

SIXTH EDITION

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Internal Medicine

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SIXTH EDITION

CASE FILES®
Internal Medicine

Eugene C. Toy, MD
Assistant Dean for Educational Programs
Director of Doctoring Courses
Professor and Vice Chair of Medical Education
Department of Obstetrics and Gynecology
McGovern Medical School at The University of Texas
Health Science Center at Houston (UTHealth)
Houston, Texas

Gabriel M. Aisenberg, MD
Associate Professor of Medicine
Department of General Internal Medicine
McGovern Medical School at The University of Texas
Health Science Center at Houston (UTHealth)
Houston, Texas

Mc Graw Hill

New York Chicago San Francisco Athens London Madrid Mexico City
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DEDICATION

To the McGovern Medical School class of 2020,
who have continued to challenge and inspire me to be the
very best teacher possible. You are the first class of our new curriculum,
and you trusted that the theoretical dreams
and abstract fancies weaving the basic and clinical sciences with the art
of medicine in the Doctoring Courses would work. Four years later,
we know it worked, primarily because each of you believed
and worked diligently to fill in the gaps that we missed.
You are each what is most special about medicine and are the reason I teach.
May you have a wonderfully fulfilling and
rewarding career, and continue to learn and heal.

—ECT

To my beloved wife, Cynthia, and my children, Lucas, Tomas, and
Carola, whose support, love, and understanding fill me
with hope, with energy, and with passion. To Dr. Herbert L. Fred,
a mentor and a friend. He may not be around,
but his light will shine forever.

—GA

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CONTENTS

Contributors / vii
Preface / xvii
Acknowledgments / xix
Introduction / xxi
Listing of Cases / xxiii

Section I
How to Approach Clinical Problems....1
Part 1. Approach to the Patient....3
Part 2. Approach to Clinical Problem-Solving....10
Part 3. Approach to Reading....13

Section II
Clinical Cases....19
Wellness (Cases 1-2)....21
Cardiovascular (Cases 3-13)....39
Pulmonary (Cases 14-19)....153
Gastrointestinal (Cases 20-23)....213
Hepatic, Gallbladder, Biliary (Cases 24-27)....255
Renal, Genitourinary (Cases 28-30)....295
Musculoskeletal (Cases 31-35)....323
Neurological (Cases 36-39)....377
Critical Care (Cases 40-41)....415
Immunological, Infectious (Cases 42-46)....435
Endocrine/Hormonal (Cases 47-53)....487
Hematological (Cases 54-58)....557
Alcohol Abuse/ Toxicology (Case 59-60)....605

Section III
Review Questions....627

Index / 641

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CONTRIBUTORS

Radhini Abeysekera, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Meningitis, Bacterial
Vascular Catheter Infection in a Patient With Neutropenic Fever

Heba Ahmad, MS3
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Anaphylaxis/Drug Reactions
Urinary Tract Infection With Sepsis in the Elderly

Kristopher Ahn, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Hepatitis

Omowunmi Aibana, MD
Assistant Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Anaphylaxis/Drug Reaction
Opioid Overdose

Madison Bangert, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute hepatitis
Hemoptysis/Lung Cancer
Pancreatitis/Gallstones

Jammie Barnes, MD
Associate Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Monoarticular Arthritis—Gout
Rheumatoid Arthritis

Christopher Bertini, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Adrenal Insufficiency
Type 2 Diabetes Diagnosis and Management
Manuscript Reviewer

Mac Bohanan, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Immune Thrombocytopenic Purpura
Symptomatic Anemia and Transfusion Medicine

Jeffrey Chen, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Immune Thrombocytopenic Purpura/Abnormal Bleeding
Symptomatic Anemia and Transfusion Medicine

Qingzheng Chen, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Aortic Dissection/Marfan Syndrome
Heart Failure due to Critical Aortic Stenosis
Manuscript Reviewer

Sujith Cherian, MD
Assistant Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Chronic Obstructive Pulmonary Disease
Chronic Cough/Asthma
Pleural Effusion, Parapneumonic

Julia Chernis, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Monoarticular Arthritis—Gout
Osteoarthritis/Degenerative Joint Disease
Lead Manuscript Reviewer

Maneera T. Chopra, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Diverticulitis
Chronic Diarrhea
Manuscript Reviewer

Amanda Clorfeine, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Community-Acquired Pneumonia

Saumil Datar, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Chronic Obstructive Pulmonary Disease
Chronic Cough/Asthma
Manuscript Reviewer

Jonathan Dau, MD
Medical Fellow
McGovern Medical School at UTHealth in Houston
Houston, Texas
Neutropenic Fever in a Patient With Vascular Catheter Infection
Meningitis, Bacterial

Joy M. Davis, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Review Questions

Olivia Drummond, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Transient Ischemic Accident
Oligomenorrhea Caused by Hypothyroidism and Hyperprolactinemia

Kim Du, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Thyrotoxicosis/Graves Disease
Manuscript Reviewer

Renee Flores, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Iron-Deficiency Anemia
Parkinson Disease

John Foringer, MD
Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Hypercalcemia/Multiple Myeloma
Hyponatremia, Syndrome of Inappropriate Secretion of Diuretic Hormone

Jinesh Gheeya, MD, PhD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Diverticulitis
Chronic Diarrhea

Rohit Goswamy, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Parkinson Disease
Tuberculosis (Pulmonary), Cavitary Lung Lesions

Renato A. Guerrieri, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Glomerulonephritis
Painless Jaundice, Pancreatic Cancer
Manuscript Reviewer

Andrew Gulde, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Coronary Syndrome
Hypertension, Outpatient
Manuscript Reviewer

Absalon Gutierrez, MD
Associate Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Adrenal Insufficiency
Oligomenorrhea Caused by Hypothyroidism and Hyperprolactinemia
Type 2 Diabetes Diagnosis and Management

Katie Guttenberg, MD
Assistant Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Osteoporosis, Cushing Syndrome

Carissa Huq, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Liver Cirrhosis, Probably Alcoholic
Limb Ischemia (Peripheral Vascular Disease)
Peptic Ulcer Disease
Colitis and Inflammatory Bowel Disease

Michael Hust, MD
Medical Fellow
McGovern Medical School at UTHealth in Houston
Houston, Texas
Aortic Dissection/Marfan Syndrome
Heart Failure due to Aortic Stenosis

Marina Kristy Ibraheim, MS3
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Diabetic Ketoacidosis, Type 1 Diabetes

Jill Jacoby, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Iron-Deficiency Anemia

Aman Jaiswal, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Manuscript Reviewer

Alyssa Kahl, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Headache/Temporal Arteritis
Health Maintenance
Manuscript Reviewer

Maha Khalid, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Pleural Effusion, Parapneumonic
Pulmonary Embolism
Manuscript Reviewer

Luana Kohnke, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Atrial Fibrillation/Mitral Stenosis
Syncope and Heart Block
Manuscript Reviewer

Alexandria Lawrence, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Low Back Pain
Rheumatoid Arthritis
Manuscript Reviewer

Jeffrey Lofgran, MD
Assistant Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Atrial Fibrillation
Hypertensive Encephalopathy/Pheochromocytoma
Syncope and Heart Block
Urinary Tract Infection With Sepsis in the Elderly

Kristine McAndrews, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Kidney Injury
Nephrotic Syndrome and Diabetic Nephropathy
Manuscript Reviewer

Daniel McNavish, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Pancreatitis/Gallstones
Hemoptysis/Lung Cancer
Manuscript Reviewer

Annika Medhus, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Sickle Cell Crisis

Lauren Mellor-Crummey, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Manuscript Reviewer

Avni Mody, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Osteoporosis, Cushing Syndrome

Tyler Novy, MS3
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Hypercalcemia/Multiple Myeloma
Hyponatremia, Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Vivian Okirie, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Community-Acquired Pneumonia
HIV/AIDS and Pneumocystis *Pneumonia*
Syphilis

Justin M. Olivas, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Peptic Ulcer Disease
Colitis and Inflammatory Bowel Disease
Manuscript Reviewer

Elizabeth Park, MD
Assistant Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Diabetic Ketoacidosis, Type 1 Diabetes
Thyrotoxicosis/Graves Disease

Nicola Park, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Pericardial Effusion/Tamponade Caused by Malignancy
Acute Pericarditis caused by Systemic Lupus Erythematosus

Anish Patnaik, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Limb Ischemia (Peripheral Vascular Disease)
Manuscript Reviewer

Abin Puravath, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Peptic Ulcer Disease
Colitis and Inflammatory Bowel Disease

Saher Rabadi, MD
Assistant Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Hypertension, Outpatient
Acute Coronary Syndrome

Nayana Ramachandra, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Hypertensive Encephalopathy/Pheochromocytoma
Manuscript Reviewer

Chelsea T. Ratliff, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Tuberculosis (Pulmonary), Cavitary Lung Lesions
Manuscript Reviewer

Tiffany Robles, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Endocarditis (Tricuspid)/Septic Pulmonary Emboli

Daniel Rongo, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Alzheimer Disease/Dementia
Delirium/Alcohol Withdrawal
Transient Ischemic Attack

Monica Rosales Santillan, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Headache/Temporal Arteritis
Health Maintenance

Jennifer Swails, MD
Associate Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Metabolic Syndrome
Polycythemia Vera

Tuan Tang, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Alzheimer Disease/Dementia
Manuscript Reviewer

Jade Teakell, MD
Assistant Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Kidney Injury
Nephrotic Syndrome and Diabetic Nephropathy

Evangelia Valilis, MD
Medical Resident
McGovern Medical School at UTHealth in Houston
Houston, Texas
Syphilis

Connor Vershel, MS4
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
Delirium/Alcohol Withdrawal
Manuscript Reviewer

Robby Wesley, MD
Associate Professor of Medicine
McGovern Medical School at UTHealth in Houston
Houston, Texas
Acute Glomerulonephritis
Painless Jaundice, Pancreatic Cancer

Jacqueline Woloski, MS3
Medical Student
McGovern Medical School at UTHealth in Houston
Houston, Texas
HIV/AIDS and Pneumocystis *Pneumonia*

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PREFACE

I have been deeply amazed and grateful to see how the *Case Files®* books have been so well received and have helped students to learn more effectively. In the 16 short years since *Case Files® Internal Medicine* was first printed, the series has now multiplied to span most of the clinical and the basic science disciplines and has been translated into over a dozen foreign languages. Numerous students have sent encouraging remarks, suggestions, and recommendations. Six completely new cases have been written. The cases have retained the organ system organization for better ability to integrate knowledge. Case correlation references are also used in this edition. This sixth edition has been a collaborative work with my wonderful coauthors and contributors and with the suggestions from six generations of students. We utilized focus groups of students to create a more user-friendly format for the digital platform, such as bullet points for the case summary for faster reading and more plentiful use of subheadings throughout the text. We have used entrustable professional activities (EPA) corresponding to the learning objectives. The multiple-choice questions (MCQs) have been carefully reviewed and rewritten to ensure that they comply with the National Board and the US Medical Licensing Examination format. Truly, the enthusiastic encouragement from students throughout not only the United States but also the world provides me the inspiration and energy to continue to write. It is thus with humility that I offer my sincere thanks to students everywhere … for without students, how can a teacher teach?

Eugene C. Toy

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The curriculum that evolved into the ideas for this series was inspired by Philbert Yau and Chuck Rosipal, two talented and forthright students, who have since graduated from medical school. It has been a tremendous joy to work with my excellent coauthor, Dr. Gabriel Aisenberg, who exemplifies the qualities of the ideal physician—caring, empathetic, and avid teacher, and who is intellectually unparalleled. He had "big shoes" to fill in taking over from my dear friend and colleague Dr. John Patlan, who has retired from academics and is currently in private practice. We owe John a great debt for setting such a "high bar" with five excellent editions of this book. Dr. Aisenberg would like to acknowledge Dr. Herbert Fred, a master educator, teacher of the value of hard work and skepticism. Dr. Aisenberg and I would like to express appreciation to Julia Chernis, who helped to coordinate the assignment of cases and served as our student representative, including a thorough student review for each case and careful reading of content, readability, and questions/explanations. Julia is a special person and will succeed wherever she goes. Julia would like to acknowledge Michael Kuhlmeier for his never-ending love and support, as well as her amazing grandmother, Dr. Nadya Natanzon, whose stories of her pediatric practice inspired her to pursue a career in medicine.

I am greatly indebted to Bob Boehringer, whose experience and vision helped to support this series. I appreciate McGraw Hill's believing in the concept of teaching through clinical cases. I am also grateful to Catherine Saggese for her excellent production expertise, and Madison Tucky for her wonderful and meticulous role as editorial assistant. I cherish the ever-organized and precise project manager, Sarika Gupta. It has been a privilege and honor to work with one of the brightest medical students I have encountered, Joy Davis, who directed the review questions and answers and gave input on the explanations for all the comprehension questions. As always, my daughter Allison serves as the assistant editor for the Case Files Collection and has been meticulous and insightful concerning her review and editing of this manuscript; she is like the key enzyme of the case files chemical reactions, without whom all meaningful activity ceases and with whom the words and concepts leap off the page with vigor and life. Most of all, I appreciate my ever-loving wife, Terri, and our four wonderful children, Andy and his wife Anna, Michael and his wife Nadine, Allison, and Christina and her husband Andy, for their patience and understanding.

Eugene C. Toy

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Mastering the cognitive knowledge within a field such as internal medicine is a formidable task. It is even more difficult to draw on that knowledge, procure and filter through the clinical and laboratory data, develop a differential diagnosis, and, finally, make a rational treatment plan. To gain these skills, the student learns best at the bedside, guided and instructed by experienced teachers, and inspired toward self-directed, diligent reading. Clearly, there is no replacement for education at the bedside. Unfortunately, clinical situations usually do not encompass the breadth of the specialty. Perhaps the best alternative is a carefully crafted patient case designed to stimulate the clinical approach and the decision-making process. In an attempt to achieve that goal, we have constructed a collection of clinical vignettes to teach diagnostic or therapeutic approaches relevant to internal medicine.

Most importantly, the explanations for the cases emphasize the mechanisms and underlying principles, rather than merely rote questions and answers. This book is organized for versatility: It allows the student "in a rush" to go quickly through the scenarios and check the corresponding answers, and it allows the student who wants thought-provoking explanations to obtain them. The answers are arranged from simple to complex: the bare answers, an analysis of the case, an approach to the pertinent topic, a comprehension test at the end, clinical pearls for emphasis, and a list of references for further reading. The clinical vignettes are organized by system to help students compare and contrast, and integrate information. A listing of cases is included later in this section to aid the student who desires to test his or her knowledge of a certain area, or to review a topic, including basic definitions. Finally, we intentionally did not use a multiple-choice question format in the case scenarios because clues (or distractions) are not available in the real world.

HOW TO GET THE MOST OUT OF THIS BOOK

Each case is designed to simulate a patient encounter with open-ended questions. At times, the patient's complaint is different from the most concerning issue, and sometimes extraneous information is given. The answers are organized into four different parts, discussed next.

CLINICAL CASE FORMAT: PART I

1. **Summary:** The salient aspects of the case are identified, filtering out the extraneous information. Students should formulate their summary from the case before looking at the answers. A comparison to the summation in the answer will help to improve their ability to focus on the important data, while appropriately discarding the irrelevant information—a fundamental skill in clinical problem-solving.
2. **A straightforward Answer** is given to each open-ended question.

Table 1 • SYNOPSIS OF ENTRUSTABLE PROFESSIONAL ACTIVITIES	
EPA 1	Gather a history and perform a physical examination
EPA 2	Prioritize a differential diagnosis following a clinical encounter
EPA 3	Recommend and interpret common diagnostic and screening tests
EPA 4	Enter and discuss orders and prescriptions
EPA 5	Document a clinical encounter in the patient record
EPA 6	Provide an oral presentation of a clinical encounter
EPA 7	Form clinical questions and retrieve evidence to advance patient care
EPA 8	Give or receive a patient handover to transition care responsibly
EPA 9	Collaborate as a member of a interprofessional team
EPA 10	Recognize a patient requiring urgent or emergent care and initiate evaluation and management
EPA 11	Obtain informed consent for tests and/or procedures
EPA 12	Perform general procedures as a physician
EPA 13	Identify system failures and contribute to a culture of safety and improvement

3. **The Analysis of the case** comprises two parts:
   a. **Objectives of the Case:** A listing of the two or three main principles that are crucial for a practitioner to manage the patient. Again, the students are challenged to make educated "guesses" about the objectives of the case upon initial review of the case scenario, which helps to sharpen their clinical and analytical skills. We have included the entrustable professional activities (EPA) corresponding to the objective for instructors and curriculum overseers (see Table 1).
   b. **Considerations:** A discussion of the relevant points and brief approach to the specific patient.

PART II

Approach to the Disease Process: It consists of two distinct parts:
   a. **Definitions:** Terminology pertinent to the disease process.
   b. **Clinical Approach:** A discussion of the approach to the clinical problem in general, including tables, figures, and algorithms.

PART III

Comprehension Questions: Each case contains several multiple-choice questions, which reinforce the material or which introduce new and related concepts. Questions about material not found in the text will have explanations in the answers.

PART IV

Clinical Pearls: Several clinically important points are reiterated as a summation of the text. This allows for easy review, such as before an examination.

LISTING BY CASE NUMBER

CASE NO.	SYSTEM	CASE TOPIC	PAGE NUMBER
	Wellness		
1		Health Maintenance	22
2		Metabolic Syndrome	30
	Cardiovascular		
3		Acute Coronary Syndrome	40
4		Heart Failure due to Critical Aortic Stenosis	56
5		Aortic Dissection/Marfan Syndrome	66
6		Hypertension, Outpatient	76
7		Hypertensive Encephalopathy/ Pheochromocytoma	90
8		Atrial Fibrillation/Mitral Stenosis	100
9		Syncope and Heart Block	110
10		Acute Pericarditis Caused by Systemic Lupus Erythematosus	119
11		Pericardial Effusion/Tamponade Caused by Malignancy	126
12		Endocarditis (Tricuspid)/Septic Pulmonary Emboli	134
13		Limb Ischemia (Peripheral Vascular Disease)	144
	Pulmonary		
14		Pulmonary Embolism	154
15		Chronic Obstructive Pulmonary Disease	164
16		Chronic Cough/Asthma	174
17		Pleural Effusion, Parapneumonic	185
18		Hemoptysis/Lung Cancer	194
19		Community-Acquired Pneumonia	204
	Gastrointestinal		
20		Peptic Ulcer Disease	214
21		Colitis and Inflammatory Bowel Disease	222
22		Acute Diverticulitis	232
23		Chronic Diarrhea	242
	Hepatic, Gallbladder, Biliary		
24		Liver Cirrhosis, Probably Alcoholic	256

25	Pancreatitis/Gallstones	266
26	Acute Hepatitis	276
27	Painless Jaundice, Pancreatic Cancer	288
	Renal, Genitourinary	
28	Acute Glomerulonephritis	296
29	Nephrotic Syndrome and Diabetic Nephropathy	306
30	Acute Kidney Injury	314
	Musculoskeletal	
31	Osteoarthritis/Degenerative Joint Disease	324
32	Low Back Pain	332
33	Acute Monoarticular Arthritis—Gout	342
34	Rheumatoid Arthritis	354
35	Osteoporosis, Cushing Syndrome	364
	Neurological	
36	Transient Ischemic Attack	378
37	Alzheimer Disease/Dementia	388
38	Headache/Temporal Arteritis	398
39	Parkinson Disease	406
	Critical Care	
40	Anaphylaxis/Drug Reactions	416
41	Urinary Tract Infection With Sepsis in the Elderly	426
	Immunological, Infectious	
42	Vascular Catheter Infection in a Patient With Neutropenic Fever	436
43	Meningitis, Bacterial	444
44	Tuberculosis (Pulmonary), Cavitary Lung Lesions	457
45	Syphilis	466
46	HIV/AIDS and *Pneumocystis* Pneumonia	477
	Endocrine/Hormonal	
47	Hyponatremia, Syndrome of Inappropriate Secretion of Antidiuretic Hormone	488
48	Oligomenorrhea Caused by Hypothyroidism and Hyperprolactinemia	498
49	Adrenal Insufficiency	508
50	Hypercalcemia/Multiple Myeloma	517
51	Type 2 Diabetes Diagnosis and Management	526
52	Diabetic Ketoacidosis, Type 1 Diabetes	536
53	Thyrotoxicosis/Graves Disease	548

	Hematological	
54	Iron-Deficiency Anemia	558
55	Symptomatic Anemia and Transfusion Medicine	570
56	Immune Thrombocytopenic Purpura/ Abnormal Bleeding	578
57	Polycythemia Vera	588
58	Sickle Cell Crisis	598
	Alcohol Abuse/Toxicology	
59	Delirium/Alcohol Withdrawal	606
60	Opioid Overdose	616

LISTING BY DISORDER (ALPHABETICAL)

CASE NO.	CASE TOPIC	PAGE NUMBER
3	Acute Coronary Syndrome	40
22	Acute Diverticulitis	232
28	Acute Glomerulonephritis	296
26	Acute Hepatitis	276
30	Acute Kidney Injury	314
33	Acute Monoarticular Arthritis—Gout	342
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37	Alzheimer Disease/Dementia	388
40	Anaphylaxis/Drug Reactions	416
5	Aortic Dissection/Marfan Syndrome	66
8	Atrial Fibrillation/Mitral Stenosis	100
16	Chronic Cough/Asthma	174
23	Chronic Diarrhea	242
15	Chronic Obstructive Pulmonary Disease	164
21	Colitis and Inflammatory Bowel Disease	222
19	Community-Acquired Pneumonia	204
59	Delirium/Alcohol Withdrawal	606
52	Diabetic Ketoacidosis, Type 1 Diabetes	536
12	Endocarditis (Tricuspid)/Septic Pulmonary Emboli	134
38	Headache/Temporal Arteritis	398
1	Health Maintenance	22
4	Heart Failure due to Critical Aortic Stenosis	56

18	Hemoptysis/Lung Cancer	194
46	HIV/AIDS and *Pneumocystis* Pneumonia	477
50	Hypercalcemia/Multiple Myeloma	517
6	Hypertension, Outpatient	76
7	Hypertensive Encephalopathy/Pheochromocytoma	90
47	Hyponatremia, Syndrome of Inappropriate Secretion of Antidiuretic Hormone	488
56	Immune Thrombocytopenic Purpura/Abnormal Bleeding	578
54	Iron-Deficiency Anemia	558
13	Limb Ischemia (Peripheral Vascular Disease)	144
24	Liver Cirrhosis, Probably Alcoholic	256
32	Low Back Pain	332
43	Meningitis, Bacterial	444
2	Metabolic Syndrome	30
29	Nephrotic Syndrome and Diabetic Nephropathy	306
48	Oligomenorrhea Caused by Hypothyroidism and Hyperprolactinemia	498
60	Opioid Overdose	616
31	Osteoarthritis/Degenerative Joint Disease	324
35	Osteoporosis, Cushing Syndrome	364
27	Painless Jaundice, Pancreatic Cancer	288
25	Pancreatitis/Gallstones	266
39	Parkinson Disease	406
20	Peptic Ulcer Disease	214
11	Pericardial Effusion/Tamponade Caused by Malignancy	126
17	Pleural Effusion, Parapneumonic	185
57	Polycythemia Vera	588
14	Pulmonary Embolism	154
34	Rheumatoid Arthritis	354
58	Sickle Cell Crisis	598
55	Symptomatic Anemia and Transfusion Medicine	570
9	Syncope and Heart Block	110
45	Syphilis	466
53	Thyrotoxicosis/Graves Disease	548
36	Transient Ischemic Attack	378
44	Tuberculosis (Pulmonary), Cavitary Lung Lesions	457
51	Type 2 Diabetes Diagnosis and Management	526
41	Urinary Tract Infection With Sepsis in the Elderly	426
42	Vascular Catheter Infection in a Patient With Neutropenic Fever	436

SECTION I

How to Approach Clinical Problems

Part 1 Approach to the Patient

Part 2 Approach to Clinical Problem-Solving

Part 3 Approach to Reading

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Part 1. Approach to the Patient

The transition from the textbook or journal article to the clinical situation is one of the most challenging tasks in medicine. Retention of information is difficult; organization of the facts and recall of myriad data in precise application to the patient are crucial. The purpose of this text is to facilitate in this process. The first step is gathering information, also known as establishing the database. This includes taking the history (asking questions), performing the physical examination, and obtaining selective laboratory and/or imaging tests. Of these, the historical examination is the most important and useful. Sensitivity and respect should always be exercised during the interview of patients.

CLINICAL PEARL

- The history is the single most important tool in obtaining a diagnosis. All physical findings and laboratory and imaging studies are first obtained and then interpreted in the light of the pertinent history.

HISTORY

1. **Basic information:** Age, gender, and ethnicity must be recorded because some conditions are more common at certain ages; for instance, pain on defecation and rectal bleeding in a 20-year-old may indicate inflammatory bowel disease, whereas the same symptoms in a 60-year-old would more likely suggest colon cancer.

2. **Chief complaint:** What is it that brought the patient into the hospital or clinic? Is it a scheduled appointment or an unexpected symptom? The patient's own words should be used if possible, such as, "I feel like a ton of bricks are on my chest." The chief complaint, or reason for seeking medical attention, may not be the first subject the patient talks about (in fact, it may be the last thing), particularly if the subject is embarrassing, such as a sexually transmitted disease, or highly emotional, such as depression. It is often useful to clarify exactly what the patient's concern is; for example, the patient may fear the headaches represent an underlying brain tumor.

3. **History of present illness:** This is the most crucial part of the entire database. The questions one asks are guided by the differential diagnosis one begins to consider the moment the patient identifies the chief complaint, as well as the clinician's knowledge of typical disease patterns and their natural history. The duration and character of the primary complaint, associated symptoms, and exacerbating/relieving factors should be recorded. Sometimes, the history will be convoluted and lengthy, with multiple diagnostic or therapeutic interventions at different locations. For patients with chronic illnesses, obtaining prior medical records is invaluable. For example, when extensive evaluation of

a complicated medical problem has been done elsewhere, it is usually better to first obtain those results than to repeat a "million-dollar workup." When reviewing prior records, it is often useful to review the primary data (eg, biopsy reports, echocardiograms, serologic evaluations) rather than to rely upon a diagnostic label applied by someone else, which then gets replicated in medical records and, by repetition, acquires the aura of truth, when it may not be fully supported by data. Some patients will be poor historians because of dementia, confusion, or language barriers; recognition of these situations and querying of family members are useful. When little or no history is available to guide a focused investigation, more extensive objective studies are often necessary to exclude potentially serious diagnoses.

4. **Past history:**
   a. **Illness:** Any illnesses such as hypertension, hepatitis, diabetes mellitus, cancer, heart disease, pulmonary disease, and thyroid disease should be elicited. If an existing or prior diagnosis is not obvious, it is useful to ask exactly how it was diagnosed, that is, what investigations were performed. Duration, severity, and therapies should be queried.
   b. **Hospitalization:** Any hospitalizations and emergency room visits should be listed with the reason(s) for admission, the intervention, and the location of the hospital.
   c. **Blood transfusion:** Transfusions with any blood products should be listed, including any adverse reactions.
   d. **Surgeries:** The year and type of surgery should be elucidated and any complications documented. The type of incision and any untoward effects of the anesthesia or the surgery should be noted.

5. **Allergies:** Reactions to medications should be recorded, including severity and temporal relationship to the medication. An adverse effect (eg, nausea) should be differentiated from a true allergic reaction.

6. **Medications:** Current and previous medications should be listed, including dosage, route, frequency, and duration of use. Prescription, over-the-counter, and herbal medications are all relevant. Patients often forget their complete medication list; thus, asking each patient to bring in all their medications—both prescribed and nonprescribed—allows for a complete inventory.

7. **Family history:** Many conditions are inherited or are predisposed in family members. The age and health of siblings, parents, grandparents, and others can provide diagnostic clues. For instance, an individual with first-degree family members with early-onset coronary heart disease is at risk for cardiovascular disease.

8. **Social history:** This is one of the most important parts of the history in that the patient's functional status at home, social and economic circumstances, and goals and aspirations for the future are often the critical determinant in what the best way to manage a patient's medical problem is. Living arrangements,

economic situations, and religious affiliations may provide important clues for puzzling diagnostic cases or suggest the acceptability of various diagnostic or therapeutic options. Marital status and habits such as alcohol, tobacco, or illicit drug use may be relevant as risk factors for disease. More specifically in the domain of infectious diseases, understanding how many people the patient cohabitates with, whether those people are known to be sick, the presence of pets at home, and the recent travel history are noteworthy.

9. **Review of systems:** A few questions about each major body system ensure that problems will not be overlooked. The clinician should avoid the mechanical "rapid-fire" questioning technique that discourages patients from answering truthfully because of fear of "annoying the doctor."

PHYSICAL EXAMINATION

The physical examination begins as one is taking the history, by observing the patient and beginning to consider a differential diagnosis. When performing the physical examination, one focuses on body systems suggested by the differential diagnosis and performs tests or maneuvers with specific questions in mind; for example, does the patient with jaundice have ascites? When the physical examination is performed with potential diagnoses and expected physical findings in mind ("one sees what one looks for"), the utility of the examination in adding to diagnostic yield is greatly increased, as opposed to an unfocused "head-to-toe" physical examination.

1. **General appearance:** A great deal of information is gathered by observation, as one notes the patient's body habitus, state of grooming, nutritional status, level of anxiety (or perhaps inappropriate indifference), degree of pain or comfort, mental status, speech patterns, and use of language. This forms your impression of "who this patient is."

2. **Vital signs:** Vital signs like temperature, blood pressure, heart rate, respiratory rate, height, and weight are often placed here. Blood pressure can sometimes be different in the two arms; initially, it should be measured in both arms. In patients with suspected hypovolemia, pulse and blood pressure should be taken in lying and standing positions to look for orthostatic hypotension. It is quite useful to take the vital signs oneself, rather than relying upon numbers gathered by ancillary personnel using automated equipment, because important decisions regarding patient care are often made using the vital signs as an important determining factor.

3. **Head and neck examination:** Facial or periorbital edema and pupillary responses should be noted. Fundoscopic examination provides a way to visualize the effects of diseases such as diabetes on the microvasculature; papilledema can signify increased intracranial pressure. Estimation of jugular venous pressure is very useful to estimate volume status. The thyroid should be palpated for a goiter or nodule and carotid arteries auscultated for bruits. Cervical (common) and supraclavicular (pathologic) nodes should be palpated.

4. **Breast examination:** Inspect for symmetry and for skin or nipple retraction with the patient's hands on her hips (to accentuate the pectoral muscles) and also with arms raised. With the patient sitting and supine, the breasts should then be palpated systematically to assess for masses. The nipple should be assessed for discharge, and the axillary and supraclavicular regions should be examined for adenopathy.

5. **Cardiac examination:** The point of maximal impulse should be ascertained for size and location, and the heart should be auscultated at the apex and at the base. Heart sounds, murmurs, and clicks should be characterized. Murmurs should be classified according to intensity, duration, timing in the cardiac cycle, and changes with various maneuvers. Systolic murmurs are very common and often physiologic; diastolic murmurs are uncommon and usually pathologic. The patient's body habitus and the environmental noise limit the quality of the heart auscultation; always search for a quiet place to examine the patient's heart.

6. **Pulmonary examination:** The lung fields should be examined systematically and thoroughly. Wheezes, rales, rhonchi, and bronchial breath sounds should be recorded. Percussion of the lung fields may be helpful in identifying the hyperresonance of tension pneumothorax or the dullness of consolidated pneumonia or a pleural effusion.

7. **Abdominal examination:** The abdomen should be inspected for scars, distension, or discoloration (eg, the Grey Turner sign of discoloration at the flank areas indicating intra-abdominal or retroperitoneal hemorrhage). Auscultation of bowel sounds can identify normal versus high pitched and hyperactive versus hypoactive. Percussion of the abdomen can be utilized to assess the size of the liver and spleen and to detect ascites by noting shifting dullness. Careful palpation should begin initially away from the area of pain, involving one hand on top of the other, to assess for masses, tenderness, and peritoneal signs. Tenderness should be recorded on a scale (eg, 1–4 where 4 is the most severe pain). Guarding, and whether it is voluntary or involuntary, should be noted.

8. **Back and spine examination:** The back should be assessed for symmetry, tenderness, and masses. The flank regions are particularly important to assess for pain on percussion, which might indicate renal disease.

9. **Genitalia:**
    a. **Females:** The pelvic examination should include an inspection of the external genitalia and, with the speculum, evaluation of the vagina and cervix. A Papanicolaou test (Pap smear) and/or cervical cultures may be obtained. A bimanual examination to assess the size, shape, and tenderness of the uterus and adnexa is important.
    b. **Males:** An inspection of the penis and testes is performed. Evaluation for masses, tenderness, and lesions is important. Palpation for hernias in the inguinal region with the patient standing and coughing to increase intra-abdominal pressure is useful.

10. **Rectal examination:** A digital rectal examination is generally performed for those individuals with possible colorectal disease or gastrointestinal bleeding. Masses should be assessed, and stool for occult blood should be tested. In men, the prostate gland can be assessed for enlargement and for nodules.
11. **Extremities:** An examination for joint effusions, tenderness, edema, and cyanosis may be helpful. Clubbing of the nails might indicate pulmonary diseases such as lung cancer or chronic cyanotic heart disease.
12. **Neurologic examination:** Patients who present with neurologic complaints usually require a thorough assessment, including mental status, cranial nerves, motor strength, sensation, and reflexes.
13. **Skin examination:** The skin should be carefully examined for evidence of pigmented lesions (melanoma), cyanosis, or rashes that may indicate systemic disease (malar rash of systemic lupus erythematosus).

LABORATORY AND IMAGING ASSESSMENT

1. **Laboratory:**
   a. **Complete blood count** (CBC): The CBC is used to assess for anemia and thrombocytopenia.
   b. **Serum chemistry:** A chemistry panel is most commonly used to evaluate renal and liver function, as well as glucose levels.
   c. **Hemoglobin A_{1c}:** this fraction of the total hemoglobin represents the addition of glucose residues, which is proportional to the serum glucose levels, but more stable than they are, thus providing with a more thorough assessment of the control of diabetes mellitus.
   d. **Lipid panel:** The lipid panel is particularly relevant in cardiovascular diseases.
   e. **Urinalysis:** Urinalysis is often referred to as a "liquid renal biopsy" because the presence of cells, casts, protein, or bacteria provides clues about underlying glomerular or tubular diseases.
   f. **Infection:** Gram stain and culture of urine, sputum, and cerebrospinal fluid, as well as blood cultures, are frequently useful to isolate the cause of infection.
2. **Imaging procedures:**
   a. **Chest radiography:** Chest radiography is extremely useful in assessing cardiac size and contour, chamber enlargement, pulmonary vasculature and infiltrates, and the presence of pleural effusions.
   b. **Ultrasonographic examination:** Ultrasonographic examination is useful for identifying fluid-solid interfaces and for characterizing masses as cystic, solid, or complex. It is also very helpful in evaluating the biliary tree, kidney size, and evidence of ureteral obstruction and can be combined with Doppler flow to identify deep venous thrombosis. Ultrasonography is noninvasive and has no radiation risk, but it cannot be used to penetrate through bone or air and is less useful in obese patients.

CLINICAL PEARL

- Ultrasonography is helpful in evaluating the biliary tree, looking for ureteral obstruction, and evaluating vascular structures, but it has limited utility in obese patients.

c. **Computed tomography:** Computed tomography (CT) is helpful in possible intracranial bleeding, abdominal and/or pelvic masses, and pulmonary processes and may help to delineate the lymph nodes and retroperitoneal disorders. CT exposes the patient to radiation and requires the patient to be immobilized during the procedure. Generally, CT requires administration of a radiocontrast dye, which can be nephrotoxic.

d. **Magnetic resonance imaging:** Magnetic resonance imaging (MRI) identifies soft-tissue planes very well and provides the best imaging of the brain parenchyma. When used with gadolinium contrast (which is not nephrotoxic), MR angiography (MRA) is useful for delineating vascular structures. MRI does not use radiation, but the powerful magnetic field prohibits its use in patients with ferromagnetic metal in their bodies, for example, many prosthetic devices.

e. **Cardiac procedures:**

   i. **Echocardiography:** Echocardiography uses ultrasonography to delineate the cardiac size, function, ejection fraction, and presence of valvular dysfunction.

   ii. **Angiography:** Radiopaque dye is injected into various vessels, and radiographs or fluoroscopic images are used to determine the vascular occlusion, cardiac function, or valvular integrity.

   iii. **Stress treadmill tests:** Individuals at risk for coronary heart disease are monitored for blood pressure, heart rate, and chest pain, and an electrocardiogram (ECG) is performed while increasing oxygen demands on the heart, such as running on a treadmill, are made. Nuclear medicine imaging of the heart can be added to increase the sensitivity and specificity of the test. Individuals who cannot run on the treadmill (eg, those with severe arthritis) may be given medications such as adenosine or dobutamine to "stress" the heart.

INTERPRETATION OF TEST RESULTS: USING PRETEST PROBABILITY AND LIKELIHOOD RATIO

Because no test is 100% accurate, it is essential when ordering a test to have some knowledge of the test's characteristics, as well as how to apply the test results to an **individual patient's clinical** situation. Let us use the example of a patient with chest pain. The first diagnostic concern of most patients and physicians regarding chest pain is **angina pectoris**, that is, the pain of myocardial ischemia caused by coronary insufficiency. Distinguishing angina pectoris from other causes of chest pain relies

upon two important factors: the clinical history and an understanding of how to use objective testing. In making the diagnosis of angina pectoris, the clinician must establish whether the pain satisfies the **three criteria for typical anginal pain**: (1) retrosternal in location, (2) precipitated by exertion, and (3) relieved within minutes by rest or nitroglycerin. Then, the clinician considers other factors, such as patient age and other risk factors, to determine a **pretest probability** for angina pectoris.

After a pretest probability is estimated by applying some combination of statistical data, epidemiology of the disease, and clinical experience, the next decision is whether and how to use an objective test. **A test should only be ordered if the results would change the posttest probability high enough or low enough in either direction that it will affect the decision-making process.** For example, a 21-year-old woman with chest pain that is not exertional and not relieved by rest or nitroglycerin has a very low pretest probability of coronary artery disease (CAD), and any positive results on a cardiac stress test are very likely to be false positive. Any test result is unlikely to change her management; thus, the test should not be obtained. Similarly, a 69-year-old diabetic smoker with a recent coronary angioplasty who now has recurrent episodes of typical angina has a very high pretest probability that the pain is a result of myocardial ischemia. One could argue that a negative cardiac stress test is likely to be falsely negative, and that the clinician should proceed directly to a coronary angiography to assess for a repeat angioplasty. **Diagnostic tests, therefore, are usually most useful for those patients** in the midranges of pretest probabilities in whom a positive or negative test will move the clinician past some decision threshold.

In the case of diagnosing a patient with atherosclerotic CAD, one test that is frequently used is the exercise treadmill test. Patients are monitored on an ECG while they perform graded exercise on a treadmill. A positive test is the development of ST-segment depression during the test; the greater the degree of ST depression, the more useful the test becomes in raising the posttest probability of CAD. In the example illustrated by Figure I–1, if a patient has a pretest probability of CAD of 50%, then the test result of 2 mm of ST-segment depression raises the posttest probability to 90%.

If one knows the sensitivity and specificity of the test used, one can calculate the **likelihood ratio** of the positive test as **sensitivity/(1 – specificity)**. Posttest probability is calculated by multiplying the positive likelihood ratio by the pretest probability, or plotting the probabilities using a nomogram (see Figure I–1).

Thus, knowing something about the characteristics of the test you are employing and how to apply them to the patient at hand are essential in reaching a correct diagnosis and to avoid falling into the common trap of "positive test = disease" and "negative test = no disease." Stated another way, **tests do not make diagnoses; providers do, considering test results quantitatively in the context of their clinical assessment.**

CLINICAL PEARL

- If test result is positive,

  Posttest Probability = Pretest Probability × Likelihood Ratio
  Likelihood Ratio = Sensitivity/(1 – Specificity)

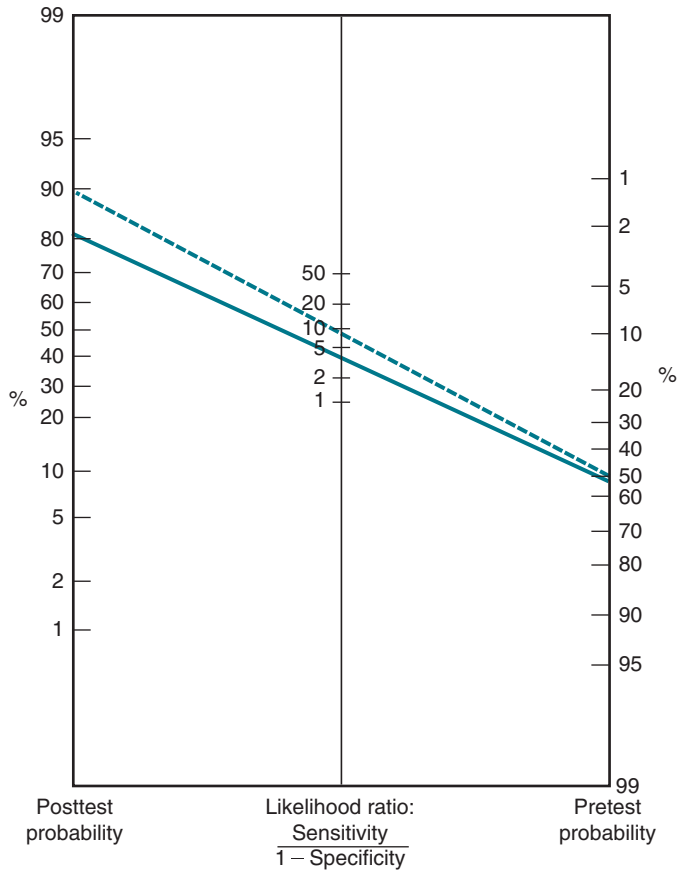


Figure I–1. Nomogram illustrating the relationship between pretest probability, posttest probability, and likelihood ratio. (Reproduced with permission, from Braunwald E, Fauci AS, Kasper KL, et al. *Harrison's Principles of Internal Medicine*. 16th ed. 2005. Copyright © McGraw Hill LLC. All rights reserved.)

Part 2. Approach to Clinical Problem-Solving

There are typically four distinct steps to the systematic solving of clinical problems:

1. Making the diagnosis
2. Assessing the severity of the disease (stage)
3. Rendering a treatment based on the stage of the disease
4. Following the patient's response to the treatment

MAKING THE DIAGNOSIS

There are two ways to make a diagnosis. Experienced clinicians often make a diagnosis very quickly using **pattern recognition**, that is, the features of the patient's

illness match a scenario the provider has seen before. If it does not fit a readily recognized pattern, then one has to undertake several steps in diagnostic reasoning:

1. The first step is to **gather information with a differential diagnosis in mind**. The clinician should start considering diagnostic possibilities with initial contact with the patient; these possibilities are continually refined as information is gathered. Historical questions and physical examination tests and findings are all tailored to the potential diagnoses one is considering. This is the principle that "you find what you are looking for." When one is trying to perform a thorough head-to-toe examination, for instance, without looking for anything in particular, one is much more likely to miss findings.

2. The next step is to try to move from subjective complaints or nonspecific symptoms to focus on objective abnormalities in an effort to **conceptualize the patient's objective problem with the greatest specificity one can achieve.** For example, a patient may come to the physician complaining of pedal edema, a relatively common and nonspecific finding. Laboratory testing may reveal that the patient has renal failure, a more specific cause of the many causes of edema. Examination of the urine may then reveal red blood cell casts, indicating glomerulonephritis, which is even more specific as the cause of the renal failure. The patient's problem, then, described with the greatest degree of specificity, is glomerulonephritis. The clinician's task at this point is to consider the differential diagnosis of glomerulonephritis rather than that of pedal edema.

3. The last step is to **look for discriminating features** of the patient's illness. This means the features of the illness, which by their presence or their absence narrow the differential diagnosis. This is often difficult for junior learners because it requires a well-developed knowledge base of the typical features of disease so the diagnostician can judge how much weight to assign to the various clinical clues present. For example, in the diagnosis of a patient with a fever and productive cough, the finding by chest x-ray of bilateral apical infiltrates with cavitation is highly discriminatory. There are few illnesses besides tuberculosis that are likely to produce that radiographic pattern. A negatively predictive example is a patient with exudative pharyngitis who also has rhinorrhea and cough. The presence of these features makes the diagnosis of streptococcal infection unlikely as the cause of the pharyngitis. Once the differential diagnosis has been constructed, the clinician uses the presence of discriminating features, knowledge of patient risk factors, and the epidemiology of diseases to decide which potential diagnoses are most likely.

CLINICAL PEARL

- There are three steps in diagnostic reasoning:
  1. Gathering information with a differential diagnosis in mind
  2. Identifying the objective abnormalities with the greatest specificity
  3. Looking for discriminating features to narrow the differential diagnosis

Once the most specific problem has been identified and a differential diagnosis of that problem is considered using discriminating features to order the possibilities, the next step is to consider using diagnostic testing, such as laboratory, radiologic, or pathologic data, to confirm the diagnosis. Quantitative reasoning in the use and interpretation of tests was discussed in Part 1. Clinically, the timing and effort with which one pursues a definitive diagnosis using objective data depend on several factors: the potential gravity of the diagnosis in question, the clinical state of the patient, the potential risks of diagnostic testing, and the potential benefits or harms of empiric treatment. For example, if a young man is admitted to the hospital with bilateral pulmonary nodules on chest x-ray, there are many possibilities, including metastatic malignancy, and aggressive pursuit of a diagnosis is necessary, perhaps including a thoracotomy with an open-lung biopsy. The same radiographic findings in an elderly bed-bound woman with advanced Alzheimer dementia who would not be a good candidate for chemotherapy might be best left alone without any diagnostic testing. Decisions like this are difficult, require solid medical knowledge, as well as a thorough understanding of one's patient and the patient's background and inclinations. Thus, this combination of skills constitute the art of medicine.

ASSESSING THE SEVERITY OF THE DISEASE

After ascertaining the diagnosis, the next step is to characterize the severity of the disease process; in other words, it is describing "how bad" a disease is. There is usually prognostic or treatment significance based on the stage. With malignancy, this is done formally by cancer staging. Most cancers are categorized from stage I (localized) to stage IV (widely metastatic). Some diseases, such as congestive heart failure, may be designated as mild, moderate, or severe based on the patient's functional status, that is, their ability to exercise before becoming dyspneic. With some infections, such as syphilis, the staging depends on the duration and extent of the infection and follows along the natural history of the infection (ie, primary syphilis, secondary, latent period, and tertiary/neurosyphilis).

RENDERING A TREATMENT BASED ON THE STAGE OF THE DISEASE

Many illnesses are stratified according to severity because prognosis and treatment often vary based on the severity. If neither the prognosis nor the treatment was affected by the stage of the disease process, there would not be a reason to subcategorize as mild or severe. As an example, a man with mild chronic obstructive pulmonary disease (COPD) may be treated with inhaled bronchodilators as needed and advice for smoking cessation. However, an individual with severe COPD may need round-the-clock oxygen supplementation, scheduled bronchodilators, and possibly oral corticosteroid therapy.

The treatment should be tailored to the extent or **"stage" of the disease.** In making decisions regarding treatment, it is also essential that the clinician identify the therapeutic objectives. When patients seek medical attention, it is generally because they are bothered by a symptom and want it to go away. When clinicians institute therapy, they often have several other goals besides symptom relief, such as

prevention of short- or long-term complications or a reduction in mortality. For example, patients with congestive heart failure are bothered by the symptoms of edema and dyspnea. Salt restriction, loop diuretics, and bed rest are effective at reducing these symptoms. However, heart failure is a progressive disease with high mortality, so other treatments, such as angiotensin-converting enzyme inhibitors and some beta-blockers, are also used to reduce mortality in this condition. It is essential that the clinician know what the therapeutic objective is so that one can monitor and guide therapy.

CLINICAL PEARL

- The clinician needs to identify the objectives of therapy: symptom relief, prevention of complications, or reduction in mortality.

FOLLOWING THE PATIENT'S RESPONSE TO THE TREATMENT

The final step in the approach to disease is to follow the patient's response to the therapy. The "measure" of response should be recorded and monitored. Some responses are clinical, such as the patient's abdominal pain, temperature, or pulmonary examination. Obviously, the student must work on being more skilled in eliciting the data in an unbiased and standardized manner. Other responses may be followed by imaging tests, such as CT scan of a retroperitoneal node size in a patient receiving chemotherapy, or a tumor marker such as the prostate-specific antigen (PSA) level in a man receiving chemotherapy for prostatic cancer. For syphilis, it may be the nonspecific treponemal antibody test rapid plasma reagent (RPR) titer over time. The student must be prepared to know what to do if the measured marker does not respond according to what is expected. Is the next step to re-treat, to repeat the metastatic workup, or to follow up with another more specific test?

Part 3. Approach to Reading

The clinical problem-oriented approach to reading is different from the classic "systematic" research of a disease. Patients rarely present with a clear diagnosis; hence, the student must become skilled in applying the textbook information to the clinical setting. Furthermore, one retains more information when one reads with a purpose. In other words, the student should read with the goal of answering specific questions. There are several fundamental questions that facilitate **clinical thinking**. These questions are as follows:

1. What is the most likely diagnosis?
2. What should be the next step?
3. What is the most likely mechanism for this process?

4. What are the risk factors for this condition?
5. What are the complications associated with the disease process?
6. What is the best therapy?
7. How would you confirm the diagnosis?

CLINICAL PEARL

- Reading with the purpose of answering the seven fundamental clinical questions improves retention of information and facilitates the application of "book knowledge" to "clinical knowledge."

WHAT IS THE MOST LIKELY DIAGNOSIS?

The method of establishing the diagnosis was discussed in the previous part. One way of attacking this problem is to develop standard "approaches" to common-clinical problems. It is helpful to understand the most common causes of various presentations, such as "the most common causes of pancreatitis are gallstones and alcohol." (See the **Clinical Pearls** at end of each case.)

The clinical scenario would entail something such as

A 28-year-old pregnant woman complains of severe epigastric pain radiating to the back, nausea and vomiting, and an elevated serum amylase level. What is the most likely diagnosis?

With no other information to go on, the student would note that this woman has a clinical diagnosis of pancreatitis. Using the "most common cause" information, the student would make an educated guess that the patient has gallstones, because being female and pregnant are risk factors. If, instead, cholelithiasis is removed from the equation of this scenario, a phrase may be added, such as

"The ultrasonogram of the gallbladder shows no stones."

CLINICAL PEARL

- Knowing how diseases present and the most common conditions in certain populations can point to likely diagnoses.

Now, the student would use the phrase, "patients without gallstones who have pancreatitis most likely abuse alcohol." Aside from these two causes, there are many other etiologies of pancreatitis.

WHAT SHOULD BE THE NEXT STEP?

The question, "what is the next step" is difficult because the next step may be more diagnostic information, staging, or therapy. It may be more challenging than "the most likely diagnosis" because there may be insufficient information to make

a diagnosis, and the next step may be to pursue more diagnostic information. Another possibility is that there is enough information for a probable diagnosis, and the next step is to stage the disease. Finally, the most appropriate action may be to treat. Hence, from clinical data, a judgment needs to be rendered regarding how far along one is on this road:

Make a diagnosis → Stage the disease → Treatment based on stage → Follow response

Frequently, the student is taught to regurgitate the same information that someone has written about a particular disease but is not skilled at giving the next step. This talent is learned optimally at the bedside, in a supportive environment, with freedom to make educated guesses, and with constructive feedback. A sample scenario may describe a student's thought process as follows:

1. **Make the diagnosis:** "Based on the information I have, I believe that Mr. Smith has stable angina because he has retrosternal chest pain when he walks three blocks, but it is relieved within minutes by rest and with sublingual nitroglycerin."
2. **Stage the disease:** "I don't believe that this is severe disease because he does not have pain lasting for more than 5 minutes, angina at rest, or congestive heart failure."
3. **Treatment based on stage:** "Therefore, my next step is to treat with aspirin, beta-blockers, and sublingual nitroglycerin as needed, as well as lifestyle changes."
4. **Follow response:** "I want to follow the treatment by assessing his pain (I will ask him about the degree of exercise he is able to perform without chest pain), performing a cardiac stress test, and reassessing him after the test is done."

In a similar patient, when the clinical presentation is unclear or more severe, perhaps the best "next step" may be diagnostic in nature, such as a thallium stress test or even coronary angiography. The **next step** depends upon the **clinical state of the patient** (if unstable, the next step is therapeutic), the **potential severity** of the disease (the next step may be staging), or the **uncertainty of the diagnosis** (the next step is diagnostic).

Usually, the vague question, "What is your next step?" is the most difficult question because the answer may be diagnostic, staging, or therapeutic.

WHAT IS THE MOST LIKELY MECHANISM FOR THIS PROCESS?

The question of the most likely mechanism for the process not only goes further than making the diagnosis, but it also requires the student to understand the underlying mechanism for the process. For example, a clinical scenario may describe an "18-year-old woman who presents with several months of severe epistaxis, heavy menses, petechiae, and a normal CBC except for a platelet count of 15,000/mm^3." Answers that a student may consider to explain this condition include immune-mediated platelet destruction, drug-induced thrombocytopenia, bone marrow suppression, and platelet sequestration as a result of hypersplenism.

The student is advised to learn the mechanisms for each disease process and not merely memorize a constellation of symptoms. In other words, rather than solely committing to memory the classic presentation of idiopathic thrombocytopenic purpura (ITP) (isolated thrombocytopenia without lymphadenopathy or offending drugs), the student should understand that ITP is an autoimmune process whereby the body produces immunoglobulin (Ig) G antibodies against the platelets. The platelet-antibody complexes are then taken from the circulation in the spleen. Because the disease process is specific for platelets, the other two cell lines (erythrocytes and leukocytes) are normal. Also, because the thrombocytopenia is caused by excessive platelet peripheral destruction, the bone marrow will show increased megakaryocytes (platelet precursors). Hence, treatment for ITP includes oral corticosteroid agents to decrease the immune process of antiplatelet IgG production, and, if refractory, then splenectomy.

WHAT ARE THE RISK FACTORS FOR THIS PROCESS?

Understanding the risk factors helps the practitioner to establish a diagnosis and to determine how to interpret tests. For example, understanding the risk factor analysis may help to manage a 45-year-old obese woman with sudden onset of dyspnea and pleuritic chest pain following an orthopedic surgery for a femur fracture. This patient has numerous risk factors for deep venous thrombosis and pulmonary embolism. The clinician may want to pursue angiography even if the ventilation/perfusion scan result is low probability. Thus, the number of risk factors helps to categorize the likelihood of a disease process.

For infrequent diseases (eg, lung cancer), the risk factors are identified as odds ratios: These represent the probability of the event (lung cancer) in the presence of an exposure (smoking), divided by that probability in absence of the exposure. We know now not only that smoking is more common in patients with lung cancer, but also the mechanisms that explain the causality. Nevertheless, odds ratios can be explained as follows: If your patient has lung cancer, it is more likely that he or she smokes than he or she does not. Most smokers **do not** have lung cancer.

CLINICAL PEARL

- Risk factors help clinicians to have a higher index of suspicion for disease and perhaps modify their diagnostic strategy.

WHAT ARE THE COMPLICATIONS ASSOCIATED WITH THE DISEASE PROCESS?

A clinician must understand the complications of a disease so that one may monitor the patient. Sometimes, the student has to make the diagnosis from clinical clues and then apply his or her knowledge of the sequelae of the pathologic process. For example, the student should know that chronic hypertension may affect various end organs, such as the brain (encephalopathy or stroke), the eyes (vascular changes),

the kidneys, and the heart. Understanding the types of consequences also helps the clinician to be aware of the dangers to a patient. The clinician is acutely aware of the need to monitor for the end-organ involvement and undertakes the appropriate intervention when involvement is present.

WHAT IS THE BEST THERAPY?

To answer this question, the clinician needs to reach the correct diagnosis, assess the severity of the condition, and weigh the situation to reach the appropriate intervention. For the student, knowing exact dosages is not as important as understanding the best medication, route of delivery, mechanism of action, and possible complications. It is important for the student to be able to verbalize the diagnosis and the rationale for the therapy. A common error is for the student to "jump to a treatment," like a random guess, and therefore be given "right or wrong" feedback. In fact, the student's guess may be correct, but for the wrong reason; conversely, the answer may be a very reasonable one, with only one small error in thinking. Instead, the student should verbalize the steps so that feedback may be given at every reasoning point.

For example, if the question is, "What is the best therapy for a 25-year-old man who complains of a nontender penile ulcer?" the incorrect manner of response is for the student to blurt out "azithromycin." Rather, the student should reason it out in a way similar to this: "The most common cause of a nontender infectious ulcer of the penis is syphilis. Nontender adenopathy is usually associated. Therefore, the best treatment for this man with probable syphilis is intramuscular penicillin (but I would want to confirm the diagnosis). His partner also needs treatment."

Frequently, clinicians face the need for rapid decision-making. With little evidence in their hands, they need to decide whether an acutely ill-appearing patient needs treatment for a likely, yet unproven, diagnosis. The clinician's experience plays an essential role in deciding when to start a treatment before the final diagnosis is established.

CLINICAL PEARL

- Therapy should be logically based on the severity of disease. Antibiotic therapy should be tailored for specific organisms.

HOW WOULD YOU CONFIRM THE DIAGNOSIS?

In the previous scenario, the man with a nontender penile ulcer is likely to have syphilis. Confirmation may be achieved by serology (RPR or Venereal Disease Research Laboratory [VDRL] test); however, there is a significant possibility that patients with primary syphilis may not have developed antibody response yet and have negative serology. Thus, confirmation of the diagnosis is attained with dark-field microscopy. Knowing the limitations of diagnostic tests and the manifestations of disease aids in this area.

SUMMARY

1. There is no replacement for a careful history and physical examination.
2. There are four steps to the clinical approach to the patient: making the diagnosis, assessing severity, treatment based on severity, and following response.
3. Assessment of pretest probability and knowledge of test characteristics are essential in the application of test results to the clinical situation.
4. There are seven questions that help to bridge the gap between the textbook and the clinical arena.

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SECTION II

Clinical Cases

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CASE 1

A 66-year-old woman comes in for a routine physical examination. She reports going through menopause at age 51. Her other medical and family history is unremarkable. Social history is remarkable for a 30 pack-year smoking history. On examination, she is found to have a blood pressure of 120/70 mm Hg, heart rate of 70 beats per minute (bpm), and temperature of 98 °F. Her weight is 140 lb, and her height is 5 ft 4 in. The thyroid is normal to palpation. Breast examination reveals no masses or discharge. Abdominal, cardiac, and lung evaluations are within normal limits. Pelvic examination shows a normal multiparous cervix, a normal-sized uterus, and no adnexal masses. She had undergone a mammogram 3 months ago. The patient states that she has regular Papanicolaou (Pap) smears and that the last one, performed 1 year ago, was normal.

- What is your next step?
- What would be the most common cause of mortality for this patient?

ANSWERS TO CASE 1:
Health Maintenance

Summary: A 66-year-old woman presents with

- 30 pack-year smoking history
- Mammogram performed 3 months ago
- Last Pap smear, normal, a year ago

Next step: Each of the following should be performed: colorectal cancer screening, lung cancer screening, dyslipidemia and blood glucose screening, immunizations (pneumococcal vaccine, herpes zoster vaccine, influenza vaccine, tetanus vaccine [if not within 10 years]), and smoking cessation counseling.

Most common cause of mortality: Cardiovascular disease.

ANALYSIS

Objectives

1. Describe which health maintenance studies should be performed for a patient older than 65 years. (EPA 1, 3)
2. Recognize the most common cause of mortality in a woman in this age group. (EPA 12)
3. Verbalize that preventive maintenance consists of immunizations, cancer screening, and screening for common diseases. (EPA 1, 12)

Considerations

The approach to health maintenance consists of **three parts**: (1) screening for cancer, cardiovascular disease, or other conditions; (2) immunizations; and (3) behavioral counseling regarding healthy behaviors such as regular exercise and tobacco cessation. For a 66-year-old woman, cancer screening includes mammography for breast cancer screening every 2 years until age 74 and colon cancer screening every 10 years with a colonoscopy until age 75 (can also screen with fecal occult blood testing annually or flexible sigmoidoscopy every 5 years). Because this patient is a current smoker with a 30 pack-year history, lung cancer screening with low-dose computed tomographic (CT) chest scan is also warranted. Cervical cancer screening can be stopped at age 65 if all previous Pap smears have been normal. Screening for cardiovascular disease includes high blood pressure screening every year and testing for dyslipidemia in men starting at age 35 and in women starting at age 45 or sooner if there are risk factors such as family history, history of diabetes, tobacco use, or body mass index (BMI) greater than 30. Immunizations for this patient would include tetanus booster every 10 years, pneumococcal vaccine, herpes zoster vaccine, and yearly influenza immunization. Screening for abnormal blood glucose levels is also recommended. The most common cause of mortality in men or women over 65 is cardiovascular disease.

APPROACH TO:
Health Maintenance

DEFINITIONS

COST-EFFECTIVENESS: Comparison of resources expended in an intervention versus the benefit, which may be measured in life-years or quality-adjusted life-years (QALY).

PRIMARY PREVENTION: Identifying and modifying risk factors in subjects who have never had the disease of concern.

SCREENING TEST: Device used to identify asymptomatic disease in the hope that early detection will lead to an improved outcome. An optimal screening test has high sensitivity and specificity, is inexpensive, is easy to perform, and has readily available treatment for the disease being screened for.

SECONDARY PREVENTION: Actions taken to reduce the morbidity or mortality once a disease has been diagnosed.

CLINICAL APPROACH

Preventive Care

Aside from care focused on treating acute or chronic illnesses, a cornerstone of medical practice includes **preventive care.** As stated in the modern Hippocratic Oath, "I will prevent disease whenever I can, for prevention is preferable to cure." A directed approach to intervene on common pathologies helps keep patients healthy or detects disease early enough that interventions are more effective. There are several types of preventive care:

1. **Immunizations:** Aside from childhood immunizations, routine adult immunizations include influenza, pneumococcal, diphtheria, tetanus, and acellular pertussis (Td/Tdap), zoster, as well as others, such as hepatitis A or B vaccines, in certain situations.
2. **Behavioral counseling:** Inquiry and counseling regarding regular exercise, avoidance or cessation of tobacco, moderate alcohol use, and screening for depression.
3. **Chemoprevention:** Use of medication to prevent disease, such as use of statin therapy to prevent cardiovascular events.
4. **Screening:** Identification of disease or risk factors in an asymptomatic patient.

Of these preventive measures, screening requires firm medical evidence that it may offer benefit, and thoughtful consideration from the practitioner before he or she initiates screening and recommends to an asymptomatic patient that he or she undergoes a medical intervention with potential harms (eg, cost,

radiation exposure, anxiety regarding false-positive tests, biopsies, or other follow-up examinations). The World Health Organization outlined the following principles of screening:

1. The condition must be an important health problem.
2. There should be an effective treatment for the condition.
3. Facilities for diagnosis and treatment of the condition should be available to the patient.
4. There needs to be a latent or preclinical stage of the disease in which it can be detected.
5. There should be an accurate test to detect the condition.
6. The test should be acceptable to the patient or the population.
7. The natural history of the disease should be understood to guide intervention or treatment.
8. The cost of case-finding should be balanced within the context of overall medical expenditures.

Using these criteria, one may deduce that it would not be useful to screen for Alzheimer disease since there is no curative treatment and no evidence that early intervention alters the course of the disease. Regarding cost-effectiveness, health care economists perform sophisticated analysis for screening and other medical care, but one rough measure of cost-effectiveness is QALY, combining longevity with quality of life as a single measurement. In the United States, medical interventions, including cancer screening, are often considered cost-effective at a cost of $50,000 to $100,000 per QALY gained.

Health Maintenance by Age Group

Among Americans between ages 15 and 45, accidents and homicide are the leading causes of death, so preventive care may include counseling regarding behavioral risk reduction, such as seatbelt use, avoiding alcohol or texting while driving, or substance abuse. It is important to consider that the rising prevalence of obesity in younger populations may necessitate earlier screening of cardiovascular disease, including dyslipidemia, blood pressure, and abnormal blood glucose, which are reflected in newer guidelines.

After age 45, the leading causes of death are malignancy and cardiovascular disease, so screening is focused on risk factor reduction for those diseases, such as control of blood pressure and hyperlipidemia and early detection of cancers. Regarding cancer screening tests, the American Cancer Society and various subspecialty organizations publish various recommendations, which are often not in agreement. The US Preventive Services Task Force (USPSTF) is an independent panel of physicians and epidemiologists appointed by the Department of Health and Human Services to systematically review the evidence of effectiveness of clinical preventive services (though they do not consider cost-effectiveness). Offering cancer screening to older patients should consider estimated life expectancy

(typically at least 10 years), comorbid conditions, and ability or willingness to undergo cancer treatment if a cancer is detected (eg, to tolerate a hemicolectomy if a colon cancer is found). The USPSTF recommendations for cancer and other health screenings are listed in Table 1–1.

Table 1–1 • US PREVENTIVE SERVICES TASK FORCE SCREENING RECOMMENDATIONS

Health Problem	Population	Intervention
Cardiovascular disease		
Hypertension	All patients 18 y and older	Blood pressure screening
Hyperlipidemia	No risk factors: M > 35 y, F > 45 y	Check lipids
	With risk factors: M 20-35 y, F 20-45 y	Check lipids
Diabetes	Age 40-70 y with BMI > 25 kg/m^2	Check Hb A_{1C} (glycated hemoglobin), fasting glucose, oral glucose tolerance test
	Positive family history, prior gestational diabetes, polycystic ovarian syndrome, or BMI > 25 kg/m^2	Consider Hb A_{1C}, fasting glucose, oral glucose tolerance test
Abdominal aortic aneurysm:	**M age 65-75 y with history of smoking**	Ultrasound
Cancer		
Breast cancer	Women 50-74 y	Mammography every 2 y
Cervical cancer	Women 21-29 y	Pap smear every 3 y
	Women 30-65 y	Pap smear every 3 y or
		Pap smear + HPV testing every 5 y
Colorectal cancer	Patients starting age 45-50 and until 75 y	Screening: fecal occult blood testing annually, or flexible sigmoidoscopy every 5 y, colonoscopy every 10 y
Lung cancer	Patients 55-80 y, ≥ 30 pack-year smoking history (current smoker or quit < 15 y)	Low-dose CT chest annually
Prostate cancer	Men 50-69 y or high-risk men ≥ 40 y	Discuss risks and benefits of screening using serum prostate-specific antigen (PSA), individual decision
Infectious diseases		
Hepatitis C	All persons born between 1945 and 1965; persons at high risk for infection	Anti-HCV (hepatitis C virus) antibody assay (one-time screening)
HIV	Pregnant women, patients outside 15-65 y range at increased risk for infection, and all patients age 15-65 y	Rapid HIV or immunoassay

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The use of vaccinations is another important component of preventive health in older adults. Routine immunizations include annual influenza vaccine (especially important in the geriatric population since >90% of influenza-related deaths occur in patients over 60 years), pneumococcal vaccines (23-valent polysaccharide vaccine [PPSV23] and 13-valent pneumococcal conjugate vaccine [PCV13] should be given sequentially), and herpes zoster live-attenuated vaccine for immunocompetent patients over age 60 or recombinant herpes zoster vaccine for patients over age 50.

CASE CORRELATION

- See also Case 6 (Hypertension, Outpatient) and Case 51 (Type 2 diabetes diagnosis and management).

COMPREHENSION QUESTIONS

1.1 A 59-year-old woman is being seen for a health maintenance appointment. She has not seen a doctor for over 10 years. She had undergone a total hysterectomy for uterine fibroids 12 years ago. The patient takes supplemental calcium. The provider orders a fasting glucose level, lipid panel, mammogram, colonoscopy, and a Pap smear of the vaginal cuff. Which of the following statements is most appropriate regarding the screening for this patient?

A. The Pap smear of the vaginal cuff is unnecessary.

B. In general, colon cancer screening should be initiated at age 60, but this patient has very sporadic care; therefore, colonoscopy is reasonable.

C. Because the patient takes supplemental calcium, a dual-energy x-ray absorptiometry (DEXA) scan is not needed.

D. Pneumococcal vaccination should be recommended.

1.2 A 65-year-old man has had annual health maintenance appointments and has followed all the recommendations offered by his primary care provider. The practitioner counsels him about pneumococcal vaccine. Which of the following is the most appropriate statement about this vaccine?

A. It is recommended for patients who are age 60 and older.

B. The vaccination is administered in a two-dose series.

C. The pneumococcal vaccination consists of only a conjugate vaccine.

D. This vaccine is not recommended if a patient is immunocompromised.

1.3 An 18-year-old woman is being seen for a health maintenance appointment. She has not had a Pap smear previously. She currently takes oral contraceptive pills. She began sexual intercourse 6 months previously. Which of the following statements is most appropriate regarding health maintenance for this individual?

A. A Pap smear should not be performed in this patient at this time.

B. The human papilloma virus (HPV) vaccine should be administered only if she has a history of genital warts.

C. The most common cause of mortality for this patient would be suicide.

D. Hepatitis C vaccination should be offered to this patient.

ANSWERS

1.1 **A.** Cervical cytology of the vaginal cuff is unnecessary when the hysterectomy was for benign indications (not cervical dysplasia or cervical cancer) and when there is no history of abnormal Pap smears. Colon cancer screening (answer B) is generally started at age 45 or 50 and not at age 60. DEXA scan for osteoporosis (answer C) is recommended for women starting at age 65 or earlier for women with elevated fracture risk. Pneumococcal vaccine (answer D) is generally given at age 65.

1.2 **B.** The pneumococcal vaccine actually consists of two vaccines (not one, as in answer C), PCV13 vaccine and PPSV23. It is recommended to give the PCV13 vaccine at age 65 (not age 60, as in answer A), followed 1 year later by PPSV23. Conjugate vaccines induce a T-cell–dependent immune response for longer-lasting immunity, while polysaccharide vaccines induce a T-independent response that achieves relative immunity in adults and older children. It is recommended for individuals aged 65 and above and sooner for those with certain medical conditions or an immunocompromised state (answer D). It has been shown to greatly reduce the incidence of bacterial pneumonia and associated complications, such as bacteremia and meningitis. Pneumococcal disease affects 18,000 older adults every year in the United States, and growing strains of antibiotic-resistant organisms make the vaccine all the more important.

1.3 **A.** Cervical cytology should be deferred until age 21. This is due to the fact that adolescents many times will clear the HPV infection and cause an abnormal Pap smear to normalize. **The Advisory Committee on Immunization Practices (ACIP) recommends that the HPV vaccine should be recommended to both males and females between the ages of 9 and 26** (not dependent on history of genital warts, as in answer B). The most common cause of mortality for adolescent girls is motor vehicle accidents (not suicide, as in answer C). No vaccine is currently available for hepatitis C (answer D).

CLINICAL PEARLS

- The basic approach to health maintenance is age-appropriate immunizations, cancer screening, and screening for common diseases.
- The most common cause of mortality in a woman younger than 20 years is motor vehicle accidents.
- The top two causes of mortality in men or women age 45 or older are cardiovascular disease and cancer.
- Women older than 65 years should be screened for osteoporosis, heart disease, breast cancer, and depression.
- Obesity is a major concern and has numerous complications, including diabetes, hyperlipidemia, heart disease, sleep apnea, and respiratory difficulties.
- Tobacco use should be queried at each visit, and patients should be counseled actively about cessation; pharmacologic therapy is associated with a higher success rate.

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CASE 2

A 46-year-old man comes to the internal medicine clinic for an annual checkup. He has no current complaints. He has just moved from Michigan, where he was an autoworker. While living in Michigan, he regularly saw his primary care provider once a year. His previous medical records are currently unavailable. The patient reports a history of hypertension, diagnosed 6 years earlier, without known complications. He has been adherent to his prescribed medications of lisinopril/hydrochlorothiazide. He states that he checks his blood pressure weekly, and that "his numbers are normal." He smokes 10 cigarettes per day but is open to quitting. On examination, his blood pressure is 140/85 mm Hg, his pulse is regular at 70 beats per minute (bpm), and his temperature is 98 °F. His body mass index (BMI) is 27 kg/m^2. His heart examination shows normal S_1 and S_2 without murmurs, gallops, or rubs. His lungs are clear to auscultation. No bruits are heard on the neck, abdomen, or flank regions. His abdominal and neurologic exams are normal. Preclinic laboratory tests show normal cell blood count, normal liver and kidney function tests, normal urinalysis, hemoglobin A_{1c} (Hb A_{1c}) of 6%, total cholesterol of 210 mg/dL, high-density lipoprotein (HDL) cholesterol of 40 mg/dL, and low-density lipoprotein (LDL) cholesterol of 140 mg/dL.

- How do his conditions affect his cardiovascular risk?
- What is your next management step?

ANSWERS TO CASE 2:
Metabolic Syndrome

Summary: A 46-year-old man presents for a checkup with

- Elevated BMI
- Elevated blood pressure while on pharmacological treatment
- Current cigarette use
- Elevated LDL cholesterol and a borderline Hb A_{1C}

How do his conditions affect his cardiovascular risk? The patient has multiple risk factors, such as hypertension, elevated BMI, prediabetes, dyslipidemia, and current cigarette use, which increase his cardiovascular risk.

Next management step: Use the atherosclerotic cardiovascular disease (ASCVD) 10-year risk calculator to determine the patient's risk of developing cardiovascular disease (CVD), which will guide management of the patient's conditions.

ANALYSIS

Objectives

1. Define metabolic syndrome. (EPA 12)
2. Recognize the value of the ASCVD calculator for determining patient's risk. (EPA 1, 4, 7)
3. Outline the treatment options when individual or multiple cardiovascular risk factors are present. (EPA 4)

Considerations

The three most important issues for this patient are (1) the diagnosis of metabolic syndrome based on physical examination and laboratory findings, (2) identification of modifiable risk factors, and (3) incorporating lifestyle modifications and pharmacological therapies to reduce morbidity and mortality.

APPROACH TO:
Metabolic Syndrome

DEFINITIONS

ASCVD RISK CALCULATOR: Estimates the risk of developing myocardial infarction or stroke over the following 10 years. This risk estimate can help clinicians identify patients who would benefit from primary prevention. Components of the risk calculator are listed in Table 2–1.

Table 2–1 • COMPONENTS OF ASCVD RISK CALCULATOR

- Age
- Sex
- Race
- Total cholesterol
- HDL cholesterol
- Systolic blood pressure
- Treatment for hypertension
- Diabetes
- Smoker

Abbreviation: ASCVD, atherosclerotic cardiovascular disease.
Components of the pooled cohort equation to calculate the risk of developing ASCVD over next 10 years.

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD): The disease caused by atherosclerotic plaque buildup in vessel walls, which can lead to coronary artery disease, cerebrovascular disease, peripheral artery disease, and aortic disease.

BODY MASS INDEX (BMI): A measurement of the patient's body weight in kilograms over the square of height in meters. It is an inexpensive screening tool used alongside other diagnostic tests.

METABOLIC SYNDROME: Metabolic syndrome is a constellation of interconnected risk factors that increase one's chances of developing diabetes, stroke, and heart disease.

WAIST-TO-HIP RATIO: Ratio of circumference of waist to hip. It is a surrogate marker for abdominal fat distribution. Increased waist-to-hip ratio is highly correlated with increased risk of stroke, myocardial infarction, and premature death.

CLINICAL APPROACH

Epidemiology

Metabolic syndrome is a constellation of **interrelated clinical syndromes of insulin resistance, central obesity, raised triglycerides, reduced HDL, and hypertension.** Overall, the prevalence of metabolic syndrome is approximately 34% in the United States. The prevalence is over 50% in Americans older than 60. The prevalence of metabolic syndrome has been historically higher in older adults, but it is now increasing among younger patients due to increasing obesity and diabetes rates. There are also significant variations in the prevalence of metabolic syndrome among different ethnicities. Native Americans, African Americans, and Mexican Americans have higher rates of metabolic syndrome as compared to age-matched non-Hispanic white Americans or Chinese Americans, likely due more to social factors than genetic predisposition. In addition, there are geographic variations in the rates of diabetes, obesity, hypertension, and dyslipidemia. The 500 Cities project, a collaboration between the Centers for Disease Control and Prevention (CDC), the CDC Foundation, and the Robert Wood Johnson Foundation, revealed significant differences in the rates of chronic diseases and health

outcomes among 500 of the largest cities in the United States (https://www.cdc.gov/500cities/index.htm). For example, the prevalence of hypertension is 35.2% in Charleston, West Virginia, compared to 10.7% in College Station, Texas. This varying prevalence of chronic conditions may lead to significantly different local prevalence of metabolic syndrome compared to national averages. Those with metabolic syndrome are five times more likely to develop diabetes mellitus (DM), three times more likely to develop ASCVD, and two times more likely to develop chronic kidney disease; therefore, it is imperative to screen and treat patients in the primary care setting.

Pathophysiology

The pathophysiology of metabolic syndrome is not well understood, but it is likely multifactorial. The most well-accepted hypothesis is that metabolic syndrome stems from resistance of peripheral tissue to insulin, which in turn causes the pancreas to release more insulin to maintain euglycemia. This hyperinsulinemia leads to increased lipolysis and the release of more free fatty acids (FFAs). Increased circulation of FFAs not only further reduces insulin sensitivity of the peripheral tissue but also leads to increased production of glucose and triglycerides, as well as altered cholesterol metabolism in the liver. In addition, FFAs generate reactive oxygen species, which causes endothelial dysfunction. Hyperinsulinemia can activate the sympathetic nervous system. These mechanisms together can likely lead to the hypertension, hyperlipidemia, and hyperglycemia observed in patients with metabolic syndrome.

Clinical Presentation

There are no specific clinical symptoms associated with metabolic syndrome. A patient may present to the primary care clinic with symptoms associated with **obesity, insulin resistance, hypertension, and dyslipidemia.** Diagnostic criteria for metabolic syndrome are listed in Table 2–2.

Table 2–2 • DIAGNOSTIC CRITERIA FOR METABOLIC SYNDROME

Central obesity with increased waist circumference • ≥ 37 in for men • ≥ 31 in for women
Triglycerides ≥ 150 mg/dL
Fasting blood sugars ≥ 100 mg/dL
Hypertension with systolic blood pressure ≥ 130 mm Hg and diastolic blood pressure ≥ 85 mm Hg
Reduced HDL • ≤ 40 mg/dL in men • ≤ 50 mg/dL in women

Diagnostic criteria per International Diabetes Foundation (IDF) worldwide definition of metabolic syndrome. The diagnosis of metabolic syndrome requires three of the five criteria. Of note, the criteria for central obesity are country and ethnicity specific, and the United States specific guidelines are listed in the table. Please refer to IDF consensus guidelines for other country-specific central obesity cutoffs.

Data from International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. 2020.

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Patients often seek medical care due to obesity. Though imperfect, BMI is a non-invasive and an inexpensive screening tool that has been correlated with adverse cardiovascular events. As the BMI measurement does not account for body composition, gender, or age, BMI may not be accurate in elderly patients (who tend to have more adipose tissue compared to younger patients), women (who have higher total body fat for the equivalent BMI), or muscular individuals (who have lower body fat for the equivalent BMI). Recent studies have demonstrated that **waist circumference, waist-to-hip ratio, and neck circumference** are additional surrogate markers that are associated with increased risk of insulin resistance, diabetes, and coronary artery disease. In addition, patients may present to the clinic for an evaluation of menstrual cycle abnormalities, hirsutism, daytime sleepiness, or chronic fatigue due to polycystic ovary syndrome and obstructive sleep apnea.

Patients with severe insulin resistance may have **acanthosis nigricans**. Those who have already developed DM may have polyuria, polydipsia, polyphagia, blurry vision, peripheral neuropathy, or recurrent urinary tract infections. Uncontrolled hypertension may manifest as visual disturbances or episodic headaches.

In addition to hypertension and obesity on the physical examination, the patient's blood work may reveal elevated fasting serum glucose, Hb A_{1C}, triglycerides, LDL, or reduced HDL. Patients who have diabetes or hypertension may also have proteinuria on urinalysis.

Treatment

Screening. Patients at risk of developing metabolic syndrome should be screened routinely. In addition to measuring BMI, waist circumference, blood pressure, fasting blood glucose levels, and lipid panel, level and intensity of daily physical activity and typical food intake should be assessed. In the absence of management recommendations based on randomized controlled trials, clinicians should focus on individual components of metabolic syndrome to reduce the risk of developing CVD and DM.

Lifestyle Modification. Lifestyle modification is the mainstay of treatment. Smoking is one of the biggest modifiable risk factors for developing CVD. Patients' **tobacco use** should be assessed at every visit, and smoking cessation interventions should be provided to all patients. The United States Preventive Services Task Force recommends the 5A approach for smoking cessation: **Ask** about tobacco use, **Advise** to quit, **Assess** willingness to quit, **Assist** to quit, and **Arrange** for follow-up. Patients who are ambivalent about quitting may benefit from a brief motivational interview, which can help resolve a patient's ambivalence about smoking cessation. A combination of counseling and pharmacologic therapy, including nicotine replacement therapy, bupropion, or varenicline, is more effective than either counseling or medications alone.

Multiple studies have shown that **moderate-intensity physical activity** for at least 150 minutes per week is associated with weight loss. Modest weight loss of 5% to 10% has been shown to improve insulin sensitivity, fasting blood glucose, HDL, and triglyceride levels as well as hypertension. In addition to physical activity, diets rich in fruits, vegetables, fiber, unsaturated fats, and complex carbohydrates in

which patients avoid saturated fats and sodium can prevent development of CVD and DM.

Pharmacotherapy. Though the lifestyle modifications are offered as a first-line option, they are often insufficient in addressing metabolic syndrome. **Patients should be offered pharmacologic therapies for dyslipidemia, hypertension, and diabetes to prevent the development of CVD, myocardial infarction, and cerebrovascular accidents.** Using the ASCVD risk calculator, a patient's 10-year risk of developing CVD should be assessed. Those with borderline risk (5%-7.5%) and chronic kidney disease, metabolic syndrome, DM, HIV, rheumatoid arthritis, psoriasis, or South Asian ethnicity should be started on moderate-intensity statins. Patients who have intermediate risk (7.5%-20%) should also be placed on moderate- or high-intensity statins. All high-risk patients (> 20%) should be prescribed high-intensity statin therapy.

Clinicians should consider initiating metformin for patients who have impaired glucose tolerance (IGT). Metformin suppresses hepatic glucose production and enhances peripheral tissue insulin sensitivity. A large cohort study in the United Kingdom showed that treatment of patients with IGT with metformin delayed development of metabolic syndrome and DM. Thiazolidinediones have also been shown to improve insulin sensitivity and delay onset of DM in patients with prediabetes. Newer agents such as glucagon-like peptide-1 (GLP1) receptor agonists and sodium glucose transport-2 (SGLT2) inhibitors may potentially be useful in treatment of metabolic syndrome as they cause weight loss, improve insulin sensitivity, and reduce ASCVD; however, more studies are needed to assess their efficacies.

Similarly, pharmacologic therapies should be considered in patients with blood pressure > 140/90 mm Hg. An ACE inhibitor (ACEI) and angiotensin receptor blockers (ARBs) may be useful particularly in patients with metabolic syndrome or DM. Angiotensin II affects hypertension by increasing reactive oxygen species production and impairing nitric oxide generation. Furthermore, angiotensin II augments hepatic gluconeogenesis and insulin resistance. A large-scale metanalysis has shown that ACEi and ARBs not only improve hypertension but also reduce development of new-onset DM.

Bariatric Surgery. Patients with BMI > 35 and DM, hypertension, or severe sleep apnea—for whom lifestyle modifications have been insufficient—should be offered bariatric surgery. Bariatric surgery was associated with improvement in fasting glucose, blood pressure, obesity, waist circumference, and cholesterol. As patients with morbid obesity have increased perioperative complications with bariatric surgeries, patients should be advised on perioperative as well as long-term risks associated with the procedure.

CASE CORRELATION

- See also Case 1 (Health Maintenance), Case 6 (Hypertension, Outpatient), and Case 51 (Type 2 Diabetes Diagnosis and Management).

COMPREHENSION QUESTIONS

2.1 A 51-year-old man is being seen for an annual physical examination. The patient's BMI is 28 kg/m^2, blood pressure is 141/72 mm Hg, and heart rate is 73 bpm. Laboratory tests showed normal complete blood count (CBC), normal basic metabolic panel (BMP), Hb A_{1C} of 7%, and total cholesterol of 245 mg/dL. The patient has smoked 1 pack per day for the last 30 years. He exercises 30 minutes daily. What is the best step in management of this patient?

A. Calculate the patient's ASCVD risk score
B. Initiate statin therapy
C. Initiate metformin therapy
D. Assess readiness for smoking cessation
E. Schedule an appointment for a blood pressure check in 1 week

2.2 A 38-year-old woman is being seen by her primary care provider for a regular follow-up. The patient's BMI is 34 kg/m^2 with significant abdominal adiposity. The patient has hypothyroidism, hypertension, diabetes, and hyperlipidemia, which are well controlled with levothyroxine, lisinopril, metformin, and atorvastatin. She works as an executive assistant. She has never smoked cigarettes and does not drink alcohol. What is the next best step in management of the patient's metabolic syndrome?

A. Recheck Hb A_{1C}, fasting lipid panel, triiodothyronine (T_3), and thyroid-stimulating hormone (TSH)
B. Refer the patient for bariatric surgery
C. Encourage the patient to perform moderate-intensity physical exercise
D. Obtain an electrocardiogram (ECG)

2.3 A 55-year-old man is presenting for an annual examination. The patient's BMI is 24 kg/m^2. His blood pressure is 123/77 mm Hg with a heart rate of 71 bpm. The patient's total cholesterol is 171 mg/dL, HDL is 45 mg/dL, and LDL is 90 mg/dL. Last year, his Hb A_{1C} was 5.2% and 10-year ASCVD risk score was 4.8%. Laboratory tests drawn today are unremarkable except for elevated Hb A_{1C} at 7%. He currently takes no medications. He does not smoke or drink. What is the next best step in management?

A. Start statin therapy
B. Start metformin therapy
C. Start statin and metformin therapy
D. No further changes necessary

2.4 A 28-year-old woman is presenting to the primary care clinic for an annual physical. Her BMI is 48 kg/m^2, blood pressure is 145/91 mm Hg, and Hb A_{1C} is 8.4%. Her past medical history is remarkable for hypertension, dyslipidemia, DM, and obstructive sleep apnea. She is currently taking lisinopril, hydrochlorothiazide, atorvastatin, and insulin. The patient's weight has remained unchanged since the last visit despite starting moderate-intensity exercise and dietary modifications. The patient endorses chronic fatigue and daytime somnolence. Which of the following is the next best step for management of metabolic syndrome?

A. Refer the patient for bariatric surgery

B. Increase insulin dose

C. Add nifedipine

D. Prescribe continuous positive airway pressure (CPAP) therapy

ANSWERS

2.1 **D.** The patient should be evaluated for readiness to quit smoking. If appropriate, the patient should be counseled on smoking cessation and prescribed nicotine replacement therapy. Smoking is one of the biggest risk factors for developing CVD, and smoking cessation is the most appropriate next step in managing this patient.

2.2 **C.** The patient has metabolic syndrome as she has hypertension, diabetes, abdominal obesity, and hyperlipidemia. Lifestyle modification is the first step of metabolic syndrome treatment. Studies have shown that 150 minutes of moderate-intensity exercise per week can significantly improve hypertension, obesity, diabetes, and hyperlipidemia.

2.3 **C.** This patient is presenting with a new-onset diabetes. The patient had a 10-year ASCVD risk score of 4.8% last year, which has now increased to 9.8% with newly diagnosed diabetes. In addition to encouraging moderate-intensity exercise, pharmacologic therapies for dyslipidemia and diabetes are indicated in this patient. Metformin is a first-line agent to treat diabetes. Per the American Heart Association guidelines, a 10-year ASCVD risk score between 7.5% and 20% is considered intermediate risk and would necessitate moderate-intensity statins to lower LDL.

2.4 **A.** This patient has metabolic syndrome (obesity, hypertension, dyslipidemia, and DM). Though lifestyle modifications are the first-line interventions for metabolic syndrome, they are often insufficient. Patients with uncontrolled diabetes, hypertension, and dyslipidemia remain at increased risk of developing CVD. To reduce cardiovascular morbidities and mortality, these patients should be offered bariatric surgery evaluation. Bariatric surgery can improve fasting glucose level, lipid profile, hypertension, and obesity.

CLINICAL PEARLS

- Metabolic syndrome is a constellation of interconnected risk factors that increase one's chances of developing diabetes, stroke, and heart disease.
- Abdominal obesity, elevated triglycerides, reduced HDL, insulin resistance, and hypertension are the hallmarks of metabolic syndrome.
- Lifestyle modifications are the mainstay of treatment. Pharmacologic therapy should be offered if lifestyle modifications are insufficient.
- Smoking is the key risk factor for developing CVD. Smoking cessation can be promoted with counseling and pharmacologic interventions.
- Metformin has been shown to delay onset of DM in patients with IGT.
- ACE inhibitors and ARBs are noted to improve hypertension and insulin sensitivity.
- An ASCVD risk calculator can be used to estimate a patient's 10-year risk of developing CVD.

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CASE 3

A 56-year-old man with a history of hypercholesterolemia and a 40-pack-year smoking history comes to the emergency department complaining of chest discomfort. He describes the discomfort as a severe, retrosternal pressure that woke him from sleep 3 hours earlier. On examination, he appears uncomfortable and diaphoretic, with a heart rate of 116 beats per minute (bpm), blood pressure of 166/102 mm Hg, respiratory rate of 22 breaths per minute, and oxygen saturation of 96% on room air. Jugular venous pressure appears normal. Auscultation of the chest reveals clear lung fields, a regular rhythm with an S_4 gallop, and no murmurs or rubs. A chest radiograph shows clear lungs and a normal cardiac silhouette. The electrocardiogram (ECG) is shown in Figure 3–1.

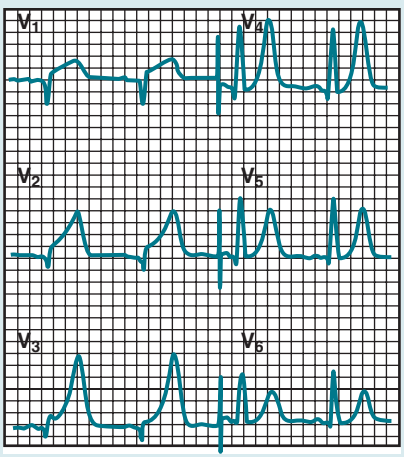


Figure 3–1. Electrocardiogram. (Reproduced with permission, from Braunwald E, Fauci AS, Kasper KL, et al. *Harrison's Principles of Internal Medicine*. 16th ed. 2005. Copyright © McGraw Hill LLC. All rights reserved.)

- What is the most likely diagnosis?
- What is the next step in therapy?

ANSWERS TO CASE 3:

Acute Coronary Syndrome

Summary: A 56-year-old man presents with

- Cardiovascular risk factors (hypertension and tobacco use)
- Acute onset of retrosternal pressure, tachycardia, hypertension, and diaphoresis
- S_4 on cardiac auscultation, reflecting a stiff left ventricle (LV), which may result from ischemic myocardium
- ECG showing ST elevations and T-wave changes

Most likely diagnosis: Acute ST-segment elevation myocardial infarction (MI) (STEMI).

Next step in therapy: Administer aspirin and a beta-blocker and assess whether he is a candidate for rapid reperfusion of the myocardium, that is, treatment with thrombolytics or percutaneous coronary intervention.

ANALYSIS

Objectives

1. List the diagnostic criteria for acute MI. (EPA 3, 10)
2. Identify patients who benefit from thrombolytics or percutaneous coronary intervention. (EPA 4, 10)
3. Describe the complications of MI and their treatment options. (EPA 4, 10)
4. Describe post-MI risk stratification and secondary prevention strategies. (EPA 12)

Considerations

The three most important issues for this patient are (1) the **suspicion of acute MI** based on the clinical and ECG findings, (2) deciding whether the patient has indications or contraindications for **thrombolytics or primary percutaneous coronary intervention**, and (3) **excluding other diagnoses** that might mimic acute MI but would not benefit from or might be worsened by anticoagulation or thrombolysis (eg, acute pericarditis, aortic dissection).

APPROACH TO:

Suspected Acute MI

DEFINITIONS

ACUTE CORONARY SYNDROME (ACS): An umbrella term for conditions of acute cardiac ischemia, usually caused by formation of a thrombus in a coronary artery. ACS is subdivided into three separate conditions: **unstable angina, NSTEMI**

(non–ST-segment elevation myocardial infarction), and **STEMI.** These three conditions are distinguished from each other by biomarkers (troponins, CK-MB [creatine kinase myocardial band]) and ECG changes.

NON–ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (NSTEMI): Acute cardiac ischemia *with* death of cardiac myocytes. Death of myocytes results in intracellular proteins like troponins being leaked into the blood. Thus, NSTEMI is characterized by **presence of troponins without ST elevation on ECG.**

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI): Acute cardiac ischemia with *transmural* cardiac infarction, resulting in ST-segment elevations of more than 0.1 mV in two or more contiguous leads AND elevated cardiac biomarkers. STEMI is the most severe form of ACS and is more likely to cause cardiogenic shock acutely.

THROMBOLYTICS: Drugs such as tissue plasminogen activator (tPA), streptokinase, and reteplase (recombinant plasminogen activator [r-PA]), which act to lyse fibrin thrombi in order to restore patency of the coronary artery when percutaneous coronary intervention (PCI) is contraindicated or is not available.

UNSTABLE ANGINA: Acute cardiac ischemia without death of cardiac myocytes. In unstable angina, a typical patient is experiencing chest pain but **without serum troponin elevation and without ST elevation on ECG.**

CLINICAL APPROACH

Pathophysiology

Acute coronary syndromes, which exist on a continuum ranging from **unstable angina pectoris** to **NSTEMI** to **STEMI**, are usually caused by **in situ thrombosis** at the site of a ruptured atherosclerotic plaque in a coronary artery. Occasionally, they are caused by embolic occlusion, coronary vasospasm, vasculitis, aortic root or coronary artery dissection, or cocaine use (which promotes both vasospasm and thrombosis). The resultant clinical syndrome is related to both the degree of atherosclerotic stenosis in the artery and the duration and extent of sudden thrombotic occlusion of the artery. If the occlusion is incomplete or if the thrombus undergoes spontaneous lysis, unstable angina occurs. If the occlusion is complete for longer than 30 minutes, infarction occurs. In contrast, the mechanism of chronic stable angina is a flow-limiting stenosis usually caused by atherosclerotic plaque that causes ischemia during exercise without acute thrombosis (Table 3–1).

Table 3–1 • THE ACUTE CORONARY SYNDROMES

	Biomarkers (+)	ST Elevation	Typical Cause
Unstable angina	No	No	Nonocclusive thrombus
NSTEMI	Yes	No	Nonocclusive thrombus
STEMI	Yes	Yes	Occlusive thrombus

Table 3–2 • CLINICAL MANIFESTATIONS OF CORONARY ARTERY DISEASE

Vessel Architecture	Blood Flow	Clinical Manifestation
Early plaque	Unobstructed	Asymptomatic
Critical coronary artery stenosis > 70%	Blood flow limited during exertion	Stable angina
Unstable plaque rupture	Platelet thrombus begins to form and spasm limits blood flow at rest	Unstable angina
Unstable platelet thrombus on ruptured plaque	Transient or incomplete vessel occlusion (lysis occurs)	Non–ST-segment elevation (subendocardial) myocardial infarction
Platelet thrombus on ruptured plaque	Complete vessel occlusion (no lysis)	ST-segment elevation (transmural) myocardial infarction

Clinical Presentation

Signs and Symptoms. Chest pain is the cardinal feature of MI, even though it is not universally present (Table 3–2). It is similar to angina pectoris—described as heavy, squeezing, or crushing—and is localized to the retrosternal area or epigastrium, sometimes radiating to the arm, lower jaw, or neck. **Unlike stable angina, however, it persists for more than 30 minutes and is not relieved by rest.** The pain often is accompanied by sweating, nausea, vomiting, and/or the sense of impending doom. In some patients, chest pain may not be prominent. Diabetics and older patients may present with only vague discomfort or have sudden dyspnea, pulmonary edema, or ventricular arrhythmias as their initial presentation. There are **no specific physical findings** in a patient with an acute MI. Many patients are anxious and diaphoretic. Cardiac auscultation may reveal an S_4 gallop, reflecting myocardial noncompliance because of ischemia; an S_3 gallop, representing severe systolic dysfunction; or a new apical systolic murmur of mitral regurgitation caused by ischemic papillary muscle dysfunction.

Electrocardiogram. The ECG is often critical in diagnosing an acute MI and guiding therapy. A series of ECG changes reflects the evolution of the infarction (Figure 3–2).

1. The earliest changes are tall, positive, **hyperacute T waves** in the ischemic vascular territory.
2. This is followed by **elevation of the ST segments** (myocardial "injury pattern").
3. Over hours to days, **T-wave inversion** frequently develops.
4. Finally, diminished R-wave amplitude or **Q waves** occurs, representing significant myocardial necrosis and replacement by scar tissue.

When acute ischemia is limited to the **subendocardium**, **ST-segment depression**, rather than ST-segment elevation, develops. **ST-segment elevation indicates that the full thickness of the wall has been affected (ie, "transmural" infarction).**

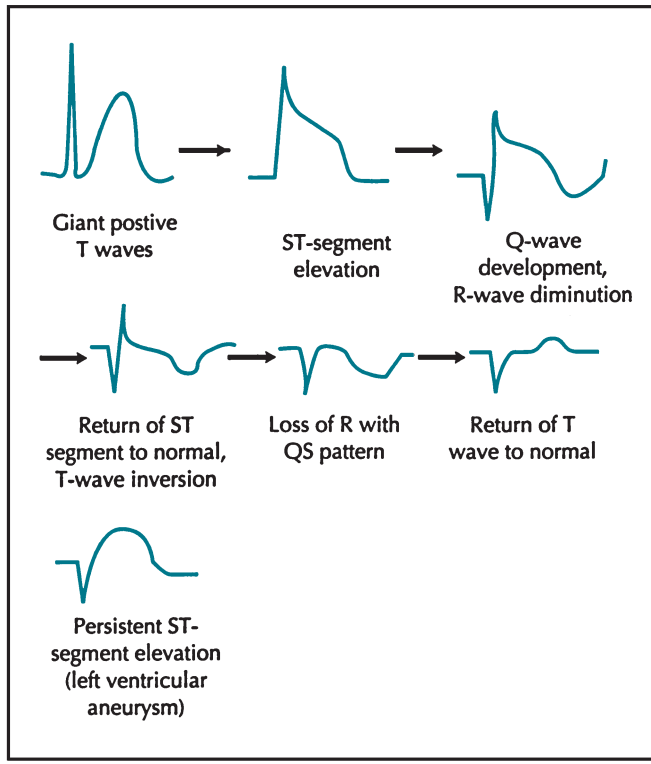


Figure 3–2. Temporal evolution of ECG changes in acute MI. Note tall hyperacute T waves and loss of R-wave amplitude, followed by ST-segment elevation, T-wave inversion, and development of Q waves. Persistent ST-segment elevation suggests LV aneurysm. (Reproduced with permission, from Alpert JS. *Cardiology for the Primary Care Physician*. 2nd ed. 1998. Copyright © Appleton & Lange. All rights reserved.)

From the ECG we can localize the ischemia related to a vascular territory supplied by one of the three major coronary arteries. **STEMI** is defined as ST-segment elevation more than 0.1 mV in two or more contiguous leads (ie, in the same vascular territory) and/or a new left bundle branch block (LBBB) (which obscures usual ST-segment analysis). As a general rule, **leads II, III, and aVF** correspond to the **inferior** surface of the heart supplied by the **right coronary artery** (RCA); leads **V_2 to V_4** correspond to the **anterior** surface supplied by the **left anterior descending coronary artery** (LAD); and **leads I, aVL, V_5, and V_6** correspond to the **lateral** surface, supplied by the **left circumflex coronary artery** (LCX).

Cardiac Biomarkers. Certain proteins, referred to as cardiac biomarkers, are released into blood from necrotic heart muscle after an acute MI. The creatine phosphokinase (CK) level rises within 4 to 8 hours and returns to normal by 48 to 72 hours. Creatine phosphokinase is found in skeletal muscle and other tissues, but the CK-MB isoenzyme is not found in significant amounts outside of heart muscle, so elevation of this fraction is more specific for myocardial injury. Cardiac-specific

troponin I (cTnI) and cardiac-specific troponin T (cTnT) are more specific to heart muscle and are the preferred markers of myocardial injury. These protein levels rise approximately from 3 to 5 hours after infarct. The cTnI levels may remain elevated for 7 to 10 days and cTnT levels for 10 to 14 days. They are very sensitive and fairly specific indicators of myocardial injury, and their levels may be elevated with even small amounts of myocardial necrosis. Generally, two sets of normal troponin levels 6 to 8 hours apart exclude MI.

Differential Diagnosis. The diagnosis of **acute MI** is made by finding **at least two of the following three features**: typical **chest pain persisting for more than 30 minutes**, typical **ECG findings**, and **elevated cardiac biomarker levels.** Because of the urgency in initiating treatment, diagnosis often rests on the clinical history and the ECG findings while determination of cardiac biomarker levels is pending. During the initial evaluation, other conditions that present with chest pain but could impair with the treatment of ACS should be excluded. Two such conditions are aortic dissection and acute pericarditis. **Aortic dissection** often presents with unequal pulses or blood pressures in the arms, a new murmur of aortic insufficiency, or a widened mediastinum on chest x-ray film. Acute pericarditis often presents with chest pain and a pericardial friction rub, but the ECG findings show **diffuse ST-segment elevation** rather than those limited to a vascular territory.

Treatment

Once an acute MI has been diagnosed based on history, ECG, or cardiac biomarkers, several therapies are initiated. Because the process is caused by acute thrombosis, antiplatelet agents such as **aspirin** and anticoagulation with **heparin** are used. To limit infarct size, **beta-blockers** are used to decrease myocardial oxygen demand, and **nitrates** are given to increase coronary blood flow. All of these therapies appear to reduce mortality in patients with acute MI. In addition, morphine may be given to reduce pain and the consequent tachycardia. Patients are also placed on supplemental oxygen (Figure 3–3). After this medical management, reperfusion therapy should be considered. The major options are thrombolytics or PCI.

Percutaneous coronary intervention. PCI is effective in restoring perfusion in patients with acute STEMI and, if performed by experienced operators in dedicated medical centers, has been shown in multiple trials to provide a greater survival benefit and lower risk for serious bleeding compared to thrombolytics. **If patients with an acute STEMI present within 2 to 3 hours of symptom onset and can receive PCI within 90 minutes, then PCI is the recommended reperfusion therapy**. PCI can also be used in patients with a contraindication to thrombolytic therapy or who are hypotensive or in cardiogenic shock, for whom thrombolytics offer no survival benefit. PCI is accomplished by cardiac catheterization, in which a guidewire is inserted into the occluded coronary artery and a small balloon threaded over the guidewire and inflated in an attempt to open the blockage and restore blood flow. Sometimes intraluminal expandable stents are deployed, which may improve vessel patency. Use of primary PCI may be limited by the availability of the facilities and personnel required to perform the procedure in a timely fashion.

Thrombolytics. If PCI is not available, patients with STEMI should receive thrombolytics, which have been shown to reduce mortality and preserve

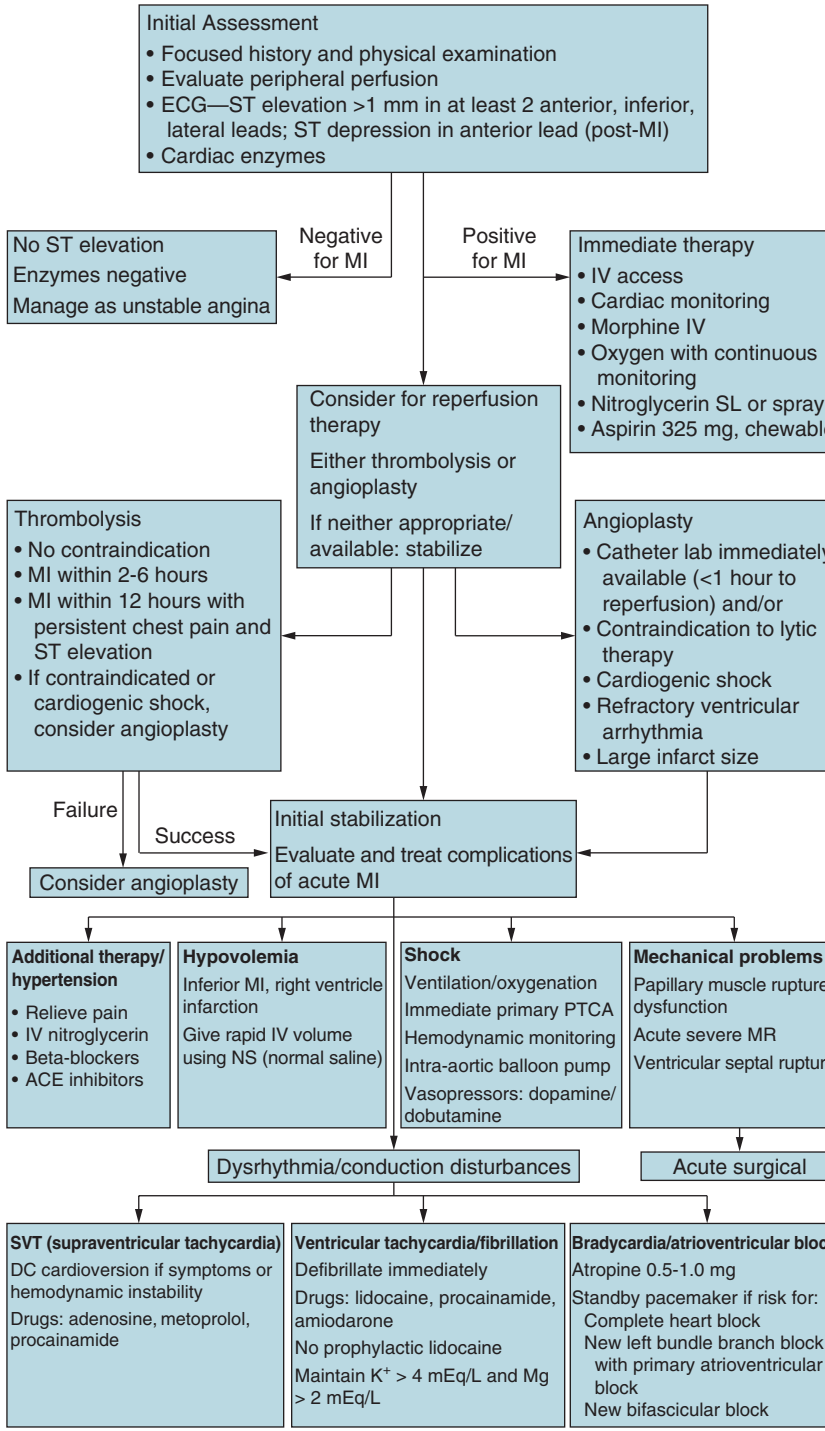


Figure 3–3. Sample algorithm for assessment and treatment of chest pain.

myocardial function. In patients without ST-segment elevation, thrombolytics have not demonstrated the same mortality benefit. Because myocardium can be salvaged only before it is irreversibly injured ("time is muscle"), patients benefit maximally when the drug is given early (eg, within 1-3 hours after the onset of chest pain), and the relative benefits decline with time. The major risk of thrombolytics is bleeding, which can lead to potentially disastrous situations, such as intracranial hemorrhages. The risk of hemorrhage is relatively constant, so the risk begins to outweigh the benefit by 12 hours, at which time most infarctions are completed, and the at-risk myocardium is dead. Thrombolytic therapy is indicated if all of the following criteria are met:

1. Clinical complaints are consistent with ischemic-type chest pain.
2. ST-segment elevation more than 1 mm is present in at least two anatomically contiguous leads.
3. There are no contraindications to thrombolytic therapy.
4. Patient is younger than 75 years (greater risk of hemorrhage if > 75).

Contraindications to thrombolytics are related to the patient's bleeding risk and include recent major surgery, active internal bleeding, suspected aortic dissection, severe hypertension, or a prior history of a hemorrhagic stroke.

Complications

In acute MI, **mortality is usually a result of ventricular arrhythmias or myocardial pump failure and resultant cardiogenic shock** (Table 3–3)**.**

Ventricular Arrhythmias. Life-threatening **ventricular arrhythmias,** such as **ventricular tachycardia** (**VT**) and **ventricular fibrillation** (**VF**), are common, especially in the first 24 hours. Historically, most deaths from acute MI occurred in the first hour and were caused by VT/VF. This has diminished in recent years with earlier, more aggressive treatment of ischemia and arrhythmias. Premature ventricular contractions (PVCs) are very common but generally not treated with antiarrhythmic agents unless they occur very frequently, are sustained, or induce hemodynamic

Table 3–3 • POST-MI COMPLICATIONS

Time Frame		
< 24 Hours: Rhythm Disturbance	**< 1 Week: Mechanical Complications**	**> 2 Weeks: Late Complications**
Cardiogenic shock	Mitral regurgitation	Ventricular aneurysm
Ventricular arrhythmia	Papillary muscle rupture	Dressler syndrome
Accelerated idioventricular rhythm	Ventricular septal rupture	
Premature ventricular contractions	Ventricular free wall rupture	
AV node disease		
New bundle branch block		

compromise. Sustained VT (> 30 seconds) and VF are life threatening because they prevent coordinated ventricular contraction, causing cardiovascular collapse. They are treated with **defibrillation,** followed by infusion of intravenous antiarrhythmics such as **amiodarone.** Electrolyte deficiencies, such as hypokalemia or hypomagnesemia, can potentiate ventricular arrhythmias and should be corrected.

One benign ventricular arrhythmia that is generally not suppressed by antiarrhythmics is the **accelerated idioventricular rhythm.** This is a wide-complex escape rhythm between 60 and 110 bpm that frequently accompanies reperfusion of the myocardium but causes no hemodynamic compromise.

Supraventricular and Atrial Tachyarrhythmias. **Supraventricular or atrial tachyarrhythmias** are much less common after acute MI, but they can worsen ischemia and cause infarct extension as a consequence of the rate-related increase in myocardial oxygen demand. When they cause hemodynamic instability, they also are treated with immediate direct current (DC) cardioversion.

Bradyarrhythmias. Other frequent rhythm disturbances are bradyarrhythmias. **Sinus bradycardia** is frequently seen in inferior MI because the RCA supplies the sinoatrial node, but the condition generally requires no treatment unless it causes hypotension. If the heart rate is slow enough to cause cardiac output and blood pressure to fall, intravenous **atropine** is usually administered.

Bradyarrhythmias can also be caused by atrioventricular (AV) conduction disturbances. **First-degree AV block** (PR interval prolongation) and **Mobitz I second-degree AV block** (gradual prolongation of the PR interval before a nonconducted P wave) are often caused by AV nodal dysfunction, for example, nodal ischemia caused by inferior MI. Patients who are symptomatic can be treated with **atropine.**

Conduction Dysfunctions. Conduction disturbances below the AV node typically produce a widened QRS complex. Examples include **Mobitz II second-degree AV block** (nonconducted P waves not preceded by PR prolongation) and **third-degree AV block** (complete AV dissociation with no P-wave conduction). Third-degree AV block also can be caused by AV nodal dysfunction. These arrhythmias are described more fully in other cases. Conduction disturbances caused by involvement of the bundle of His include **LBBB** or **right bundle branch block (RBBB) with left anterior hemiblock.** Conduction disturbances below the AV node generally have a worse prognosis than AV nodal dysfunction because they are generally seen with anterior infarction in which a significant amount of myocardium is damaged. When symptomatic bradycardias such as third-degree AV block develop, they may be treated with external pacing but can require placement of a temporary transvenous pacemaker if the patient is in cardiogenic shock from complete heart block. Patients in persistent complete heart block will require placement of a permanent pacemaker.

Cardiac pump failure and cardiogenic shock. Cardiogenic shock in acute MI usually is the most severe form of LV pump failure, manifested by end-organ hypoperfusion. Ischemic reduction in ventricular diastolic compliance may lead to transient pulmonary congestion, associated with elevated left-sided filling pressures. Extensive myocardial necrosis and less contracting heart muscle may cause systolic failure and reduced cardiac output. Patients with hypotension frequently are evaluated by

pulmonary artery (Swan-Ganz) catheterization to assess hemodynamic parameters. **Cardiogenic shock** is diagnosed when the patient has **hypotension** with systolic arterial pressure less than 80 mm Hg, **markedly reduced cardiac index** less than **1.8 L/min/m^2**, and **elevated LV filling pressure** (measured indirectly with a pulmonary capillary wedge pressure > 18 mm Hg). Clinically, such patients appear hypotensive, with cold extremities because of peripheral vasoconstriction, pulmonary edema, and elevated jugular venous pressure, reflecting high left- and right-sided filling pressures. Supportive treatment includes hemodynamic monitoring, adequate ventilation and oxygenation, and blood pressure support with vasopressors such as dobutamine and dopamine. These patients also may require mechanical assistance to augment blood pressure while providing afterload reduction, using intra-aortic balloon counterpulsation. Cardiogenic shock may require urgent revascularization with primary PCI or coronary artery bypass surgery.

Hypotension may also be seen in patients with **right ventricular (RV) infarction**, which is a complication of RCA occlusion and inferior infarction. In this case, LV function is not impaired, but LV filling is dramatically reduced because of the right-sided ventricular failure (the left heart can only pump out what it receives from the right heart). These patients can be recognized clinically as **hypotensive, with markedly elevated jugular venous pressure but clear lung fields** and no pulmonary edema seen radiographically (in contrast to the pulmonary edema seen in patients with hypotension to LV failure). The diagnosis is confirmed by observation of ST-segment elevation in a right-sided ECG. In this setting, RV function is impaired and highly dependent on adequate preload, so treatment consists of volume replacement with crystalloid or colloid solution. Diuretics or nitrates should be avoided in these patients because they lower preload, which can cause catastrophic cardiovascular collapse. Patients with RV dysfunction or failure may require inotropic support to increase blood delivery to the LV.

Mechanical Problems. A number of mechanical problems can complicate acute MI, usually presenting within the first week with a **new systolic murmur**. The most common is **papillary muscle dysfunction** caused by LV ischemia or infarction, leading to **mitral regurgitation,** which may or may not be hemodynamically significant. This is in contrast with **papillary muscle rupture**, which produces a flail mitral leaflet and acute mitral regurgitation with development of heart failure and cardiogenic shock. **Ventricular septal rupture** can also occur, possibly leading to development of acute heart failure and shock. Transthoracic echocardiography can be used to distinguish among these conditions. In all of them, stabilization of cardiogenic shock is accomplished using afterload reduction with intravenous nitroglycerin or nitroprusside and sometimes with intra-aortic balloon counterpulsation until definitive, urgent, surgical repair can be accomplished. Other modalities of mechanical circulatory support may be used for temporary support in cardiogenic shock, including a LV assist device or venous-arterial extracorporeal membrane oxygenation (ECMO).

The most catastrophic mechanical complication is **rupture of the ventricular free wall**. As blood fills the pericardium, cardiac tamponade develops rapidly, with sudden pulselessness, hypotension, and loss of consciousness. This complication nearly always is fatal.

Post-MI Risk Stratification. Post-MI, patients should be stratified to identify patients who are at high risk for subsequent cardiac events and who might benefit from revascularization. The initial evaluation involves noninvasive testing. **Submaximal exercise stress testing** is generally performed in stable patients before hospital discharge to detect residual ischemia or ventricular ectopy and to provide a guideline for exercise in the early recovery period. **Evaluation of LV systolic function**, usually with echocardiography, is routinely performed. High-risk patients include those with impaired systolic function, large areas of ischemic myocardium on stress testing, postinfarction angina, or ventricular ectopy. These patients might benefit from coronary angiography to evaluate for revascularization. PCI can be performed to reduce anginal symptoms, and **coronary artery bypass surgery** should be considered for patients with **multivessel atherosclerotic stenosis** and **impaired systolic function** because the surgery may reduce symptoms and prolong survival. Post-STEMI patients with **LV dysfunction** (LV ejection fraction [EF] < 40%) are at **increased risk for sudden cardiac death** from **ventricular arrhythmias** and may benefit from placement of an implanted cardioverter-defibrillator (ICD).

Secondary Prevention of Ischemic Heart Disease. Medical therapy to reduce modifiable risk factors is the cornerstone of post-MI care. In addition to symptom relief, the major goal of medical therapy is to prevent cardiac events: fatal or nonfatal MI. By far, the **most important risk factor is smoking cessation**. Quitting tobacco use can reduce the risk of fatal or nonfatal cardiac events by more than 50%, more than any other medical or surgical therapy available.

A number of other therapies reduce the risk of recurrent cardiovascular events and prolong survival in patients with coronary artery disease. Antiplatelet agents such as **aspirin** and **clopidogrel** reduce the risk of thrombus formation. **Beta-blockers** reduce myocardial oxygen demand and may help suppress ventricular arrhythmias. **Statins** improve serum cholesterol levels and may stabilize vascular plaque, reducing the number of coronary events and prolonging survival. **Angiotensin-converting enzyme (ACE) inhibitors** decrease ventricular remodeling and reduce mortality and are recommended for all patients after STEMI. **Aldosterone antagonists** such as spironolactone or eplerenone reduce mortality in patients with LV EF < 40% and clinical heart failure or diabetes. Finally, **screening for depression** is appropriate, as depression is common (~20%) post-MI and has been associated with increased rates of hospitalization and death.

CASE CORRELATION

- See also Case 2 (Metabolic Syndrome), Case 10 (Acute Pericarditis Caused by Systemic Lupus Erythematosus), and Case 13 (Limb Ischemia, Peripheral Vascular Disease)

COMPREHENSION QUESTIONS

3.1 A 36-year-old woman has severe burning chest pain that radiates to her neck. The pain occurs particularly after meals, especially when she lies down, and is not precipitated by exertion. She is admitted for observation. Serial ECG and troponin I levels are normal. Which of the following is the best next step?

A. Stress thallium treadmill test

B. Initiation of a proton pump inhibitor

C. Coronary angiography

D. Initiation of an antidepressant such as a selective serotonin reuptake inhibitor (SSRI)

3.2 A 56-year-old man is admitted to the hospital for chest pain of 2-hour duration. His heart rate is 42 bpm, with sinus bradycardia on ECG, as well as ST-segment elevation in leads II, III, and aVF. Which of the following is the most likely diagnosis?

A. Left-circumflex territory infarction

B. Inferior wall infarction

C. LV aneurysm

D. Anterior wall infarction

3.3 A 59-year-old diabetic woman had suffered an acute anterior wall MI. Five days later, she gets into an argument with her husband and complains of chest pain. Her initial ECG shows no ischemic changes, but serum cardiac troponin I levels are drawn and return mildly elevated at this time. Which of the following is the best next step?

A. Use thrombolytic therapy.

B. Treat with percutaneous coronary intervention.

C. Perform coronary artery bypass.

D. Perform serial ECGs and obtain CK-MB.

3.4 A 59-year-old male smoker complains of severe retrosternal squeezing chest pain of 30 minutes' duration. The paramedics have given sublingual nitroglycerin and oxygen by nasal cannula. His blood pressure is 110/70 mm Hg, and heart rate is 90 bpm on arrival to the Emergency Department. The ECG is normal. Which of the following is the best next step?

A. Echocardiography

B. Thallium stress test

C. Aspirin

D. Coronary angiography

E. Coronary artery bypass

ANSWERS

3.1 **B.** It is appropriate to evaluate chest pain to first rule out cardiac ischemia. One of the most common causes of "chest pain," particularly in a younger patient, is gastroesophageal reflux or esophageal spasm. This patient has classic symptoms of reflux esophagitis and is best treated with a proton pump inhibitor. If the chest pain has the characteristics of angina pectoris (retrosternal location, precipitated by exertion, relieved by rest or nitroglycerin), it should be investigated with a stress test (answer A) or coronary angiography (answer C). SSRIs may be used to treat panic disorder, which can present with chest pain and palpitations; however, there are no indications for an SSRI in this patient (answer D).

3.2 **B.** Sinus bradycardia is often seen with inferior wall MI because the RCA supplies the inferior wall of the LV and the sinoatrial node. The ischemic changes in leads II, III, and aVF are in the region of the inferior leads. A circumflex-territory infarction (answer A) usually leads to a lateral wall infarction, involving leads I, aVL, V_5, and V_6. LV aneurysm (answer C) can be a late complication of MI, associated with persistence of ST elevation for weeks after an MI. Anterior wall infarction (answer D) is associated with ST elevation in leads V1 through V_4.

3.3 **D.** Diabetic patients can have myocardial ischemia or infarction with atypical or absent symptoms. Clinical suspicion and a liberal use of cardiac enzyme testing are required. Troponin levels often remain elevated for 7 to 10 days and should not be used to diagnose reinfarction, especially if the levels are trending downward. New ECG findings or rapidly rising markers such as serum myoglobin or CK-MB can be used in this setting. Thrombolytics, PCI, or coronary artery bypass grafting (CABG) (answers A, B, and C) are not indicated in this patient at this time, as her elevated troponins are likely due to prior infarct, and she does not meet criteria for STEMI or NSTEMI currently.

3.4 **C.** Aspirin is the first agent that should be used after oxygen and nitroglycerin. Aspirin use decreases mortality in the face of an acute coronary event. Because initial ECGs and cardiac enzymes may be normal in an acute MI, serial studies are needed to definitively rule out MI. Echocardiography or coronary angiography (answers A and D) may be appropriate in working up this patient's chest pain, but the first priority is to administer aspirin. Stress tests (answer B) are used to determine if patients with moderate pretest probability of coronary artery disease have it or not. Stress tests are never part of the acute management of cardiac chest pain. CABG (answer E) is premature in this patient, who does not have any indications for the procedure at this time.

CLINICAL PEARLS

- Acute coronary syndromes (unstable angina or acute MI) occur when a thrombus forms at the site of rupture of an atherosclerotic plaque and acutely occludes a coronary artery.
- Acute MI is diagnosed based on the presence of at least two of three criteria: typical symptoms, ECG findings, and cardiac enzymes.
- ECG findings can further stratify MI into STEMI or NSTEMI. Initial ECG and enzyme levels may be normal, so serial studies are necessary.
- Typical initial treatment of ACS includes aspirin, beta-blockers, nitrates, heparin, and morphine. Nitrates and beta-blockers should be used cautiously as they lower cardiac output.
- Early reperfusion with PCI or thrombolytics reduces mortality and preserves ventricular function in patients who have ST-segment elevation, have no contraindications, and receive treatment within the first 6 to 12 hours.
- The goal of secondary prevention after MI is to prevent recurrent cardiac events and death. Smoking cessation, antiplatelet medications, beta-blockers, ACE inhibitors, statins, and aldosterone antagonists all reduce the rate of events and mortality.
- After MI, PCI can be performed to reduce ischemia and anginal symptoms. Bypass surgery may be indicated for patients with multivessel stenosis and impaired systolic function to reduce symptoms and prolong survival.
- The ECG can indicate the location of the ischemia or infarction: anterior (leads V_2 through V_4); lateral (leads I, aVL, V_5, and V_6); inferior (leads II, III, and aVF); and posterior (R waves in leads V_1 and V_2).
- STEMI is characterized by ischemic discomfort along with ST-segment elevation on ECG and biomarkers.
- Unstable angina and NSTEMI will not have ST-segment elevation; NSTEMI is diagnosed by positive cardiac biomarkers.

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CASE 4

A 72-year-old man presents to the clinic complaining of worsening exertional dyspnea. Previously, he had been able to work in his garden and mow the lawn, but now he feels short of breath after walking 100 ft. He does not have chest pain at rest but has experienced retrosternal chest pressure with strenuous exertion. He occasionally feels light-headed while climbing a flight of stairs, as if he were about to faint, but this resolves after sitting down. He now uses three pillows when he sleeps; otherwise, he wakes up at night feeling short of breath, which is relieved within minutes by sitting upright in bed. He notes occasional swelling of his lower extremities. He denies any significant medical history, takes no medications, and prides himself on the fact that he has not seen a doctor in years. He does not smoke or drink alcohol.

On physical examination, he is afebrile, with a heart rate of 86 beats per minute (bpm), blood pressure of 115/92 mm Hg, and respiratory rate of 16 breaths per minute. Examination of the head and neck reveals a normal thyroid gland and distended neck veins. Bibasilar inspiratory crackles are appreciated. On cardiac examination, his heart rhythm is regular with a normal S_1 and S_2, with an S_4 at the apex, a leftward displaced apical impulse, and a late-peaking systolic murmur at the right upper sternal border that radiates to his carotids. The carotid upstrokes have diminished amplitude.

- What is the most likely diagnosis?
- What test would confirm the diagnosis?

ANSWERS TO CASE 4:
Heart Failure due to Critical Aortic Stenosis

Summary: A 72-year-old man presents with

- Angina-like chest pressure with strenuous exertion and near-syncope while climbing a flight of stairs
- Orthopnea and paroxysmal nocturnal dyspnea, pedal edema, elevated jugular venous pressure (JVP), and crackles suggesting pulmonary edema
- A late systolic murmur radiating to his carotids, the paradoxical splitting of his second heart sound, and the diminished carotid upstrokes suggesting severe aortic stenosis

Most likely diagnosis: Heart failure (HF), likely as a result of aortic valve stenosis.

Diagnostic test: Echocardiogram to assess the aortic valve area as well as the left ventricular (LV) systolic function, chest x-ray, electrocardiogram (ECG), and B-type natriuretic peptide (BNP) levels.

ANALYSIS

Objectives

1. Identify the causes of chronic HF (eg, ischemia, hypertension, valvular disease, alcohol abuse, cocaine, and thyrotoxicosis). (EPA 1, 3)
2. Understand the treatment of acute and chronic HF. (EPA 4)
3. Discuss the evaluation of aortic stenosis and the indications for valve replacement. (EPA 1, 4, 7)
4. Identify preventive measures for general patients at risk for heart failure (HF) to avoid progression. (EPA 4)

Considerations

This is an elderly patient with symptoms and signs of aortic stenosis. The valvular disorder has progressed from previous angina and presyncopal symptoms to HF, reflecting worsening severity of the stenosis and worsening prognosis for survival. This patient should undergo urgent evaluation of his aortic valve surface area and coronary artery status to assess the need for valve replacement.

APPROACH TO: Heart Failure

DEFINITIONS

ACUTE HF: Acute (hours, days) presentation of cardiac decompensation with pulmonary edema and low cardiac output, which may proceed to cardiogenic shock; can be superimposed onto chronic HF.

CARDIAC REMODELING: Changes to cardiac myocytes due to changing cardiac parameters leading to cardiac dysfunction. Some medications can prevent or even reverse the remodeling.

CHRONIC HF: Chronic (months, years) presence of cardiac dysfunction; symptoms may range from minimal to severe.

DIASTOLIC DYSFUNCTION: Increased diastolic filling pressures caused by impaired diastolic relaxation and decreased ventricular compliance, but with preserved ejection fraction (EF) > 40% to 50%. Etiologies may include uncontrolled hypertension, constrictive pericarditis, restrictive cardiomyopathy, and cardiac tamponade, among others.

LEFT-SIDED HF: HF due to left ventricular dysfunction; also known as "forward" HF.

RIGHT-SIDED HF: HF due to right ventricular dysfunction; also known as "backward" HF.

SYSTOLIC DYSFUNCTION: Low cardiac output caused by impaired systolic function (low EF < 40%). Etiologies may include myocardial infarction, myocarditis, and dilated cardiomyopathy resulting from multiple diseases, among others.

CLINICAL APPROACH TO HEART FAILURE

Pathophysiology

Heart failure is found in 1% to 2% of the US population, with disproportionately higher rates in African Americans, Native Americans, and Hispanics. **HF** is a **clinical syndrome** that is produced when the heart is **unable to meet the metabolic needs of the body while maintaining normal ventricular filling pressures.** A series of **neurohumoral responses** develops, including activation of the renin-angiotensin-aldosterone axis and increased sympathetic activity, which initially may be compensatory but ultimately cause further cardiac decompensation. The most common cause of HF overall is ischemic cardiomyopathy. Systolic dysfunction is classified via transthoracic echocardiogram (TTE) by reduction of contractility (reduction in EF), in contrast to diastolic dysfunction, in which EF is preserved.

Clinical Presentation

Types of HF. Symptoms may be a result of **forward failure** (low cardiac output or systolic dysfunction), including **fatigue, lethargy, and even hypotension**, or **backward failure** (increased filling pressures or diastolic dysfunction), including **dyspnea,**

peripheral edema, and ascites. Some patients have isolated diastolic dysfunction with preserved left ventricular ejection fraction (LVEF > 40%-50%), most often as a consequence of hypertension or simply of aging. Half of patients with HF have impaired systolic dysfunction (LVEF < 40%) with associated increased filling pressures. Some patients have isolated **right-sided HF, which typically presents predominantly with symptoms of peripheral congestion.** These include pitting edema of extremities, hepatomegaly and congestion, ascites, and jugular venous distention. On the other hand, **left-sided HF, which often progresses to biventricular failure, exhibits pulmonary symptoms** before progressing to signs of peripheral volume overload. These include pulmonary edema, paroxysmal nocturnal dyspnea, orthopnea, and cardiac asthma.

History and Physical Examination. Obtaining a thorough history and physical examination is critical in the evaluation of possible HF. A history should focus on exertional symptoms and triggers, alcohol and drug use, and recent viral infections. Physical exam should involve assessment for rales, displaced apical impulse, JVP, hepatojugular reflux, hepatomegaly, and extremity pitting edema. The presence of pulmonary edema more likely supports a diagnosis of left HF. **Auscultatory findings may include an S_4 (atrial gallop) or an S_3 (ventricular gallop)**, low-pitched heart sound that is heard best with the bell of the stethoscope.

Diagnostic Workup. Workup should include an **ECG, chest x-ray, TTE, and BNP levels.** An ECG may reveal ventricular hypertrophy or previous myocardial infarction. Chest x-ray may show signs of pulmonary congestion, cardiomegaly, and other lung pathology. An echocardiogram is useful for assessment of EF, wall motion abnormalities, valvular disease, and possible pericardial fluid collection. BNP levels can be used to support clinical suspicion for HF. **BNP values > 400 pg/mL are relatively sensitive for HF.** Other appropriate investigations may include cardiac stress testing or coronary angiography if there are signs of myocardial ischemia.

Staging. HF is a **chronic and progressive syndrome** that can be assessed by following the patient's exercise tolerance, as done by the **New York Heart Association (NYHA) functional classification** (Table 4–1). This functional classification carries prognostic significance. Individuals in class III who have low oxygen consumption during exercise have an annual mortality rate of 20%; in class IV, the rate is 60% annually. Patients with a low ventricular ejection fraction (LVEF < 20%) also have very high mortality risks. Death associated with HF may occur from the underlying disease process, cardiogenic shock, or sudden death as a result of ventricular arrhythmias.

Chronic Heart Failure Treatment

Although HF has many causes (Table 4–2), identification of the underlying treatable or reversible causes of disease is essential. For example, HF related to

Table 4–1 • NEW YORK HEART ASSOCATION FUNCTIONAL CLASSIFICATION

Class I:	No limitation during ordinary physical activity
Class II:	Slight limitation of physical activity. Develops fatigue or dyspnea with moderate exertion
Class III:	Marked limitation of physical activity. Even light activity produces symptoms
Class IV:	Symptoms at rest. Any activity causes worsening

Table 4–2 • SELECTED CAUSES OF HEART FAILURE

Myocardial injury • Adriamycin • Alcohol use • Cocaine • Ischemic cardiomyopathy (atherosclerotic coronary artery disease) • Rheumatic fever • Viral myocarditis
Chronic pressure overload • Aortic stenosis • Hypertension
Chronic volume overload • Mitral regurgitation
Infiltrative diseases • Amyloidosis • Hemochromatosis
Chronic tachyarrhythmia or bradyarrhythmia

tachycardia, alcohol consumption, or viral myocarditis may be reversible with removal of the inciting factor. In patients with underlying multivessel atherosclerotic coronary disease and a low EF, revascularization with coronary artery bypass grafting improves cardiac function and prolongs survival. The three major treatment goals for patients with chronic HF are **relief of symptoms, prevention of disease progression, and a reduction in mortality risk.**

Relief of Symptoms. The HF symptoms, which are mainly caused by low cardiac output and fluid overload, usually are relieved with lifestyle modifications and diuretics. Lifestyle changes may include reducing sodium intake to < 3 g daily, fluid restriction, establishing an exercise regimen, smoking cessation, and reduction of alcohol intake.

Preventing Disease Progression. Because HF has such a substantial mortality, measures to halt or reverse disease progression are necessary. Reversible causes should be aggressively sought and treated.

Decreasing Mortality Risk. Use of **angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and some beta-blockers,** such as carvedilol (CAR), metoprolol, or bisoprolol, **have been shown to reduce mortality in patients with impaired systolic function and moderate-to-severe symptoms.** In patients who cannot tolerate ACE inhibition (or in black patients in whom ACE inhibitors appear to confer less benefit), the use of **hydralazine with nitrates** has been shown to decrease mortality. **Aldosterone antagonists such as spironolactone may be added to patients with NYHA class III or IV HF with persistent symptoms, but patients should be monitored for hyperkalemia.** Digoxin can be added to these regimens for persistent symptoms, but it provides no survival benefit and can confer significant toxicity at supratherapeutic levels. The mechanisms of these various agents are outlined in Table 4–3. On the other hand, there are certain medications that are relatively contraindicated in HF; some examples include the nondihydropyridine calcium channel blockers (verapamil and diltiazem), which reduce

Table 4–3 • SELECTED MEDICATIONS FOR HF

Medication	Mechanism of Action
Beta-blockers	Prevent and reverse adrenergically mediated intrinsic myocardial dysfunction and remodeling.
ACE inhibitors/ARBs	Reduce preload and afterload, thereby reducing right atrial, pulmonary arterial, and pulmonary capillary wedge pressures along with systemic vascular resistance. Prevent remodeling. These agents are the initial drugs of choices in treating HF due to survival advantage.
Nitrates and nitrites	Reduce preload and clear pulmonary congestion. Decreases mortality in HF when associated with hydralazine.
Hydralazine	Unclear. Vasodilator.
Diuretics	Decrease preload. Especially useful in acute settings.
Digoxin	Improves cardiac contractility. Also slows conduction at atrioventricular (AV) node. It has a narrow therapeutic window.
Aldosterone antagonists	Block the action of aldosterone. Spironolactone has antiandrogenic effects, while eplerenone does not.

cardiac contractility, and the **thiazolidinediones, a class of diabetes medications that can exacerbate HF.**

Some devices may also be useful in reducing symptoms and mortality in patients with HF. Patients with depressed EF and advanced symptoms often have a widened QRS > 120 ms, indicating dyssynchronous ventricular contraction. Placement of a biventricular pacemaker, called **cardiac resynchronization therapy** (**CRT**), to stimulate both ventricles to contract simultaneously can improve symptoms and reduce mortality. Since patients with class II–III HF and depressed EF < 35% have elevated risk of sudden cardiac death due to ventricular arrhythmias, placement of an **implanted cardioverter-defibrillator** (**ICD**) should be considered.

Acute Decompensated Heart Failure Treatment

In patients with acute decompensated HF, the initial treatment goals are to **stabilize the patient's hemodynamic derangements** and to **identify and treat reversible factors** that may have precipitated the decompensation, such as arrhythmias or myocardial ischemia. Symptomatic treatment may include the use of oxygen, nitrates, and furosemide.

Regarding hemodynamics, if patients appear to have elevated LV filling pressures, they often require intravenous vasodilators such as nitroglycerin infusion, and patients with decreased cardiac output may require inotropes such as dobutamine; hypotensive patients may require vasoconstrictors such as dopamine.

Another complication that may arise is **cardiorenal syndrome**, a process that results from reductions in glomerular filtration rate due to renal hypoperfusion and renal venous congestion. Management includes treatment of the underlying HF and acute kidney injury.

CLINICAL APPROACH TO AORTIC STENOSIS

Pathophysiology

The history and physical findings presented in the scenario suggest that this patient's HF may be a result of aortic stenosis. This is the **most common symptomatic valvular abnormality in adults**. Most cases occur in men. The causes of the valvular stenosis vary depending on the typical age of presentation: Stenosis in patients **younger than 30 years** usually is caused by a **congenital bicuspid valve**; in patients 30 to 70 years old, it usually is caused by congenital stenosis or acquired rheumatic heart disease; and in patients **older than 70 years, it usually is caused by degenerative calcific stenosis.**

Clinical Presentation

Typical physical findings of critical aortic stenosis include a **narrow pulse pressure**, a soft S_2, a **harsh late-peaking systolic murmur** heard best at the right second intercostal space with radiation to the carotid arteries, and a delayed, slow-rising carotid upstroke (*pulsus parvus et tardus*). The ECG often shows LV hypertrophy. Doppler echocardiography reveals a thickened abnormal valve and can estimate aortic valve area and the transvalvular pressure gradient to determine severity. As the valve orifice narrows, the pressure gradient increases in an attempt to maintain cardiac output. **Severe** aortic stenosis is defined as a **calcified valve** with decreased systolic opening, an **aortic velocity > 4 m/s**, and a **mean pressure gradient > 40 mg Hg; valve areas are typically less than 1 cm**^{2} (normal 3–4 cm^2).

Symptoms of aortic stenosis develop as a consequence of LV hypertrophy as well as diminished cardiac output from flow-limiting valvular stenosis. The first symptom typically is **angina pectoris**, that is, retrosternal chest pain precipitated by exercise and relieved by rest. As the stenosis worsens and cardiac output falls, patients may experience **syncopal episodes**, typically precipitated by exertion. Finally, because of the low cardiac output and high diastolic filling pressures, patients develop clinically apparent **HF** as described previously. The prognosis for patients worsens as symptoms develop. The mean survival with angina, syncope, or HF is 5 years, 3 years, and 2 years, respectively.

Treatment

Patients with severe stenosis who are symptomatic or have a LVEF < 50% should be considered for aortic valve replacement (AVR). Indications for AVR are outlined in Table 4–4. Preoperative cardiac catheterization is routinely performed to provide definitive assessment of the aortic valve area and the pressure gradient, as well as to assess the coronary arteries for significant stenosis. There are three primary approaches to AVR: surgery, transcatheter aortic valve replacement (TAVR), and catheter balloon valvuloplasty. In patients who are not good candidates for valve replacement, the stenotic valve can be enlarged using balloon valvuloplasty, but this will provide only temporary relief of symptoms, as there is a high rate of restenosis. TAVR is a new technique that has been developed for patients who have an unacceptably high surgical risk, and catheter-based aortic valves have now been approved for use in both Europe and the United States.

Table 4–4 • INDICATIONS FOR AORTIC VALVE REPLACEMENT*

Aortic valve replacement is recommended for patients with severe aortic stenosis and any of the following: • LVEF < 50% • Symptoms • Undergoing cardiac surgery for other indications
Severe aortic stenosis criteria: • Decreased systolic opening of a calcified valve • Aortic velocity > 4 m/s • Mean pressure gradient > 40 mm Hg

**Data from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease.* J Am Coll Cardiol. *2014; 63(22): e57-e185.*

Because the most common cause of HF is ischemic cardiomyopathy, the importance of preventive measures to reduce the likelihood of progressive cardiac dysfunction cannot be overstated. Primary prevention includes modification of risk factors: hypertension, hyperlipidemia, diabetes, poor dietary habits, physical activity, alcohol intake, and smoking. Maintaining an effective regimen for hypertension is critical to prevention of diastolic dysfunction, as uncontrolled hypertension can progress to concentric hypertrophy and diastolic failure. Elevated low-density lipoprotein levels > 190 mg/dL or a 10-year atherosclerotic coronary vascular disease (ASCVD) risk of > 7.5% should prompt the initiation of high-intensity statin therapy. Patients with diabetes should be on a regimen that aims to maintain a hemoglobin A_{1C} between 7% and 8% while balancing the risk of hypoglycemia. Dietary changes should include reduction of salt intake and red meats with an increase in vegetables and whole grains. Adherence to an exercise regimen that includes 150 minutes of moderate-intensity aerobic activity weekly is recommended. Reduction of alcohol intake and smoking cessation are also beneficial risk management strategies.

CASE CORRELATION

- See also Case 3 (Acute Coronary Syndrome) and Case 6 (Hypertension, Outpatient)

COMPREHENSION QUESTIONS

4.1 A 55-year-old man is noted to have moderately severe HF with impaired systolic function. Which of the following drugs would most likely lower his risk of mortality?

A. ACE inhibitors

B. Loop diuretics

C. Digoxin

D. Aspirin

4.2 In the United States, which of the following is most likely to have caused the HF in the patient described in Question 4.1?

A. Diabetes
B. Atherosclerosis
C. Alcohol
D. Rheumatic heart disease

4.3 A 75-year-old man is noted to have chest pain with exertion and has been passing out recently. On examination, he is noted to have a harsh systolic murmur. Which of the following is the best therapy for his condition?

A. Coronary artery bypass
B. Angioplasty
C. Valve replacement
D. Carotid endarterectomy

4.4 A 55-year-old man is noted to have HF and states that he is comfortable at rest but becomes dyspneic when he walks to the bathroom. On echocardiography, he is noted to have an EF of 50%. Which of the following is the most accurate description of this patient's condition?

A. Diastolic dysfunction (HF with preserved EF)
B. Systolic dysfunction (HF with reduced EF)
C. Dilated cardiomyopathy
D. Pericardial disease

ANSWERS

4.1 **A.** ACE inhibitors and beta-blockers decrease the risk of mortality for patients who have HF with impaired systolic function. For this reason, these agents are the initial therapies of choice to treat HF. They both prevent and can even, in some circumstances, **reverse cardiac remodeling.**

4.2 **B.** In the United States, the most common cause of HF associated with impaired systolic function is ischemic cardiomyopathy due to coronary atherosclerosis.

4.3 **C.** The symptoms of aortic stenosis classically progress through angina, syncope, and, finally, HF, which has the worst prognosis for survival. This patient's systolic murmur is consistent with aortic stenosis. An evaluation should include echocardiography to confirm the diagnosis and then AVR. **The patient meets criteria for valve replacement because he is exhibiting symptoms.**

4.4 **A.** When the EF is 50%, there is likely diastolic dysfunction with stiff ventricles. The stiff, thickened ventricles do not accept blood very readily. This patient has symptoms with mild exertion that are indicative of functional class III. The worst class is level IV, manifested as symptoms at rest or with minimal

exertion. ACE inhibitors, ARBs, and beta-blockers are important agents in patients with diastolic dysfunction. The current nomenclature uses the terms *preserved* and *reduced* EF to replace *diastolic* and *systolic* HF, respectively.

CLINICAL PEARLS

- Heart failure is a clinical syndrome that is always caused by some underlying heart disease, most commonly ischemic cardiomyopathy as a result of atherosclerotic coronary disease, or hypertension.
- HF can be caused by impaired systolic function (EF < 40%) or impaired diastolic function (with preserved systolic function).
- Chronic HF is a progressive disease with a high mortality. A patient's functional class (exercise tolerance) is the best predictor of mortality and often guides therapy.
- The primary goals of therapy are to relieve congestive symptoms with salt restriction, diuretics, and vasodilators.
- ACE inhibitors, beta-blockers, and aldosterone antagonists can decrease mortality in patients with HF.
- Cardiac resynchronization therapy and placement of an ICD can reduce symptoms and improve mortality in patients with advanced HF and low EF < 35%.
- Aortic stenosis produces progressive symptoms such as angina, exertional syncope, and HF, with increasingly higher risk of mortality. Valve replacement should be considered for patients with severe aortic stenosis who exhibit symptoms or have an LVEF < 50%.

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CASE 5

A 42-year-old man is brought to the emergency department (ED) by ambulance after a sudden onset of severe retrosternal chest pain that began one hour ago while he was at home mowing the lawn. He initially described the pain as a tearing sensation that is now sharp, constant, referred to his back, and unrelated to movement. Three doses of sublingual nitroglycerin administered by the paramedics while en route to the hospital did not relieve the pain. He has never had symptoms like this before. His only medical history is hypertension, for which he takes enalapril. There is no cardiac disease in his family. He does not smoke, drink alcohol, or use illicit drugs. He is a basketball coach at a local high school and is usually very physically active.

On physical examination, he is a tall man with long extremities, appearing uncomfortable and diaphoretic while lying on the stretcher with his eyes closed. He is afebrile, with a heart rate of 118 beats per minute (bpm) and blood pressure of 156/64 mm Hg in the right arm and 188/74 mm Hg in the left arm. His head and neck examinations are unremarkable. His chest is clear to auscultation bilaterally, and an incidental note is made of pectus excavatum. His heart rate is tachycardic and regular. A soft, early diastolic murmur is auscultated at the right sternal border with bounding pulses. His abdominal examination is benign, and neurologic examination is nonfocal. His chest x-ray shows a widened mediastinum.

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 5:
Aortic Dissection/Marfan Syndrome

Summary: A 42-year-old tall man with pectus excavatum presents with

- Severe chest pain unrelieved by nitroglycerin
- Asymmetrically elevated blood pressure in his arms
- New murmur of aortic insufficiency
- Chest x-ray that shows a widened mediastinum

Most likely diagnosis: Aortic dissection, likely secondary to Marfan syndrome.

Next step: Administer an intravenous beta-blocker to lower blood pressure and arterial shear stress, then perform a noninvasive imaging procedure, such as transesophageal echocardiography (TEE), computed tomography (CT) angiography, or magnetic resonance angiography (MRA).

ANALYSIS

Objectives

1. Understand the clinical and radiographic features of aortic dissection as well as complications of dissection. (EPA 3)
2. Identify the risk factors for aortic dissection. (EPA 1, 2, 7)
3. Identify common genetic syndromes associated with aortic dissection. (EPA 2, 12)
4. Understand the management of dissection and the indications for surgical versus medical treatment. (EPA 4, 10)
5. Recognize other aortic diseases, such as abdominal aortic aneurysm (AAA), and the role of surveillance and indications for surgical repair. (EPA 1, 4, 7, 10)

Considerations

Most patients with chest pain seek medical attention because of the concern about myocardial infarction (MI). Differentiating other conditions of chest pain is important because some underlying conditions, such as aortic dissection, could be worsened by an MI treatment algorithm, for example, by anticoagulation with heparin or use of thrombolytics. In hypertensive patients with dissection, urgent blood pressure lowering is indicated to limit propagation of the dissection.

The aorta is the largest conductance vessel in the body. It receives most of the shear forces generated by the heart with every heartbeat throughout the lifetime of an individual. The wall of the aorta is composed of three layers: the intima, the media, and the adventitia. These specialized layers allow the aortic wall to distend under the great pressure created by every heartbeat. The vessel walls expand and accommodate the forward flow of blood ejected from the heart during each cardiac

cycle, thus storing kinetic energy as potential energy and creating large amounts of tensile stress. Pathologic processes arise when the vessel wall is unable to accommodate this tension.

APPROACH TO:
Aortic Aneurysm and Dissection

DEFINITIONS

AORTIC ANEURYSM: Defined as a pathologic dilation of more than 1.5 times the normal diameter of the aorta. Aneurysms can occur anywhere in the thoracic or abdominal aorta, but the large majority occur in the abdomen, below the renal arteries and above the bifurcation of the iliac vessels.

AORTIC DISSECTION: Tear or ulceration of the aortic intima that allows pulsatile aortic flow to dissect longitudinally along elastic planes of the media, creating a false lumen or channel for blood flow.

CLINICAL APPROACH TO AORTIC DISSECTION

Epidemiology

Cystic degeneration of the elastic media predisposes patients to aortic dissection. This occurs in various connective tissue disorders that cause cystic medial degeneration, such as Marfan syndrome and Ehlers-Danlos syndrome. Examine for characteristic features of Marfan, including tall stature, long extremities, joint hypermobility, pectus deformity, and scoliosis. Other genetic syndromes and gene mutations may accelerate development of aneurysms and dissection and are described in Table 5–1.

Other factors predisposing to aortic dissection are hypertension, aortic valvular abnormalities such as aortic stenosis and congenital bicuspid aortic valve, coarctation of the aorta, the third trimester of pregnancy, atherosclerotic disease, vasculitis, amphetamines/cocaine, and trauma. Aortic dissection may also occur iatrogenically after cardiac surgery or catheterization. More recently, the use of **fluoroquinolones** has been associated with an **increased risk of aneurysm and dissection**; care should be taken to choose alternative antibiotic regimens, if possible. Causes are outlined in Table 5–2.

Pathophysiology

A dissection occurs when there is a sudden intimal tear or rupture followed by the formation of a dissecting hematoma within the aortic media, separating the intima from the adventitia and propagating distally. **The presence of hypertension and associated shear forces is the most important factor causing propagation of the dissection.** Aortic dissection can produce several devastating or fatal complications. It can produce an intraluminal intimal flap, which can occlude branch arteries and cause organ ischemia or infarction. The hematoma may rupture into the pericardial sac, causing cardiac tamponade, or into the pleural space, causing hemothorax

Table 5–1 • GENETIC SYNDROMES ASSOCIATED WITH ANEURYSM AND DISSECTION[a]

Syndrome	Genetic Mutation	Protein Affected	Aortic Segments Affected
Marfan	*FBN1, TGFβR2*	Fibrillin-1, transforming growth factor beta receptor 2	Ascending aorta
Ehlers-Danlos	*COL3A1*	Collagen alpha-1 chain	Aortic arch, descending thoracic aorta, abdominal aorta
Homocystinuria	CBS	Cystathionine beta-synthase	Abdominal aorta
Turner	Loss of X chromosome (45X)	N/A	Aortic root dilation, aortic coarctation
Noonan	*PTPN11, KRAS, RAF1, SOS1*	Tyrosine-protein phosphatase nonreceptor type 11, GTPase KRas, RAF proto-oncogene serine/threonine protein kinase, son of sevenless homolog 1	Aortic coarctation
Hurler	*IDUA*	Alpha-L-iduronidase	Aortic coarctation
Osteogenesis imperfecta	*COL1A1, COL1A2*	Collagen alpha-1 or alpha-2 chain	Ascending aorta
Loeys-Dietz	*TGFβR1, TGFβR2*	Transforming growth factor beta receptors 1 and 2	Aortic root dilation > ascending aorta
ADPKD	*PKD1, PKD2*	Polycystin 1, polycystin 2	Thoracic aorta
Pseudoxanthoma elasticum	*ABCC6*	ATP-binding cassette transporter C6	Abdominal aorta > arch and thoracic aorta

[a]*Other genes that have been implicated in nonsyndromic arterial dissection include TAAD1, FAA1, TAAD2, and MYH11.*

Table 5–2 • CONDITIONS PREDISPOSING TO AORTIC DISSECTION

Acquired	Congenital
Hypertension Deceleration injury Aortic vasculitis (eg, syphilis) Atherosclerosis Pregnancy (third trimester) Amphetamines and cocaine Cardiac surgery/catheterization Ciprofloxacin	Bicuspid aortic valve Coarctation of the aorta Connective tissue diseases (Marfan, Ehlers-Danlos)

Table 5–3 • CLINICAL MANIFESTATIONS OF AORTIC DISSECTION

Complication	Mechanism
Horner syndrome	Compression of the superior cervical ganglion
Myocardial infarction	Occlusion of coronary artery ostia
Hemopericardium, pericardial tamponade	Thoracic dissection with retrograde flow into the pericardium
Aortic regurgitation	Thoracic dissection involving the aortic root
Bowel ischemia, hematuria	Dissection involving the mesenteric arteries or renal arteries
Hypertension, different blood pressures in arms	Thoracic dissection involving brachiocephalic artery
Hemiplegia	Carotid artery involvement

and/or exsanguination. It can produce severe acute aortic regurgitation, leading to fulminant heart failure.

Clinical Presentation

Clinical features typically include a **sudden onset of ripping or tearing chest pain, radiating to the back.** However, the pain may radiate to the neck or extremities as the dissection extends (Table 5–3). Differentiating the pain of dissection from the pain of myocardial ischemia or infarction is essential because **the use of anticoagulation or thrombolytics in a patient with a dissection may be devastating.** In contrast to anginal pain, which often builds over minutes, the pain of dissection is **often maximal at onset.** In addition, myocardial ischemia pain is usually relieved by nitrates, whereas the pain of dissection is not. Also, because most dissections begin very close to the aortic valve, a dissection may produce an **early diastolic murmur characteristic of aortic insufficiency.** If it occludes aortic branch arteries, such as the brachiocephalic artery, it can produce dramatically different pulses and blood pressures in the extremities. Most patients with dissection are hypertensive; if hypotension is present, one must suspect aortic rupture, cardiac tamponade, or dissection of the subclavian artery supplying the arm where the blood pressure is being measured. **Often, a widened superior mediastinum (> 8 cm) is noted on plain chest film because of dissection of the ascending aorta.**

Diagnostic Approach. When aortic dissection is suspected, confirming the diagnosis with an **imaging study** is essential. Conventional aortography was the traditional diagnostic "gold standard," but in recent years, very sensitive noninvasive studies, such as TEE, dynamic CT scanning, and magnetic resonance imaging (MRI), have gained widespread use. Because of the emergent nature of the condition, the best initial study is the one that can be obtained and interpreted quickly in the given hospital setting**. If the patient is hemodynamically unstable or has renal insufficiency, TEE is the best test. Otherwise, CT angiography is widely used.**

Classification. Several classification schemes describe the different types of aortic dissections. Figure 5–1 shows the Stanford classification. Type A dissection

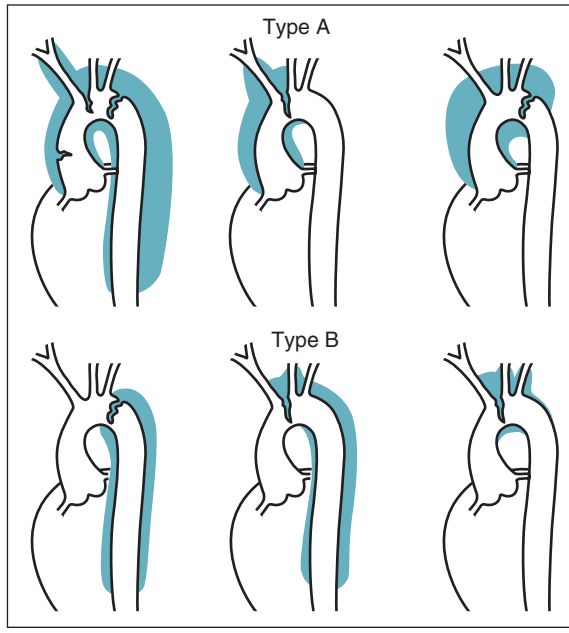


Figure 5–1. Classification of aortic aneurysms. (Reproduced with permission, from Braunwald E, Fauci AS, Kasper KL, et al. *Harrison's Principles of Internal Medicine*. 17th ed. 2008. Copyright © McGraw Hill LLC. All rights reserved.)

always involves the ascending aorta but may extend to any other part. Type B dissection does not involve the ascending aorta. The alternative method of classification, the DeBakey classification scheme, splits type A dissections into types 1 and 2 and splits type B dissections into types 3a and 3b.

Treatment

Two-thirds of aortic dissections originate in the ascending aorta only centimeters above the aortic valve. The classification system is important because it guides therapy. Virtually all **type A (proximal or ascending) dissections require urgent surgical therapy** with replacement of the involved aorta and sometimes the aortic valve. Without surgery, the mortality rate for type A dissections is 90%. Type B dissections do not involve the ascending aorta and typically originate in the aortic arch distal to the left subclavian artery. Usually, type B dissections are first managed medically, with surgery reserved only for complications such as rupture or ischemia caused by occlusion of an aortic branch.

The aim of medical therapy is to prevent propagation of the dissection by reducing mean arterial pressure and the rate of rise (dP/dT) of arterial pressure, which correlates with arterial shear forces. **Beta-blockers (ie, metoprolol, esmolol, labetalol) are used as first-line treatment** to lower systolic blood pressure to < 120 mm Hg and achieve a heart rate of 60 bpm, ultimately reducing shear forces. If hypertension is refractory, sodium nitroprusside may be used; it is generally not used initially due to risks of causing cyanide toxicity, especially in patients with renal insufficiency.

CLINICAL APPROACH TO ABDOMINAL AORTIC ANEURYSMS

Epidemiology

Abdominal aortic aneurysms are found in 1.5% to 3% of older adults but in 5% to 10% of higher risk patients, such as those with known atherosclerotic disease. AAA is a degenerative condition typically found in older white men (> 50 years), most commonly in smokers, who often have atherosclerotic disease elsewhere, such as coronary artery disease or peripheral vascular disease. **Smoking has been found to be the most significant risk factor for the development of AAAs. Thus, it is recommended that men between the ages of 65 and 75 who have a history of smoking should be screened for AAA with ultrasound.**

Pathophysiology

In marked contrast to the dramatic presentation of dissection of the thoracic aorta, patients with **AAA are typically asymptomatic**; AAAs are often found by physical examination with detection of a midline pulsatile mass and auscultation of an abdominal bruit or noted incidentally on imaging (ie, ultrasound). AAA is usually defined as a dilation of the aorta with a diameter greater than 3 cm, typically below the renal vasculature and above the bifurcation of the common iliacs.

One complication of AAAs is **atheroembolic disease**—small thrombi may form within the aneurysm due to turbulent blood flow and can embolize to extremities, leading to signs of distal ischemia. Findings can range from blue toe syndrome to livedo reticularis. However, the feared complication of AAA is **spontaneous rupture**, which can be visualized with ultrasound or contrast CT. If AAA ruptures anteriorly into the peritoneal cavity, the patient usually exsanguinates and dies within minutes. If AAA ruptures posteriorly and the bleeding is confined to the retroperitoneum, the peritoneum can produce local tamponade, and the patient will present with severe lower back or midabdominal pain. Skin findings of rupture may include Grey Turner sign, which is ecchymosis of the flank, and Cullen sign, which is periumbilical ecchymosis. Overall, the mortality rate of ruptured AAA is 80%, with 50% of patients dying before they reach the hospital. **The risk of rupture is related to the size of the aneurysm**: The annual rate of rupture is low if the aneurysm is smaller than 5 cm but is at least 10% to 20% for 6-cm aneurysms.

Treatment

The risk of rupture must be weighed against the surgical risk of elective repair, which traditionally requires excision of the diseased aorta and replacement with a Dacron graft, although endovascular treatment with placement of an aortic stent graft is now commonly performed. **Operative repair of AAAs is indicated for aneurysms 5.5 cm or greater** in diameter, aneurysms expanding more than 1 cm per year, or symptomatic aneurysms. Postoperative complications may include bowel ischemia, infection, and rarely, aorto-enteric fistula. As for surveillance of AAAs, the current recommendations are that patients undergo some sort of imaging of the aneurysm (MRI, CT scan, or ultrasound study) at 6-month to 3-year intervals, depending on the risk of rupture. Surveillance guidelines are outlined in Table 5–4.

Table 5–4 • SURVEILLANCE FOR ABDOMINAL AORTIC ANEURYSM

Diameter (cm)	Frequency of Imaging
2.5-2.9	Rescreen after 10 years
3-3.9	Ultrasound every 3 years
4-4.9	Ultrasound annually
5-5.4	Ultrasound every 6 months
> 5.5	Surgical repair indicated

Data from Chaikof EL, Dalman RL, Eskandari MK, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. *2018;67(1):2-77.e2.*

CASE CORRELATION

- See also Case 3 (Acute Coronary Syndrome), Case 6 (Hypertension, Outpatient), and Case 7 (Hypertensive Encephalopathy/Pheochromocytoma).

COMPREHENSION QUESTIONS

5.1 A 59-year-old man complains of severe chest pain that radiates to his back. His brachial pulses appear unequal between his right and left arms. He appears hemodynamically stable. On chest radiography, he has a widened mediastinum. Which of the following is the best next step?

A. Initiate thrombolytic therapy.

B. Obtain CT of chest with intravenous contrast.

C. Initiate aspirin and heparin.

D. Measure serial cardiac enzyme levels.

5.2 A 45-year-old woman with new-onset aortic regurgitation is found to have aortic dissection of the ascending aorta and aortic arch by TEE. She is relatively asymptomatic. Which of the following is the best management?

A. Oral atenolol therapy and monitor the dissection

B. Angioplasty

C. Surgical repair of the dissection

D. Oral warfarin (Coumadin) therapy

5.3 A healthy 75-year-old man undergoing an ultrasound examination for suspected gallbladder disease is found incidentally to have a 4.5-cm abdominal aneurysm of the aorta. Which of the following is the best management for this patient?

A. Surgical repair of the aneurysm

B. Serial ultrasound examinations every 6 months

C. Urgent MRI

D. Beta-agonist therapy

5.4 A 45-year-old man with a past medical history of diabetes, hyperlipidemia, and hypertension has smoked one pack of cigarettes a day for the past 15 years and drinks four glasses of wine every weekend. He is found to have an AAA incidentally on CT imaging of the abdomen. Which of the following is the most important predisposing factor for the development of his AAA?

A. Hypertension
B. Smoking
C. Hyperlipidemia
D. Alcohol use

ANSWERS

5.1 **B.** This clinical presentation of severe chest pain radiating to the back, unequal brachial blood pressures or pulse strengths, and a widened mediastinum on chest x-ray is consistent with acute aortic dissection. A CT scan of the chest is a quick imaging test to confirm the aortic dissection. Thrombolytic therapy (answer A) or anticoagulation (answer C) can worsen the process. Measuring serial cardiac enzyme levels (answer D) would only delay the therapy and endanger the patient.

5.2 **C.** Surgery is urgently required in the event of aortic root or other proximal (type A) dissections. An unrecognized, and hence untreated, aortic dissection can quickly lead to exsanguination and death. Medical therapy such as beta-blockers (answer A) can help to decrease the risk of dissection while getting the patient urgently to the operating room, but a type A dissection should not merely be monitored since it has a very high mortality rate without surgery. Angioplasty (answer B) may be indicated in a case of MI, but not in aortic dissection. Anticoagulation (answer D) is not appropriate in this scenario.

5.3 **B.** When an AAA reaches 5.5 cm or greater, surgery (answer A) is usually required because of the high risk of aneurysm rupture. For asymptomatic aneurysms smaller than 5 cm, the 5-year risk of rupture is less than 1% to 2%, so serial noninvasive monitoring is an alternative strategy. Further imaging such as with CT or MRI (answer C) is not warranted with the ultrasound diameter being less than the threshold. Answer D (beta-agonist therapy) is indicated when there is aortic dissection, to prepare for intervention, but not in this patient with an indolent and chronic AAA.

5.4 **B.** Risk factors for AAA include smoking, hypertension (answer A), and peripheral vascular disease. However, the single greatest risk factor for developing AAA is smoking history. Thus, it is recommended that all men with a history of smoking undergo a one-time screening for AAA between the ages of 65 and 75. Although hyperlipidemia (answer C) and alcohol use (answer D) are risk factors for the development of AAA, these factors are not as strongly associated with AAA as smoking.

CLINICAL PEARLS

- Hypertension is an underlying factor that predisposes to aortic dissection in most cases. Other patients at risk include those with Marfan syndrome, patients with congenital aortic anomalies, or otherwise normal women in the third trimester of pregnancy.
- Chest pain in the presence of a widened mediastinum on chest x-ray should suggest aortic dissection.
- Medical therapy for aortic dissection includes intravenous beta-blockers such as metoprolol, esmolol, or labetalol to lower cardiac contractility, arterial pressure, and shear stress, thus limiting propagation of the dissection.
- Urgent surgical repair is indicated for type A (ascending) aortic dissections. Uncomplicated, stable, type B (transverse or descending) aortic dissections can be managed medically.
- Aortic dissection may be complicated by rupture, occlusion of any branch artery of the aorta, or retrograde dissection with hemopericardium and cardiac tamponade.
- Men between the ages of 65 and 75 with a smoking history should be screened for AAA by ultrasound.
- The risk of rupture of AAAs increases with size. Aneurysms larger than 5.5 cm should undergo elective surgical repair; those smaller than 5.5 cm can be monitored with serial ultrasonography.

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CASE 6

A 56-year-old man comes into your clinic as a new patient. Seven years ago at a work-related health screening, he was diagnosed with hypertension and hypercholesterolemia. At that time, he saw a physician who prescribed a diuretic and encouraged him to lose weight, modify his diet, and exercise. Since that time, he has not followed up with any clinician. Last month, a routine optometry examination showed hypertensive retinopathy, and he was instructed to follow up with a physician. He brings the optometry report to this visit, which describes arteriovenous crossing defects and increased arteriolar light reflex. He denies chest pain, shortness of breath, dyspnea on exertion, or paroxysmal nocturnal dyspnea. He smokes one pack of cigarettes per day and has done so since he was 15 years old. He typically drinks two glasses of wine with dinner. On examination, the patient is obese; you calculate his body mass index (BMI) as 30 kg/m^2. His blood pressure is 168/98 mm Hg in the right arm and 170/94 mm Hg in the left arm, and his heart rate is 84 beats per minute (bpm). He has no thyromegaly or carotid bruits. Cardiac examination reveals an S_4 gallop. No cardiac murmurs are auscultated. Lung and abdomen examinations are normal.

- What is the most likely diagnosis?
- What are your next steps?

ANSWERS TO CASE 6:
Hypertension, Outpatient

Summary: A 56-year-old man is being evaluated as a new patient with

- Blood pressure of 168/98 mm Hg in the right arm and 170/94 mm Hg in the left arm
- Fundoscopic examination revealing hypertensive retinopathy
- Cardiac fourth heart sound, consistent with a thickened, noncompliant ventricle
- Multiple cardiovascular risk factors, including his age, obesity, and smoking

Most likely diagnosis: Stage 2 hypertension with end-organ damage (left ventricular hypertrophy and hypertensive retinopathy).

Next steps:

1. Use laboratory evaluation and a baseline electrocardiogram (ECG) to assess for end-organ damage.
2. Assess patient's overall cardiovascular risk status, including lipid profile.
3. Rule out secondary causes of hypertension.

ANALYSIS

Objectives

1. Underline the initial evaluation of a patient with hypertension. (EPA 1, 3)
2. List the most common antihypertensive medications and their indications and cautions regarding their usage. (EPA 4, 12)
3. Describe the various causes of secondary hypertension and when to pursue these diagnoses. (EPA 2, 3)

Considerations

This is a 56-year-old man with severe hypertension who has physical examination evidence of hypertensive end-organ damage (hypertensive retinopathy and left ventricular hypertrophy). He has multiple risk factors for atherosclerotic disease. The most likely diagnosis is essential hypertension, but secondary causes still must be considered. Although you have measured his blood pressure only once in your clinic, he has been told before that he is hypertensive, and he already appears to have end-organ damage of hypertension. His blood pressure is above 160 mm Hg systolic or 100 mm Hg diastolic which places him in **stage 2 hypertension.** He should be started on two-drug therapy without further delay.

APPROACH TO: Hypertension

DEFINITIONS

DIEATRY APPROACHES TO STOP HYPERTENSION (DASH) DIET: Diet rich in fruits, vegetables, legumes, and low-fat dietary products and low in snacks, sweets, meat, and saturated fat, with an emphasis of a sodium intake lower than 2300 mg/d.

ELEVATED BLOOD PRESSURE: Systolic blood pressures 120 to 129 mm Hg and diastolic < 80 mm Hg.

ESSENTIAL HYPERTENSION: Elevated blood pressure without a known cause, also called primary or idiopathic hypertension. It comprises approximately 80% to 95% of all cases of hypertension.

LIFESTYLE MODIFICATION: A cornerstone in the treatment of hypertension, consisting of regular aerobic activity, weight loss, decreased salt intake, and adherence to a DASH–type dietary plan. Alcohol consumption should be moderated, no more than two glasses of wine per day for men and one glass per day for women.

SECONDARY HYPERTENSION: Elevated blood pressure with a known underlying cause, such as renal artery stenosis or primary aldosteronism. Prevalence is approximately 5% to 20% of all cases of hypertension.

STAGE 1 HYPERTENSION: Blood pressures 130–139/80–89 mm Hg.

STAGE 2 HYPERTENSION: Blood pressures equal to or greater than 140/90 mm Hg.

CLINICAL APPROACH

Background and Epidemiology

Hypertension is not diagnosed based on one blood pressure measurement. In general, a diagnosis of hypertension requires repeatedly elevated measurements, ideally including measurements outside of the clinic setting. This can involve the patient checking their blood pressures at home or **ambulatory blood pressure monitoring (ABPM)**. ABPM consists of sending a patient home with an automated blood pressure cuff that measures over a 24-hour period. Either of these methods gives a more accurate measurement of a patient's overall blood pressure than clinic readings alone.

One well-described phenomenon is "white coat hypertension," in which patients have elevated blood pressures in the clinic, but normal blood pressures by ABPM or home measurement. The clinical significance and treatment goals for white coat hypertension are currently unclear. The inverse of white coat hypertension is "masked hypertension," in which a patient has normal clinic blood pressures but elevated measurements on ABPM or home measurement. These patients have

Table 6–1 • SECONDARY CAUSES OF HYPERTENSION

Renal diseases
• Parenchymal (glomerulonephritis, polycystic kidney disease, renal tumors)
• Renovascular (atherosclerosis or fibromuscular dysplasia)
Endocrine
• Primary aldosteronism
• Cushing syndrome
• Pheochromocytoma
• Hyperthyroidism
• Growth hormone excess (acromegaly)
Miscellaneous
• Obstructive sleep apnea
• Coarctation of the aorta
• Increased intravascular volume (posttransfusion)
• Hypercalcemia
• Medications (sympathomimetics, glucocorticoids, high-dose estrogen, NSAIDs)

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

an elevated risk of cardiovascular morbidity and mortality and should be treated despite normal clinic measurements.

Cardiovascular **risk factors** and **hypertensive target organ damage should be identified.** The **major risk factors** for cardiovascular disease (CVD) are **age, cigarette smoking, dyslipidemia, diabetes mellitus, obesity, kidney disease, and a family history of premature CVD.**

Pathophysiology

Underlying causes of hypertension must then be considered. Essential or idiopathic hypertension is the most common form of hypertension, comprising 80% to 95% of cases, but approximately 5% to 20% of cases of hypertension have secondary causes (Table 6–1). To identify the secondary (and potentially reversible) causes of hypertension, the clinician must be aware of the clinical and laboratory manifestations of the processes. A secondary cause of hypertension should be suspected and worked up when patients have any of the following clinical features: age of onset before 25 or after 55, presentation with evidence of end-organ damage, refractory hypertension requiring three or more antihypertensive medications, hypertension that has suddenly become uncontrolled, a rising creatinine level with the use of angiotensin-converting enzyme (ACE) inhibitors, or other clinical signs of a secondary cause.

Clinical Presentation

Target organ damage of hypertension includes left ventricular hypertrophy, nephropathy, retinopathy, and cerebrovascular disease. A complete history and physical examination, including fundoscopic examination; auscultation of the major arteries for bruits; palpation of the abdomen for enlarged kidneys, masses, or an enlarged abdominal aorta; evaluation of the lower extremities for edema and perfusion; and a neurologic examination, should be standard. Some initial

Table 6–2 • BASIC TESTS FOR INITIAL EVALUATION OF HYPERTENSION

Urinalysis, to evaluate for hematuria, and albumin/creatinine ratio to screen for proteinuria
Serum sodium, potassium, calcium, and creatinine to estimate glomerular filtration rate
Fasting glucose; total, HDL, and LDL cholesterol; triglycerides to evaluate cardiovascular risk
Electrocardiogram
Consider thyroid-stimulating hormone, echocardiogram, and evaluation for secondary causes of hypertension, as guided by history and clinical findings

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

laboratory testing is also indicated for a patient with a new diagnosis of hypertension (Table 6–2).

Treatment

Therapy Based on Staging. Initial therapy should be based on the stage or degree of hypertension. For those with **elevated blood pressure** (blood pressure 120–129/< 80 mm Hg), lifestyle modifications and 3- to 6-month follow-up are the only interventions indicated unless they have another comorbid condition, such as heart failure or diabetes, which necessitate the use of an antihypertensive.

Patients with **stage 1 hypertension** (blood pressure 130–139/80–89 mm Hg) should be risk assessed for CVD; those with a 10-year CVD risk > 10% should be started on a single antihypertensive agent along with lifestyle modifications, whereas those with lower CVD only require lifestyle modification and 3- to 6-month follow-up.

Patients with **stage 2 hypertension** (> 140/90 mm Hg) will need lifestyle modification and antihypertensive medication. Patients starting antihypertensive agents should receive 1-month follow-up to evaluate whether the patient's blood pressure goals are being met or require intensification of therapy.

In 2015, the National Institutes of Health–sponsored systolic blood pressure intervention trial (**SPRINT trial**) showed that for patients age 50 or older with at least one other cardiovascular risk factor, a target blood pressure of **120 mm Hg** (rather than 140 mm Hg) produced a 30% risk reduction in cardiovascular events, stroke, and cardiovascular death.

Lifestyle Changes. Counseling patients on lifestyle changes is important at any blood pressure level and includes weight loss, limitation of alcohol intake, increased aerobic physical activity, reduced sodium intake (< 6 g NaCl or 2.3 g sodium), cessation of smoking, and adherence to a DASH diet.

Pharmacotherapy. For most patients with hypertension, lowering blood pressure itself reduces cardiac risk and is more important than the choice of agent. Several different drugs appear to be equally effective as initial monotherapy. **Thiazide diuretics, calcium channel blockers, ACE inhibitors, or angiotensin II receptor blockers (ARBs)** are all widely used and acceptable choices. When considering initial therapy in patients of African descent, evidence shows benefit from the use of thiazide diuretics or long-acting calcium channel blockers over other antihypertensives. ACE inhibitors or ARBs should be used for initial monotherapy in patients with diabetic nephropathy or those with nondiabetic chronic kidney disease complicated by proteinuria because of their ability to reduce intraglomerular pressure via

inhibition of angiotensin II–mediated efferent arteriolar vasoconstriction. Beta-blockers are not recommended for initial monotherapy unless there is a specific indication, such as ischemic heart disease. If patients have markedly elevated blood pressures at baseline (stage 2 hypertension), a single agent will often not be able to achieve good blood pressure control, and patients will often require combination therapy with two or more agents. Whatever drug class is used, a long-acting formulation that provides 24-hour efficacy is preferred over short-acting agents for better compliance and more consistent blood pressure control. A list of oral antihypertensive drugs is extensive (Table 6–3).

For some patients, there are specific compelling indications to use specific drug classes. **ACE inhibitors or ARBs are the agents of choice in hypertensive patients with diabetes or systolic heart failure.** Beta-blockers would be first-line agents in patients with hypertension and coronary artery disease or a history of tachyarrhythmias. Alpha-blockers may be considered in men with hypertension and benign prostatic hypertrophy. Most patients ultimately need more than one drug to control their blood pressure. It is critical to tailor the treatment to the patient's personal, financial, lifestyle, and medical factors and to periodically review compliance and adverse effects.

SELECTED CAUSES OF SECONDARY HYPERTENSION

Renal Causes

The most common cause of secondary hypertension is renal disease (renal parenchymal or renovascular). **Renal artery stenosis** is caused by atherosclerotic disease with hemodynamically significant blockage of the renal artery in older patients or by fibromuscular dysplasia in younger adults. The clinician must have a high index of suspicion, and further testing may be indicated, for instance, in an individual with diffuse atherosclerosis. Abrupt elevations in creatinine after using an ACE inhibitor or ARB, a renal bruit, recurrent pulmonary edema, or low potassium may be suggestive of renal artery stenosis. Initial imaging options include renal ultrasound, computed tomographic (CT) angiography, or magnetic resonance (MR) angiography, with MR angiography having the highest sensitivity and specificity. Captopril-enhanced radionuclide scan is less useful diagnostically (interrater variability) but may provide functional information about the stenotic kidney. Surgical or angioplastic correction of the vascular occlusion may be considered.

Polycystic kidney disease is inherited as an autosomal dominant trait. The classic clinical findings are positive family history of polycystic kidney disease, bilateral flank masses, flank pain, elevated blood pressure, and hematuria. Other causes of chronic renal disease very commonly lead to hypertension.

Endocrine causes

Primary hyperaldosteronism is an increasingly recognized cause of hypertension, contributing to as much as 5% to 10% of patients with hypertension. Although hyperaldosteronism "classically" presents with hypertension, metabolic alkalosis, and hypokalemia, more than half of patients will have normal bicarbonate and

Table 6–3 • PARTIAL LISTING OF ORAL ANTIHYPERTENSIVE AGENTS

Category	Agents	Mechanisms of Action	Side Effects	Indications	Contraindications/ Cautions
Diuretic	Thiazide diuretic: **Hydrochlorothiazide, chlorthalidone**	Sodium diuresis, volume depletion, possible lower peripheral vascular resistance	Hypokalemia, hyponatremia, carbohydrate intolerance, hyperuricemia, hyperlipidemia	Initial monotherapy or as combination with ACE inhibitor/ ARB	Diabetes mellitus, gout, hypokalemia
	Potassium sparing: **spironolactone, eplerenone**	Competitive inhibitor of aldosterone, causing renal sodium loss	**Hyperkalemia**, gynecomastia (more for spironolactone than eplerenone)	CHF with systolic dysfunction	Renal failure, hyperkalemia
Antiadrenergic	**Clonidine**	Stimulation of alpha-2 vasomotor center of brain	Postural hypotension, drowsiness, dry mouth, **rebound hypertension** with abrupt withdrawal		History of medication noncompliance (risk of rebound hypertension)
	Beta-blocker: **Metoprolol, atenolol**	Block sympathetic effect of heart and kidneys (renin)	**Bronchospasm**, hyperlipidemia, depression, erectile dysfunction	Angina, post-MI, tachyarrhythmia	Asthma, 2nd- or 3rd-degree heart block, sick sinus syndrome
	Alpha-beta-blocker: **Carvedilol**	Same as beta-blockers and also direct vasodilation	Similar to beta-blockers	Post-MI, CHF with systolic dysfunction	Similar to beta-blockers
	Alpha-blockers	Direct vasodilation	First-dose syncope, retrograde ejaculation, orthostatic hypotension, reflex tachycardia	Concomitant BPH	Increased risk of heart failure and cardiovascular events; not for monotherapy
Vasodilator	**Hydralazine**	Arterial vasodilation, produces reflex tachycardia	Headache, tachycardia, angina, lupus-like syndrome		Severe coronary artery disease

(*Continued*)

Table 6–3 • PARTIAL LISTING OF ORAL ANTIHYPERTENSIVE AGENTS (Continued)

Category	Agents	Mechanisms of Action	Side Effects	Indications	Contraindications/ Cautions
ACE inhibitor	**Lisinopril, captopril, enalapril,** ramipril	Inhibit conversion of angiotensin I to angiotensin II (powerful vasoconstrictor)	Orthostatic hypotension, **cough**, angioedema, **hyperkalemia**, acute renal failure	Post-MI, CHF with systolic dysfunction, diabetes, proteinuric chronic kidney disease	Renal failure, bilateral renal artery stenosis, pregnancy
Angiotensin receptor antagonist	**Losartan, valsartan, candesartan, irbesartan**	Competitive inhibition of the angiotensin II receptor	Similar to ACE inhibitors but no cough or angioedema	Same as ACE inhibitors	Same as ACE inhibitors
Calcium channel antagonist	Dihydropyridines: **Amlodipine, nifedipine, felodipine**	Blockade of L-channels, reducing intracellular calcium and causing vasodilation	Tachycardia, flushing, gastrointestinal side effects, hyperkalemia, **edema**		May worsen peripheral edema
	Nondihydropyridine: **Diltiazem, verapamil**	Similar to dihydropyridines	**Heart block,** constipation	Post-MI, supraventricular tachycardia	Heart failure, 2nd- or 3rd-degree heart block

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BPH, benign prostatic hypertrophy; CHF, congestive heart failure; MI, myocardial infarction.
Data from Kasper DL, Fauci AS, Hauser SL, et al. Harrison's Principles of Internal Medicine. *19th ed. 2015.* *Copyright © McGraw Hill LLC. All rights reserved.*

potassium levels. A more common presentation is severe hypokalemia provoked by diuretics. Hyperaldosteronism can be screened for with a renin/aldosterone ratio. If abnormal, further workup should be pursued to confirm the diagnosis and determine if the hyperaldosteronism is due to adrenal adenoma or adrenal hyperplasia.

Hyperthyroidism may also cause hypertension. The patient will have a widened pulse pressure with increased systolic blood pressure and decreased diastolic blood pressure, as well as a hyperdynamic precordium. The patient may have warm skin, tremor, and thyroid gland enlargement or a palpable thyroid nodule. A low level of serum thyroid-stimulating hormone (TSH) and elevated levels of thyroid hormones (eg, free T_4) are diagnostic.

Glucocorticoid excess states, including **Cushing syndrome**, and iatrogenic (treatment with glucocorticoids) classically present with thinning of the extremities, truncal obesity, round moon face, supraclavicular fat pad, purple striae, acne, and possibly psychiatric symptoms. Excess corticosteroids cause secondary hypertension due to a combination of mineralocorticoid activity and upregulating vascular sensitivity to vasoconstrictors. Dexamethasone suppression testing of the serum cortisol level aids in the diagnosis of Cushing syndrome.

Pheochromocytoma is a rare catecholamine-releasing adrenal tumor that typically produces hypertension. Classic clinical manifestations include paroxysmal headaches, palpitations, diaphoresis, pallor, and chest pain. It can be diagnosed by elevated urinary and plasma metanephrine and normetanephrine.

Other Causes

Obstructive sleep apnea (OSA) is another fairly common cause of hypertension. Obstructive sleep apnea is caused by abnormal relaxation of the upper airway musculature, resulting in hypoxic and hypercarbic episodes during sleep. Over time, this can lead to systemic vasoconstriction, systolic hypertension, and pulmonary hypertension. Strongly suspect OSA in a patient with obesity, snoring, daytime sleepiness, and a crowded palate. OSA is diagnosed with "sleep studies" (ie, polysomnography) and treated with nighttime continuous positive airway pressure.

Coarctation of the aorta is a congenital narrowing of the aortic lumen and usually is diagnosed in younger patients by finding hypertension along with discordant upper and lower extremity blood pressures. Coarctation of the aorta can cause leg claudication, cold extremities, and delayed or diminished femoral pulses as a result of decreased blood pressure in the lower extremities. Rib notching may be seen on chest x-ray due to development of collateral circulation. In children, echocardiography is often diagnostic, while adults may require CT or MR angiography.

CASE CORRELATION

- See also Case 7 (Hypertensive Encephalopathy/Pheochromocytoma).

COMPREHENSION QUESTIONS

6.1 A 30-year-old woman is noted to have blood pressures in the 160/100 mm Hg range. She also has increased obesity, especially around her abdomen, which also shows some striae. She has been bruising very easily and has increased hair growth on her face and chest. Which of the following most likely to reveal the diagnosis?

A. Thyroid-stimulating hormone
B. MR angiography of the renal vessels
C. Dexamethasone suppression test and serum cortisol
D. Urinary metanephrine

6.2 A 45-year-old man is diagnosed with essential hypertension based on two blood pressures of 150/100 and 156/102 mm Hg during two separate visits. He has no other medical problems. Which of the following would most likely provide prognostic information regarding this patient?

A. Vascular biopsy
B. End-organ effects from hypertension
C. Patient's enrollment in a clinical trial
D. Measurement of serum homocysteine levels

6.3 A 34-year-old woman contemplating pregnancy is diagnosed with stage 1 hypertension, and after an evaluation she is noted to have no complications. Which of the following antihypertensive classes may be appropriate for this individual?

A. Beta adrenergic blockers
B. Angiotensin-converting enzyme inhibitors
C. Direct renin inhibitors
D. Angiotensin receptor blockers
E. Thiazide diuretics

6.4 A 45-year-old African American man is noted to have blood pressures of 145/90 mm Hg and 150/96 mm Hg on two separate occasions. He has no other medical problems and no signs or symptoms suggestive of secondary hypertension. Which of the following is the best initial therapy for this patient?

A. Chlorthalidone
B. Lisinopril
C. Metoprolol succinate
D. Clonidine
E. Spironolactone

ANSWERS

6.1 **C.** This question addresses secondary causes of hypertension. This patient's central obesity, abdominal striae, hirsutism, and easy bruisability are consistent with Cushing syndrome, which can be diagnosed with a dexamethasone suppression test and serum cortisol. TSH (answer A) would be useful for evaluating for hyperthyroidism causing hypertension, which would present with weight loss, heat intolerance, and tremor. MR angiography (answer B) is a good diagnostic test for renal artery stenosis, which may present with a renal bruit. Urinary metanephrine (answer D) can evaluate for pheochromocytoma, which presents with paroxysmal hypertension, headaches, and diaphoresis.

6.2 **B.** The prognosis in hypertension depends on the patient's other cardiovascular risks and observed end-organ damage from hypertension, such as left ventricular hypertrophy, hypertensive retinopathy, or chronic kidney disease. Vascular biopsy (answer A) is indicated in some patients with vasculitis, which may present with a wide variety of end-organ damage and inflammatory markers. Enrollment in clinical trials (answer C) is not required for effective control of hypertension. Serum homocysteine levels (answer D) are elevated in some genetic disorders as well as B_{12} or folate deficiency.

6.3 **A.** Labetalol, which is a beta blocking agent, is widely used in pregnant women and is considered safe for the fetus. ACE inhibitors, ARBs, and direct renin inhibitors (answers B, C, and D) are contraindicated in all stages of pregnancy. Thiazide diuretics (E) can cause thrombocytopenia in the fetus and is not recommended in pregnancy. Methyldopa is an older agent less effective than labetalol.

6.4 **A.** Chlorthalidone is a thiazide-like diuretic that is preferred over hydrochlorothiazide by many hypertension experts for its longer acting effects. Recall that thiazide diuretics or calcium channel blockers are preferred initial therapy for black patients. Lisinopril (answer B) is an ACE inhibitor, which would be a reasonable choice in a non-black patient or a necessity in a patient with diabetes. Metoprolol (answer C) is not a first-line therapy for hypertension in the absence of other indications. Clonidine (answer D) is a third- or fourth-line agent for hypertension; it is not preferred due to potent rebound hypertension when a patient discontinues the medicine. Spironolactone (answer E) is an aldosterone antagonist that can be used to treat primary hyperaldosteronism; it is occasionally used in combination with other medicines to treat refractory hypertension. It is not a first-line antihypertensive and is not indicated in this patient.

CLINICAL PEARLS

- In general, the diagnosis of hypertension requires two or more blood pressure measurements on at least two visits or the use of ambulatory or home blood pressure monitoring.
- Cardiovascular disease risk evaluation consists of identifying target organ dysfunction and cardiovascular risk factors, such as diabetes and hyperlipidemia.
- Most patients with hypertension have essential hypertension, but secondary causes of hypertension should be evaluated when clinically indicated.
- A urinalysis, ECG, comprehensive metabolic panel (CMP), and lipids are indicated in patients with newly diagnosed hypertension.
- First-line agents for hypertension are thiazide diuretics, ACE inhibitors, ARBs, and dihydropyridine calcium channel blockers. Many patients will require combination therapy.
- Renal diseases, including renovascular hypertension, are the most common causes of secondary hypertension.
- Lifestyle modifications consisting of dietary changes, exercise, and moderation of alcohol intake are indicated to address hypertension control and lower overall cardiovascular risk.
- For most patients, the degree of blood pressure reduction is the major determinant of cardiovascular risk reduction, rather than the class of antihypertensive drug used.

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CASE 7

A 39-year-old man is brought to the emergency center by ambulance after he was found wandering in the street in a disoriented state. He is confused and agitated. Further history is obtained from his wife. She reports that for the last several months he has been complaining of intermittent headaches and palpitations. He has also experienced feelings of light-headedness when playing basketball. Three weeks ago, he was diagnosed with hypertension and was started on clonidine twice per day. He took the clonidine for 2 weeks, but the drug made him feel sedated. Five days ago, he was instructed by his primary care provider to stop the clonidine and to start taking metoprolol twice daily. On examination, he is afebrile, with a heart rate of 110 beats per minute (bpm), respiratory rate of 26 breaths per minute, oxygen saturation of 98% on room air, and blood pressure of 215/132 mm Hg in both arms. He is agitated and diaphoretic and is looking around the room but does not appear to recognize his wife. His pupils are dilated but reactive. On fundoscopic examination, he has papilledema and scattered retinal hemorrhages. He has no thyromegaly. Heart, lung, and abdominal examinations are normal. His pulses are bounding and equal in his arms and legs. He moves his extremities well, his reflexes are brisk and symmetric, and he is slightly tremulous. Noncontrast computed tomography (CT) of the head is negative for hemorrhage. Laboratory studies results include a normal leukocyte count and a hemoglobin level of 16.5 g/dL. Serum sodium is 139 mEq/L, potassium is 4.7 mEq/L, chloride is 105 mEq/L, HCO_3 is 29 mEq/L, blood urea nitrogen (BUN) is 32 mg/dL, and creatinine is 1.3 mg/dL. Urinalysis is normal, and a urine drug screen is negative. Lumbar puncture is performed. The cerebrospinal fluid (CSF) has no red or white blood cells or xanthochromia, and it has normal protein and glucose levels.

- What is the most likely diagnosis?
- What is the underlying etiology?
- What is the next step?

ANSWERS TO CASE 7:
Hypertensive Encephalopathy/Pheochromocytoma

Summary: A 39-year-old-man with recently diagnosed hypertension presents with

- Altered mental status
- Critically elevated blood pressures
- Previous episodes of palpitations, headaches, light-headedness
- Recent medication change from clonidine to metoprolol
- Physical examination significant for dilated pupils, papilledema, and bounding peripheral pulses
- Negative urine drug screen and no evidence of intracranial hemorrhage or infection on CT scan and CSF studies

Most likely diagnosis: Hypertensive encephalopathy as evidenced by confusion, with systolic blood pressures > 180 mm Hg and diastolic blood pressures > 110 mm Hg.

Possible etiology: Pheochromocytoma, given the age of presentation and absence of major risk factors for idiopathic hypertension and previous episodes of palpitations, headaches, and light-headedness. Consider clonidine rebound hypertension due to recent medication change.

Next step: Admit to the intensive care unit (ICU), immediately lower blood pressure with a parenteral agent, and closely monitor the arterial pressure.

ANALYSIS

Objectives

1. Define and describe the management of hypertensive emergency and urgency. (EPA 10)
2. Understand the relationship between systemic blood pressure and cerebral blood flow. (EPA 3, 12)
3. Describe how to diagnose and medically treat a patient with a pheochromocytoma. (EPA 1, 4)

Considerations

Hypertensive encephalopathy, a symptom complex of severely elevated blood pressures, confusion, increased intracranial pressure, and/or seizures, is a diagnosis of exclusion; other causes for the patient's acute mental decline, such as stroke, subarachnoid hemorrhage, meningitis, or mass lesion, must be ruled out. Knowing the specific etiology of the patient's hypertension is not necessary to treat his encephalopathy; urgent blood pressure lowering is indicated. However, it **may be harmful to normalize the blood pressure too quickly** because it may cause cerebral

hypoperfusion. **Parenteral medications should be used to lower the blood pressure to the range of 160/100 to 110 mm Hg.**

In addition, the patient has tachycardia, hypertension, diaphoresis, dilated pupils, and a slight tremor, all signs of a hyperadrenergic state. Pheochromocytoma must be considered as a possible underlying etiology of his hypertension. His antihypertensive medication changes may also be contributory—perhaps rebound due to discontinuation of clonidine. Moreover, in pheochromocytoma the use of beta-blockers promotes further hypertension due to the unopposed effect of alpha-adrenergic stimulation.

APPROACH TO:

Hypertensive Crises/Pheocromocytoma

DEFINITIONS

HYPERTENSIVE EMERGENCY: Acute elevation in blood pressure with associated end-organ damage.

HYPERTENSIVE URGENCY: Acute elevation in blood pressure to greater than 180 mm Hg systolic pressure and/or greater than 110 mm Hg diastolic pressure without evidence of end-organ damage.

CLINICAL APPROACH TO HYPERTENSIVE CRISIS AND EMERGENCY

Background

Hypertensive crises are critical elevations in blood pressure and are usually classified as either hypertensive emergencies or urgencies. The presence of **acute end-organ damage** constitutes a **hypertensive emergency**, whereas the absence of such complications is considered **hypertensive urgency**. Examples of acute end-organ damage include hypertensive encephalopathy, myocardial ischemia or infarction, aortic dissection, stroke, declining renal function with proteinuria, microangiopathic hemolytic anemia, pulmonary edema secondary to acute left ventricular failure, and vision loss with papilledema on examination.

Hypertensive emergencies require immediate reduction in blood pressure with hospitalization for close monitoring. Hypertensive urgencies also require prompt medical attention, but the blood pressure can be lowered over 1 to 2 days and monitored in the outpatient setting for patients with reliable follow-up.

Hypertensive crises are uncommon but occur most often in patients with an established history of essential hypertension (hypertension without an apparent underlying cause). A crisis may also be precipitated by use of sympathomimetic agents, such as cocaine, or by conditions that produce excess sympathetic discharge, such as clonidine withdrawal. Hypertensive crises also result

from underlying diseases that cause hypertension, such as renovascular disease (eg, renal artery stenosis), renal parenchymal disease (eg, glomerulonephritis), and pheochromocytoma.

Pathophysiology

Although the pathophysiology is not completely understood, abrupt rises in vascular resistance are met with endothelial compensation by the release of vasodilator molecules such as nitric oxide. If the increase in arterial pressure persists, the endothelial response is overwhelmed and decompensates, leading to a further rise in pressure and endothelial damage and dysfunction.

Cerebral blood flow is a good example of vascular compensation by vasodilation or vasoconstriction in response to changes in arterial pressure (Figure 7–1). In normotensive adults, cerebral blood flow remains relatively constant over a range of mean arterial pressures between 60 and 120 mm Hg because cerebral vasoconstriction limits excessive cerebral perfusion. In patients with chronic hypertension, this regulation curve is shifted to the right due to the long-term change in pressure. As the mean arterial pressure increases beyond the normal range of cerebral autoregulation, there is cerebrovascular endothelial dysfunction and increased permeability of the blood-brain barrier. This leads to **vasogenic edema and the formation of microhemorrhages** that manifest as symptoms and signs of hypertensive encephalopathy, such as lethargy, confusion, headaches, or vision changes. Typical imaging findings on magnetic resonance imaging (MRI) include posterior leukoencephalopathy, usually in the parietooccipital regions, which may or may not be seen on CT scanning. **Without therapy, hypertensive encephalopathy can lead to seizures, coma, and death.**

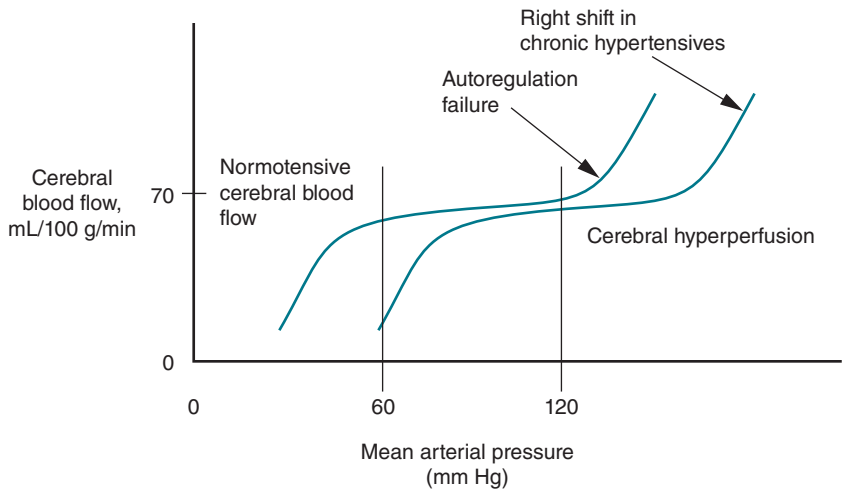


Figure 7–1. Cerebral blood flow autoregulation. Cerebral blood flow is constant over a range of blood pressures. Chronic hypertensive patients have an adaptive mechanism that shifts the curve to the right.

Treatment

The definition of hypertensive emergency does not require numerical thresholds of arterial pressure but **is based on end-organ effects.** Autoregulation failure can occur in previously normotensive individuals at blood pressures as low as 160/100 mm Hg; however, individuals with long-standing hypertension frequently develop adaptive mechanisms (eg, cerebral arterial autoregulation) and may not show clinical manifestations until the blood pressure rises to above 220/110 mm Hg. Thus, **emergent treatment of hypertensive encephalopathy** (and indeed, all hypertensive emergencies) should **focus on the symptoms** rather than the numbers. In fact, it may be dangerous to "normalize" the blood pressure of patients with chronic hypertension too quickly. Rapid lowering of blood pressures may lead to decreased perfusion to the brain due to the rightward shift in the blood pressure autoregulation curve. This results in cerebral ischemia or infarction or in renal or coronary hypoperfusion. Usually, a reasonable goal is reduction of mean arterial pressures by no more than 20% or to a diastolic blood pressure of 110 to 120 mm Hg in the first hour and further 15% reduction in the following 23 hours.

Treatment of **hypertensive emergencies usually necessitates parenteral medication without delay**; direct blood pressure monitoring with an arterial catheter often is necessary. One of the most commonly used medications for treating hypertensive emergencies is **sodium nitroprusside.** It has the advantage of nearly instantaneous onset of action, and its dose can be easily titrated for a smooth reduction in blood pressure. However, its metabolite may accumulate, resulting in **cyanide or thiocyanate toxicity** when it is given for more than 2 to 3 days. Certain clinical situations may favor the use of other medications. Intravenous loop diuretics and vasodilators such as nitroglycerin decrease the preload (central venous pressure) in acute pulmonary edema. Myocardial ischemia or infarction is treated with intravenous nitroglycerin to improve coronary perfusion and beta-blockers to reduce blood pressure, heart rate, and myocardial oxygen demand. Patients with aortic dissection benefit from medications that reduce the shear forces affecting the aorta, which will help limit propagation of the dissection. A useful technique in treating these individuals is the use of intravenous nitroprusside to lower the arterial blood pressure and a beta-blocker to blunt reflex tachycardia. Alternatively, intravenous labetalol, a combined alpha- and beta-blocker, alone can be used. **Patients presenting with acute cerebral infarction generally should not have acute blood pressure lowering unless the systolic blood pressure is greater than 220 mm Hg because of the possibility of worsening cerebral ischemia.**

CLINICAL APPROACH TO PHEOCHROMOCYTOMA

Epidemiology

The vast majority of hypertension has no discernible cause (essential hypertension), but some patients have secondary causes, such as renal artery stenosis, hyperaldosteronism, or pheochromocytoma. Less than 10% of pheochromocytomas are familial, and these tend to be bilateral. One should consider screening for the presence of the *RET* proto-oncogene seen in multiple endocrine neoplasia

type II (MEN II) or the *VHL* gene for von Hippel-Lindau syndrome, as well as screening family members for these diseases and for familial pheochromocytoma and neurofibromatosis.

Pathophysiology

Pheochromocytomas are catecholamine-producing tumors that arise from chromaffin cells of the adrenal medulla. The diagnosis of pheochromocytoma is established by measuring increased concentrations of catecholamines or their metabolites in either urine or plasma. Usually, **a 24-hour urine collection** is assayed for **metanephrines and catecholamines**. One-time measurement of plasma-free metanephrines is a convenient and fairly sensitive screening test. After the biochemical tests document the excess catecholamines, the next step is to locate the tumor for surgical removal. Approximately 90% of pheochromocytomas are in the adrenal gland, usually identified by CT or MRI. If the initial imaging is unrevealing, scintigraphic localization with ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) or an octreotide (somatostatin analog) scan is indicated.

Clinical Presentation

This patient's history of paroxysmal hypertension with headaches, palpitations, and hyperadrenergic state (dilated pupils, diaphoresis) suggests the diagnosis of **pheochromocytoma**. Other symptoms may include episodic anxiety, tremor, and orthostatic hypotension caused by volume contraction from pressure-induced natriuresis. Although uncommon, accounting for only 0.01% to 0.1% of hypertensive individuals, these tumors have important therapeutic considerations.

Treatment

The treatment of choice for these tumors is surgical resection, but it is critical to reverse the acute and chronic effects of the excess catecholamines prior to excision (Figure 7–2). **Alpha-adrenergic blocking agents, such as phenoxybenzamine, an irreversible, long-acting agent, are started 2 weeks prior to surgery to help prevent hypertensive exacerbations**, which are especially worrisome during surgery. A liberal salt diet is initiated to expand the commonly seen contracted blood volume. Sometimes a **beta-blocking** agent is started, but **only after alpha-blockade is established**. The products of pheochromocytomas stimulate both the alpha- and beta-adrenergic receptors; thus, using a beta-blocker alone may worsen the hypertension because of unopposed alpha-adrenergic stimulation. Also, beta-blockade may result in acute pulmonary edema, especially in the presence of cardiomyopathy secondary to chronic catecholamine exposure.

CASE CORRELATION

- See also Case 6 (Hypertension, Outpatient) and Case 36 (Transient Ischemic Attack).

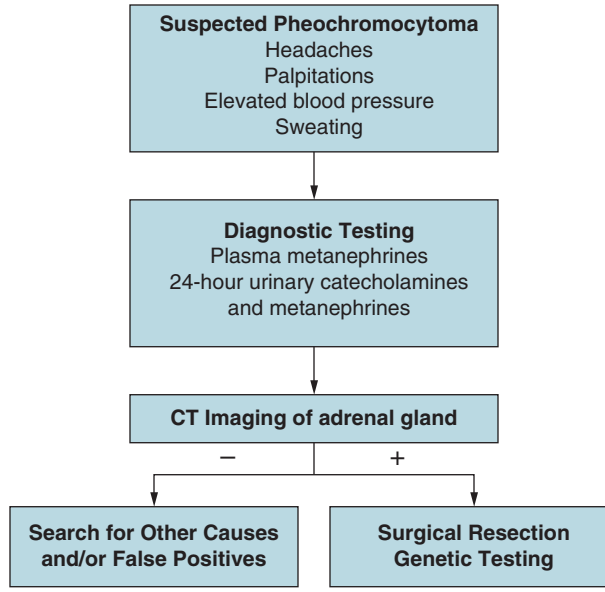


Figure 7–2. Pheochromocytoma evaluation and treatment flowchart.

COMPREHENSION QUESTIONS

7.1 A 50-year-old man with chronic hypertension presents at the clinic having run out of his medications, lisinopril and amlodipine, for more than a month. He is asymptomatic and has a blood pressure of 200/104 mm Hg. Which of the following is the best management?

A. Admit him to the hospital and initiate intravenous nitroprusside.

B. Prescribe clonidine 0.1 mg tid and recheck the blood pressure in 24 to 48 hours.

C. Restart his angiotensin-converting enzyme (ACE) inhibitor and calcium channel blocker and recheck blood pressure in 24 to 48 hours.

D. Refer to a social worker and do not prescribe any antihypertensive agent.

7.2 An 80-year-old woman with no significant past medical history undergoes surgery for a hip fracture. She tolerates the procedure well. On postoperative day 1 she reports moderate hip pain, but no chest pain, headache, shortness of breath, or palpitations. She is alert, awake, and oriented to person, place, and time. Her pulse is 95 bpm, temperature is 99.5 °F, respiratory rate is 18 breaths per minute, and blood pressure is 172/106 mm Hg. Over the past 24 hours, she has made 1000 mL of clear, yellow urine. Which of the following is the best next step?

A. Transfer the patient to the ICU, obtain cardiac enzyme levels, and lower the blood pressures to the 140/90 mm Hg range.

B. Control the pain and monitor the blood pressure.

C. Start the patient on a beta-blocker and monitor the blood pressure.

D. Restrict visitors and turn down the television, alarms, and other noise.

7.3 A 61-year-old man with a past medical history of coronary artery disease complains of progressive orthopnea, pedal edema, and dyspnea on exertion for the past 3 months. He is hospitalized with a pulse of 78 bpm, temperature of 98.6 °F, respiratory rate of 14 breaths per minute, and blood pressure of 190/105 mm Hg. He has bilateral 2+ pitting edema above the ankles. Cardiac enzyme levels and an electrocardiogram are normal, but an echocardiogram is still pending. Intravenous furosemide has been administered. Which of the following is the best next step?

A. Prescribe a beta-blocker to decrease myocardial oxygen demands.

B. Start intravenous dopamine.

C. Observe his clinical status.

D. Start an ACE inhibitor.

7.4 A 58-year-old woman with a past medical history of atrial fibrillation presents to the emergency room with aphasia and right arm weakness for the past 8 hours. She is nonadherent to her medication regimen. Pulse is 86 bpm, temperature is 99 °F, blood pressure is 162/98 mm Hg, and her respiratory rate is 14 breaths per minute. Cardiac examination shows an irregularly irregular rhythm. Pulmonary examination is normal. CT scan shows no intracranial hemorrhage. Which of the following is the best next step in management?

A. Normalize the blood pressure with beta-blockade.

B. Admit to the ICU with sodium nitroprusside.

C. Normalize the blood pressure with an ACE inhibitor.

D. Observe the blood pressure.

ANSWERS

7.1 **C.** This man has a hypertensive urgency—elevated blood pressures without end-organ symptoms. The appropriate treatment is reinitiation of blood pressure medications and reassessment in 24 to 48 hours. Answer A (hospitalization)

would be indicated if the patient had symptoms of end-organ damage such as headache, chest pain, altered mental status, and so on. Answer B (clonidine) would not be good maintenance therapy, given questions regarding his compliance with treatment and the risk of rebound hypertension. Answer D (refer to social worker and do not prescribe antihypertensives) is incorrect because it is unethical not to treat this patient with critically high blood pressures. While the patient's nonadherence should be explored and addressed, it is imperative to get the blood pressure controlled first.

7.2 **B.** Elevated blood pressure without symptoms may occur acutely after surgery, particularly because of postoperative pain. Answer C (starting beta-blocker therapy) would be appropriate only if the patient had critically elevated blood pressures (systolic blood pressure > 180 mm Hg and diastolic blood pressure > 110 mm Hg) or symptoms of end-organ damage. Blood pressure medications are usually not indicated when the pressures are below the malignant range; rather, pain control is the primary treatment. Lowering the blood pressure excessively can lead to orthostatic hypotension when the patient gets out of bed. Answer A (admitting to the ICU and obtaining cardiac enzymes) is not necessary in an asymptomatic patient whose increased blood pressure can be explained by postoperative pain. Answer D (restrict visitors, limit noise) would not treat the patient's underlying pain.

7.3 **D.** Elevated blood pressures may exacerbate congestive heart failure and must be treated. Both ACE inhibitors and oral nitrates or intravenous nitroglycerine are used to treat acute heart failure. ACE inhibition reduces afterload, and oral nitrates or intravenous nitroglycerine reduce preload. Answer A (prescribing beta-blockers) would be inappropriate for this patient; beta-blockers are generally avoided when patients are volume overloaded because beta-blockers decrease myocardial contractility and can thus worsen acute heart failure. Answer B (treatment with intravenous dopamine) would be inappropriate for this patient because the dopamine may exacerbate the increased blood pressure and peripheral resistance. Answer C (observe the clinical status) is not appropriate with a blood pressure so high.

7.4 **D.** In general, blood pressure should not be acutely decreased (unless systolic blood pressure > 220 mm Hg) in an individual suspected of having an ischemic stroke because of the concern for cerebral hypoperfusion and worsening brain ischemia. If thrombolytic therapy is considered, blood pressure should be controlled to < 185/100 mm Hg, but this patient's symptom duration precludes that consideration. In contrast, patients with intracerebral hemorrhage require urgent blood pressure decrease to values of 140 mm Hg systolic or less to decrease the propagation of the hemorrhage. Answers A (normalize the blood pressure with beta-blockade), B (admit to ICU with sodium nitroprusside), and C (normalize the blood pressure with an ACE inhibitor) are inappropriate in this patient with an ischemic stroke.

CLINICAL PEARLS

- Hypertensive urgencies are acute elevations of blood pressures > 180 mm Hg systolic and > 110 mm Hg diastolic.
- Asymptomatic patients with hypertensive urgency can be treated with an oral regimen and reassessed in the outpatient setting in 24 to 48 hours.
- A hypertensive emergency is defined as an episode of elevated blood pressure with acute end-organ damage or dysfunction.
- Patients with hypertensive emergencies require immediate hospitalization and a gradual decrease in blood pressure, with a focus on symptom resolution.
- The cerebral autoregulation curve of individuals with chronic hypertension is shifted to the right.
- Marked elevations in mean arterial pressure can exceed the ability of cerebral vessels to constrict, causing hyperperfusion, cerebral edema, and hypertensive encephalopathy.
- Pheochromocytomas may cause paroxysmal blood pressure elevation with episodic headaches, palpitations, and diaphoresis.
- Preoperative blood pressure control in pheochromocytoma resection is achieved with alpha-blockers. Beta-blockers used alone can paradoxically increase blood pressure because of unopposed alpha-adrenergic effects.

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CASE 8

A 26-year-old Nigerian woman presents to the emergency center complaining of the sudden onset of palpitations, severe shortness of breath, and coughing. She reports that she has experienced several episodes of palpitations in the past, often lasting 1 or 2 days, but never with dyspnea. She has a history of rheumatic fever at the age of 14. She is now pregnant at 20 weeks' gestation with her first child and takes prenatal vitamins. She denies the use of any other medications, tobacco, alcohol, or illicit drugs.

On examination, her heart rate ranges from 110 to 130 beats per minute (bpm), blood pressure is 92/65 mm Hg, respiratory rate is 24 breaths/min, and oxygen saturation is 94% on room air. She appears uncomfortable, with labored respirations. She is coughing and producing scant amounts of frothy sputum with a pink tint. She has ruddy cheeks and normal jugular venous pressure. She has bilateral inspiratory crackles in the lower lung fields. On cardiac examination, her heart rhythm is irregularly irregular with a loud S_1 and low-pitched diastolic murmur best heard at the apex with a nondisplaced apical impulse. Her uterine fundus is palpable at the umbilicus, and she has no peripheral edema. An electrocardiogram (ECG) is obtained (Figure 8–1).

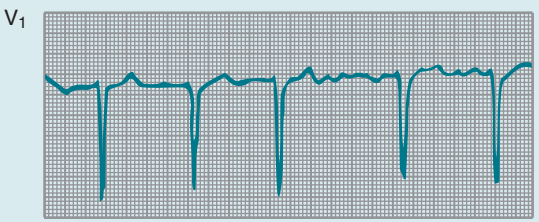


Figure 8–1. Electrocardiogram. (Reproduced with permission, from Braunwald E, Fauci AS, Kasper KL, et al. *Harrison's Principles of Internal Medicine*. 16th ed. 2005. Copyright © McGraw Hill LLC. All rights reserved.)

- What is the most likely diagnosis?
- What is your next step in management?

ANSWERS TO CASE 8:
Atrial Fibrillation/Mitral Stenosis

Summary: A 26-year-old woman presents with

- History of rheumatic fever during adolescence
- Pregnancy in the second trimester currently
- Acute onset of palpitations
- Atrial fibrillation (AF) with a rapid ventricular response
- Diastolic rumble suggestive of mitral stenosis leading to left atrial enlargement, which is the likely cause of her AF
- Increased blood volume from pregnancy, tachycardia, and loss of atrial contraction, which have likely led to pulmonary edema

Most likely diagnosis: AF caused by mitral stenosis.

Next step in management: Heart rate control with intravenous beta-blockers.

ANALYSIS

Objectives

1. Enumerate the causes of AF. (EPA 12)
2. Understand the management of AF with rapid ventricular response. (EPA 4, 10)
3. Understand the rationale for anticoagulation in chronic AF. (EPA 4, 12)
4. Describe the typical cardiac lesions of rheumatic heart disease and the physical findings in mitral stenosis. (EPA 1, 3)
5. Understand the physiologic basis of Wolff-Parkinson-White (WPW) syndrome and the special considerations in AF. (EPA 4, 12)

APPROACH TO:
Atrial Fibrillation

DEFINITIONS

ATRIAL FIBRILLATION: Irregular heart rhythm with chaotic generation of electrical signals in the atria of the heart.

DIRECT CURRENT (DC) CARDIOVERSION: Converting an abnormal rhythm of the heart to normal sinus rhythm by applying DC electrical shock.

CLINICAL APPROACH

Background and Epidemiology

Atrial fibrillation is the most common arrhythmia for which patients seek treatment; it occurs in acute, paroxysmal, and chronic forms. With AF, there is disordered atrial depolarization from multiple irritable foci, often at rates exceeding 300 to 400 bpm; these atrial impulses produce an irregular ventricular response, depending on the number of impulses that are conducted through the atrioventricular (AV) node. The ECG is characterized by the **absence of discrete P waves** and an RR interval without a repetitive pattern, commonly referred to as an **irregularly irregular** rhythm. The incidence of AF increases with age, affecting 5% to 10% of patients older than 75 years. Although many patients can maintain a normal activity level and remain essentially asymptomatic with chronic AF, there are several causes of morbidity from this arrhythmia: It may trigger a rapid ventricular rate, leading to myocardial ischemia, exacerbation of heart failure in patients with heart disease, and **thrombus formation** in the noncontractile atrial appendage, which can lead to systemic embolization (AF is a common cause of ischemic stroke).

Pathophysiology

Anything that causes atrial dilation or excessive sympathetic tone can lead to AF, but the **two most common causes** of AF are **hypertension and coronary atherosclerosis.** The common causes of AF are listed in Table 8–1.

Treatment

Acute AF. **Acute AF with rapid ventricular response must be addressed quickly.** The four major goals are (1) hemodynamic stabilization, (2) rate control, (3) anticoagulation, and (4) possible conversion to sinus rhythm. If a patient is **hemodynamically unstable** (hypotensive, angina pectoris, pulmonary edema), **urgent DC cardioversion** is indicated. If the patient is hemodynamically stable, **ventricular rate control** can generally be achieved with **intravenous beta-blockers, calcium channel blockers, or digoxin**, which slow conduction through the AV node. Once the ventricular rate has been controlled, the underlying cause (eg, thyrotoxicosis, use of adrenergic stimulants, or worsening heart failure) should be reversed so that patients can undergo **cardioversion** to sinus rhythm. This may occur spontaneously or after correction of underlying abnormalities, or it may require pharmacologic or electrical

Table 8–1 • CAUSES OF ATRIAL FIBRILLATION

Structural heart disease (hypertension, mitral valve disease)
Ischemic heart disease
Pericarditis or pericardial injury (postsurgical)
Pulmonary disease (especially pulmonary embolism)
Hyperthyroidism
Stress or increased sympathetic tone (acute illness, pheochromocytoma)
Alcohol consumption (holiday heart syndrome, alcoholic cardiomyopathy)
Sick sinus syndrome (tachy-brady syndrome)

cardioversion. If the duration of **AF exceeds 48 hours, the risk of intra-atrial thrombus formation increases.**

Rate control alone (ie, the use of agents to maintain a slow ventricular response rate) is often effective in managing the symptoms of AF, and it has been shown to be as effective as rhythm control for long-term outcomes.

However, if patients are unstable or persistently symptomatic, they may require efforts to terminate the AF and restore sinus rhythm. **The most effective method of terminating AF is electrical cardioversion.** After cardioversion, the return of coordinated atrial contraction in the presence of an atrial thrombus may result in clot embolization, leading to a cerebral infarction or other ischemic event. Therefore, after 24 to 48 hours of AF, patients should receive 3 to 4 weeks of anticoagulant therapy prior to and after cardioversion to reduce the risk of thromboembolic phenomena. Alternatively, low-risk patients can undergo transesophageal echocardiography to exclude the presence of an atrial appendage thrombus prior to cardioversion. Postcardioversion anticoagulation is still required for 4 additional weeks, because though the rhythm returns to sinus, the atria do not contract normally for some time. Pharmacologic antiarrhythmic agents, such as propafenone, sotalol, and amiodarone, may be used to try to maintain sinus rhythm.

Many patients with AF even after cardioversion do not remain in sinus rhythm. **Two important prognostic factors** are **left atrial dilation** (atrial diameter > 4.5 cm predicts failure of cardioversion) and duration of AF. The longer the patient is in AF, the more likely the patient is to stay in that rhythm as a consequence of electrical remodeling of the heart.

Chronic AF. In patients with chronic AF, the management goals are rate control, using drugs to reduce AV nodal conduction (such as digoxin or beta-blockers) as described previously, and anticoagulation. Patients with chronic AF who are not anticoagulated have a 1% to 5% per year incidence of clinically evident embolization such as stroke. Risk assessment tools such as the **CHA_2DS_2-VASc** (see Table 8–2 for definition) **score** can be used to estimate stroke risk and need for anticoagulation. The CHA_2DS_2-VASc score correlates an increasing event rate with an increasing score (Tables 8–2 and 8–3).

Table 8–2 • CHA_2DS_2-VASc SCORE

C—congestive heart failure	1
H—hypertension	1
A—age ≥ 75 years	2
D—diabetes mellitus	1
S—stroke or TIA, embolus	2
V—vascular disease (prior MI, PAD, or aortic plaque)	1
A—age 65-74 years	1
Sex category—female	1

Abbreviations: MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack.

Table 8–3 • CHA_2DS_2-VASc SCORE AND ESTIMATED ANNUAL STROKE RATE	
CHA_2DS_2-VASc Score	Estimated Annual Stroke Rate
0	0
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6-9	> 9%

For chronic AF caused by valvular disease such as mitral stenosis, the annual risk of stroke is substantially higher. AF that develops in patients younger than 60 years without evidence of structural heart disease, hypertension, or other factors for stroke is termed **lone AF**, and the **risk of stroke is very low**, so anticoagulation with warfarin is not used. Instead, aspirin may be used.

Anticoagulation reduces the risk of stroke by two-thirds in patients with chronic AF. New oral anticoagulants such as dabigatran and rivaroxaban have been developed for use in AF, but the oral vitamin K antagonist warfarin remains the most widely used medication for this purpose. Warfarin does not produce a predictable dose-related response; therefore, the level of anticoagulation needs to be monitored by regular laboratory testing using the international normalized ratio (INR). In AF not caused by valvular disease, the target INR is 2 to 3.

The most common complication of warfarin therapy is bleeding resulting from excessive anticoagulation. The risk of bleeding increases with the INR. If the INR is markedly elevated (eg, INR 6–9) but there is no apparent bleeding, the values will return to normal over several days if the warfarin is held. For higher levels of INR (> 9) without bleeding, vitamin K can be administered. If clinically significant bleeding is present, warfarin toxicity can be rapidly reversed with administration of vitamin K, fresh frozen plasma (FFP), and prothrombin complex concentrate to replace clotting factors and provide intravascular volume replacement.

Rheumatic Heart Disease

In this case, the cause of this patient's AF appears to be rheumatic mitral stenosis. **Rheumatic heart disease** is a late sequela of acute rheumatic fever, usually becoming symptomatic many years after the original illness. Valvular thickening, fibrosis, and calcifications lead to valvular stenosis. The **mitral valve is most frequently involved.** The aortic valve may also develop stenosis in combination with the mitral valve. The right side of the heart is rarely involved. Most cases of **mitral stenosis** in adults are secondary to **rheumatic heart disease**, especially in the developing world. Congenital mitral stenosis is also commonly seen.

The physical signs of mitral stenosis are a **loud S_1** and an **opening snap following S_2.** The S_2-OS (mitral valve opening snap) interval narrows as the severity of the stenosis increases. There is a **low-pitched diastolic rumble** after the **opening snap,** heard best at the apex with the bell of the stethoscope. Because of the stenotic

valve, pressure in the left atrium is increased, leading to left atrial dilation and, ultimately, pulmonary hypertension. Pulmonary hypertension can cause hemoptysis and signs of right-sided heart failure, such as peripheral edema. When AF develops, the rapid ventricular response causes shortened diastolic filling time, leading to fluid accumulation in the pulmonary system with eventual pulmonary congestion. Rate control with intravenous beta-blockers or calcium channel blockers is essential to relieve pulmonary symptoms. In this case, the mitral stenosis likely became symptomatic due to the patient's pregnancy, with increased blood volume and increased cardiac output of up to 30% to 50%.

Wolff-Parkinson-White Syndrome

Another cause of AF is the **Wolff-Parkinson-White (WPW) syndrome**. In patients with this condition, AF may be life threatening. In addition to the AV node, patients with WPW have an **accessory pathway** that provides an alternate route for electrical communication between the atria and ventricles. This alternative route leads to **pre-excitation**, an early ventricular depolarization that begins prior to normal AV nodal conduction. A portion of ventricular activation occurs over the accessory pathway, with the remainder occurring normally through the His-Purkinje system. This pre-excitation is recognized on the ECG as a **delta wave**, or early upslurring of the R wave, which both **widens the QRS complex** and **shortens the PR interval** (Figure 8–2).

Some patients with the ECG abnormalities of WPW syndrome are asymptomatic. Others have recurrent tachyarrhythmias, mostly paroxysmal supraventricular tachycardia; one-third of patients have AF. AF with conduction to the ventricles over an accessory pathway is a special case for two reasons. First, when conducted through the accessory pathway, the **widened QRS** may look like ventricular tachycardia, except that it will have the **irregular RR interval of AF**. Second, because the

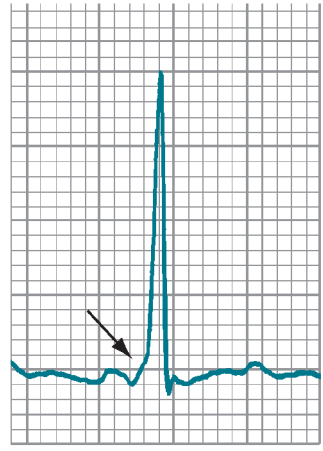


Figure 8–2. Electrocardiogram revealing the delta wave (arrow) of Wolff-Parkinson-White syndrome. (Reproduced with permission, from Stead LG, Stead SM, Kaufman MS. *First Aid for the Medicine Clerkship*, 2nd ed. 2006. Copyright © McGraw Hill LLC. All rights reserved.)

AV conduction is occurring through the accessory pathway rather than through the AV node, the ventricular rate may be very rapid, and the usual AV nodal–blocking drugs given for ventricular rate control will not affect the accessory pathway. In fact, **beta-blockers, verapamil**, and other AV nodal–blocking agents can, **paradoxically, increase the ventricular rate** and **should be avoided in WPW patients with AF**. If hemodynamically unstable, **DC cardioversion** should be performed. If hemodynamically stable, the agent of choice is procainamide or ibutilide to slow conduction and convert the rhythm to sinus.

CASE CORRELATION

- See also Case 4 (Heart Failure due to Critical Aortic Stenosis), Case 6 (Hypertension, Outpatient), and Case 36 (Transient Ischemic Attack).

COMPREHENSION QUESTIONS

8.1 A 28-year-old woman has been told she has rheumatic heart disease, specifically mitral stenosis. Which of the following murmurs is most likely present?

A. Diastolic rumble at apex of the heart
B. Early diastolic decrescendo at right upper sternal border
C. Holosystolic murmur at apex
D. Late-peaking systolic murmur at right upper sternal border

8.2 A 48-year-old woman is noted to have AF with a ventricular rate of 140 bpm. She is feeling dizzy and dyspneic, with a systolic blood pressure of 75/48 mm Hg. Which of the following is the most appropriate next step?

A. Intravenous digoxin
B. DC cardioversion
C. Vagal maneuvers
D. Intravenous diltiazem

8.3 A third-year medical student has been reading about the dangers of excessive anticoagulation and bleeding potential. He reviews the charts of several patients with AF currently taking warfarin. Which of the following patients is best suited to discontinue anticoagulation?

A. A 45-year-old man who has normal echocardiographic findings and no history of heart disease or hypertension, but a family history of hyperlipidemia
B. A 62-year-old man with mild chronic hypertension and dilated left atrium, but normal ejection fraction
C. A 75-year-old woman who is in good health except for a prior stroke, from which she has recovered nearly all function
D. A 52-year-old man with orthopnea and paroxysmal nocturnal dyspnea

8.4 A 59-year-old woman has been placed on warfarin after being found to have chronic AF. She is noted to have an INR of 5.8, is asymptomatic, and has no overt bleeding. Which of the following is the best management for this patient?

A. Transfuse with erythrocytes.

B. Give vitamin K.

C. Give fresh frozen plasma

D. Hold warfarin.

8.5 A 45-year-old woman is noted to have dizziness, a pounding feeling in her chest, and fatigue of 3 hours' duration. On examination, she is noted to have a blood pressure of 110/70 mm Hg and a heart rate of 180 bpm. On ECG, she has AF, and a prior baseline ECG showed delta waves. The emergency department provider counsels the patient regarding cardioversion, but the patient declines. Which of the following is the best therapy for her condition?

A. Digoxin

B. Angiotensin-converting enzyme inhibitor

C. Calcium channel blocker

D. Procainamide

ANSWERS

8.1 **A.** A diastolic rumble at the cardiac apex suggests mitral stenosis. The early diastolic decrescendo murmur (answer B) is typical of aortic regurgitation; holosystolic murmur at the apex (answer C) is typical of mitral regurgitation; and late-peaking systolic murmur at the upper sternal border (answer D) is typical of aortic stenosis.

8.2 **B.** This individual has significant symptoms and hypotension caused by the AF and rapid ventricular rate; this is an unstable patient, and thus DC cardioversion is the treatment of choice. The other answer choices (answer A, digoxin, and answer D, diltiazem) would take time to work, and additionally answer C (vagal maneuvers) could potentially compromise cerebral blood flow if carotid massage is used.

8.3 **A.** Clinical factors associated with a higher risk for embolic stroke include congestive heart failure, hypertension, age > 65, diabetes, or prior stroke. Echocardiographic factors include dilated left atrium or the presence of an atrial thrombus. The man in answer A has "lone AF" with a $CHADS_2$ score < 2 and has a low risk for stroke; thus, he would not benefit from anticoagulation. The other answer choices have high $CHADS_2$ scores based on age and other comorbidities.

8.4 **D.** The target INR with warfarin is 2 to 3; thus, 5.8 is markedly elevated. However, because this patient has no overt bleeding and is asymptomatic, holding the warfarin until the INR reaches the acceptable range is a reasonable approach. Answer A (transfusion) is not indicated since the patient did not

have bleeding. Patients with overt bleeding require more urgent intervention, such as administration of vitamin K (answer B), FFP (answer C), or prothrombin complex concentrate to replenish clotting factors.

8.5 **D.** This patient has AF with WPW, as indicated by the delta wave. In this setting, the typical agents (answer A, digoxin; answer B, angiotensin-converting enzyme inhibitor; and answer C, calcium channel blocker) used to treat AF that slow the AV node are contraindicated since the conduction through the accessory pathway could accelerate, leading to ventricular tachycardia. DC cardioversion is an option; however, in a hemodynamically stable patient, procainamide may be used since it will slow propagation through the accessory pathway. Because this patient declines cardioversion, procainamide is the best choice.

CLINICAL PEARLS

- The most common causes of AF are hypertension, atherosclerotic heart disease, pericardial or pulmonary disease, and hyperthyroidism.
- Acute AF is treated with direct current cardioversion if the patient is unstable. If the patient is stable, initial management is ventricular rate control with an AV nodal–blocking agent, such as beta-blockers, diltiazem, or verapamil.
- Patients with chronic AF generally require long-term anticoagulation to prevent embolic strokes. An exception is "lone AF."
- CHA_2DS_2-VASc score can help with risk stratification for both thromboembolic events and need for long-term anticoagulation.
- WPW syndrome is a ventricular pre-excitation syndrome with a delta wave, short PR interval (< 0.12 seconds), and prolonged QRS interval (> 0.12 seconds).
- WPW syndrome is associated with paroxysmal tachycardias, including AF. AF in WPW syndrome is treated with DC cardioversion or with procainamide. AV nodal–blocking agents can, paradoxically, increase the ventricular rate.
- Auscultatory findings in mitral stenosis include a loud S_1 and an opening snap following the second heart sound (S_2). The interval between S_2 and the opening snap varies inversely with the severity of the stenosis.

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CASE 9

A 72-year-old man is brought to the emergency department after fainting while in church. He stood up to sing a hymn and then fell to the floor. His wife, who witnessed the episode, reports that he was unconscious for approximately 2 or 3 minutes. When he woke up, he was groggy for another minute or two and then seemed himself. No abnormal movements were noted. This had never happened to him before, but his wife does report that for the last several months he has had to curtail activities, such as mowing the lawn, because he becomes weak and feels light-headed. His only medical history is osteoarthritis of the knees, for which he takes acetaminophen.

On examination, he is alert, talkative, and smiling. He is afebrile, his heart rate is 35 beats per minute (bpm), and his blood pressure is 118/72 mm Hg, which remains unchanged on standing. He has contusions on his face, left arm, and chest wall, but no lacerations. His chest is clear to auscultation, and his heart rhythm is regular but bradycardic with a nondisplaced apical impulse. He has no focal deficits. Laboratory examination shows negative cardiac enzymes and normal blood counts, renal function, and serum electrolyte levels. His rhythm strip is shown in Figure 9–1.

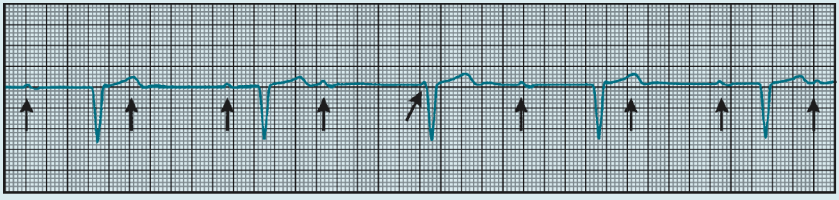


Figure 9–1. Electrocardiogram. (Reproduced with permission, from Stead LG, Stead SM, Kaufman MS. *First Aid for the Medicine Clerkship,* 2nd ed. 2006. Copyright © McGraw Hill LLC. All rights reserved.)

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 9:
Syncope and Heart Block

Summary: A 72-year-old man presents with

- A witnessed syncopal episode, brief and without seizure activity
- Decreased exercise tolerance recently because of weakness and presyncopal symptoms
- Bradycardia, with third-degree atrioventricular (AV) block on electrocardiogram (ECG)

Most likely diagnosis: Syncope as a consequence of third-degree AV block. The arrows in Figure 9–1 point to P waves.

Next step: Placement of a temporary transcutaneous or transvenous pacemaker and evaluation for placement of a permanent pacemaker.

ANALYSIS

Objectives

1. Identify the major causes of syncope and important historical clues to the diagnosis. (EPA 1, 2)
2. Understand the basic evaluation of syncope based on the history. (EPA 1, 3, 10)
3. Recognize vasovagal syncope and carotid sinus hypersensitivity. (EPA 1, 3)
4. Describe diagnosis and management of first-, second-, and third-degree AV block. (EPA 4, 10)

Considerations

There are two major considerations to the management of this patient: recognizing the cause and managing his AV block. He should be evaluated for myocardial infarction and structural cardiac abnormalities. If this evaluation is negative, he may simply have conduction system disease because of aging. Atropine or isoproterenol can be used as a temporary measure when the conduction block is at the level of the AV node. However, in this case the heart rate is less than 40 bpm and the QRS is widened, suggesting that the defect is below the AV node, in the bundles of His. A permanent pacemaker will likely be required.

APPROACH TO: Syncope

DEFINITIONS

CARDIOGENIC SYNCOPE: Syncope due to the heart's intrinsic failure to generate sufficient cardiac output.

ORTHOSTATIC SYNCOPE: Syncope due to failure of appropriate systemic vasoconstriction, measured by a 20 mm Hg decrease in systolic pressure and a 10 mm Hg decrease in diastolic pressure.

SYNCOPE: A transient loss of consciousness and postural tone with subsequent spontaneous recovery.

VASOVAGAL SYNCOPE: Fainting due to excessive vagal tone causing impaired autonomic responses such as hypotension without appropriate rise in heart rate or vasomotor tone.

CLINICAL APPROACH

Epidemiology

Syncope is a very common phenomenon, resulting in 3% of emergency center visits and 1% of subsequent hospitalizations. The causes are varied, but they all result in transiently diminished cerebral perfusion, leading to loss of consciousness. The prognosis is quite varied, ranging from a benign episode in an otherwise young, healthy person with a clear precipitating event, such as emotional stress, to a more serious occurrence in an older patient with cardiac disease. In the latter situation, syncope has been referred to as "sudden cardiac death, averted." For that reason, higher-risk patients routinely undergo hospitalization and sometimes extensive evaluation to determine the cause.

Pathophysiology

Traditionally, the etiologies of syncope have been divided into neurogenic, vasovagal, orthostatic, and cardiogenic—either arrhythmias or outflow obstruction. Table 9–1 lists the most common causes of syncope. By far, **the most useful evaluation for diagnosing the cause of syncope is the patient's history.** Because, by definition, the patient was unconscious, the patient may only be able to report preceding and subsequent symptoms, so finding a witness to describe the episode is extremely helpful.

Neurogenic Syncope

Neurogenic syncope results from **dysfunction of the autonomic function,** which leads to orthostatic hypotension as described in diabetes mellitus, multisystem atrophy, and idiopathic dysautonomia. Other neurologic diseases in the differential diagnosis for syncope include vertebrobasilar insufficiency, seizures, and transient ischemic attacks (TIAs). Vertebrobasilar insufficiency with resultant loss of

Table 9–1 • CAUSES OF SYNCOPE

Cardiogenic	Noncardiogenic
Cardiac arrhythmias • Bradyarrhythmias • Sinus bradycardia, sinoatrial block, sinus arrest, sick sinus syndrome • Atrioventricular block • Tachyarrhythmias • Supraventricular tachycardia with structural cardiac disease • Atrial fibrillation associated with the Wolff-Parkinson-White syndrome • Atrial flutter with 1:1 atrioventricular conduction • Ventricular tachycardia **Other cardiopulmonary etiologies** • Pulmonary embolism • Pulmonary hypertension • Atrial myxoma • Myocardial disease (massive myocardial infarction) • Left ventricular myocardial restriction or constriction • Pericardial constriction or tamponade • Aortic outflow tract obstruction (aortic valvular stenosis, hypertrophic obstructive cardiomyopathy)	**Vasovagal (vasodepressor, neurocardiogenic)** **Postural (orthostatic) hypotension** • Drug induced (especially antihypertensive or vasodilator drugs) • Peripheral neuropathy (diabetic, alcoholic, nutritional, amyloid) • Idiopathic postural hypotension • Neurologic disorder (Shy-Drager syndrome) • Physical deconditioning • Sympathectomy • Acute dysautonomia (Guillain-Barré syndrome variant) • Decreased blood volume (adrenal insufficiency, acute blood loss, etc) • Carotid sinus hypersensitivity **Situational** • Cough, Valsalva • Micturition, defecation • Hypoglycemia • Generalized anxiety, panic disorder, somatization

consciousness is often discussed yet rarely seen in clinical practice. Seizure episodes are a common cause of transient loss of consciousness, and distinguishing seizure episodes from syncopal episodes based on history often is quite difficult. Loss of consciousness associated with seizure typically lasts longer than 5 minutes, with a prolonged postictal period, whereas patients with syncope usually become reoriented quickly. To further complicate matters, the same lack of cerebral blood flow that produced the loss of consciousness can lead to postsyncopal seizure activity. Seizures are best discussed elsewhere, so our discussion here is confined to syncope. Syncope is essentially never a result of TIAs because syncope reflects global **cerebral** hypoperfusion, and TIAs are a result of regional ischemia.

Vasovagal Syncope

Vasovagal syncope refers to **excessive vagal tone** causing impaired autonomic responses, that is, a fall in blood pressure without appropriate rise in heart rate or vasomotor tone. This is, by far, the **most common cause of syncope** and is the usual cause of a "fainting spell" in an otherwise healthy young person. Episodes often are precipitated by physical or emotional stress or by a painful experience. There is usually a clear precipitating event by history and, often, prodromal symptoms such as nausea, yawning, or diaphoresis. The episodes are brief, lasting seconds to minutes, with a rapid recovery. Syncopal episodes also can be triggered by physiologic

activities that increase vagal tone, such as micturition, defecation, or coughing in otherwise healthy people. Vasovagal syncope needs to be differentiated from orthostatic hypotension.

Carotid sinus hypersensitivity is also **vagally mediated**. This usually occurs in older men, and episodes can be triggered by turning the head to the side, wearing a tight collar, or even shaving the neck over the area. Pressure over one or both carotid sinuses causes excess vagal activity with resultant cardiac slowing and can produce sinus bradycardia, sinus arrest, or even AV block. Less commonly, carotid sinus pressure can induce a fall in arterial pressure without cardiac slowing. When recurrent syncope as a result of bradyarrhythmia occurs, a demand pacemaker is often required.

Orthostatic Hypotension

Patients with **orthostatic hypotension** typically report symptoms related to positional changes, such as rising from a seated or recumbent position. In orthostatic hypotension, **the postural drop in systolic blood pressure by more than 20 mm Hg, or 10 mm Hg diastolic, within 3 minutes of standing,** can be demonstrated on examination. This can occur because of hypovolemia (hemorrhage, anemia, diarrhea, or vomiting) or with impaired autonomic response despite adequate circulating blood volume. The most common reason for this autonomic impairment probably is iatrogenic as a result of antihypertensive or other medications, especially in elderly persons. It also can be caused by autonomic insufficiency seen in diabetic neuropathy, in a syndrome of chronic idiopathic orthostatic hypotension in older men, or in other primary neurologic conditions (Parkinsonism or idiopathic dysautonomia). Multiple unwitnessed events (not corroborated) or those that occur only in periods of emotional upset suggest **factitious** symptoms.

Cardiogenic Syncope

Etiologies of cardiogenic syncope include **rhythm disturbances and structural heart abnormalities.** Certain structural heart abnormalities will cause obstruction of blood flow to the brain, resulting in syncope. These include aortic stenosis and hypertrophic obstructive cardiomyopathy (HOCM). Syncope due to cardiac outflow obstruction can also occur with cardiac tamponade, massive pulmonary embolism, and severe pulmonary hypertension. Syncope caused by cardiac outflow obstruction typically presents during or immediately after exertion. An echocardiogram often is obtained to elucidate such abnormalities.

Arrhythmias. **Arrhythmias, usually bradyarrhythmias, are the most common cardiac cause of syncope.** Sinus bradycardia, most often due to degenerative sinoatrial (SA) node dysfunction, and AV node block are bradyarrhythmic causes of syncope. Sick sinus syndrome (SSS) in elderly patients is one of the most common causes for pacemaker placement. Patients with SSS may experience sinus bradycardia or arrest, alternating with a supraventricular tachycardia (SVT), most often atrial fibrillation (tachycardia-bradycardia syndrome). Additionally, prolonged QT interval may induce syncope. This can be acquired due to hypokalemia, hypomagnesemia, or medication use (eg, ondansetron). Also, some patients have congenital prolonged QT syndromes. Tachyarrhythmias such as atrial fibrillation or flutter,

SVT, ventricular tachycardia, or ventricular fibrillation are more likely to produce palpitations than syncope. Often, the rhythm abnormality is apparent by routine ECG, or if it occurs paroxysmally, it can be recorded using a 24-hour Holter monitor or an event monitor. Sometimes evaluation requires invasive electrophysiologic studies to assess sinus node or AV node function or to induce supraventricular or ventricular arrhythmias.

Heart Block. There are three types of AV node block, all based on ECG findings.

First-degree AV block is a prolonged PR interval longer than 200 ms (more than one large box in ECG). This is a conduction delay in the AV node. Prognosis is good, and there is usually no need for pacing.

Second-degree AV block comes in two types. **Mobitz type I** (Wenckebach) is a progressive **lengthening of the PR interval**, until a dropped beat is produced. The resulting P wave of the dropped beat is not followed by a QRS complex. This phenomenon is caused by abnormal conduction in the AV node and may be the result of an inferior myocardial infarction. Prognosis is good, and there is generally no need for pacing unless the patient is symptomatic (ie, bradycardia, syncope, heart failure, asystole > 3 seconds). On the other hand, **Mobitz type II produces dropped beats without lengthening of the PR interval.** This is usually caused by a block within the bundle of His. Permanent pacing is often indicated in these patients because the Mobitz type II AV block may later progress to complete heart block.

Third-degree AV block is a complete heart block, where the SA node and AV node fire at independent rates. The atrial rhythm is faster than the ventricular escape rhythm. Permanent pacing is indicated in these patients, especially when associated with symptoms such as exercise intolerance or syncope.

CASE CORRELATION

- See also Case 8 (Atrial Fibrillation/Mitral Stenosis) and Case 36 (Transient Ischemic Attack).

COMPREHENSION QUESTIONS

9.1 An 18-year-old woman is brought to the emergency center because she fainted at a rock concert. She apparently recovered spontaneously, did not exhibit any seizure activity, and has no medical history. Her heart rate is 90 bpm, and blood pressure is 110/70 mm Hg. The neurologic examination is normal. A pregnancy test is negative, and an ECG shows normal sinus rhythm. Which of the following is the most appropriate management?

A. Admit to hospital for cardiac evaluation.

B. Obtain an outpatient echocardiogram.

C. Use 24-hour Holter monitor.

D. Reassure the patient and discharge home.

9.2 A 67-year-old woman has diabetes and mild hypertension. She is noted to have diabetic retinopathy, and she states that she cannot feel her legs. She has recurrent episodes of light-headedness when she gets up in the morning. She comes in now because she fainted this morning. Which of the following is the most likely cause of her syncope?

A. Carotid sinus hypersensitivity
B. Pulmonary embolism
C. Autonomic neuropathy
D. Critical aortic stenosis

9.3 A 74-year-old man with no prior medical problems faints while shaving. He has a quick recovery and has no neurologic deficits. His blood sugar level is normal, and an ECG shows a normal sinus rhythm. Which of the following is the most useful diagnostic test of his probable condition?

A. Carotid massage
B. Echocardiogram
C. Computed tomographic scan of the head
D. Serial cardiac enzymes

9.4 A 49-year-old man is admitted to the intensive care unit with a diagnosis of an inferior myocardial infarction. His heart rate is 35 bpm, and blood pressure is 90/50 mm Hg. His ECG shows a Mobitz type I heart block. Which of the following is the best next step?

A. Atropine
B. Transvenous pacer
C. Lidocaine
D. Observation

ANSWERS

9.1 **D.** A young patient without a medical history, without seizure activity, and with a history suggestive of emotionally mediated vasovagal syncope has an excellent prognosis. The other answer choices for further evaluation or hospitalization are not needed in this patient.

9.2 **C.** This diabetic patient has evidence of microvascular disease, including peripheral neuropathy, and likely has autonomic dysfunction. Although this is the most likely etiology, one must be concerned about a possible cardiac issue since the patient has numerous cardiovascular risk factors; an evaluation should include an ECG. Answer A (carotid sinus hypersensitivity) is associated with fainting when wearing a tight collar or turning one's head. Answer B (pulmonary embolism) is associated with shortness of breath and chest pain. Answer D (critical aortic stenosis) is associated with angina and a harsh systolic ejection murmur.

9.3 **A.** This patient likely has carotid hypersensitivity; thus, careful carotid massage (after auscultation to ensure no bruits are present) may be performed in an attempt to reproduce the symptoms. Carotid massage in an older patient should be used with caution because it may lead to cerebral ischemia, plaque embolization, or atrial fibrillation. Computed tomography of the head (answer C) would be appropriate if a stroke were suspected, and serial cardiac enzymes (answer D) would be indicated if angina were present or to rule out a myocardial infarction.

9.4 **A.** This patient's bradycardia is severe, probably a result of the inferior myocardial infarction. Atropine is the agent of choice in this situation. Mobitz type I block has a good prognosis (vs complete heart block), so transvenous pacing (answer B) is not usually required. Pacing would be required for a Mobitz type II block or complete heart block. Answer C (lidocaine) is usually used for ventricular ectopy such as frequent premature ventricular contractions. Answer D (observation) may be considered in a patient with mild bradycardia (such as a heart rate of 50-60 bpm) and normal BP.

CLINICAL PEARLS

- Vasovagal syncope is the most common cause of syncope in healthy young people. It often has a precipitating event, prodromal symptoms, and an excellent prognosis.
- Carotid sinus hypersensitivity causes bradyarrhythmias in older patients with pressure over the carotid bulb and sometimes requires a pacemaker.
- Syncope caused by cardiac outflow obstruction, such as aortic stenosis, occurs during or after exertion.
- Syncope is a very common problem, affecting nearly one-third of the adult population at some point, but a specific cause is identified in less than half of cases.
- Permanent pacing usually is indicated for symptomatic bradyarrhythmias (eg, sick sinus syndrome), Mobitz II AV block, or third-degree heart block.

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CASE 10

A 27-year-old woman presents to the emergency center complaining of retrosternal chest pain for the past 2 days. The pain is constant, unrelated to exertion, worsened by deep breaths, and relieved by sitting up and leaning forward. She denies any shortness of breath, nausea, or diaphoresis.

On examination, her temperature is 99.4 °F, heart rate is 104 beats per minute (bpm), and blood pressure is 118/72 mm Hg. She is sitting forward on the stretcher taking shallow breaths. Her conjunctivae are clear, and her oral mucosa is pink and notable for two aphthous ulcers. Her neck veins are not distended; her chest is clear to auscultation and is mildly tender to palpation. Her heart rhythm is regular, with a harsh scratchy sound over the apex heard during systole and diastole. Her abdominal examination is unremarkable, and her extremities show warmth and swelling of the proximal interphalangeal (PIP) joints of both hands.

Laboratory studies are significant for a white blood cell count of 2100 cells/mm^3, hemoglobin concentration 10.4 g/dL with mean corpuscular volume 94 fL, and platelet count 78,000/mm^3. Her blood urea nitrogen and creatinine levels are normal. Urinalysis shows 10 to 20 white blood cells and 5 to 10 red blood cells per high-powered field. A urine drug screen is negative.

Chest x-ray is read as normal, with a normal cardiac silhouette and no pulmonary infiltrates or effusions. The electrocardiogram (ECG) is shown in Figure 10–1.

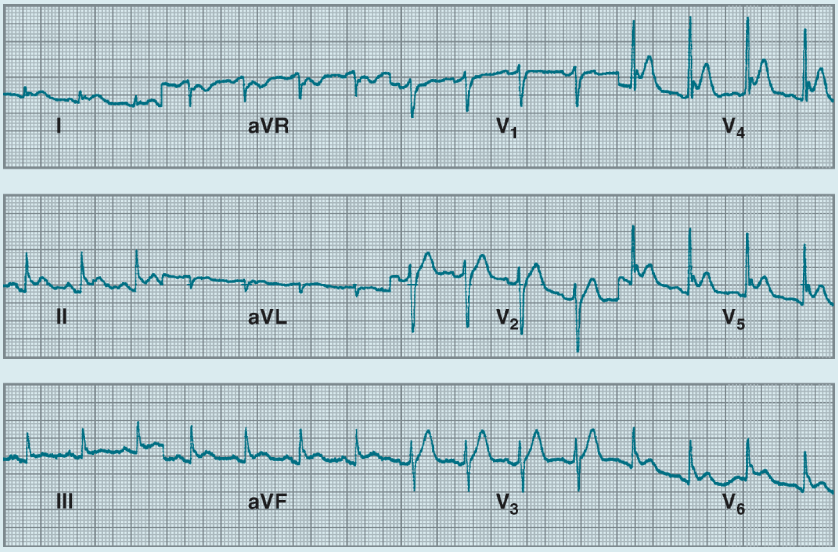


Figure 10–1. Electrocardiogram. (Reproduced with permission, from Stead LG, Stead SM, Kaufman MS. *First Aid for the Medicine Clerkship*, 2nd ed. 2006. Copyright © McGraw Hill LLC. All rights reserved.)

- What is the most likely diagnosis?
- What is the best next step?

ANSWERS TO CASE 10:
Acute Pericarditis Caused by Systemic Lupus Erythematosus

Summary: A 27-year-old woman presents with

- Nonexertional pleuritic chest pain relieved by sitting forward
- Pericardial friction rub, finger arthritis, and aphthous ulcers on examination
- Changes in the ECG (classically diffuse ST elevations and PR depressions) consistent with acute pericarditis
- No radiographic evidence of a large pericardial effusion
- No clinical signs of cardiac tamponade (water bottle sign, quiet heart sounds, jugular venous distension, etc)
- Pancytopenia, pyuria, and microhematuria

Most likely diagnosis: Acute pericarditis due to systemic lupus erythematosus (SLE).

Best next step: Echocardiogram to assess for effusion and tamponade.

ANALYSIS

Objectives

1. Recognize the clinical and ECG features of pericarditis and be able to recognize a pericardial friction rub. (EPA 1, 2, 3)
2. List the causes of pericarditis and its treatment. (EPA 4, 12)
3. List the diagnostic criteria for SLE. (EPA 3, 12)
4. Describe the major complications of SLE and its treatment. (EPA 12)

Considerations

In patients with chest pain, one of the primary diagnostic considerations is always myocardial ischemia or myocardial infarction (MI). This is particularly true when the ECG is abnormal with changes that may represent myocardial injury, such as ST-segment elevation. However, other conditions may produce ST-segment elevation, such as acute pericarditis. ECG findings can help distinguish between these two diagnoses. Pericarditis may have diffuse ST elevations and PR depressions, whereas STEMI (ST-segment elevation myocardial infarction) typically will demonstrate ST elevation consistent with an anatomic area of infarction (eg, anterolateral, inferior, posterior, or lateral). The pleuritic nature of the pain and the relief by leaning forward are clues to the diagnosis. Of the multiple possible etiologies, the case discloses some features suggestive of SLE.

APPROACH TO:
Acute Pericarditis and Systemic Lupus Erythematosus

DEFINITIONS

ACUTE PERICARDITIS: An inflammation of the pericardial sac surrounding the heart.

PERICARDIAL FRICTION RUB: Harsh, high-pitched, scratchy sound with variable intensity, usually best heard at the left sternal border by auscultation.

CLINICAL APPROACH TO ACUTE PERICARDITIS

Pathophysiology

Acute pericarditis can result from a multitude of disease processes, but the most common causes are listed in Table 10–1.

Clinical Presentation

There is a wide spectrum of clinical presentations for acute pericarditis, ranging from subclinical inflammation, to the classic presentation of acute pericarditis with chest pain, to chronic inflammation, which may persist for weeks to months. Most patients with acute pericarditis seek medical attention because of **chest pain.** The classic description is a sudden onset of retrosternal chest pain, which worsens on inspiration and with recumbence and often radiates to the trapezius ridge; the pain is **improved by sitting and leaning forward.** Other clinical features vary according to the cause of the pericarditis, but most patients are thought to have viral infection and often present with low-grade fever, malaise, or upper respiratory illness symptoms.

A **pericardial friction rub** is pathognomonic and virtually 100% specific for acute pericarditis. The sensitivity of this sign varies, however, because friction rubs may soften and return. Classically, a rub is a harsh, high-pitched, scratchy sound with variable intensity, usually best heard at the left sternal border. It can have one, two, or three components: presystolic (correlating with atrial systole), systolic, and diastolic. The large majority of rubs are triphasic (all three components) or biphasic,

Table 10–1 • COMMON CAUSES OF ACUTE PERICARDITIS

Diseases of contiguous structures, eg, during transmural myocardial infarction
Hypersensitivity/immunologic reactions, eg, Dressler syndrome
Idiopathic pericarditis: specific diagnosis unidentified, presumably either viral or autoimmune and requires no specific management
Infectious: viral, bacterial, tuberculous, parasitic
Metabolic disease, eg, uremia, Gaucher disease
Neoplasms: usually thoracic malignancies such as breast, lung, or lymphoma
Trauma: penetrating or nonpenetrating chest injury
Vasculitis: autoimmune diseases, postradiation therapy

Data from Spodick DH. Acute pericarditis: current concepts and practice. JAMA. *2003;289:1150-1153.*

Table 10–2 • PERICARDITIS VERSUS MYOCARDIAL INFARCTION

ECG Findings	Acute Pericarditis	Acute MI
ST-segment elevation	Diffuse: in limb leads as well as V_2-V_6	Regional (vascular territory), eg, inferior, anterior, or lateral
PR-segment depression	Present	Usually absent
Reciprocal ST-segment depression	Absent	Typical, eg, ST-segment depression inferiorly with anterior ischemia (ST-segment elevation)
QRS-complex changes	Absent	Loss of R-wave amplitude and development of Q waves

having a systolic and either an early or a late diastolic component. In these cases, it usually is easy to diagnose the pericardial friction rub and acute pericarditis. When the rub is monophasic (just a systolic component), it often is difficult to distinguish a pericardial friction rub from a harsh murmur, making bedside diagnosis difficult and uncertain. In these cases, one should look for ECG evidence of pericarditis (Table 10–2) and perform serial examinations because the rub may vary with time.

The classic ECG findings in **acute pericarditis** include **diffuse ST-segment elevation** in association with PR-segment depression, as seen in this patient. The opposite findings (PR-segment elevation and ST-segment depression) are often seen in leads aVR and V_1. Acute pericarditis may be confused with acute MI due to the presentation with chest pain and ST-segment elevation on ECG. This is potentially a serious problem because if a patient is treated with **thrombolytics** for infarction, the patient may develop **pericardial hemorrhage and cardiac tamponade.** Several clinical features can help to differentiate the two conditions: Acute ischemia is more likely to have a gradual onset of pain with a crescendo pattern, more likely to present with a heavy pressure or squeezing sensation (as opposed to the sharp pain of pericarditis), typically does not vary with respiration, and is relieved with nitrates (whereas the pain of pericarditis is not). In addition, several ECG features can help to make the distinction (Table 10–2). Moreover, if the ECG reveals arrhythmias or conduction abnormalities, the condition is much more likely to represent ischemia rather than pericarditis.

Treatment

Most patients with acute viral or idiopathic pericarditis have excellent prognoses. Treatment is mainly symptomatic, with aspirin or another nonsteroidal anti-inflammatory drug (NSAID), such as indomethacin, for relief of chest pain. Colchicine or corticosteroids may be used for refractory symptoms or comorbid conditions. In most patients, symptoms typically resolve within days to 2 to 3 weeks. Any form of pericarditis can cause pericardial effusion and bleeding; however, the most serious consequence would be cardiac tamponade. It is a common misconception that a pericardial friction rub cannot coexist with an effusion (both are very common in uremic pericarditis). Therefore, it is important to monitor these patients for signs of developing hemodynamic compromise resulting from cardiac tamponade.

CLINICAL APPROACH TO SYSTEMIC LUPUS ERYTHEMATOSUS

Pathophysiology

Our patient is very young and has no significant previous medical history. The presence of symmetric arthritis and laboratory findings suggest a systemic disease, such as SLE, as the cause of her pericarditis. SLE is a systemic inflammatory disease that mainly affects women. It is characterized by autoimmune multiorgan involvement, such as pericarditis, nephritis, pleuritis, arthritis, and skin disorders. To diagnose SLE, the patient must meet 4 of the 11 criteria listed in Table 10–3 (96% sensitive and 96% specific). The need of 4 out 11 criteria is imperative for the diagnosis of SLE among patients included in clinical studies; however, it is noteworthy that patients can actually be diagnosed with SLE even with fewer criteria in the right clinical context.

Our patient has serositis (pericarditis), oral ulcers, hematologic disorders (leukopenia, lymphopenia, and thrombocytopenia), arthritis, and renal involvement (hematuria)—she clearly meets the clinical criteria for SLE. Although the patient in the scenario, like most patients with SLE, sought medical attention because of the pain of arthritis or serositis, both these problems are generally manageable or self-limited. The arthritis is generally nonerosive and nondeforming, and the serositis usually resolves spontaneously without sequelae.

Complications

The major complication of SLE usually is related to renal involvement, which can cause hypertension, chronic renal failure, nephrotic syndrome, or end-stage renal disease. In the past, renal disease was the most common cause of death of SLE patients; however, currently lupus neprhritis can be treated with powerful immunosuppressants, such as high-dose corticosteroids and mycophenolate or cyclophosphamide. Other serious complications of lupus include central nervous system (CNS) disorders, which are highly variable and unpredictable and can include seizures, psychosis, stroke syndromes, and cranial neuropathies. In addition to renal failure and CNS involvement, the most common causes of death in SLE patients are infection (often related to the immunosuppression used to treat the disease) and vascular disease, for example, MI.

Table 10–3 • DIAGNOSTIC CRITERIA FOR SLE

Malar rash: fixed erythema, flat or raised over the malar area, that tends to spare nasolabial folds
Discoid rash: erythematous raised patches with adherent keratotic scaling and follicular plugging
Photosensitivity: skin rash as a result of exposure to sunlight
Oral or vaginal ulcers: usually painless
Arthritis: nonerosive, involving two or more peripheral joints with tenderness, swelling, and effusion
Serositis: usually pleuritis or pericarditis
Renal involvement: persistent proteinuria or cellular casts
Neurologic disorder: seizure or psychosis
Hematologic disorder: hemolytic anemia or leukopenia (< 4000/mm^3) on two or more occasions, or lymphopenia (< 1500/mm^3) on two or more occasions, or thrombocytopenia (< 100,000/mm^3)
Immunologic disorder: positive anti-double-stranded DNA, anti-Smith Ab, antiphospholipid Ab
Antinuclear antibody (ANA): positive ANA in absence of drugs known to induce ANA

Abbreviation: Ab, antibody; SLE, systemic lupus erythematosus.

CASE CORRELATION

- See also Case 3 (Acute Coronary Syndrome), Case 5 (Aortic Dissection, Marfan Syndrome), and Case 20 (Peptic Ulcer Disease).

COMPREHENSION QUESTIONS

10.1 A 68-year-old man with a history of end-stage renal disease is admitted to the hospital for chest pain. On examination, a pericardial friction rub is noted. His ECG shows diffuse ST-segment elevation. Which of the following is the best definitive treatment?

A. Nonsteroidal anti-inflammatory drugs
B. Dialysis
C. Steroids
D. Sodium polystyrene sulfonate (Kayexalate)

10.2 The patient described in Question 10.1 is hospitalized, but there is a delay in initiating treatment. You are called to the bedside because he has become hypotensive with a systolic blood pressure of 85/68 mm Hg, a heart rate of 122 bpm, and pulsus paradoxus. A repeat ECG is unchanged from admission. Which of the following is the most appropriate immediate intervention?

A. Draw blood cultures and initiate broad-spectrum antibiotics for suspected sepsis.
B. Give intravenous furosemide for fluid overload.
C. Perform echocardiographic-guided pericardiocentesis.
D. Perform percutaneous coronary intervention for acute MI.

10.3 A 25-year-old woman complains of pain in her PIP and metacarpophalangeal joints and reports a recent positive antinuclear antibody (ANA) laboratory test. Which of the following clinical features would **not** be consistent with a diagnosis of SLE?

A. Pleural effusion
B. Malar rash
C. Sclerodactyly
D. Urinary sediment with red blood cell casts

ANSWERS

10.1 **B.** Uremic pericarditis is considered a medical emergency and an indication for urgent dialysis. While NSAIDs (answer A) can help with pain, they do not attack the pathophysiologic underlying process. Steroids (answer C) do not offer benefit in this setting. Resins like sodium polystyrene sulfonate (answer D) are beneficial in the treatment of hyperkalemia.

10.2 **C.** The clinical picture suggests the patient has developed pericardial tamponade, which may be life threatening and often requires urgent pericardiocentesis. The question stem does not suggest sepsis or an MI, making answers A and D incorrect. Furosemide (answer B) can worsen the picture by decreasing the intravascular compartment further and is therefore contraindicated.

10.3 **C.** Sclerodactyly, which is thickened and tight skin of the fingers and toes, is a classic feature of patients with scleroderma (who may also have a positive ANA test but will likely have either anticentromere or antitopoisomerase antibodies), but it is not seen in SLE. Malar rash (answer B), serositis, and glomerulonephritis are typical of SLE but are not seen in scleroderma. The other answer choices such as pleural effusion (answer A) and red blood cell casts (answer D) would suggest lupus nephritis are often found in SLE.

CLINICAL PEARLS

- Acute pericarditis is characterized by pleuritic chest pain, a pericardial friction rub, and ECG findings of diffuse ST-segment elevation and PR-segment depression.
- Pericardial friction rub does not exclude a pericardial effusion; patients with acute pericarditis should be monitored for development of effusion and tamponade.
- Treatment of pericarditis is directed at the underlying cause; for example, uremic pericarditis requires urgent dialysis. For viral or inflammatory causes, treatment is NSAIDs or corticosteroids for refractory cases.
- Systemic lupus erythematosus can be diagnosed if a patient has four of the following features: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disease, neurologic manifestations, hematologic cytopenias, immunologic abnormalities (eg, false-positive Venereal Disease Research Laboratory [VDRL] test), or positive ANA.
- The major morbidity and mortality of SLE result from renal disease, CNS involvement, or infection.

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CASE 11

A 42-year-old man presents complaining of 2 days of worsening chest pain and dyspnea. Six weeks ago, he was diagnosed with non-Hodgkin lymphoma with lymphadenopathy of the mediastinum and was treated with mediastinal radiation therapy. His most recent treatment was 1 week ago. He has no other medical or surgical history and takes no medications. His chest pain is constant and unrelated to activity. He becomes short of breath with minimal exertion. He is afebrile; heart rate is 115 beats per minute (bpm) with a thready pulse, respiratory rate is 22 breaths per minute, and blood pressure is 108/86 mm Hg. Systolic blood pressure drops to 86 mm Hg on inspiration. He appears uncomfortable and is diaphoretic. His jugular veins are distended to the angle of the jaw, and his chest is clear to auscultation. He is tachycardic, his heart sounds are faint, and no extra sounds are appreciated. The chest x-ray is shown in Figure 11–1.

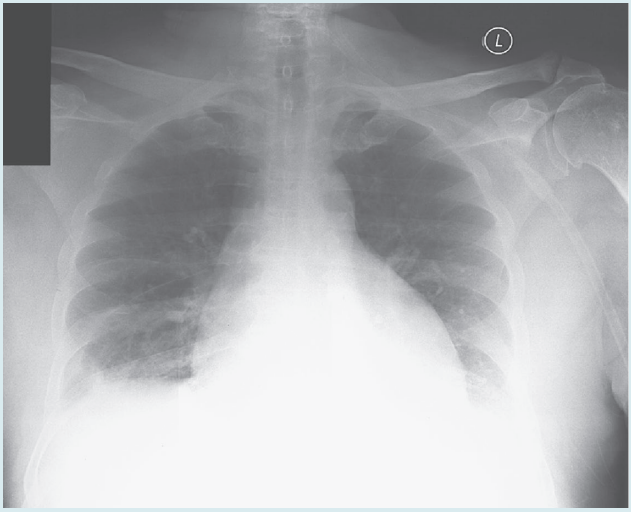


Figure 11–1. Chest x-ray. (Courtesy of Dr. Jorge Albin.)

- What is the most likely diagnosis?
- What is your next step in therapy?

ANSWERS TO CASE 11:
Pericardial Effusion/Tamponade Caused by Malignancy

Summary: A 42-year-old man presents with

- A thoracic malignancy and history of radiotherapy to the mediastinum
- Complaints of chest pain and dyspnea
- Jugular venous distention, distant cardiac sounds, and pulsus paradoxus on examination
- Cardiac enlargement on chest x-ray (which could represent cardiomegaly or pericardial effusion)

Most likely diagnosis: Pericardial effusion causing cardiac tamponade.

Next therapeutic step: Urgent pericardiocentesis or surgical pericardial window.

ANALYSIS

Objectives

1. Recognize pericardial tamponade and pulsus paradoxus. (EPA 1, 10)
2. Identify the features of cardiac tamponade, constrictive pericarditis, and restrictive cardiomyopathy and how to distinguish among them. (EPA 1, 3)
3. Understand the treatment of each of these conditions. (EPA 4, 10)
4. Describe the potential cardiac complications of thoracic malignancies and radiation therapy. (EPA 4, 12)

Considerations

A patient with thoracic malignancy and history of radiation therapy, like this patient, is at risk for diseases of the pericardium and myocardium. The jugular venous distention, distant heart sounds, and pulsus paradoxus all are suggestive of cardiac tamponade. The major diagnostic considerations in this case, each with very different treatment, are pericardial effusion causing cardiac tamponade, constrictive pericarditis, and restrictive cardiomyopathy. All of these conditions can impede diastolic filling of the heart and lead to cardiovascular compromise. Urgent differentiation among these conditions is required because the treatment is very different, and the consequences of mistreating these diseases can be immediately fatal. Clinically, the patient's fall in systolic blood pressure with inspiration (pulsus paradoxus) is suggestive of cardiac tamponade, which would be treated with evacuation of the pericardial fluid via pericardiocentesis.

APPROACH TO:
Cardiac Tamponade

DEFINITIONS

CARDIAC TAMPONADE: Increased pressure within the pericardial space caused by an accumulating effusion, which compresses the heart and impedes diastolic filling.

PERICARDIAL EFFUSION: Fluid that fills the pericardial space, which may be due to infection, hemorrhage, or malignancy. A rapidly accumulating effusion may lead to cardiac compromise.

CLINICAL APPROACH

Pathophysiology

Cardiac tamponade refers to increased pressure within the pericardial space caused by an accumulating effusion, which compresses the heart and impedes diastolic filling. Because the heart can only pump out during systole what it receives during diastole, severe restriction of diastolic filling leads to a marked decrease in cardiac output, culminating in hypotension, cardiovascular collapse, and death. If pericardial fluid accumulates slowly, the sac may dilate and hold up to 2000 mL (producing notable cardiomegaly on chest x-ray) before causing diastolic impairment. If the fluid accumulates rapidly, as in a hemopericardium caused by trauma or surgery, as little as 200 mL can produce tamponade.

Clinical Presentation

The classic description of **Beck's triad (hypotension, elevated jugular venous pressure, and small, quiet heart)** is a description of **acute tamponade** with rapid accumulation of fluid, as in the cases of cardiac trauma or ventricular rupture. If the fluid accumulates slowly, the clinical picture may look more like heart failure, with cardiomegaly on chest x-ray (although there should be no pulmonary edema), dyspnea, elevated jugular pressure, hepatomegaly, and peripheral edema. A high index of suspicion is required: Cardiac tamponade should be considered in any patient with hypotension and elevated jugular venous pressure.

The **most important physical sign** to look for **in cardiac tamponade** is **pulsus paradoxus**. This refers to a **drop in systolic blood pressure of more than 10 mm Hg during inspiration.** Although called "paradoxical," this drop in systolic blood pressure is not contrary to the normal physiologic variation with respiration; it is an exaggeration of the normal small drop in systolic pressure during inspiration. Although not a specific sign of tamponade (ie, it is often seen in patients with disturbed intrathoracic pressures during respiration, eg, those with obstructive lung disease), pulsus paradoxus is fairly sensitive for hemodynamically significant tamponade.

To test for this, one must use a manual blood pressure cuff that is inflated above systolic pressure and deflated very slowly until the first Korotkoff sound is heard during expiration and then, finally, during both phases of respiration.

The difference between these two pressure readings is the pulsus paradoxus. When the pulsus paradoxus is severe, it may be detected by palpation as a diminution or disappearance of peripheral pulses during inspiration.

Treatment

Acute treatment of cardiac tamponade consists of relief of the pericardial pressure, by either percutaneous pericardiocentesis (possibly echocardiographically guided) or a surgical approach. The choice between percutaneous versus surgical effusion relief is dependent on clinical and institutional expertise. Resection of the diseased pericardium is the definitive treatment of constrictive pericarditis. There is no effective treatment for restrictive cardiomyopathy. Any patient with evidence of cardiovascular compromise (ie, cardiac tamponade) should have immediate drainage of effusion in the pericardium. If there is no evidence of hemodynamic collapse, then urgent drainage is not necessary. Patients with large effusions who are hemodynamically stable may require close monitoring, serial echocardiography, and careful volume status regulation with management directed to treat the underlying cause of the effusion. Beyond its described therapeutic benefit, pericardiocentesis can offer diagnostic value when the presumed etiology cannot be established.

Complications

Constrictive pericarditis is a complication of a prior episode of acute or chronic fibrinous pericarditis. The inflammation with resultant granulation tissue forms a **thickened fibrotic adherent sac** that gradually contracts, encasing the heart and **impairing diastolic filling.** In the past, tuberculosis was the most common cause of this problem, but now that is a rare cause in the United States. Currently, this is **most commonly caused by radiation therapy, cardiac surgery**, or any cause of acute pericarditis, such as **viral infection, uremia, or malignancy.** The pathophysiology of constrictive pericarditis is similar to that of cardiac tamponade in the restricted ability of the ventricles to fill during diastole because of the thickened noncompliant pericardium.

Because the process is **chronic**, patients with **constrictive pericarditis** generally do not present with acute hemodynamic collapse but rather with **chronic and slowly progressive weakness, fatigue, and exertional dyspnea.** Patients commonly have what appears to be right-sided heart failure, that is, chronic lower extremity edema, hepatomegaly, and ascites. Like patients with tamponade, they have elevated jugular venous pressures, but **pulsus paradoxus usually is absent.** Examination of neck veins shows an increase in jugular venous pressure during inspiration, termed the **Kussmaul sign.** This is easy to see because it is the opposite of the normal fall in pressure as a person inspires. Normally, the negative intrathoracic pressure generated by inspiration increases blood flow into the heart, but because of the severe diastolic restriction, the blood cannot enter the right atrium or ventricle, so it fills the jugular vein. Another physical finding characteristic of constrictive pericarditis is a **pericardial knock**, which is a high-pitched, early diastolic sound occurring just after aortic valve closure. Chest radiography frequently shows cardiomegaly and a calcified pericardium. Table 11–1 compares features of

Table 11–1 • FEATURES OF CARDIAC TAMPONADE, ACUTE PERICARDITIS, RESTRICTIVE CARDIOMYOPATHY, AND CONSTRICTIVE PERICARDITIS

Disease	Pathophysiology	Clinical Features	ECG Findings
Cardiac tamponade	Increased pressure in pericardial space due to effusion, impeding diastolic filling	**Pulsus paradoxus,** hypotension, elevated jugular venous distention, small quiet heart	Low voltage diffusely, electrical alternans
Constrictive pericarditis	Inflammation and granulation tissue forms a thickened fibrotic adherent sac, commonly caused by radiation, viral infection, uremia	Absent pulsus paradoxus, **Kussmaul sign,** pericardial knock, chronic and slow progressive weakness, and exertional dyspnea	Low voltage
Acute pericarditis	Acute inflammation of the parietal pericardium and superficial myocardium	Chest pain, fever, pericardial rub	ST-segment elevation, low voltage diffusely
Restrictive cardiomyopathy	Myocardial fibrosis, hypertrophy, or infiltration leading to impaired diastolic filling	No pulsus paradoxus or Kussmaul sign; progressive exertional dyspnea and dependent edema	

cardiac tamponade, acute pericarditis, restrictive cardiomyopathy, and constrictive pericarditis.

Restrictive cardiomyopathy, like the previous diagnoses, is primarily a problem of impaired diastolic filling, usually with preserved systolic function. This is a relatively uncommon problem in the Western world. The **most common causes are amyloidosis**, an infiltrative disease of the elderly, in which an abnormal fibrillar amyloid protein is deposited in heart muscle, or fibrosis of the myocardium following radiation therapy or open-heart surgery. In **Africa**, restrictive cardiomyopathy is much more common because of a process called **endomyocardial fibrosis**, characterized by fibrosis of the endocardium along with fever and marked eosinophilia, accounting for up to 25% of deaths due to heart disease.

Clinically, it may be very difficult to distinguish restrictive cardiomyopathy from constrictive pericarditis, and various echocardiographic criteria have been proposed to try to distinguish between them. In addition, magnetic resonance imaging (MRI) can be very useful to visualize or exclude the presence of the thickened pericardium typical of constrictive pericarditis and absence in restrictive cardiomyopathy. **Kussmaul sign** can be seen in both restrictive cardiomyopathy and constrictive pericarditis. Nevertheless, it may be necessary to obtain an **endomyocardial biopsy** to make the diagnosis. Differentiation between the two is essential because constrictive pericarditis is a potentially curable disease, whereas very little effective therapy is available for either the underlying conditions or the cardiac failure of restrictive cardiomyopathy.

CASE CORRELATION

- See also Case 3 (Acute Coronary Syndrome), Case 4 (Heart Failure Due to Critical Aortic Stenosis), Case 8 (Atrial Fibrillation/Mitral Stenosis), and Case 10 (Acute Pericarditis Caused by Systemic Lupus Erythematosus).

COMPREHENSION QUESTIONS

11.1 A 35-year-old woman is being seen for shortness of breath of 2 weeks' duration. She denies a history of asthma, smoking, or cough. On examination, her heart rate is 100 bpm, blood pressure is 90/60 mm Hg, and respiratory rate is 20 breaths per min. Her jugular venous pulse was noted at rest to be 2 cm above the sternal notch, increasing to 6 cm above the sternal notch with deep inspiration. Which of the following conditions does she most likely have?

A. Constrictive pericarditis
B. Cardiac tamponade
C. Dilated cardiomyopathy
D. Diabetic ketoacidosis

11.2 A 53-year-old man has been undergoing dialysis for end-stage renal disease due to long-standing diabetes mellitus. He is being seen in the emergency center for progressive dyspnea on exertion. On examination, he is found to have a heart rate of 105 bpm, blood pressure of 90/60 mm Hg, and respiratory rate of 20 breaths per minute. After examination, the clinician suspects cardiac tamponade. Which of the following is the most sensitive finding in this condition?

A. Disappearance of radial pulse during inspiration
B. Drop in systolic blood pressure more than 10 mm Hg during inspiration
C. Rise in heart rate more than 20 bpm during inspiration
D. Distant heart sounds

11.3 A 35-year-old man is brought into the emergency department after a knife injury to the chest. He is noted to be hypotensive with a blood pressure of 80/40 mm Hg and an elevated jugular venous pulse. Bedside ultrasound examination confirms a large cardiac effusion. While awaiting pericardiocentesis, which of the following is the most important intervention for the patient to receive?

A. Diuresis with furosemide
B. Intravenous fluids
C. Nitrates to lower venous congestion
D. Morphine to relieve dyspnea

11.4 Which of the following is most likely to cause restrictive cardiomyopathy?

A. Endomyocardial fibrosis
B. Viral myocarditis
C. Beriberi (thiamine deficiency)
D. Doxorubicin therapy

ANSWERS

11.1 **A.** This patient has shortness of breath and an increase in the jugular venous pulse with deep inspiration, which is called the Kussmaul sign. This increase in neck veins with inspiration is seen with constrictive pericarditis (and restrictive cardiomyopathy) and is due to the impaired diastolic dysfunction and inability of blood to enter the right ventricle. Normally, the jugular venous pulse *decreases* with inspiration since the negative intrathoracic pressure "pulls" the blood into the chest. The other answer choices (B, cardiac tamponade; C, dilated cardiomyopathy; and D, diabetic ketoacidosis) are not associated with Kussmaul sign. Cardiac tamponade is associated with a distended jugular venous pulse at baseline.

11.2 **B.** Cardiac tamponade is caused by an effusion in the pericardial space that does not allow for cardiac filling. This patient likely has a pericardial effusion due to uremia. Pulsus paradoxus is a sensitive yet nonspecific sign for cardiac tamponade. Other clinical features include hypotension, elevated jugular venous distention, and soft heart sounds. Answer A (disappearance of radial pulse during inspiration) is possible in severe tamponade but not common. Answer C (rise in heart rate more than 20 bpm during inspiration) is not seen in tamponade. Answer D (distant heart sounds) is found in pericardial effusion with or without tamponade.

11.3 **B.** Patients with cardiac tamponade are preload dependent; therefore, diuretics (answer A), nitrates (answer C), or morphine (answer D) may cause them to become hypotensive. In contrast, volume expansion with intravenous fluids helps maintain intravascular volume and cardiac output.

11.4 **A.** Endomyocardial fibrosis is an etiology of restrictive cardiomyopathy. It is common in developing countries and is associated with eosinophilia. The other disease processes mentioned (answer B, viral myocarditis; answer C, beriberi; and answer D, doxorubicin therapy) are causes of dilated cardiomyopathy.

CLINICAL PEARLS

- Elevated jugular venous pressure and pulsus paradoxus are features of cardiac tamponade.
- Kussmaul sign and right-sided heart failure are features of constrictive cardiomyopathy, but pulsus paradoxus is not.
- Cardiac tamponade requires urgent treatment by pericardiocentesis or a pericardial drainage.
- Constrictive pericarditis may show calcifications of the pericardium on chest x-ray or thickened pericardium on echocardiography. Definitive therapy is resection of the pericardium.
- Restrictive cardiomyopathy is most often caused by amyloidosis or radiation therapy in the western hemisphere. There is no effective therapy.

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CASE 12

A 28-year-old man comes to the emergency center complaining of 6 days of fever with shaking chills. Over the past 2 days, he has also developed a productive cough with greenish sputum, occasionally streaked with blood. He reports no dyspnea, but sometimes he experiences chest pain with deep inspiration. He does not have a headache, abdominal pain, urinary symptoms, vomiting, or diarrhea. He has no significant past medical history. He smokes cigarettes and marijuana regularly, drinks several beers daily, and denies intravenous drug use.

On examination, his temperature is 102.5 °F, heart rate is 109 beats per minute (bpm), blood pressure is 128/76 mm Hg, and respiratory rate is 23 breaths per minute. He is alert and talkative. He has no oral lesions, and fundoscopic examination reveals no abnormalities. His jugular veins show prominent V waves. He is tachycardic with a regular rhythm and has a harsh holosystolic murmur at the left lower sternal border that becomes louder with inspiration. Chest examination reveals inspiratory rales bilaterally. He has linear streaks of induration, hyperpigmentation, and a few small nodules overlying the superficial veins on either forearm, but no erythema, warmth, or tenderness.

Laboratory examination is significant for an elevated white blood cell count of 17,500/mm^3, with 84% polymorphonuclear cells, 7% band forms, and 9% lymphocytes; a hemoglobin concentration of 14 g/dL; hematocrit of 42%; and platelet count of 189,000/mm^3. Liver function tests and urinalysis are normal. A chest radiograph shows multiple peripheral, ill-defined nodules, some with cavitation.

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 12:
Endocarditis (Tricuspid)/Septic Pulmonary Emboli

Summary: A 28-year-old man presents with

- Complaints of shaking chills, fever, and a productive cough
- Denial of intravenous drug use
- A new holosystolic murmur at the left lower sternal border that increases with inspiration
- Linear streaks of induration on both forearms
- Chest radiograph showing multiple ill-defined nodules

Most likely diagnosis: Infective endocarditis involving the tricuspid valve, with probable septic pulmonary emboli.

Next step: Obtain serial blood cultures and institute empiric broad-spectrum antibiotics.

ANALYSIS

Objectives

1. Describe the differences in clinical presentation between acute and subacute endocarditis and between left-sided versus right-sided endocarditis. (EPA 1, 2)
2. Identify the most common organisms that cause endocarditis, including "culture-negative" endocarditis. (EPA 2, 3, 4)
3. Review the diagnostic approach to infective endocarditis, including the indications for valve replacement. (EPA 4)
4. Understand the complications of endocarditis, which include valvular and embolic sequelae. (EPA 4, 10)
5. Discuss management principles for infectious endocarditis and implications for antibiotic and anticoagulant use. (EPA 4, 12)

Considerations

Although this patient denied intravenous drug use, the track marks on the forearms are very suspicious for intravenous drug abuse. This type of addiction carries a social stigma, which is the usual reason for patients not to disclose it. A polite, nonjudgmental approach makes patients more open to discuss this medical problem. This patient has fever, a new heart murmur very typical of tricuspid regurgitation, and a chest radiograph suggestive of multiple septic pulmonary emboli. Serial blood cultures, ideally obtained before antibiotics are started, are essential to establish the diagnosis of infective endocarditis. The rapidity with which antibiotics are started depends on the clinical presentation of the patient: A septic, critically ill

patient needs antibiotics immediately, whereas a patient with a subacute presentation can wait many hours while cultures are obtained.

APPROACH TO: Endocarditis

DEFINITIONS

D-DIMERS: Protein fragments present in the blood after a blood clot gets degraded during fibrinolysis, used for suspicion of deep vein thrombosis, pulmonary embolism, or disseminated intravascular coagulation.

INFECTIOUS ENDOCARDITIS: A microbial inflammation of the endocardium, usually involving the heart valves.

JANEWAY LESIONS: Painless hemorrhagic macules on the palms and soles thought to be caused by **septic emboli**, resulting in microabscesses.

LOW-MOLECULAR-WEIGHT HEPARIN: A class of anticoagulants that works by activating antithrombin, which decreases factor Xa in the coagulation cascade, preventing the formation of a clot.

OSLER NODES: Painful, palpable, erythematous lesions most often involving the pads of the fingers and toes, representing **vasculitic** lesions caused by **immune complexes**.

ROTH SPOTS: Hemorrhagic retinal lesions with white centers thought to be an immune complex–mediated vasculitis. While this term is widely accepted, the description of these lesions should actually be attributed not to Roth, but to Litten.

CLINICAL APPROACH

Pathophysiology and Clinical Presentation

The clinical presentation of infectious endocarditis varies between patients depending on which valves are involved (left sided vs right sided), as well as the virulence of the organism. Highly virulent species, such as *Staphylococcus aureus*, produce a rapidly progressive endocarditis. Conversely, less virulent organisms, such as *Streptococcus viridans* or *mutans*, produce a more subacute endocarditis, which may evolve over weeks. **Fever is present in 95% of all cases**. For **acute endocarditis**, patients often present with high fever, acute valvular regurgitation, and embolic phenomena (eg, to the extremities or to the brain, causing stroke). **Subacute endocarditis** is more often associated with constitutional symptoms such as anorexia, weight loss, night sweats, and findings attributable to immune complex deposition and vasculitis; these include petechiae, splenomegaly, and glomerulonephritis. Classic peripheral lesions, such as **Osler nodes**, **Janeway lesions, and Roth spots**, although frequently discussed, are seen in only 20% to 25% of cases. **Splinter hemorrhages** under the nails may also be seen, but this finding is very nonspecific. A common mnemonic

used to remember the clinical features of bacterial endocarditis is "FROM JANE," which stands for fever, Roth spots, Osler nodes, murmur, Janeway lesions, anemia, nail bed hemorrhage, and emboli.

Right-sided endocarditis usually involves the **tricuspid** valve, causing **pulmonary** emboli, rather than involving the systemic circulation. Accordingly, patients develop pleuritic chest pain, purulent sputum, or hemoptysis, and radiographs may show multiple peripheral nodular lesions, often with cavitation. The murmur of tricuspid regurgitation may not be present, especially early in the illness.

In all cases of endocarditis, the critical finding is bacteremia, which usually is sustained. The initiating event is a transient bacteremia, which may be a result of mucosal injury, **such as a dental extraction**, or a complication from the use of intravascular catheters. Bacteria are then able to seed valvular endothelium. Previously damaged, abnormal, or prosthetic valves form vegetations, which are composed of platelets and fibrin and are relatively avascular sites where bacteria may grow protected from immune attack.

An uncommon situation in which routine cultures fail to grow is most likely a result of prior **antibiotic** treatment, **fungal** infection (fungi other than *Candida* spp often require special culture media), or **fastidious** organisms. These organisms can include *Abiotrophia* spp, *Bartonella* spp, *Coxiella burnetii, Legionella* spp, *Chlamydia*, and the **HACEK organisms** (*Haemophilus aphrophilus/paraphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*).

Serial blood cultures are the most important step in the diagnosis of endocarditis. Acutely ill patients should have **three blood cultures** obtained over a **2- to 3-hour** period prior to initiating antibiotics. In **subacute** disease, **three blood cultures over a 24-hour** period maximize the diagnostic yield. If patients are critically ill or hemodynamically unstable, initiation of antibiotic therapy should not be delayed while cultures are obtained. Because sustained bacteremia is the hallmark of infective endocarditis, blood cultures are commonly positive for microorganisms. Table 12–1 lists typical organisms, frequency of infection, and associated conditions.

Clinical features and echocardiography are also used to diagnose cases of infective endocarditis using the highly sensitive and specific **Duke criteria**. Endocarditis is considered to definitely be present if the patient satisfies two major criteria, one major and three minor criteria, or five minor criteria (Table 12–2). It should be noted that transesophageal echocardiography (TEE) rather than transthoracic echocardiography (TTE) is the method of choice in assessing these vegetations due to better image quality and fewer intervening structures. If concerns for systemic embolization arise, D-dimer testing is helpful, with an elevated level indicating significant blood clot formation and breakdown in the body.

Treatment

Antibiotics. Antibiotic treatment is usually begun in the hospital, but because of the prolonged nature of therapy, it is often completed on an outpatient basis once the patient is clinically stable. **Treatment generally lasts 4 to 6 weeks.** If the organism is susceptible to beta-lactams, such as **most *Streptococcus* species, penicillin G** is the

Table 12–1 • ORGANISMS CAUSING ENDOCARDITIS

Organism	Frequency	Associated Conditions
Staphylococcus aureus	30%-40% of native valve infection	Intravascular catheter, intravenous drug use (tricuspid valve endocarditis)
Coagulase-negative staphylococci	30%-35% of early prosthetic valve infection	Neonates, prosthetic valves
Streptococcus viridans	40%-60% of native valve infection	Oral flora, after dental surgery
Enterococci	15%, usually in older patients	Previous genitourinary tract disease or instrumentation
Streptococcus bovis	5%-10%	Elderly patients, often with underlying GI mucosal lesion, eg, adenoma or malignancy
***Candida* spp**	5%-10%	Intravascular catheters, intravenous drug use

agent of choice. For ***S. aureus*, nafcillin** is the drug of choice, often used in combination with **gentamicin**, initially for synergy, to help resolve bacteremia. Therapy for intravenous drug users should be directed against *S. aureus*. **Vancomycin** is used when **methicillin-resistant *S. aureus* or coagulase-negative staphylococci** are present. **Ceftriaxone is the usual therapy for the HACEK** group of organisms. Deciding appropriate therapy for culture-negative endocarditis may be challenging and depends on the clinical situation.

Surgery and Anticoagulation. Table 12–3 summarizes the commonly recognized indications for surgical intervention: valve excision and replacement. For patients with isolated or newly diagnosed infectious endocarditis, routine anticoagulation is not recommended unless there is a preexisting or coexisting condition warranting treatment, such as atrial fibrillation, stroke, deep vein thrombosis, or pulmonary embolism. At this time, if there are no other contraindications to anticoagulation, low-molecular-weight heparin, fondaparinux, or oral factor Xa inhibitors can be used.

Table 12–2 • DUKE CRITERIA FOR DIAGNOSIS OF ENDOCARDITIS

Major criteria

- Isolation of typical organisms (viridans streptococci, *Staphylococcus aureus*, enterococci, *Streptococcus bovis*, or one of the HACEK organisms) from two separate blood cultures or persistently positive blood cultures with other organisms
- Evidence of endocardial involvement: either echocardiographic evidence of endocarditis (eg, oscillating intracardiac mass) or new valvular regurgitation

Minor criteria

- Predisposing valvular lesion or intravenous drug use
- Fever > 100.4 °F (38 °C)
- Vascular phenomena: arterial or septic pulmonary emboli, mycotic aneurysm, Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, positive rheumatoid factor
- Positive blood cultures not meeting major criteria

Table 12–3 • INDICATIONS FOR SURGICAL MANAGEMENT OF ENDOCARDITIS

Intractable congestive heart failure caused by valve dysfunction, > 1 serious systemic embolic episode, or large (> 10 mm) vegetation with high risk for embolism
Uncontrolled infection (eg, positive cultures after 7 d of therapy)
No effective antimicrobial therapy (eg, fungal endocarditis)
Most cases of prosthetic valve endocarditis, especially *Staphylococcus aureus* prosthetic valve infection
Local suppurative complications (eg, myocardial abscess)

Antibiotic Prophylaxis. Patients at high risk for developing infective endocarditis benefit from antibiotic prophylaxis prior to dental procedures. The most recent American Heart Association guidelines (2007) specify individuals the following conditions

- Prosthetic heart valves
- Previous infective endocarditis
- Congenital heart disease (unrepaired cyanotic coronary heart disease [CHD], including palliative shunts and conduits)
- CHD completely repaired with prosthetic material or a device during the first 6 postoperative months
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device
- Valve regurgitation caused by a structurally abnormal valve in cardiac transplant recipients

Amoxicillin is the drug of choice for prophylaxis unless the patient is allergic to penicillin or unable to take medications by mouth. In these situations, alternative antibiotics such as cephalosporins and clindamycin can be used.

Complications

One life-threatening complication of endocarditis is **congestive heart failure**, usually as a consequence of **infection-induced valvular damage.** Other cardiac complications are intracardiac abscesses and conduction disturbances caused by septal involvement by infection. Systemic arterial embolization may lead to splenic or renal infarction, as well as abscess formation. Vegetations may embolize to the coronary circulation, causing a myocardial infarction, or to the brain, causing a cerebral infarction. A **stroke syndrome** in a **febrile** patient should always suggest the possibility of **endocarditis.** Infection of the vasa vasorum may weaken the wall of major arteries and produce mycotic aneurysms, which occur most commonly in the cerebral circulation, sinuses of Valsalva, or abdominal aorta. These aneurysms may leak or rupture, producing sudden intracranial hemorrhage or exsanguination.

CASE CORRELATION

- See also Case 3 (Acute Coronary Syndrome), Case 5 (Aortic Dissection/Marfan Syndrome), and Case 9 (Syncope and Heart Block).

COMPREHENSION QUESTIONS

12.1 A 68-year-old man was hospitalized with persistent fever and a new heart murmur and diagnosed with *Streptococcus bovis* endocarditis of the mitral valve. After receiving 10 days of intravenous antimicrobial therapy, he is noted to be afebrile and with symptoms resolved. At this time, which of the following is the most important next step?

A. Good dental hygiene and proper denture fitting to prevent reinfection of damaged heart valves from oral flora.

B. Repeat echocardiography in 6 weeks to ensure the vegetations have resolved.

C. Colonoscopy to look for mucosal lesions.

D. Mitral valve replacement to prevent systemic emboli such as cerebral infarction.

12.2 A 24-year-old intravenous drug user is admitted to the hospital with 4 weeks of fever. He has three blood cultures positive for growth of *Candida* species. After 2 days in the hospital, he develops a cold, blue right great toe. Which of the following is the appropriate next step?

A. Repeat echocardiography to see if the large aortic vegetation previously seen has now embolized.

B. Cardiovascular surgery consultation for aortic valve replacement.

C. Aortic angiography to evaluate for a mycotic aneurysm, which may be embolizing.

D. Switch from fluconazole to amphotericin B.

12.3 A patient with which of the following conditions requires antimicrobial prophylaxis before dental surgery?

A. Atrial septal defect

B. Mitral valve prolapse without mitral regurgitation

C. Previous coronary artery bypass graft

D. Previous infective endocarditis

ANSWERS

12.1 **C.** Colonoscopy is necessary because a significant number of patients with *S. bovis* endocarditis have a colonic cancer or premalignant polyp, which leads to seeding of the valve by gastrointestinal (GI) flora. Heart valves damaged by endocarditis are more susceptible to infection, so good dental hygiene (answer A) is important, but in this case, the organism came from the intestinal tract, not the mouth, and the possibility of malignancy is most important to address. Serial echocardiography (answer B) would not add to the patient's care after successful therapy because vegetations become organized and persist for months or years without late embolization. Prophylactic valve

replacement (answer D) would not be indicated because the prosthetic valve is even more susceptible to reinfection than the damaged native valve and would actually increase the risk of cerebral infarction or other systemic emboli as a consequence of thrombus formation, even if adequately anticoagulated.

12.2 **B.** Fungal endocarditis, which occurs in intravenous drug users or immunosuppressed persons with indwelling catheters, frequently gives rise to large, friable vegetations with a high risk of embolization (often to the lower extremities) and is very difficult to cure with medical therapy (antifungal medications). Valve replacement is usually necessary. Repeat echocardiography (answer A) would not add to the patient's care because the clinical diagnosis of peripheral embolization is almost certain, and it would not change the management. Mycotic aneurysms (answer C) may occur in any artery as a consequence of endocarditis and can cause late embolic complications, but in this case, the source probably is the heart. Medical therapy with any antifungal agent (answer D) is unlikely to cure this infection.

12.3 **D.** Prior endocarditis damages valvular surfaces, and these patients are at increased risk for reinfection during a transient bacteremia, as may occur during dental procedures or some other GI or genitourinary tract procedures. All of the other conditions mentioned (answer A, atrial septal defect; answer B, mitral valve prolapse without mitral regurgitation; and answer C, previous coronary artery bypass graft) have a negligible risk of endocarditis, the same as in the general population, and antibiotic prophylaxis is not recommended by the American Heart Association.

CLINICAL PEARLS

- Suspect endocarditis in a patient with a fever or signs of bacteremia and a new heart murmur.
- Infective endocarditis is diagnosed in patients with sustained bacteremia and evidence of endocardial involvement, usually by echocardiography.
- Right-sided endocarditis may be difficult to diagnose due to the lack of systemic emboli seen in left-sided endocarditis and because a tricuspid regurgitation murmur is often not heard.
- Left-sided native valve endocarditis usually is caused by *Streptococcus viridans*, *S. aureus*, and *Enterococcus*. The vast majority of right-sided endocarditis is caused by *S. aureus*.
- Valve replacement usually is necessary for persistent infection, recurrent embolization, or when medical therapy is ineffective, for example, in cases of large vegetations as seen in fungal endocarditis.
- Culture-negative endocarditis is usually caused by prior administration of antibiotics before obtaining blood cultures or by infection with fungi or fastidious organisms, such as the HACEK group.

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CASE 13

A 58-year-old man presents to the emergency center (EC) complaining of severe pain in his left calf and foot that woke him from his sleep. He has a history of chronic stable angina, hypercholesterolemia, and hypertension, for which he takes aspirin, atenolol, and simvastatin. For several years, he has experienced pain in both calves and feet with walking. The pain has gradually progressed so that he can now walk only 100 ft before he has to stop. He occasionally has experienced mild pain in his feet at night, but the pain usually gets better when he sits up and hangs his feet off the bed. This time, the pain was more severe and did not improve, and he now feels like the foot is numb, and he cannot move his toes.

On physical examination, he is afebrile, with a heart rate of 72 beats per minute (bpm) and a blood pressure of 125/74 mm Hg. Head and neck examination is significant for a right carotid bruit. His chest is clear to auscultation; his heart rhythm is regular with a nondisplaced apical impulse, an S_4 gallop, and no murmurs. His abdomen is benign, with no tenderness or masses. He has bilateral femoral bruits, and his femoral and popliteal pulses are palpable bilaterally. His pedal pulses are diminished; they are present on the right but absent on the left. The left distal leg and foot are pale and cold to touch, with very slow capillary refill.

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 13:
Limb Ischemia (Peripheral Vascular Disease)

Summary: A 58-year-old man presents with

- Severe pain and numbness of his left foot
- Angina and a carotid bruit suggesting systemic atherosclerotic disease
- Femoral bruits bilaterally and bilateral calf claudication
- Sudden onset of pain, pallor, and pulselessness in the left foot

Most likely diagnosis: Acute limb ischemia, either thrombotic arterial occlusion or embolism from a more proximal source.

Next step: Angiogram of the lower extremity.

ANALYSIS

Objectives

1. Understand the clinical presentation of a patient with atherosclerotic peripheral vascular disease, including acute limb ischemia. (EPA 1)
2. Describe the evaluation and medical management of peripheral vascular disease. (EPA 3, 4)
3. Understand the indications for extremity revascularization. (EPA 4, 10, 12)

Considerations

This patient has diffuse atherosclerotic vascular disease, including coronary artery disease, carotid disease, and peripheral vascular disease. His **history of calf pain with ambulation and resolution with rest is classic for claudication**. Recently, the perfusion of his left leg likely was worsening, requiring his waking up and dangling his leg to enable blood flow and to help the pain. **Rest pain is a warning sign of possible critical limb vascular insufficiency**. The patient complains of the sudden onset of **pain, pallor, and pulselessness**, indicative of acute arterial occlusion. His limb ischemia may result from acute arterial occlusion caused by an embolus possibly originating from a thrombus in the heart, the aorta, or a large proximal artery such as the iliac. Magnetic resonance (MR) or computed tomography (CT) angiography, or possibly a conventional arteriogram, would be needed to first determine the arterial anatomy and define the best mode of revascularization. Then, depending on the level of occlusion, the patient may require urgent arterial thromboembolectomy.

APPROACH TO:
Peripheral Vascular Disease

DEFINITIONS

ANKLE-BRACHIAL INDEX (ABI): Ratio of ankle to brachial systolic blood pressure, determined clinically or by using Doppler ultrasound flow. Normal ratio is 0.9–1.4.

CLAUDICATION: Pain, ache, or cramp in muscles that increases with walking or leg exertion in a predictable manner and resolves with rest.

"6 P's" OF PERIPHERAL VASCULAR DISEASE: Pain, pallor, paresthesia, poikilothermia (coolness), pulselessness, and paralysis.

CLINICAL APPROACH

Pathophysiology

Although atherosclerosis is a systemic disease, clinicians often focus on the coronary circulation and pay less attention to the extremities. Yet, atherosclerotic peripheral arterial disease (PAD) is estimated to affect up to 16% of Americans who are 55 years and older and may exist without clinically recognized coronary or cerebrovascular disease. Furthermore, PAD confers the same risk of cardiovascular death as in persons with a prior myocardial infarction or stroke. **The most important risk factors** for PAD are **cigarette smoking and diabetes mellitus**. Hypertension, dyslipidemia, and elevated homocysteine levels also play significant roles.

Less common causes of chronic peripheral arterial insufficiency include thromboangiitis obliterans, or **Buerger disease**, an inflammatory condition of small- and medium-sized arteries that may affect the upper or lower extremities. It is found almost exclusively in smokers, especially men younger than 40 years. **Fibromuscular dysplasia** is a hyperplastic disorder **affecting medium and small arteries that usually occurs in women.** Generally, the renal or carotid arteries are involved, but when the arteries to the limbs are affected, the clinical symptoms are identical to those of atherosclerotic PAD. **Takayasu arteritis** is an inflammatory condition, seen primarily in younger women, that usually affects branches of the aorta, most commonly the subclavian arteries, and causes **arm claudication and Raynaud phenomenon**, along with constitutional symptoms such as **fever** and **weight loss**.

Patients with chronic peripheral arterial insufficiency who present with sudden unremitting pain may have an **acute arterial occlusion**, most commonly the result of **embolism** or **in situ thrombosis. The heart is the most common source of emboli;** conditions that may cause cardiogenic emboli include atrial fibrillation, dilated cardiomyopathy, and endocarditis. Artery-to-artery embolization of atherosclerotic debris from the aorta or large vessels may occur spontaneously or, more often, after an intravascular procedure, such as arterial catheterization. Emboli tend to lodge at the bifurcation of two vessels, most often in the femoral, iliac, popliteal, or tibioperoneal arteries. Arterial thrombosis may occur in atherosclerotic vessels at the site of stenosis or in an area of aneurysmal dilation, which may also complicate atherosclerotic disease.

Clinical Presentation

Patients with **acute arterial occlusion** may present with a number of signs, which can be remembered as **six P's: pain, pallor, pulselessness, paresthesias, poikilothermia (coolness), and paralysis.** The first five signs occur fairly quickly with acute ischemia; paralysis will develop if the arterial occlusion is severe and persistent.

The most common symptom associated with **chronic arterial insufficiency** caused by PAD is **intermittent claudication** (pain, achiness, fatigue, or other discomfort that occurs in one or both legs during exercise and is relieved with rest). It is ischemic pain and occurs distal to the site of the arterial stenosis, most commonly in the calves. The symptoms often are progressive and may severely limit a patient's activities and reduce the patient's functional status. An individual with proximal stenosis, such as aortoiliac disease, may complain of exertional pain in the buttocks and thighs. Severe occlusion may produce **rest pain**, which often occurs at night and may be relieved by sitting up and dangling the legs, using gravity to assist blood flow to the feet.

On physical examination, palpation of the **peripheral pulses may be diminished** or absent below the level of occlusion; **bruits** may indicate accelerated blood flow velocity and turbulence at the sites of stenosis. Bruits may be heard in the abdomen with aortoiliac stenosis and in the groin with femoral artery stenosis. **Elevation of the feet** above the level of the heart in the supine patient (known as the Buerger test) often induces **pallor in the soles.** If the legs are then placed in the dependent position, they frequently develop rubor as a result of reactive hyperemia. Chronic arterial insufficiency may cause **hair loss on the legs and feet**, thickened and brittle toenails, and shiny atrophic skin. Severe ischemia may produce ulcers or gangrene, typically at the distal extremities.

When PAD is suspected, the test most commonly used to evaluate for arterial insufficiency is the **ABI.** Systolic blood pressures are measured by Doppler ultrasonography in each arm and in the dorsalis pedis and posterior tibial arteries in each ankle. Normally, blood pressures in the large arteries of the legs and arms are similar. In fact, blood pressures in the legs often are higher than in the arms because of an artifact of measurement, so the **normal ratio of ankle-to-brachial pressures is 0.9–1.4.** Patients with claudication typically have ABI values ranging from 0.41 to 0.90, and those with **critical leg ischemia** have **ABI values less than or equal to 0.40.** Further evaluation with exercise treadmill testing can clarify the diagnosis when symptoms are equivocal, allow for assessment of functional limitations (eg, maximal walking distance), and evaluate for concomitant coronary artery disease. Additional imaging, such as magnetic resonance angiography (MRA) or computed tomography angiography (CTA), is not used in routine diagnostic evaluation but can help determine arterial anatomy before a revascularization procedure.

Treatment

The goals of therapy include reductions in cardiovascular morbidity, improvement in quality of life by alleviating symptoms, and preservation of limb viability.

Risk Factor Modification. The first step in managing patients with PAD is risk factor modification. Because of the likelihood of coexisting atherosclerotic vascular disease such as coronary artery disease, patients with **symptomatic PAD** have an

estimated **mortality** rate of **50% in 10 years**, most often as a consequence of cardiovascular events. **Smoking** is, by far, the **single most important risk factor** impacting both claudication symptoms and overall cardiovascular mortality. Besides slowing the progression to critical leg ischemia, **tobacco cessation reduces the risk of fatal or nonfatal myocardial infarction by as much as 50%,** more than any other medical or surgical intervention. In addition, treatment of hypercholesterolemia, control of hypertension and diabetes, and use of antiplatelet agents such as aspirin or clopidogrel all have been shown to improve cardiovascular health and may have an effect on peripheral arterial circulation. Carefully supervised exercise programs can improve muscle strength and prolong walking distance by promoting the development of collateral blood flow.

Medications for Claudication. Specific medications for improving claudication symptoms have been used with some benefit. Pentoxifylline, a substituted xanthine derivative that increases erythrocyte elasticity, has been reported to decrease blood viscosity, thus allowing improved blood flow to the microcirculation; however, results from clinical trials are conflicting, and the benefit of pentoxifylline, if present, appears small. Cilostazol, a phosphodiesterase inhibitor with vasodilatory and antiplatelet properties, has been approved by the Food and Drug Administration for treatment of claudication. It has been shown in randomized controlled trials to improve maximal walking distance and quality of life. Figure 13–1 shows an algorithm for management of PAD.

Revascularization. Patients with **critical leg ischemia**, defined as **ABI** less than **0.40, severe or disabling claudication, unremitting rest pain**, or **nonhealing ulcers**, should be **evaluated for a revascularization procedure**. This can be accomplished by percutaneous angioplasty, with or without placement of intra-arterial stents, or surgical bypass grafting. Angiography (either conventional arteriogram or MRA) should be performed to define the flow-limiting lesions prior to any vascular procedure. Ideal candidates for arterial revascularization are those with discrete stenosis of large vessels; diffuse atherosclerotic and small-vessel disease responds poorly.

Managing acute arterial occlusions. **Rapid restoration of arterial supply is mandatory** in patients with an **acute arterial occlusion that threatens limb viability**. Initial management includes anticoagulation with heparin to prevent propagation of the thrombus. The affected limb should be placed below the horizontal plane without any pressure applied to it. Conventional arteriography is used to identify the location of the occlusion and to plan for the method of revascularization. Surgical removal of an embolus or arterial bypass may be performed, particularly if a large proximal artery is occluded. A balloon catheter may also be used to remove the clot. Alternatively, a catheter can be used to deliver intra-arterial thrombolytic therapy directly into the thrombus, sometimes in conjunction with stent placement. In comparison to systemic fibrinolytic therapy, localized infusion is associated with fewer bleeding complications.

CASE CORRELATION

- See also Case 2 (Metabolic Syndrome), Case 3 (Acute Coronary Syndrome), and Case 6 (Hypertension, Outpatient).

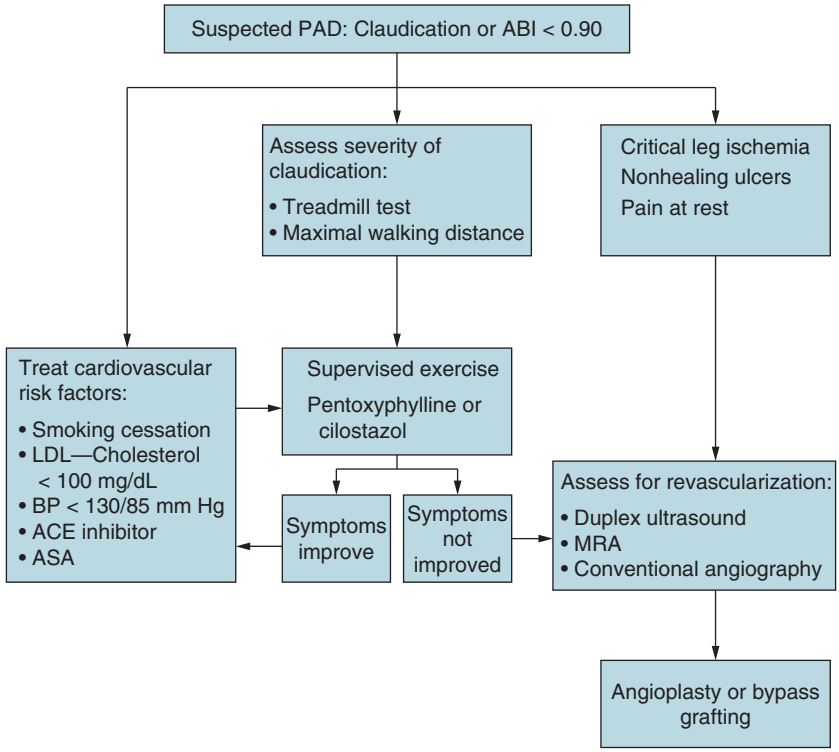


Figure 13–1. Algorithm for management of peripheral arterial disease. ABI, ankle-brachial index; ACE, angiotensin-converting enzyme; ASA, aspirin; BP, blood pressure; LDL, low-density lipoprotein; MRA, magnetic resonance angiography; PAD, peripheral arterial disease. (Data from Hiatt W. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med.* 2001;344:1608-1621.)

COMPREHENSION QUESTIONS

13.1 A 49-year-old smoker with hypertension, diabetes, and hypercholesterolemia comes to the clinic complaining of pain in his calves when he walks two to three blocks. Which of the following therapies might offer him the greatest benefit in symptom reduction and in overall mortality?

A. Aspirin

B. Limb revascularization procedure

C. Cilostazol

D. Smoking cessation

E. Pravastatin

13.2 A 31-year-old male smoker presents with resting pain in his legs and a nonhealing foot ulcer. Which of the following is the most likely cause of arterial insufficiency in this patient?

A. Cholesterol embolism
B. Fibromuscular dysplasia
C. Thromboangiitis obliterans (Buerger disease)
D. Takayasu arteritis
E. Psychogenic pain

13.3 A 21-year-old woman presents with fever, fatigue, and unequal pulses and blood pressures in her arms. Which of the following is the most likely cause of arterial insufficiency in this patient?

A. Cholesterol embolism
B. Fibromuscular dysplasia
C. Thromboangiitis obliterans (Buerger disease)
D. Takayasu arteritis
E. Psychogenic pain

13.4 A 62-year-old man presents with livedo reticularis and three blue toes, including one with gangrene following cardiac catheterization. Which of the following is the most likely cause of this patient's findings?

A. Cholesterol embolism
B. Fibromuscular dysplasia
C. Thromboangiitis obliterans (Buerger disease)
D. Takayasu aortitis
E. Psychogenic pain

13.5 A 67-year-old woman is noted to have significant peripheral vascular disease. She is evaluated by the cardiovascular surgeon but not felt to be a surgical candidate. Which of the following conditions is likely to be present in this patient?

A. Diffuse atherosclerotic disease
B. Leg pain at rest
C. Symptoms that do not improve with pharmacologic management
D. Nonhealing ulcers of the ankle

ANSWERS

13.1 **D.** Tobacco cessation is the most important intervention to improve cardiovascular morbidity and mortality in high-risk patients, such as those with PAD, and to improve claudication symptoms. Cilostazol (answer C) may help with claudication symptoms but will not affect cardiovascular mortality. Aspirin (answer A), angiotensin-converting enzyme inhibitors, and beta-hydroxy-beta-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are important adjuncts for risk factor modification and for relief of symptoms, but their benefits pale in comparison to smoking cessation.

13.2 **C.** Thromboangiitis obliterans, or Buerger disease, is a disease of young male smokers and may cause symptoms of chronic arterial insufficiency in either legs or arms. Cholesterol embolisms (answer A) are most likely to occur after a vascular procedure, including cardiac catheterization. Location of arterial insufficiency is also important for differentiation of the cause. For example, fibromuscular dysplasia (answer B) is more likely to involve the renal arteries and extracranial cerebrovascular arteries rather than peripheral arteries of the extremities. Takayasu arteritis (answer D) is a large-vessel vasculitis that primarily affects the aorta and the primary branches.

13.3 **D.** Takayasu arteritis is associated with symptoms of inflammation such as fever, and it most often affects the subclavian arteries, producing stenotic lesions that may cause unequal blood pressures, diminished pulses, and ischemic pain in the affected limbs. The other answer choices typically do not cause fever.

13.4 **A.** Embolism of cholesterol and other atherosclerotic debris from the aorta or other large vessels to small vessels of skin or digits may complicate any intra-arterial procedure. Signs may include livedo reticularis, ulcers, gangrene, renal involvement, and ocular involvement. Eosinophilia may be found on laboratory work. The other answer choices may be associated with pain, but not sudden onset of ischemia.

13.5 **A.** Surgical therapy is reserved for those with severe symptoms after exercise despite pharmacologic agents or in cases where quality of life is impaired. Pain at rest (answer B), refractoriness to medical therapy (answer C), and the presence of nonhealing ulcers and/or gangrene (answer D) are some indications for surgical intervention. Duplex ultrasound can help discern whether the patient is a potential surgical candidate. Arteriography may also be performed. Diffuse atherosclerotic disease is a contraindication for surgery since bypass would not help in the face of significant and widespread disease.

CLINICAL PEARLS

- Smoking cessation is the single most important intervention for atherosclerotic peripheral vascular disease. Other treatments include pentoxifylline or cilostazol, structured regular exercise, and cardiovascular risk factor modification.
- Revascularization by angioplasty or bypass grafting may be indicated for patients with debilitating claudication, ischemic rest pain, or tissue necrosis.
- Acute arterial occlusion that threatens limb viability is a medical emergency and requires immediate anticoagulation and investigation with conventional arteriography.
- Acute severe ischemia of an extremity causes the "six P's": *pain, pallor, pulselessness, paresthesias, poikilothermia*, and *paralysis*.
- Chronic incomplete arterial occlusion may result only in exertional pain or fatigue, pallor on elevation of the extremity, and rubor on dependency.

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CASE 14

A 48-year-old woman is brought to the emergency center complaining of a sudden onset of dyspnea. She reports that she was standing in the kitchen making dinner when she suddenly felt as if she could not get enough air. Also, her heart started racing, she became light-headed, and she felt as if she would faint. She denies chest pain or cough. Her medical history is significant only for a cholecystectomy performed 2 weeks earlier for gallstones. The procedure was complicated by a wound infection, requiring her to stay in the hospital for 8 days. She takes no medications regularly and only takes acetaminophen as needed for pain at her abdominal incision site.

On examination, she is tachypneic with a respiratory rate of 28 breaths/min, oxygen saturation of 84% on room air, heart rate of 124 beats per minute (bpm), and blood pressure of 118/89 mm Hg. She appears uncomfortable, diaphoretic, and frightened. Her oral mucosa is slightly cyanotic, her jugular venous pressure is elevated, and her chest is clear to auscultation. Her heart rhythm is tachycardic but regular with a loud second sound in the left second intercostal space, without gallop or murmurs. Her abdominal examination is benign, with a clean incision site without signs of infection. Her right leg is moderately swollen from her midthigh to her foot, and her thigh and calf are mildly tender to palpation. Laboratory studies, including cardiac enzymes, are normal; her electrocardiogram (ECG) reveals only sinus tachycardia, and her chest x-ray is interpreted as normal.

- What is the most likely diagnosis?
- What is the most appropriate diagnostic step?
- What are the common risk factors for this condition?

ANSWERS TO CASE 14:
Pulmonary Embolism

Summary: A 48-year-old woman presents with

- Recent surgery and hospitalization
- Acute onset of dyspnea
- Tachypnea, tachycardia, and hypoxemia
- Elevated jugular venous pressure and an accentuated pulmonic component of S_2, suggestive of elevated pulmonary pressures
- A clear chest radiograph

Most likely diagnosis: Pulmonary embolism (PE) due to acute-onset dyspnea with history of recent hospitalization and immobilization.

Most appropriate diagnostic step: Chest computed tomography pulmonary angiogram (CTPA) with intravenous contrast or V/Q (ventilation/perfusion) scan.

Common risk factors: Recent surgery, immobilization, malignancy, pregnancy, certain medications (eg, oral contraceptives), and genetic factors.

ANALYSIS

Objectives

1. Understand the factors that predispose patients to develop thromboembolic disease. (EPA 12)
2. Recognize the clinical presentation of PE. (EPA 1, 2)
3. Describe the strategies to diagnose PE. (EPA 3)
4. Understand the goals and methods of treatment of thromboembolism. (EPA 4, 10, 12)

Considerations

Pulmonary embolism is a difficult diagnosis to establish because of the nonspecificity of presenting signs and symptoms and the probabilistic nature of the most common noninvasive diagnostic tests. In patients with suspected PE, initial treatment is supportive to maintain adequate oxygenation and hemodynamic stability while efforts are undertaken to diagnose the cause of the patient's symptoms. Often, a series of diagnostic tests is necessary to determine the likely diagnosis. Specific treatment of PE may include thrombolysis or surgical embolectomy for unstable patients and initiation of anticoagulation as a long-term measure to prevent recurrence.

APPROACH TO:
Pulmonary Embolism

DEFINITIONS

D-DIMER: A major fibrin degradation product that is released upon fibrinolysis. Elevated plasma levels of D-dimer indicate recent or ongoing intravascular coagulation and fibrinolysis.

DEEP VENOUS THROMBOSIS (DVT): Blood clot in the deep venous system that usually affects the lower extremities or pelvic veins.

LOW-MOLECULAR-WEIGHT HEPARIN (LMWH): A fragment of the larger mucopolysaccharide, heparin, that activates antithrombin III, inhibiting the final common pathway of the coagulation cascade.

PULMONARY EMBOLISM: A clot (usually originating from the lower extremity veins) that travels through the venous circulation and becomes lodged in the pulmonary artery or one of its branches. PE causes acute pulmonary hypertension and is labeled "massive PE" if it causes hemodynamic instability; it is labeled "submassive" or "moderate" if it causes right ventricular enlargement, strain, or dysfunction but is not associated with hemodynamic instability.

CLINICAL APPROACH

Epidemiology

Diagnosis and management of PE require a combination of clinical suspicion and appropriate use of diagnostic tools. Pulmonary emboli usually arise from DVTs and occasionally from less common sources, including air, fat, amniotic fluid, or tumor thrombus. More than 100 years ago, **Rudolf Virchow** postulated three factors that predispose to venous thrombus: **local trauma to vessel wall, a state of hypercoagulability**, and **venous stasis**. Genetic predisposition to hypercoagulability accounts for approximately 20% of PEs. **The most common inherited conditions** are the **factor V Leiden mutation** and the **prothrombin gene mutations**. Malignancy is also a predisposing condition for DVT. Neoplastic cells are thought to generate thrombin or to synthesize various procoagulants. Surgery and prolonged immobilization also increase the risk of PE up to 1 month postoperatively.

Pathophysiology

When venous thrombi dislodge from their site of formation, they may embolize to the pulmonary arteries, causing PEs. The **deep proximal lower extremity veins** are the **most common sites of clot formation**, although thromboses in pelvic, calf, and upper extremity veins may also embolize. **Emboli to the pulmonary artery cause vascular obstruction and release of vasoactive agents such as serotonin, thereby elevating pulmonary vascular resistance.** The resulting increase in alveolar dead space and subsequent redistribution of blood flow create areas of V/Q mismatch and impair gas exchange. Reflex bronchoconstriction increases airway resistance. This cascade

can result in pulmonary edema, hemorrhage, or loss of surfactant, further decreasing lung compliance. As pulmonary vascular resistance increases, right heart wall tension rises, resulting in dilation and dysfunction that ultimately may impair left heart function. **Progressive right heart failure is the usual cause of death from PE.**

Clinical Presentation

Physical Examination. PE can often mimic other cardiopulmonary diseases, making the diagnosis challenging. Acute onset of dyspnea is the most common symptom of PE, and tachypnea is the most frequently observed sign. Severe dyspnea accompanied by syncope, hypotension, or cyanosis may indicate massive PE, whereas pleuritic pain, cough, or hemoptysis may suggest a smaller, more peripheral embolus causing infarction of lung tissue. Classic findings on physical examination include tachycardia and signs of right ventricular dysfunction, including increased jugular venous pressure, accentuated pulmonic component of the second heart sound, and systolic murmur that increases with inspiration. Findings suggestive of DVT include pain, swelling, and erythema of the lower extremity, particularly the back of the leg below the knee. Some patients complain of calf tenderness.

D-dimer Test. The most useful nonimaging diagnostic test is the serum **D-dimer** enzyme-linked immunosorbent assay (ELISA). It is elevated (> 500 ng/mL) in more than 95% of patients with PE, reflecting the breakdown of fibrin and thrombolysis. Although the D-dimer ELISA has a high negative predictive value and thus is useful in excluding PE, one should keep in mind that it lacks specificity if the pretest probability of PE is low. **Elevations may be seen in patients with myocardial infarction, pneumonia, heart failure, cancer, or sepsis.** Additional laboratory tests can assist in risk stratification of submassive PE, including brain natriuretic peptide (BNP) and cardiac troponins. Abnormalities on the ECG are less useful in the evaluation of PE. The most common finding is sinus tachycardia. The $S_1Q_3T_3$ (S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III, respectively) is often discussed but seen only in a minority of patients. When present, it is relatively specific.

Imaging Modalities. Radiologic studies are critical in the diagnosis of PE and DVT. A chest x-ray is the first study indicated in a symptomatic patient with new-onset dyspnea. A normal or near-normal chest x-ray is the most common finding in PE, sometimes with nonspecific abnormalities, such as atelectasis. In general, **acute onset of hypoxemia in a patient with a normal chest x-ray should be interpreted as PE until otherwise proven.** Classic abnormalities associated with PE include Westermark sign (decreased pulmonary vascularity distal to the clot), Hampton hump (peripheral wedge-shaped density above the diaphragm), and Palla sign (enlargement of the right descending pulmonary artery). The chest radiograph probably is more important in identifying other significant pulmonary parenchymal disease (pneumonia, pulmonary edema) and cardiac disease (cardiomyopathy) as alternative causes of the respiratory symptoms.

For any imaging modality, the most accurate diagnosis will be achieved in combination with the clinical suspicion. The **Wells score** is a useful clinical calculator to clinically estimate pretest probability of PE. A point score less than 4 *with* a negative D-dimer assay indicates a low probability for PE. A score

Table 14–1 • CLINICAL PREDICTION SCORE FOR ESTIMATING LIKELIHOOD OF PE

Clinical Variable	Score
Symptoms of DVT	3.0
Alternative Dx less likely than PE	3.0
Heart rate > 100 bpm	1.5
Immobilization > 3 days, surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Presence of malignancy (advanced disease or treatment within 6 months)	1.0

DX, diagnosis.
7 points or more = high probability for PE.
Less than 4 points, with negative D-dimer = low probability for PE.
Data from Wells PS, Anderson DR, Rodger M, et. al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. *2000;83(3):416-420.*

of 2 to 6 points indicates moderate probability, and more than 6 points is high probability (Table 14–1).

Chest computed tomography angiogram (CTA) with intravenous contrast is now the principal imaging modality to diagnose suspected PE. Current-generation spiral CT can acquire high-resolution images in a single breath hold and can visualize small branch artery emboli. In addition, the chest CT has the additional benefit of visualizing other abnormalities, such as pneumonia, aortic abnormalities, or pulmonary masses, that may not have been apparent on routine chest radiograph and may provide an alternative diagnosis for the patient's symptomatology. The main caveats in the use of CT are the image quality and the experience of the center in interpreting this type of scan. In general, however, CT has been shown to be at least as accurate as the previously accepted standard imaging modality, V/Q lung scanning.

In patients in whom a CT with radiocontrast cannot be obtained or is contraindicated (such as in cases of advanced renal insufficiency or severe contrast allergy), a **V/Q scan** remains a useful tool. This study evaluates the circulation of air (distribution of inhaled xenon-133) and blood (distribution of technetium-99 aggregates with albumin) in the lungs. A segmental or lobar area with proper air distribution but with no perfusion is diagnostic of PE. A normal scan or a low-probability scan with a low clinical suspicion for PE effectively excludes the diagnosis.

If the CT and/or V/Q scan are nondiagnostic and yet the clinical suspicion remains high, other imaging modalities may be obtained. A **lower extremity venous ultrasound** demonstrating an acute DVT in a patient with signs and symptoms of PE would be sufficient to diagnose and treat PE (especially since the treatment with anticoagulation is the same). It should be noted, though, that a normal ultrasound does not exclude the diagnosis of PE since most patients with PE do not have evidence of residual DVT and since in many cases the clot has already embolized.

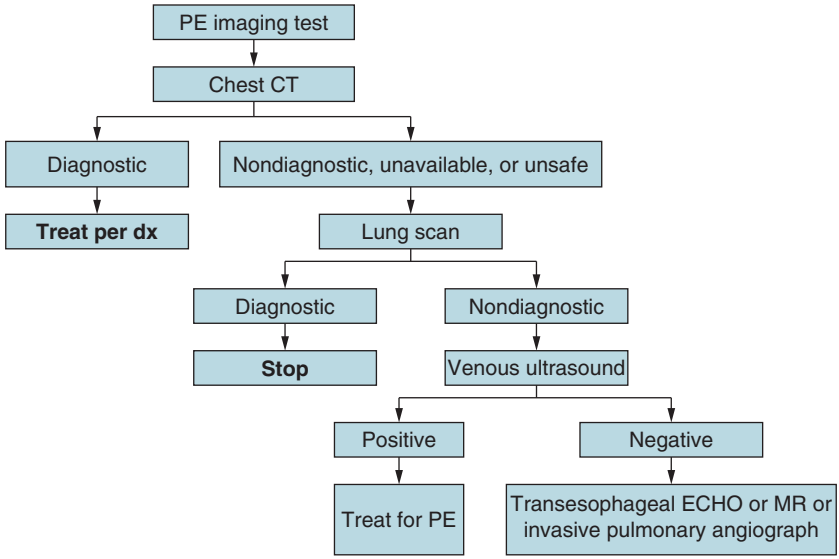


Figure 14–1. Diagnostic algorithm for patients with suspected pulmonary embolism. CT, computed tomography; ECHO, echocardiography; MR, magnetic resonance; PE, pulmonary embolism. (Adapted with permission, from Braunwald E, Fauci AS, Kasper KL, et al. *Harrison's Principles of Internal Medicine*. 17th ed. 2008. Copyright © McGraw Hill LLC. All rights reserved.)

Other imaging studies, such as **contrast-enhanced magnetic resonance imaging (MRI)** or **echocardiography** (especially transesophageal echocardiography) may be used when the clinical suspicion remains high, but other diagnostic studies are inconclusive. Pulmonary artery angiography used to be the gold standard, but the methods described previously are as sensitive, specific, and less invasive; thus, it is no longer preferred. Figure 14–1 shows a diagnostic algorithm for suspected PE.

Treatment

Treatment options can be categorized in terms of primary and secondary therapy based on different management goals. **Primary therapy** consists of clot dissolution or **thrombolysis (with tissue plasminogen activator [tPA]) or removal of the clot by surgical embolectomy.** Primary therapy is usually reserved for patients with a high risk for adverse outcomes if the clot remains, that is, those with evidence of **right heart failure or hemodynamic instability. The main criterion for thrombolytic administration is a systolic blood pressure < 90 mm Hg in the absence of absolute contraindications to tPA.** The main complications of thrombolytic administration are bleeding, **a very small percentage of which can be devastating intracerebral hemorrhages. Patients who have conventional surgical embolectomy performed emergently for "rescue" have a higher mortality (approaching 50%); however in less urgent circumstances, mortality rates are about 7%.**

Newer therapies include half-dose thrombolytics and catheter-directed thrombolysis for submassive PE. Patients with hemodynamic collapse may require mechanical circulatory support with venoarterial extracorporeal membrane oxygenation

(ECMO), which provides cardiac and pulmonary support, but this should only be employed in patients who are likely to improve with a definitive therapy (ie, surgical embolectomy).

For patients who are normotensive with normal RV function, the treatment is with **anticoagulation**, with the goal of **secondary prevention** of thrombus extension or recurrence. Anticoagulation does not dissolve an existing thrombus, but it allows for endothelialization and organization, which begins within days of treatment. Immediate anticoagulation should be initiated with intravenous **unfractionated heparin** (UFH), subcutaneous **LMWH** (eg, enoxaparin or tinzaparin), or the direct factor Xa inhibitor **fondaparinux**. While UFH requires a continuous infusion and frequent laboratory monitoring every 4 to 6 hours, LMWH and fondaparinux have similar efficacy and safety profiles. Both LMWH and fandaparinux provide rapid onset of action and predictable dose response, and laboratory monitoring is generally not required. Non–vitamin K antagonist oral anticoagulants (NOACs), which include direct thrombin inhibitors (dabigatran) and Xa inhibitors (rivaroxaban, apixaban and edoxaban), are now approved for the treatment of DVT and also do not require laboratory monitoring.

While patients are still on heparin, they can start therapy with the oral vitamin K antagonist **warfarin**. Because its biological effect is unpredictable, warfarin requires routine monitoring of the prothrombin time, standardized across laboratories as the international normalized ratio (**INR**). The target therapeutic INR is usually 2–3. When initiating warfarin therapy, the usual course is to use UFH, LMWH, or fondaparinux for at least 5 days while overlapping with warfarin (commonly referred to as "bridging") until the INR has been therapeutic for 2 consecutive days. Rivaroxaban and apixaban have the added advantage that a bridging dose of heparin is not required.

The duration of treatment relates to the risk of recurrence. One factor in assessing this risk is whether the DVT or PE was provoked (ie, occurred due to a readily identifiable and transient event, eg, trauma or surgery) or unprovoked. For provoked DVT of the calf or upper extremity, 3 months of anticoagulation are recommended. Six months are recommended for patients with provoked proximal leg DVT or PE. For patients with idiopathic or unprovoked DVT or PE or with ongoing risk factors, such as malignancy or antiphospholipid syndrome, the duration of therapy is controversial, but indefinite anticoagulation may be required.

Inferior vena cava filter placement to prevent recurrent PE is recommended when there is active bleeding or other contraindication to anticoagulation or when there is recurrent DVT or PE despite therapeutic anticoagulation.

CASE CORRELATION

- See also Case 3 (Acute Coronary Syndrome), Case 5 (Aortic Dissection/Marfan Syndrome), Case 10 (Acute Pericarditis Caused by Systemic Lupus Erythematosus), Case 15 (Chronic Obstructive Pulmonary Disease), and Case 16 (Chronic Cough/Asthma).

COMPREHENSION QUESTIONS

14.1 A 35-year-old woman presents with calf tenderness and acute dyspnea. The arterial blood gas reveals a partial pressure of oxygen (Po_2) of 76 mm Hg. Which of the following is the most common physical examination finding of PE?

A. Wheezing
B. Increased pulmonary component of the second heart sound
C. Tachypnea
D. Calf swelling
E. Pulmonary rales

14.2 A 39-year-old man is noted to have a DVT without any known risk factors. He notes that his brother also developed a PE at age 45, and his mother developed a "clot in the leg" when she was in her 30s. Which of the following is the most likely inherited disorder in this patient?

A. Protein S deficiency
B. Antithrombin III deficiency
C. Factor V Leiden mutation
D. Antiphospholipid antibody syndrome
E. Familial malignancy syndrome

14.3 A 54-year-old woman is being evaluated in the emergency center with shortness of breath of 12 hours' duration. She also has significant vaginal bleeding of 1 month's duration. On examination, she is found to have significant pallor of her sclera and skin. Speculum examination showed a large necrotic and exophytic mass of the cervix. The hemoglobin level is 7 g/dL. Her left leg is swollen and markedly different from her right leg. Doppler investigation reveals a DVT of the left leg. Which of the following is the best treatment for the thrombus?

A. Intravenous unfractionated heparin
B. Fractionated subcutaneous heparin
C. Subcutaneous unfractionated heparin
D. Oral warfarin (Coumadin)
E. Vena cava filter

ANSWERS

14.1 **C.** Tachypnea is the most common physical sign associated with PE. Calf or thigh pain and/or swelling (answer D) occurs less frequently than tachypnea. Other common clinical manifestations of pulmonary embolus in decreasing frequency include pleuritic pain, cough, and orthopnea. Wheezing (answer A), a sound caused by narrowing of the airway as seen in asthma or chronic obstructive pulmonary disease (COPD), can occur in PE but is less common.

Rales (answer E) are rattling or crackling noises heard on auscultation of the lungs due to fluid or exudate in the alveoli. It is an uncommon sign in patients with PE. An increased pulmonary component of S_2 (answer B) is also a possible sign in PE due to increased pressures in the pulmonary vasculature, but it is not the most common sign.

14.2 **C.** Factor V Leiden mutation is the most common hereditary thrombophilia. It is inherited in an autosomal dominant fashion and therefore will affect both men and women. The other answer choices (answer A, protein S deficiency; answer B, antithrombin III deficiency; answer D, antiphospholipid antibody syndrome; and answer E, familial malignancy syndrome) are all causes of hereditary thrombophilia with increased risk of PE but are less common causes.

14.3 **E.** This patient likely has cervical cancer with significant vaginal bleeding and anemia. This is a relative contraindication for anticoagulation (answers A [intravenous UFH]; answer B [fractionated subcutaneous heparin]; answer C [subcutaneous UFH]; and answer D [oral warfarin]) since these agents would exacerbate the bleeding. Thus, a vena cava filter is the most appropriate choice in this patient; the filter ideally prevents thrombi from traveling to the lungs.

CLINICAL PEARLS

- Acute onset of dyspnea or hypoxemia with a normal chest x-ray should be considered caused by a PE until proven otherwise.
- Diagnosis of PE is usually established using imaging tests such as chest CT pulmonary angiogram in light of clinical pretest probability.
- The clinical suspicion guides the pursuit of diagnosis of thromboemboli.
- The primary therapy of DVT or PE is anticoagulation, with the goal of preventing recurrence.

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CASE 15

A 58-year-old man comes to your office because of shortness of breath. He has experienced mild dyspnea on exertion for a few years, but more recently he has noted worsening shortness of breath with minimal exercise and the onset of dyspnea at rest. He has difficulty reclining; as a result, he spends the night sitting up in a chair trying to sleep. He reports a cough with production of yellowish-brown sputum every morning throughout the year. He denies chest pain, fever, chills, or lower extremity edema. He has smoked about two packs of cigarettes per day since age 15. He does not drink alcohol. A few months ago, the patient went to an urgent care clinic for evaluation of his symptoms, and he received a prescription for some inhalers, the names of which he does not remember. He was also told to find a primary care provider for further evaluation. On physical examination, his blood pressure is 135/85 mm Hg, heart rate is 96 beats per minute (bpm), respiratory rate is 28 breaths/min, and temperature is 97.6 °F. He is sitting in a chair, leaning forward, with his arms braced on his knees. He appears uncomfortable, with labored respirations and cyanotic lips. He is using accessory muscles of respiration, and chest examination reveals wheezes and rhonchi bilaterally, but no crackles are noted. The anteroposterior (AP) diameter of the chest wall appears increased, and he has inward movement of the lower rib cage with inspiration. Cardiovascular examination reveals distant heart sounds but with a regular rate and rhythm, and his jugular venous pressure (JVP) is normal. His extremities show no cyanosis, edema, or clubbing.

- What is the most likely diagnosis?
- What are the next best diagnostic tests?
- What is the best initial treatment?

ANSWERS TO CASE 15:
Chronic Obstructive Pulmonary Disease

Summary: A 58-year-old man presents with

- Worsening shortness of breath with minimal exercise and the onset of dyspnea at rest with difficulty reclining
- History of smoking two packs of cigarettes per day since age 15
- Reports of a productive cough with yellowish-brown sputum every morning throughout the year
- Sitting in a characteristic "tripod" position to facilitate use of accessory muscles of respiration
- The appearance of an airway obstruction with respiratory distress, lower chest retractions, and bilateral wheezes and rhonchi
- Perioral cyanosis suggesting hypoxemia
- An increased appearance of the anteroposterior diameter of the chest wall

Most likely diagnosis: Chronic obstructive pulmonary disease (COPD) with acute exacerbation.

Next diagnostic steps: Arterial blood gas (ABG) to assess oxygenation and acid-base status and chest x-ray.

Best initial treatment: Oxygen by nasal cannula, followed closely by bronchodilators and steroids for airway inflammation.

ANALYSIS

Objectives

1. Define chronic bronchitis, COPD, and emphysema. (EPA 1, 2)
2. Describe spirometry and flow-volume loops and their value for the diagnosis and management of obstructive and restrictive lung diseases. (EPA 3)
3. Describe the treatment of stable COPD, as well as management of acute exacerbations, including the indications for mechanical ventilation. (EPA 4, 10, 12)

Considerations

This 58-year-old, long-time smoker likely has COPD. He is now in respiratory distress with labored respirations, cyanosis, and wheezing. The urgent issue is his current respiratory status. Rapid clinical assessment is critical in case this patient is headed toward respiratory failure, perhaps necessitating endotracheal intubation and mechanical ventilation. An ABG will quickly provide information regarding the adequacy of oxygenation status (Pao_2) and ventilation ($Paco_2$). A chest x-ray will determine the underlying status of the lung parenchyma and whether a trigger for the current situation can be identified.

APPROACH TO:

Chronic Obstructive Pulmonary Disease

DEFINITIONS

CHRONIC BRONCHITIS: COPD component that is diagnosed clinically and is characterized by excessive secretion of bronchial mucus and productive cough for 3 months or more in at least 2 consecutive years in the absence of any other disease that might account for this symptom.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): Chronic airflow obstruction caused by chronic bronchitis or emphysema. COPD is a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the lungs to noxious particles and gases. Diagnosis in the right clinical setting is usually supported by FEV_1/FVC ratio less than 0.7. Severity of COPD on spirometry is based on the level of FEV_1/FVC ratio compared to the predicted value. The severity of airflow limitation can be classified based on postbronchodilator FEV_1 (Table 15–1).

EMPHYSEMA: COPD component that inferred clinically, and is diagnosed pathologically with abnormal, permanent enlargement of air spaces distal to the terminal bronchioles, with destruction of their walls and without obvious fibrosis.

FEV_1/FVC: Ratio involving volume expired in the first second and the vital capacity (VC) in maximal effort, reduced in obstructive lung disease.

FORCED EXPIRATORY VOLUME IN 1 SECOND (FEV_1): Volume of air expired in the first second during maximal expiratory effort. FEV_1 is reduced in both obstructive lung disease (increased airway resistance) and restrictive lung disease (low VC).

FORCED VITAL CAPACITY (FVC): Total volume of air expired after full inspiration. FVC is reduced in restrictive lung disease.

OBSTRUCTIVE LUNG DISEASE: Chronic pulmonary disorder that is characterized by a disproportional decrease in maximal airflow from the lung in relation

Table 15–1 • CLASSIFICATION OF SEVERITY OF COPD BASED ON THE RESPONSE OF FEV_1 TO BRONCHODILATORS

Stage	Severity	FEV_1 (% predicted)
GOLD 1	Mild	> 80%
GOLD 2	Moderate	50%-79%
GOLD 3	Severe	30%-49%
GOLD 4	Very severe	< 30%

Abbreviations: FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

to maximal volume that can be displaced from the lung. Typically, FEV_1 will be decreased relative to FVC; therefore, the FEV_1/FVC will be decreased. The most common types of obstructive lung disease are asthma and COPD.

PULMONARY FUNCTION TEST (PFT): Complete PFTs comprise respiratory tests of spirometry, lung volumes, and diffusion.

RESTRICTIVE LUNG DISEASE: Chronic pulmonary disorder characterized by low lung volumes. Can be due to intrinsic factors, such as changes in the lung parenchyma, or extrinsic factors, such as alterations of the chest wall, pleura, or respiratory muscles. Typically, the FVC and FEV_1 are reduced, but the FEV_1/FVC is normal. The diagnosis is best made by a reduced total lung capacity (TLC).

SPIROMETRY: Method of evaluating respiratory flow volumes and flow rates to assess pulmonary function.

CLINICAL APPROACH

Pathophysiology

The most common **etiology** for COPD is inhalation injury, specifically **cigarette smoking**. Another important cause is **alpha-1 antitrypsin deficiency**, which is hereditary; pulmonary disease may become evident by age 40 and may occur without cough or smoking history. Therapy by replacement of alpha-1 antitrypsin enzyme is available. Characteristically, patients with COPD present with progressively worsening dyspnea (first on exertion, then with activity, then at rest). Patients may vary in appearance from a "blue bloater" (chronic bronchitis, overweight, edematous, cyanotic) to a "pink puffer" (emphysema, thin, ruddy cheeks).

Arterial blood gases often are normal in the early phase of the disease; however, in more advanced disease, there is evidence of hypoxemia and hypercapnia, often with a chronic compensated respiratory acidosis as a consequence of CO_2 retention. Such chronic stable patients may have a Pao_2 near 50 mm Hg and a $Paco_2$ near 50 mm Hg, but a near-normal pH (the "50-50" club). During an acute exacerbation, more severe hypoxemia or hypercapnia, or respiratory acidosis noted on ABG, may be an indication of impending respiratory failure and need for ventilatory support. Given an appropriate clinical context, general indications for measuring ABGs include low oxygen saturation on pulse oximetry (< 92%), depressed level of consciousness, acute exacerbation, or assessment of hypercapnia in at-risk patients 30 to 60 minutes after supplemental oxygen is initiated.

Spirometry is the most basic, inexpensive, widely valuable PFT to diagnose pulmonary diseases (Figure 15–1). Spirometric tracings of **forced expiration** (Figure 15–2) and **flow-volume loops** (Figure 15–3) help to identify the type of lung disease (obstructive vs restrictive), as well as potential reversibility of airflow obstruction. **Restrictive lung diseases tend to have lower lung volumes (decreased TLC and VC)**, whereas **obstructive diseases have larger lung volumes (TLC normal or increased) with decreased expiratory flow rates (reduced FEV_1 < 80% expected, and FEV_1/FVC < 0.7)**. Specific parameters help to classify the type and degree of lung dysfunction (Table 15–2). Reduced FEV_1/FVC with minimal response to bronchodilators is the hallmark of COPD.

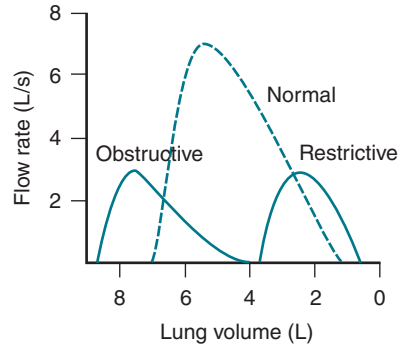


Figure 15–1. Expiratory flow-volume loops of normal, obstructive, and restrictive lung disease.

Treatment

Management of severe COPD exacerbations focuses simultaneously on relieving airway obstruction and correcting life-threatening abnormalities of gas exchange. Bronchodilators (beta-agonist and anticholinergic agents) are administered via handheld nebulizers; systemic glucocorticoids accelerate the rate of improvement in lung function among these patients. Antibiotics should be given if there is suspicion of a respiratory infection. Controlled oxygen administration with nasal oxygen at low flows or oxygen with Venturi masks will correct hypoxemia without causing severe hypercapnia. **It is prudent to watch for CO_2 retention and consequent apnea in these patients due to the effects of oxygen causing increased V/Q mismatch, loss of**

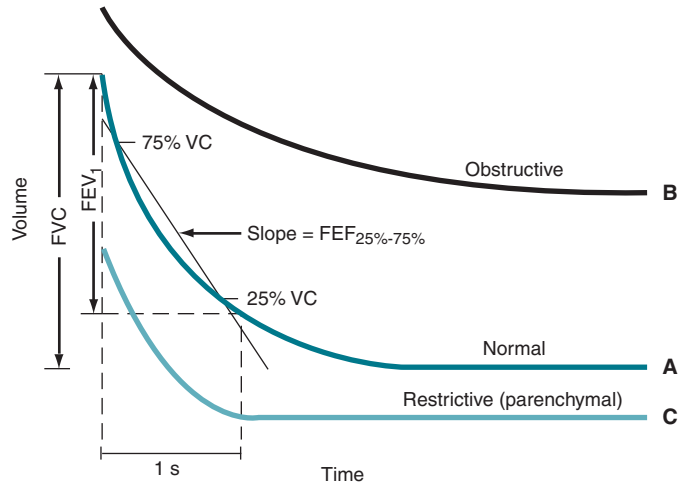


Figure 15–2. Spirographic tracing of forced expiration, comparing normal tracing (**A**) with that of patients with obstructive (**B**) and restrictive (**C**) lung disease. Calculations of FVC, FEV_1, and forced expiratory flow (FEF) (25%-75%) are shown for the normal tracing. The curves are positioned to show the relative starting lung volumes in each of these different conditions. Lung volumes increase to the left on the horizontal axis. *FEV_1*, forced expiratory volume in first second; FVC, forced vital capacity; VC, vital capacity. (Reproduced with permission, from Braunwald E, Fauci AS, Kasper KL, et al. *Harrison's Principles of Internal Medicine*. 17th ed. 2008. Copyright © McGraw Hill LLC. All rights reserved.)

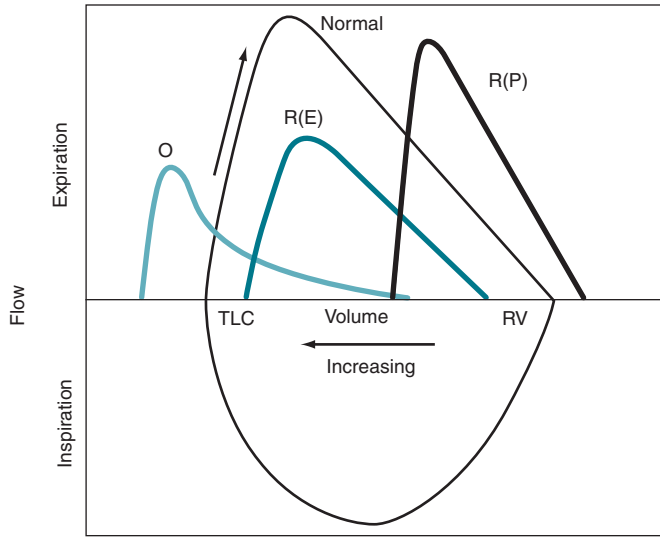


Figure 15–3. Flow-volume curves showing forced inspiratory and expiratory volumes in lung disease: O, obstructive lung disease (eg, COPD); R(P), parenchymal restrictive disease (eg, pulmonary fibrosis); R(E), extraparenchymal restrictive disease (eg, chest wall deformity) with limitation of both inspiration and expiration. Lung volumes increase to the left on the horizontal axis. TLC, total lung capacity. (Reproduced with permission, from Braunwald E, Fauci AS, Kasper KL, et al. *Harrison's Principles of Internal Medicine*. 17th ed. 2008. Copyright © McGraw Hill LLC. All rights reserved.)

hypoxemic respiratory drive, and Haldane effect. The Haldane effect describes how the binding of O_2 to hemoglobin reduces hemoglobin CO_2 affinity. Deoxygenation of blood increases the ability of hemoglobin to carry CO_2, whereas oxygenated blood has reduced capacity for CO_2.

Positive pressure mask ventilation, such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), offers an alternative to

Table 15–2 • OBSTRUCTIVE AND RESTRICTIVE LUNG DISEASE CHARACTERISTICS

	Obstructive Lung Disease	Restrictive Lung Disease	
Pulmonary Function Tests	$FEV_1/FVC < 0.7$; TLC usually normal or increased; residual volume usually increased	Decreased lung volumes: decreased VC and TLC (this is diagnostic hallmark) FEV_1/FVC is normal	
Example of Diseases	**B**ronchiectasis (ie, cystic fibrosis) **A**sthma **B**ronchitis (chronic) **E**mphysema	Extrapulmonary: poor breathing mechanics **P**oliomyelitis **M**yasthenia gravis **S**coliosis	Pulmonary: poor lung expansion **P**neumonia **A**RDS **P**ulmonary edema **I**nterstitial fibrosis

Abbreviations: ARDS, acute respiratory distress syndrome; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; VC, vital capacity.

intubation and mechanical ventilation in the treatment of cooperative patients with an acute exacerbation of COPD and severe hypercapnia. Signs of **acute respiratory failure** include **tachypnea** (respiratory rate > 40 breaths/min), **inability to speak** because of dyspnea, **accessory muscle use with fatigue** despite maximal therapy, confusion, restlessness, agitation, lethargy, **a rising $Paco_2$ level**, and extreme **hypoxemia**. Acute respiratory failure is generally treated with endotracheal intubation and mechanical ventilatory support to correct the gas exchange disorders. Complications of mechanical ventilation include difficulty in extubation, ventilator-associated pneumonia, and pneumothorax.

Other therapies such as inhaled bronchodilators (beta-agonists and/or anticholinergics) or inhaled glucocorticoids are used for symptomatic relief and to reduce the frequency of exacerbations. **Therapeutic recommendations** are **based on the disease stage**, per the Global Initiative for Chronic Obstructive Lung Disease (**GOLD**) **guidelines** (Table 15–3).

Table 15–3 • THERAPY AT EACH STAGE OF COPD

Stage	Characteristics	Recommended Treatment
All		Avoidance of risk factors Influenza vaccination
0: At risk	Chronic symptoms: cough/sputum Exposure to risk factors Normal spirometry	
1: Mild COPD	$FEV_1/FVC < 0.7$ $FEV_1 > 80\%$ predicted With or without symptoms	Short acting, on-demand bronchodilators
2: Moderate COPD	2A: $FEV_1/FVC < 0.7$ $FEV_1 > 50\%$ and/or $< 80\%$ predicted With or without symptoms 2B: $FEV_1/FVC < 0.7$ $FEV_1 > 30\%$ and/or $< 50\%$ predicted With or without symptoms	Regular treatment with one or more bronchodilators Rehabilitation Inhaled glucocorticosteroids if significant symptoms and lung function response Regular treatment with one or more bronchodilators Rehabilitation Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations
3: Severe COPD	$FEV_1/FVC < 0.7$ $FEV_1 < 30\%$ predicted, or respiratory failure, or right heart failure	Regular treatment with one or more bronchodilators Inhaled glucocorticosteroids if significant symptoms and lung function response or if repeated exacerbations Treatment of complications Rehabilitation Long-term oxygen therapy if respiratory failure Consider surgical treatments

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Complications

Long-term complications of COPD from hypoxemia can cause pulmonary hypertension, secondary erythrocytosis, exercise limitation, and impaired mental functioning. For patients with COPD who are stable, only **smoking cessation, supplemental oxygen therapy for patients with chronic hypoxemia, and lung volume reduction surgery** in selected patients have been shown to **alter the natural history of the disease** and provide a **reduction in mortality**. Patients with resting hypoxemia (Pao_2 < 55 mm Hg or arterial oxygen saturation [Sao_2arterial oxygen saturation] < 88%) generally benefit from home oxygen therapy, which must be utilized at least 18 h/d.

CASE CORRELATION

- See also Case 14 (Pulmonary Embolism), Case 16 (Chronic Cough/Asthma), Case 17 (Pleural Effusion, Parapneumonic), and Case 19 (Community-Acquired Pneumonia).

COMPREHENSION QUESTIONS

15.1 A 65-year-old man is being seen in the office for shortness of breath of 1 day's duration. He has smoked 1.5 packs of cigarettes per day for 35 years. On examination, he is cachectic and breathes with pursed lips. His chest is barrel-shaped, and the AP diameter is enlarged. Which of the following is the most likely physical examination finding in this patient?

A. Diffuse expiratory wheezing
B. Clubbing of the fingers
C. Bibasilar inspiratory crackles with increased JVP
D. Inspiratory stridor
E. Third heart sound

15.2 A 56-year-old woman is being seen in the office for a history of shortness of breath that has worsened over the past month. She admits to a 60 pack-year smoking history. She complains of fatigue and dyspnea with minimal exertion and a productive cough each morning. Pulmonary function testing is ordered. Which of the following is the most likely finding in this patient?

A. Higher diffusing capacity of lung for carbon monoxide (DLCO)
B. Decreased residual volume
C. Normal FEV_1
D. Decreased FEV_1/FVC
E. Decreased FVC

15.3 Which of the following therapies is most likely to provide the greatest benefit to a patient with chronic stable emphysema and a resting oxygen saturation of 86%?

A. Inhaled tiotropium daily
B. Inhaled albuterol as needed
C. Oral prednisone daily
D. Supplemental oxygen used at night
E. Supplemental oxygen used continuously

ANSWERS

15.1 **A.** COPD is characterized by chronic airway obstruction, with most airflow resistance occurring in small airways of the lower respiratory tract, producing expiratory wheezing. Inspiratory stridor (answer D) would occur with upper airway, usually extrathoracic, obstruction. Clubbing (answer B) is not generally a feature of COPD unless there is long-standing cyanosis and should prompt investigation for another disease process, such as a bronchogenic carcinoma. Crackles and elevated JVP (answer C), as well as an S_3 (answer E), are signs of heart failure.

15.2 **D.** This patient likely has COPD, based on the smoking history and symptoms. A decrease in the FEV_1/FVC ratio is the hallmark of airflow obstruction. The FEV_1 is decreased in obstructive and restrictive lung disease, and therefore answer C (normal FEV_1) is incorrect. The diffusing capacity is typically decreased (answer A) in COPD as well as intrinsic restrictive lung disease. The DLCO indicates the adequacy of the alveolar-capillary membrane; the residual volume is the volume of air remaining in the lungs after a maximal expiratory effort and is usually increased (answer B) in COPD due to air trapping. The FVC is typically normal to increased with COPD, which is why answer E is incorrect.

15.3 **E.** For patients with chronic hypoxemia, supplemental oxygen has a significant impact on mortality, with a greater benefit with continuous usage rather than intermittent or nocturnal-only usage (answer D). Bronchodilators such as tiotropium (answer A) and albuterol (answer B) improve symptoms and FEV_1 but offer no mortality benefit. Chronic use of oral corticosteroids (answer C) should be avoided because of unfavorable side effects, such as osteoporosis, glucose intolerance, and gastrointestinal (GI) side effects.

CLINICAL PEARLS

- Patients with obstructive lung disease have airflow limitation on expiration (reduced FEV_1/FVC), whereas patients with restrictive lung disease have difficulty in expanding their lung volumes in response to exercise (reduced TLC).
- The mainstay for treatment of COPD exacerbations includes bronchodilators, oxygen, and glucocorticoids, as well as antibiotics if infection is suspected.
- Controlled supplemental oxygen along with positive pressure mask ventilation (BiPAP) may prevent respiratory failure requiring endotracheal intubation.
- Smoking cessation and supplemental oxygen to treat chronic hypoxemia are the only medical therapies shown to decrease mortality among persons with COPD.
- In both obstructive and restrictive lung disease, the FEV_1 is decreased; the FEV_1/FVC is decreased in obstructive processes and normal in restrictive processes.
- The hallmark of restrictive lung disease is decreased lung capacity, particularly the TLC but also the VC.

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CASE 16

A 37-year-old man presents to your office with a complaint of cough. The cough began approximately 3 months prior to this appointment, and it has become progressively more annoying to the patient. The cough is nonproductive and worse at night and after exercise. The patient has had a sedentary lifestyle but recently started an exercise program, including jogging, and he says he is having a much harder time with exertion. He "runs out of breath" earlier than he did previously and "coughs a lot". He has not had any fever, blood-tinged sputum, or weight loss. He denies nasal congestion and headaches. He does not smoke and has no significant medical history. His examination is notable for a blood pressure of 134/78 mm Hg and lung findings of occasional expiratory wheezes on forced expiration. A chest radiograph is read as normal.

- What is the most likely diagnosis?
- How would you confirm the diagnosis?

ANSWERS TO CASE 16:
Chronic Cough/Asthma

Summary: A 37-year-old man presents to the office with

- A 3-month nonproductive cough that worsens at night and with exercise
- No fevers or other symptoms to suggest infection
- Occasional expiratory wheezes on forced expiration
- A normal chest radiograph
- No history of smoking

Most likely diagnosis: Bronchial asthma.

Confirmation of diagnosis: Spirometry with testing for bronchodilator responsiveness and bronchoprovocation testing if indicated.

ANALYSIS

Objectives

1. Discuss the differential diagnosis of chronic cough in adult patients. (EPA 2)
2. Understand the stepwise approach to finding the cause of cough in these patients. (EPA 1, 3)
3. Recognize how to diagnose and treat asthma. (EPA 3, 4)

Considerations

This is a 37-year-old man who presents with a chronic cough of more than 8 weeks' duration. With the history of exercise intolerance, worsening cough at night, and occasional wheezes on examination, asthma is the most likely diagnosis in this patient. A chest radiograph is important to evaluate for other processes such as tumor, infection, or other etiologies of lung injury. A focused history should look for exposure to environmental irritants, medications such as angiotensin-converting enzyme (ACE) inhibitors, or other etiologies such as postnasal drip or gastroesophageal reflux disease (GERD).

APPROACH TO: Chronic Cough

DEFINITIONS

ACUTE COUGH: Cough lasting less than 3 weeks, most commonly caused by acute upper respiratory infection but may also be caused by heart failure, pneumonia, allergic rhinitis, or exacerbation of existing structural lung disease.

ASTHMA: Condition of bronchial hyperactivity and smooth muscle hypertrophy leading to a chronic inflammatory condition of the airways associated with wide spread bronchospasm that has characteristically reversible obstruction on pulmonary function tests.

CHRONIC COUGH: Cough that often lasts more than 8 weeks. In a smoker, chronic cough is usually a symptom of chronic obstructive pulmonary disease, but bronchogenic carcinoma would be in the differential diagnosis in this population. In a nonsmoker with a normal chest radiograph and absence of ACE inhibitor use, it may be due to upper airway cough syndrome (UACS), which is usually due to postnasal drip syndrome (PNDS), GERD, or asthma.

SUBACUTE COUGH: Cough that is typically defined as lasting 3 to 8 weeks in duration and is most often infectious or postinfectious in etiology. Infectious etiologies of subacute cough include bacteria and viruses, such as respiratory syncytial virus, influenza, and adenovirus. Bacterial infections causing subacute cough are usually due to pertussis, *Chlamydia*, or mycoplasma.

CLINICAL APPROACH

Pathophysiology

Chronic cough is a common complaint and accounts for a large portion of health care expenditures. Physiologically, cough is a reflexive defense mechanism to clear the upper airways. The action of a cough serves two main functions: (1) to protect the lungs against aspiration and (2) to clear secretions or other material into more proximal airways to be expectorated from the tracheobronchial tree. Evaluation begins with a detailed history and physical examination, including smoking habits, complete medication list, environmental and occupational exposures, and any history of lung disease. Specific questions regarding the precipitating factors and duration and nature of the cough should be elicited. Although the physical examination or nature of the cough rarely identifies the cause, meticulous review of the ears, nose, throat, and lungs may suggest a particular diagnosis. For example, a cobblestone appearance of the oropharynx (representing lymphoid hyperplasia) or boggy erythematous nasal mucosa can be consistent with UACS. **End-expiratory wheezing suggests active bronchospasm, whereas localized wheezing may be consistent with a foreign body or a bronchogenic tumor.**

In more than 90% of cases, a normal chest radiograph in an immunocompetent nonsmoker guides the clinician to one of three diagnoses: **UACS, asthma, or GERD.**

Chronic cough in an immunocompromised patient is beyond the scope of this discussion. In the outpatient setting, the mainstay of diagnosis relates to the response with empiric therapy, and multiple etiologies (UACS and GERD) are often simultaneously addressed. Often, a definitive diagnosis for chronic cough depends on observing a successful response to therapy. A rational approach includes discontinuing an ACE inhibitor if the patient is using one, obtaining a chest radiograph, and avoiding environmental irritants. If persistent, then UACS, asthma, and GERD should be considered. Referral to a pulmonologist is recommended when the diagnostic and empiric therapy options are exhausted. If suspicion for carcinoma is high, a high-resolution computed tomography (CT) scan of the thorax or bronchoscopy should be pursued. A diagnosis of psychogenic cough should be one of exclusion. See Figure 16–1 for an example of an algorithm.

Upper Airway Cough Syndrome

Upper airway cough syndrome can be attributed to sinusitis and the following types of rhinitis, alone or in combination: nonallergic, allergic, postinfectious, vasomotor, drug induced, and environmental irritant induced. Since the symptoms may be nonspecific (eg, frequent throat clearing, nasal discharge, or sensation of liquid in the throat), no definitive diagnostic criteria exist for UACS, and response to therapy confirms the diagnosis. Initial treatment for a nonallergic etiology usually includes combination treatment with a first-generation antihistamine and a decongestant for 3 weeks. For allergic rhinitis, a newer-generation antihistamine, along with a nasal corticosteroid, should be used. If the patient's symptoms do not improve, sinus radiographs may be ordered. Opacification, air-fluid levels, or mucosal thickening could suggest sinusitis, which can be treated with antibiotics when indicated.

Asthma

Asthma is a chronic inflammatory disease of the airways characterized by air way obstruction, bronchial hyperresponsiveness, and mucus hypersecretion with recurring symptoms. These symptoms are often reversible spontaneously or with treatment.

Although wheezing is considered a classic sign of asthma, **cough is often the only symptom.** Cough-variant asthma usually presents with a dry cough that occurs throughout the day and night, and is worsened by airway inflammation from viral infections of the upper respiratory tract, allergies, cold air, or exercise. Although the history may be suggestive of asthma, the diagnosis should be confirmed with pulmonary function tests. Spirometry can confirm airflow obstruction with reduced forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC); spirometry will also demonstrate reversibility with improved FEV_1 after inhalation of a bronchodilator, typically a beta-agonist. Positive bronchodilator responsiveness is defined as reversible obstruction with an increase in FEV_1 or FVC of more than 12% and an increase of 200 mL of volume after bronchodilator treatment. If the diagnosis is in doubt, bronchial hyperresponsiveness (the fundamental pathophysiologic abnormality in asthma) can be confirmed by a reduction in FEV_1 after

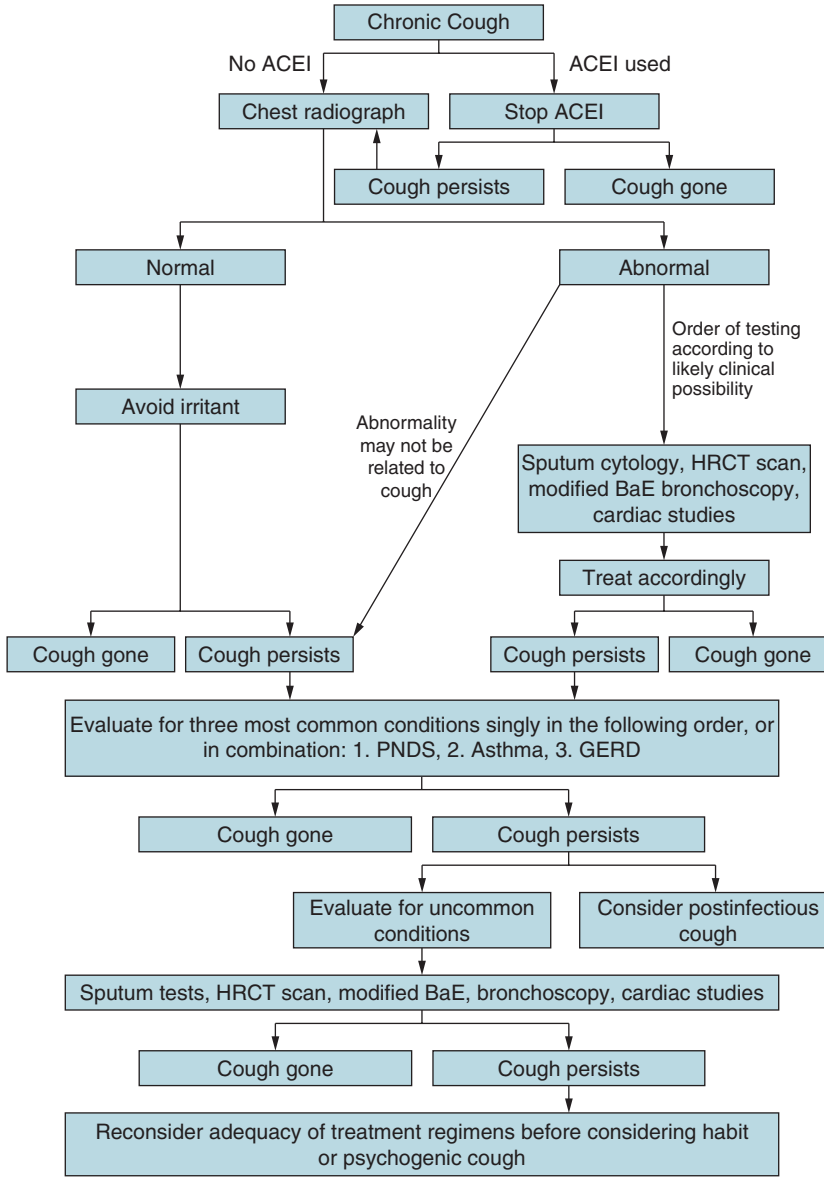


Figure 16–1. Algorithm for diagnosis and treatment of chronic cough. ACEI, angiotensin-converting enzyme inhibitor; BaE, barium esophagography; GERD, gastroesophageal reflux disease; HRCT, high-resolution computed tomography; Hx, history; PE, pulmonary embolism; PNDS, postnasal drip syndrome. (Data from Irwin RS, Boulet L-P, Cloutier MM, et al. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. *Chest*. 1998;114[Suppl]:133S-181S.)

Table 16–1 • GUIDELINES FOR DIAGNOSIS AND MANAGEMENT OF ASTHMA

Classification	Step	Days With Symptoms	Nights With Symptoms	Daily Medication	Quick Relief Medication
Severe persistent	4	Continual	Frequent	High-dose inhaled steroids and long-acting inhaled beta-2 agonist; if needed, add oral steroids	Short-acting inhaled beta-2 agonist, as needed; oral steroids may be required
Moderate persistent	3	Daily	> 1/wk	Low- to medium-dose inhaled steroids and long-acting beta-2 agonist (preferred) or medium-dose inhaled steroids or low- to medium-dose inhaled steroids and either leukotriene modifier or theophylline	Short-acting inhaled beta-2 agonist, as needed; oral steroids may be required
Mild persistent	2	> 2/wk, but < 1 time/d	> 2/mo	Low-dose inhaled steroids (preferred) or cromolyn, leukotriene modifier, or nedocromil	Short-acting inhaled beta-2 agonist, as needed; oral steroids may be required
Mild intermittent	1	< 2/wk	< 2/mo	No daily medications	Short-acting inhaled beta-2 agonist, as needed; oral steroids may be required

challenge with a provocative agent such as methacholine or histamine. If methacholine is used, a positive test is defined as a 20% fall in FEV_1. Approach to asthma management is stepwise with use of asthma controllers such as inhaled corticosteroids (and if needed systemic corticosteroids), which inhibit airway inflammation, and bronchodilators for rapid relief of symptoms. Current guidelines emphasize a preventive approach and a stepwise approach to therapy based on asthma severity and control (Table 16–1).

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease often can be clinically inapparent. It may be the primary or coexisting cause of the cough, such as the result of aspiration and vagal stimulation. Initial treatment includes lifestyle modification along with medical

therapy. Recommendations include a low-fat diet, elevation of the head of the bed, avoidance of offending foods (caffeine, alcohol, chocolate), smoking cessation, and weight reduction. If the cough does not resolve with lifestyle changes, daily treatment should be initiated with an H_2 receptor antagonist, such as famotidine, or a proton pump inhibitor, such as omeprazole. If acid suppression does not resolve the symptoms and if there are other symptoms of dyspepsia, a gastric motility stimulant such as metoclopramide may be considered.

Patients who remain symptomatic after maximal medical treatment may benefit from 24-hour esophageal pH monitoring to confirm the diagnosis. An esophagogastroduodenoscopy showing esophagitis or an upper gastrointestinal radiographic series demonstrating reflux further supports the diagnosis. Of note, gastrointestinal symptoms may resolve prior to resolution of the cough, and full resolution may require 2 to 3 months of intensive medical therapy.

CASE CORRELATION

- See also Case 14 (Pulmonary Embolism), Case 15 (Chronic Obstructive Pulmonary Disease), Case 17 (Pleural Effusion, Parapneumonic), and Case 19 (Community-Acquired Pneumonia).

COMPREHENSION QUESTIONS

16.1 A 21-year-old man with known asthma has been placed on a regimen consisting of inhaled corticosteroids and intermittent (short-acting) beta-2-agonist. He is being seen in the office with a new complaint of nocturnal awakenings secondary to cough and occasional wheezing. These episodes occur three to four times per week. Six months ago, his pulmonary function testing revealed an FEV_1 of 80% of predicted, and FEV_1/FVC of 70% of predicted. Which of the following is the best next step?

A. Oral steroids
B. Leukotriene inhibitors
C. Long-acting beta-2-agonists (LABAs)
D. Theophylline
E. Antireflux therapy

16.2 Which of the following is most accurate?

A. Cough caused by captopril may resolve with switching to enalapril.
B. Initial treatment of a chronic cough should include codeine or a similar opiate derivative to suppress the cough.
C. Cough caused by reflux can be effectively ruled out by a negative history of heartburn or dyspepsia.
D. More than one condition is often responsible for causing chronic cough in a given patient.

16.3 A 22-year-old woman presents with fatigue, arthralgias, and a nagging dry cough for the past 6 weeks, but no shortness of breath. On physical examination, her lungs are clear to auscultation, and she has bilateral pretibial tender erythematous raised nodules. Which of the following is your best next step?

A. Chest radiograph
B. High-resolution CT
C. Empiric treatment for postnasal drip
D. Antinuclear antibody test
E. Initiation of antituberculosis therapy

16.4 An obese 50-year-old man with a history of asthma is being seen in the clinic with complaints of occasional dyspepsia and nocturnal cough. He notes that he wakes up in the morning with a sour taste in his mouth. His current medications include an inhaled corticosteroid and a short-acting beta-2-agonist. Which of the following should be your next step?

A. 24-hour esophageal pH monitoring
B. Chest radiograph
C. Initiation of omeprazole
D. Short course of oral corticosteroids
E. Initiation of allergy desensitization

ANSWERS

16.1 **C.** Long-acting beta-2-agonists are indicated in this situation. The asthma would be classified as moderate persistent because of the exacerbations more than once a week and nocturnal symptoms more than once a week; the recommended treatment is addition of LABAs (such as salmeterol) to the inhaled corticosteroids. LABA therapy is particularly helpful with nocturnal symptoms. The logical augmentation therapy following guidelines makes the other options (answer A, oral steroids; answer B, leukotriene inhibitors; and answer D, theophylline) less useful (see Table 16–1). This patient does not show signs of GERD, so answer E (antireflux therapy) is not the best choice.

16.2 **D.** Often, more than one condition is responsible for causing chronic cough in a given patient. Cough from ACE inhibitors (answer A) is class dependent, and change to another class of antihypertensives is more appropriate. The etiology of chronic cough should be determined prior to suppression of the cough (answer B) because treatment of the underlying condition is the most effective approach. A patient with GERD (answer C) may present with the sole manifestation of cough, sometimes with no perceivable acid reflux.

16.3 **A.** The patient has clinical features suggestive of sarcoidosis given the new cough, arthralgias, and description of erythema nodosum. The initial, most cost-effective study is a chest radiograph. Hilar lymphadenopathy with

or without interstitial infiltrates would solidify a diagnosis of sarcoidosis. A high-resolution CT (answer B) may be ordered if the patient has interstitial lung disease, but it is not the first study of choice. Treating postnasal drip (answer C) does not investigate the patient's other symptoms. An antinuclear antibody test (answer D) would not necessarily identify the cause of the cough or provide a diagnosis. Antituberculosis therapy (answer E) is indicated in a patient with suspected tuberculosis. The clinical presentation of tuberculosis includes fever, night sweats, productive or bloody cough, weight loss, and exposure to a patient with tuberculosis.

16.4 **C.** The dyspepsia and the sour taste suggest GERD. Omeprazole is an oral proton pump inhibitor, which is a noncompetitive inhibitor of the H^+-K^+-ATPase (adenosine triphosphatase) pump in parietal cells and is useful in patients with GERD. Aside from acid suppression, other recommendations include dietary modifications and weight reduction. Esophageal pH monitoring for 24 hours (answer A) is indicated only if there is no response to treatment, and it is not indicated initially. Chest radiography (answer B) is only indicated if there are symptoms of cough or aspiration such as pneumonia. Answer D (short course of oral corticosteroids) is indicated with an acute exacerbation that does not respond to nebulized beta-adrenergic agonist therapy. Answer E (allergy desensitization) is indicated with patients with moderate-to-severe asthma when there is evidence of allergic reaction to various antigens.

CLINICAL PEARLS

- A normal chest radiograph excludes most, **but not all**, of the serious and uncommon causes of chronic cough.
- The three most common causes of chronic cough in immunocompetent nonsmokers who are not taking ACE inhibitors are UACS, asthma, and GERD.
- Cough caused by ACE inhibitors can be triggered after the first dose or may occur after months of therapy.
- Treatment of asthma is a stepwise process based on frequency of symptoms and response to prescribed medications.
- Asthma can be the cause of cough in a patient with a normal examination and pulmonary function tests. If suspicion is high, a positive methacholine challenge has a high predictive value.
- Definitive diagnosis of the etiology of chronic cough is not always necessary for successful treatment.

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CASE 17

A 32-year-old woman presents to the emergency center complaining of a productive cough, fever, and chest pain for 4 days. She was seen 2 days ago in her primary care provider's clinic with the same complaints; she was diagnosed clinically with pneumonia and was sent home with oral azithromycin. Since then, her cough has diminished in quantity. However, the fever has not abated, and she still experiences left-sided chest pain, which is worse when she coughs or takes a deep breath. In addition, she has started to feel short of breath when she walks around the house. She has no other medical history. She does not smoke and has no history of occupational exposure. She has not traveled outside of the United States and has no sick contacts.

On physical examination, her temperature is 103.4 °F, heart rate is 116 beats per minute (bpm), blood pressure is 128/69 mm Hg, and respiratory rate is 24 breaths/min and shallow. Her pulse oximetry is 94% saturation on room air. Physical examination is significant for decreased breath sounds in the lower half of the left lung fields posteriorly, with dullness to percussion between the fifth and eighth intercostal spaces at the midclavicular line. There are a few inspiratory crackles in the midlung fields, and her right lung is clear to auscultation. She has sinus tachycardia with no murmurs. She has no cyanosis. Figure 17–1 shows her chest x-ray films.

- What is the most likely diagnosis?
- What is your next step in management?
- What are the most common causes of this condition?

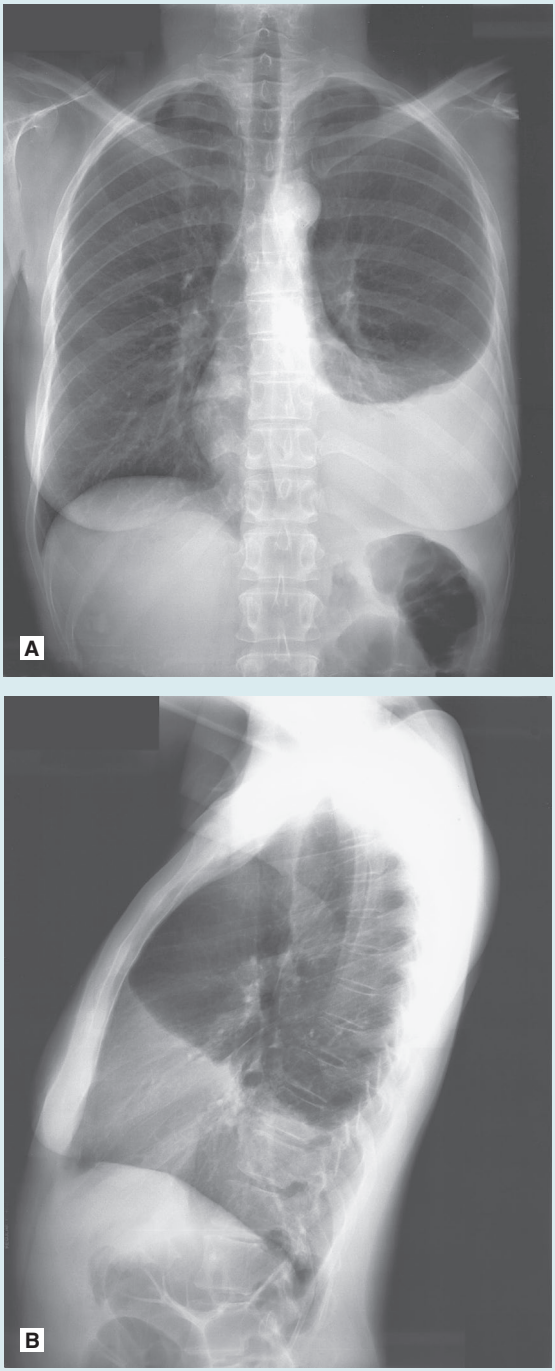


Figure 17–1. (**A**) Posteroanterior film of the chest. (**B**) Lateral chest film of the same patient. (Courtesy of Dr. Jorge Albin.)

ANSWERS TO CASE 17:
Pleural Effusion, Parapneumonic

Summary: A 32-year-old previously healthy woman presents with

- A 4-day history of productive cough, fever, and chest pain
- Clinical diagnosis of community-acquired pneumonia, not improved with oral azithromycin
- Vital signs: febrile, tachycardic, tachypneic with hypoxemia on room air
- Diminished breath sounds and left-sided dullness to percussion
- Chest radiography confirming a large left-sided pleural effusion
- Effusion that is likely caused by infection in the adjacent lung parenchyma and that may be the cause of her failure to improve on antibiotics

Most likely diagnosis: Parapneumonic effusion as a complication of pneumonia.

Next step: Diagnostic thoracentesis to help diagnose the cause of the pleural effusion and to determine the necessity for fluid drainage.

Most common causes: Underlying pneumonia, malignancy, pulmonary embolism, tuberculosis.

ANALYSIS

Objectives

1. Understand the use of Light criteria to distinguish transudative effusions from exudative effusions as a guide to the etiology of the effusion. (EPA 1, 3)
2. Describe the pleural fluid characteristics that suggest a complicated parapneumonic effusion or empyema and the need for drainage. (EPA 3, 4)
3. State the treatment of a complicated parapneumonic effusion that does not improve after thoracentesis. (EPA 4, 10)

Considerations

If the pleural effusion is large and free flowing, which can be evaluated with a lateral decubitus film, then diagnostic thoracentesis can easily be accomplished. It is important to determine if the effusion is, in fact, caused by the pneumonia, and, if so, whether it is likely to resolve with antibiotics alone or will require drainage with tube thoracostomy.

APPROACH TO:
Pleural Effusion

DEFINITIONS

EMPYEMA: Collection of pus in the pleural cavity.

EXUDATE: Effusion caused by inflammatory or malignant causes, with high protein or high lactate dehydrogenase (LDH) levels.

PLEURAL EFFUSION: Accumulation of fluid in the pleural space.

TRANSUDATE: Effusion caused by alteration of hydrostatic and oncotic forces, with low protein and low LDH levels.

CLINICAL APPROACH

Pathophysiology

Pleural effusions occur in 40% of patients with an underlying bacterial pneumonia. Most of these effusions should resolve with appropriate antibiotic treatment, but if the fluid characteristics predict a **"complicated" parapneumonic** effusion, urgent tube drainage is indicated to prevent formation of fibrous peels, which may need surgical decortication.

Diagnostic thoracentesis should be considered for every patient who presents with a pleural effusion with unknown cause. An exception to this rule is if the patient is known to have heart failure (HF) with equal bilateral effusions or if the effusion is too small—that is, less than 10 mm—on lateral decubitus film. However, if the pleural effusion of HF does not significantly improve after a trial of diuresis, a diagnostic thoracentesis should be performed. Another exception would be in patients with fluid overload states, such as in end-stage renal disease or nephrotic syndrome, where dialysis will help with the clearing of effusions. Table 17–1 gives

Table 17–1 • PLEURAL FLUID APPEARANCE AND DIFFERENTIAL DIAGNOSIS

Pleural Fluid Appearance	Diagnoses to Consider
Clear yellow	Transudative, eg, secondary to heart failure, cirrhosis, nephrotic syndrome
Frank pus	Empyema
Bloody	If hematocrit (Hct) of pleural fluid is > 50% of Hct in peripheral blood: hemothorax, secondary to trauma (most likely), rupture of blood vessel, or malignancy—these conditions often require tube thoracostomy If Hct < 50% of peripheral blood: cancer, pulmonary embolism, tuberculosis
Milky, turbid	Chylothorax triglycerides > 110 mg/dL (secondary to disruption of thoracic duct), cholesterol effusion
Dark green	Biliothorax

the correlations of pleural fluid appearance. As little as 5 to 10 mL can be visualized on a lateral decubitus film (it is more reliable in detecting smaller effusions), and fluid volume more than 500 mL usually obscures the whole hemidiaphragm. Ultrasound is an additional tool that can be easily used to identify pleural effusions.

Transudate Versus Exudate. Transudative and exudative fluids can be differentiated by the amount of measured protein and LDH, which correlate with the pathophysiology of the fluid formation. Approximately 12 mL of pleural fluid is formed every day by the parietal pleural capillaries and absorbed also by the parietal pleura (lymphatics). Processes that disturb this equilibrium lead to fluid accumulation. Clinical settings in which the hydrostatic pressure is increased (HF and constrictive pericarditis), the oncotic pressure is decreased (nephrotic syndrome and cirrhosis), or the intrapleural pressure is reduced (atelectasis), lead to the formation of a "transudate." In contrast, "exudates" are more a result of local inflammation and increased capillary permeability—for example, infection, malignancy, and connective tissue diseases, which cause proteins to leak into the pleural space. Less commonly, impaired lymphatic drainage, as occurs in chylothorax or lymphangitic spread of a malignancy, may cause an exudative fluid. Pulmonary emboli can cause both exudative and transudative effusions (exudative is much more common). Tables 17–2 and 17–3 list the etiologies of transudative and exudative pleural effusions, respectively.

Light Criteria. The most widely used criteria to distinguish between a transudative and exudative fluid are the Light criteria first described in 1997. For a fluid to be labeled an **exudate**, it must meet **at least one of the following criteria** (transudates meet none of these criteria):

1. Pleural fluid protein/serum protein ratio > 0.5
2. Pleural fluid LDH/serum LDH ratio > 0.6
3. Pleural fluid LDH > 2/3 the upper limit of normal for serum LDH

Pleural LDH correlates with the degree of **pleural inflammation** and, along with **fluid protein**, should always be sent in the initial evaluation.

Table 17–2 • CAUSES OF TRANSUDATIVE PLEURAL EFFUSIONS

Transudate	Clinical Correlates or Radiographic Features
Heart failure	Most commonly bilateral and symmetric, at times isolated right-sided effusion
Nephrotic syndrome	Bilateral and subpulmonic effusion; due to hypoalbuminemia, third spacing
Cirrhosis	Likely with significant ascites
Myxedema	Uncommon; usually occurs along with ascites, signs of heart failure in advanced hypothyroidism
Pulmonary embolism	May also be exudative or bloody; rarely large

Table 17–3 • CAUSES OF EXUDATIVE PLEURAL EFFUSIONS

Exudate	Comment
Infection	Bacterial pneumonia, viral etiology, fungal infection, parasitic (eosinophilic) involvement; subdiaphragmatic abscesses
Tuberculosis	One-third have parenchymal involvement; lymphocytes > 80%; adenosine deaminase > 40 U/L; total protein > 4.0 g/dL; diagnostic yield of fluid for acid-fast bacilli < 10%; pleural biopsy increases yield to between 80% and 90%
Malignancy	Lymphocytic predominant and occasionally bloody; cytologic examination positive in > 50% of cases (especially adenocarcinoma and small-cell carcinoma); usually indicative of very poor prognosis
Connective tissue disease	Rheumatoid pleurisy: very low glucose, rheumatoid factor > 1:320 and LDH > 700 IU/L; more common in men
Lupus	Lupus pleuritis: lupus erythematosus cells are highly specific; pleural fluid/serum antinuclear antibody > 1.0; usually responsive to steroid treatment
Pancreatitis	Elevated pancreatic amylase isoenzyme; salivary isoenzyme seen in esophageal rupture with associated low pH
Chylothorax	Triglycerides > 110 mg/dL
Asbestos exposure	Spectrum of disease ranges from pleural plaques to effusion and malignancy; may be eosinophilic

Treatment

In contrast to the simple "diagnostic" thoracentesis that can be performed to evaluate the contents of the fluid, a "therapeutic" thoracentesis may also be performed if the patient is dyspneic as a result of a significant amount of fluids. The purpose is to remove large volumes of fluid (up to 1.5 L) for patient comfort and clinical improvement. Of note, removal of large amounts of fluid puts the patient at risk for developing reexpansion pulmonary edema.

If tube thoracostomy drainage is required, a chest tube is placed until the drainage rate has decreased to less than 50 mL/d. Postdrainage imaging must be obtained to confirm complete drainage of fluid and to assess the need for placement of a second tube if the fluid has not been adequately drained (as is often seen if the effusion is loculated). The following fluid characteristics suggest the need for chest tube drainage:

- **Most sensitive: pH < 7.20 (normal pH 7.6)**
- Positive Gram stain or culture of fluid
- Presence of loculations
- **Empyema (frank pus in the pleural space)**
- Glucose less than 60 mg/dL
- LDH more than 1000 U/L

If the patient does not meet the criteria for immediate drainage, a 1-week trial of antibiotics is indicated, with close reevaluation of those patients who do not respond or who clinically deteriorate.

In empyema, 4 to 6 weeks of antibiotic therapy are necessary for complete sterilization. Poorly draining or multiloculated empyemas are treated further by administering a combination of fibrinolytic agents such as tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) through the chest tube. Video-assisted thoracoscopic surgery with debridement and drainage is the next option if the combination of tPA and DNase fail in clearing the loculations. Thus, surgical referral is encouraged within a week of failure of medical therapy (tube thoracostomy with or without tPA and DNase).

CASE CORRELATION

- See also Case 14 (Pulmonary Embolism), Case 15 (Chronic Obstructive Pulmonary Disease), and Case 16 (Chronic Cough/Asthma).

COMPREHENSION QUESTIONS

17.1 A 55-year-old man with HF presents to the emergency department with a 1-week history of dyspnea on exertion and swelling in both ankles. He has had no fever or cough. Chest radiography shows bilateral pleural effusions. Which of the following is the most likely pleural fluid characteristic if thoracentesis is performed?

A. Pleural fluid LDH 39, LDH ratio 0.2, protein ratio 0.7
B. Pleural fluid LDH 39, LDH ratio 0.2, protein ratio 0.1
C. Pleural fluid LDH 599, LDH ratio 0.9, protein ratio 0.1
D. Pleural fluid LDH 599, LDH ratio 0.9, protein ratio 0.7

17.2 A 39-year-old man develops a moderate free-flowing pleural effusion following a left lower lobe pneumonia. Thoracentesis reveals straw-colored fluid with gram-positive diplococci on Gram stain, pH 6.9, glucose 32 mg/dL, and LDH 1890. Which of the following is the best next step?

A. Send the fluid for culture.
B. Continue treatment with antibiotics for pneumococcal infection.
C. Drain the effusion via tube thoracostomy.
D. Schedule a follow-up chest x-ray in 2 weeks to document resolution of the effusion.

17.3 A 69-year-old man is being seen in the emergency center for gradually worsening dyspnea and a nagging cough over the past 3 months. He denied feeling warm or having fever. The chest radiograph shows a right-sided pleural effusion. A diagnostic thoracentesis reveals gross blood in the fluid. Which of the following is the most likely diagnosis?

A. Parapneumonic effusion

B. Malignancy in the pleural space

C. Rupture of aortic dissection into the pleural space

D. Pulmonary embolism with pulmonary infarction

ANSWERS

17.1 **B.** Heart failure is commonly associated with bilateral pleural effusions, which are **transudative**, as a consequence of alteration of Starling forces. The effusions of heart failure are best managed by treating the heart failure, for example, with diuretics, and typically do not require thoracentesis. Per Light criteria, the other answer choices would be classified as an exudative pleural effusion. Exudative effusion criteria include pleural fluid: serum protein > 0.5; pleural fluid: serum LDH > 0.6; and pleural fluid LDH > 2/3 upper limits for serum.

17.2 **C.** Drainage with chest thoracostomy is the best treatment for this patient. The positive Gram stain, low pH, low glucose, and markedly elevated LDH all suggest that this parapneumonic effusion is "complicated," that is, it is unlikely to resolve with antibiotic therapy; this effusion is likely to produce loculated pockets of pus, which will require drainage with tube thoracostomy. While continuing the therapy with antibiotics (answer B) is appropriate, it is also insufficient in the case of an empyema, which is the situation at present with this patient. Answer A (Send the fluid for culture) is usually performed, but it often is negative for growth; although antibiotics and culture are important adjuvant measures, the most important intervention is fluid drainage. Answer D (Schedule a follow-up chest x-ray in 2 weeks) is inappropriate and will lead to patient decompensation.

17.3 **B.** The most common causes of hemorrhagic pleural effusion are trauma, malignancy, and pulmonary embolism. Pulmonary embolism (answer D) would be suggested by acute onset of dyspnea and pleuritic chest pain rather than this subacute presentation. Aortic rupture (answer C) can produce a hemothorax but would have an acute presentation with chest and back pain and hemodynamic compromise. Parapneumonic effusion (answer A) is a collection of purulent fluid that arises from pneumonia, lung abscess, or bronchiectasis; the aspirated fluid would be purulent and not bloody.

CLINICAL PEARLS

- Transudative effusions meet **none** of the following criteria (exudative effusions meet at least one): (a) pleural fluid protein/serum protein ratio more than 0.5; (b) pleural fluid LDH/serum LDH ratio more than 0.6; (c) pleural fluid LDH greater than two-thirds normal serum LDH.
- Tube thoracostomy or more aggressive drainage of parapneumonic effusion usually is required with gross pus (empyema), positive Gram stain or culture, glucose less than 60 mg/dL, pH less than 7.20, and loculations.
- The most common cause of pleural effusion is HF, which typically results in bilateral symmetric transudative effusions and is best treated with diuresis.
- The most common causes of bloody pleural effusion (in the absence of trauma) are malignancy and pulmonary embolism with infarction.

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CASE 18

A 68-year-old woman is brought to the emergency center after coughing up several tablespoons of bright red blood. For the previous 3 to 4 months, she has had a chronic nonproductive cough but no fevers. More recently, she has noticed some scant blood-streaked sputum. She also reports increased fatigue, decreased appetite, and a 25-lb weight loss in the past 3 months. She denies chest pain, fever, chills, or night sweats. The patient drinks two martinis every day and has smoked one pack of cigarettes per day for the past 35 years. Other than alcohol and tobacco use, she has not had any additional medical issues. She worked in a library for 35 years and has no history of occupational exposures. She does not take any medication except for one low-dose aspirin per day.

The patient is a mildly anxious appearing, thin woman who is alert and oriented. Her blood pressure is 150/90 mm Hg, heart rate is 88 beats per minute (bpm), respiratory rate is 16 breaths/min, and temperature is 99.2 °F. Neck examination reveals no lymphadenopathy, thyromegaly, or carotid bruit. The chest has scattered rhonchi bilaterally, with no wheezes or crackles. Cardiovascular examination reveals a regular rate and rhythm, without rubs, gallops, or murmurs. The abdomen is benign with no hepatosplenomegaly. Examination of her extremities reveals no cyanosis; there is finger clubbing. Neurologic examination is normal.

- What is your next step?
- What is the most likely diagnosis?
- What is the major risk factor?

ANSWERS TO CASE 18:
Hemoptysis/Lung Cancer

Summary: A 68-year-old woman presents with

- A history of smoking one pack of cigarettes per day for the past 35 years
- A chronic, nonproductive cough with recent blood-streaked sputum
- Increased fatigability, reduced appetite, and 3 months of unintentional weight loss
- Absence of fever, chills, and night sweats
- Physical examination revealing scattered rhonchi bilaterally and digital clubbing

Next step: Chest imaging, either x-ray or computed tomography (CT) scan.

Most likely diagnosis: Lung cancer is the most likely diagnosis due to the presence of hemoptysis, unintentional weight loss, and clubbing of the fingers in an individual with significant smoking history.

Major risk factor: Smoking, especially for longer than 30 years.

ANALYSIS

Objectives

1. Describe the differential diagnosis for hemoptysis. (EPA 2, 10)
2. Be familiar with the risk factors for and the clinical presentation of lung cancer (including superior vena cava [SVC] syndrome and Horner syndrome). (EPA 1, 3, 12)
3. Know the workup of the solitary pulmonary nodule. (EPA 3)
4. List the general principles of the treatment of lung cancer. (EPA 4, 9)

Considerations

The most likely diagnosis in this case is lung cancer. On physical examination, there is finger clubbing, which is an enlargement of the terminal digital phalanges with loss of the nail bed angle. In pulmonary disease, clubbing of the fingers is most commonly seen in patients with lung cancer, interstitial pulmonary fibrosis, or chronic septic conditions, such as bronchiectasis or lung abscess. This patient will require imaging studies such as a chest x-ray and likely CT of the chest and, if abnormalities are seen, a biopsy procedure to establish a tissue diagnosis. In the meantime, she will benefit from rest and cough suppression to minimize her hemoptysis, which may be acutely life threatening if massive bleeding occurs. Though it may not affect prognosis, it is advisable that she also stop smoking at this time.

APPROACH TO:
Hemoptysis and Lung Cancer

DEFINITIONS

HORNER SYNDROME: Symptoms are ptosis, loss of pupillary dilation (miosis), and loss of sweating on the ipsilateral side (anhidrosis) caused by compression of the superior cervical ganglion and resultant loss of sympathetic innervation. This is usually related to a superior sulcus tumor.

HEMOPTYSIS: An expectoration of blood from the respiratory tract.

MASSIVE HEMOPTYSIS: A consensus definition has not been established but typically is defined as 250 mL or more of fresh blood coughed up in 24 hours.

SUPERIOR VENA CAVA (SVC) SYNDROME: Obstruction of venous drainage, usually by extrinsic compression of the SVC, leading to edema of the face, neck, and upper part of the torso, and formation of prominent collateral veins on the upper chest.

CLINICAL APPROACH TO HEMOPTYSIS

Pathophysiology

Hemoptysis is an alarming symptom, both because it may be a manifestation of a serious underlying diagnosis, such as malignancy, and because massive hemoptysis itself can be deadly by filling up alveolar air spaces and causing asphyxiation. Hemoptysis, particularly if in large amounts or recurrent, is a potentially fatal event, thus requiring an immediate search for the cause and precise location of the bleeding. Hemoptysis must be differentiated from hematemesis and epistaxis. Currently, **the most common causes of hemoptysis in the United States are bronchitis and lung cancer**. In prior eras, the most common causes have been tuberculosis, lung abscess, and bronchiectasis. As stated previously, a good history is an important diagnostic step: Blood-streaked purulent sputum suggests bronchitis; **chronic copious sputum production suggests bronchiectasis. Hemoptysis with an acute onset of pleuritic chest pain and dyspnea** suggests a **pulmonary embolism**.

Clinical Presentation

History. A targeted history for patients presenting with hemoptysis is an essential diagnostic step, as it may direct the subsequent steps. It is important to discern how much blood has been expectorated in the past 24 hours and how often the hemoptysis as occurred. These questions are essential in evaluating the acuity and severity of the hemoptysis and may prompt additional questions, such as whether the patient's airway needs to be protected emergently. It is also necessary to probe about a past history of chronic respiratory disease or respiratory problems (chronic obstructive pulmonary disease, cystic fibrosis, chronic bronchitis, interstitial lung fibrosis, recurrent pneumonia). Specific lung diseases may predispose to bronchiectasis and to airway diseases more prone to hemoptysis. Questions regarding an

infectious etiology are also imperative. Is the blood mixed with phlegm? Is that sputum clear or purulent? Additionally, fevers, chills, and night sweats may lead to either an infectious or malignant root cause depending on severity and frequency. Smoking history and environmental exposures should also be assessed. These questions should be followed up by asking about degree and duration of exposure.

Physical examination. Examination of a patient can reveal many cues regarding what the underlying diagnosis may be. When presenting with hemoptysis, the lung examination is of particular importance, but additional hints may be supplied by a complete physical examination. Pulmonary examination may reveal rhonchi or low-pitched continuous sounds that suggest secretions in the airway, and/or wheezes or high-pitched continuous sounds with a hissing quality that suggest narrowed airways. Crackles (rales) are considered intermittent discontinuous sounds and may point to several different ailments, such as heart failure, pneumonia, bronchitis, or bronchiectasis. Clubbing of the fingers is defined as enlargement of the terminal digital phalanges with loss of the nail bed angle. In pulmonary disease, clubbing of the fingers is most commonly seen in patients with lung cancer, interstitial pulmonary fibrosis, or chronic septic conditions, such as bronchiectasis or lung abscess.

Laboratory Tests/Imaging. Every patient with hemoptysis should undergo a chest x-ray or CT to look for a mass lesion, evidence of bronchiectasis, or parenchymal lung disease. If the chest imaging reveals a lung mass, the patient should undergo fiber-optic bronchoscopy to localize the site of bleeding and to visualize and attempt to biopsy any endobronchial lesion.

Treatment

Patients with massive hemoptysis require urgent measures to maintain their airway and to prevent spilling of blood into unaffected areas of the lungs. These patients should be kept at rest with cough suppressants. If the bleeding is localized to one lung, the affected side should be placed in a dependent position so that bleeding does not flow into the contralateral side. They may also require endotracheal intubation and rigid bronchoscopy for better airway control and suction capacity. Urgent referral to interventional radiology for bronchial artery embolization or thoracic surgery for resection may also be required if bleeding is not amenable to bronchoscopic intervention.

CLINICAL APPROACH TO LUNG CANCER

Pathophysiology

Primary lung cancer, or bronchogenic carcinoma, is the leading cause of cancer deaths in both men and women. Approximately 85% of lung cancers of all cell types are linked to smoking. Of the 15% of lung cancers that are not related to smoking, the majority are found in women for reasons that are unknown. Thoracic radiation exposure and exposure to occupational or environmental toxins, such as asbestos or radon, are also associated with increased risk of developing lung cancer.

Data from the National Lung Screening Trial demonstrated a reduction in lung cancer mortality in select high-risk patients who undergo an annual low-dose CT scan of the chest; these high-risk patients include adults 55 to 80 years old with a 30 pack-year smoking history who are current smokers, or quit within the last 15 years, and do not have other life-limiting diseases.

Clinical Presentation

Only 5% to 15% of patients with lung cancer are asymptomatic when diagnosed. In these cases, a lung nodule usually is found incidentally on chest x-ray or CT.

Endobronchial tumors may present with cough or with hemoptysis. Chest pain is also a possible symptom of lung cancer and suggests pleural involvement or neoplastic invasion of the chest wall. Constitutional symptoms like weight loss, malaise, and fatigue usually develop later in the disease course. Malignant pleural effusion is common and may lead to presenting symptoms of shortness of breath and chest pain. Two well-known syndromes are associated with lung cancer: Horner syndrome and SVC syndrome. **Horner syndrome** is caused by the invasion of the cervicothoracic sympathetic nerves and occurs with apical tumors (P**ancoast tumor**). Phrenic nerve invasion may cause diaphragmatic paralysis. SVC obstruction is produced by direct extension of the tumor or by compression from the neighboring lymph nodes. **SVC syndrome** has a dramatic clinical presentation and is a medical emergency requiring urgent care. The clinical presentation is facial swelling, hoarseness of voice, arm swelling, stridor, and nasal stuffiness.

Once a patient presents with symptoms or radiographic findings suggestive of lung cancer, the next steps are as follows:

1. Tissue diagnosis to establish malignant diagnosis and histologic type
2. Staging to determine resectability or curative potential
3. Cancer treatment: surgery, radiotherapy, traditional chemotherapy, or targeted therapies

Classification. Histologically, primary lung cancer can be divided into two major categories with important therapeutic implications: **small cell lung cancer** (SCLC) and **non–small cell lung cancer** (NSCLC). NSCLC accounts for approximately 86% of all primary lung cancers compared to only 14% for SCLC. NSCLC is further classified into three or more major histologic types, including squamous cell carcinoma (SCC), adenocarcinoma, large-cell carcinoma, and others.

SCC usually does not metastasize early. It is usually a central/hilar lesion with local extension that may present with symptoms caused by bronchial obstruction, such as atelectasis and pneumonia. SCC is the most likely lung cancer to cavitate and may be seen on x-ray as a central cavitary lesion. It may also produce parathyroid hormone–related protein, which causes hypercalcemia.

Adenocarcinoma and large-cell cancer are peripheral lesions. Adenocarcinoma metastasizes early, especially to the central nervous system (CNS), bones, and adrenal glands. **Adenocarcinoma has the lowest association with smoking** and a stronger association with pulmonary scars/fibrosis. **Large-cell cancer** is usually a peripheral lesion and tends to metastasize to the CNS and mediastinum. **It can cause SVC**

Table 18–1 • LUNG CANCER CHARACTERISTICS

	Small Cell	Squamous Cell	Adenocarcinoma	Large Cell
Location	Central	Central	Peripheral	Peripheral
Associated with smoking	Yes	Yes	Often not associated	Yes
Cavitation	Never	Common	Rare	Uncommon
Metastases	Early	Late	Early	Late
Extrapulmonary manifestations	SIADH, ectopic ACTH, Eaton-Lambert, Cushing, peripheral neuropathy	Hypercalcemia	Thrombophlebitis	SVC syndrome or hoarseness

Abbreviations: ACTH, corticotropin (adrenocorticotropic hormone); SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SVC, superior vena cava.

syndrome or hoarseness as a consequence of laryngeal nerve paralysis. Individually, the other NSCLC subtypes represent only a fraction of total lung cancer cases and have a varied presentation.

Small-cell carcinoma is made up of poorly differentiated neuroendocrine cells. It is extremely aggressive but in general responds better to chemotherapy than NSCLC. The primary lesion is typically central. Eighty percent of patients have metastasis at the time of diagnosis, so its treatment generally differs from that of other lung cancers. Contrary to other lung cancers, cavitation never occurs in small-cell cancer. **SCLC can cause paraneoplastic syndromes, including syndrome of inappropriate secretion of antidiuretic hormone (SIADH), ectopic adrenocorticotropic hormone (ACTH; corticotropin) production, and Lambert-Eaton syndrome.** Table 18–1 lists typical characteristics of various cell types.

SCLC is initially very responsive to chemotherapy and radiation therapy, but unfortunately, most SCLC relapses. Additionally, SCLC has almost always spread at time of diagnosis, so surgical treatment with curative intent is not possible. In contrast, NSCLC is much less responsive to chemotherapy or to radiation, but tumors that are localized at time of diagnosis may be treated with curative surgery or with radiation therapy. The majority of NSCLC subtypes have similar treatment and prognoses at similar stages.

Treatment

Treatment of lung cancer consists of surgical resection, chemotherapy, and/or radiation therapy in different combinations, depending on the tissue type and extent of the disease, and may be performed with either curative or palliative intent. Targeted therapies against mutations prevalent in adenocarcinoma subtypes are increasingly being used with variable success.

Once the diagnosis of NSCLC is made, the next step is to stage the disease to decide whether the cancer is resectable and thus potentially curable. Patients may be candidates for resection if the cancer is localized to one hemithorax, which may

include ipsilateral, but not contralateral, hilar and mediastinal lymph nodes, and there are no major anatomic barriers to successful resection.

SCLC is nearly always metastatic at time of diagnosis and, therefore, not eligible for surgical resection. It is staged as either **limited**, disease confined to one hemithorax that can be treated within a radiotherapy port, or **extensive**, disease with contralateral lung involvement or distant metastases that is treated with systemic therapies. Patients with untreated, advanced SCLC have a poor prognosis, with survival generally measured in weeks. Approximately 20% to 30% of patients with limited-stage disease can be cured with radiotherapy and chemotherapy; however, the prognosis for relapsed patients is poor.

Because most lung cancer occurs in older patients who have been smokers, patients with lung cancer frequently have underlying cardiopulmonary disease and require preoperative evaluation, including pulmonary function testing, to predict whether they have sufficient pulmonary reserve to tolerate a lobectomy (removal of one lung lobe) or pneumonectomy (removal of one lung). Performance status, or general well-being of the patient, is also taken into consideration when deciding if a patient is even a candidate for therapy or what type of therapy is appropriate.

Solitary Pulmonary Nodule. The solitary pulmonary nodule is defined as a nodule surrounded by normal parenchyma. Most incidentally discovered nodules are benign, but differentiation between benign etiologies and early-stage malignancy can be challenging. Proper management of a solitary nodule in an individual patient depends on a variety of elements: age, risk factors, presence of calcifications, and size of the nodule. Of these factors, size is highly predictive. Larger lesions are more likely to be malignant than smaller lesions. In one study, the likelihood of malignancy was 0.2% for nodules smaller than 3 mm, 0.9% for nodules 4 to 7 mm, 18% for nodules 8 to 20 mm, and 50% for nodules larger than 20 mm. Put another way, greater than 99% of nodules measuring less than 8 mm are benign.

The presence and type of calcification on a solitary pulmonary nodule can be helpful. "Popcorn" and "bull's-eye" calcifications suggest a benign process, whereas absence of calcification increases the likelihood of malignancy.

Professional organizations such as the Fleischner Society offer a widely accepted algorithm for follow-up imaging of solitary pulmonary nodules. Generally speaking, for lesions 8 mm or less, serial CT imaging is an acceptable strategy to monitor for growth. Radiographic stability for 2 years or longer is strong evidence of benign etiology. For lesions 1 cm or greater, additional studies, such as positron emission tomography scan, transthoracic needle biopsy, or bronchoscopic evaluation, may be indicated.

CASE CORRELATION

- See also Case 15 (Chronic Obstructive Pulmonary Disease), Case 16 (Chronic Cough/Asthma), Case 17 (Pleural Effusion, Parapneumonic), and Case 19 (Community-Acquired Pneumonia).

COMPREHENSION QUESTIONS

18.1 A 67-year-old man presents to the office with a 3-day history of headaches and progressive swelling of his face and right arm. He has a 50 pack-year smoking history and was diagnosed with chronic obstructive pulmonary disease 15 years ago. On examination, he is found to have redness and edema of his face and his right arm, which is of recent onset. Which of the following is the most likely diagnosis?

A. Angioedema
B. Hypothyroidism
C. Superior vena cava syndrome
D. Trichinosis

18.2 A 64-year-old woman is being seen in the office complaining of a hoarse voice for 4 months. She denies fever, sore throat, or cough. On examination, her respiratory rate is 26 breaths/min, temperature is 98 °F, and heart rate is 100 bpm. She has expiratory wheezes in her left midlung fields bilaterally. Which of the following is the best next step the management of this patient?

A. Prescribe antibiotics for bronchitis.
B. Order a chest x-ray.
C. Advise gargling with saltwater solution.
D. Prescribe an albuterol inhaler.

18.3 A 33-year-old woman is being seen in the office for a dry cough that has persisted for 3 months. She has lost 30 lb without intention over the past 3 months. On examination, she is noted to be cachectic. Examination shows clear lung fields. A chest x-ray shows a 3-cm lung mass. Bronchoscopic biopsy is performed. Which of the following lung cancers is the most likely cell type?

A. Squamous cell
B. Adenocarcinoma
C. Small cell
D. Large cell

18.4 A 52-year-old previously healthy man presents to the emergency center with progressively worsening dyspnea over the past 2 months. Examination shows decreased breath sounds on the right lung zone and dullness on percussion on that side. Chest x-ray shows a 4-cm hilar mass and a large ipsilateral right pleural effusion. Which of the following is the best next step in the management of this patient?

A. CT scan of the chest, head, and abdomen for cancer staging.
B. Pulmonary function testing to evaluate pulmonary reserve to evaluate for pulmonectomy.
C. Biopsy and pathologic evaluation of the hilar mass.
D. Initiate palliative radiation because the patient is not a candidate for curative resection.

ANSWERS

18.1 **C.** The patient has features of SVC syndrome, caused by compression of the SVC, almost always by a thoracic malignancy. Urgent diagnosis and treatment are mandatory because of impaired cerebral venous drainage and resultant increased intracranial pressure or possibly fatal intracranial venous thrombosis. Angioedema (answer A), hypothyroidism (answer B), and trichinosis (answer D) all may cause facial swelling, but not the redness (plethora) or swelling of the arm.

18.2 **B.** This patient has chronic hoarseness and unilateral wheezing. This suggests an intrathoracic mass causing bronchial obstruction and impairment of the recurrent laryngeal nerve, causing vocal cord paralysis. Thus, an imaging study of the chest is essential. If the chest x-ray is negative, the voice hoarseness still needs to be pursued, such as by laryngoscopy, to assess for pathology of the vocal cords or larynx. Answer A (antibiotics for bronchitis) may be appropriate in the clinical setting of 1-2 weeks of cough and voice hoarseness; however, once voice hoarseness has lasted longer 3 weeks, investigation for cancer must be undertaken. Similarly, answer C (Saltwater gargling) and answer D (Albuterol inhaler) are symptomatic measures, and more aggressive diagnostic interventions are required.

18.3 **B.** The most common form of lung cancer found in nonsmokers, young patients, and women is adenocarcinoma. Of note, 85% of patients with lung cancer of *all* histologic types have a smoking history.

18.4 **C.** Biopsy of the hilar mass is important because tissue diagnosis is essential for proper treatment of any malignancy; for this reason, biopsy should generally be the first step. Once a specific tissue diagnosis is obtained, the cancer is staged (answer A) for prognosis and to guide therapy. Therapeutic options may be surgical resection, chemotherapy, or radiotherapy. Questions for this patient include the tissue type, location of spread, and whether the pleural effusion is caused by malignancy. Answer B (Pulmonary function tests) are not indicated until a diagnosis is determined to see what treatment is needed. Answer D (Palliative radiation) is not indicated until cancer is diagnosed.

CLINICAL PEARLS

- Most patients with hemoptysis require evaluation with bronchoscopy. Massive hemoptysis may result in death by asphyxiation.
- Lung cancer is the leading cause of cancer deaths in men and women.
- A solitary pulmonary nodule measuring 8 mm or less can be followed radiographically. For larger lesions, a biopsy, whether bronchoscopic, percutaneous, or surgical, should be considered.
- Steps in management of a patient with suspected lung cancer include tissue diagnosis, staging, preoperative evaluation, and treatment with surgery, radiotherapy, or chemotherapy.
- Small cell lung cancer usually is metastatic at the time of diagnosis and not resectable. NSCLC may be curable by resection if it is early stage and the patient has sufficient pulmonary reserve.

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CASE 19

A 44-year-old man presents to the emergency department with sudden onset of shaking chills, fever, and productive cough. He was in his usual state of good health until 1 week ago, when he developed mild nasal congestion and generalized achiness. Last night he became feverish and fatigued, and he developed a cough associated with nonbloody sputum production and right-sided chest pain. The patient also expressed mild exertional dyspnea when walking his dog this morning. His medical history is remarkable only for mild, intermittent asthma, hypertension, and hyperlipidemia. His medications are lisinopril and atorvastatin. The patient admits to smoking a pack per day for the last 20 years. He states he drinks a glass of wine two or three times a week and denies drug use. In your office, his vital signs are normal except for a temperature of 39 °C (102.2 °F). His oxygen saturation is 100% on room air. Physical examination shows a mostly comfortable man (except when he coughs) with bronchial breath sounds and end-inspiratory crackles in the right lower lung field. The remaining examination is unremarkable. A chest x-ray demonstrates a homogeneous opacity with bronchogram on the right lower pulmonary field.

- What is the most likely diagnosis?
- What is the most likely etiology of this disease process?
- What is your next step?
- What are risk factors for this condition?

ANSWERS TO CASE 19:
Community-Acquired Pneumonia

Summary: A 44-year-old man presents with

- Sudden onset of shaking chills, fever, dyspnea on exertion, and productive cough with pleuritic chest pain
- A 102.2 °F fever without tachypnea or hypoxia
- Bronchial breath sounds and end-inspiratory crackles in the right lower lung field
- Consolidation on the right pulmonary base on chest x-ray

Most likely diagnosis: Community-acquired pneumonia (CAP).

Most likely etiology: The etiologies of CAP within this patient's demographic include *Haemophilus influenzae, Staphylococcus aureus,* group A streptococci, *Moraxella catarrhalis,* viruses, *Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia psittaci,* and *Legionella* species; however, the most common isolate is *Streptococcus pneumoniae*.

Next step: Chest x-ray. If the images confirm the suspicion of pneumonia, then start antibiotic therapy, pain relievers, antipyretics, and cough suppressants for relief of symptoms. Close outpatient follow-up (in 1-2 weeks) is also important.

Risk factors: Common CAP risk factors include alcohol abuse, smoking, Chronic obstructive pulmonary disease (COPD), immunosuppression, and recent influenza infection.

ANALYSIS

Objectives

1. Identify the causative organisms in CAP and the appropriate therapeutic regimens. (EPA 3, 4)
2. Differentiate the clinical criteria indicating inpatient versus outpatient therapy. (EPA 4, 7, 10)
3. Analyze the role of radiologic and laboratory evaluation in the diagnosis of pneumonia. (EPA 3)
4. Compare and contrast the difference between chemical pneumonitis and infectious aspiration pneumonia. (EPA 1, 2)

Considerations

This previously healthy 44-year-old man displayed clinical and radiographic evidence of a focal lung consolidation, which is consistent with a bacterial process, such as a *S. pneumoniae* infection. The specific causative organism is usually not definitively established, so empiric antimicrobial therapy will need to be initiated and the patient response monitored. It will also be necessary to risk stratify the

patient to determine whether he can safely be treated as an outpatient or requires hospitalization.

APPROACH TO:
Community-Acquired Pneumonia

DEFINITIONS

COMMUNITY-ACQUIRED PNEUMONIA (CAP): An infection of the alveoli, distal airways, and interstitium of the lungs that is acquired outside the hospital setting, affecting individuals of all ages.

HEALTH CARE–ASSOCIATED PNEUMONIA (HCAP): Pneumonia developing 48 hours after admission that was not present prior to admission. The previous concept of HCAP has since fallen out of favor due to its inability to be sensitive or specific in identifying patients who might be at risk. HCAP was previously defined as pneumonia occurring in a nonhospitalized patient with extensive health care contact, including one of the following: intravenous therapy, wound care, intravenous chemotherapy within the prior 30 days, those who live in a nursing home or other long-term care facility, hospitalization in an acute care hospital for 2 or more days within the prior 90 days, or attendance at a hospital or hemodialysis clinic within the prior 30 days. Recently, terminology has changed so that nursing home patients who develop pneumonia is called CAP.

PNEUMONIA: Inflammation of the lung parenchyma, which may be caused by bacteria, viruses, fungi, or rarely protozoa or noninfectious diseases. In the day-to-day medical language, it refers to an infection affecting the lung.

VENTILATOR-ASSOCIATED PNEUMONIA: Pneumonia that develops 48 hours after intubation.

CLINICAL APPROACH

Pathophysiology

Community-acquired pneumonia, as opposed to HCAP, in adults is most commonly caused by *S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *C. pneumoniae*, or respiratory viruses, such as influenza and adenovirus. Despite a careful history and physical, routine laboratory tests, and radiographic investigation, it remains difficult to determine a specific pathogen in most cases. Epidemiologic risk factors and certain exposures may provide additional clues: *C. psittaci* is associated with bird exposure, coccidioidomycosis is associated with travel to the American southwest, and histoplasmosis is endemic to the Mississippi Valley and common in spelunkers. In a patient with acquired immunodeficiency syndrome (AIDS) or immunosuppression, *Pneumocystis jiroveci* should instantly be added to the differential diagnosis. Tuberculosis should always be considered a possibility in patients with a history suggestive of exposure or predisposition (ie, homelessness or exposure to shelters,

previous incarceration, emigration from countries of high endemicity, unvaccinated or immunocompromised state) to this disease.

Pathogens in HCAP include methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter* spp, and multidrug-resistant *Enterobacteriaceae*. Empiric antibiotic therapy should be directed accordingly.

Clinical Presentation

Pneumonia represents inflammation, commonly infectious of the lung parenchyma. Patients may present with any combination of cough, fever, pleuritic chest pain, sputum production, shortness of breath, hypoxia, and respiratory distress. Certain clinical presentations are associated with particular infectious agents. For example, characteristics of "typical" pneumonia include sudden onset of fever, cough with productive sputum, pleuritic chest pain, and occasionally **rust-colored sputum**. This describes the classic presentation of pneumococcal pneumonia.

The **"atypical" pneumonia** is recognized by a **more insidious onset, a dry cough**, and prominent extrapulmonary symptoms such as **headache, myalgias, and sore throat.** In addition, a chest radiograph usually appears much worse than the clinical or auscultatory findings. ***M. pneumoniae*** remains the most commonly identified pathogen attributed to "atypical" pneumonia. Although these characterizations are of some diagnostic value, there are no features that can distinguish between typical and atypical pneumonia based on the clinical history and physical examination alone. Therefore, pneumonias are typically classified according to the immune status of the host, the radiographic findings, and the setting in which the infection was acquired in an attempt to identify the most likely causative organisms and to guide initial empiric therapy.

Risk Stratification. Once the clinical diagnosis of infectious pneumonia has been made, the next step is to **risk stratify** the patients to determine which patients can be treated safely as outpatients with oral antibiotics and which require hospitalization. Two major risk stratification tools are currently employeds: the Pneumonia Severity Index (PSI) and the CURB-65. The **PSI** stratifies patients into five groups based on a 30-day all-cause mortality in those with radiographically proven pneumonia. This two-step processes involves first using patient demographic factors:— age > 50, medical history comorbidities, and physical examination findings—to determine low-risk patients (risk class I: outpatient treatment). Patients possessing these factors progress to step 2, which utilizes objective laboratory findings to further classify patients in classes II to IV based on the number of points assigned per risk factor. Scoring is determined by taking the age (subtract 10 in women) and adding a point for each risk factor. The other stages are as follows: class II (scores < 70), class III (score 71-90), class IV (scores 91-130), and class V (scores > 130). Patients in classes I and II have a predicted mortality of less than 0.6% and are suitable for outpatient treatment, while patients in class V have a 30-day mortality risk of 27%. Calculating PSI is laborious.

The **CURB-65** serves as a simplified prognostic score using five variables:

Confusion (1 point)

Urea greater than 20 mg/dL (1 point)

Respiratory rate greater than 30 breaths/min (1 point)

Blood pressure, systolic less than 90 mm Hg (1 point)

Age greater than **65** (1 point)

Patients with a score of 0 to 1 have a 30-day mortality below 3%, and they can usually be safely treated as outpatients with oral antibiotics. However, further analysis should be performed to ensure the patient's ability to take oral medications and the availability of outpatient support. Scores of 2 or greater require hospitalization, and those of 3 or greater should be assessed for intensive care unit (ICU) admission. Patients with a score of 3 or greater have a 30-day mortality of 15% to 40%. Compared to PSI, CURB-65 assigns no points to comorbid illnesses; another limitation of CURB-65 is that it assumes that the confusion is related to the acute pneumonia.

Although outpatients usually are diagnosed and empiric therapy is started based on clinical findings, further diagnostic evaluation is necessary in hospitalized patients. Chest radiography is required to diagnose CAP, to define the extent of the pneumonia, and to look for complications, such as parapneumonic effusion or lung abscess. Unless the patient cannot mount an immune response, as in severe neutropenia, significant dehydration, or early in the disease process, **every patient with pneumonia will have a visible pulmonary consolidation**.

Imaging. The pattern of infiltration can yield diagnostic clues. Infection with ***S. pneumoniae*** classically presents with a **dense lobar consolidation**, often with an associated parapneumonic effusion. Diffuse interstitial opacities are common in *Pneumocystis* pneumonia and viral processes. Conversely, pleural effusions are almost never seen in *Pneumocystis* pneumonia. Bilateral apical alveolar opacities (with or without cavitation) suggest tuberculosis. Appearance of **cavitation** suggests a necrotizing infection such as *S. aureus*, tuberculosis, or gram-negative organisms like *P. aeruginosa* or *Klebsiella pneumoniae*. Serial chest radiography of inpatients usually is unnecessary because many weeks are required for the infiltrate to resolve; serial chest radiography typically is performed if the patient does not show clinical improvement, has a pleural effusion, or has a necrotizing infection. Infiltrates that are not resolving or that are relapsing on the same lung field represent a red flag for obstruction of the bronchus corresponding with that area; malignancy is usually the culprit.

Laboratory Results. Microbiologic studies, such as blood cultures and sputum Gram stain and culture, should be obtained to try to establish the etiology. Sputum samples are frequently contaminated by oral flora, limiting their value, though their diagnostic yield increases when sputum is purulent (> 25 polymorphonuclear cells and < 10 epithelial cells per low-power field). Additionally, blood cultures can further classify the etiology of pneumonia, especially since 30% to 40% of pneumococcal pneumonia patients are bacteremic on admission. Further serologic studies can diagnose patients who are infected with organisms not easily cultured, for example, *Legionella*, *Mycoplasma*, or *C. pneumoniae*.

Bronchoscopy. Finally, fiber-optic bronchoscopy with bronchoalveolar lavage is often performed in seriously ill patients, the immunocompromised, and patients who are not responding to therapy. This procedure obtains specimens from the

lower respiratory tract for routine Gram stain and culture, as well as direct fluorescent antibody testing for organisms such as *Legionella* or *P. jiroveci*.

Treatment

Initially, empiric treatment is based on the most common organisms given the clinical scenario. Macrolide antibiotics (azithromycin), doxycycline, or antipneumococcal fluoroquinolones (moxifloxacin or levofloxacin) are good choices for **outpatient treatment** of CAP caused by *S. pneumoniae*, *M. pneumoniae*, and other common bacterial organisms. Keep in mind that increasing community resistance patterns alter available antibiotic coverage. In regard to outpatient therapy duration, antibiotics should be administered for a minimum of 5 days. **Hospitalized patients** with CAP usually require **intravenous third-generation cephalosporin plus a macrolide** (or antipneumococcal fluoroquinolone). For immunocompetent patients with hospital-acquired or ventilator-associated pneumonias, initial antibiotic coverage is broader, with more serious antibiotic coverage. Some common antimicrobials chosen include piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem. In addition, for patients with risk factors for MRSA infection (ie, prior intravenous antibiotic use, intravenous drug usage, recent ventilatory support), empiric coverage for MRSA such as vancomycin or linezolid should be added. Vaccination for influenza and pneumococcus should be considered for all who meet the criteria. Smoking cessation is also an integral part of postrecovery care.

Other Pulmonary Syndromes

Three other commonly confused pulmonary syndromes deserve mention at this point: aspiration pneumonia, chemical pneumonitis, and mechanical obstruction.

Aspiration Pneumonia. Aspiration pneumonia refers to the inflammation promoted by infectious agents that results from abnormal entry of fluids or secretions into the lower airways when defensive mechanisms of the upper airway fail. It should be noted that many healthy adults frequently aspirate small volumes of oropharyngeal secretions while sleeping (this is the primary way that bacteria gain entry to the lungs), but the material is cleared by coughing, ciliary transport, or normal immune defenses so that no clinical infection results. The affected lobe of the lung depends on the patient's position: In recumbent patients, the posterior segments of the upper lobes and superior segments of the lower lobes are most common.

Chemical Pneumonitis. Chemical pneumonitis refers to the aspiration of toxic substances (the most common being gastric acid) into the lower airway without the development of bacterial infection. The inflammation is proportional to the volume of the aspirate and the acidity of the content. The clinical presentation can go from minor dyspnea and low-grade fever to severe respiratory distress and a pulmonary infiltrate that is apparent within 4 to 6 hours and typically resolves within 48 hours. Aspiration of gastric contents is most likely to occur in patients with a depressed level of consciousness, such as with anesthesia, drug overdose, intoxication, or a postictal state. This process has also been described among victims of smoke inhalation. Treatment for chemical pneumonitis is usually supportive and involves positive pressure breathing, intravenous fluids, and tracheal suction.

Infectious pneumonia should be considered in those who fail to show clinical improvement after 48 hours of presumed chemical pneumonitis; those with significant comorbidities can be started on antibiotics initially. In contrast to chemical pneumonitis, where aspiration of vomitus may be witnessed, the aspiration of oral secretions typically is silent and should be suspected when any institutionalized patient with dysphagia presents with respiratory symptoms and pulmonary infiltrate in a dependent segment of the lung.

Antibiotic therapy for presumed bacterial aspiration (infectious) pneumonia is similar to that of other pneumonias; antibiotics should cover typical respiratory pathogens such as oral anaerobes, gram-negative organisms, *S. pneumoniae,* and *H. influenzae*. When anaerobes are likely, first-line therapy is ampicillin-sulbactam, amoxicillin-clavulanate, or the combination of metronidazole plus amoxicillin or penicillin G. Clindamycin use has declined secondary to increased resistance; however, it can still be used in those with penicillin allergies.

Airway Obstruction. Airway obstruction refers to the inhalation of nontoxic fluid or matter causing obstruction or closure of distal airways. The most common aspirated items include water, saline, barium, and food. The fluids/matter can result in a reversible hypoxemia. Treatment involves removal of the obstruction with supportive care.

CASE CORRELATION

- See also Case 14 (Pulmonary Embolism), Case 15 (Chronic Obstructive Pulmonary Disease), Case 16 (Chronic Cough/Asthma), Case 17 (Pleural Effusion, Parapneumonic), and Case 18 (Hemoptysis/Lung Cancer).

COMPREHENSION QUESTIONS

19.1 A 65-year-old man with a medical history of uncontrolled hypertension, mild biventricular systolic heart failure, and a 40 pack-year smoking history presents to the emergency room with 1 week of worsening cough, fever, and dyspnea at rest. His symptoms also include diffuse myalgia, abdominal pain, nonbloody diarrhea, and a rapidly worsening nonproductive cough. He denies alcohol or drug history and endorses being married to his wife for 40 years. On admission, his vital signs are: temperature of 38 °C, blood pressure (BP) 160/82 mm Hg, heart rate 89 beats per minute (bpm), respiratory rate (RR) 25 breaths/min, and SpO_2 (oxygen saturation as measured by pulse oximetry) is 94% on room air. Which of the most likely organisms is the etiology of his illness?

A. *Aspergillus fumigatus*
B. *Chlamydia pneumoniae*
C. Coccidioidomycosis
D. *Legionella pneumophila*
E. *Mycoplasma pneumoniae*

19.2 An 85-year-old nursing home resident with a medical history of diastolic heart failure, hypertension, diabetes mellitus, and dementia requiring assistance in all activities of daily life presents with a 3-day history of fever and nonbloody, productive cough. Her mental status was found to be more altered than usual. On admission, her vital signs show the following: temperature of 39 °C, BP 105/70 mm Hg, heart rate 93 bpm, RR 32 breaths/min, and SpO_2 94% on room air. Chest x-ray reveals a right middle lobe consolidation. Which of the following is the best medical treatment of the patient?

A. Admit to the floor and start intravenous cefepime and linezolid.

B. Admit to the floor and start intravenous azithromycin and ceftriaxone.

C. Admit to the ICU and start intravenous vancomycin and linezolid.

D. Discharge home with a prescription of oral amoxicillin and cefpodoxime.

E. Discharge home with oral azithromycin and oral cefpodoxime.

19.3 A 56-year-old man with a medical history of hypertension, chronic kidney disease stage III, gout, and alcohol dependence is brought in by emergency medical services after being found down on the ground. He smells strongly of ethanol and has a prior history of delirium tremens based on previous medical records. He is admitted to the ICU with concern for alcohol withdrawal. His vitals on admission are: temperature 37 °C, BP 110/74 mm Hg, heart rate 77 bpm, RR 12 breaths/min, and SpO_2 of 94% on room air. Due to concern for inability to protect his airway, he is intubated in the emergency room. The next day, he shows significant clinical improvement and is extubated. Later that day, he goes into withdrawal with altered mental status, and aspirates while eating. What is the next best step in management?

A. Obtain chest x-rays and continue to monitor for symptoms.

B. Obtain chest x-rays and start azithromycin therapy.

C. Obtain chest x-rays and start vancomycin and cefepime.

D. Obtain chest x-rays, perform bronchoscopy, and initiate steroid treatment.

ANSWERS

19.1 **D.** *Legionella* typically presents with diffuse myalgias, abdominal pain, diarrhea, and severe pneumonia. Tobacco dependence increases susceptibility to *Legionella* as well. Typically, it is associated with hyponatremia on laboratory tests. *C. pneumoniae* (answer B) typically presents in older patients with more indolent symptoms and associated pharyngitis, hoarseness, and/or sinus involvement. *M. pneumonia* (answer E) tends to appear in young adults, with significantly fewer toxic symptoms; this is why it is also known as walking pneumonia. **Bullous myringitis** (blisters seen on the tympanic membrane) is frequently associated. Coccidioidomycosis (answer C) is endemic in the southwestern United States and causes a subclinical infection, often after dust exposure. *Aspergillus* (answer A) is more common in immunocompromised individuals and can present with hemoptysis and lung infarction.

19.2 **B.** This nursing home resident would be considered to have CAP, with a similar infectious rate as individuals not residing in nursing homes. Using CURB-65, the patient would have three points (confusion for her worsening mental status, respiratory rate > 30 breaths/min, and her age). These criteria indicate the need for hospitalization with possible consideration for ICU admission; thus, discharging this patient home (answers D and E) would be inappropriate. The use of ceftriaxone (or other third-generation cephalosporins) and azithromycin would be appropriate therapy. Vancomycin and linezolid (answer C) cover gram-positive organisms only.

19.3 **A.** The patient did aspirate; however, this does not automatically mean aspiration pneumonia will develop. The first steps are to obtain imaging and monitor closely. If symptoms (fevers or purulent sputum production) develop or the patient fails to improve after 48 hours, then ampicillin-sulbactam, amoxicillin-clavulanate, or metronidazole plus amoxicillin can be started to cover anaerobic mouth bacteria. Azithromycin (answer B) is indicated for CAP but is not the appropriate therapy for aspiration pneumonia. Vancomycin and cefepime (answer C) would not need to be started unless necrotizing pneumonia is suspected. Last, bronchoscopy (answer D) is typically not required for aspiration pneumonitis diagnosis, and steroids are not used.

CLINICAL PEARLS

- It is difficult to reliably distinguish clinically between typical and atypical causes of pneumonia. Therefore, diagnosis and empiric treatment of pneumonia are based on the setting in which it was acquired (CAP or HCAP) and the immune status of the host.
- Clinical criteria, such as patient's age, vital signs, mental status, renal function, and additional comorbidities can be used to risk stratify patients with pneumonia to decide who can be treated as an outpatient and who requires hospitalization with intravenous antibiotics.
- Although initial antibiotic therapy is empiric, the etiologic agent frequently can be identified based on chest radiography, blood cultures, or sputum Gram stain and culture. Once determined, antibiotics can be deescalated for more specific coverage.
- Chemical pneumonitis is a noninfectious, chemically induced inflammation caused by inhalation of acidic gastric contents in patients with a decreased level of consciousness, such as seizure or overdose; however, if patients fail to improve within 48 hours, antibiotic interventions can be started. It can also be seen in victims of smoke inhalation.
- Aspiration (infectious) pneumonia is a pulmonary infection caused by aspiration of colonized oropharyngeal secretions and is seen in patients with impaired swallowing, such as stroke victims. The treatment is antibiotics.

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CASE 20

A 37-year-old executive returns to your clinic for follow-up of recurrent upper abdominal pain. He had been experiencing a "burning" epigastric pain intermittently for more than 2 years but did not seek medical attention until recently, when the pain increased in frequency and severity over the past 2 months. The pain now occurs three to four times per week, is more noticeable "on an empty stomach," and often awakens him at night. The pain is usually relieved immediately after eating or using over-the-counter antacids, but it recurs within 2 to 3 hours. He admits to experiencing increased stress at work, drinking more caffeine, and frequently eating take-out foods because of his busy schedule. His medical history and review of systems are otherwise unremarkable. He takes no medications besides the occasional use of antacids. His physical examination is normal, including a stool guaiac test, which was negative for occult blood. Results of the laboratory tests performed at his initial visit show no anemia, but his serum *Helicobacter pylori* antibody test is positive.

- What is the most likely diagnosis?
- What are the main risk factors for developing this condition?
- What is your next step?

ANSWERS TO CASE 20:
Peptic Ulcer Disease

Summary: A 37-year-old man presents with

- "Burning" abdominal pain located in the epigastrium that is relieved with meals but recurs 2 to 3 hours later
- No evidence of gastrointestinal (GI) bleeding
- Serologies positive for *H. pylori* infection

Most likely diagnosis: Peptic ulcer disease (PUD) since the patient has recurrent, burning epigastric pain and positive serologies for *H. pylori*.

Risk factors: Infection with *H. pylori* or chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Next step: Triple therapy (PPI, amoxicillin, clarithromycin) for *H. pylori*.

ANALYSIS

Objectives

1. Differentiate common causes of abdominal pain by historical clues. (EPA 1, 2)
2. Recognize clinical features of duodenal ulcers and gastric ulcers and "alarm symptoms" that increase concern for gastric cancer. (EPA 1, 3)
3. Understand the association between *H. pylori* infection and the use of NSAIDs in the development of PUD. (EPA 2, 12)
4. Understand and interpret the laboratory tests used for diagnosing *H. pylori* infection. (EPA 3)

Considerations

This is a 37-year-old man whose symptoms are suggestive of a duodenal ulcer. He does not demonstrate alarm symptoms, such as weight loss, bleeding, or anemia. Moreover, his young age and chronicity of complaints make gastric malignancy a less likely diagnosis. ***H. pylori* is the most common cause of PUD,** requiring eradication to promote ulcer healing and to prevent development of gastric cancers (eg, **gastric adenocarcinoma, mucosa-associated lymphoid tissue [MALT] lymphoma**).

APPROACH TO:
Peptic Ulcer Disease

DEFINITIONS

DYSPEPSIA: Pain or discomfort located in the upper abdomen (**"epigastrium"**), which may be associated with fullness, early satiety, bloating, or nausea. Dyspepsia can be intermittent or continuous and may be related to meals.

FUNCTIONAL (NONULCER) DYSPEPSIA: Symptoms as described for dyspepsia, persisting for at least 12 weeks but **without evidence of ulcer on endoscopy**.

***HELICOBACTER PYLORI*:** A gram-negative microaerophilic bacillus that resides within the gastric mucosa and causes chronic inflammation. It is **urease positive**, capable of hydrolyzing urea into ammonia carbonate, thus alkalinizing the local pH and allowing it to survive in an acidic environment. *H. pylori* is associated with 30% to 60% of gastric ulcers and with 50% to 70% of duodenal ulcers.

PEPTIC ULCER DISEASE (PUD): Presence of gastric or duodenal mucosal ulceration, visualized by endoscopy or by upper gastrointestinal barium study.

TRIPLE THERAPY: Treatment for PUD caused by *H. pylori*; consists of amoxicillin, clarithromycin, and a PPI (replace amoxicillin with metronidazole if penicillin allergy is present).

QUADRUPLE THERAPY: Alternative treatment for PUD caused by *H. pylori*, in setting of clarithromycin resistance; consists of metronidazole, a tetracycline, a bismuth compound, and a PPI.

CLINICAL APPROACH

Pathophysiology

Upper abdominal pain is one of the most common complaints encountered in primary care. Many patients have benign functional disorders (ie, no specific pathology can be identified after diagnostic testing), but others have potentially more serious conditions, such as PUD or gastric cancer. Historical clues, knowledge of the epidemiology of diseases, and some simple laboratory assessments can help to separate benign from serious causes of pain. However, endoscopy is often necessary to confirm the diagnosis.

The two major risk factors for developing PUD are chronic infection with ***H. pylori*** and the use of **NSAIDs**. Certain virulence factors of *H. pylori* are important for producing ulcer formation and include urease, adhesins, and cytotoxins. **Urease** is an enzyme that hydrolyzes urea into ammonium carbonate, thus producing an alkaline environment, and is an essential virulent factor for *H. pylori* to survive in the stomach. **Adhesins** (BabA, OipA) facilitate the attachment of *H. pylori* to the gastric epithelium. Almost all *H. pylori* contain the ***vacA* gene**, which encodes for a vacuolating cytotoxin that causes gastrointestinal inflammation. However, not all *H. pylori* express the vacA protein. Therefore, the role of this specific gene in the pathogenesis of PUD remains unclear.

Use of NSAIDs is another major risk factor for the development of PUD, primarily mediating ulcer formation by inhibiting the constitutively expressed **cyclooxygenase 1 (COX-1)–derived prostaglandins.** Inhibition of these prostaglandins is associated with impaired gastric defenses within the host, such as **decreased vasodilation of mucosal blood vessels** and **low secretion of gastric mucus and bicarbonate.** The risk of ulcer formation due to NSAIDs is dose dependent and may even occur within days of NSAID use.

Zollinger-Ellison syndrome (ZES) is a rare, yet highly tested, cause of ulceration that involves a **gastrin-producing tumor** ("gastrinoma"; usually located in the **pancreas**), resulting in **acid hypersecretion.** This condition should be suspected if patients have **ulcers refractory to standard medical therapy**, ulcers in **unusual locations** (eg, jejunum), or ulcers without a history of NSAID use or *H. pylori* infection. Endoscopy shows multiple gastric ulcers and prominent rugae of the gastric mucosa. About 25% of gastrinomas occur in patients with **multiple endocrine neoplasia I (MEN I) syndrome**, an **autosomal dominant** genetic disorder characterized by **parathyroid**, **pancreatic**, and **pituitary** neoplasms. To diagnose ZES, the first step is to measure a **fasting gastrin level**, followed by a **secretin stimulation test**, which paradoxically **elevates gastrin levels (> 1000 pg/mL).** Once ZES is suspected, an imaging study (eg, **abdominal computed tomography [CT]**) is used to localize the tumor.

Clinical Presentation

Dyspepsia refers to upper abdominal pain or discomfort, which may be produced by several gastrointestinal disorders, including PUD. **Gastroesophageal reflux disease (GERD)** typically produces "heartburn," a burning epigastric or chest pain, associated with regurgitation of gastric content, usually occurring after meals and worsening with recumbency. Patients with GERD may also complain of a chronic dry cough, secondary to aspiration of gastric contents and stimulation of cough receptors in the lower respiratory tract. **Biliary colic** is characterized by an acute onset of right upper quadrant pain, lasting 30 to 60 minutes, and precipitated by fatty meals. Biliary colic is more common in **fertile, middle-aged women. Irritable bowel syndrome (IBS)** is a diagnosis of exclusion, characterized by chronic dysmotility symptoms (bloating, cramping) and **relieved with defecation.** Patients report a mixture of constipation and diarrhea without weight loss or GI bleeding.

PUD manifests when gastric acid erodes the mucosal and muscularis layers of the gastrointestinal tract, leading to the formation of an ulcer. These ulcers are most commonly located in the stomach (**gastric ulcer**) or duodenum (**duodenal ulcer**). Patients typically present with a **gnawing/burning pain**, located in the **epigastrium** *without* radiation to the back and relieved by antacids (ie, calcium carbonate, aluminum-magnesium hydroxide). Other associated symptoms may vary, depending on the location of the ulcer. Gastric ulcers typically present with **postprandial abdominal pain**, leading to an aversion of food, nausea, vomiting, and **weight loss.** Patients with duodenal ulcers may experience **weight gain** because the pain associated with these ulcers is **initially relieved during meals**, when ingestion of food stimulates bicarbonate secretion into the duodenum. The pain, however, **worsens 2 to 5 hours later**, when acidic gastric contents are emptied from the stomach and

enter the duodenum, directly irritating the ulcer. Pain associated with duodenal ulcers may also **worsen at night** due to circadian stimulation of acid secretion.

Young patients without alarm features may undergo **noninvasive testing**, such as serology for *H. pylori* antibody, urea breath test, or fecal *H. pylori* antigen test. The **urea breath test** and **serology for the *H. pylori* antibody** are the most commonly used noninvasive tests to detect active infection. However, serologic testing for *H. pylori* is only useful if the patient has never been previously treated for *H. pylori* since antibodies will be positive for life, even after successful treatment.

Treatment

Chronic infection with *H. pylori* is the most common cause for both gastric and duodenal ulcers. Therefore, the standard of care is to test the patient for infection and treat with triple or quadruple therapy if present. Although **triple therapy** has traditionally been the gold standard for *H. pylori* eradication, **clarithromycin-resistant strains of *H. pylori*** have been identified, resulting in decreased efficacy of triple therapy. **Quadruple therapy** is preferred if the patient has ever had **exposure to macrolides** for any reason, if **local clarithromycin resistance rates are > 15%**, or if **eradication rates with triple therapy are < 85%**. A follow-up visit within 4 to 8 weeks is recommended to ensure *H. pylori* eradication. **Fecal *H. pylori* antigen testing** may be used to **confirm eradication** following treatment. If the **patient is older (> 45 years)** or presents with **alarm symptoms**, an **esophagogastroduodenoscopy (EGD)** with or without biopsy, depending on gastric (high risk) versus duodenal (low risk) ulcer, should be performed to rule out malignancy.

Treatment for **PUD caused by NSAIDs** consists of **discontinuing the offending agent** and **initiating a PPI** to reduce acid secretion and promote ulcer healing.

Complications

Approximately 70% of peptic ulcers are asymptomatic and may go unnoticed until complications develop. **The most common severe complication of PUD is hemorrhage.** Patients may complain of **hematemesis** ("coffee ground emesis") or **melena**. Chronic ulcers may result in **gastric outlet obstruction** symptoms due to formation of strictures. Similarly, ulcers located near the pyloric channel may also cause obstructive symptoms due to mass effect. Transmural ulcers may cause perforation within the gastrointestinal tract. Ulcers that perforate the **lesser curvature of the stomach** or **posterior wall of the duodenum** may cause **hemorrhage** due to involvement of the **left gastric artery** and **gastroduodenal artery**, respectively. Perforation of the **anterior wall of the duodenum** may lead to **peritonitis** (eg, rebound tenderness, involuntary guarding) and **referred pain to the shoulder** due to phrenic nerve irritation caused by free air accumulation below the diaphragm. Perforation near the pancreas may result in pancreatitis. **Both obstructive and peritoneal symptoms are indications for surgery.**

Moreover, unlike duodenal ulcers, which have a low propensity for malignant transformation, approximately 5% to 10% of **gastric ulcers** are **malignant** (eg, gastric adenocarcinoma). Gastric ulcers should be evaluated endoscopically with an **EGD** and **biopsied** to exclude gastric cancer, which may also present as nausea/vomiting, dysphagia, and early satiety. Chronic *H. pylori* infection may also result in the development of a **gastric MALT tumor**.

In general, **patients older than 45 years** who present with **new-onset dyspepsia** should undergo endoscopy since the risk of malignancy increases with age. Furthermore, patients with **alarm symptoms** (eg, weight loss, recurrent vomiting, dysphagia, evidence of GI bleeding, or iron-deficiency anemia) or who **fail to respond to empiric therapy** should also be referred for prompt endoscopic evaluation.

CASE CORRELATION

- See also Case 3 (Acute Coronary Syndrome), Case 5 (Aortic Dissection/Marfan Syndrome), Case 10 (Acute Pericarditis Caused by Systemic Lupus Erythematosus), Case 22 (Acute Diverticulitis), and Case 25 (Pancreatitis/Gallstones).

COMPREHENSION QUESTIONS

20.1 A previously healthy 42-year-old overweight woman presents to the emergency department complaining of sudden, right upper abdominal pain that "comes and goes," lasting approximately 45 minutes after eating at a fast-food restaurant. The patient has vomited twice since the pain started, and any attempt to eat worsens the pain. She is sexually active with one male partner, uses condoms regularly, and denies drug use. Which of the following is the most likely cause?

A. Gastric ulcer
B. Cholelithiasis
C. Duodenal ulcer
D. Acute hepatitis

20.2 A 34-year-old man is being seen in the office for follow-up for epigastric pain and suspected PUD. Serum antibodies are positive for *H. pylori*. Which of the following is the most accurate statement regarding this infection?

A. It is more common in North America than in the developing world.
B. It is associated with the development of colon cancer.
C. Eradication of *H. pylori* eliminates most cases of nonulcer dyspepsia.
D. It is believed to be sexually transmitted.
E. It is a cause of both duodenal and gastric ulcers.

20.3 A 45-year-old man was brought to the emergency department after vomiting bright red blood. He has a blood pressure of 88/46 mm Hg and heart rate of 120 bpm. Which of the following is the best next step?

A. Intravenous fluid resuscitation and preparation for a transfusion
B. Administration of a PPI
C. Guaiac test of the stool
D. Treatment for *H. pylori*

20.4 Which one of the following patients should be promptly referred for endoscopy?

A. A 65-year-old man with new onset of epigastric pain and weight loss

B. A 32-year-old patient whose symptoms are not relieved with ranitidine

C. A 29-year-old *H. pylori*–positive patient with dyspeptic symptoms

D. A 49-year-old woman with intermittent right upper quadrant pain following meals

ANSWERS

20.1 **B.** This patient demonstrates risk factors for biliary colic secondary to cholelithiasis (**4 F's: "fat, fertile, female, forty"**). Acute right upper abdominal pain occurring after a fatty meal ("fast food") and producing nausea/vomiting is most suggestive of biliary colic due to gallstones. Gastric and duodenal ulcers (answers A and C) cause a gradual, "gnawing/burning" pain, most commonly located in the midepigastrium. Moreover, the pain associated with duodenal ulcers is relieved with meals. The patient does not demonstrate risk factors for acute hepatitis (answer D) such as intravenous drug use, recent travel, and risky sexual activity.

20.2 **E.** *Helicobacter pylori* infection is more common in *developing* countries (answer A). It is associated with poor hygiene and transmitted via ingestion of the bacteria (contaminated food or water—not sexually [answer D]). *H. pylori* is associated with the development of gastric adenocarcinoma and MALT lymphoma, not colon cancer (answer B). The association between *H. pylori* and nonulcer dyspepsia (answer C) remains unclear. Fewer than 10% of patients with nonulcer dyspepsia improve after *H. pylori* treatment.

20.3 **A.** This patient is *hemodynamically unstable* with hypotension (systolic blood pressure < 90 mm Hg) and tachycardic because of the acute blood loss. Immediate volume resuscitation with crystalloid solution (eg, normal saline), followed by blood transfusion, if necessary, are the best initial steps to prevent irreversible shock and death. Only after the patient is stabilized would it then be appropriate to investigate the cause of instability (eg, hemorrhage or ulcer perforation [answers B, C, and D]).

20.4 **A.** The patient in answer A has "red flag" symptoms, prompting immediate endoscopic evaluation: He is *older than 45 years* and *has new-onset symptoms* suggesting possible malignancy (eg, weight loss). The patient in answer B is young and may benefit from a PPI rather than an H_2 blocker. The patient in answer C is also young and may benefit from triple or quadruple therapy for *H. pylori* eradication. If this initial therapy does not improve symptoms, endoscopic examination would then be appropriate to investigate other causes of dyspepsia. The patient in answer D is most likely experiencing a biliary colic. A right upper quadrant ultrasound would be the best next step in order to evaluate for gallstones.

CLINICAL PEARLS

- The most common causes of duodenal and gastric ulcers are *H. pylori* infection and the use of NSAIDs.
- *Helicobacter pylori* is associated with duodenal and gastric ulcers, chronic active gastritis, gastric adenocarcinoma, and gastric MALT lymphoma.
- Treatment of peptic ulcers requires acid suppression with a PPI to heal the ulcer and antibiotic therapy for eradication *of H. pylori*, if present, to prevent recurrence.
- Patients with dyspepsia who have red flag symptoms (new dyspepsia after the age of 45, weight loss, dysphagia, evidence of bleeding, or anemia) should be referred for endoscopic examination.
- Patients without red flag symptoms may undergo noninvasive testing for *H. pylori* first. The urea breath test may demonstrate active infection. Serologies may be used only if the patient has never been treated for *H. pylori* since antibodies will remain present even after successful treatment.
- Triple or quadruple therapy is used for the treatment of PUD secondary to *H. pylori*. Triple therapy consists of amoxicillin (or metronidazole if penicillin allergy is present), clarithromycin, and a PPI. Quadruple therapy is preferred in the setting of suspected clarithromycin-resistant strains of *H. pylori,* and it consists of a tetracycline, metronidazole, a bismuth compound, and a PPI.

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CASE 21

A 28-year-old man comes to the emergency center complaining of abdominal pain and diarrhea for 2 days. He claims to defecate frequently, usually 10 to 12 times per day, consisting of small-volume stools. Blood and mucus are occasionally visualized in the stool. These episodes are preceded by a sudden urge to defecate. The abdominal pain is crampy, diffuse, moderately severe, and not relieved with defecation. In the past 6 to 8 months, he has experienced similar episodes of abdominal pain that were milder, resolved within 24 to 48 hours, and were associated with loose, mucoid, bloody stools. He has no other medical history and takes no medications. He has neither traveled out of the United States nor had contact with anyone experiencing similar symptoms. He works as an accountant and does not smoke or drink alcohol. The patient denies any family history of gastrointestinal (GI) problems.

On examination, his temperature is 99 °F, heart rate (HR) is 98 beats per minute (bpm), and blood pressure (BP) is 118/74 mm Hg. He appears uncomfortable and is lying still on the stretcher. His sclerae are anicteric, and his oral mucosa is pink without ulceration. His chest is clear to auscultation, and his heart rhythm is regular, without murmurs. His abdomen is soft and mildly distended with hypoactive bowel sounds. There is a mild diffuse tenderness upon palpation, but no guarding or rebound tenderness is elicited.

Laboratory studies are significant for a white blood cell (WBC) count of 15,800/mm^3 with 82% polymorphonuclear leukocytes, hemoglobin 10.3 g/dL, and platelet count 754,000/mm^3. The human immunodeficiency virus (HIV) assay is negative. Renal function and liver function tests are normal. A plain film radiograph of the abdomen shows a mildly dilated, air-filled colon 4.5 cm in diameter without air-fluid levels or evidence of pneumoperitoneum.

- What is the most likely diagnosis?
- What complications are associated with this disease?
- What is the next best step in establishing the diagnosis?
- What is the most appropriate treatment at this time?

ANSWERS TO CASE 21:
Colitis and Inflammatory Bowel Disease

Summary: A 28-year-old man presents with

- Chronic, "crampy" abdominal pain that is not relieved with defecation
- Tenesmus
- Bloody/mucoid stools
- Colon distention, visualized on abdominal x-ray
- No history of foreign travel

Most likely diagnosis: Colitis, secondary to inflammatory bowel disease (IBD; eg, ulcerative colitis [UC], Crohn disease [CD]) because the patient is young, experiencing crampy abdominal pain not relieved with defecation, bloody/mucoid stools, and an increase in stool frequency and urgency.

Associated complications: Complications associated with IBD are toxic megacolon, bowel perforation with peritonitis, abscesses, and fistula formation (eg, enterovesical fistula).

Next step to confirm diagnosis: After obtaining stool samples to exclude infection, colonoscopy would be appropriate to confirm the diagnosis of IBD.

Most appropriate treatment: Admit the patient to the hospital and begin treatment with corticosteroids (eg, budesonide, prednisone).

ANALYSIS

Objectives

1. Describe the typical presentation of IBD. (EPA 1, 2)
2. Recognize the differences between CD and UC. (EPA 2, 3)
3. Describe the treatment of IBD. (EPA 4)

Considerations

Although the likelihood in this patient is low, infection must be excluded. Common organisms that cause colitis are *Entamoeba histolytica*, *Salmonella*, *Shigella*, *Escherichia coli*, *Campylobacter*, and *Clostridium difficile*, which can occur even in the absence of prior antibiotic exposure. The main consideration in this case would be IBD versus infectious colitis. The absence of travel history and sick contacts and the chronicity of the illness all point away from infection.

This patient does not appear to have any life-threatening complications of colitis, such as a perforation or toxic megacolon. However, close monitoring is imperative, and surgical consultation may be helpful in the event that such complications arise during hospitalization.

APPROACH TO:

Colitis and Inflammatory Bowel Disease

DEFINITIONS

COLITIS: Inflammation of the colon, which may be due to infectious, autoimmune, ischemic, or idiopathic causes.

CROHN DISEASE: Inflammatory disease of the bowel that involves the full thickness of the bowel wall and can affect the intestines anywhere from esophagus to anus, although the ileum is most commonly affected.

INFLAMMATORY BOWEL DISEASE: An autoimmune condition characterized by inflammation of the intestinal tract; may be further subdivided into CD or UC.

TENESMUS: Feeling an urge to defecate.

ULCERATIVE COLITIS: Inflammatory disease affecting the mucosa of the bowel, principally the large bowel.

CLINICAL APPROACH TO COLITIS

Pathophysiology

The differential diagnosis for colitis includes ischemic colitis, infectious colitis (*C. difficile*, *E. coli*, *Salmonella*, *Shigella*, and *Campylobacter*), radiation colitis, and IBD (CD vs UC).

Ischemic colitis (eg, mesenteric colitis) usually presents in people older than 50 years with **known atherosclerotic vascular disease** (eg, peripheral vascular disease, coronary artery disease). The pain is usually acute, commonly **after a meal** ("intestinal angina") and not associated with fevers.

Patients with **infectious colitis** usually present with fever, leukocytosis, abdominal pain, and diarrhea, which may be categorized as either *invasive diarrhea* ("dysentery") or *watery diarrhea*. The stools associated with **dysentery** are hemorrhagic, appearing grossly bloody (**hematochezia**) or black/tar-like (**melena**). Infectious colitis associated with **profuse watery diarrhea** is usually indicative of ***C. difficile*** infection and presents in the setting of **antibiotic use.** The initial workup for infectious colitis includes **stabilizing the patient with normal saline** if hypovolemic shock is present (systolic BP < 90 mm Hg), obtaining a **stool culture**, and **sampling for bacterial toxins** (Shiga toxin, *C. difficile* toxins).

Radiation enteritis presents as abdominal pain associated with nausea/vomiting, diarrhea, and lower GI bleeding, 3 or more months after completing radiation therapy. Imaging studies, such as abdominal computed tomography, or endoscopic studies (eg, colonoscopy) would demonstrate segmental bowel inflammation in regions of a known radiation field.

Treatment

Antimicrobial therapy (eg, azithromycin, ciprofloxacin) is recommended for treatment of severe dysentery caused by *Campylobacter* and entero-hemorrhagic or entero-toxigenic *E. coli*. Antibiotic therapy for the treatment of Shiga toxin–producing strains of *E. coli* remain controversial. *C. difficile* infection requires treatment with ***oral* vancomycin**. Although antimotility drugs (eg, loperamide) may improve symptoms of watery diarrhea, these agents should be avoided in cases of bloody diarrhea. Risk factors for infectious colitis include **recent history of foreign travel** (*E. histolytica*), **consumption of raw/undercooked meat** (*Shigella, E. coli* O157:H7, *Salmonella, Campylobacter*), and **antibiotic use** (*C. difficile*).

CLINICAL APPROACH TO INFLAMMATORY BOWEL DISEASE

Epidemiology

IBD is an autoimmune condition characterized by chronic inflammation of the intestinal tract. Disease incidence is bimodal, most commonly presenting in young patients between the ages of 15 and 35, with a second peak between the ages of 60 and 70. Although patients may initially complain of GI symptoms (eg, chronic abdominal pain, bloody diarrhea), systemic symptoms may also be present, such as fever, weight loss, and anemia, either due to iron deficiency (chronic GI blood loss) or anemia of chronic disease. IBD encompasses two major disorders, UC and CD, each demonstrating their own clinical and pathologic characteristics, yet with substantial overlap.

Pathophysiology

UC is the **most common subtype of IBD** and is a chronic inflammatory condition that is **limited to the mucosal and submucosal surface** of the **colon**. The exact mechanism for developing UC remains unclear but is thought to be caused by a dysregulated immune response to a microbial pathogen in the intestine, resulting in colonic inflammation. The inflammation associated with UC **always begins at the rectum**, is **circumferential**, and **extends proximally**, involving other portions of the colon in a **continuous** pattern. Different terms may be used to describe the degree of colonic extension. For example, ulcerative proctitis refers to inflammation limited to the rectum. Ulcerative proctosigmoiditis refers to inflammation limited to the rectum and sigmoid colon. Left-sided colitis refers to inflammation extending proximally from the rectum to the splenic flexure. Symptoms of UC progress gradually, consisting of **bloody diarrhea**, increased stool frequency, urgency, tenesmus, and **left lower quadrant (LLQ) abdominal pain** due to rectum/colonic involvement. Abdominal imaging is not required for the diagnosis of UC. However, barium x-rays may show a "**lead pipe colon**" due to colonic inflammation and edema. Colonoscopy with visualization of ulcers is the gold standard for diagnosing UC. Biopsy of these lesions demonstrates crypt atrophy with **polymorphonuclear cell infiltration ("crypt abscesses")**.

CD is the other subtype of IBD and is characterized by **transmural inflammation**, which may arise at **any portion of the GI tract**, from the mouth to the perianal area. Unlike UC, the inflammation in CD is **noncontinuous** and most

Table 21–1 • COMPARISON OF CROHN DISEASE VERSUS ULCERATIVE COLITIS

	Crohn Disease	Ulcerative Colitis
Site of origin	Terminal ileum (most common)	Rectum
Pattern of progression	"Skip" lesions/irregular	Continuous; extends proximally from rectum
Thickness of inflammation	Transmural	Submucosa or mucosa
Symptoms	Crampy abdominal pain with or without bloody diarrhea	Bloody diarrhea
Complications	Fistula, abscess, obstruction	Hemorrhage, toxic megacolon, cancer
Radiographic findings	String sign on barium x-ray	Lead pipe colon on barium x-ray
Surgery	For complications such as stricture	Curative
Smoking	Increases risk for developing CD	Decreases risk for developing UC

commonly affects the **terminal ileum**, resulting in **right lower quadrant (RLQ) abdominal pain.** Other symptoms associated with CD are fever, weight loss, and prolonged diarrhea with or without gross bleeding. Like UC, abdominal imaging is not required to diagnose CD. However, the **"string sign"** is a classic finding on barium x-rays, correlating to strictures in the lower GI tract. Endoscopic evaluation with visualization of GI inflammation is the gold standard for diagnosing CD. Grossly, the intestinal lumen classically reveals **"cobblestoning"** of the mucosa, with biopsy of these lesions demonstrating **noncaseating granulomas.** Tables 21–1 and 21–2 summarize features seen in UC and CD.

Treatment

The treatment for UC is aimed at reducing colonic inflammation and varies depending on disease severity. For mild-to-moderate inflammation, **sulfasalazine** or other 5-aminosalicylic acid (ASA) compounds, such as **mesalamine,** are used. **Corticosteroids** (oral, rectal, or intravenous) are used for the initial treatment of **severe UC flares** and are gradually tapered once remission is achieved to avoid side effects. **Immune modulators** (eg, 6-mercaptopurine, azathioprine, methotrexate, infliximab) are used for **refractory cases**, but they may reactivate latent infections (eg, tuberculosis). Since inflammation is limited to the colon in UC, **total colectomy is curative** but is reserved for medically intractable disease, management of acute complications, or treatment of colorectal cancer/dysplasia.

Treatment of CD is similar to that of UC, but it does have some major differences. Like UC, **remission** of an acute CD flare is also achieved with **corticosteroids** (eg, budesonide, prednisone), which are tapered once remission is achieved. A **thiopurine** (eg, azathioprine, 6-mercaptopurine) or biologic agent (eg, **infliximab**) may be added to maintain remission. However, unlike UC, **treatment of CD with colectomy is not curative** since these lesions may occur at any portion of the GI tract and are not limited to the colon.

Table 21–2 • EXTRAINTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

	Crohn Disease	Ulcerative Colitis
Skin manifestations	**Erythema nodosum**: 15% Pyoderma gangrenosum: rare	**Erythema nodosum**: 10% **Pyoderma gangrenosum**: 1%-12%
Rheumatologic	Arthritis (polyarticular, asymmetric): common **Ankylosing spondylitis**: 10%	Arthritis: less common Ankylosing spondylitis: less common
Ocular	Uveitis: more common (photophobia, blurred vision, headache)	Uveitis: 3%-4% (photophobia, blurred vision, headache)
Hepatobiliary	**Cholelithiasis**: common Primary sclerosing cholangitis: rare	**Fatty liver: common** **Primary sclerosing cholangitis: 5%**
Urologic	**Nephrolithiasis** (eg, **calcium oxalate;** 10%-20%) after small bowel resection or ileostomy due **to increased enteric oxalic acid absorption and renal excretion**	

Complications

Ulcerative Colitis. Ulcerative colitis is associated with both acute and chronic complications. Acute complications include **severe hemorrhage**, **fulminant colitis/toxic megacolon**, and colonic **perforation.** Patients with severe bleeding may present with hemorrhagic shock (systolic BP < 90 mm Hg) and have anemia. Symptoms associated with fulminant colitis include profound increase in stool frequency (> 10 stools/d), abdominal pain, distention, and severe **toxic symptoms**, such as **fever**, **leukocytosis**, **tachycardia**, **hypotension**, and **altered mental status**. These patients are at increased risk for developing toxic megacolon, which is characterized by colonic diameter > 6 cm or cecal diameter > 9 cm in the presence of systemic toxicity. Colonic perforation with **peritonitis** is the most severe complication of UC, usually resulting from untreated toxic megacolon, and it is associated with 50% mortality in patients with UC. Management involves providing prompt **intravenous fluids** and **nasogastric decompression**, ensuring the patient receives **nothing by mouth** (**NPO**), and referring for a surgical evaluation for **colectomy**. Broad-spectrum antibiotics and systemic corticosteroids are also administered to reduce inflammation.

Patients with **UC** also have a marked **increase in the incidence of colon cancer** compared to the general population. The risk of cancer increases over time and is related to disease duration and extent. **Annual or biennial colonoscopy is advised in patients with UC, beginning 8 years after diagnosis,** and random biopsies should be sent for evaluation. If colon cancer or dysplasia is found, a colectomy is recommended.

Crohn Disease. Complications associated with CD are **fistula formation**, **perianal disease**, and **malabsorption**. Chronic transmural inflammation may cause a sinus tract to gradually form within the bowel wall, which may predispose to fistula

formation if the sinus tract penetrates through the serosa and connects to another epithelial-lined organ. Clinical manifestations of fistula formation vary depending on organ involvement. For example, fistulas connecting the bowel to bladder (enterovesical fistulas) present with recurrent urinary tract infections and pneumaturia. Enterovaginal fistulas may present with gas or feces emanating from the vaginal vault.

Other complications associated with CD include **perianal disease** and **malabsorption**. More than one-third of patients with CD complain of perianal disease. Symptoms may include large perianal **skin tags**, fissures, or abscesses, which may evolve into fistulas. Terminal ileum involvement may cause **malabsorption** of **bile salts**, resulting in **deficiency of fat-soluble vitamins** (**A, D, E, K**), and/or malabsorption of **vitamin B_{12}**, corresponding to **megaloblastic anemia** with possibly subacute combined degeneration of the spinal cord.

CASE CORRELATION

- See also Case 22 (Acute Diverticulitis) and Case 23 (Chronic Diarrhea).

COMPREHENSION QUESTIONS

21.1 A 32-year-old woman is being seen in the office for follow-up of her systemic inflammatory condition. She has a history of chronic diarrhea and gallstones. Today, she complains of 3 days' duration of "brown, foul-smelling discharge" leaking from her vagina. The clinician believes that the vaginal condition is related to her primary disease. Which of the following is the most likely diagnosis?

A. Crohn disease
B. Ulcerative colitis
C. Systemic lupus erythematosus
D. Sarcoidosis

21.2 A 45-year-old man with a history of UC is admitted to the hospital with 2 to 3 weeks of right upper quadrant abdominal pain, jaundice, and pruritus. He states that he has not had these symptoms previously. He has no fever and has a normal WBC count. Endoscopic retrograde cholangiopancreatography (ERCP) shows stricture formation of intrahepatic and extrahepatic bile ducts with intervening segments of normal and dilated ducts. Which of the following is the most likely diagnosis?

A. Primary biliary cirrhosis (PBC)
B. Cholangiocarcinoma
C. Primary sclerosing cholangitis (PSC)
D. Choledocholithiasis with resultant biliary strictures

21.3 A 25-year-old man is hospitalized for an exacerbation of UC. He complains of abdominal pain and fever. On examination, he is found to have a temperature of 101 °F, HR 110 bpm, and BP 100/60 mm Hg. His abdomen is distended. On abdominal x-ray, he is noted to have bowel distention with a transverse colonic dilation of 7 cm. Which of the following is the best next step?

A. 5-ASA

B. Oral steroids

C. Intravenous antibiotics and prompt surgical consultation

D. Infliximab

21.4 A 35-year-old woman complains of chronic crampy abdominal pain, intermittent constipation, and diarrhea. She denies weight loss or GI bleeding. Her abdominal pain is usually relieved with defection. Colonoscopy and upper endoscopy with biopsies are normal, and stool cultures are negative. Which of the following is the most likely diagnosis?

A. Infectious colitis

B. Irritable bowel syndrome

C. Crohn disease

D. Ulcerative colitis

ANSWERS

21.1 **A.** This patient likely has an enterovaginal fistula based on the history of stool leaking into the vaginal area. Fistulas (eg, rectovaginal fistulas) are common with CD because of transmural inflammation. Fistulas can occur between bowel, between the bowel and other organs (bladder, vagina), or between the bowel and skin (enterocutaneous). In contrast, the mucosal inflammation seen in UC (answer B) is not associated with fistulas. Gallstones are common in patients with CD due to bile salt malabsorption, which is necessary to increase cholesterol solubility in bile. Systemic lupus erythematosus (answer C) is more commonly associated with joint pain, alopecia, serositis, rash, anemia, central nervous system findings, and renal dysfunction. Sarcoidosis (answer D) is associated with pulmonary findings such as shortness of breath and cough, neurologic manifestations, and systemic findings (fever, weight loss). Neither systemic lupus erythematosus nor sarcoidosis is associated with fistulas.

21.2 **C.** The ERCP shows the typical appearance for PSC, which is associated with IBD (predominantly UC) in 75% of cases. PSC is more common in men. Antibodies against perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are also common. Stone-induced strictures such as those due to choledocholithiasis (answer D) are extrahepatic and unifocal. Cholangiocarcinoma (answer B) is less common but may develop in 10% of patients

with PSC. PBC (answer A) is an autoimmune disorder characterized by destruction of intrahepatic bile ducts, presenting with jaundice and extensive pruritus secondary to cholestasis. PBC is more common in women and is associated with antimitochondrial antibodies.

21.3 **C.** Colonic dilation greater than or equal to 6 cm with signs of systemic toxicity (ie, fever) makes the diagnosis of toxic megacolon more likely. With toxic megacolon, antibiotics and surgical intervention are often necessary and lifesaving. Medical therapy includes bowel rest with total parenteral nutrition, intravenous steroids, and antibiotics. Sulfasalazine and 5-ASA compounds (answer A) are not recommended for the treatment of toxic megacolon. The other answer choices are medical therapy (answer B, oral steroids and answer D, infliximab) and would only delay addressing the possible emergency.

21.4 **B.** Irritable bowel syndrome is characterized by intermittent diarrhea and/or constipation and crampy abdominal pain often relieved with defecation. Weight loss, fecal blood, and intestinal biopsies are negative. It is a diagnosis of exclusion once other conditions, such as IBD and parasitic infection (eg, giardiasis), have been excluded. The other diseases (answer A, infectious colitis; answer C, Crohn disease; answer D, ulcerative colitis) are associated with fever, weight loss and systemic symptoms.

CLINICAL PEARLS

- Ulcerative colitis always involves the rectum and may extend proximally in a continuous distribution.
- Crohn disease most commonly involves the distal ileum, but it may involve any portion of the GI tract in a noncontinuous ("skip lesions") distribution.
- Crohn disease is often complicated by fistula formation and malabsorption of fat-soluble vitamins and vitamin B_{12}.
- Toxic megacolon is associated with UC and characterized by dilation of the colon with symptoms of systemic toxicity; failure to improve with medical therapy may require surgical intervention.
- Ulcerative colitis is associated with increased risk of colon cancer; the risk increases with duration and extent of disease.
- Both UC and CD can be associated with extraintestinal manifestations, such as uveitis, erythema nodosum, pyoderma gangrenosum, arthritis, and PSC.

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CASE 22

A 61-year-old man comes to the emergency center complaining of 3 days of worsening abdominal pain. The pain is localized to the left lower quadrant of his abdomen. It began as an intermittent crampy pain and now has become steady and moderately severe. He feels nauseated, but he has not vomited. He had a small loose stool at the beginning of this illness, but he has had not had any bowel movements over past 2 days. He has never experienced these symptoms before, and he does not have any history of gastrointestinal (GI) illnesses.

On examination, his temperature is 100.2 °F, heart rate is 98 beats per minute (bpm), and blood pressure is 110/72 mm Hg. He has no pallor or jaundice. His chest is clear, and his heart rhythm is regular without murmurs. His abdomen is mildly distended with hypoactive bowel sounds and marked left lower quadrant tenderness with voluntary guarding. Rectal examination reveals tenderness, and his stool is negative for occult blood.

Laboratory studies are significant for a white blood cell count of 12,800/mm^3 with 74% polymorphonuclear leukocytes, 22% lymphocytes, and a normal hemoglobin and hematocrit. A plain film of the abdomen shows no pneumoperitoneum and a nonspecific bowel gas pattern.

- What is the most likely diagnosis?
- What are risk factors for developing this condition?
- What are the most appropriate next steps in management?

ANSWERS TO CASE 22:
Acute Diverticulitis

Summary: A 61-year-old man presents with

- A 3-day history of worsening new-onset abdominal pain
- Low-grade fever
- Abdominal distention, hypoactive bowel sounds, and voluntary guarding
- Leukocytosis with normal hemoglobin and no occult blood
- Normal x-ray of the abdomen

Most likely diagnosis: Acute sigmoid diverticulitis.

Risk factors: Frequent red meat consumption, Western diet, and low-fiber diets.

Most appropriate next steps: This patient shows voluntary guarding, which is concerning for peritoneal inflammation, likely due to complicated diverticulitis. The patient should be admitted to the hospital for intravenous antibiotics, imaging, and close monitoring. Computed tomographic (CT) scan of the abdomen will be very useful to confirm the diagnosis and to exclude pericolic abscess or other complications, such as fistula formation.

ANALYSIS

Objectives

1. Describe the complications of diverticular disease. (EPA 1, 10)
2. Recognize the appropriate therapy of acute diverticulitis, which is dependent on the age of the patient and the severity of the disease presentation. (EPA 1, 4)
3. List the complications of diverticulitis and the indications for surgical intervention. (EPA 4, 10)
4. Differentiate between inpatient and outpatient management of diverticulitis. (EPA 1, 2, 9)
5. Discuss strategies for prevention and follow-up in acute diverticulitis. (EPA 7, 12)

Considerations

This 61-year-old man presents with new-onset, progressively worsening, severe, lower left abdominal pain. The most likely diagnosis is acute diverticulitis, but the differential diagnosis for these symptoms is broad; several key diagnoses that carry significant morbidity and mortality for the patient must be excluded. These include bowel perforation, ischemic colitis, and colon cancer. This patient had an x-ray that showed no free air in the abdomen. This makes pneumoperitoneum secondary to bowel perforation, which is a surgical emergency, less likely. Ischemic colitis

is another diagnostic consideration in an older patient, but it usually is associated with signs of bleeding and a history of atherosclerotic disease and pain out of proportion to the physical examination findings. As colon cancer can present with abdominal pain and bleeding per rectum, the patient must receive age-appropriate colon cancer screening once acute diverticulitis has resolved.

APPROACH TO: Diverticulitis

DEFINITIONS

COLONIC DIVERTICULUM: Herniation of the mucosa and submucosa through a weakness of the muscle lining of the colon.

DIVERTICULITIS: Inflammation of a colonic diverticulum, typically on the left colon, such as the sigmoid.

DIVERTICULOSIS: Presence of diverticular disease in the colon without inflammation; it is often asymptomatic or may present with painless bright red rectal bleeding.

RECURRENT DIVERTICULITIS: Subsequent diverticulitis episode(s) after the resolution of the first attack of acute diverticulitis, which may not be as severe.

SMOLDERING DIVERTICULITIS: Symptomatic, uncomplicated diverticulitis that persists after the initial episode and is refractory to medical treatment.

CLINICAL APPROACH

Pathophysiology

Diverticulosis is extremely common, affecting 50% to 80% of people older than 80 years. Colonic diverticula are, in fact, *pseudodiverticula* through weakness in the muscle lining, typically at areas of vascular penetration to the smooth muscle. Therefore, their walls do not contain the muscle layers surrounding the colon. They are typically 5 to 10 mm in diameter and occur mainly in the distal colon. The development of diverticula has been linked to insufficient dietary fiber, leading to a slower colonic transit and increased resting colonic intraluminal pressure. Most patients will remain asymptomatic. Some patients, however, will have chronic symptoms (eg, nonspecific lower abdominal pain aggravated by eating and relieved upon defecation, bloating, constipation, or diarrhea) resembling those of irritable bowel syndrome. A patient with diverticulosis may even present with acute symptoms that could be confused with acute diverticulitis, but upon further workup there is no evidence of inflammation. This entity has been named "painful diverticular disease without diverticulitis."

Acute diverticulitis is a common complication of diverticulosis, developing in approximately 20% of all patients with diverticula. The risk of diverticulitis is increased in patients who use medications such as aspirin and nonsteroidal

Table 22–1 • PRESENTATION OF DIVERTICULITIS	
Uncomplicated (75%)	Abdominal pain, fever, leukocytosis, anorexia, constipation/obstipation
Complicated (25%)	Abscess (15%) Perforation (10%) Stricture (5%) Fistula (1%)

anti-inflammatory drugs, patients who are obese, or those who lead sedentary lifestyles. Patients often present with acute abdominal pain and signs of peritoneal irritation localizing to the left lower quadrant, often **presenting like "left-sided appendicitis."** Inspissated stool particles (fecaliths) appear to obstruct the diverticular neck, causing more inflammation and diminished venous outflow, as well as bacterial overgrowth, which ultimately leads to abrasion and perforation of the thin diverticular wall. Most cases are uncomplicated and may be medically managed in an outpatient setting, but 25% of cases develop complications that may require hospitalization or surgical intervention (Table 22–1).

Clinical Presentation

Patients usually present with visceral pain that localizes later to the **left lower quadrant** and may be associated with fever, nausea, vomiting, dysuria, diarrhea, or constipation. A right lower quadrant presentation would not exclude this diagnosis because diverticulitis can also affect the ascending colon or cecum. On examination, the patient may have localized left lower quadrant tenderness or more diffuse abdominal tenderness with peritoneal irritation signs, such as guarding or rebound tenderness. The patient may also have a palpable mass or abdominal distension on examination. On rectal examination, the patient may exhibit tenderness if there is an abscess present. Laboratory testing will show neutrophil-predominant leukocytosis.

Plain film radiographs, including abdominal erect and supine films with a chest x-ray, are routinely performed but usually are not diagnostic. These films can help to identify patients with pneumoperitoneum and assess their cardiopulmonary status, especially in patients with other comorbid conditions. Barium enemas are contraindicated for fear of perforation and spillage of contrast into the abdominal cavity, a catastrophic complication. Endoscopy is also relatively contraindicated in the acute phase due to risk of perforation and usually is reserved for use at least 6 weeks after resolution of the acute episode. The purpose of the colonoscopy is to confirm the presence of diverticuli and to exclude colonic neoplasia.

CT scan is typically the **preferred modality of choice for diagnosing diverticulitis.** Findings consistent with diverticulitis include inflamed sigmoid diverticula, thickening of the bowel wall to more than 4 mm, pericolic fat stranding signifying inflammation, or the finding of a diverticular abscess. Although these findings have high specificity for diverticulitis, they have low sensitivity, and only 50% of patients will have these characteristics on CT. Pregnant patients

can undergo ultrasonography to avoid the harmful effects of ionizing radiation to the fetus.

Treatment

Outpatient Therapy. Patients with **uncomplicated diverticulitis** can usually be managed conservatively with **bowel rest and antibiotics**. Select patients with less severe presentation, ability to tolerate oral antibiotic medications, and absence of significant comorbid conditions may be managed as outpatients. There is weak evidence supporting the use of antibiotic therapy in uncomplicated diverticulitis. Several studies showed that antibiotics do not affect recovery time or prevent future complications in uncomplicated diverticulitis. However, antibiotics are often prescribed as a part of the standard practice. Antibiotic therapy should cover a broad spectrum and should especially target gram-negative rods and anaerobes. Oral antibiotics may include a quinolone plus metronidazole, or amoxicillin-clavulanate for 7 to 10 days. Patients should be instructed to take clear liquids only and advance their diet slowly only if clinical improvement is evident after 2 to 3 days.

Inpatient Therapy. Factors that advocate for **inpatient** therapy include elderly or immunosuppressed patients, those with significant comorbidities, those with high fever or significant leukocytosis, and those in need for narcotics to control pain. Patients requiring hospitalization can be treated with clear liquids or given nothing by mouth (NPO) with intravenous hydration, depending on the severity of symptoms. Intravenous empiric antibiotics with broad-spectrum activity against gram-negative rods and anaerobic organisms such as piperacillin/tazobactam or ceftriaxone plus metronidazole should be started. Pain, fever, and leukocytosis are expected to diminish with appropriate management in the first few days of treatment, at which point the dietary intake can be advanced gradually. CT imaging is indicated to identify complications (Table 22–2), such as abscess, stricture, or obstruction in the patient with persistent fever or pain. The patient can be discharged once able to tolerate an oral diet, their vital signs are stable, and their abdominal pain has resolved.

Surgical Therapy. **Surgical management** such as sigmoid resection is indicated for **low surgical risk** patients with **complicated diverticulitis**. Patients who have suffered two or more episodes of uncomplicated diverticulitis are often treated surgically, but medical management may also be continued without increased risk of perforation. Indications for **emergent surgical intervention** include **generalized peritonitis, uncontrolled sepsis, perforation, and clinical deterioration**. Surgical interventions include abdominal washout, CT-guided percutaneous drainage of abscesses, and bowel resection.

Prevention and Recurrence. Once the acute phase has resolved, medical management to prevent symptoms includes a high-fiber diet, anti-inflammatory medications such as mesalamine for chronic low-grade inflammation, and probiotics. Treatment of diverticulosis consists of changing dietary habits, especially increasing fiber intake. Avoidance of nuts or foods with small seeds (eg, strawberries) is traditionally advised, although data supporting this recommendation is lacking. Patients should be encouraged to exercise routinely and counseled to stop smoking. Colonoscopy is commonly performed at least 6 weeks after an attack

Table 22–2 • COMPLICATIONS OF DIVERTICULITIS

Complication	Characteristics	Treatment
Abscess	Suspected in patients with a tender mass on examination, persistent fever and leukocytosis in spite of adequate therapy, or a suggestive finding on imaging studies.	Conservative management for small pericolic abscesses. CT-guided percutaneous drainage or surgical drainage for other abscesses depending on the size, content, location, and peritoneal contamination.
Fistulas	Majority are colovesical with male predominance (because of bladder protection by the uterus in females). Others include colovaginal, coloenteric, colouterine, and coloureteral. Colocutaneous fistulas are extremely rare.	Single-stage surgery with fistula closure and primary anastomosis.
Obstruction	Either acute or chronic. Ileus or pseudo-obstruction is more likely than complete mechanical obstruction. Small-bowel obstruction may occur if a small-bowel loop was incorporated in the inflamed mass.	Usually amenable to medical management (NPO, gastric decompression). If not, prompt surgical intervention is required.
Strictures	Occur as a result of recurrent attacks of diverticulitis. Insidious-onset colonic obstruction is likely. Colonoscopy is important for an accurate diagnosis and to exclude a stenosing neoplasm as the cause of the stricture.	A trial of endoscopic therapy (bougienage, balloon, laser, electrocautery, or a blunt dilating endoscope) can be attempted. Surgery is indicated if neoplasm could not be excluded or if such trial has failed.

Abbreviations: CT, computed tomography; NPO, nothing by mouth.

of diverticulitis to evaluate for colorectal carcinoma, which may mimic the clinical presentation of diverticulitis.

Some patients may continue to have symptoms after an initial attack, leading to a **subacute phase called "smoldering diverticulitis."** These patients may develop chronic symptoms that last longer than 6 months without progressing to acute diverticulitis or other complications. About a third of the patients with one episode of diverticulitis will develop recurrent disease. Though those with uncomplicated diverticulitis are not at increased risk of recurrence, patients with complicated disease are 1.5 times more likely to develop recurrence. Patients without significant other comorbidities who have chronic smoldering diverticulitis or recurrent or complicated diverticulitis should be offered surgical intervention.

Complications

Complications include hemorrhage and obstruction. **Diverticular hemorrhage is the most common cause of hematochezia in patients older than 60 years** and typically presents as **painless passage of bright red blood**. Only 20% of patients with diverticulosis will experience GI bleeding. Generally, hemorrhage is **abrupt in onset and resolution.** The diagnosis may be established by finding diverticula on

colonoscopy without other pathology. Most diverticular hemorrhages are self-limited, and treatment is supportive, with intravenous fluid or blood product transfusion as needed. For patients with recurrent or chronic bleeding, resection of the affected colonic segment may be indicated. Bowel obstruction is rare and can be due to acute inflammation leading to partial obstruction of the bowel lumen or, less commonly, chronic inflammation leading to stricture formation. Sometimes surgical therapy is needed if medical treatment is ineffective.

CASE CORRELATION

- See also Case 20 (Peptic Ulcer Disease), Case 21 (Colitis and Inflammatory Bowel Disease), Case 23 (Chronic Diarrhea), and Case 25 (Pancreatitis/Gallstones).

COMPREHENSION QUESTIONS

22.1 A 48-year-old woman is admitted to the hospital with left lower quadrant abdominal pain, leukocytosis, and a CT scan showing sigmoid wall thickening consistent with a pericolic abscess. Her medical history is significant for a similar hospitalization with the same diagnosis less than 1 year previously. Which of the following is the most appropriate next step in management?

A. Surgical consultation for exploratory laparotomy and sigmoid resection
B. Intravenous antibiotics and colonoscopy for evaluation for colon cancer
C. Intravenous antibiotics and barium enema to evaluate for possible colonic malignancy
D. Intravenous antibiotics and recommendations for postdischarge diet high in fiber with whole grains and nuts to minimize the risk of diverticular progression

22.2 A 78-year-old is woman is hospitalized for a 2-day history of progressive fever and chills, decreased mentation, and lower abdominal pain. On examination, her blood pressure is 120/70 mm Hg, heart rate is 110 bpm, and temperature is 101 °F. Examination shows severe right lower quadrant abdominal tenderness and guarding. Which of the following is the most likely diagnosis?

A. Ruptured diverticulitis
B. Meningitis
C. Ruptured appendicitis
D. Ischemic bowel
E. Sepsis secondary to urinary tract infection

22.3 A 58-year-old man presents to the emergency room for evaluation of a 2-day history of left lower quadrant abdominal pain. The patient notes that during this time he has had fevers, chills, and constipation. His vital signs show a temperature of 102 °F, pulse of 90 bpm, and respiratory rate of 20 breaths/min. Physical examination shows abdominal pain localizing to the left lower quadrant and mild rebound tenderness. There are no abnormalities on cardiopulmonary examination. Which of the following diagnostic tests is the best next step?

A. Barium enema

B. Flexible sigmoidoscopy

C. CT imaging of the abdomen

D. Laparoscopic examination

E. Observation

22.4 A 74-year-old man presents to the emergency room due to severe abdominal pain that started 2 hours ago. He has had three bloody stools during this time. The patient has a past medical history of diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease. He recalls that he recently had heart surgery to repair a vessel with a weak wall. He has a 30 pack-year history of smoking but quit several years ago. His diet consists of red meats and low fiber. He drinks one or two glasses of wine a week. The patient's temperature is 101.2 °F, pulse is 110 bpm, and blood pressure is 90/58 mm Hg. On physical examination, his abdomen is distended and diffusely tender to palpation. Bowel sounds are absent. What is the likely etiology of this patient's condition?

A. Inflammation of herniated colonic wall mucosa

B. Ischemia and necrosis of the watershed areas of the colon

C. GI bleed due to arteriovenous malformation

D. Neoplasia of columnar epithelium in the colon

22.5 An 85-year-old woman presents to the emergency department with severe left lower abdominal pain that began several hours ago. The patient has a past medical history of hypertension, osteoporosis, and rheumatoid arthritis. She was brought in by a caretaker at a nursing home. The patient's temperature is 103.8 °F, pulse is 115 bpm, and blood pressure is 135/80 mm Hg. She is mildly confused but alert and answers questions. Her heart and lung examinations are normal. Abdominal examination shows tenderness to palpation of the left lower quadrant with guarding, but no peritoneal signs. Her hemoglobin is 11.2 g/dL, leukocyte count is 14,000/mm^3, and platelet count is 280,000/mm^3. What is the best next step in the management of this patient?

A. Outpatient management, oral amoxicillin-clavulanate, and follow-up in 2 to 3 days

B. Outpatient management, no antibiotics, and bowel rest

C. Inpatient management, oral amoxicillin-clavulanate, and NPO with intravenous hydration

D. Inpatient management, intravenous piperacillin/tazobactam, and NPO with intravenous hydration

ANSWERS

22.1 **A.** This patient has complicated diverticulitis, with recurrent disease (as defined by two or more complicated episodes); she is a low surgical risk and thus should be evaluated for resection. Barium enema (answer C) is contraindicated due to risk of perforation, and dietary recommendations regarding nuts and seeds (answer D) are unsupported by data. Colonoscopy (answer B) should be postponed until at least 6 weeks after the acute case of diverticulitis to avoid perforation.

22.2 **C.** This patient has right lower abdominal tenderness and fever, which is most likely due to acute appendicitis. The most common cause of an acute abdomen at any age is appendicitis. Ischemic bowel (answer D) usually presents with severe abdominal pain out of proportion to abdominal examination findings and often with a history of atherosclerotic vascular disease. Sepsis due to a urinary tract infection (answer E) is a common cause of septic shock and hypotension, but it usually does not cause abdominal findings; flank tenderness or merely generalized sepsis is more common.

22.3 **C.** CT imaging is the modality of choice in evaluating diverticulitis. Barium enema (answer A) and endoscopy tend to increase intraluminal pressure and can worsen diverticulitis or lead to colonic rupture. Colonoscopy and flexible sigmoidoscopy (answer B) are also contraindicated in the acute setting and should be delayed until 6 weeks after to rule out a neoplasm. Observation (answer E) is not appropriate in this patient before a complete evaluation is performed.

22.4 **B.** This patient has ischemic colitis, which is suggested by his acute presentation of bloody stools, diffuse abdominal pain, absent bowel sounds, and hypotension. This patient has several risk factors for ischemic colitis, such as coronary artery disease and history of aortic aneurysm repair (weakening of vessel wall). Although arteriovenous malformation (answer C) and angiodysplasia are common causes of lower GI bleeds, they do not usually present with severe abdominal pain and shock, and the patient usually has a history of renal disease. Colorectal cancer (answer D) is a chronic condition that may present with lower GI bleed, anemia, changes in bowel habits, and weight loss.

22.5 **D.** This elderly patient is quite ill. Although her current blood pressure is normal, her temperature of 103.8 °F, tachycardia, and leukocytosis portend serious illness. The patient should be admitted to the hospital for inpatient management. The physical findings point toward an abdominal process. Regardless of the etiology, this patient should be treated within 1 hour (optimally after blood and urine cultures). Treatment includes intravenous antibiotics that are broad spectrum and target gram-negative rods as well as anaerobic bacteria, intravenous fluids, and serum lactate level. A CT scan of the abdomen is important to assess the etiology of the abdominal pain and decide appropriate therapy based on the findings. Answers A and B

CLINICAL PEARLS

- Acute diverticulitis usually presents with left lower quadrant pain, fever, leukocytosis, and constipation and often with signs of peritoneal inflammation.
- Inpatient management of diverticulitis is indicated in patients with complications such as peritonitis, abscess, and strictures or in patients who are at high risk of morbidity and mortality.
- Some patients can be managed on an outpatient basis and should be reevaluated in 2 to 3 days to monitor resolution of symptoms.
- Uncomplicated diverticulitis can be treated medically with antibiotics and bowel rest.
- Diverticulitis can be complicated by perforation with peritonitis; pericolic abscess; fistula formation, often to the bladder; and strictures with colonic obstruction. Complicated diverticulitis may require hospitalization, intravenous antibiotics, and possibly surgical intervention.
- Enemas and endoscopy are usually avoided in the acute setting because of the risk of perforation.
- Prevention includes incorporation of dietary fiber, eating less meat, smoking cessation, and routine exercise.

(outpatient treatment) are not appropriate options for this patient due to the seriousness of the infection. Similarly, oral antibiotics (answer C) are not acceptable due to the patient's condition.

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CASE 23

A 38-year-old man without a significant medical history presents for an evaluation. He reports a 9- to 12-month history of intermittent diarrhea associated with mild cramping. He reports that his stools are usually large volume, nonbloody, and greasy. He has unintentionally lost more than 20 lb during this period but says that his appetite and oral intake have been good. He has tried taking a proton pump inhibitor daily for the last several months, but it has not improved his symptoms. He also tried refraining from any intake of dairy products, but that did not affect the diarrhea either. He has not experienced fever or any other constitutional symptoms. He does not smoke and drinks an occasional beer on the weekends, but not regularly. He is married, is monogamous, and does not know his family medical history due to being adopted.

On examination, he is afebrile, normotensive, and comfortable appearing. He has some glossitis but no oral lesions. His chest is clear to auscultation, and his heart is regular in rate and rhythm. On abdominal examination, his bowel sounds are active; no tenderness, masses, or organomegaly are evident on palpation. Rectal examination is negative for occult blood. He has some patches of papulovesicular lesions on his elbows, knees, and abdomen with some excoriations; he says it is very itchy.

- What is the most likely diagnosis?
- What is the next step in management?
- What is the best diagnostic test?
- What are the risk factors for this condition?
- What is the best treatment?

ANSWERS TO CASE 23:
Chronic Diarrhea

Summary: A 38-year-old man presents with

- Chronic diarrhea
- Nonbloody, greasy stools suggestive of fat malabsorption
- Unintentional weight loss without systemic symptoms
- Glossitis suggestive of vitamin deficiency
- Rash on extensor surfaces consistent with dermatitis herpetiformis (papules and blisters that are very itchy)

Most likely diagnosis: Chronic diarrhea due to celiac disease.

Next step in management: Check serum tissue transglutaminase (tTG)–Ig (immunoglobulin) A and endomysial (EMA)–IgA antibody.

Best diagnostic test: Endoscopic examination with small-bowel biopsy.

Risk Factors: Family history of celiac disease, autoimmune conditions (type 1 diabetes, autoimmune thyroiditis), Down syndrome, Turner syndrome.

Best treatment: Adherence to a gluten-free diet to improve small-intestine mucosal morphology.

ANALYSIS

Objectives

1. Describe the initial evaluation and management of acute infectious diarrhea. (EPA 1, 3, 4)
2. List the indications for antibiotic treatment of acute diarrhea. (EPA 4)
3. Recognize the pathophysiology of chronic diarrhea. (EPA 2, 12)
4. Understand the diagnosis, management, and complications of celiac disease. (EPA 1, 4, 10)

Considerations

This patient has chronic diarrhea with worrisome features such as weight loss and nutritional deficiency secondary to malabsorption. It is important to distinguish between functional causes of chronic diarrhea, such as irritable bowel syndrome (IBS), and more significant causes of diarrhea, such as inflammatory diseases and malabsorption, that may lead to complications or adverse long-term sequelae. Some of the red flags that indicate a pathologic etiology include weight loss, fever, fatigue, bloody diarrhea, systemic symptoms such as joint pain, and nutritional deficiencies. Celiac disease, an autoimmune sensitivity to gluten, is an important diagnosis to consider because the clinical manifestations may be subtle. This patient's rash, which is very suspicious for dermatitis herpetiformis (raised red papules that can

erupt into blisters and is very pruritic), is strongly associated with celiac disease. Once a diagnosis is established, most patients can be managed with dietary modification to improve symptoms and prevent complications.

APPROACH TO: Diarrhea

DEFINITIONS

ACUTE DIARRHEA: Diarrhea of duration less than 14 days.

CELIAC DISEASE: Small-bowel disorder characterized by symptoms of malabsorption and an abnormal small-bowel biopsy; it occurs with exposure to dietary gluten and improves after elimination of gluten from the diet.

CHRONIC DIARRHEA: Diarrhea of more than a 4 weeks' duration; it is sometimes called persistent diarrhea.

DIARRHEA: Passage of abnormally liquid or unformed stool at increased frequency.

INFLAMMATORY DIARRHEA: Diarrhea that can be osmotic, secretory, or mixed in presentation and presents with systemic symptoms.

INVASIVE DIARRHEA: Diarrhea consisting of bloody stools or mucus; it is also called dysentery. This may occur with fever and abdominal pain.

OSMOTIC DIARRHEA: Diarrhea that occurs due to water drawn into the gut lumen by a poorly absorbed or unabsorbed substance. This type of diarrhea has a high stool osmotic gap.

SECRETORY DIARRHEA: Diarrhea that results from secretion of water and electrolytes or decreased absorption and is characterized by a low stool osmotic gap.

STEATORRHEA: Characterized by greasy or oily stools that are difficult to flush. Patients with steatorrhea may often have nutritional deficiency secondary to malabsorption.

CLINICAL APPROACH TO ACUTE DIARRHEA

Pathophysiology

Diarrheal illnesses are extremely common, affecting nearly one in three people in the United States each year. In developing countries, acute infectious diarrhea is one of the leading causes of mortality. In the developed world, **90% of cases of acute diarrhea are infectious**, but the large majority of those illnesses are mild and self-limited. Most causes of acute diarrhea in developed countries do not require antibiotic treatment and resolve with symptomatic treatment. High-risk groups include travelers, immunocompromised patients, and people who are hospitalized or institutionalized.

Most patients with mild-to-moderate illness do not require specific evaluation, and their symptoms can be managed with an oral sugar-electrolyte solution or with antimotility agents such as loperamide. Bismuth subsalicylate can also reduce symptoms of nausea and diarrhea. A more severe illness is suggested by any of the following findings: profuse watery diarrhea with signs of hypovolemia, grossly bloody stools, fever, symptoms lasting longer than 48 hours, severe abdominal pain, age > 70, hospitalization, or recent use of antibiotics.

For these patients, an evaluation should be performed to **distinguish between inflammatory and noninflammatory** causes of diarrhea. Routine evaluation includes testing for **fecal leukocytes** or **fecal lactoferrin** (a more sensitive marker of fecal leukocytes) and performing a **routine stool culture** (for *Salmonella*, *Shigella*, and *Campylobacter*). Additional testing might include the following:

- Examination of **stool for ova and parasites**, which may be considered in cases of persistent diarrhea, especially if the patient has exposure to infants in a day care setting (*Giardia*, *Cryptosporidium*) or if there is a known community waterborne outbreak of these infections.
- Nonroutine cultures, such as for ***Escherichia coli* O157:H7**, may be performed in cases of acute bloody diarrhea, especially if there is a known local outbreak or if the patient develops hemolytic uremic syndrome (HUS).
- Stool may also be tested for the ***Clostridium difficile* toxin** in patients with recent antibiotic use.

Treatment

Patients with inflammatory diarrhea may present with bloody stools, fever, or other signs suggestive of invasive bacterial or viral infections. The most common etiologies of inflammatory diarrhea are *Salmonella, Campylobacter, Shigella, Entamoeba histolytica,* and *E. coli* O157:H7. A patient with suspected inflammatory diarrhea often receives empiric antibiotics such as quinolones. An exception to this strategy is in patients with suspected **enterohemorrhagic *E. coli* (EHEC)** infection. There is no evidence of benefit from antibiotics for EHEC infections, such as those caused by the O157:H7 strain. **Antibiotics are not recommended** due to concerns for increased risk of HUS from an increase in the production of Shiga toxin.

If testing suggests a **noninflammatory diarrhea**, most cases are due to viral infection (Norwalk, rotavirus) food poisoning (*Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*) or giardiasis. Viral infections and food poisoning are generally self-limited and are treated with **supportive care.** Giardiasis is treated with metronidazole or tinidazole.

CLINICAL APPROACH TO CHRONIC DIARRHEA

Unlike acute diarrhea, most cases of chronic diarrhea are not infectious. To evaluate and manage patients with chronic diarrhea, it is useful to classify the causes of chronic diarrhea by their pathophysiologic mechanism (Table 23–1 and Figure 23–1).

Table 23–1 • CAUSES OF CHRONIC DIARRHEA

Secretory
Bacterial or parasitic infections, eg, *Giardia*, microsporidia
Hormone-producing tumors (carcinoid, VIPoma, medullary cancer of thyroid, gastrinoma)
Exogenous stimulant laxatives
Idiopathic secretory diarrhea
Bowel resection, disease, or fistula (inadequate absorptive surface)
Congenital electrolyte absorption defects
Cholerrheic diarrhea (excess bile acid entering colon stimulates secretion, eg, postcholecystectomy)
Osmotic
Osmotic laxatives (magnesium, phosphate, sulfate)
Lactase deficiencies
Nonabsorbable carbohydrates (sorbitol, lactulose, polyethylene glycol)
Steatorrhea
Chronic pancreatitis (exocrine insufficiency)
Cystic fibrosis
Bacterial overgrowth
Celiac disease
Whipple disease
Tropical sprue
Mycobacterium avium-intracellulare (AIDS patients)
Amyloidosis
First- or second-degree lymphatic obstruction
Inflammatory causes
Inflammatory bowel disease (Crohn, ulcerative colitis)
Lymphocytic and collagenous colitis
Eosinophilic gastroenteritis
Graft-vs-host disease
Infections (invasive bacteria, viruses, and parasites, Brainerd diarrhea)
Radiation enteritis
Dysmotility
Irritable bowel syndrome
Visceral neuromyopathies (diabetic diarrhea)
Hyperthyroidism
Drugs (prokinetic agents such as metoclopramide or erythromycin)

Abbreviation: VIPoma, vasoactive intestinal peptide tumor.

Secretory Diarrhea

Secretory diarrhea is caused by a disruption of the water and electrolyte transport across the intestinal epithelium. The diarrhea is typically described as **large volume, watery, without significant abdominal pain, and with no evidence of stool fat or fecal leukocytes**. Secretory diarrhea can occur while the patient is fasting or asleep.

Hormone-producing tumors are less common but important causes of secretory diarrhea. **Carcinoid** tumors typically arise in the small bowel and may present with diarrhea, episodic flushing, wheezing from bronchospasm, and right-sided heart failure. Diagnosis is established by demonstration of elevated serotonin levels, usually through finding high concentrations of its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in a 24-hour urine collection. **Gastrinomas** are uncommon

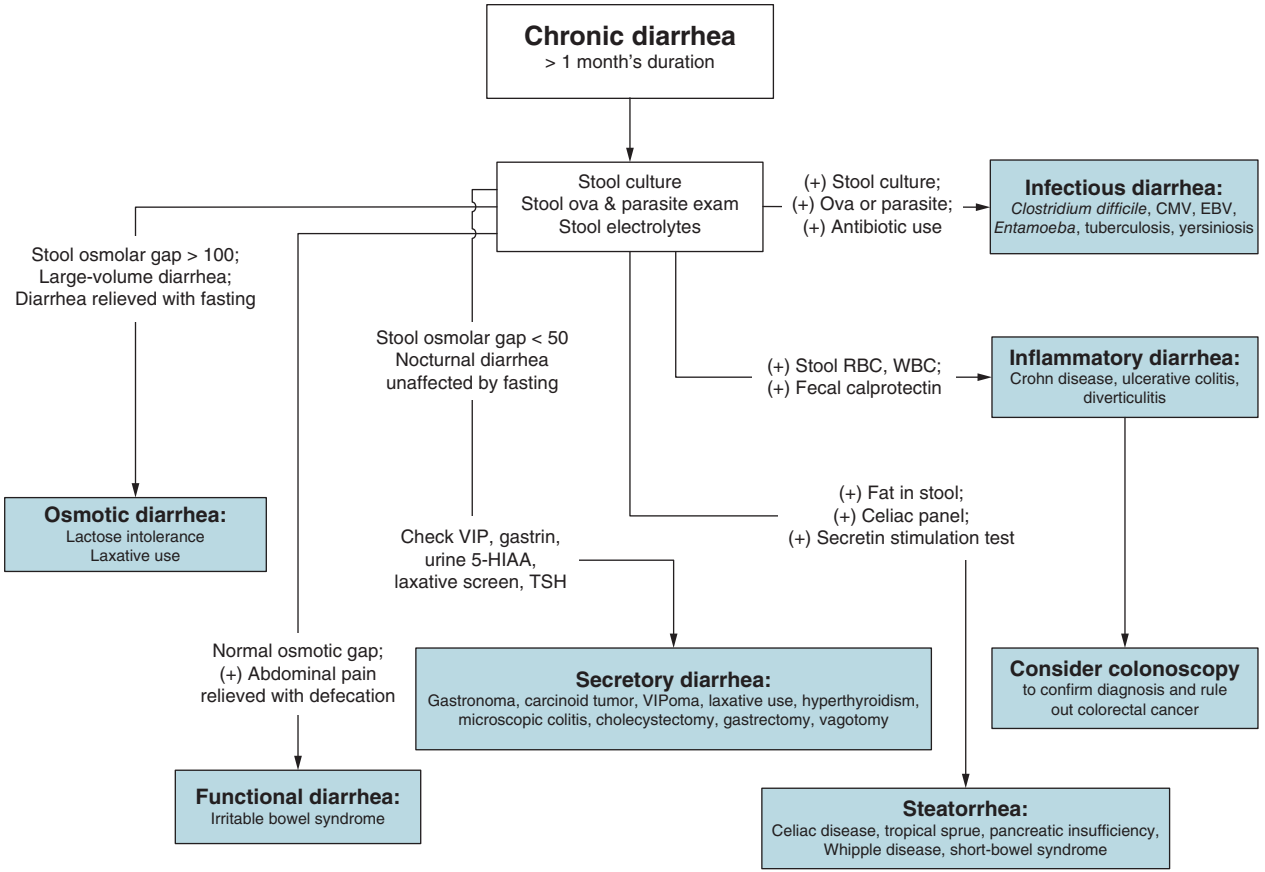


Figure 23–1. Diagnostic schema for chronic diarrhea.

neuroendocrine tumors that are usually located in the pancreas. These tumors secrete gastrin, which causes high gastric acid levels and manifests as recurrent peptic ulcers and diarrhea. Chronic diarrhea may be the presenting feature in 10% of cases. Initial diagnostic testing includes finding a markedly elevated fasting gastrin level. **VIPoma** is a rare pancreatic neuroendocrine tumor that secretes vasoactive intestinal peptide (VIP) as well as other peptide hormones that cause profuse, sometimes massive, watery diarrhea with profound dehydration and hypokalemia, as gastrointestinal (GI) secretions are rich in potassium.

Osmotic Diarrhea

Osmotic diarrhea occurs with ingestion of large amounts of poorly absorbed, osmotically active solute that draws water into the intestinal lumen. Common solutes include unabsorbed carbohydrates (sorbitol, lactulose, or lactose in patients with lactase deficiency), orlistat, or divalent ions (magnesium or sulfate, often used in laxatives). Low fecal pH < 6 suggests carbohydrate malabsorption. Other features of osmotic diarrhea include a high stool osmotic gap (> 75 mOsm/kg) and low sodium concentration (< 70 mEq/L). The fecal water output is proportional to the solute load, so the diarrhea can be large or small volume. An important clinical clue to distinguish between osmotic and secretory diarrhea is that **secretory diarrhea will persist during a 24- to 28-hour fast**, whereas **osmotic diarrhea should abate with fasting** or when the patient stops ingesting the poorly absorbed solute.

The **most common cause of osmotic diarrhea** is **lactose intolerance**, which affects the large majority of the world's nonwhite population and approximately 20% to 30% of the US population. Most people lose the brush border lactase enzyme with age and can no longer digest lactose by adulthood. Diagnosis is made clinically, by history, and with a trial of lactose avoidance. Symptoms are managed by avoiding dairy products or providing supplementation with oral lactase enzyme.

Inflammatory Diarrhea

Inflammatory diarrhea is characterized by systemic symptoms such as fever, abdominal pain, and blood in the stool. Stool studies will typically show fecal leukocytes and an elevation of fecal calprotectin, which is released by neutrophils. The most common and important causes are the inflammatory bowel diseases, ulcerative colitis and Crohn disease. Microscopic colitis is another cause of inflammatory diarrhea that occurs in older adults and presents with frequent watery stools. Colonoscopy usually reveals normal colonic mucosa macroscopically, while biopsy shows lymphocytic infiltration.

Dysmotility

Dysmotility represents altered bowel motility due to a secondary cause, such as hyperthyroidism, prokinetic medications, or visceral autonomic dysregulation like diabetes. An extremely common but poorly understood dysmotility disorder is **IBS**. It is characterized by chronic abdominal pain and altered bowel habits without a clear organic cause. Pain is typically relieved with defecation, and there is often mucus discharge with stools and a sensation of incomplete voiding. Presence of any of the following findings is **not characteristic of IBS** and should prompt

investigation for an organic cause of diarrhea: large-volume diarrhea, bloody stools, greasy stools, significant weight loss, anemia, occult or overt GI bleeding, or nocturnal awakening with pain or diarrhea.

Malabsorption/Steatorrhea

Malabsorption, or impaired absorption of nutrients, can be caused by either intraluminal maldigestion or mucosal epithelial defects. In conditions causing malabsorption, steatorrhea is commonly assessed as an indicator of global malabsorption primarily because the process of fat absorption is complex and is sensitive to interference from absorptive disease processes. Significant fat malabsorption produces greasy, foul-smelling diarrhea. Hydroxylation by gut bacteria leads to increased concentration of intraluminal fatty acids, causing an osmotic effect and increased stool output.

The **most common cause of intraluminal maldigestion** is pancreatic exocrine insufficiency due to **chronic pancreatitis**, most often due to alcohol abuse. Patients present with chronic abdominal pain, steatorrhea, and pancreatic calcifications on imaging and may often have diabetes due to pancreatic endocrine dysfunction and insulin deficiency. Other causes of chronic pancreatitis include hypertriglyceridemia, smoking, cystic fibrosis, and autoimmune pancreatitis. Treatment of malabsorption is with oral pancreatic enzyme supplementation.

The **most common and important cause of mucosal malabsorption** is **celiac disease.** It was originally described in pediatric patients with severe diarrhea and failure to thrive. It is now understood that this condition is much more common than previously recognized and **affects approximately 1% of the population,** with highest incidence in people of northern European ancestry. Patients with severe disease may present with classic manifestations of malabsorption: greasy, voluminous, foul-smelling stools; weight loss; severe microcytic anemia; neurologic disorders from deficiencies of B vitamins; and osteopenia from deficiency of vitamin D and calcium. However, this spectrum of findings is relatively uncommon, even in generalized mucosal disease. **Adult patients with undiagnosed celiac disease rarely present with profuse diarrhea and severe metabolic disturbances.** The majority of patients have relatively mild GI symptoms, which often mimic more common disorders, such as IBS, and may present solely with symptoms that are attributable to a nutritional deficiency or watery diarrhea. For example, patients with **unexplained iron deficiency anemia, especially if it fails to correct adequately with iron supplementation, should be suspected to have celiac disease.**

The exact pathophysiology of celiac disease is uncertain, but the current understanding is that **genetically predisposed** individuals, especially those with *HLA-DQ2* and *HLA-DQ8* gene subtypes, develop this **immune disorder** that is triggered by exposure to the **gliadin component of gluten**, which is a protein composite found in foods processed from wheat and related grain species like barley and rye.

In patients for whom there is a **high clinical suspicion of disease**, one should proceed to **endoscopic evaluation with small-bowel biopsy, and a serologic evaluation.** On an endoscopic examination, patients have characteristic mucosal changes involving

villous atrophy and crypt hyperplasia in the proximal small bowel. **IgA anti-EMA antibodies** and **anti- tTG antibodies** are highly specific and reasonably sensitive tests for celiac disease. However, antigliadin antibodies have a lower specificity (between 2% and 12%). Patients who have no family history of celiac disease or no clinical or laboratory evidence of malabsorption have a low clinical suspicion of disease. In those cases, only serologic evaluation is sufficient for diagnosis. Negative serology adequately excludes the diagnosis in such patients. Note that **all testing should be done with patients on a gluten-rich diet** for at least several weeks, as the mucosal abnormalities may disappear and serologic titers fall after gluten withdrawal from the diet.

The mainstay of treatment of celiac disease is **adherence to a gluten-free diet**. Referral to a nutritionist may be appropriate, and there are a number of gluten-free foods that are commercially available. In addition, nutritional deficiencies should be corrected, and patients should be evaluated for bone loss using a dual-energy x-ray absorptiometric (DEXA) scan. Patients with celiac disease may also have a higher risk of GI tract malignancies and T-cell lymphoma, so one should maintain a high index of suspicion.

CASE CORRELATION

- See also Case 21 (Colitis and Inflammatory Bowel Disease) and Case 22 (Acute Diverticulitis).

COMPREHENSION QUESTIONS

23.1 A 24-year-old woman comes to the clinic due to intermittent diarrhea associated with abdominal pain for several months. She reports that her stools are watery and she sometimes sees mucus in the toilet. The episodes of diarrhea occur four to six times a day and last for a few days at a time. The patient denies any weight loss or fever. When questioned about her diet, the patient states that she eats a well-balanced diet and drinks three cups of coffee a day. Physical examination and rectal examination are normal. What is the most likely cause for this patient's symptoms?

A. Altered mucosal permeability and GI motility

B. Transmural inflammation and tissue damage to intestinal walls

C. Decreased absorption of disaccharides in the small intestine

D. Exocrine insufficiency resulting in maldigestion

E. Immunologic response resulting in intestinal mucosal atrophy and crypt hyperplasia

23.2 A 65-year-old man presents to his provider because of watery diarrhea for the last 4 months. He denies passing bloody stools, but he has had up to nine large-volume bowel movements a day. He noticed that he has lost 10 lb in the last month, which he attributes to lack of appetite and nausea. He has had extreme fatigue and finds it difficult to go about his daily routine. The patient also complains of numbness and tingling of his lower extremities. He is afebrile and has a blood pressure reading of 105/70 mm Hg. On physical examination, the patient has mild, diffuse tenderness to palpation of the abdomen without guarding. The provider notes that the patient's mucous membranes appear dry. Abnormal laboratory tests include a K^+ level of 3.1 mmol/L and Ca^{2+} level of 11.2 mg/dL. What is the most appropriate next step in diagnosis?

A. Computed tomographic (CT) scan of the abdomen
B. Serum VIP level
C. Gallium Ga-68 DOTATATE positron emission tomographic (PET)/CT scan
D. Somatostatin receptor scintigraphy
E. Endoscopic ultrasound
F. Exploratory laparotomy

23.3 Which of the following patients is not a good candidate for evaluation for celiac disease with either endoscopy or serologic testing?

A. A 26-year-old woman who experiences intermittent abdominal bloating but no diarrhea and is found to have osteopenia and vitamin D deficiency.
B. A 19-year-old college freshman with bulky, foul-smelling, floating stools and excessive flatulence who has lost 20 lb unintentionally.
C. A thin, 39-year-old man with a family history of celiac disease who has been adhering to a gluten-free vegetarian diet for the last 3 years and now complains of gassiness and reflux.
D. A 42-year-old man who was found to have iron deficiency anemia but has no GI symptoms and recently had a negative colonoscopy.

23.4 A 29-year-old man presents to the clinic due to 3 days of abdominal cramps and diarrhea. His diarrhea was initially watery but progressed to bloody episodes. He has had a low-grade fever and reports two episodes of vomiting. The patient says that he recently returned from a trip to Mexico. Physical examination shows mild dehydration and minimal blood in the rectal vault. What is the most appropriate treatment for this patient?

A. Metronidazole
B. Azithromycin
C. Vancomycin and cefepime
D. Piperacillin-tazobactam
E. Observation and supportive care

ANSWERS

23.1 **A.** This patient's symptoms are most suggestive of IBS. IBS is diagnosed based on the Rome IV criteria, which include abdominal pain at least 1 day per week for at least 3 months associated with two or more of the following criteria: (1) pain related to defecation, (2) change in frequency of stool, and (3) change in appearance of stool. IBS is a diagnosis of exclusion and should not be made if the patient has "alarm" symptoms (hematochezia, weight loss, anemia). This patient has mucus in her stools, which is a common complaint. IBS causes altered gut motility, although the pathophysiology is not clear. Transmural inflammation (answer B) is seen in Crohn disease, which would also present with systemic symptoms. Lactose intolerance is caused by decreased absorption of disaccharides (answer C). Chronic pancreatitis presents with exocrine insufficiency and maldigestion (answer D). Celiac disease causes an immunologic response to gliadin, which leads to crypt hyperplasia and villous atrophy (answer E).

23.2 **B.** This patient presents with voluminous watery diarrhea, dehydration, weight loss, hypokalemia, and hypercalcemia, which suggest VIPoma. VIPomas are caused by autonomous VIP secretion leading to stimulation of intestinal epithelial cells and fluid secretion into the lumen. This tumor can lead to iron and vitamin B_{12} deficiencies. The best initial step to confirm diagnosis is to obtain a serum VIP level. After diagnosis is confirmed, a CT scan of the abdomen (answer A) is usually obtained to confirm location of the tumor as well as help with staging; an initial CT scan is not indicated without a diagnosis. DOTATATE scans (answer C) and somatostatin receptor scintigraphy (answer D) are used if other imaging is inconclusive. In addition to initial workup and repletion of electrolytes, this patient may require testing for multiple endocrine neoplasia type I syndrome. The other answer choices, endoscopic ultrasound (answer E) and exploratory laparotomy (answer F), are not useful for this condition.

23.3 **C.** While GI symptoms in a patient with a family history of celiac disease are reasonable to investigate, the fact that he has been on a gluten-free diet for a prolonged period greatly diminishes the sensitivity of both endoscopic and serologic testing. Unexplained osteopenia and vitamin D deficiency in a young woman (answer A), unexplained iron deficiency anemia (answer D) in any patient, and the classic presentation with steatorrhea and weight loss (answer B) should all be investigated.

23.4 **E.** Acute diarrhea that progresses to bloody diarrhea and a history of recent travel suggests EHEC infection. Empiric antibiotics (answers A-D) are not used in EHEC infections due to the risk of developing HUS. Although there is less data in adults, the risk for HUS in children rises as high as 25% when treated with antibiotics. Antibiotics have also not been shown to reduce GI upset symptoms. The best treatment for a patient with suspected EHEC infection is supportive care with isotonic fluids.

CLINICAL PEARLS

- Most cases of acute infectious diarrhea in the United States cause mild-to-moderate illness that is self-limited and can be managed with oral rehydration solution or with antimotility agents such as loperamide.
- Empiric treatment with quinolone antibiotics is usually indicated for acute inflammatory diarrhea. An exception is for EHEC infection, where antibiotics may increase the risk of HUS.
- Symptoms of malabsorption include greasy, voluminous stools; weight loss; anemia; neurologic disorders from deficiencies of B vitamins; and osteopenia from deficiency of vitamin D and calcium.
- Adults with undiagnosed celiac disease often present with relatively mild GI symptoms and may only present with unexplained nutritional deficiency, such as refractory iron deficiency anemia.
- If there is a high clinical suspicion for celiac disease, patients should undergo endoscopic evaluation with small-bowel biopsy and serologies for IgA anti-EMAs and anti-tTG antibodies.

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CASE 24

A 60-year-old man presents to the emergency department complaining of a 4-week history of progressive abdominal swelling and diffuse discomfort. He has no other gastrointestinal (GI) symptoms. He is a construction worker who spends at least 8 hours a day working outside. He reports that he drinks beer when he gets thirsty, usually drinking 12 cans per day. He states that he never felt the need to stop drinking alcohol. He denies illicit intravenous drug use. Over the last few months, he has noted dark colored urine, but he has not seen skin or mucosal color changes. On examination, his temperature is 100.3 °F, heart rate is 90 beats per minute, and blood pressure is 90/60 mm Hg. He is thin appearing, with telangiectasias noted on his cheeks and upper anterior chest. Yellow discoloration can be seen under his tongue and on his sclera but is not evident on his skin. His heart and lung examinations are unremarkable. The abdomen is distended, with mild diffuse tenderness, hypoactive bowel sounds, diffuse dullness to percussion, and a fluid wave. He has no peripheral or pitting edema. Laboratory studies are normal except for Na 129 mEq/L (normal 135-145); albumin 2.8 g/dL (normal 3.5-5 g/dL); total bilirubin 2 mg/dL; prothrombin time 15 seconds (normal 11-13.5); hemoglobin 11 g/dL with mean cell volume 102 fL (normal 78-95); and platelet count 78,000/mm^3 (normal 150,000-500,000).

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 24B:
Liver Cirrhosis, Probably Alcoholic

Summary: A 60-year-old man presents with

- New, progressive abdominal distention
- Heavy alcohol use daily
- Scleral and mucosal icterus with physical findings consistent with ascites
- Low serum albumin and sodium
- Bilirubin slightly elevated
- Low platelet count and macrocytic anemia

Most likely diagnosis: Ascites caused by portal hypertension as a complication of hepatic cirrhosis, most likely related to alcohol abuse.

Next step: Perform a diagnostic paracentesis to evaluate the fluid to determine the likely etiology of the ascites, as well as evaluate for a known possible complication of spontaneous bacterial peritonitis (SBP).

ANALYSIS

Objectives

1. Explain how liver cirrhosis is diagnosed. (EPA 1, 3)
2. Recognize the possible etiologies of liver cirrhosis. (EPA 2)
3. Understand the utility of the serum ascites-albumin gradient (SAAG) to differentiate causes of ascites. (EPA 3)
4. Outline the diagnosis of SBP. (EPA 1, 10)

Considerations

This 60-year-old man had been in good health until recently, when he noted increasing abdominal swelling and discomfort. He has drunk significant amounts of alcohol for an imprecise period of his life. Currently, he also has a low-grade fever and mild abdominal tenderness; both signs suggest a possible infection. Bacterial infection of the ascitic fluid must be considered and evaluated because untreated cases have a high mortality. Although most patients with ascites and jaundice have cirrhosis, other etiologies of the ascites must be considered, including malignancy. Diagnostic paracentesis can be used to assess for infection as well as to seek an etiology of the ascites.

APPROACH TO:
Liver Cirrhosis

DEFINITIONS

ASCITES: Abnormal accumulation (> 25 mL) of fluid within the peritoneal cavity.

CIRRHOSIS: Histologic diagnosis reflecting irreversible chronic hepatic injury, which includes extensive fibrosis and formation of regenerative nodules.

PORTAL HYPERTENSION: Increased pressure gradient (> 5 mm Hg) in the hepatic portal vein, usually resulting from resistance to portal flow and most commonly caused by cirrhosis.

SPONTANEOUS BACTERIAL PERITONITIS: Bacterial infection of ascitic fluid without any primary intra-abdominal source of infection. Occurs in 10% to 20% of cirrhotic patients with ascites.

CLINICAL APPROACH

Pathophysiology

Cirrhosis represents the end stage of chronic hepatocellular injury that results in **fibrosis** and architectural distortion with **nodular regeneration**. With ongoing hepatocyte destruction, activated hepatic stellate cells promote collagen deposition, resulting in a hardened, nodular liver that shrinks in size. Alcoholic cirrhosis is one of the most common forms of cirrhosis encountered in the United States. Quantity and duration of alcohol intake, as well as gender, genetic predispositions, and concurrent chronic hepatitis C virus (HCV) infection, contribute to the progression of alcoholic liver disease to cirrhosis. Other causes of cirrhosis are listed in Table 24–1.

When cirrhosis is suspected, patients should have an ultrasound of the right upper quadrant to assess for parenchymal changes, nodularity, hepatic cysts, and biliary ductal dilation. Histologic evaluation of tissue via percutaneous liver biopsy may be utilized for the pathologic diagnosis of cirrhosis and to differentiate the

Table 24–1 • CAUSES OF CHRONIC HEPATITIS AND LIVER CIRRHOSIS

Cause	Test
Hepatitis C	Anti-HCV Ab, presence of HCV RNA
Hepatitis B	Persistent HBsAg, presence of HBeAg
Autoimmune	ANA, anti-LKM (liver kidney microsomal)
Hemochromatosis	High-transferrin saturation (> 45%), high ferritin
Wilson disease	Low serum ceruloplasmin
Alpha$_1$-antitrypsin deficiency	Low alpha$_1$-antitrypsin enzyme activity

Abbreviations: Ab, antibody; ANA, antinuclear antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

etiology when it is not clear by history alone. This can be helpful to diagnose hemochromatosis, Wilson disease, and autoimmune hepatitis. Increasingly, noninvasive methods of diagnosis are being utilized, including elastography to assess the stiffness of liver tissue, which correlates with hepatocellular fibrosis. Another noninvasive test utilizes blood serum biomarker measurements to assign a fibrosis score correlating with the severity of the liver fibrosis.

Clinical Presentation

Advanced liver disease will show mild elevations in AST (aspartate aminotransferase) and ALT (alanine aminotransferase), with the AST:ALT ratio greater than 2 in alcoholics, although advanced cirrhosis may eventually show normal transaminase levels due to loss of hepatocyte function. Total and direct bilirubin and alkaline phosphatase may be elevated as well. Cirrhosis will also show elevated prothrombin time, serum hypoalbuminemia, hyponatremia usually with ascites, and possibly electrolyte disturbances or impaired renal function. Patients also usually will have low platelets and macrocytic anemia.

Cirrhotic patients are classified by the presence or absence of complications (Table 24–2). **Compensated cirrhosis** refers to patients without clinical symptoms beyond minor fatigue, muscle cramps, and itching. **Decompensated cirrhosis** refers to the presence of cirrhosis with complications, such as jaundice, ascites, hepatic encephalopathy, variceal bleeding, SBP, and hepatorenal syndrome. Many of these complications are driven by **portal hypertension**, which results from hepatocyte fibrosis causing sinusoidal resistance to portal venous flow, as well as increased splanchnic flow related to splanchnic vascular bed vasodilation.

Loss of functioning hepatic mass leads to jaundice as well as impaired synthesis of albumin (leading to edema) and clotting factors (leading to coagulopathy). Decreased liver production of steroid hormone-binding globulin leads to an increase in unbound estrogen manifested by spider angiomata, palmar erythema, and testicular atrophy and gynecomastia in men. Portal hypertension can also result in hypersplenism and splenomegaly, resulting in platelet sequestration.

Ascites may result as a consequence of portal venous hypertension related to cirrhosis. However, it may also be a result of exudative causes, such as infection (eg, tuberculous peritonitis) or malignancy. It is important to distinguish the cause of ascites in order to look for serious and/or reversible causes, such as malignancy, and to guide therapy. Ascitic fluid is obtained by paracentesis and examined for protein, albumin, cell count with differential, and culture. The first step in trying to determine the cause of ascites is to determine whether it is caused by portal hypertension or by an exudative process by calculating the SAAG (Table 24–3).

Treatment

The **treatment of ascites that is secondary to liver cirrhosis usually consists of dietary sodium restriction coupled with diuretics**. Loop diuretics are often combined with spironolactone to provide effective diuresis and to maintain normal potassium levels.

Alcohol cessation is critical for those with alcoholic liver disease to prevent progression to advanced cirrhosis. Sustained abstinence after diagnosis of cirrhosis

Table 24–2 • COMPLICATIONS OF CIRRHOSIS

Disorder	Diagnosis	Clinical Presentation	Treatment
Portal hypertension	Development of clinical features, visualization of varices and splenomegaly on imaging, and evaluation of portal blood flow using Doppler ultrasonography	Ascites, splenomegaly, hypersplenism, encephalopathy, and bleeding varices	Nonselective beta-blockers such as propranolol lower portal pressure; for acute variceal bleed, intravenous octreotide causes splanchnic vasoconstriction. When medically refractory, a transjugular intrahepatic portosystemic shunt (TIPS) can be inserted.
Ascites	Finding of free peritoneal fluid on physical examination or on an imaging study	Abdominal distention, sometimes with peripheral edema	Sodium restriction, spironolactone; loop diuretics; large-volume paracentesis
Spontaneous bacterial peritonitis	Ascitic fluid contains > 250 neutrophils/mm^3 and confirmed with a positive culture; most common organisms are *Escherichia coli*, *Klebsiella*, other enteric flora, enterococci	Abdominal pain, distention, fever, decreased bowel sounds, or sometimes few abdominal symptoms but worsening encephalopathy	Intravenous antibiotics, such as cefotaxime or ampicillin/sulbactam
Hepatic encephalopathy	Clinical. The most serious cases occur when overt **proof of liver failure** is present; when that is not the case, **consider alternative diagnoses**. Elevated serum ammonia levels are usually present (nonspecific).	Confusion, lethargy, flapping hand tremor (asterixis); initially just fatigue, inversion of sleep / awakening cycle	Cathartics (lactulose, polyethylene glycol) to promote excretion of the amino acid precursors of ammonia generation

should also be maintained to allow for possible modest reversal of fibrosis, which is occasionally seen. Ultimately, liver transplantation is the only definitive treatment for those with cirrhosis.

Patients being considered for **transplant** are stratified according to scoring systems to estimate disease severity and survival. The Model for End-Stage Liver Disease (**MELD**) score uses a patient's laboratory values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time to predict survival. An older scoring system, the **Child-Turcotte-Pugh system**, also classifies severity of disease, with class A having the best prognosis and class C the worst.

Prevention. Men who consume > 14 alcoholic drinks per week and women who consume > 7 drinks per week should be counseled on alcohol use. A CAGE questionnaire (Cut down, Annoyed, Guilty, Eye-opener) should be utilized to assess for

Table 24–3 • DIFFERENTIAL DIAGNOSIS OF ASCITES BASED ON SAAG[a]

High gradient > 1.1 g/dL: Portal hypertension
• Cirrhosis
• Portal vein thrombosis
• Budd-Chiari syndrome
• Congestive heart failure
• Constrictive pericarditis
Low gradient < 1.1 g/dL: Nonportal hypertension
• Peritoneal carcinomatosis
• Tuberculous peritonitis
• Pancreatic ascites
• Bowel obstruction or infarction
• Serositis, eg, as in lupus
• Nephrotic syndrome

[a]*SAAG, serum ascites-albumin gradient = serum albumin – ascitic albumin.*

readiness and willingness to adopt abstinence, with referral to alcohol abstinence programs.

Complications

Spontaneous Bacterial Peritonitis. SBP is a relatively common complication of ascites. It is thought to be caused by translocation of gut flora into the peritoneal fluid. Symptoms include fever and abdominal pain, but often there is paucity of signs and symptoms. **Diagnosis is established by paracentesis** and finding more than 250 neutrophils/mm^3 OR by a positive culture. Culture of ascitic fluid often fails to yield the organism (inserting fluid in a blood culture bottle raises the sensitivity from 40% to 90%). However, when positive, fluid cultures usually reveal a single organism, most often gram-negative enteric flora but occasionally enterococci or pneumococci. This is in contrast to **secondary peritonitis** (eg, as a consequence of intestinal perforation), which usually is polymicrobial. Empiric therapy includes coverage for gram-positive cocci and gram-negative rods, such as intravenous ampicillin/sulbactam, or a third-generation cephalosporin such as cefotaxime. Oral fluoroquinolones may also be used for uncomplicated SBP, but should be avoided in patients who were taking quinolones for SBP prophylaxis, as their organisms may be resistant. Patients who have had SBP in the past, or are considered high risk for SBP, should be maintained on a prophylactic regimen with an oral fluoroquinolone.

Esophageal and Gastric Variceal Bleeding. Other complications of advanced cirrhosis with portal hypertension include esophageal and gastric variceal bleeding, which can result in massive hemorrhage and hemodynamic instability. Treatment may include infusion of **octreotide** to cause splanchnic vasoconstriction and reduce portal pressure. Esophageal varices can also be treated endoscopically with ligation or banding to treat or prevent bleeding or with sclerotherapy for active bleeding. In patients presenting with upper GI variceal bleed, the incidence of SBP is higher, and these patients should be initiated on antibiotic prophylaxis. **Surgical or transjugular intrahepatic portosystemic shunt (TIPS)** may also be placed to decompress portal pressure and reduce the bleeding risk as the patient awaits liver transplantation.

Hepatorenal Syndrome. **Hepatorenal syndrome**, which typically presents as **progressive decline in renal function** in patients with significant ascites, can also present in advanced cirrhosis. The pathogenesis is poorly understood, though it is thought to be related to multifactorial renal vasoconstriction. Treatment is difficult, and prognosis is often poor unless patients proceed for liver transplantation.

Hepatic Encephalopathy. **Hepatic encephalopathy is characterized by mental status changes, asterixis, and elevated ammonia levels** related to loss of hepatic function. It may be precipitated by numerous factors, including infection such as SBP, electrolyte disturbances (hypokalemia), increased dietary protein load, and GI bleeding; it can also occur just after a TIPS procedure. *Diagnosis* is a clinical one based on history and physical examination and by excluding other causes of confusion. Ammonia levels are variable in patients with hepatic encephalopathy and should not be relied on to make the diagnosis. *Treatment* is aimed at correcting underlying causes, as well as administration of lactulose, a nonabsorbable disaccharide that causes colonic acidification and elimination of nitrogenous waste. Other cathartic agents are also effective. Poorly absorbed antibiotics such as neomycin and rifaximin are used as adjuncts in refractory cases of hepatic encephalopathy.

CASE CORRELATION

- See also Case 26 (Acute Hepatitis) and Case 27 (Painless Jaundice, Pancreatic Cancer).

COMPREHENSION QUESTIONS

24.1 A 54-year-old man with an unknown medical history is brought to the emergency department by his brother with reports that the patient has been feeling dizzy and lightheaded. His brother states that the patient has been depressed since his divorce and has been binge drinking nearly daily for the last 6 months. Last night, he came home after drinking heavily and vomited multiple times, with some blood-tinged vomit. He does not take any medications and has no known medical problems. On examination, the patient is alert but tired-appearing. Blood pressure is 94/60 mm Hg, heart rate is 126 beats per minute, respiratory rate is 16 breaths/min, and temperature is 99.3 °F. Lungs are clear to auscultation, and he is tachycardic with regular rhythm. His abdomen is distended, though soft, with quiet bowel sounds and positive shifting dullness to percussion. While being examined, the patient has a large bowel movement of black stool. Which of the following is the next best step?

A. Administer intravenous fluids.

B. Await results of hemoglobin and hematocrit.

C. Call surgery for an emergency laparotomy.

D. Give him an antiemetic for his nausea.

E. Start a proton pump inhibitor.

24.2 A 55-year-old woman with a history of decompensated alcoholic cirrhosis was admitted to the hospital 5 days ago with melena. An esophagogastroduodenoscopy (EGD) was performed, and bleeding varices were banded. The patient was started on antibiotics with ceftriaxone to prevent SBP in the setting of bleeding. Despite that fact, she developed SBP on day 3. On daily labs, her creatinine has been steadily increasing and now is at 3.1 mg/dL (1.5 on the day of admission). Despite treatment with antibiotics, holding diuretics on the day of admission, and administration of fluids and albumin, her kidney function continues to worsen. Her vital signs are normal. Physical examination shows significant ascites. Urine analysis is normal without hematuria or proteinuria. Urine Na is low (< 10 mEq/L). A renal ultrasound does not show any evidence of obstruction to urine flow. Which of the following is the definitive treatment for her condition?

A. Changing antibiotics from ceftriaxone to vancomycin and cefepime
B. Performing a TIPS procedure
C. Starting the patient on dialysis
D. Liver transplantation

24.3 A 49-year-old woman with a history of obesity and type 2 diabetes mellitus presents to the outpatient clinic with 2 to 3 months of fatigue, abdominal distention, and bilateral edema of the legs. On examination, her vital signs are normal and ascites is present, as is bilateral pitting edema of the legs. She is jaundiced and has several spider angiomas on her trunk. Her laboratory work shows mild macrocytic anemia, thrombocytopenia, and low albumin. Her liver enzymes are normal. Her liver ultrasound shows findings suggestive of fatty liver. The patient denies ever drinking alcohol. Workup of viral hepatitis is negative. What would be the best test to establish the presence of liver cirrhosis and its etiology?

A. Magnetic resonance imaging of the liver
B. Measurement of alpha-fetoprotein
C. Liver biopsy
D. CT scan of abdomen and pelvis-liver protocol

ANSWERS

24.1 **A.** The patient likely has an upper GI bleed from ruptured esophageal varices, related to undiagnosed alcoholic cirrhosis, based on his binge drinking history and notable ascites on examination. He is tachycardic and hypotensive, and the first step should be volume resuscitation. Awaiting laboratory results before acting would not be appropriate (answer B). He will benefit from initiation of octreotide, a somatostatin analog to decrease portal pressures, followed by early upper endoscopy. A proton pump inhibitor will not be helpful for bleeding varices (answer E). Antiemetics may improve his nausea, but it is not the most important first step (answer D). A laparotomy is not indicated for melena related to bleeding varices (answer C).

24.2 **D.** The patient has likely hepatorenal syndrome, and liver transplantation is the definitive treatment for this. While SBP is a known trigger for hepatorenal syndrome, antibiotics alone are unlikely to improve renal function (answer A). TIPS (answer B) will reduce portal hypertension, and dialysis (answer C) can be used to treat complications of renal failure in the setting of hepatorenal syndrome; however, neither is a definitive treatment. They can be implemented while the patient is waiting for liver transplantation.

24.3 **C.** The presence of diabetes mellitus and the absence of an obvious explanation for this patient's liver dysfunction suggest liver disease resulting from fatty deposition. A liver biopsy differentiates alcoholic from nonalcoholic fatty liver, and the innocuous fatty liver from nonalcoholic steatohepatitis (which frequently progresses to cirrhosis and hepatocellular carcinoma). Despite its diagnostic value, a liver biopsy seldom alters therapeutic options. Imaging (answers A and D) and alpha-fetoprotein (answer B) have no specific etiologic diagnostic value.

CLINICAL PEARLS

- Alcoholic cirrhosis is one of the most common forms of cirrhosis encountered in the United States, with other notable causes including viral hepatitis and nonalcoholic fatty liver disease.
- Cirrhotic patients are classified by the presence or absence of complications associated with their liver dysfunction, most of which are driven by portal hypertension.
- An SAAG greater than 1.1 g/dL suggests the ascites is caused by portal hypertension, as seen in cirrhosis.
- All patients with ascites presenting to the hospital should have diagnostic paracentesis to rule out SBP, a complication of ascites and cirrhosis carrying a high mortality.
- SBP is characterized by the presence of greater than 250 polymorphonuclear cells/mm^3 in the ascitic fluid, occasionally accompanied by positive monomicrobial culture.
- TIPS may be placed to decompress portal pressure to prevent esophageal variceal bleeding, but this may trigger hepatic encephalopathy.
- Hepatic transplant is the only cure for advanced liver cirrhosis.
- All patients who drink alcohol should be screened for alcohol use disorder with a CAGE questionnaire and counseled on abstinence to prevent development of alcoholic cirrhosis.

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CASE 25

A 42-year-old woman presents to the emergency department complaining of 24 hours of severe, steady epigastric abdominal pain radiating to her back with several episodes of nausea and vomiting. She has experienced similar painful episodes in the past, usually in the evening following heavy meals, but the prior episodes always resolved spontaneously within an hour or two. This time the pain did not improve, so she sought medical attention. She has no medical history and takes no medications. She is married, has three children, and does not drink alcohol or smoke cigarettes.

On examination, she is afebrile with tachycardia of 104 beats per minute (bpm), a blood pressure of 115/74 mm Hg, and shallow respirations at a rate of 22 breaths/min. She is moving uncomfortably on the stretcher. Her skin is warm and diaphoretic, and she has scleral icterus. Her abdomen is soft, mildly distended with marked right upper quadrant (RUQ) and epigastric tenderness to palpation, hypoactive bowel sounds, and no palpable masses or organomegaly. Her stool is negative for occult blood. Laboratory studies are significant for an elevated total bilirubin (9.2 g/dL) with a direct fraction of 4.8 g/dL, alkaline phosphatase 285 IU/L, aspartate aminotransferase (AST) 78 IU/L, alanine aminotransferase (ALT) 92 IU/L, and elevated serum lipase level. Her leukocyte count is 16,500/mm^3 with 82% polymorphonuclear cells and 16% lymphocytes. Serum electrolytes, blood urea nitrogen (BUN), and creatinine are normal. A plain film of the abdomen shows a nonspecific gas pattern and no pneumoperitoneum, and chest x-ray is normal.

- What is the most likely diagnosis?
- What is the most likely underlying etiology?
- What is your next diagnostic step?
- What is the most important immediate therapeutic step?

ANSWERS TO CASE 25:
Pancreatitis/Gallstones

Summary: A 42-year-old woman presents with

- A prior history consistent with symptomatic cholelithiasis (gallstones)
- Epigastric pain and nausea for 24 hours
- Hyperbilirubinemia and an elevated alkaline phosphatase level
- Elevated serum lipase levels

Most likely diagnosis: Acute pancreatitis is the most likely diagnosis based on her history of persistent epigastric pain radiating to her back with associated nausea and vomiting.

Most likely etiology: Choledocholithiasis (common bile duct stone) based on the hyperbilirubinemia.

Next diagnostic step: RUQ and abdominal ultrasonography and assessment for complications of pancreatitis, such as electrolyte, bicarbonate, calcium, and glucose levels.

Most important immediate therapeutic step: Intravenous fluid hydration to support the blood pressure and replace electrolytes.

ANALYSIS

Objectives

1. Describe the causes, clinical features, and prognostic factors in acute pancreatitis. (EPA 1, 2)
2. List the principles of treatment and complications of acute pancreatitis. (EPA 4, 10)
3. Recognize the complications of gallstones. (EPA 10, 12)
4. Understand the medical treatment of a patient with biliary sepsis and the indications for endoscopic retrograde cholangiopancreatography (ERCP) or surgical intervention. (EPA 4, 10)

Considerations

This 42-year-old woman complained of intermittent episodes of short duration of mild RUQ abdominal pain with heavy meals in the past. This is very consistent with biliary colic. However, this episode is different in severity and location of pain (now radiating straight to her back and accompanied by nausea and vomiting). The elevated lipase level confirms the clinical impression of acute pancreatitis likely caused by a stone in the common bile duct. Biliary obstruction is suggested by the elevated bilirubin and alkaline phosphatase levels. She is moderately ill but is hemodynamically stable and has only one prognostic feature to predict mortality.

Table 25–1 • SIRS CRITERIA	
Temperature	≤ 36 °C or ≥ 38 °C
Heart rate	≥ 90 bpm
Respiratory rate	≥ 20 breaths/min **or** $Paco_2$ < 32 mm Hg
White blood cell count	≥ 12,000 or ≤ 4000 cells/mm^3 **or** > 10% bands

Abbreviation: $Paco_2$, partial pressure of carbon dioxide.
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She meets criteria for systemic inflammatory response syndrome (SIRS) and should be monitored closely for signs of clinical deterioration (Table 25–1).

APPROACH TO:

Acute Pancreatitis and Cholelithiasis

DEFINITIONS

ACUTE PANCREATITIS: An inflammatory process in which pancreatic enzymes are activated and cause autodigestion of the pancreas.

PANCREATIC PSEUDOCYST: Fluid collection within the pancreas **not lined by epithelial cells**, appearing several days after some cases of acute pancreatitis and often associated with chronic pancreatitis.

CLINICAL APPROACH TO ACUTE PANCREATITIS

Pathophysiology

Acute pancreatitis can be caused by many conditions, although gallstones and alcohol are implicated in up to two-thirds of cases. The passage of **gallstones into the common bile duct** is the most common cause and is responsible for approximately 40% to 70% of cases. **Alcohol use** is the next most common cause (25%-35% of cases in the United States), with episodes often precipitated by binge drinking. **Hypertriglyceridemia** is another common cause (1%-14% of cases) and occurs when serum triglyceride levels are more than 1000 mg/dL, as is seen in patients with familial dyslipidemias or diabetes (etiologies are given in Table 25–2). Acute pancreatitis can also be induced by **ERCP**, occurring after 5% to 10% of such procedures. Less common etiologies include genetic predisposition, medication, infections, hypercalcemia, toxins, vascular disease, or anatomic/physiologic anomalies of the pancreas. When patients appear to have "idiopathic" pancreatitis, that is, no gallstones are seen on ultrasonography and no other predisposing factor can be

Table 25–2 • CAUSES OF ACUTE PANCREATITIS

Biliary tract disease (eg, gallstones)
Alcohol use
Drugs (eg, the antiretroviral didanosine [DDI], pentamidine, thiazides, furosemide, sulfonamides, azathioprine, L-asparaginase)
Surgical manipulation of the gland, or ERCP
Hypertriglyceridemia/hypercalcemia
Infections, eg, mumps or cytomegalovirus
Trauma, eg, blunt abdominal trauma
Congenital/anatomic (pancreas divisum)

found, biliary tract disease is still the most likely cause, either biliary sludge (microlithiasis) or sphincter of Oddi dysfunction.

Epigastric pain and/or RUQ pain can have a variety of etiologies. Other diagnoses that may be considered during the workup of acute pancreatitis include peptic ulcer disease, bowel perforation, intestinal obstruction, mesenteric ischemia, diabetic ketoacidosis, or hepatitis. Many additional diagnoses that should be considered are directly related to gallstone production, including biliary colic, choledocholithiasis, cholangitis, and cholecystitis.

Clinical Presentation

Abdominal pain is the cardinal symptom of pancreatitis and often is severe, typically in the **upper abdomen with radiation to the back**. The pain is often relieved by sitting up and leaning forward and is exacerbated by food. Patients **commonly experience nausea and vomiting** that is precipitated by oral intake. They **may have low-grade fever** (if temperature is > 101 °F, one should suspect infection) and are often volume depleted because of the vomiting and inability to tolerate oral intake. The inflammatory process may cause third spacing, with sequestration of large volumes of fluid in the peritoneal cavity additionally leading to intravascular depletion. Hemorrhagic pancreatitis with blood tracking along fascial planes would be suspected if periumbilical ecchymosis (**Cullen sign**) or flank ecchymosis (**Grey Turner sign**) is present.

During the physical examination, those with acute pancreatitis may appear noticeably uncomfortable. On initial and repeat examinations, it is important to take note of the vitals since fever, hypotension, hypoxia, and tachypnea may alter subsequent management and diagnosis. Common findings on examination include epigastric pain with or without pain in the RUQ; pain can vary greatly in severity. Jaundice, abdominal distention, and presence or absence of bowel sounds are also important to note.

The common test used to diagnose pancreatitis is an **elevated serum lipase level**. It is **more specific than serum amylase to support the diagnosis of acute pancreatitis. Levels remain elevated in the bloodstream longer than amylase**. Serum amylase is not specific to the pancreas, however, and can be elevated as a consequence of many other abdominal processes, such as **gastrointestinal ischemia with infarction**

or perforation; even just the vomiting associated with pancreatitis can cause elevated amylase of **salivary origin**. It is released from the inflamed pancreas within hours of the attack and remains elevated for 3 to 4 days. When the diagnosis is uncertain or when complications of pancreatitis are suspected, **computed tomographic (CT) imaging of the abdomen is highly sensitive** for showing the inflammatory changes in patients with moderate-to-severe pancreatitis.

Treatment

Treatment is **mainly supportive** and includes "pancreatic rest," that is, **withholding food or liquids by mouth until symptoms subside**, and adequate **narcotic analgesia. Intravenous fluids** are necessary for maintenance and to replace any deficits. In patients with severe pancreatitis who sequester large volumes of fluid in their abdomen as pancreatic ascites, considerable amounts of parenteral fluid replacement are necessary to maintain intravascular volume. ERCP with papillotomy to remove bile duct stones may lessen the severity of gallstone pancreatitis and is usually done within 24 to 48 hours. When pain has largely subsided and the patient has bowel sounds, oral clear liquids can be started and the diet advanced as tolerated.

Most patients with acute pancreatitis will recover spontaneously and have a relatively uncomplicated course. Several scoring systems have been developed in an attempt to identify the 15% to 25% of patients who will have a more complicated course, including the Bedside Index for Severity of Acute Pancreatitis (BISAP) score and Acute Physiology And Chronic Health Evaluation II (APACHE II) score. Patients with severe acute pancreatitis may require management in a monitored or intensive care unit. **The most common cause of early death in patients with pancreatitis is hypovolemic shock**, which is multifactorial: third spacing and sequestration of large fluid volumes in the abdomen, as well as increased capillary permeability. Others develop pulmonary edema, which may be noncardiogenic due to acute respiratory distress syndrome (ARDS) or cardiogenic as a consequence of myocardial dysfunction.

Complications

Pancreatic complications include a **phlegmon**, which is a solid mass of inflamed pancreas, often with patchy areas of necrosis. Sometimes, extensive areas of **pancreatic necrosis** develop within a phlegmon. Either necrosis or a phlegmon can become secondarily infected, resulting in **pancreatic abscess**. Abscesses typically develop 2 to 3 weeks after the onset of illness and should be suspected if there is fever or leukocytosis. If pancreatic abscesses are not drained, mortality approaches 100%. Pancreatic necrosis and abscess are the leading causes of death in patients after the first week of illness. A **pancreatic pseudocyst** is a collection of inflammatory fluid and pancreatic secretions; unlike true cysts, these do not have an epithelial lining. Most pancreatic pseudocysts resolve spontaneously within 6 weeks, especially if they are smaller than 6 cm. However, if they are causing pain, are large or expanding, or become infected, they usually require drainage. Any of these local complications of pancreatitis should be suspected if persistent pain, fever, abdominal mass, or persistent hyperamylasemia occurs.

CLINICAL APPROACH TO CHOLELTHIASIS

Pathophysiology

Gallstones usually form as a consequence of precipitation of cholesterol microcrystals in bile. They are very common, occurring in 10% to 20% of patients older than 65 years. Patients are often asymptomatic. When discovered incidentally, they can be followed without intervention, as only 10% of patients will develop any symptoms related to their stones within 10 years. When patients do develop symptoms because of a stone in the cystic duct or Hartmann pouch, the typical attack of **biliary colic** is sudden in onset, often precipitated by a large or fatty meal, with severe steady pain in the RUQ or epigastrium, lasting between 1 and 4 hours. They may have mild elevations of the alkaline phosphatase level and slight hyperbilirubinemia, but elevations of the bilirubin level over 3 g/dL suggest a common duct stone. The first diagnostic test in a patient with suspected gallstones usually is an **ultrasonogram.** The test is noninvasive and very sensitive for detecting stones in the gallbladder as well as intrahepatic or extrahepatic biliary duct dilation.

Treatment

Patients with asymptomatic gallstones do not require treatment; they can be observed and treated if symptoms develop. Cholecystectomy is performed for patients with symptoms of biliary colic or for those with complications.

One of the most common complications of gallstones is **acute cholecystitis**, which occurs when a stone becomes impacted in the cystic duct, and edema and inflammation develop behind the obstruction. This is apparent ultrasonographically as gallbladder wall thickening and pericholecystic fluid; it is characterized clinically as a persistent RUQ abdominal pain, with fever and leukocytosis. Cultures of bile in the gallbladder often yield enteric flora such as *Escherichia coli* and *Klebsiella*. If the diagnosis is in question, nuclear scintigraphy with a **hepatobiliary iminodiacetic acid (HIDA) scan** may be performed. The positive test shows visualization of the liver by the isotope, but nonvisualization of the gallbladder may indicate an obstructed cystic duct. Treatment of acute cholecystitis usually involves making the patient *nil per os* (NPO; nothing by mouth), intravenous fluids and antibiotics, and early cholecystectomy within 48 to 72 hours.

Another complication of gallstones is cholangitis, which occurs when there is intermittent obstruction of the common bile duct, allowing reflux of bacteria up the biliary tree, followed by development of purulent infection behind the obstruction. If the patient is septic, the condition requires urgent decompression of the biliary tree, either surgically or by ERCP, to remove the stones endoscopically after performing a papillotomy, which allows the other stones to pass.

CASE CORRELATION

- See also Case 20 (Peptic Ulcer Disease), Case 21 (Colitis and Inflammatory Bowel Disease), and Case 22 (Acute Diverticulitis).

COMPREHENSION QUESTIONS

25.1 A 43-year-old man is admitted to the hospital with a diagnosis of acute pancreatitis. His family shares that he is a heavy user of alcohol. He is given intravenous hydration and is placed NPO. Which of the following findings is the highest predictor of mortality?

A. His age
B. Initial serum glucose level of 60 mg/dL
C. BUN of 18 mg/dL
D. Disorientation, with Glasgow Coma Scale score of 10
E. Amylase level of 1000 IU/L

25.2 A 37-year-old woman was being followed by her primary provider for symptomatic gallstones, which were confirmed on ultrasonography. She was placed on a low-fat diet and was doing well for the past 3 months. However, today, she presents to the emergency center with severe RUQ pain and nausea. On examination, her temperature is 102.3 °F, heart rate 100 bpm, and blood pressure 120/70 mm Hg. Her abdominal examination reveals marked RUQ tenderness and guarding. There is no rebound tenderness. Which of the following is the most likely diagnosis?

A. Acute cholangitis
B. Acute cholecystitis
C. Acute pancreatitis
D. Acute perforation of the gallbladder

25.3 A 45-year-old man was admitted for acute pancreatitis, thought to be a result of blunt abdominal trauma. After 3 months, he still has epigastric pain but is able to eat solid food. His amylase level is elevated at 260 IU/L. Which of the following is the most likely diagnosis?

A. Recurrent pancreatitis
B. Diverticulitis
C. Peptic ulcer disease
D. Pancreatic pseudocyst

ANSWERS

25.1 **D.** Impaired mental status is a poor prognostic sign. Other findings associated with higher mortality include a BUN > 25 mg/dL (not 18 mg/dL, as in answer C), presence of SIRS, age over 60 (not 43 years of age, as in answer A), and presence of a pleural effusion. Notably, the amylase level (answer E) does not correlate with the severity of the disease. Thus, although the serum amylase level or lipase level helps to make a diagnosis of pancreatitis, it is the presence of other findings that dictates prognosis. Hyperglycemia with a

serum glucose exceeding 200 mg/dL indicates significant pancreatic dysfunction and is a poor prognostic factor; this patient's glucose level of 60 mg/dL (answer B) is therefore not a significant prognostic indicator.

25.2 **B.** Acute cholecystitis is one of the most common complications of gallstones. This patient with fever, RUQ pain, and a history of gallstones likely has acute cholecystitis. Acute cholangitis (answer A) usually presents with Charcot triad (RUQ pain, jaundice, and fever/chills) due to an ascending infection proximal to an obstructed bile duct. There is no description of icterus. Acute pancreatitis (answer C) is a complication of gallstones, but affected patients typically present with midline epigastric pain radiating to the back. Acute perforation of the gallbladder (answer D) is a rare complication of cholecystitis that is life threatening; associated findings include high fever, nausea, vomiting, and severe abdominal tenderness with rebound. Treatment is generally surgical, and early diagnosis is important to reduce mortality.

25.3 **D.** A pancreatic pseudocyst has a clinical presentation of abdominal pain and mass and persistent hyperamylasemia in a patient with prior pancreatitis. The fact that the patient's pain has largely abated and he is able to eat food speaks against recurrent pancreatitis (answer A). Acute diverticulitis (answer B) usually presents with the acute onset of left lower quadrant abdominal tenderness, fever, and nausea. Peptic ulcer disease (answer C) presents with burning epigastric pain that radiates to the back.

CLINICAL PEARLS

- The three most common causes of acute pancreatitis in the United States are gallstones, alcohol consumption, and hypertriglyceridemia.
- Acute pancreatitis usually is managed with pancreatic rest, intravenous hydration, and analgesia, often narcotics.
- Pancreatic complications (phlegmon, necrosis, abscess, pseudocyst) should be suspected if persistent pain, fever, abdominal mass, or persistent hyperamylasemia occurs.
- Patients with asymptomatic gallstones do not require treatment; they can be observed and treated if symptoms develop. Cholecystectomy is performed for patients with symptoms of biliary colic or for those with complications.
- Acute cholecystitis is best treated with antibiotics and then cholecystectomy, generally within 48 to 72 hours.

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CASE 26

A 28-year-old man comes to your clinic complaining of a 5-day history of nausea, vomiting, diffuse abdominal pain, fever, and muscle aches. He has lost his appetite, but he is able to tolerate liquids and has no diarrhea. He has no significant medical or family history, and he has not traveled outside the United States. He admits to having 12 different lifetime sexual partners with inconsistent barrier protection use. He denies illicit drug use and reports drinking alcohol occasionally, but not since this illness began. He takes no medications or supplements. However, he has taken 30 tablets of acetaminophen per day over the past 2 days for fever and body aches. On examination, his temperature is 100.8 °F, heart rate is 98 beats per minute (bpm), and blood pressure is 120/74 mm Hg. He is alert and oriented but appears uncomfortable. Jaundice is noted. His chest is clear to auscultation, and his heart rhythm is regular without murmurs. His liver size is estimated to be 12 cm upon percussion and is noted to be smooth but slightly tender to palpation. He has no abdominal distention or peripheral edema. Laboratory values are significant for a normal complete blood count, creatinine 1.1 mg/dL, alanine aminotransferase (ALT) 3440 IU/L, aspartate aminotransferase (AST) 2705 IU/L, total bilirubin 24.5 mg/dL, direct bilirubin 18.2 mg/dL, alkaline phosphatase 349 IU/L, serum albumin 3.0 g/dL, and prothrombin time 14 seconds.

- What is the most likely diagnosis?
- What is the most important immediate diagnostic test?
- What is an important management consideration for this patient?

ANSWERS TO CASE 26:
Acute Hepatitis

Summary: A 28-year-old man presents with

- No past medical history
- Five days of nausea, vomiting, diffuse abdominal pain, fever, and myalgias
- Twelve different lifetime sexual partners
- Recent history of taking large amounts of acetaminophen
- Icteric appearance with a low-grade fever and tender hepatomegaly
- Laboratory results consistent with severe hepatocellular injury

Most likely diagnosis: Acute hepatitis, either viral infection or toxic injury, possibly exacerbated by acetaminophen use due to the patient's young age, sexual history, lack of medication/supplement use, and pattern of liver study results.

Most important immediate diagnostic test: Acetaminophen level, as acetaminophen toxicity may greatly exacerbate liver injury but is treatable.

Important management consideration: If fulminant liver failure is suspected, the patient should be transferred to a liver transplant center to be evaluated, as fulminant liver failure may be rapidly fatal. Evaluate for encephalopathy in conjunction with hepatic synthetic dysfunction.

ANALYSIS

Objectives

1. Understand the use of viral serologic studies for diagnosing hepatitis A, B, and C infections. (EPA 3)
2. Recognize the prognosis for acute viral hepatitis and recognize fulminant hepatic failure. (EPA 1, 12)
3. List measures to prevent hepatitis A and B infections. (EPA 12)
4. Understand the use of the acetaminophen nomogram and the treatment of acetaminophen hepatotoxicity. (EPA 3, 4)

Considerations

This patient has an acute onset of hepatic injury and systemic symptoms that predate his acetaminophen use. The markedly elevated hepatic transaminases and bilirubin levels are consistent with viral hepatitis or toxic injury. This patient denied intravenous drug use, which would be a risk factor for hepatitis B and C infections.

However, his sexual history does place him at higher risk for these infections. The degree and pattern of transaminase ALT and AST elevation provide clues to help differentiate possible etiologies. Transaminase levels more than 1000 IU/L are seen in conditions that produce extensive hepatic necrosis, such as toxic injury, viral hepatitis, and ischemia ("shock liver"). Meanwhile, patients with alcoholic hepatitis almost always have levels less than 500 IU/L and often have an AST/ALT ratio of 2:1. In this case, it is important to consider the possibility of acetaminophen toxicity, both because the condition can produce fatal liver failure and because an effective antidote is available. By obtaining a serum acetaminophen level and knowing the time of his last ingestion, the provider can plot the data on a nomogram (Figure 26–1) to help predict acetaminophen-related liver damage and the possible need for *N*-acetylcysteine (NAC), which is the antidote.

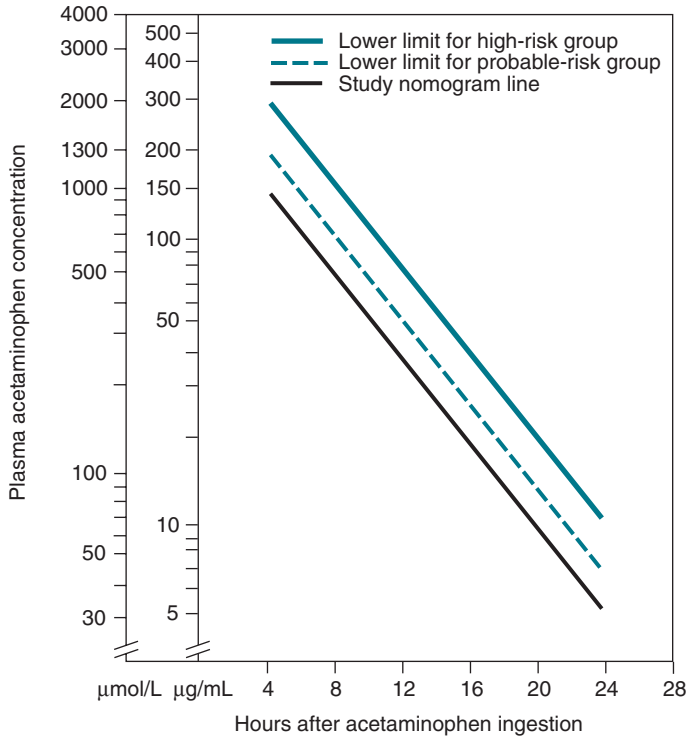


Figure 26–1. Acetaminophen nomogram. (Reproduced with permission, from Braunwald E, Fauci AS, Kasper DL, et al., eds. *Harrison's Principles of Internal Medicine*, 15th ed. 2001. Copyright © McGraw Hill LLC. All rights reserved.)

APPROACH TO:
Viral and Acetaminophen Hepatitis

DEFINITIONS

ACUTE HEPATITIS: Inflammation of the liver that may be caused by infection, ischemia, autoimmune state, or toxic exposure for a duration of less than 26 weeks. At least six viruses that cause hepatitis have been identified, referred to as hepatitis A, B, C, D, E, and G. Hepatitis A, C, D, E, and G are RNA viruses, while hepatitis B is a DNA virus.

CHRONIC HEPATITIS: A syndrome that is defined clinically by evidence of liver disease with inflammation and necrosis for at least 26 weeks, most commonly with hepatitis B, C, and D infections.

CIRRHOSIS: Diffuse damage to hepatocytes, which show evidence of chronic inflammation with fibrosis and loss of hepatocyte function.

FULMINANT HEPATIC FAILURE: A rare, but devastating, syndrome that rapidly progresses within 8 weeks of symptom onset. Normal hepatic function is arrested, and clinical manifestations include markedly elevated serum transaminases, jaundice, coagulopathy, and hepatic encephalopathy.

CLINICAL APPROACH TO VIRAL HEPATITIS

Epidemiology

Most cases of acute hepatitis are caused by infection with one of the five viruses: **hepatitis A, B, C, D, or E.** These viruses produce virtually indistinguishable clinical syndromes, although it is unusual to observe acute hepatitis C. Affected individuals often complain of a prodrome of nonspecific constitutional symptoms, including fever, nausea, fatigue, arthralgias, myalgias, headache, and sometimes pharyngitis and coryza, which is then followed by the onset of jaundice caused by hyperbilirubinemia and dark urine caused by hyperbilirubinuria. The liver may be enlarged (hepatomegaly) and tender. The clinical course and prognosis vary based on the type of virus causing the hepatitis.

The differential diagnosis for acute hepatitis includes viral, toxic, ischemic, or autoimmune injury. Viral hepatitis can originate from infection by the several viruses described in the material that follows; less commonly, it be caused by Epstein-Barr virus, herpes simplex virus, varicella zoster virus, cytomegalovirus, and adenovirus, among others. Toxic injury may be the result of medications (ie, acetaminophen, statins, phenytoin, ketoconazole), alcohol, supplements (ie, black cohosh, kava), or mushroom poisoning (ie, *Amanita phalloides*). Ischemic injury may occur during episodes of severe, acute hypoperfusion. Budd-Chiari and veno-occlusive disease may also lead to acute hepatitis. Additional causes include Wilson disease, leptospirosis, malignant infiltration, or heatstroke.

Pathophysiology

Hepatitis A and **E** both are very contagious and transmitted either by the **fecal-oral route**, usually through contaminated food or water where sanitation is poor, or from person to person, such as in day care settings by children. **Hepatitis A** is found worldwide and is the **most common cause of acute viral hepatitis in the United States. Hepatitis E** is much less common and is found in Asia, Africa, Central America, and the Caribbean. Both hepatitis A and E infections usually lead to self-limited illnesses and generally resolve within weeks. Almost all patients with hepatitis A recover completely and have no long-term complications. Less than 1% of those infected with hepatitis A develop fulminant liver disease resulting in hepatic failure, and those patients are generally > 50 years old and have some underlying chronic liver disease. Most patients with **hepatitis E** also have uncomplicated courses, but some patients, particularly **pregnant women**, have been reported to develop **severe hepatic necrosis and fatal liver failure**.

Hepatitis B is the second most common type of viral hepatitis in the United States and is **usually sexually transmitted.** It also may be acquired parenterally, such as by intravenous drug use, or during birth from chronically infected mothers. The outcome depends on the age at which the infection was acquired. Up to 90% of infected newborns develop chronic hepatitis B infection, which places the affected infant at significant risk of hepatocellular carcinoma later in adulthood. For individuals infected later in life, approximately 95% of patients will recover completely without sequelae. Between 5% and 10% of patients will develop chronic hepatitis, which may progress to cirrhosis. A chronic carrier state may be seen in which the virus continues to replicate, but it does not cause irreversible hepatic damage in the host.

Hepatitis C is transmitted **parenterally by blood transfusions or intravenous drug use** and less commonly by sexual contact. The mode of transmission is unknown in approximately 40% of cases. It is uncommonly diagnosed as a cause of acute hepatitis, often producing subclinical infection, but is frequently diagnosed later as a cause of **chronic hepatitis** with or without the presence of liver cirrhosis. The majority of hepatitis C infection leads to chronic hepatitis, but the development of newer medications can lead to the cure of many patients; for this reason, most preventive guidelines recommend screening for hepatitis C infection at least once during adulthood and more often in high-risk individuals.

Hepatitis D is a defective RNA virus that requires the presence of the hepatitis B virus to replicate. It can be acquired as a **coinfection simultaneously with acute hepatitis B** or as a later superinfection in a person with a chronic hepatitis B infection. Patients afflicted with chronic hepatitis B virus who then become infected with hepatitis D may suffer clinical deterioration; in 10% to 20% of these cases, individuals develop severe fatal hepatic failure.

Clinical Presentation

Since there are many causes of acute hepatitis, a good history is vital. The history should include targeted questions about the patient's drug use, sexual contacts, and travel history. Additional questions should investigate possible exposures

to toxins and supplements. Timing of symptoms may also help elucidate an etiology.

Examination findings may include jaundice, right upper quadrant tenderness, ascites, and signs of intravascular depletion, such as orthostatic vitals. It is important to perform a complete neurologic examination on the patient to assess for encephalopathy. If encephalopathy is present, then it should be graded I-IV. Grade I may be evident by confusion, abnormal behavior, changes in sleeping patterns, or slurred speech. This may be difficult to distinguish from grade II, which has progressive lethargy. Profound confusion, incoherent speech, and increased sleeping may be signs of grade III encephalopathy, while grade IV is hallmarked by coma. Findings on physical examination may not help distinguish the etiology of acute hepatic failure, and further studies are usually needed.

Serologic studies are generally used to establish a diagnosis. Anti-hepatitis A immunoglobulin M (IgM) establishes an acute hepatitis A infection. Anti-hepatitis C antibody is present in acute hepatitis C, but the test result may be negative for several weeks. The hepatitis C RNA assay, which becomes positive earlier in the disease course, often aids in the diagnosis. Acute hepatitis B infection is diagnosed by the presence of hepatitis B surface antigen (HBsAg) in the clinical context of elevated serum transaminase levels and jaundice. **HBsAg later disappears when the antibody (anti-HBs) is produced** (Figure 26–2). There is often an interval of a few weeks between the disappearance of HBsAg and the appearance of anti-HBsAb. This period is referred to as the **"window period."** During this interval, the presence of anti-hepatitis B core antigen IgM (anti–HBc IgM) is indicative of an acute hepatitis B infection. A positive hepatitis B precore antigen **(HBeAg) represents a high level of viral replication and high infectivity**. It is almost always present during acute infection, but its persistence after 6 weeks of illness is a sign of chronic infection

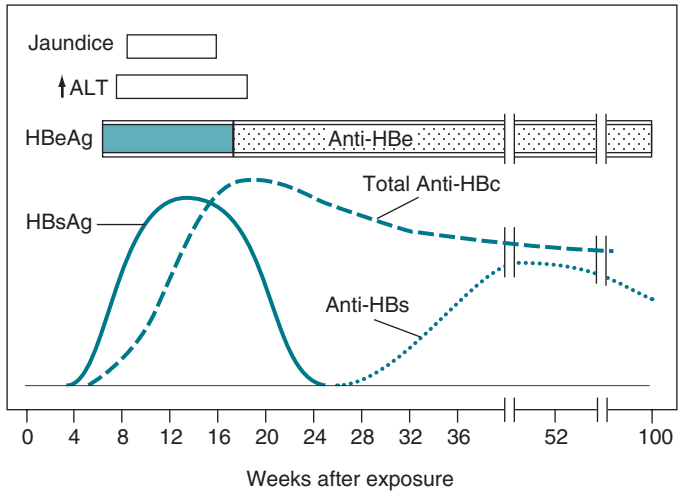


Figure 26–2. Serologic markers in acute hepatitis B infection. Note: Total Anti-HBc = both IgG and IgM. (Reproduced with permission, form Braunwald E, Fauci AS, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*, 16th ed. 2005. Copyright © McGraw Hill LLC. All rights reserved.)

and high infectivity. Persistence of HBsAg or HBeAg is a marker for chronic hepatitis or a chronic carrier state; elevated versus normal serum transaminase levels distinguish between these two entities, respectively. Patients who have been vaccinated against hepatitis B will have a positive HBsAb but no other positive serology.

Treatment and Complications

Fortunately, in most cases of acute viral hepatitis, patients recover completely, so the treatment is generally supportive. However, **fulminant hepatic failure** due to massive hepatic necrosis may progress over a period of weeks and is usually caused by infections from the hepatitis B and D viruses or from toxins. **Toxin- or drug-induced liver injury is the most common cause of acute liver failure** and can be a result of direct toxic effects of substances on the liver parenchyma (acetaminophen, *A. phalloides*) or idiosyncratic reactions of medications (halothane, isoniazid, phenytoin). Direct toxic effects are predictable and dose dependent, but idiosyncratic reactions are not.

Acute hepatic failure is characterized by rapid progression of encephalopathy from confusion or somnolence to coma. Patients also have markedly high serum aminotransferase levels, worsening coagulopathy, rising bilirubin levels, ascites and peripheral edema, hypoglycemia, hyperammonemia, and lactic acidosis. Fulminant hepatic failure carries a poor prognosis (the mortality for comatose patients is 80%) and often is fatal without an emergent liver transplant.

Prevention. The efficacy of the **hepatitis A vaccine** (available in two doses given 6 months apart) exceeds 90%. It is indicated for individuals planning to travel to endemic areas, along with those with chronic hepatitis B or C. Postexposure prophylaxis with hepatitis A immunoglobulin, along with the first injection of the vaccine, should be given to household and intimate contacts within 2 weeks of exposure. The **hepatitis B vaccine** (given in three doses over 6 months) provides effective immunity in more than 90% of patients. It is recommended for health care workers, those with chronic hepatitis C, and all infants in the United States. Hepatitis B immunoglobulin (HBIg) is given after exposure, such as to health care providers after a needlestick injury from an infected patient, or to newborns of infected mothers. The first inoculation of the vaccine is usually given concurrently. There is no immunization and no proven postexposure prophylaxis for persons exposed to hepatitis C. Interferon and nucleos(t)ide analogs, such as entecavir, tenofovir, or lamivudine, are used to treat patients with chronic hepatitis B. **Treatment for chronic hepatitis C** has undergone major advancement with utilization of direct acting antivirals (DAAs), sometimes in combination with ribavirin or interferon, allowing for high rates of curative treatment of chronic hepatitis C. Examples of DAA selections include sofosbuvir, a nucleoside analog of the hepatitis C virus, and simeprevir, a protease inhibitor specific to proteins on the hepatitis C virus. Regimens for treatment are based on hepatitis C genotyping, with genotype I being the most common, along with history of prior treatment failure and comorbidities.

CLINICAL APPROACH TO ACETAMINOPHEN HEPATITIS

Pathophysiology

Acetaminophen poisoning is among the most common types of medication-induced toxicity and death. Acetaminophen-induced hepatocellular injury may result after a single, large ingestion, as in a suicide attempt, or by chronic use of over-the-counter acetaminophen-containing preparations for treatment of pain or fever. **Hepatic toxicity** most often occurs after an acute ingestion of **10 g or more**, but lower doses (4 g in 24 hours) may cause injury to patients with pre-existing liver disease, particularly in those who abuse alcohol. Acetaminophen is metabolized in the liver by the cytochrome P450 enzyme system, which produces a toxic metabolite. This metabolite is detoxified by binding to glutathione. Risk of hepatic injury is greater when P450 activity is augmented by drugs such as ethanol or phenobarbital or when less glutathione is available, as in alcoholism, malnutrition, or acquired immunodeficiency syndrome (AIDS). Acetaminophen levels are measured between 4 and 24 hours after an acute ingestion and plotted on a **nomogram** to predict possible hepatotoxicity and determine if treatment is necessary. Sometimes, empiric therapy is started even before laboratory results return.

Treatment

Treatment of the acetaminophen toxicity is dependent on time of presentation. Patients who present promptly after ingestion of large amounts of acetaminophen may benefit from gastric decontamination with charcoal if no additional contraindications exist. Gastric decontamination is most beneficial if performed within the first 4 hours after ingestion. If acetaminophen levels are above the level that predisposes to hepatic injury or if there is a significant risk of hepatotoxicity, administration of **NAC** is indicated. NAC functions as an antidote to acetaminophen toxicity by providing cysteine to **replenish glutathione stores**. Ideally, NAC should be started prior to evidence of liver injury and within the first 10 hours of ingestion in attempt to prevent liver damage; it is continued for 72 hours. Meanwhile, the patient should not receive any medications that are known to be hepatotoxic. It is equally important to ensure that patients are receiving adequate supportive therapy based on the severity of disease presentation. Patients may require fluid resuscitation, airway support, vasopressors, dialysis, and/or management of cerebral edema.

CASE CORRELATION

- See also Case 24 (Liver Cirrhosis, Probably Alcoholic) and Case 27 (Painless Jaundice, Pancreatic Cancer).

COMPREHENSION QUESTIONS

26.1 A 25-year-old medical student is stuck with a hollow needle during a procedure performed on a patient known to have hepatitis B and C viral infections, but who is HIV negative. The student's baseline laboratory studies include serology: HBsAg negative, anti-HBsAb positive, and anti-HBc IgG negative. Which of the following regarding this medical student's hepatitis status is true?

A. Prior vaccination with hepatitis B vaccine
B. Acute infection with hepatitis B virus
C. Prior infection with hepatitis B virus
D. The student was vaccinated for hepatitis B but is not immune

26.2 What postexposure prophylaxis (if any) should the student described in Question 26.1 receive?

A. HBIg
B. Oral tenofovir
C. Immunoglobulin
D. Reassurance

26.3 In a suicide attempt, an 18-year-old woman took 4 g of acetaminophen, approximately 8 hours previously. On examination, she is drowsy but oriented and answers questions appropriately. Her blood pressure is 120/70 mm Hg and heart rate is 90 bpm. She is anicteric. Her heart, lung, and abdominal examinations are normal. Her acetaminophen level is 30 mcg/mL. Which of the following is the best next step to be performed for this patient?

A. Immediately start NAC
B. Observation
C. Alkalinize the urine
D. Administer intravenous activated charcoal

ANSWERS

26.1 **A.** This student's serology is most consistent with vaccination and not prior infection. Like all health care workers, the student should have been vaccinated against the hepatitis B virus, which induces anti-HBs IgG antibody, and is thought to be protective. Not all people receiving the vaccine develop an adequate antibody titer; if none were detected, it would indicate the need for revaccination (answer D). Patients with prior hepatitis B infection (answer C) also have anti-HBsAb but will additionally have anti-HBc IgG. Acute infection (answer B) would be established by the presence of either HBsAg or anti-HBc IgM.

26.2 **D.** No postexposure prophylaxis is definitively indicated. The student has detectable protective antibody levels against the hepatitis B virus, and if the levels are judged to be adequate, the student is protected against infection. Thus, the key point in this question is that the presence of anti-HBsAg antibody is protective. Oral tenofovir (answer B) is a treatment for chronic hepatitis B infection and is part of an antiretroviral prophylaxis if the patient were HIV positive. There is no effective prophylaxis for hepatitis C exposure. Seroconversion against this virus needs to be retested at a later time. Thus, passive immunization with HBIg (answer A) is not needed. Answer C (immunoglobulin) is indicated for hepatitis A exposure but not hepatitis B.

26.3 **B.** The serum acetaminophen level of 30 mcg/mL, with last ingestion 8 hours previously, is plotted on the nomogram and falls below the "danger zone" of possible hepatic injury. Thus, this patient should be observed. Sometimes, patients will take more than one medication, and serum and/or urine drug testing may be worthwhile. Gastrointestinal activated charcoal, not intravenous charcoal (answer D), is used for other ingestions. Initiation of NAC (answer A) is recommended when the normogram suggests possible hepatic injury. Alkalinization (answer C) of the urine is helpful to enhance excretion of acidic toxins such as aspirin but does not have a role in acetaminophen toxicity.

CLINICAL PEARLS

- The most common cause of acute hepatic failure is toxin or drug injury, which may be due to direct toxic effects or an idiosyncratic reaction.
- The likelihood of toxic acetaminophen injury and the need for treatment can be predicted from a nomogram based on serum level and the time since last ingestion.
- The majority of adults with acute hepatitis B infection recover completely. However, 5% to 10% develop chronic hepatitis.
- Vaccination for hepatitis B should produce measurable HBsAb. Presence of anti-HBc IgG indicates evidence of prior infection. Anti-HBc IgM can be positive during the "window period" of acute infection.
- Prevention of hepatitis B viral infection hinges on long-term immunity with a highly effective recombinant vaccine or postexposure prophylaxis with HBIg. There is no vaccine or postexposure prophylaxis for hepatitis C.

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CASE 27

A 57-year-old man comes to the clinic complaining of malaise for several weeks. He says that he has not been feeling well for some time, with fatigue, depressed mood, loss of appetite, and a 20-lb unintentional weight loss. In addition, he has been bothered by generalized itching of his skin and has tried moisturizing lotions and creams without improvement. He denies fevers, abdominal pain, nausea, vomiting, or diarrhea. He does think his stools have been lighter in color recently. He has also noticed his urine is darker. He has no other medical history and takes no medications except for a multivitamin. He drinks alcohol occasionally and smokes cigars.

On examination, he is afebrile, with heart rate of 68 beats per minute (bpm) and blood pressure of 128/74 mm Hg. He has a flat affect and a somewhat disheveled appearance. He has noticeable icterus of his sclera and skin. His chest is clear, and his heart rhythm is regular without murmurs. His abdomen is soft and nontender with active bowel sounds, a liver span of 10 cm, and no splenomegaly or masses. His skin has a few excoriations on his arms and back, but no rashes or telangiectasias are present.

Blood is obtained for laboratory analysis; the results are available the next day. His serum albumin is 3.1 g/dL, alkaline phosphatase 588 IU/L, total bilirubin 8.5 mg/dL, direct bilirubin 6 mg/dL, alanine aminotransferase (ALT) 175 IU/L, and aspartate aminotransferase (AST) 140 IU/L. His hemoglobin level is 13.5 g/dL. Prothrombin time (PT) is 15 seconds, international normalized ratio (INR) is 1.2, and partial thromboplastin time is 32 seconds.

- What is the most likely diagnosis?
- What is the next diagnostic step?
- What risk factors are associated with the most likely diagnosis?

ANSWERS TO CASE 27:
Painless Jaundice, Pancreatic Cancer

Summary: A 57-year-old man presents with

- Pruritus and weight loss
- Light-colored stools and dark urine
- Painless jaundice
- Elevated alkaline phosphatase level and conjugated hyperbilirubinemia

Most likely diagnosis: Biliary obstruction, most likely caused by malignancy.

Next diagnostic step: Imaging procedure of his biliary system, initially ultrasonography followed by computed tomographic (CT) scan.

Risk factors for pancreatic cancer: Smoking, alcohol use, obesity, age, and diabetes.

ANALYSIS

Objectives

1. Describe the causes and evaluation of a patient with unconjugated hyperbilirubinemia. (EPA 1, 2, 3)
2. Distinguish between hepatocellular disease and biliary obstruction. (EPA 3)
3. Evaluate patients with cholestasis. (EPA 1, 3)
4. List the treatment and complications of biliary obstruction. (EPA 4, 10)

Considerations

In patients with jaundice, one must try to distinguish between hepatocellular and biliary disease. In a patient with painless biliary obstruction, one should be suspicious of malignancy or strictures. The findings in this case, such as generalized pruritis and icterus, point toward cholestasis. The light-colored or acholic stools suggest the cholestasis is most likely due to biliary obstruction since bile is what causes stool to have its darker color. The absence of abdominal pain makes gallstone disease less likely, and in fact, nontender jaundice is suspicious for pancreatic cancer.

APPROACH TO:
Painless Jaundice

DEFINITIONS

CHOLESTASIS: Deficient bile flow that can result from intrahepatic disease or extrahepatic obstruction.

CONJUGATED BILIRUBIN (DIRECT-REACTING BILIRUBIN): Bilirubin that has entered the liver and has been enzymatically bound to glucuronic acid, forming the water-soluble bilirubin monoglucuronide or diglucuronide.

JAUNDICE OR ICTERUS: Yellowing of the skin or whites of the eyes, indicating hyperbilirubinemia.

UNCONJUGATED BILIRUBIN (INDIRECT-REACTING BILIRUBIN): Bilirubin that has not been enzymatically bound to glucuronic acid by the liver and is in the serum reversibly and noncovalently bound to albumin.

CLINICAL APPROACH

Pathophysiology

Jaundice, or icterus, is the visible manifestation of **hyperbilirubinemia** and usually can be noticed by physical examination when the serum bilirubin level exceeds 2.0 to 2.5 mg/dL. Traditional instruction regarding the jaundiced patient divides the mechanism of hyperbilirubinemia into prehepatic (excessive production of bilirubin), intrahepatic, or extrahepatic (as in biliary obstruction). For most patients with jaundice, the focus should be on hepatic or biliary diseases that cause conjugated (direct) hyperbilirubinemia because they represent the most clinically important causes of jaundice.

The term **unconjugated (indirect) hyperbilirubinemia** is used when the conjugated (or direct-reacting fraction) does not exceed 15% of the total bilirubin. In adults, it is almost always caused by hemolysis or Gilbert syndrome. In these conditions, the serum bilirubin level almost always is less than 5 mg/dL, and there are usually no other clinical signs of liver disease. In addition, there should be no bilirubinuria (only conjugated bilirubin can be filtered and renally excreted). **Hemolysis** usually is clinically apparent, as in sickle cell disease or autoimmune hemolytic anemia. **Gilbert syndrome** is a benign condition caused by a deficiency of hepatic enzymatic conjugation of bilirubin, which results in intermittent unconjugated hyperbilirubinemia. Total bilirubin is usually less than 4 g/dL and is often precipitated by events such as stress, fasting, and febrile illnesses. It is not associated with liver dysfunction and requires no therapy.

Conjugated (direct) hyperbilirubinemia almost always reflects either hepatocellular disease or biliary obstruction. These two conditions can be differentiated by the pattern of elevation of the liver enzymes. Elevation of serum AST and ALT levels is characteristic of hepatocellular disease as a result of the inflammation/destruction of the hepatocytes and the release of these enzymes into the blood.

The serum alkaline phosphatase level is elevated in cholestatic disease as a consequence of inflammation, destruction, or obstruction of the intrahepatic or extrahepatic bile ducts with relative sparing of the hepatocytes. The serum AST and ALT levels may be mildly elevated in cholestasis but usually not to the levels seen in primary acute hepatocellular disease. Other tests, such as serum albumin or PT, generally reflect the capacity of hepatocytes to synthesize proteins such as clotting factors. When they are abnormal, they most often reflect hepatocellular disease. Table 27–1 summarizes the liver test patterns seen in various categories of hepatobiliary disorders.

Differential Diagnosis. The patient discussed in this case has a pattern consistent with cholestasis, and the **first diagnostic test in a patient with cholestasis usually is an ultrasound.** It is noninvasive and is very sensitive for detecting stones in the gallbladder as well as intrahepatic or extrahepatic biliary ductal dilation. The **most common cause of biliary obstruction in the United States is gallstones**, which may become lodged in the common bile duct. Obstructing stones causing jaundice usually are associated with epigastric or right upper quadrant colicky pain. Extrahepatic dilation without evidence of stones warrants further study with CT, magnetic resonance cholangiopancreatography, or endoscopic retrograde cholangiopancreatography (ERCP). These imaging techniques may detect occult stones, strictures, or malignancies that include cholangiocarcinoma, pancreatic cancer, and ampullary cancer (ampulla of Vater).

Other possible causes of obstruction include strictures, which can result from prior biliary surgery, prior inflammatory conditions such as pancreatitis (rarely), inflammatory diseases of the biliary tree, and infection in the setting of acquired immunodeficiency syndrome (AIDS). Two important primary biliary conditions are **primary sclerosing cholangitis** and **primary biliary cirrhosis**. Table 27–2 compares features of these two entities.

The complications of biliary obstruction include development of acute cholangitis as a result of ascending infection, or secondary hepatic cirrhosis if the obstruction is chronic or recurrent. The patient in this case scenario has painless jaundice, liver enzymes consistent with a cholestatic process, and light-colored stools, suggesting obstruction of bile flow into the intestine. Because he has no history of abdominal or biliary surgery that might have caused a stricture, malignancy is the most likely cause of his biliary obstruction. The most common malignancy with this clinical presentation is **pancreatic cancer**. The patient should undergo an imaging procedure of his abdomen, including a right upper quadrant ultrasound to evaluate the biliary tree, as well as a **CT scan** or magnetic resonance imaging (MRI) to visualize the pancreas. Endoscopic ultrasound with fine-needle aspiration of the pancreas is highly accurate in establishing a tissue diagnosis.

Treatment

Pancreatic cancer is the fifth leading cause of cancer death in the United States. Peak incidence is in the seventh decade of life, with two-thirds of cases occurring in persons older than 65 years. The median survival is 9 months, with a dismal overall 5-year survival rate of 3%. Clinically apparent metastatic disease is found in 80% of patients at the time of diagnosis. For patients without obvious metastases, the best

Table 27–1 • LABORATORY FINDINGS IN HEPATOBILIARY DISORDERS

Type of Disorder	Bilirubin	Aminotransferases	Alkaline Phosphatase	Albumin	Prothrombin Time
Hemolysis/Gilbert syndrome	Normal to 5 mg/dL; 85% due to indirect fractions. No bilirubinuria.	Normal	Normal	Normal	Normal
Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)	Both fractions may be elevated. Peak usually follows aminotransferases. Bilirubinuria.	Elevated, often > 500 IU/L; ALT > AST	Normal to < 3 times normal elevation	Normal	Usually normal. If > 5 times above control and not corrected by vitamin K, suggests poor prognosis
Chronic hepatocellular disease (cirrhosis, cancer)	Both fractions may be elevated. Bilirubinuria.	Elevated but usually < 300 IU/L	Normal to < 3 times normal elevation	Often decreased	Often prolonged; fails to correct with parenteral vitamin K
Intra- and extrahepatic cholestasis (obstructive jaundice)	Both fractions may be elevated. Bilirubinuria.	Normal to moderate elevation, rarely > 500 IU/L	Elevated, often > 4 times normal elevation	Normal, unless chronic	Normal; if prolonged, will correct with parenteral vitamin K
Infiltrative diseases (tumor, granulomata): partial bile duct obstruction	Usually normal.	Normal to slight elevation	Elevated, often > 4 times normal elevation fractionate, may confirm liver origin with 5′-nucleotidase, or gamma-glutamyl transpeptidase	Normal	Normal

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Table 27–2 • COMPARISON OF PRIMARY SCLEROSING CHOLANGITIS AND PRIMARY BILIARY CIRRHOSIS

Disease	Primary Sclerosing Cholangitis	Primary Biliary Cirrhosis
Gender/age distribution	Younger males	Older females
Location of disease	Larger intra- and extrahepatic ducts	Smaller intrahepatic bile ducts
Associated conditions	Ulcerative colitis	Autoimmune diseases, eg, rheumatoid arthritis
Serologic markers	None	Antimitochondrial antibody (AMA)
Complications	Stricture; infection (cholangitis); cholangiocarcinoma	Cirrhosis

hope for cure is surgical resection by pancreaticoduodenectomy (Whipple procedure), which in experienced hands has a perioperative mortality rate of less than 5%. Even when the cancer is resectable, there is a high rate of recurrence. As such, many treatment programs include neoadjuvant chemotherapy. Palliative measures may include common bile duct stenting to relieve biliary obstruction. Several serum markers for pancreatic cancer have been evaluated, the most useful of which is CA 19-9. This marker has prognostic value and is also used as an indicator of response to treatment and/or disease progression.

Unfortunately, there is no cure for primary biliary cirrhosis, but ursodeoxycholic acid, steroids, and immunosuppressive agents can slow the progression of the disease; ultimately, liver transplantation is the only option for end-stage disease.

CASE CORRELATION

- See also Case 24 (Liver Cirrhosis, Probably Alcoholic) and Case 26 (Acute Hepatitis).

COMPREHENSION QUESTIONS

For Questions **27.1** to **27.4**, choose the one diagnosis (A-F) that best matches with the most likely clinical situation.

A. Hemolysis
B. Alcoholic hepatitis
C. Gilbert disease
D. Pancreatic cancer
E. Gallstones
F. Primary sclerosing cholangitis

27.1 A 38-year-old man with an alcohol history of 12 beers per day presents with jaundice, ascites, and dark urine. His laboratory results are AST 350 U/mL, ALT 150 U/mL, alkaline phosphatase 120 U/mL, total bilirubin 25 mg/dL, direct bilirubin 18 mg/dL, and albumin 2.1 g/dL.

27.2 A 40-year-old moderately obese woman presents with abdominal pain after eating and mild conjunctival icterus. Her laboratory results are AST 200 U/L, ALT 150 U/L, alkaline phosphatase 355 U/L, total bilirubin 3.5 mg/dL, direct bilirubin 1.8 mg/dL, and albumin 3.5 g/dL.

27.3 A 25-year-old man presents with 3 days of conjunctival icterus but has been otherwise feeling well. His laboratory results are AST 45 U/L, ALT 48 U/L, alkaline phosphatase 100 U/L, total bilirubin 3.2 mg/dL, direct bilirubin 0.2 mg/dL, and albumin 3.5 g/dL. Complete blood cell count and lactate dehydrogenase are normal.

27.4 A 32-year-old man with a 5-year history of episodic bloody diarrhea and abdominal cramping pain presents with conjunctival icterus and fever. His laboratory results are AST 100 U/L, ALT 125 U/L, alkaline phosphatase 550 U/L, total bilirubin 5.5 mg/dL, direct bilirubin 3.0 mg/dL, and albumin 2.9 g/dL.

ANSWERS

27.1 **B.** The patient's laboratory results show a conjugated hyperbilirubinemia with evidence of hepatocellular disease (hypoalbuminemia, ascites). The AST and ALT levels show the 2:1 ratio consistent with alcohol-related liver disease.

27.2 **E.** The patient's laboratory results show a conjugated hyperbilirubinemia consistent with an obstructive pattern. She has the risk factors for gallstones (female, obese, middle age) and has symptoms of postprandial abdominal pain.

27.3 **C.** The patient's laboratory results show an unconjugated hyperbilirubinemia without other abnormality. He is otherwise healthy and without symptoms of systemic disease or hemolytic anemia; this is suggestive of Gilbert disease. No treatment is necessary.

27.4 **F.** The patient's laboratory results show a conjugated hyperbilirubinemia with an obstructive pattern. The history is consistent with inflammatory bowel disease, which is associated with primary sclerosing cholangitis. The initial evaluation should include ultrasonography to rule out gallstones; if negative, ERCP could confirm the diagnosis by demonstrating multiple strictures of the extrahepatic bile ducts. Treatment options include stenting of the larger bile duct strictures and immunosuppression to slow the progression of the disease.

CLINICAL PEARLS

- Unconjugated (indirect) hyperbilirubinemia usually is caused by hemolysis or Gilbert syndrome.
- Conjugated (direct) hyperbilirubinemia is commonly caused by hepatocellular disease, with elevated AST and ALT levels, or biliary obstruction, with elevated alkaline phosphatase level.
- An imaging procedure such as ultrasonography is the initial study of choice in a patient with cholestasis to evaluate for intrahepatic or extrahepatic biliary obstruction.
- The most common causes of biliary obstruction are gallstones, which are painful if obstructing, and strictures or neoplasms, which may be painless.
- Pancreatic cancer is initially diagnosed and staged by CT; the best hope for cure is resection by a pancreaticoduodenectomy (Whipple procedure).

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CASE 28

A 27-year-old man presents to the outpatient clinic complaining of facial and hand swelling for 2 days. Additionally, he noticed that his urine appears reddish-brown and that he has had less urine output over the last several days. He has no significant medical history. His only medication is ibuprofen, which he took 2 weeks ago for fever and a sore throat that have since resolved. On examination, he is afebrile, with a heart rate of 85 beats per minute (bpm) and blood pressure of 164/98 mm Hg. He has periorbital edema; his fundoscopic examination is normal without arteriovenous nicking or papilledema. His chest is clear to auscultation, his heart rhythm is regular with a nondisplaced point of maximal impulse, and he has no abdominal masses or bruits. He has edema of his feet, hands, and face. A dipstick urinalysis in the clinic shows specific gravity of 1.025 with 3+ blood and 2+ protein, but it is otherwise negative.

- What is the most likely diagnosis?
- What is the next diagnostic step?

ANSWERS TO CASE 28:
Acute Glomerulonephritis

Summary: A 27-year-old man presents with

- Chief complaint of several days of facial and hand swelling
- Reddish-brown urine of decreased volume
- Dipstick urinalysis that shows hematuria and proteinuria
- History of fever and sore throat 2 weeks ago for which he took ibuprofen
- Hypertensive but afebrile state
- Normal fundoscopic, cardiac, pulmonary, and abdominal examinations
- Edema of the feet, hands, and face, including periorbital edema

Most likely diagnosis: Acute glomerulonephritis (GN).

Next diagnostic step: Examine a freshly spun urine specimen to look for red blood cell (RBC) casts or dysmorphic RBCs, as these are signs of inflammation if present.

ANALYSIS

Objectives

1. Be able to differentiate glomerular from nonglomerular hematuria. (EPA 2, 3)
2. Understand the clinical features of GN. (EPA 1, 3)
3. Evaluate and treat a patient with GN. (EPA 1, 4)
4. Be familiar with the evaluation of a patient with nonglomerular hematuria. (EPA 1, 7)

Considerations

A young man without a significant medical history now presents with new onset of hypertension, edema, and hematuria following an upper respiratory tract infection. He has no history of renal disease, does not have manifestations of chronic hypertension, and has not received any nephrotoxins. He does not have other symptoms of inflammatory diseases such as systemic lupus erythematosus (SLE). The presentation of acute renal failure, hypertension, edema, and hematuria in a young man with no significant medical history is highly suggestive of glomerular injury. He likely has acute GN, either postinfectious (streptococcal) or immunoglobulin (Ig) A nephropathy. The reddish-brown appearance of the urine could represent hematuria, which was later suggested by dipstick urinalysis (3+ blood); hence, microscopic examination of the urine for RBCs is very important. Together, the history and examination suggest that the patient likely has acute GN, either primary GN of unknown etiology (no concomitant systemic disease is mentioned)

Table 28–1 • SEROLOGIC MARKERS OF GLOMERULONEPHRITIS

Complement levels (C3, C4): low in complement-mediated GN (SLE, MPGN, infective endocarditis, poststreptococcal/postinfectious GN, cryoglobulin-induced GN)
Antineutrophil cytoplasmic antibody levels (MPO-ANCA and PR3-ANCA): PR3-ANCA positive in GPA (granulomatosis with polyangiitis, formerly Wegener), MPO-ANCA positive in microscopic polyangiitis and Churg-Strauss
ANA: positive in SLE (anti-dsDNA, anti-Smith)
Antiglomerular basement membrane (anti-GBM) antibody levels: positive in anti-GBM GN and Goodpasture
ASO titers: elevated in poststreptococcal GN
Blood cultures: positive in infective endocarditis
Cryoglobulin titers: positive in cryoglobulin-induced GN
Hepatitis serologies: hepatitis C and hepatitis B associated with cryo-induced GN

or secondary GN as a result of recent upper respiratory infection (postinfectious GN). The next logical step in diagnosing GN should be to examine the precipitate of a freshly spun urine sample for active sediment (cellular components, red cell casts, dysmorphic red cells). If present, these are signs of inflammation and establish the diagnosis of acute GN. Although likely to be present, these markers do not distinguish among the distinct immune-mediated causes of GN; they merely allow us to make the diagnosis of acute GN (primary or secondary). Further evaluation with serologic markers, such as complement levels and antistreptolysin-O (ASO) titers (Table 28–1), may help to further classify the GN.

APPROACH TO: Glomerulonephritis

DEFINITIONS

GROSS HEMATURIA: Blood in the urine visible to the eye.

HEMATURIA: Presence of blood in the urine.

MICROSCOPIC HEMATURIA: RBCs in the urine that require microscopy for diagnosis.

CLINICAL APPROACH

Pathophysiology

Hematuria. Direct visualization of a urine sample (gross hematuria) or dipstick examination (positive blood) can be helpful; however, the **diagnosis of hematuria is made by microscopic confirmation of the presence of red blood cells** (microscopic hematuria). The first step in evaluating a patient who complains of

Table 28–2 • COMMON CAUSES OF HEMATURIA

Intrarenal hematuria
• Kidney trauma
• Renal stones and crystals
• Glomerulonephritis
• Infection (pyelonephritis)
• Neoplasia (renal cell carcinoma)
• Vascular injury (vasculitis, renal thrombosis)
Extrarenal hematuria
• Trauma (Foley placement)
• Infections (urethritis, prostatitis, cystitis)
• Nephrolithiasis (ureteral stones)
• Neoplasia (prostate, bladder)

red-dark urine is to differentiate between true hematuria (presence of RBCs in urine) and pigmented urine (red-dark urine). The breakdown products of muscle cells and RBCs (myoglobin and hemoglobin, respectively) are heme-containing compounds capable of turning the color of urine dark red or brown in the absence of true hematuria (RBCs). **A dipstick urinalysis positive for blood without the presence of RBCs (negative microscopic cellular sediment) is suggestive of hemoglobinuria or myoglobinuria.**

After confirmation, the etiology of the hematuria should be determined. **Hematuria** can be classified into two broad categories: **intrarenal and extrarenal** (Table 28–2). The history and physical examination are very helpful in the evaluation (age, fever, pain, family history). Laboratory analysis and imaging studies often are necessary, and considering the potential clinical implications, the etiology of hematuria should be pursued in all cases. First, examination of the cellular urine sediment can help to differentiate glomerular from nonglomerular hematuria. The presence of **dysmorphic/fragmented RBCs or red cell casts** is indicative of **glomerular origin** (GN). Second, the urine Gram stain and culture can aid in the diagnosis of infectious hematuria. Third, the urine sample should be sent for cytologic evaluation when the diagnosis of malignancy is suspected. Finally, renal imaging via ultrasound or CT scan can help in the visualization of the renal parenchyma and vascular structures. Cystoscopy can be used to assess the bladder.

Differential Diagnosis for Glomerular Disease. The approach to the patient with glomerular disease should be systematic and undertaken in a stepwise fashion. The history should be approached meticulously, looking for evidence of preexisting renal disease, exposure to nephrotoxins, and especially any underlying systemic illness. Serologic markers of systemic diseases should be obtained, if indicated (Figure 28–1) in order to further classify the GN. Once the appropriate serologic tests have been reviewed, a kidney biopsy may be required. A biopsy sample can be examined under the light microscope in order to determine the primary histopathologic injury to the nephron (membranoproliferative glomerulonephritis [MPGN], crescentic GN, etc). Further examination of an immunofluorescent-stained sample for immune recognition (IgG, IgA, IgM, C3, C4, or pauci-immune staining)

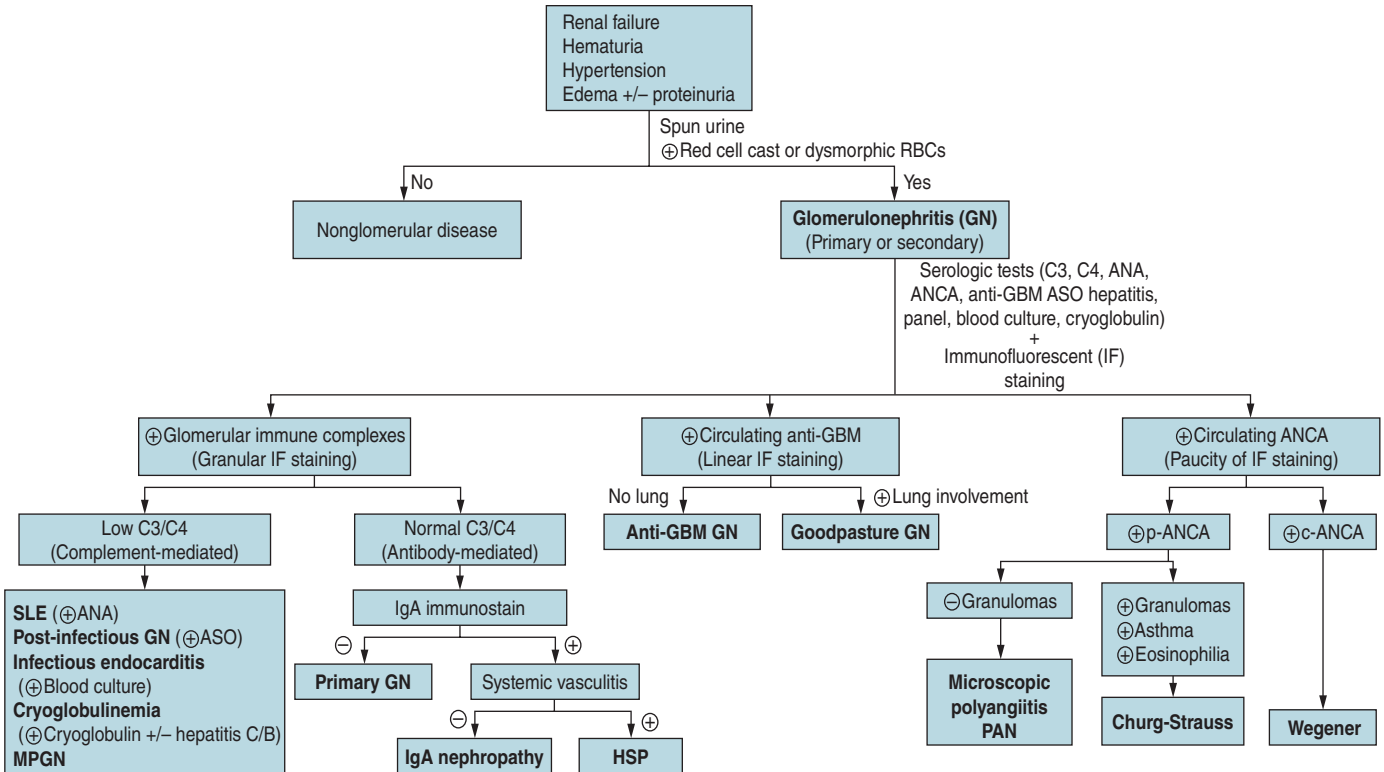


Figure 28–1. Algorithm of approach to the patient with acute glomerulonephritis. Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin-O; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; HSP, Henoch-Schönlein purpura; MPGN, membranoproliferative glomerulonephritis; MPO-ANCA, perinuclear antineutrophil cytoplasmic antibody; p-ANCA, perinuclear antineutrophil cytoplasmic antibodies; PAN, periarteritis nodosa; SLE, systemic lupus erythematosus.

of the affected glomerular membrane (capillary, epithelial, etc) and inspection under electron microscopy for characteristic patterns of immune deposition (granular, linear GN) may provide a definitive diagnosis of the immune-mediated injury to the glomeruli. Figure 28–1 shows an algorithmic approach to the patient with acute GN.

A common clinical scenario is the need to distinguish between **postinfectious (usually streptococcal) GN** and **IgA nephropathy**. Both illnesses can present with GN occurring after an upper respiratory illness. The history can sometimes provide a clue. In poststreptococcal GN (PSGN), the GN typically does not set in until several weeks after the initial infection. In contrast, IgA nephropathy may present with pharyngitis and GN at the same time. In addition, **PSGN classically presents with hypocomplementemia (predominantly low C3),** and if the patient undergoes a renal biopsy, there is evidence of an immune complex–mediated process. In contrast, **IgA nephropathy** has normal complement levels and negative ASO titer (IgA levels may be elevated in about a third of patients, but this is nonspecific), and **the renal biopsy will show mesangial IgA.**

Clinical Presentation

Glomerular disease is encountered **mainly in the form of two distinct syndromes: nephritic or nephrotic** (or sometimes an overlap of the two syndromes). **Nephritis** (nephritic syndrome) is defined as an **inflammatory** renal syndrome that presents as hematuria, edema, hypertension, and a low degree of proteinuria (< 1-2 g/d). **Nephrosis** (or nephrotic syndrome) is a **noninflammatory** (no active sediment in the urine) glomerulopathy that causes heavy proteinuria. Nephrotic syndrome is distinguished by four features: (1) edema, (2) hypoalbuminemia, (3) hyperlipidemia, and (4) proteinuria (> 3 g/d). Glomerular injury may result from a variety of insults and presents either as the sole clinical finding in a patient (primary renal disease) or as part of a complex syndrome of a systemic disorder (secondary glomerular disease). For the purpose of this discussion, GN includes only the inflammatory glomerulopathies.

Nephritic Syndrome. The presentation of acute renal failure with associated hypertension, hematuria, and edema is consistent with acute GN. Acute kidney injury, as manifested by a decrease in urine output and azotemia, results from impaired urine production and ineffective filtration of nitrogenous waste by the glomerulus. Common signs suggesting an inflammatory glomerular cause of renal failure (ie, acute GN) include hematuria (caused by ruptured capillaries in the glomerulus), proteinuria (caused by altered permeability of the capillary walls), edema (caused by salt and water retention), and hypertension (caused by fluid retention and disturbed renal homeostasis of blood pressure). The presence of this constellation of signs in a patient makes the diagnosis of GN very likely. However, it is important to note that often patients present with an overlap syndrome, sharing signs of both nephritis and nephrosis. Moreover, the presence of hematuria in itself is not pathognomonic for GN because there are multiple causes of hematuria of nonglomerular origin. Therefore, confirmation of the presumptive diagnosis of acute GN requires microscopic examination of a urine sample from the patient.

Table 28–3 • CLASSIFICATION OF GLOMERULONEPHRITIS

Primary renal disorders (based on histopathology)
Membranoproliferative glomerulonephritis (MPGN, types I and II)
Mesangioproliferative glomerulonephritis (MSGN)
Crescentic glomerulonephritis
Immune deposit (anti-GBM)
Pauci-immune (ANCA)
Fibrillary glomerulonephritis
Proliferative glomerulonephritis (IgA nephropathy)
Secondary renal disorders (based on clinical presentation)
Lupus nephritis
Postinfectious glomerulonephritis (poststreptococcal GN)
Hepatitis C/hepatitis B–related glomerulonephritis (cryo-GN)
Vasculitis-related glomerulonephritis (granulomatosis with polyangiitis, Churg-Strauss, polyarteritis nodosa, microscopic polyangiitis, Henoch-Schönlein purpura)
Infective endocarditis-related glomerulonephritis

The presence of **red cell casts** (inflammatory casts) or **dysmorphic RBCs** (caused by filtration through damaged glomeruli) in a sample of spun urine establishes the diagnosis of GN.

Once the diagnosis of acute GN is made, it can be broadly classified as either *primary* (present clinically as a renal disorder) or *secondary* (renal injury caused by a systemic disease). The specific diagnosis can usually be established by clinical history and serologic evaluation and often requires a kidney biopsy (Table 28–3).

Treatment

Treatment depends on the diagnosis of the GN, whether it is a primary renal disease or secondary to a systemic illness. When appropriate, the underlying disease should be treated (infective endocarditis, hepatitis, SLE, or vasculitis). The use of steroids and cyclophosphamide has been advocated in the treatment of GN induced by antineutrophil cytoplasmic antibody, while other antibody-mediated GNs might require plasmapheresis in order to eliminate the inciting antibody-immune complex. Treatment for PSGN is usually supportive, with control of hypertension and edema, with a very good prognosis. There is no clearly defined treatment for IgA nephropathy. However, general interventions to slow progression include blood pressure control with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, as well as corticosteroids and immunosuppressive agents to reduce underlying inflammatory disease.

CASE CORRELATION

- See also Case 29 (Nephrotic Syndrome and Diabetic Nephropathy) and Case 30 (Acute Kidney Injury).

COMPREHENSION QUESTIONS

28.1 An 18-year-old marathon runner has been training during the summer. He is brought to the emergency department disoriented after collapsing on the track. His temperature is 102 °F. A Foley catheter is placed and reveals reddish urine with 3+ blood on dipstick and no cells seen microscopically. Which of the following is the most likely explanation for his urine?

A. Underlying renal disease
B. Prerenal azotemia
C. Myoglobinuria
D. Glomerulonephritis

28.2 An 8-year-old boy is brought into the pediatrician's office for fatigue, pain of the joints, and red-brown colored urine of 2 days. On examination, the blood pressure is 140/92 mm Hg, and heart rate is 90 beats per minute. He has facial swelling and pedal edema. The heart, lung, and abdominal examinations are normal. His mother states that about 3 weeks ago he had a sore throat and fever. Which of the following laboratory findings would most likely be present?

A. Elevated serum complement levels
B. Positive antinuclear antibody titers
C. Elevated ASO titers
D. Positive blood cultures
E. Positive cryoglobulin titers

28.3 A 22-year-old man complains of acute hemoptysis over the past week. He denies smoking, fever, or preexisting lung disease. His blood pressure is 130/70 mm Hg, and his physical examination, including lung examination, is normal. His urinalysis shows microscopic hematuria and RBC casts. Which of the following is the most likely etiology?

A. Metastatic renal cell carcinoma to the lungs
B. Acute tuberculosis of the kidneys and lungs
C. Systemic lupus erythematosus
D. Goodpasture disease (antiglomerular basement membrane)

ANSWERS

28.1 **C.** This individual is suffering from heat exhaustion, which can lead to rhabdomyolysis and release of myoglobin. Myoglobinuria leads to a reddish appearance and positive urine dipstick reaction for blood, but microscopic analysis of the urine likely will demonstrate no red cells. Based on the history, this diagnosis is most likely, and the other answer choices (answer A, underlying renal disease; answer B, prerenal azotemia; and answer D, glomerulonephritis) are not as likely.

28.2 **C.** This child most likely has postinfectious GN based on the fever and pharyngitis 3 weeks previously and now with hypertension, facial and pedal edema, and hematuria. The ASO titers typically are elevated, and serum complement levels are decreased (not increased, as in answer A) in PSGN. Answer B (positive antinuclear antibody titers) would be more likely seen in a patient with lupus nephritis along with decreased complement levels (C3 and C4). Answer D (positive blood cultures) is more likely in a patient with GN secondary to endocarditis, where valvular disease would also be present. Answer E (positive cryoglobulin titers) is indicative of GN secondary to cryoglobulinemia, where the patient is also likely to test positive for hepatitis C.

28.3 **D.** Goodpasture (antiglomerular basement membrane) disease typically affects young males, who present with hemoptysis and hematuria. Antibody against type IV collagen, expressed in the pulmonary alveolar and glomerular basement membrane, leads to the pulmonary and renal manifestations. Granulomatosis with polyangiitis typically affects older adults and includes more systemic symptoms such as arthralgias, myalgias, and sinonasal symptoms; these patients are positive for ANCA. Metastatic renal cell carcinoma to the lungs (answer A) is not as likely due to the patient's young age and since he is not a smoker. Acute tuberculosis of the lungs and kidneys (answer B) is not usual, and since the patient does not have a travel history, night sweats, weight loss, or fever, this is not likely. Systemic lupus erythematosus (answer C) can cause GN (hematuria) but not hemoptysis; pleuritis is the typical pulmonary manifestation.

CLINICAL PEARLS

- Finding RBC casts or dysmorphic RBCs on urinalysis differentiates glomerular bleeding (eg, GN) from nonglomerular bleeding (eg, kidney stones).
- Glomerulonephritis is characterized by hematuria, edema, and hypertension caused by volume retention.
- Gross hematuria following an upper respiratory illness suggests either IgA nephropathy or PSGN.
- Patients with nonglomerular hematuria and no evidence of infection should undergo investigation with imaging (noncontrast helical computed tomography, ultrasound, or intravenous pyelogram) or cystoscopy to evaluate for stones or malignancy.

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CASE 29

A 58-year-old woman presents to your office complaining of persistent swelling of her feet and ankles. She first noted mild ankle swelling approximately 2 to 3 months ago. Now, she cannot put on her shoes. She borrowed a few diuretic pills from a friend and they seemed to help, but she has run out. She also reports that she gained 20 to 25 lb over the last few months, despite regular exercise and trying to adhere to a healthy diet. Her medical history is significant for a 27-year history of type 2 diabetes mellitus, for which she takes a sulfonylurea agent. However, she neither sees a doctor regularly nor monitors her blood glucose at home. She denies dysuria, increased urinary frequency, or urgency. She does report that her urine appears foamy. She denies recent fevers, joint pain, skin rashes, or gastrointestinal symptoms.

Her physical examination is significant for mild periorbital edema and pitting edema of her hands, feet, and legs. Her lungs are clear, heart rhythm is regular without murmurs, and abdominal examination is benign. She has diminished sensation to light touch in her feet and legs to midcalf. Fundoscopic examination shows multiple hard exudates with dot hemorrhages. A urine dipstick performed in the office shows 2+ glucose, 3+ protein, and negative leukocyte esterase, nitrates, and blood.

- What is the most likely diagnosis?
- What is the strongest risk factor for this condition?
- What might have prevented this condition?
- What is the best intervention to slow disease progression?

ANSWERS TO CASE 29:
Nephrotic Syndrome and Diabetic Nephropathy

Summary: A 58-year-old woman presents with

- A history of long-standing, uncontrolled type 2 diabetes mellitus
- Diabetic retinopathy and peripheral neuropathy
- Edema and significant proteinuria
- No other findings suggestive of other systemic disease

Most likely diagnosis: Nephrotic syndrome as a consequence of diabetic nephropathy.

Strongest risk factor: Long-standing diabetes without tight glycemic control.

Possible prevention: Regular visits with her primary care provider and better glycemic control with regular hemoglobin A_{1C} measurements.

Best intervention to slow disease progression: Angiotensin inhibition with either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

ANALYSIS

Objectives

1. Recognize the clinical features and complications of nephrotic syndrome. (EPA 1, 10)
2. List the most common causes of nephrotic syndrome. (EPA 2, 3)
3. Understand the natural history of diabetic renal disease and how to diagnose and manage it. (EPA 1, 4)
4. Discuss the principles of treatment of nephrotic syndrome. (EPA 4, 12)

Considerations

Patients develop significant proteinuria as a result of glomerular damage, which can result from many systemic diseases. It is important to screen for diseases such as human immunodeficiency virus (HIV), viral hepatitis, autoimmune diseases, and malignancy by history. Physical examination and laboratory investigation can usually determine the underlying cause of the renal manifestations, but sometimes kidney biopsy is required.

APPROACH TO:
Nephrotic Syndrome

DEFINITION

NEPHROTIC SYNDROME: Urine protein excretion greater than 3.5 g over 24 hours, serum hypoalbuminemia (< 3 g/dL), hyperlipidemia, and edema.

CLINICAL APPROACH

Pathophysiology

Normally, the kidneys do not excrete appreciable amounts of protein (< 150 mg/d) because serum proteins are excluded from the urine by the glomerular membrane filter due to both their large size and their net negative charge. Thus, significant proteinuria suggests glomerular disease with disruption of its normal barrier function. **Proteinuria in excess of 3 to 3.5 g of protein per day is considered to be in the nephrotic range.** The key feature of nephrotic syndrome is the heavy proteinuria, which leads to loss of albumin and other serum proteins. The hypoalbuminemia and decreased intravascular oncotic pressure lead to renal sodium and fluid retention. This results in tissue edema, which usually starts in dependent areas, such as the feet, but may involve the face, the hands, and ultimately the whole body (anasarca). Both increased synthesis and decreased clearance of lipoproteins may lead to hyperlipidemia.

Clinical Presentation

Patients typically present complaining of the edema and have the laboratory features described previously. Urinalysis usually shows few or no cellular elements (bland sediment) and may show waxy casts or oval fat bodies (which look similar to Maltese crosses under polarized light) if hyperlipidemia is present.

One-third of adult patients with nephrotic syndrome have a systemic disease that involves the kidneys, such as diabetes mellitus or systemic lupus erythematosus (SLE). The rest have a primary renal disease, with one of four pathologic lesions: minimal change disease, membranous nephropathy, focal segmental glomerulosclerosis, or membranoproliferative glomerulonephritis. Thus, **a new diagnosis of nephrotic syndrome warrants further investigation into an underlying systemic disease.** Common tests include serum glucose and glycosylated hemoglobin levels to evaluate for diabetes, antinuclear antibody to screen for SLE, serum and urine protein electrophoresis to look for multiple myeloma or amyloidosis, and viral serologies because HIV and hepatitis B or C can cause nephrosis. Less common causes include various cancers, medications such as nonsteroidal anti-inflammatory drugs, heavy metals such as mercury, and hereditary renal conditions. The most common cause of nephrotic syndrome is diabetes mellitus.

Adults with nephrotic syndrome usually undergo renal biopsy, especially if the underlying diagnosis is unclear or if there is a possibility of a treatable or reversible condition. **Patients with advanced diabetes who have heavy proteinuria and evidence of microvascular disease, such as retinopathy, and no active cellular components in their urinary sediment are generally presumed to have diabetic nephropathy.**

These patients typically do not undergo renal biopsy because the nephrotic proteinuria represents irreversible glomerular damage.

Treatment

Treatment is as follows: (1) treat the underlying disease, (2) if present, manage the edema and hypertension, and (3) limit the progression of the renal disease. For edema, all patients require strict **salt restriction**, but most patients will also need **diuretics**. Thiazide and loop diuretics are highly protein bound. Thus, in cases of nephrotic syndrome with very low serum protein levels, there is reduced delivery of these diuretics to the kidney, often creating the need for very large doses to manage the edema. **Dietary protein restriction** is usually recommended for patients with moderate proteinuria and chronic kidney disease and is thought to protect against the progression of glomerular scarring.

Tight glycemic control with a **goal hemoglobin A_{1C} less than 7%** has been shown to slow or prevent the progression of renal disease in patients with microalbuminuria. Once macroalbuminuria has developed, however, it is not clear whether improved glycemic control affects the course of renal disease. In addition, as renal function declines, insulin requirements typically fall, and some oral medications, such as sulfonylureas and metformin, can be dangerous in advanced renal insufficiency.

Strict blood pressure control with a goal less than 130/80 mm Hg in all patients with diabetes is essential to slow progression, as recommended by the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines. **Angiotensin inhibition, with either an ACE inhibitor or ARB**, has been shown to reduce the progression of renal disease independent of blood pressure control by reducing intraglomerular filtration and proteinuria. If additional blood pressure control is needed, nondihydropyridine calcium channel blockers, beta-blockers, or diuretics may be added.

In addition, because cardiovascular disease is the major cause of death of diabetics, aggressive risk factor reduction should be attempted, including smoking cessation and reduction of hypercholesterolemia. Patients with diabetes are regarded as the highest risk category and should be treated with diet and **statin agents.** Previously, expert guidelines advised a goal of low-density lipoprotein (**LDL**) **cholesterol less than 100 mg/dL**. Currently, there is debate about the use of discrete goals versus the initiation of moderate- or high-intensity statin agents for those without cardiovascular disease based on cardiovascular risk (calculator: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/). In general, diabetics aged 40 and above should receive a statin agent because of the strong evidence of cardiovascular primary prevention. If diabetic patients are known to have atherosclerotic coronary disease, they should achieve an LDL goal of less than 70 mg/dL.

Complications

Patients with nephrotic syndrome have consequences of renal protein wasting other than edema. They have **decreased levels of antithrombin III and proteins C and S** and are often **hypercoagulable.** This can lead to venous thromboembolism, including renal vein thrombosis characterized by sudden flank pain, hematuria, and increased proteinuria. Patients with evidence of thrombus formation require anticoagulation, often for life. Other complications include hypogammaglobulinemia with **increased infection risk**

(especially pneumococcal infection), iron deficiency anemia caused by hypotransferrinemia, and vitamin D deficiency because of loss of vitamin D–binding protein.

During the progression of diabetic nephropathy, the glomerular filtration rate (GFR) initially increases and then declines over time. The earliest stages of diabetic nephropathy can be detected as **microalbuminuria**. This is defined as urine albumin excretion between 30 and 300 mg/d. It is possible to measure this in a random urine sample rather than a timed collection because a ratio of albumin (in milligrams) to creatinine (in grams) of 30 to 300 usually correlates with the total excretion described. When albuminuria exceeds 300 mg/d, it is detectable on ordinary urine dipsticks (macroalbuminuria), and the patient is said to have **overt nephropathy**.

After the development of microalbuminuria, most patients will remain asymptomatic. However, the glomerulopathy will continue to progress over the subsequent 5 to 10 years until overt nephropathy develops. At this point, many patients have some edema, and nearly all patients have developed hypertension. The presence of hypertension will markedly accelerate the decline of renal function. If left untreated, patients progress to **end-stage renal disease** (**ESRD**), usually requiring dialysis or transplant within a 5- to 15-year period.

The development of nephropathy and proteinuria is significant because they are associated with a much higher risk for cardiovascular disease, which is the leading cause of death in patients with diabetes. By the time patients with diabetes develop ESRD and require dialysis, the average life expectancy is shorter than 2 years.

CASE CORRELATION

- See also Case 28 (Acute Glomerulonephritis) and Case 30 (Acute Kidney Injury).

COMPREHENSION QUESTIONS

29.1 A 49-year-old woman with type 2 diabetes presents to your office for new-onset swelling in her legs and face. She has no other medical problems. However, she says that she was told the diabetes had started to affect her eyes at her last ophthalmologic appointment. She takes glyburide daily for her diabetes. Physical examination shows a blood pressure of 140/82 mm Hg. The rest of the examination is normal except for hard exudates and dot hemorrhages on fundoscopic examination and diminished sensation up to the midshin bilaterally. Urine analysis shows 2+ protein and 2+ glucose (otherwise negative). Which of the following is the best treatment for this patient?

A. Have the patient return in 6 weeks and check a repeat urine analysis at that time.

B. Start metoprolol.

C. Change the glyburide to glipizide and have the patient return for follow-up in 6 weeks.

D. Start lisinopril.

E. Refer the patient to a cardiologist.

29.2 A 19-year-old man was seen at the university student health clinic a week ago complaining of pharyngitis and now returns because he has noted discoloration of his urine. He is noted to have elevated blood pressure (178/110 mm Hg), and urinalysis reveals red blood cell (RBC) casts, dysmorphic RBCs, and 1+ proteinuria. Which of the following is the most likely diagnosis?

A. Systemic lupus erythematosus
B. Amyloidosis
C. Postinfectious glomerulonephritis
D. HIV nephropathy
E. Diabetic nephropathy

29.3 Which of the following is the best screening test for early diabetic nephropathy?

A. Urine microalbuminuria
B. Dipstick urinalysis
C. Renal biopsy
D. Fasting blood glucose
E. Twenty-four hour urine collection for creatinine clearance

29.4 A 58-year-old Caucasian man with type 2 diabetes that is controlled with metformin is being seen in the office for follow-up. He has no known cardiac disease and denies chest pain. He has never smoked and is currently not taking aspirin. On examination, his blood pressure is 110/70 mm Hg. The remainder of the physical examination is unremarkable. Laboratory findings include a hemoglobin A_{1C} level of 6%, baseline creatinine of 1.4 mg/dL, and a fasting lipid profile of triglycerides 205 mg/dL, total cholesterol 220 mg/dL, high-density lipoprotein 35 mg/dL, and LDL 148 mg/dL. What is the most appropriate treatment?

A. Niacin
B. Low-protein diet
C. Gemfibrozil
D. Simvastatin

ANSWERS

29.1 **D.** The most significant finding in this patient is the presence of proteinuria, which is a foreboding sign of diabetic nephropathy. Starting an ACE inhibitor to decrease proteinuria is the best choice for initial treatment for this patient. Changing from one sulfonylurea to another (answer C) is of no benefit because all of the agents are essentially equally efficacious. There is no indication for referral to a cardiologist (answer E) based on the information

provided in the vignette. Returning for another urinalysis in 6 weeks (answer A) is not prudent since there is already evidence of significant proteinuria. Metoprolol (answer B) will not help with the proteinuria and can also mask the symptoms of hypoglycemia.

29.2 **C.** This patient has hypertension and urinary sediment consistent with a nephritic rather than nephrotic syndrome (RBC casts, mild degree of proteinuria). Given his recent episode of pharyngitis, the most likely cause would be postinfectious, probably due to streptococcal infection. SLE (answer A) can produce a variety of renal diseases with both nephritic and nephrotic manifestations. However, SLE would be unlikely in a male patient, especially without other clinical manifestations of lupus, such as arthritis. Amyloidosis (answer B), diabetes (answer E), and HIV (answer D) all cause renal disease, but they more commonly cause nephrotic syndrome.

29.3 **A.** Although a 24-hour urine collection for creatinine (answer E) may be useful in assessing declining GFR, it is not the best screening test for the diagnosis of early diabetic nephropathy. In the outpatient setting, a dipstick urinalysis (answer B) is readily available but will detect only patients with overt nephropathy (proteinuria > 300 mg/d). Thus, a random urinary albumin/creatinine ratio of 30/300 is the best test to screen for early diabetic nephropathy. A fasting blood glucose (answer D) may aid in the diagnosis of diabetes but not nephropathy. Finally, although most patients with nephrotic syndrome require a renal biopsy (answer C) for diagnosis, a patient with worsening renal function who has had long-standing diabetes is assumed to have renal disease secondary to diabetic nephropathy. Most of these patients do not undergo a renal biopsy.

29.4 **D.** This patient should be started on a statin agent. Patients with diabetes are considered at high risk for the development of coronary artery disease, and a statin agent should be initiated unless contraindicated. Previously, strong consideration was given for strict LDL goals such as LDL of less than 100 mg/dL for primary prevention of cardiac disease; however, the ACC currently recommends the use of a 10-year atherosclerotic cardiovascular disease (ASCVD) risk calculator and moderate-dose versus high-intensity dose statin therapy based on risk. This patient's 10-year ASCVD risk result is 15%, and the recommendation would be that a statin agent of moderate intensity be initiated. Additionally, statin agents have been shown to be effective in primary prevention of cardiovascular disease in type 2 diabetics aged 40 to 75. Answer A (niacin) has been shown to lower LDL cholesterol, but it has not been shown to reduce mortality. Answer C (gemfibrozil) is used primarily to treat a mixed dyslipidemia such as hypertriglyceridemia and high LDL; however, this agent is not as efficacious in reducing cardiovascular mortality as statin agents. Answer B (low-protein diet) is not indicated in this situation since the patient has no proteinuria and a normal serum creatinine level.

CLINICAL PEARLS

- Nephrotic syndrome is characterized by proteinuria greater than 3.5 g over 24 hours, hypoalbuminemia, and edema. Often, hypercoagulability and hyperlipidemia are present.
- Nephrotic syndrome can be a result of a primary renal disease but is often a manifestation of a systemic disease such as diabetes, viral hepatitis, HIV infection, autoimmune disease, or malignancy.
- Patients with diabetes mellitus should be screened for microalbuminuria (albumin excretion 30-300 mg/d); if present, treatment should be initiated with an ACE inhibitor or ARB even if the patient is normotensive.
- Patients with diabetic nephropathy are at a very high risk for cardiovascular disease. Aggressive risk factor reduction, such as use of statins with a goal LDL less than 100 mg/dL, is very important.

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CASE 30

A 54-year-old man with a history of type 2 diabetes mellitus and coronary artery disease is admitted to the coronary care unit with worsening angina and hypertension. His pain is controlled with intravenous nitroglycerin, and he is treated with aspirin, beta-blockers to lower his heart rate, and angiotensin-converting enzyme (ACE) inhibitors to lower his blood pressure. Cardiac enzymes are normal. He undergoes coronary angiography, which reveals no significant stenosis. By the next day, his urine output has diminished to 200 mL over 24 hours. Examination at that time reveals that he is afebrile with heart rate of 56 beats per minute (bpm) and blood pressure 109/65 mm Hg. His neck veins are flat, chest is clear, and heart rhythm is normal with an S_4 gallop and no murmur or friction rub. His abdomen is soft without masses or bruits. He has no peripheral edema or rashes, with normal pulses in all extremities. His fundoscopic examination reveals dot hemorrhages and hard exudates. Current laboratory studies include Na 140 mEq/L, K 5.3 mEq/L, Cl 104 mEq/L, CO_2 19 mEq/L, and blood urea nitrogen (BUN) 69 mg/dL. His creatinine (Cr) level has risen to 2.9 mg/dL from 1.6 mg/dL on admission.

- What is the patient's new clinical problem?
- What is the strongest risk factor for this condition?
- What might have prevented this condition?
- What is your next diagnostic step?

ANSWERS TO CASE 30:
Acute Kidney Injury

Summary: A 54-year-old man presents with

- Coronary artery disease and diabetes mellitus type 2 with retinopathy
- Angina and hypertension, for which he is receiving oral aspirin, beta-blockers, an ACE inhibitor, and nitroglycerin
- No significant stenosis upon coronary angiography using contrast dye
- Currently normotensive state with likely diabetic nephropathy
- Creatinine increased to 2.9 mg/dL from 1.6 mg/dL on admission
- Oliguria

New clinical problem: Acute kidney injury (AKI) evidenced by increased creatinine from baseline values and oliguria.

Strongest risk factor: Existing kidney disease—elevated baseline creatinine.

Possible prevention: Intravenous hydration with normal saline prior to angiography.

Next diagnostic step: Urinalysis and urine chemistries to determine whether the process is prerenal, intrinsic renal, or less likely postrenal.

ANALYSIS

Objectives

1. Identify the common causes, evaluation, and prevention of AKI in hospitalized patients. (EPA 1, 2, 3)
2. Appraise urinalysis and serum chemistry values in the diagnostic approach of AKI to be able to categorize the etiology as prerenal, renal, or postrenal. (EPA 3)
3. Discuss the management of hyperkalemia and indications for acute dialysis. (EPA 4, 9, 10)

Considerations

A 54-year-old man with diabetes, retinopathy, and some chronic kidney disease develops AKI in the hospital, as indicated by the elevated serum creatinine level of 2.9 mg/dL and BUN of 69 mg/dL. He has undergone several medical therapies and procedures, all of which might be potentially contributory: acute lowering of his blood pressure, ACE inhibitor, iodinated radiocontrast media, and arterial catheterization with possible atheroemboli. The mortality rate associated with critically ill patients who develop AKI is high; thus, identifying and treating the underlying etiology of this patient's kidney failure and taking measures to protect the kidneys from further damage are essential.

APPROACH TO:
Acute Kidney Injury

DEFINITIONS

ACUTE KIDNEY INJURY: Abrupt decline in kidney function, measured as decreased glomerular filtration rate (GFR). True GFR is difficult to measure, so we rely on increases in serum creatinine levels **or decreases in urine production** to indicate a fall in GFR.

ANURIA: Less than 50 mL of urine output in 24 hours. Acute obstruction, cortical necrosis, and vascular catastrophes, such as aortic dissection, should be considered in the differential diagnosis.

OLIGURIA: Less than 400 mL of urine output in 24 hours. Physiologically, it is the lowest amount of urine a person on a normal diet can make if he or she is severely dehydrated and does not retain uremic waste products. **Oliguria is a poor prognostic sign in AKI.** Patients with **oliguric renal failure have higher mortality rates** and worse renal recovery than patients who are nonoliguric.

UREMIA: Nonspecific symptoms of fatigue, weakness, nausea with early morning vomiting, itchiness, confusion, pericarditis, and coma attributed to the retention of waste products in renal failure but do not always correlate with the BUN level. A highly malnourished patient with renal failure may have a modestly elevated BUN and be uremic. Another patient may have a highly elevated BUN and be asymptomatic. Elevated BUN without symptoms is called **azotemia.**

CLINICAL APPROACH

Pathophysiology

The differential diagnosis of AKI proceeds from consideration of three basic pathophysiologic mechanisms: **prerenal failure, postrenal failure, and intrinsic renal failure.**

Individuals with **prerenal failure** experience diminished GFR as a result of a marked **decreased renal blood perfusion** so that less glomerular filtrate is formed. Sometimes, the clinical presentation is straightforward, such as volume depletion from gastrointestinal fluid loss or hemorrhage; other times, the presentation of patients with prerenal failure can be more confusing. For example, a patient with severe nephrotic syndrome may appear to be volume overloaded because of the massive peripheral edema present; however, the effective arterial blood volume is very low as a consequence of severe hypoalbuminemia, resulting in a prerenal AKI. Similarly, a patient with severe congestive heart failure may have prerenal failure because of a low cardiac ejection fraction, yet at the same time be fluid overloaded with peripheral and pulmonary edema. **The key is to assess "what the kidneys see" versus the remainder of the body.** Typically, the BUN:Cr ratio is greater than 20 in prerenal failure. Medications such as aspirin, nonsteroidal anti-inflammatory drugs, and ACE inhibitors can alter intrarenal blood flow and

Table 30–1 • CAUSES OF PRERENAL ACUTE KIDNEY INJURY

True volume depletion • Gastrointestinal losses • Renal losses (diuretics, diabetes insipidus)
Reduced effective arterial blood volume • Nephrotic syndrome • Cirrhosis with portal hypertension • Severe burns • Sepsis • SIRS
Medications • ACE inhibitors • NSAIDs
Decreased cardiac output • Congestive heart failure • Pericardial tamponade

Abbreviations: ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug ; SIRS, Systemic inflammatory response syndrome.

result in prerenal failure. Table 30–1 provides an abbreviated listing of the etiologies of prerenal failure.

Postrenal failure, also referred to as obstructive nephropathy, implies **blockage of urinary flow**. The site of obstruction can be anywhere along the urinary system, including the intratubular region (crystals), ureters (stones, extrinsic compression by tumor), bladder, or urethra. By far, the most common causes of obstructive nephropathy are ureteral obstruction due to malignancy or urethral obstruction due to benign or malignant prostatic hypertrophy. The patient's symptoms depend on whether or not both kidneys are involved, the degree of obstruction, and the time course of the blockage. This is usually diagnosed by observing **hydronephrosis or bladder distension on ultrasound**.

Intrinsic renal failure is caused by disorders that injure the renal glomeruli or tubules directly. These include glomerulonephritis, tubulointerstitial nephritis, and acute tubular necrosis (ATN) from ischemia, sepsis, or nephrotoxic agents. Table 30–2 lists major causes of intrinsic AKI.

Clinical Presentation

A thorough history and physical examination are important. Questions that are important to ask include

- Does the patient have signs or symptoms of a systemic disease, such as heart failure or cirrhosis, that could cause prerenal failure?
- Does the patient have symptoms of a disease, such as lupus, that could cause a glomerulonephritis?
- Did the patient receive something in the hospital that could cause ATN, such as intravenous contrast or an aminoglycoside?

Table 30–2 • CAUSES OF INTRINSIC ACUTE KIDNEY INJURY

Acute tubular necrosis
- Nephrotoxic agents
  - Aminoglycosides
  - Radiocontrast
  - Chemotherapy
- Sepsis
- Ischemia
  - Hypotension
  - Vascular catastrophe

Glomerulonephritis
- Postinfectious
- Vasculitis
- Immune complex diseases (lupus, MPGN [mesangioproliferative glomerulonephritis], cryoglobulinemia)
- Cholesterol emboli syndrome
- Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura

Tubulointerstitial nephritis
- Medications (cephalosporins, methicillin, rifampin)
- Infection (pyelonephritis, HIV)

- Did the patient present with severe infection and systemic inflammatory response syndrome that could lead to septic ATN?
- While in the operating room, did the patient become hypotensive from hemorrhage causing ischemic ATN?
- Is the patient receiving an antibiotic causing allergic interstitial nephritis?

In addition to the history and physical examination, **urinalysis and measurement of urinary electrolytes** are helpful in making the diagnosis.

Urinalysis. The urine findings based on testing with reagent paper and microscopic examination help with the diagnosis of AKI (Table 30–3). In **prerenal failure**, urinalysis usually reveals a **high specific gravity** and **normal microscopic findings.** Individuals with **postrenal failure** are typically **unable to concentrate the urine**, so the urine osmolality is equal to the serum osmolality (**isosthenuria**), and the **specific gravity is 1.010.** The **microscopic findings vary** depending on the cause of the obstruction: hematuria (crystals or stones), leukocytes (prostatic hypertrophy), or normal (extrinsic ureteral compression from a tumor). Urinalysis of various intrinsic renal disorders may be helpful. **Ischemic, septic, and nephrotoxic ATN** are usually associated with urine that is **isosthenuric**, often with **proteinuria**, and containing **"muddy brown" granular casts** on microscopy. In **glomerulonephritis**, the urine generally reveals moderate-to-severe **proteinuria**, sometimes in the nephrotic range, and **microscopic hematuria and red blood cell casts. Tubulointerstitial nephritis** classically produces urine that is **isosthenuric** (the tubules are unable to concentrate the urine) with **mild proteinuria.** On microscopy, it usually reveals **leukocytes, white cell casts, and sometimes urinary eosinophils.**

Table 30–3 • EVALUATION OF ACUTE RENAL FAILURE

Etiology of Renal Failure	Urinalysis	FE_{Na}	U_{Na}
Prerenal failure	Concentrated (high specific gravity) with normal sediment	< 1%	< 20 mEq/L
Acute tubular necrosis	Isosthenuric with muddy brown granular casts	> 1%	> 20 mEq/L
Glomerulonephritis	Moderate-to-severe proteinuria with red blood cells and red blood cell casts	< 1%	Variable
Interstitial nephritis	Mild-to-moderate proteinuria with red and white blood cells and white blood cell casts	> 1%	> 20 mEq/L
Postrenal failure	Variable depending on cause	< 1% (early) > 1% (later)	< 20 mEq/L (early) > 20 mEq/L (later)

Abbreviations: FENa, fractional excretion of sodium; U_{Na}, urinary concentration of sodium.
NOTE: Though it remains widely used, the reliability of FENa to assess renal failure is poor since its conclusions arise from a very small study. It is important to highlight that, if there is suspicion for hypovolemia, rather than measuring FENa, it is more practical to assess the patient's response to fluid resuscitation.

Urinary Electrolytes. Calculation of the fractional excretion of sodium (FE_{Na}) was devised to differentiate oliguric prerenal failure from oliguric ATN; it is of little use in other circumstances. FE_{Na} represents the amount of sodium filtered by the kidneys that is not reabsorbed. The **kidneys of a healthy person on a normal diet** typically reabsorb more than 99% of the sodium that is filtered, with a corresponding **FE_{Na} less than 1%**. Normally, the excreted sodium represents the dietary intake of sodium as a result of the maintenance of sodium homeostasis. In prerenal failure, decreased renal perfusion leads to a diminished GFR; if the renal tubular function is intact, FE_{Na} remains less than 1%. Furthermore, because the patient has either true volume depletion or "effective" volume depletion, serum aldosterone will stimulate the kidneys to retain sodium, and the urinary sodium will be low (< 20 mEq/L). On the other hand, in oliguric ATN, the renal failure is caused by tubular injury. Hence, there is **tubular dysfunction** with an associated **inability to reabsorb sodium**, leading to a FE_{Na} greater than **2%** and a **urinary sodium** exceeding **20 mEq/L**.

Measurements of FE_{Na} and urinary sodium are less helpful in other circumstances. For example, in nonoliguric ATN, the injury is usually less severe, so the kidneys may maintain normal sodium reabsorption and a FE_{Na} less than 1%. Diuretic medications, which interfere with sodium reabsorption, are often used for congestive heart failure or nephrotic syndrome. Although these patients may have prerenal failure, the use of diuretics will increase the urinary sodium and FE_{Na}. In acute glomerulonephritis, the kidneys often avidly resorb sodium, leading to very low urinary sodium levels and FE_{Na}. Early in the course of postobstructive

renal failure caused by ureteral obstruction, the afferent arteriole typically undergoes intense vasoconstriction, with consequent low urinary sodium levels (Table 30–3).

Treatment

AKI is managed by identifying and reversing the underlying cause. Intravenous isotonic fluids are a mainstay of treatment for any prerenal AKI caused by true volume depletion. Diuretics, on the other hand, would be used to treat prerenal AKI in the setting of venous congestion in heart failure. Other common interventions include removing nephrotoxic medications, optimizing blood pressure and electrolytes, and administering diuretics. If the AKI is severe, the patient may require **urgent hemodialysis.**

The **indications for dialysis** in AKI include **fluid overload (such as pulmonary edema), metabolic acidosis, hyperkalemia, uremic pericarditis, severe hyperphosphatemia, and uremic symptoms** refractory to medical treatment. Because of the risk of fatal cardiac arrhythmias, severe hyperkalemia is considered an emergency best treated acutely medically, not with dialysis.

An urgent electrocardiogram should be performed on any patient with suspected hyperkalemia. If the classic **peaked or "tented" T waves** are present, intravenous calcium should be administered immediately. Although it will not lower the serum potassium level, the calcium will oppose the membrane effects of the high potassium concentration on the heart, allowing time for other interventions to lower the potassium level. One of the most effective methods for treating hyperkalemia is administration of intravenous insulin (usually 10 units), along with 50 to 100 mL of 50% glucose solution to prevent hypoglycemia. Insulin drives potassium into cells, lowering levels within 30 minutes. Potassium can also be driven intracellularly with a beta-agonist nebulizer, such as albuterol. In the presence of a severe metabolic acidosis, administration of intravenous sodium bicarbonate also promotes an intracellular shift of potassium, albeit less effectively. All three therapies have only a transient effect of lowering serum potassium levels because the total body potassium balance is unchanged, and the potassium eventually leaks back out of the cells. Definitive treatment of hyperkalemia, removal of potassium from the body, is accomplished by one of three methods: (1) administration of a loop diuretic (eg, furosemide) to increase urinary flow and excretion of potassium; (2) administration of potassium-binding cationic exchange resin (eg, sodium polystyrene sulfonate, patiromer, or sodium zirconium cyclosilicate) to prevent gastrointestinal absorption of potassium; or, finally, (3) dialysis.

Dose adjustment of medications that are excreted through the kidneys is necessary to prevent dose-related toxicity, even if the toxicity affects other organs.

CASE CORRELATION

- See also Case 28 (Acute Glomerulonephritis) and Case 29 (Nephrotic Syndrome and Diabetic Nephropathy).

COMPREHENSION QUESTIONS

30.1 A 63-year-old woman with a history of cervical cancer treated with a hysterectomy and pelvic irradiation now presents with acute oliguric renal failure. On physical examination, she has normal jugular venous pressure, is normotensive without orthostasis, and has a benign abdominal examination. Her urinalysis shows a specific gravity of 1.010, with no cells or casts on microscopy. Urinary FE_{Na} is 2%, and the Na level is 35 mEq/L. Which of the following is the best next step?

A. Bolus of intravenous fluids

B. Renal ultrasound

C. Computed tomographic scan of the abdomen with intravenous contrast

D. Administration of furosemide to increase her urine output

30.2 A 49-year-old man with a long-standing history of chronic renal failure as a consequence of diabetic nephropathy is brought to the emergency room for nausea, lethargy, and confusion. His physical examination is significant for an elevated jugular venous pressure, clear lung fields, and harsh systolic and diastolic sounds heard over the precordium. Serum chemistries reveal K 5.1 mEq/L, CO_2 17 mEq/L, BUN 145 mg/dL, and creatinine 9.8 mg/dL. Which of the following is the most appropriate next step in therapy?

A. Administer intravenous insulin and glucose

B. Administer intravenous sodium bicarbonate

C. Administer intravenous furosemide

D. Begin hemodialysis urgently

30.3 A 62-year-old diabetic man underwent an abdominal aortic aneurysm repair 2 days ago. He is being treated with gentamicin for a urinary tract infection. His urine output has fallen to 300 mL over 24 hours, and his serum creatinine has risen from 1.1 mg/dL on admission to 1.9 mg/dL. Which of the following laboratory values would be most consistent with a prerenal etiology of his renal insufficiency?

A. FE_{Na} of 3%

B. Urinary sodium level of 10 mEq/L

C. Central venous pressure reading of 10 mm Hg

D. Gentamicin trough level of 4 μg/mL

ANSWERS

30.1 **B.** Renal ultrasound is the next appropriate step to assess for hydronephrosis and to evaluate for bilateral ureteral obstructions, which are common sites of metastases of cervical cancer. Her physical examination and urine studies (showing a FE > 1%) are inconsistent with hypovolemia, so intravenous infusion (answer A) is unlikely to improve her renal function. Use of loop diuretics (answer D) may increase her urine output somewhat but does not help to diagnose the cause of her renal failure or to improve her outcome. Further imaging (answer C) may be necessary after the ultrasound, but use of intravenous contrast at this point may actually worsen her renal failure.

30.2 **D.** The patient has uremia, hyperkalemia, and (likely) uremic pericarditis (harsh systolic and diastolic sounds of friction rub), which may progress to life-threatening cardiac tamponade unless the underlying renal failure is treated with dialysis. If the threat of tamponade is significant, pericardiocentesis may need to be performed prior to dialysis. As for the other treatments, insulin plus glucose (answer A) would treat hyperkalemia, and bicarbonate (answer B) would help with both metabolic acidosis and hyperkalemia, but this patient's potassium and bicarbonate levels are only mildly abnormal and are not immediately life threatening. Furosemide (answer C) will not help because the patient does not have pulmonary edema; additionally, due to the renal insufficiency, the furosemide likely would not lead to much potassium excretion.

30.3 **B.** This elderly man has findings of renal insufficiency with two possible causes: prerenal due to volume depletion and acute kidney injury due to gentamicin/hypotension. The patient's urinary sodium of 10 mEq/L points to a prerenal cause. Prerenal insufficiency connotes insufficient blood volume, typically with FE_{Na} less than 1% (not answer A, 3%) and urinary sodium less than 20 mEq/L. Supporting data would include a low central venous pressure reading (normal central venous pressure is 4-8 mm Hg), not an elevated reading of 10 mm Hg (answer C). The gentamicin level of 4 μg/mL is elevated (normal < 2 μg/mL) and may predispose to kidney damage, but intrarenally, thus ruling out answer D.

CLINICAL PEARLS

- The two main causes of AKI in hospitalized patients are prerenal azotemia from volume depletion and ATN.
- In the acutely anuric patient, one must quickly determine if the kidneys are obstructed or if the vascular supply is interrupted.
- Treatment of prerenal failure is volume replacement unless the cause is severe systolic heart failure; treatment of postrenal failure is relief of the obstruction.
- The main causes of postrenal failure are obstruction caused by prostatic hypertrophy in men and bilateral ureteral obstruction caused by abdominal or pelvic malignancy in either gender.
- Uremic pericarditis is an indication for urgent hemodialysis. Other indications include hyperkalemia, metabolic acidosis, severe hyperphosphatemia, and volume overload when refractory to medical management.
- Treatment of hyperkalemia can be remembered by the mnemonic **C BIG K** (calcium, bicarbonate/beta-agonist, insulin, glucose, Kayexalate [polystyrene sulfonate]).
- Hyperkalemia is treated initially with calcium to stabilize cardiac membranes (if there are electrocardiographic abnormalities); insulin and beta-agonists to redistribute potassium intracellularly (sodium bicarbonate if there is a severe metabolic acidosis); and then loop diuretics, a potassium exchange resin, or hemodialysis to remove excess potassium from the body.
- Indications for dialysis can be remembered by the mnemonic **AEIOU** (acidosis, electrolyte disturbances, ingestions of toxins, overload, uremia).

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CASE 31

A 56-year-old woman presents to the office complaining of gradually progressive, nonpainful enlargement of the terminal joint on her left hand over a 9-month period. She has some stiffness with typing, usually in the afternoons. She also reports pain in her right knee, which occasionally "locks up." The right knee hurts more after long walks. On examination, her blood pressure is 130/85 mm Hg, heart rate is 80 beats per minute (bpm), height is 5'8", and weight is 285 lb with a body mass index (BMI) of 43.3 kg/m^2. Examination reveals only a nontender enlargement of her left distal interphalangeal (DIP) joint, and the right knee is noted to have crepitus and slightly decreased range of motion (ROM). Those joints were not red or swollen.

- What is your next step?
- What is the most likely diagnosis?
- What is the best initial treatment?
- What are the most important risk factors for this condition?
- What is the most effective way to prevent this condition?

ANSWERS TO CASE 31:
Osteoarthritis/Degenerative Joint Disease

Summary: A 56-year-old woman presents with

- Normal vital signs
- Obesity
- Joint pain in the left DIP and right knee that worsens with activity
- Crepitus and slightly decreased ROM of the right knee
- No synovitis on examination

Next step: Obtain erythrocyte sedimentation rate (ESR) and plain x-rays of the hand and knee.

Most likely diagnosis: Osteoarthritis (OA), because the patient is obese and has pain that worsens with activity.

Best initial treatment: Nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen for pain management.

Risk factors: Obesity, repeated trauma.

Prevention: Weight loss, regular exercise.

ANALYSIS

Objectives

1. Identify the major clinical characteristics of OA. (EPA 1, 2)
2. Describe the management of OA. (EPA 4)
3. Understand the major classes of medications used for OA. (EPA 4)
4. Differentiate OA from inflammatory arthritis. (EPA 1, 2)

Considerations

This patient's history and examination are characteristic of OA. Laboratory work, typically negative for inflammatory arthritis, and x-rays would support the diagnosis, mostly by making other diagnoses less likely. The most important features are the gradual onset, the lack of active synovitis, and the fact that her symptoms worsen with activity. If there were evidence of inflammation or joint effusion, then the best next step would be to aspirate the fluid from the joint and send it for various studies, including Gram stain and culture to assess for infection, crystal analysis to assess for gout or pseudogout, and cell count to assess for inflammation.

APPROACH TO: Osteoarthritis

DEFINITIONS

BOUCHARD NODES: Bony enlargement of proximal interphalangeal (PIP) joints, often asymptomatic.

CREPITUS: A creaking or hook-and-loop (Velcro)–like sound made by a joint in motion, typically not painful.

HEBERDEN NODES: Bony enlargement of DIP joints, often asymptomatic.

SYNOVITIS: Inflammation of the joint space characterized by redness, swelling, and tenderness to touch.

CLINICAL APPROACH

Pathophysiology

OA is the most common joint disease in adults. It is uncommon before age 40 but highly prevalent after age 60. The disease affects women more often than men. OA begins insidiously, progresses slowly, and eventually may lead to disability, recurrent falls, inability to live independently, and significant morbidity.

It is **critical to differentiate OA from other conditions that may present similarly since treatment is different.** Periarticular pain that is not reproduced with passive motion suggests bursitis or tendonitis. Prolonged pain lasting for more than 1 hour after awakening points toward an inflammatory arthritis. Intense inflammation suggests one of the microcrystalline diseases (gout/pseudogout) or infectious arthritis. Systemic constitutional symptoms, such as weight loss, fatigue, fever, anorexia, and malaise, indicate an underlying inflammatory condition and generally demand aggressive evaluation; these underlying conditions include polymyalgia rheumatica, rheumatoid arthritis (RA), systemic lupus erythematosus, and malignancy.

Clinical Presentation

Patients with **OA** often experience **joint stiffness, which occurs with activity** or after inactivity ("gel phenomena") and lasts for less than 15 to 30 minutes. This is in contrast to the morning stiffness of patients with an inflammatory arthritis, such as RA, which often lasts for 1 to 2 hours in the morning, upon wakening, and often requires warming, such as soaking in a hot tub, to improve. In early OA, there are no obvious findings. The knees and hips are the most commonly affected joints, followed by the hand and finger joints.

There may be some **crepitus** in the joint. Unlike in inflammatory arthritis, there is often no or minimal tissue swelling (except in the most advanced disease). Bony prominences, especially in the DIP/PIP joints, can occur later. Hard or bony swelling in the DIP joints are called Heberden nodes, whereas those affecting the PIP joints are called Bouchard nodes. Figure 31–1 shows a typical joint involvement in

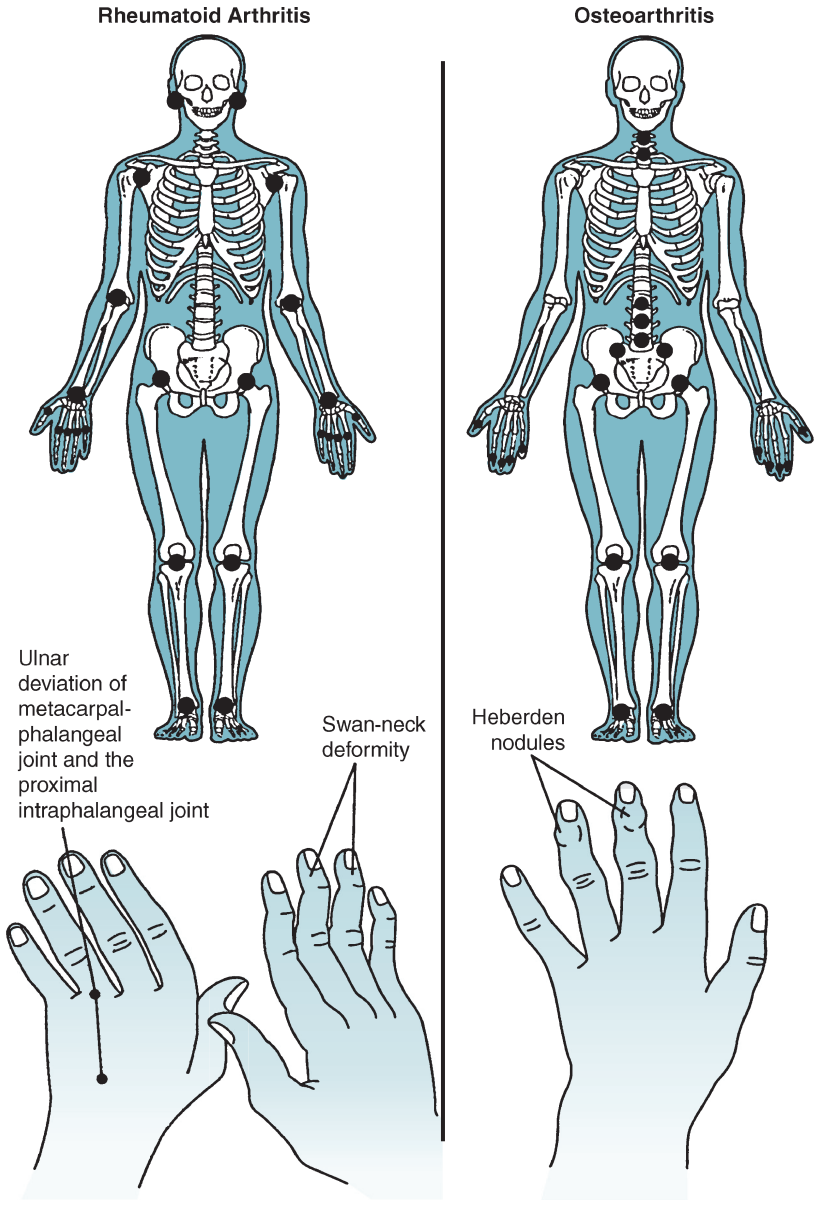


Figure 31–1. Joint involvement in rheumatoid arthritis (left) and osteoarthritis (right).

OA versus RA. Pain seen in OA typically can be reproduced with passive motion of the joint.

Labs/Imaging. Laboratory examination typically is unremarkable; inflammatory markers such as ESR, C-reactive protein, and white blood cells (WBCs) all are normal. Likewise, autoimmune studies such as antinuclear antibody (ANA),

rheumatoid factor, and complement levels also are normal. If the joint is aspirated, examination of the synovial fluid also reflects a lack of inflammation: WBCs less than 2000/mm^3, protein lower than 45 mg/dL, absence of crystals, and glucose equal to that in the serum. X-ray evaluation in OA **may show osteophytes, which are the most specific finding of this disease.** However, osteophytes **may not be present in early stages** of OA. Other characteristics seen on x-rays include joint space narrowing, subchondral sclerosis, and subchondral cysts.

Treatment

Education is critical. Encourage the patient to stay active because not using the joint can cause further immobility. Multiple short periods of rest throughout the day are better than one large period. In patients with OA who are overweight, **weight loss** of even modest degree may produce improvement in lower extremity joint pain and function. Other methods of unloading an osteoarthritic joint include canes and walkers, which can reduce joint forces at the hip by as much as 50% and are helpful in reducing the frequency of falls. Physical therapy in the form of heat applied to the affected joints in early disease is often helpful. Moist superficial heat can raise the threshold for pain, produce analgesia by acting on free nerve endings, and decrease muscle spasm.

Perhaps the most important intervention is having the patient **maintain full/near-full ROM with regular exercise.** Physical therapy and exercise improve functional outcome and pain in OA by improving flexibility and by strengthening muscles that support the affected joints.

Nonpharmacologic interventions should be tried first for pain management, for functional capacity, and for slowing the process of joint damage. Pharmacologic interventions should then be added for patients with inadequate symptom relief to further decrease the pain burden. The standard of care involves starting with oral or topical NSAIDs. NSAID use is contraindicated in patients with a history of peptic ulcers, cardiovascular disease (stroke, myocardial infarction), uncontrolled hypertension, kidney disease, or women in their third trimester of pregnancy due to premature closure of the patent ductus arteriosus. NSAIDs have a higher risk of gastrointestinal irritation and bleeding, and both NSAIDs and cyclooxygenase 2 (COX-2) inhibitors are associated with increased risk of adverse cardiovascular effects. Because of these risks, NSAIDs or COX-2 inhibitors should be used in the lowest dose necessary and for the shortest period in order to achieve symptom control. Nevertheless, **NSAIDs are superior to acetaminophen** in controlling pain among patients with OA.

Topical medications such as diclofenac, lidocaine, or capsaicin may be considered in patients who cannot tolerate oral NSAIDs or for those at higher risk for adverse effects (eg, patients over 75 years or those with significant cardiovascular disease). Duloxetine, a serotonin and norepinephrine reuptake inhibitor, has also been approved for knee OA.

The use of glucosamine and chondroitin for OA has been controversial, and results of randomized trials have varied. Though these medications appear to be safe, most studies suggest that glucosamine and chondroitin have little benefit in patients with OA.

Oral steroids are generally **not** used to treat OA. Intra-articular steroids are used for patients seeking short-term pain relief for moderate-to-severe pain flare-ups but are not useful for long-term treatment due to their relatively short duration of action (up to 6 weeks) and the possibility that long-term use may increase the rate of cartilage loss.

Surgery is reserved for only the most severe cases, which include patients who have major instability, a loose body in the joint (known as a joint mouse), intractable pain of advanced disease, or severe functional limitation. Arthroscopic debridement is widely used for those with symptomatic OA of the knee, especially with a meniscal tear, but clinical benefit is not supported by randomized clinical trials. Total joint arthroplasty (eg, knee replacement) is recommended for patients with severe symptomatic OA who fail to respond to optimal nonpharmacologic and medical therapy and for whom OA causes significant impairment in quality of life.

CASE CORRELATION

- See also Case 32 (Low Back Pain), Case 33 (Acute Monoarticular Arthritis—Gout), and Case 34 (Rheumatoid Arthritis).

COMPREHENSION QUESTIONS

31.1 A 62-year-old woman presents to the office with severe knee pain that has been progressing over the past 5 years. The patient states that the current medications are ineffective. The provider has diagnosed the condition as advanced OA. Assuming that the diagnosis is correct, which of the following is most likely to be found in this patient?

A. Disability with recurrent falls and inability to live alone
B. Joints with redness and effusion
C. Best treated with oral steroids
D. Improvement throughout the day after approximately 1 to 2 hours of "unfreezing the joint"

31.2 A 72-year-old man with history of uncontrolled hypertension complains of painful joints in his hips and knees and the hands. Examination of the knees reveals pain with palpation and some crepitus upon movement, but no effusion or redness. The DIP and PIP joints are mainly affected in the hands; they similarly do not demonstrate effusion. Which of the following is the best initial treatment for this patient?

A. Naproxen sodium
B. Celecoxib
C. Oral prednisone
D. Intra-articular prednisone
E. Acetaminophen

Match the following disease processes (A-F) to the clinical setting described in Questions **31.3** to **31.6**.

A. Gonococcal arthritis
B. Gout
C. Pseudogout
D. Osteoarthritis
E. Rheumatoid arthritis
F. Systemic lupus erythematosus

31.3 Symmetric bilateral ulnar deviation of both hands in a 42-year-old woman

31.4 Painful, swollen metatarsophalangeal great toe (unilateral) with redness and warmth after eating a steak and shrimp dinner in a 45-year-old man

31.5 Acute onset of unilateral elbow swelling, warmth, and tenderness and cervical discharge in a 25-year-old woman

31.6 Unilateral nontender bony enlargement of the first DIP and activity-related right hip pain in a 68-year-old woman

ANSWERS

31.1 **A.** This patient is presumed to have advanced OA. OA is a major cause of decreased functional status in elderly patients and requires ongoing treatment and evaluation by the clinician to try to improve symptoms and to promote mobility. Steroids are not a treatment of OA since it is not an inflammatory condition. Improvement with oral steroids (answer C) and activity throughout the day (answer D) are more characteristic of RA. Joints that exhibit redness and effusion (answer B) are more likely due to crystalline or septic arthritis.

31.2 **E.** Based on this patient having noninflamed joints and with the DIP and PIP joints of the hands affected, the most likely diagnosis is OA. RA would affect the knees and hips also, but usually with inflammation and effusion; in the hands, RA classically affects the metacarpophalangeal (MP) and PIP joints of the hands. Acetaminophen is the first agent of choice in the treatment of early OA. NSAIDs are superior in the treatment of OA; however, given this patient's comorbidity of cardiovascular disease, NSAIDs (answers A and B) are relatively contraindicated. This is because of the association between NSAIDs and cardiovascular and renal disease. Thus, acetaminophen or topical NSAIDs would be better. Because this patient has a noninflammatory condition, neither oral nor intra-articular steroids are indicated (answers C and D).

31.3 **E.** Rheumatoid arthritis gives the ulnar deviation of the fingers by affecting the MP joints (in fact, one of the hallmarks of the disease). Other deformities associated with RA include the swan neck (MP flexion with PIP hyperextension and DIP flexion) and boutonniere (PIP flexion, DIP hyperextension) deformities.

CLINICAL PEARLS

- Osteoarthritis is the most common articular disease of adults, most often affecting the DIP joints, PIP joints, knees, hip joints, and cervical and lumbar spine.
- The pathophysiology of OA is a "wear and tear" of the joint, leading to intra-articular cartilage erosion and decreased joint space on radiograph.
- Pain in OA is worsened with activity and is not associated with morning stiffness.
- Current pharmacologic agents do not modify or stop disease progression. Treatment is aimed at symptom relief.
- Initial pharmacologic therapy should be NSAIDs, unless a contraindication, such as cardiovascular disease, gastric ulcers, or chronic kidney disease, is present.
- Joint replacement for severe OA is reserved for patients with intractable pain despite medical therapy and for those with severe functional limitations.

31.4 **B.** Gouty arthritis often affects the first metatarsophalangeal joint of the feet and can be precipitated by alcohol or foods high in nucleic acids, like meats. There is often a familial predisposition. Uric acid crystals form in the joints and cause a severe inflammatory condition, redness, and pain.

31.5 **A.** Cervical discharge and inflammatory joint are consistent with gonococcal arthritis, which can also present as a migratory arthritis of large joints; this is an inflammatory condition with redness, pain, fever, and effusion.

31.6 **D.** The location and asymmetry of joint involvement, lack of inflammatory signs, and worsening with exertion all are characteristic of OA. RA is typically symmetric.

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CASE 32

A 45-year-old woman presents with low back pain and requests an x-ray. She states she works cleaning homes and has had this pain off and on for several years; however, for the past 2 days it is worse than it has ever been. It started after she vigorously vacuumed a rug; the pain is primarily on the right lower side, radiates down her posterior right thigh to her knee, but is not associated with any numbness or tingling. It is relieved by lying flat on her back with her legs slightly elevated and lessened somewhat when she takes ibuprofen 400 mg. Upon examination, she is a well-appearing, moderately obese woman. She has difficulty maneuvering onto the examination table because of pain; the rest of her examination is fairly normal. The only abnormality you note is a positive straight leg raise test, with raising the right leg eliciting more pain than the left. Her strength, sensation, and deep tendon reflexes in all extremities are normal.

- What is the most likely diagnosis?
- What is your next step in management?

ANSWERS TO CASE 32:
Low Back Pain

Summary: A 45-year-old woman presents with

- Acute worsening of chronic low back pain
- Pain radiating down her right leg
- Positive straight leg raise test, with raising the right leg eliciting more pain than the left
- Obesity
- Normal physical examination

Most likely diagnosis: Musculoskeletal low back pain, possible sciatica without neurologic deficits.

Next step: Encourage continuation of usual activity, avoiding twisting motions or heavy lifting. Using nonsteroidal anti-inflammatory drugs (NSAIDs) on a scheduled basis is helpful; you can also recommend muscle relaxants, although these drugs may cause sleepiness. Massage or physical therapy might be helpful. Follow up in 4 weeks. Long-term advice includes weight loss and back-strengthening exercises.

ANALYSIS

Objectives

1. Describe the history and physical examination findings that help to distinguish benign musculoskeletal low back pain from more serious causes of low back pain. (EPA 1, 2)
2. List the treatment options and their effectiveness in low back pain. (EPA 4)
3. Describe the indications for laboratory and imaging tests in evaluating low back pain. (EPA 3)

Considerations

This 45-year-old patient with chronic back pain has an acute exacerbation with pain radiating down her leg, which may indicate possible sciatic nerve compression. She has no other neurologic abnormalities, such as sensory deficits, motor weakness, or "red flag" symptoms of more serious etiologies of back pain, which if present would demand a more urgent evaluation. Thus, this individual has a good prognosis for recovery with conservative therapy, perhaps with time being the most important factor. If she does not improve after 4 to 6 weeks, imaging studies can be considered.

APPROACH TO:
Low Back Pain

DEFINITIONS

CAUDA EQUINA SYNDROME: Lower back pain, saddle anesthesia, and bowel or bladder dysfunction with possible lower extremity weakness and loss of reflexes caused by compression of multiple sacral nerve roots. Cauda equina syndrome is a surgical emergency.

HERNIATED DISK (NUCLEUS PULPOSUS): Condition in which the annulus fibrosus (outer layer) of the vertebral disk is torn, which allows the nucleus portion to herniate and compress the nerve fibers adjacent, leading to paresthesia, dysesthesia, and sometimes weakness.

SCIATICA: Pain in the distribution of the sciatic nerve, made up by the roots of the lumbar nerves L4 and L5, and the sacral nerves S1, S2, and S3; it can present with or without motor or sensory deficits.

SPINAL STENOSIS: Narrowing of the spinal canal, nerve root, or intervertebral foramina due to spondylosis and degenerative disk disease. Symptoms include back pain with numbness or tingling of the legs, which increases with activity and is better with sitting, lying down, or leaning forward.

SPONDYLOLISTHESIS: Anterior displacement of a vertebra on the one beneath it, which can cause symptoms and signs of spinal stenosis.

SPONDYLOSIS: Osteoarthritic spine disease, typically affecting cervical and lumbosacral spine, seen radiographically as disk space narrowing and arthritic changes of the facet joints.

CLINICAL APPROACH

Epidemiology

Low back pain is experienced by two-thirds of all adults at some point in their lives. There are approximately 20 million annual ambulatory visits because of low back pain. This complaint is most common in adults in their working years, usually affecting patients between 30 and 60 years, with a prevalence of 80%. Although it is common in workers required to perform lifting and twisting, it is also a common complaint in those who sit or stand for prolonged periods. Low back pain is a recurrent symptom that tends to be mild in younger patients, often resolving within 2 weeks, but it can be more severe and prolonged as the patient ages. It is one of the most common reasons for young adults to seek medical care, second only to upper respiratory infections, and millions of health care dollars are expended on this problem each year.

Pathophysiology

In evaluating patients with low back pain, the clinician needs to exclude potentially serious conditions, such as **malignancy, infection, inflammatory back pain**

Table 32–1 • CAUSES OF LOWER BACK PAIN

Structural	• Mechanical or nonspecific (90% of cases) • Facet joint arthritis • Prolapsed disk • Annular tear • Spondylosis • Spinal stenosis (3%)
Infectious	• Diskitis • Osteomyelitis • Paraspinal abscess
Neoplasm	• Primary or secondary (metastasis)
Inflammatory	• Spondylarthropathies • Sacroiliitis
Referred pain to spine	• From major viscera, retroperitoneal structures, genitourinary, aorta, or hip
Metabolic	• Osteoporotic vertebral collapse (3%-6%) • Paget disease • Osteomalacia • Hyperparathyroidism

(eg, ankylosing spondyloarthritis), and dangerous neurologic processes, such as **spinal cord compression or cauda equina syndrome.** Individuals without these conditions are initially managed with conservative therapy. Nearly all patients recover spontaneously within 4 to 6 weeks, but a small percentage develops chronic mechanical low back pain. If patients do not improve within 4 weeks with conservative management, another etiology of the back pain might be present, and further evaluation may be necessary, especially in patients with localized pain, nocturnal pain, or sciatica.

The potential causes of back pain are numerous (Table 32–1). Pain can emanate from the bones, ligaments, muscles, or nerves. Rarely, it can be a result of referred pain from a visceral organ or other structure. Back pain with **radiation down the back of the leg** suggests **sciatic nerve root compression**, generally caused by a herniated intervertebral disk at the **L4–L5** or **L5–S1** level. Patients typically report aching pain in the buttock and paresthesias radiating into the posterior thigh and calf or lateral foreleg. When pain radiates below the knee as opposed to just the posterior thigh, it is more likely to indicate a true radiculopathy than radiation only to the posterior thigh. A history of persistent leg numbness or weakness further increases the likelihood of neurologic involvement.

Most cases of back pain are idiopathic, referred to as nonspecific low back pain, and usually of musculoskeletal origin. **In patients with back pain < 4 weeks' duration and no associated symptoms, imaging studies and other diagnostic tests are generally not beneficial.** Studies have shown that the history and physical examination can help separate the majority of patients with simple and self-limited musculoskeletal back pain from the minority with more serious underlying causes. **Most patients with low back pain have nonserious causes, and the pain will resolve with rest; however, some conditions can be life threatening.** Searching for "red flag" symptoms can

help the clinician use diagnostic tests in a more judicious manner. **Major red flag symptoms include weight loss, fever, young age, constant pain, neurologic symptoms, history of cancer, injection drug use, and nonmechanical pain.** The following section discusses clinical examples of nonmechanical back pain.

In patients with **systemic symptoms who have pain at night or pain that is not relieved by lying** in a supine position, **malignancy** should be considered. **Primary cancers** that commonly metastasize to the spine include **lung, breast, prostate, lymphoma, and gastrointestinal tumors and melanoma. Multiple myeloma** affects the skeleton diffusely; the spinal compromise frequently manifests as back pain.

Ankylosing spondyloarthritis usually presents in young patients (age < 45); the back pain improves with activity and can awaken the patient from sleep. Characteristic x-ray findings include sacroiliitis and "bamboo spine."

Diskitis, spinal osteomyelitis, and sometimes **epidural abscesses** present with fever, constant back pain, and history of intravenous drug use or intravascular catheters (hemodialysis patients). Rapid workup with blood cultures, spinal magnetic resonance imaging (MRI), and rapid initiation of **antibiotics** are indicated. Some cases require surgery. Table 32–2 describes the recommended workup for some concerning causes of low back pain.

Clinical Presentation

When the patient has worrisome symptoms or signs, the most effective **initial evaluation** includes plain anteroposterior and lateral radiographs of the involved area

Table 32–2 • RECOMMENDED WORKUP IN PATIENTS WITH LOWER BACK PAIN

Cancer	• Consider multiple myeloma or bony metastasis from prostate, lung, or breast cancer • Obtain CBC, ESR, C-reactive protein, and MRI
Compression fracture	• Consider this in patients with osteoporosis, steroid use, or the elderly • Obtain an x-ray
Ankylosing spondyloarthritis	• Consider in patients with inflammatory symptoms, younger patients, and those with early morning pain • Obtain an x-ray
Radicular pain	• Consider in patients with symptoms in the L4, L5, or S1 distribution • Obtain imaging in patients eligible for surgery
Infection	• Consider in patients with accompanying fever, those with a history of intravenous drug use, and those with persistent pain • Obtain MRI, CBC, CMP, and blood cultures
Spinal canal stenosis	• Consider in patients with accompanying buttock pain, claudication (neurogenic), and older age • Obtain MRI in patients eligible for surgery

Abbreviations: CBC, complete blood count; CMP, comprehensive metabolic panel; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging.

of the spine, a sedimentation rate test, and a complete blood count (CBC). More advanced imaging, such as MRI, should be reserved for those patients for whom surgery is being considered (concerning neurologic symptoms, without surgical contraindications). Imaging studies often have abnormal findings, even in patients without low back pain, making it difficult to correlate symptoms with imaging findings.

During the physical examination, palpable point tenderness over the spinous processes may indicate a destructive lesion of the spine itself; in contrast, those with musculoskeletal back pain most often have tenderness in the muscular paraspinal area. Strength, sensation, and reflexes should be assessed, especially in those with complaints of radicular or radiating pain. **Straight leg raise testing**, in which the examiner holds the patient's ankle and passively elevates the patient's leg to 45 degrees, is helpful if it elicits pain in the lower back, suggesting nerve root compression. However, it is **not a very sensitive or specific test**. The Patrick maneuver, also known as a flexion abduction external rotation (FABER) test, can help distinguish pain emanating from the sacroiliac joint. In this test, the patient externally rotates the hip, flexes the knee, and crosses the knee of the other leg with the ankle (like a number 4) while the examiner simultaneously presses down on the flexed knee and the opposite side of the pelvis. **Pain produced anteriorly on the flexed side suggests a hip disorder, while contralateral posterior pain suggests sacroiliac pathology.**

Treatment

In treating idiopathic low back pain, various modalities have been shown to be equally effective in the long run. Randomized, controlled trials have shown that encouraging the patient to continue his or her **usual activity is superior to recommendations for bed rest**. Therefore, patients without disability and without evidence of nerve root compression probably can maintain judicious activity. Bed rest probably is appropriate only for individuals with severe pain or neurologic deficits.

Nonsteroidal anti-inflammatory medications (on a scheduled rather than on an as-needed basis), nonaspirin analgesics, and muscle relaxants may help in the acute phase. Because most cases of disk herniation with radiculopathy resolve spontaneously within 4 to 6 weeks without surgery, conservative measures are the initial regimen recommended for these patients as well. Narcotic analgesics may be an option in cases of very severe pain; however, because idiopathic low back pain is often a chronic problem, prolonged narcotic use beyond the initial phase is highly discouraged. Chiropractic therapy, physical therapy, massage therapy, and acupuncture have been studied in trials of varying quality, with results comparable to traditional approaches. **Referral** to a surgeon may be considered for those patients with radicular pain, with or without neuropathy, that **does not resolve with 4 to 6 weeks of conservative management.**

Patients with concerning clinical features, such as a history of malignancy, fever, or examination findings suggestive of spinal cord compression or cauda equina syndrome, should be referred for urgent imaging, either MRI or computed tomography of the spine, to evaluate for conditions such as vertebral metastases, vertebral osteomyelitis, or spinal epidural abscesses that require urgent treatment.

CASE CORRELATION

- See also Case 31 (Osteoarthritis/Degenerative Joint Disease), Case 33 (Acute Monoarticular Arthritis—Gout), and Case 34 (Rheumatoid Arthritis).

COMPREHENSION QUESTIONS

32.1 A 35-year-old woman presents with 1 week of lower back pain. Her history and examination are without red flag symptoms and completely normal. Her blood pressure is 120/70 mm Hg, heart rate is 90 beats per minute, and temperature is 98 °F. Her body mass index (BMI) is 36 kg/m^2. The physical examination is normal, and the straight leg raise test is negative. Neurologic examination of the lower extremities does not show any deficits. Which of the following is the best next step for this patient?

A. Regular doses of ibuprofen and activity as tolerated
B. Six weeks of bed rest
C. MRI of the lumbar spine
D. Plain film x-ray of the lumbosacral spine

32.2 A 28-year-old woman from Nigeria presents with a 6-month history of persistent lower lumbar back pain, associated with a low-grade fever and night sweats. She denies any extremity weakness or human immunodeficiency virus (HIV) risk factors. Her examination is normal except for point tenderness over the spinous processes of L4–L5. Which of the following is the most likely diagnosis?

A. *Staphylococcus aureus* osteomyelitis
B. Tuberculous osteomyelitis
C. Given her age, idiopathic low back pain
D. Metastatic breast cancer
E. Multiple myeloma

32.3 A 70-year-old woman presents with a 4-week history of low back pain, generalized weakness, and a 15-lb weight loss over the last 2 months. Her medical history is unremarkable, and her examination is normal except that she has generalized weakness with strength rated as 4/5 in all extremities. Initial laboratory tests reveal an erythrocyte sedimentation rate (ESR) of 80 mm/h (normal < 35), hemoglobin of 10 g/dL, creatinine level 1.8 mg/dL (nl 0.5-1.3), and calcium level 11.2 mg/dL (normal 8.5–10.5). Which of the following is the most likely diagnosis?

A. Osteoporosis with compression fractures
B. Renal failure with osteodystrophy
C. Multiple myeloma
D. Lumbar strain
E. Osteomyelitis

32.4 A 45-year-old man presents to the office for lower back pain of 2 weeks' duration related to a motor vehicle collision. After the collision, he did not initially seek medical care and took acetaminophen over the counter. However, for the past day, he has complained of decreased sensation in his buttock area, problems voiding (urine dribbling), and inability to achieve an erection. On examination, he has decreased anal sphincter tone and decreased ankle reflexes bilaterally. Which of the following is the next best step in management?

A. Bed rest and follow-up in 4 to 6 weeks

B. Plain film x-ray of lumbosacral spine

C. Determination of sedimentation rate and CBC

D. Immediate referral for advanced imaging and surgical evaluation

ANSWERS

32.1 **A.** This is a patient who has no red flag signs of back pain and class 2 obesity (severe obesity with BMI 35-39.9 kg/m^2). Regular (scheduled) doses of NSAIDs and resuming activity as normal (as tolerated) are the recommended therapy. Bed rest (answer B) has not been shown to improve outcomes in idiopathic low back pain compared to encouraging mild-to-moderate activity, and it increases the risk of deep venous thrombosis. Imaging (answers C and D) is not necessary with uncomplicated back pain.

32.2 **B.** The patient's country of origin, the chronic and slowly progressive nature of the pain in association with fever, and night sweats are highly suggestive of tuberculous osteomyelitis of the spine or Pott disease. Bacterial osteomyelitis (answer A) presents more acutely, often with high, spiking fevers. Metastatic breast cancer (answer D) and multiple myeloma (answer E) are extremely rare in this age group. The fevers, night sweats, and persistent and progressive nature of her back pain make a musculoskeletal cause (answer C) unlikely.

32.3 **C.** This patient likely has multiple myeloma. She has many "red flag" symptoms in her presentation: her age, new-onset pain, and history of weight loss. The markedly elevated ESR suggests an inflammatory condition or situation with high levels of proteins (in this case, immunoglobulins). The elevated calcium level and mild renal failure are also suggestive of multiple myeloma. Plain radiographs of the axial and appendicular skeleton may illustrate the lytic bone lesions often seen in this disease. Because the lesions are purely osteolytic, serum levels of alkaline phosphatase are normal, and bone scans do not detect them. Osteoporosis and compression fractures (answer A) are common in postmenopausal women but they are either asymptomatic or lead to some localized pain of the spine; the other red flags such as fever, trauma, urinary dysfunction, and saddle anesthesia are not present. Answer B (renal failure with osteodystrophy) can occur due to secondary hyperparathyroidism; this occurs due to decreased levels of vitamin D and, thus, decreased calcium absorption. The elevated ESR and weight loss do not occur with this condition; also, this patient's creatinine level of 1.8 mg/dL is not high

enough to suggest this etiology. Answer D (lumbar strain) is not associated with an elevated ESR or weigh loss; also, the patient should recall the injury. Answer E (osteomyelitis) usually manifests as fever and can elevate the ESR, but usually there is point tenderness at the site of infection.

32.4 **D.** Most patients with lower back pain have self-limited symptoms and improve with conservative measures. However, some red flag conditions are important to monitor. This patient, for instance, has bladder and buttocks sensory dysfunction and erectile dysfunction, which are highly suggestive of cauda equina syndrome. Immediate assessment by MRI or myelography and prompt surgical decompression should be accomplished to avoid long-term nerve denervation and incontinence/lower extremity weakness. Answers A (bed rest and follow-up in 4-6 weeks), B (x-ray of lumbosacral spine), and C (sedimentation rate and CBC) all delay treatment.

CLINICAL PEARLS

- Acute low back pain, even with sciatic nerve involvement, resolves within 4 to 6 weeks in 90% of patients.
- Analgesics, such as NSAIDs or acetaminophen, muscle relaxants, and attempts at maintaining some level of activity are helpful in managing acute low back pain; bed rest does not help.
- Pain that interferes with sleep, significant unintentional weight loss, or fever suggests an infectious or neoplastic cause of back pain.
- Imaging studies, such as MRI, are useful only if surgery is being considered (persistent pain and neurologic symptoms after 4-6 weeks of conservative care in patients with herniated disks) or if neoplastic, inflammatory, or infectious causes of back pain are being considered.
- Signs for cauda equina syndrome are a clinical emergency and require immediate referral to surgery for decompression.

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CASE 33

A 48-year-old man comes to your office complaining of severe right knee pain for 8 hours. He states that the pain started abruptly at 2 am and woke him from his sleep. The pain is so severe that even the weight of the bed sheets on his knee was unbearable. By the morning, the knee had become warm, swollen, and tender. He prefers to keep his knee bent since straightening the knee causes the pain to worsen. He has never had pain, surgery, or injury to his knees. A year ago, he did have some pain and swelling at the base of his great toe on the left foot, which was not as severe as this episode, and the previous pain resolved in 2 or 3 days after taking ibuprofen. His only medical history is hypertension, which is controlled with hydrochlorothiazide. He is a nonsmoker and reports moderate social alcohol use.

On examination, his temperature is 99.4 °F, heart rate is 104 beats per minute (bpm), blood pressure (BP) is 136/78 mm Hg, weight is 212 lb, and height is 5'11". His head and neck examinations are unremarkable, his chest is clear to auscultation, and his heart is tachycardic but regular, with no gallops or murmurs. His right knee is swollen, with a moderate effusion, and appears erythematous, warm, and very tender to palpation. He is unable to fully extend the knee because of pain. He has no other joint swelling, pain, or deformity and no skin rashes.

- What is the most likely diagnosis?
- What is your next step?
- What is the best initial treatment?
- What are the most important risk factors for this condition?
- What is the most effective way to prevent this condition?

ANSWERS TO CASE 33:
Acute Monoarticular Arthritis—Gout

Summary: A 48-year-old man presents with

- Acute onset of severe right knee pain
- Swollen, erythematous right knee with effusion and limited range of motion that is tender to palpation
- No previous surgery or injury to his knees
- Previous episode of pain and swelling at the base of his great toe that resolved with ibuprofen
- History of hypertension, for which he takes hydrochlorothiazide

Most likely diagnosis: Acute monoarticular arthritis, likely crystalline or infectious. Most likely to be gout due to history of pain in the great toe and hydrochlorothiazide use.

Next step: Aspiration of the knee joint to send fluid for cell count, culture, and crystal analysis.

Best initial treatment: If the joint fluid analysis is consistent with infection, he needs drainage of the infected fluid by aspiration and administration of antibiotics. If analysis is suggestive of crystal-induced arthritis, he can be treated with colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids.

Most important risk factors: Hyperuricemia (obesity, idiopathic, renal failure, thiazide diuretics, tumor lysis syndrome).

Most effective prevention: Diet modification, allopurinol, febuxostat.

ANALYSIS

Objectives

1. Differentiate synovial fluid features to determine the etiology of arthritis. (EPA 3)
2. Describe the stages of gout and the appropriate treatment for each stage. (EPA 1, 4)
3. Describe the similarities and differences between different types of crystalline arthritis. (EPA 2)

Considerations

A middle-aged man presents with an acute attack of monoarticular arthritis, as evidenced by knee effusion, limited range of motion, and signs of inflammation (low-grade fever, erythema, warmth, tenderness). The two most likely causes are infection (eg, *Staphylococcus aureus*) and crystalline arthritis. If the patient is at risk, gonococcal arthritis is also a possibility. The previous less severe episode involving

his first metatarsophalangeal (MTP) joint sounds like **podagra**, the most common presentation of gout. The rapid onset of severe symptoms during the current attack is consistent with acute gouty arthritis. In this patient, the attack could have been precipitated by the use of alcohol, which increases uric acid production, and his use of thiazide diuretics, which decrease renal excretion of uric acid.

Although the first attack was typical of gout, which makes this episode very likely to also be acute gouty arthritis, the current presentation could also be consistent with bacterial infection. Untreated septic arthritis could lead to rapid destruction of the joint, so joint aspiration and empiric antibiotic therapy are appropriate until his cultures and crystal analysis are available.

APPROACH TO:
Monoarticular Arthritis

DEFINITIONS

ACUTE CALCIUM PYROPHOSPHATE (CPP) CRYSTAL ARTHRITIS: Arthritis caused by deposition of calcium pyrophosphate dihydrate (CPPD) crystals. Previously known as "pseudogout."

GOUT: A disturbance of uric acid metabolism occurring mainly in men, characterized by hyperuricemia and the deposition of monosodium urate crystals in the joints and connective tissue.

MONOARTHRITIS: Inflammation of a single joint.

CLINICAL APPROACH

Pathophysiology

Almost any joint disorder may begin as monoarthritis; however, the primary concern is always **infectious arthritis** because it may lead to **joint destruction and resultant severe morbidity**. For that reason, **acute monoarthritis should be considered a medical emergency** and investigated and treated aggressively.

Accurate diagnosis starts with a good history and physical examination supplemented by additional diagnostic testing, such as **synovial fluid analysis, radiography**, and occasionally **synovial biopsy**. Patients with crystal-induced arthritis may give a history of recurrent, self-limited episodes. Precipitation of an attack by surgery or some other stress can occur with both crystalline disorders, but **gout is far more common than acute CPP crystal arthritis**. The clinical course can provide some clues to the etiology: Septic arthritis usually worsens unless treated; osteoarthritis worsens with physical activity. Gout classically progresses through four stages (Table 33–1). Interestingly, the presence of completely asymptomatic periods (intercritical gout) between monoarthritic attacks is so uncommon, except in crystalline arthritis, that it is often used as a diagnostic criterion for gout.

Table 33–1 • STAGES OF GOUT

Stage	Symptoms and Signs	Comments
Stage 1: Asymptomatic hyperuricemia	• Elevated uric acid levels without arthritis or kidney stones • Majority of patients never develop symptoms	The higher the uric acid level and the longer the duration of hyperuricemia, the greater the likelihood of the patient developing gouty arthritis.
Stage 2: Acute gouty arthritis	• Most often involves the acute onset of severe **monoarticular pain** • Pain usually occurs at night in the first MTP joint, ankle, or knee and rapidly progresses to joint swelling and erythema • Systemic symptoms, such as fever and chills, are occasionally present	Usually follows decades of asymptomatic hyperuricemia. Attacks may last hours or up to 2 weeks.
Stage 3: Intercritical gout	• Period between acute attacks • Patients generally completely asymptomatic	Another acute attack will occur in 60%-70% of patients within 1-2 years.
Stage 4: Chronic tophaceous gout	• Intercritical periods no longer asymptomatic • Involved joints have chronic swelling and discomfort that worsens over time • Subcutaneous tophaceous deposits of monosodium urate are developed	Usually occurs after 10 or more years of acute intermittent gout.

Clinical Presentation

History and Physical Examination. Affected patients complain of the spontaneous onset of severe pain, edema, and redness of the joint. There is often a family history. Triggers can include dietary consumption of high purine foods, dehydration, or medications that increase uric acid levels.

Gout most commonly involves the **first MTP joint (podagra), ankle, midfoot, or knee**. Acute CPP crystal arthritis most commonly affects the large joints, such as the knee; it may also affect the wrist or the first MTP joint. In **gonococcal** arthritis, there are often **migratory arthralgias and tenosynovitis**, often involving the wrist and hands, associated with **pustular skin lesions**. These may progress to purulent monoarthritis or oligoarthritis. Nongonococcal causes of septic arthritis often involve large weight-bearing joints, such as the knee and hip. The most common bacterial pathogen comes from skin flora, such as *S. aureus*.

The basic approach in physical examination is to differentiate arthritis from inflammatory conditions adjacent to the joint, such as cellulitis or bursitis. **True arthritis** is characterized by **swelling and redness around the joint and painful limitation of motion in all planes** during **active and passive motion. Joint movement that is**

not limited by passive motion suggests **a soft tissue disorder such as bursitis** rather than arthritis.

Laboratory Tests/Imaging. Synovial fluid analysis helps to differentiate between inflammatory and noninflammatory causes of arthritis. **Diagnostic arthrocentesis is usually necessary when evaluating an acute monoarthritis and is essential when infection is suspected.** Fluid analysis typically includes gross examination, cell count and differential, Gram stain and culture, and crystal analysis. Figure 33–1 shows the typical results that can help one distinguish between noninflammatory conditions such as osteoarthritis, inflammatory arthritis such as crystalline disease, and septic arthritis, which is most often a bacterial infection.

Normal joints contain a small amount of fluid that is essentially acellular. Noninflammatory effusions should have a white blood cell (WBC) count less than 1000 to 2000/mm^3 with less than 25% to 50% polymorphonuclear (PMN) cells. **If the fluid is inflammatory, the joint should be considered infected until proven otherwise**, especially if the patient is febrile.

Crystal analysis requires the use of a polarizing light microscope. Monosodium urate crystals, the cause of **gout**, are **needle shaped**, typically **intracellular** within a PMN cell, and are **negatively birefringent, appearing yellow** under the polarizing microscope as seen in Figure 33–2. CPPD crystals, the cause of **acute CPP crystalline arthritis**, are **short and rhomboid** and are **weakly positively birefringent**, appearing blue under polarized light. **Even if crystals are seen, infection must be excluded when the synovial fluid is inflammatory.** Crystals and infection may coexist in the same joint, and chronic arthritis or previous joint damage, such as occurs in gout, may predispose that joint to hematogenous infection.

In septic arthritis, Gram stain and culture of the synovial fluid is positive in 60% to 80% of cases. False-negative results may be related to prior antibiotic use or fastidious microorganisms. For example, in **gonococcal arthritis, joint fluid cultures typically are negative, whereas cultures of blood or the pustular skin lesions may be positive.** Sometimes the diagnosis rests on demonstration of gonococcal infection in another site, such as urethritis, with the typical arthritis-dermatitis syndrome. **Synovial biopsy** may be required when the cause of monoarthritis remains unclear, and it is usually **necessary to diagnose arthritis caused by tuberculosis or hemochromatosis.**

Plain radiographs usually are unremarkable in cases of inflammatory arthritis; the typical finding is soft tissue swelling. **Chondrocalcinosis** or linear calcium deposition in joint cartilage as seen in Figure 33–3 suggests acute CPP arthritis.

Treatment

Generally, patients require initiation of treatment before all test results are available. When septic arthritis is suspected, the clinician should culture the joint fluid and start antibiotic therapy; the antibiotic choice should be initially based on the Gram stain and, when available, the culture results. If the Gram stain is negative, the clinical picture should dictate antimicrobial selection. For example, if the patient has the typical presentation of **gonococcal arthritis, intravenous ceftriaxone is the usual initial therapy,** usually with rapid improvement in symptoms. Nongonococcal septic arthritis usually is caused by gram-positive organisms,

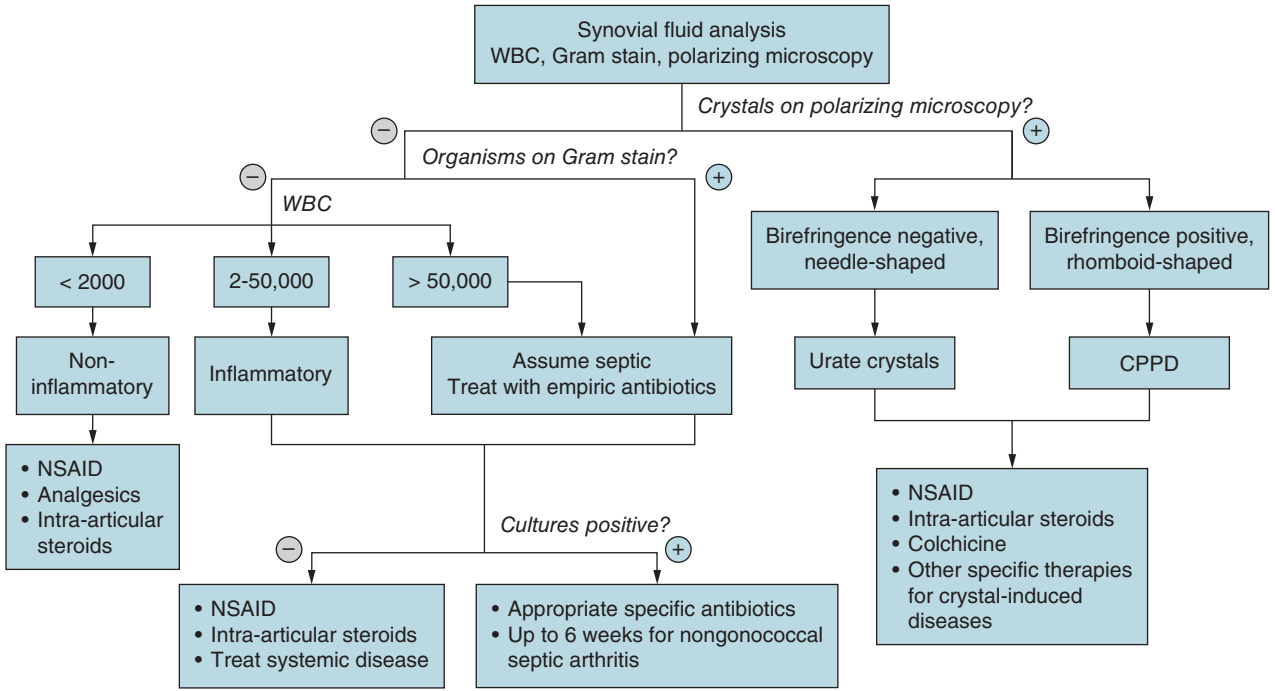


Figure 33–1. Algorithm for diagnosing acute monoarticular arthritis based on synovial fluid.

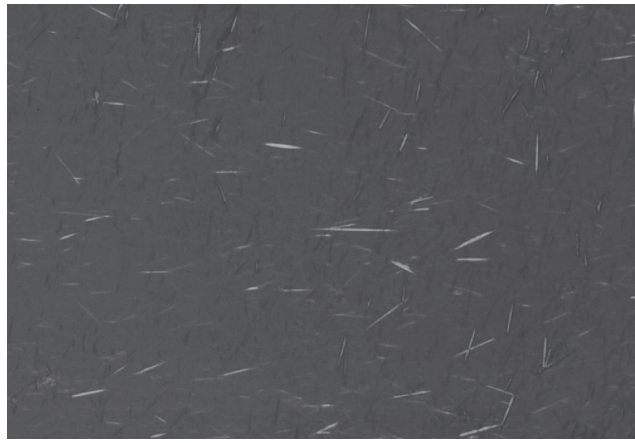


Figure 33–2. Synovial fluid microscopy showing negatively birefringent crystals. Reproduced with permission, from Strasinger SK, Di Lorenzo MS. *Urinalysis and Body Fluids*. 5th ed. 2008. Copyright © F.A. Davis Company. All rights reserved.

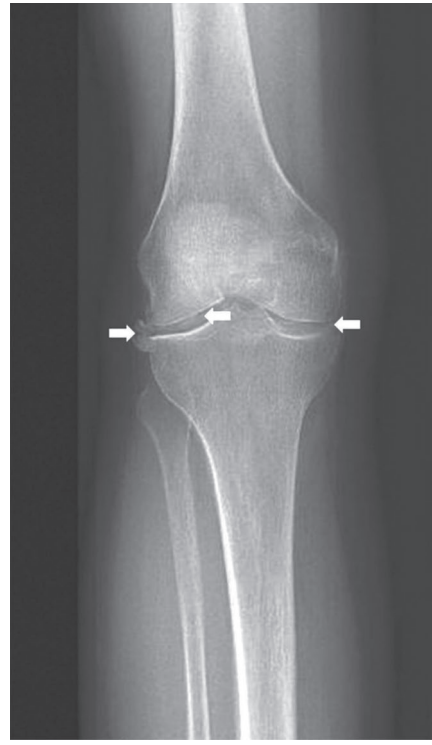


Figure 33–3. X-ray of knee showing chondrocalcinosis. Arrows point to the calcification of the menisci with calcium pyrophosphate dehydrate crystal deposition. Reproduced with permission, from McKean SC, Ross JJ, Dressler DD, et al., eds. *Principles and Practice of Hospital Medicine*, 2nd ed. 2017. Copyright © McGraw Hill LLC. All rights reserved.

most often ***S. aureus***, so treatment would involve an **antistaphylococcal antibiotic such as vancomycin, daptomycin, or linezolid.** If cultures demonstrate organisms that are sensitive to beta-lactams, antibiotic therapy can be guided by the culture and susceptibility results. **It is essential to drain the purulent joint fluid, usually by repeated percutaneous aspiration.** Open surgical drainage or arthroscopy is required when joint fluid is loculated or when shoulders, hips, or sacroiliac joints are involved.

In general, **asymptomatic hyperuricemia requires no specific treatment**. Lowering the urate level does not necessarily prevent the development of gout, and most of these patients will never develop any symptoms.

In patients with symptomatic hyperuricemia (patients who have uric acid kidney stones, more than two acute gout attacks per year, or tophi), recommended treatment is with urate-lowering therapy, which is discussed in the material that follows. Acute gouty arthritis is treated with therapies to reduce the inflammatory reaction to the presence of the crystals, all of which are most effective if started early in the attack. **Potent NSAIDs, such as indomethacin, are the mainstay of therapy** during an acute attack. Alternatively, oral colchicine can be taken three times daily until the joint symptoms abate, but dosing is limited by gastrointestinal side effects such as nausea and diarrhea. For individuals affected by acute joint pain with **renal insufficiency** (for which an **NSAID or colchicine** is relatively **contraindicated**), **intra-articular glucocorticoid injection or oral steroid therapy** is usually beneficial. Steroids should be used only if infection has been excluded. Treatment to lower uric acid levels is inappropriate during an acute episode because any sudden increase or decrease in urate levels may precipitate further attacks.

Patients with tophaceous gout are managed as previously described during acute attacks and subsequently treated with allopurinol to help tophaceous deposits resolve. A new agent, pegloticase, is an intravenous medication that is a recombinant form of urate-oxidase enzyme that will rapidly dissolve tophi in patients with treatment-resistant tophaceous gout. Surgery may be indicated if the mass effect of tophi causes nerve compression, joint deformity, or chronic skin ulceration with resultant infection.

Prognosis and Prevention. During intercritical gout, the focus shifts to **preventing further attacks by lowering uric acid levels to less than 6 mg/dL**. Dietary restriction is mainly aimed at avoiding organ-rich foods, such as liver, and alcohol. Patients taking thiazide diuretics should be switched to another antihypertensive if possible. Urate lowering can be accomplished by therapy to increase uric acid excretion by the kidney, such as with probenecid. Uricosuric agents such as probenecid are ineffective in patients with renal failure, however, and are contraindicated in patients with a history of uric acid kidney stones. In these patients, **allopurinol** can be used to diminish uric acid production, but it must be given at a lower dose in patients with renal disease. **Febuxostat** is a new xanthine oxidase inhibitor that does not require dose adjustment in renal insufficiency.

Patients with acute CPP arthritis are treated similarly for acute attacks (NSAIDs, colchicine, and systemic or intra-articular steroids). Prophylaxis with colchicine may be helpful in patients with chronic recurrent attacks, but there is no effective therapy for preventing CPPD crystal formation or deposition.

CASE CORRELATION

- See also Case 31 (Osteoarthritis/Degenerative Joint Disease), Case 32 (Low Back Pain), and Case 34 (Rheumatoid Arthritis).

COMPREHENSION QUESTIONS

33.1 A previously healthy 18-year-old college freshman presents to the student health clinic complaining of pain on the dorsum of her left wrist and in her right ankle, fever, and a pustular rash on the extensor surfaces of both her forearms. She has mild swelling and erythema of her ankle and pain on passive flexion of her wrist. Less than 1 mL of joint fluid is aspirated from her ankle and shows 8000 PMN cells per high-power field (hpf) but no organisms on Gram stain. Which of the following is the best initial treatment?

A. Indomethacin orally
B. Intravenous nafcillin
C. Colchicine orally
D. Intra-articular prednisone
E. Intravenous ceftriaxone

33.2 Which of the following laboratory tests is most likely to confirm the diagnosis for the case in Question 33.1?

A. Crystal analysis of the joint fluid
B. Culture of joint fluid
C. Blood culture
D. Cervical samples for DNA amplification tests

33.3 A 30-year-old man is seen in the emergency department for complaints of severe right knee pain of 1 day's duration that has worsened throughout the day. He denies trauma, prior joint pain, skin rash, or penile discharge. On examination, his BP is 140/80 mm Hg, heart rate is 100 bpm, and temperature is 98 °F. He has no skin rashes. The right knee is swollen, red, and very painful to the touch and to move. Joint aspirate reveals 55,000 leukocytes/mm^3 with a predominance of PMN leukocytes, but no organisms on Gram stain. Analysis shows few negatively birefringent crystals. Which of the following is the best initial treatment for this patient?

A. Oral corticosteroids
B. Intra-articular corticosteroids
C. Intravenous antibiotic therapy
D. Oral colchicine

ANSWERS

33.1 **E.** The patient described best fits the picture of disseminated gonococcal infection. She has the corresponding pustular rash, which typically is located on extensor surfaces of distal extremities. Pain on passive flexion of her wrist indicates likely tenosynovitis of that area. The fluid is inflammatory (high number of leukocytes), but gonococci are typically not seen on Gram stain; if they are seen, they are gram-negative intracellular diplococci. Intravenous ceftriaxone is the usual treatment of choice for gonococcal infection and because of the possibility of resistance, oral zithromycin is added. Treatment is usually at least for 1 week. **Gonococcal arthritis is the most common cause of infectious arthritis in patients younger than 40 years.** Nafcillin (answer B) would be useful for staphylococcal arthritis and would be the more likely choice if she were older, had some chronic joint disease such as rheumatoid arthritis, or were immunocompromised. Indomethacin (answer A) or colchicine (answer C) would be useful if she had a crystalline arthritis, but that is unlikely in this clinical picture. Intra-articular prednisone (answer D) is contraindicated until infectious arthritis is ruled out.

33.2 **D.** Synovial fluid analysis and cultures (answers A and B) usually are sterile in gonococcal arthritis (in fact, the arthritis is more likely caused by immune complex deposition than by actual joint infection), and blood cultures (answer C) are positive less than 50% of the time. Diagnosis is more often made by finding gonococcal infection through nucleic acid amplification tests in a more typical site, such as the urethra, cervix, or pharynx.

33.3 **C.** This patient presents with an acute inflammatory arthritis, which should be treated as possible a septic arthritis until final cultures return. The inflammatory arthritis as shown by markedly elevated leukocyte count in the synovial fluid. The Gram stain of the joint aspirate is suspicious for infection, even with no organisms seen on Gram stain. In other words, the sensitivity of Gram stain for a septic arthritis is low; however, the positive predictive value if organisms are present is high. Although the presence of crystals may suggest a crystalline arthritis, it does not eliminate the possibility of a concurrent infection. Typically, crystalline arthritis is associated with a synovial white cell count in the range of 5000 to 40,000/mm^3, and the typical cell count for infectious arthritis is > 50,000 cells/mm^3. These are general tendencies and not hard and fast rules. Importantly, if intravenous antibiotics are not administered in the setting of a septic joint, then the patient may lose function of the joint or even die. Thus, antibiotics should be administered to this patient until infection is ruled out. Corticosteroids—either oral (answer A) or intra-articular (answer B)—should not be used until infection is ruled out. Answer D (colchicine) can be given for pseudogout but is not as important as antibiotics. NSAIDs, rest, ice, and pain control should be instituted in addition to intravenous antibiotics. Synovial cultures should return in 48 hours.

CLINICAL PEARLS

- In the absence of trauma, acute monoarthritis is most likely to be caused by septic or crystalline arthritis.
- In a febrile patient with a joint effusion, diagnostic arthrocentesis is mandatory. Inflammatory fluid (WBC count more than 2000/mm^3) should be considered infected until proven otherwise.
- Gonococcal arthritis usually presents as a migratory tenosynovitis, often involving the wrists and hands, with few vesiculopustular skin lesions.
- Nongonococcal septic arthritis is most often caused by *S. aureus* and most often affects large weight-bearing joints.
- Monosodium urate crystals in gout are needle shaped and negatively birefringent (yellow) under the polarizing microscope. CPPD crystals in pseudogout are rhomboid and positively birefringent (blue).
- Treatment of gout depends on the stage: NSAIDs (specifically indomethacin), colchicine, or steroids for an acute gouty arthritis, and urate-lowering therapy with probenecid, allopurinol, or febuxostat during the intercritical period.

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CASE 34

A 32-year-old nurse presents to your office with a complaint of intermittent episodes of pain, stiffness, and swelling in both hands and wrists for approximately 1 year. The episodes last for several weeks and then resolve. More recently, she noticed similar symptoms in her knees and ankles. Joint pain and stiffness are making it harder for her to get out of bed in the morning and are interfering with her ability to perform her duties at work. The joint stiffness usually lasts for several hours before improving. She also reports malaise and easy fatigability for the past few months, but she denies having fever, chills, skin rashes, and weight loss.

Physical examination reveals a well-developed woman, with blood pressure 120/70 mm Hg, heart rate 82 beats per minute (bpm), and respiratory rate 14 breaths per minute. Her skin does not reveal any rashes. Head, neck, cardiovascular, chest, and abdominal examinations are normal. There is no hepatosplenomegaly. The joint examination reveals the presence of bilateral swelling, redness, and tenderness of the most proximal interphalangeal (PIP) joints, metacarpophalangeal (MP) joints, the wrists, and the knees. Laboratory studies show a mild anemia with hemoglobin 11.2 g/dL, hematocrit 32.5%, mean corpuscular volume 85.7 fL, white blood cell count 7900/mm^3 with a normal differential, and platelet count 300,000/mm^3. The urinalysis is clear with no protein and no red blood cells. The erythrocyte sedimentation rate (ESR) is 75 mm/h, and the kidney and liver function tests are normal.

- What is the most likely diagnosis?
- What is your next diagnostic step?

ANSWERS TO CASE 34:
Rheumatoid Arthritis

Summary: A 32-year-old woman presents with

- A 1-year history of symmetric polyarticular arthritis and morning stiffness
- Bilateral swelling, redness, and tenderness of her PIP joints, MCP joints, wrists, and knees
- Mild normocytic anemia
- Normal complete blood count (CBC), urinalysis, renal, and liver function tests
- Elevated ESR, suggesting an inflammatory cause of her symptoms

Most likely diagnosis: Rheumatoid arthritis (RA).

Next diagnostic step: Rheumatoid factor (RF) and anti-CCP (cyclic citrullinated peptide) antibodies.

ANALYSIS

Objectives

1. Differentiate the clinical presentation of RA from other symmetric polyarthritis syndromes. (EPA 1, 2)
2. Describe the clinical course of RA. (EPA 1, 12)
3. Review the different treatment options for RA. (EPA 4, 7, 9)

Considerations

This patient's history, including the symmetric peripheral polyarthritis and duration of symptoms, is suggestive of RA. RA is a systemic autoimmune disorder of unknown etiology. Its major distinctive feature is a chronic, symmetric, and erosive synovitis of peripheral joints, which, if untreated, leads to deformity and destruction of joints due to erosion of cartilage and bone. The MP joints of the hands are often affected, and ulnar deviation of the fingers is a common finding. The diagnosis of RA is a clinical one, based on the presence of a combination of clinical findings, laboratory abnormalities, and, in later stages, if untreated, radiographic erosions.

APPROACH TO:
Polyarticular Arthritis

DEFINITIONS

ANTI-CCP (CYCLIC CITRULLINATED PEPTIDE) ANTIBODIES: Autoantibodies that are found early in RA and have greater specificity than RF.

POLYARTHRITIS: Inflammation of five or more joints.

CLINICAL APPROACH

Clinical Findings

The first and most important step in evaluating a patient with polyarticular joint pain is determining whether or not **synovitis/arthritis** is present, producing soft tissue swelling, joint effusion, tenderness, warmth of the joint, and limitation of both active and passive range of motion. If the only finding is pain without inflammatory changes, then the diagnostic considerations include noninflammatory diseases such as osteoarthritis (OA), fibromyalgia, hypothyroidism, neuropathic pain, and depression. The presence of soft tissue swelling and tenderness with limited active range of motion but normal passive range of motion suggests the problem is extra-articular soft tissue inflammation, such as bursitis or tendonitis.

If there is active synovitis/arthritis, it is clinically useful to distinguish between monoarticular/oligoarticular arthritis and polyarticular arthritis. In polyarticular disease, the next diagnostic clue is the duration of symptoms. If symptoms are relatively acute (< **6 weeks**), the major considerations are arthritis due to **viral infection** (such as hepatitis B or C, rubella, or parvovirus B19) or the earliest manifestation of a true rheumatic disease. Viral serologies and compatible clinical history of exposure often can make the diagnosis at this point and obviate need for further rheumatologic evaluation. Treatment of a viral arthritis usually is limited to symptom relief with nonsteroidal anti-inflammatory drugs (NSAIDs) because the conditions are generally self-limited.

Differential Diagnosis

Symmetric peripheral polyarthritis is the most characteristic feature of RA. It can also be seen in other autoimmune rheumatic diseases, such as systemic lupus erythematosus and psoriatic arthritis. **Lupus**, which may present with a symmetric polyarthritis, usually is characterized by the presence of other symptoms, such as malar rash, serositis (pleuritis and pericarditis), renal disease with proteinuria or hematuria, central nervous system manifestations, and hematologic disorders, such as hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia. **Rheumatic fever**, which can cause symmetric polyarthritis, is an acute febrile illness lasting only 6 to 8 weeks. In **psoriatic arthritis,** the pattern of joint involvement varies widely. The vast majority of patients have peripheral joint involvement of more than five joints. Others have a pauciarticular asymmetric arthritis or exclusive distal interphalangeal (DIP) involvement. Inflammation is not limited to the joints but also

occurs at the periosteum, along tendons, and at the insertion points into the bone, resulting in the development of **dactylitis** or **"sausage digits," which are typical of psoriatic arthritis and reactive arthritis**. Although the arthritis can precede the development of a skin rash, the definite diagnosis of psoriatic arthritis cannot be made without the evidence of skin or nail changes typical of psoriasis (nail pitting, scaly plaques). **Reactive arthritis** is an asymmetric inflammatory arthritis that follows infection of the gastrointestinal (GI) or genitourinary tract with bacteria such as *Salmonella, Shigella, Campylobacter, Yersinia*, or *Chlamydia*. Reactive arthritis can present with the **triad of arthritis, uveitis, and urethritis**.

The peripheral polyarthritis of **RA** most typically involves the wrists, MTP joints of the feet, and the MP or **PIP joints** of both hands; the DIP joints usually are spared. It is useful to contrast the typical pattern of joint involvement of RA with that of degenerative OA. Degenerative joint disease may affect multiple joints, but it occurs in older age groups, is usually not associated with inflammation or constitutional symptoms, and tends not to be episodic. Also, in **OA** the hand joints most commonly involved are the **DIP joints**, where the formation of **Heberden nodes** can be noted (Figure 34–1). In RA, **ulnar deviation of the MP joints** is often associated with **radial deviation of the wrists; swan-neck deformities** as well as the **boutonnière deformity** can develop (Figure 34–2). Swan-neck deformity results from contracture of the interosseous and flexor muscles and tendons, which causes a flexion contracture of the MP joint, hyperextension of the PIP joint, and flexion of the DIP joint. In the boutonnière deformity, there is a flexion of the PIP and hyperextension of the DIP joints. These findings are typical of advanced RA.

Clinical Presentation

Morning stiffness or stiffness after any prolonged inactivity is a common feature of many arthritic disorders. However, stiffness that lasts more than 1 hour is seen only in inflammatory conditions such as RA and reflects the severity of joint inflammation.

Rheumatoid nodules are subcutaneous nodules typically found over extensor surfaces of the proximal ulna or other pressure points. They only occur in 20% to 30% of patients with RA but are believed to have a high diagnostic specificity for RA.

RFs are **immunoglobulins** (Ig's) that react to the **F_C portion of IgG molecules**. The usual serologic tests used in clinical laboratories detect immunoglobulin M (IgM) RFs, which are found in 80% to 85% of patients with RA. RF is not specific for RA, as it is found in 5% of healthy patients, but it can support the diagnosis when clinical features are suggestive. High RF titers have a prognostic utility for more severe systemic and progressive disease.

Antibodies to **anti-CCP** are now recognized as very useful biomarkers with diagnostic and prognostic significance. Anti-CCP antibodies have the same sensitivity as RF but are highly specific, about 95%. The presence of anti-CCP also portends worse outcomes in RA. Current classification criteria for the diagnosis of RA are listed in Table 34–1.

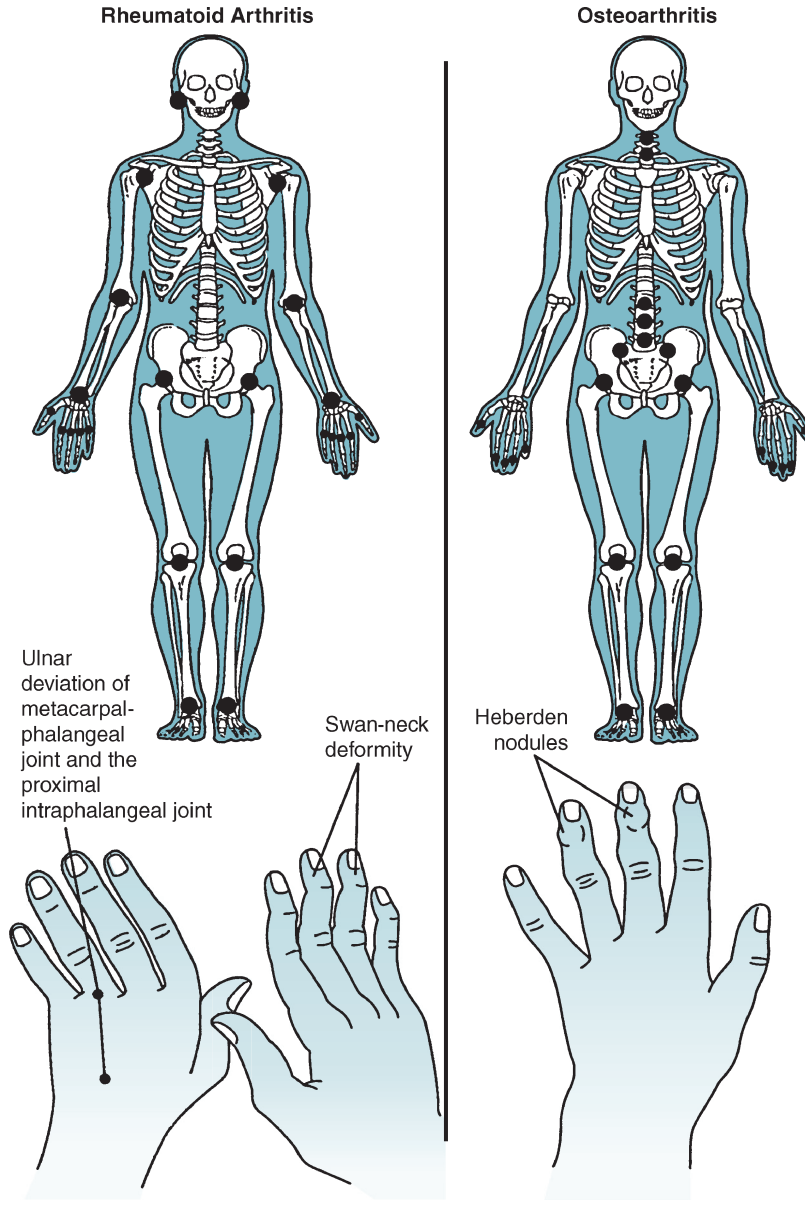


Figure 34–1. Rheumatoid arthritis versus osteoarthritis.

Radiologic findings in RA, such as erosion of periarticular bone and cartilage destruction with loss of joint space, may support the diagnosis. Usually, though, the typical x-ray findings do not develop until later in the disease process after a diagnosis has been made based on clinical findings. Joint deformities in RA occur from several different mechanisms, all related to synovitis and pannus formation

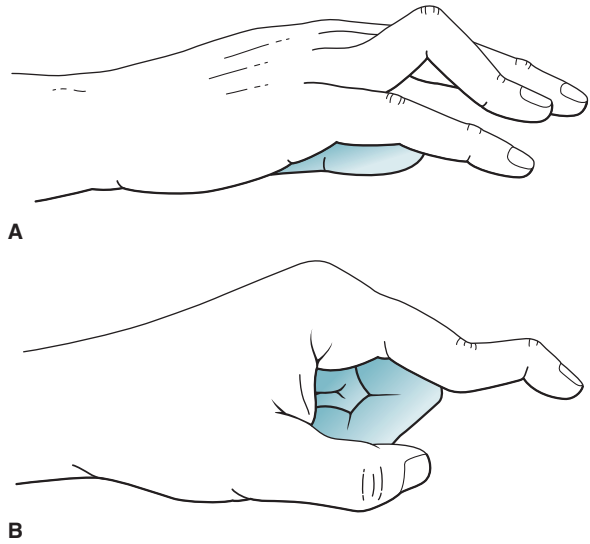


Figure 34–2. Boutonnière (A) and swan-neck (B) deformities.

with resulting cartilage destruction and erosion of periarticular bone. The structural damage to the joint is irreversible and worsens with disease progression.

There are several **extra-articular manifestations in RA**, including: vasculitic lesions with the development of ischemic ulcers, which imply systemic

Table 34–1 • 2010 ACR/EULAR CLASSIFICATION OF RHEUMATOID ARTHRITIS

Domain	Points
Number and site of involved joints	
2-10 large joints (from shoulders, elbows, hips, knees, ankles)	1
1-3 small joints (from metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joints, wrists)	2
4-10 small joints	3
> 10 joints (including at least 1 small joint)	5
Serologic abnormality (rheumatoid factor or anticitrullinated protein antibody)	
Low positive (above upper limit of normal)	2
High positive (> 3 times the upper limit of normal)	3
Elevated acute-phase reactants (ESR or CRP) above the upper limit of normal	1
Symptom duration of at least 6 weeks	1
Definitive diagnosis: synovitis in at least 1 joint, absence of alternative diagnosis, and a score of at least 6 of a possible 10 from individual scores in the following 4 domains.	

Abbreviations: ACR/EULAR, American College of Rheumatology/European League Against Rheumatism Collaborative Initiative; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Data from Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid Arthritis Classification Criteria. Arth & Rheum *2010:62(9):2569-2581.*

involvement, ocular manifestations with symptoms of **keratoconjunctivitis sicca** (Sjögren syndrome), respiratory manifestations caused by **interstitial lung disease**, cardiac manifestations, and several neurologic manifestations, such as myelopathy, related to cervical spine instability. Although not common, the continuous bone erosion may result in an atlantoaxial subluxation with cervical dislocation and spinal cord compression. Entrapment neuropathy may develop, such as carpal tunnel syndrome. Hematologic manifestations include anemia, typically anemia of chronic disease. The combination of **RA, splenomegaly, leukopenia, lymphadenopathy**, and **thrombocytopenia** is called **Felty syndrome**. Felty syndrome is most common with severe nodule-forming RA.

At this stage in the disease process, our patient is presenting with joint complaints, fatigue, and malaise. No other extra-articular manifestations have developed yet. At the very onset of RA, the characteristic symmetric inflammation of the joints and the typical serologic findings may not be evident. Therefore, initially distinguishing RA from other conditions, such as lupus, may be difficult. Usually, the development of extra-articular phenomena allows the clinician to make a more specific diagnosis.

Treatment

Several drugs are currently used for treatment of RA. **NSAIDs** or cyclooxygenase 2 (COX-2) inhibitors such as celecoxib may control local inflammatory symptoms but do not treat the underlying disease. **Corticosteroids** have an immediate and dramatic effect on joint symptoms but were historically thought not to alter the natural progression of the disease. Recent evidence suggests that low-dose corticosteroids may retard the progression of bone erosions.

Disease-modifying antirheumatic drugs (**DMARDs**) may have a favorable impact on the natural course of the disease, reducing joint inflammation and disease activity and slowing or preventing the structural progression of RA. The nonbiologic DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, minocycline, and leflunomide. There is controversy regarding which DMARD is the most effective, but **methotrexate** is often used as the first drug of choice because of its rapid onset of action and higher tolerability and patient compliance. Toxicity of the various DMARDs is often the most important determinant of which drug is used, and if the patient fails to respond or develops unacceptable side effects, the patient may be tried on a different agent.

In the last decade, the **biologic DMARDs** have revolutionized the treatment of RA. **Tumor necrosis factor** (**TNF**) **antagonists** (etanercept, infliximab, adalimumab, golimumab, and certolizumab) have been found to reduce disease activity within weeks, unlike other DMARDs, which may take several months to act. TNF antagonists may also control signs and symptoms that have failed to respond to conventional DMARD therapy. Side effects of TNF blockers may include increased risk of infection, such as reactivation tuberculosis (TB), so all patients should first be screened for latent TB. Other biologics currently in use include **anakinra**, a recombinant interleukin (IL) 1 receptor antagonist; **abatacept**, a soluble fusion protein of IgG and human cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4); **rituximab**, a chimeric monoclonal antibody against CD20, a cell-surface molecule of B lymphocytes;

tocilizumab, a monoclonal antibody against IL-6; and **tofacitinib** and **baricitinib**, Janus kinase (JAK) inhibitors.

CASE CORRELATION

- See Case 31 (Osteoarthritis/Degenerative Joint Disease) and Case 33 (Acute Monoarticular Arthritis—Gout).

COMPREHENSION QUESTIONS

34.1 A 26-year-old day care worker presents to her provider because of pain and swelling in her hands located at the MPs and wrist joints bilaterally for about 2 weeks. She has an otherwise negative review of systems. She had a complete blood count (CBC) and comprehensive metabolic panel (CMP) that were normal. She also had a serum RF drawn, and the results were negative. Which of the following other types of arthritis is most likely to be the diagnosis in this patient?

A. Parvovirus-associated arthritis
B. Osteoarthritis
C. Fibromyalgia syndrome
D. Celiac disease–associated arthritis

34.2 A long-term patient with RA presents to your clinic for follow-up. She has been on treatment for several years, but she does have some chronic changes in her hands. You expect to find which of the following radiographic changes in her hands?

A. Pencil-in-cup deformities
B. Osteophyte formation
C. Marginal erosions
D. Syndesmophytes

34.3 A 42-year-old man presents to clinic for follow-up of his RA. He is on methotrexate and adalimumab for treatment of his RA. He has been doing very well with respect to his arthritis, and he is considered to be in disease remission. However, he has been having some night sweats, cough, and weight loss for the past 3 months. He has not traveled recently, and he lives and works full time in Houston, Texas. Which of the following studies would you order next for evaluation of these symptoms?

A. Parvovirus titers
B. Acute hepatitis C titers
C. Influenza virus
D. Acid-fast bacilli culture

34.4 A 36-year-old woman is being seen by her physician in the office due to pain in her hands, wrists, and knees that has progressed over the past 6 months. She has tried over-the-counter ibuprofen without relief. Based on the distribution of the joint involvement, she is diagnosed with RA. Which of the following treatments will reduce joint inflammation and slow progression of this patient's disease?

A. NSAIDs
B. Joint aspiration
C. Methotrexate
D. Systemic corticosteroids

ANSWERS

34.1 **A.** Parvovirus presents with a symmetric arthritis in the small joints of the hands that resembles RA. In adults who contract the virus, the arthritis is usually self-limiting. Children with parvovirus usually present with a rash on the face and often have no arthritis. The patient is young for OA (answer B), and the wrong joints (usually the DIP and PIP joints of the hands in OA) are affected. She does not describe widespread pain, which would be a feature of fibromyalgia syndrome (answer C). In addition, she has some systemic features, such as anemia, and she has not had GI symptoms suggestive of celiac disease (answer D). Celiac disease can be associated with arthritis as well that might mimic RA.

34.2 **C.** Marginal erosions, periarticular osteopenia, and uniform joint space narrowing are classic for RA. Pencil-in-cup radiographic changes (answer A) are seen in psoriatic arthritis. Osteophyte formation (answer B) is seen in OA, and syndesmophytes (answer D) are seen in ankylosing spondyloarthritis.

34.3 **D.** Acid fast studies should be obtained to assess for tuberculosis. This patient has been on treatment with an anti-TNF inhibitor, adalimumab, and has developed a cough and fever for 3 months. Therefore, it is possible the patient has reactivated TB, a known complication of the drug. Parvovirus (answer A) and acute hepatitis C (answer B) are not associated with a cough. The duration of symptoms is likely too long for influenza (answer C), making screening for TB the best choice. It is also important to remember that there are still active cases of TB in the United States, and one does not have to travel to contract TB.

34.4 **C.** Although NSAIDs (answer A) and corticosteroids (answer D) may help to relieve symptoms, they typically do not slow or prevent structural progression of disease. DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, and biologic agents. Of these agents, methotrexate is usually the drug of choice and is the anchor drug of most combination therapies. Joint aspiration (answer B) may relieve the acute symptoms of inflammation; it also will not slow the natural history of the disease.

CLINICAL PEARLS

- Rheumatoid arthritis is a chronic systemic inflammatory disorder characterized by the insidious onset of symmetric polyarthritis and extra-articular symptoms.
- Rheumatoid factor is found in the serum of 85% of patients with RA but is less specific than anti-CCP antibodies (specificity 95%).
- In nearly all patients with RA, the wrist, MP joints, and PIP joints are affected, whereas the DIP joints are spared.
- Distal interphalangeal joints and large weight-bearing joints are most commonly involved in OA.
- The typical x-ray finding in RA—periarticular osteopenia and the periarticular bone erosion—may not develop until later in the disease process, when the diagnosis has already been made based on clinical findings.
- DMARDs for RA include methotrexate, TNF antagonists, and other biologic agents.

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CASE 35

A 57-year-old man is referred to the internal medicine clinic for a right radius/ulnar fracture that occurred 1 week ago from an incidental contact with the car door. X-rays showed marked demineralization of the bones. He also has fatigue, weakness, and a 20-lb weight gain over the last 2 years, particularly around the abdomen. He has noticed these symptoms for around 3 months. He denies suffering from any medical condition, although his last visit to a primary care provider was more than 5 years ago. He reports a 30 pack-year history of cigarette smoking and denies alcohol or illicit drug consumption. On examination, his blood pressure is 155/95 mm Hg, pulse rate is 80 beats per minute (bpm), respiratory rate is 20 breaths per minute, and temperature is 99 °F. His body mass index (BMI) is 28 kg/m^2. His neck, abdomen, and upper back look full, with reddish-purple striae on his abdomen and thighs. His heart examination shows regular sounds S_1 and S_2, without murmurs or gallops. Lung examination shows a slightly decreased vesicular breath sound on the right hemithorax, without adventitious sounds. His abdomen is nontender and shows no organomegaly. His right arm is in a short arm cast. Laboratory tests show a hemoglobin A_{1c} (Hb A_{1c}) of 8.5%, serum sodium of 140 mmol/L (normal 135-145), serum potassium of 3.3 mmol/L (normal 3.5-5.1), and serum bicarbonate of 30 mmol/L (normal 24).

- What is the cause of the patient's bony problem?
- What is the most likely diagnosis?
- What are your next diagnostic steps?

ANSWERS TO CASE 35 B:
Osteoporosis, Cushing Syndrome

Summary: A 57-year-old man presents with

- A history of heavy smoking
- Decreased bone mineral density (BMD) and recent fragility fracture
- Fatigue, weakness, and weight gain
- BMI of 28 kg/m^2 (noted to be overweight)
- Hypertension, centripetal fat distribution, and reddish-purple striae
- Laboratory testing that shows hypokalemia, metabolic alkalosis, and elevated Hb A_{1c}

Cause of bony problem: Likely osteoporosis or osteopenia due to high corticosteroid levels.

Most likely diagnosis: Cushing syndrome, possibly paraneoplastic.

Next diagnostic step:

- Once Cushing syndrome is suspected, one of three tests should be obtained: 24-hour urine-free cortisol (UFC), late-night salivary cortisol, or the low-dose (1 mg) overnight dexamethasone suppression test (DST).
- If any of the above is abnormal, obtain a chest x-ray or contrast-enhanced computed tomography (CT) of the chest. There is high suspicion for ectopic adrenocorticotropic hormone (ACTH) syndrome from a small-cell lung carcinoma due to the history of heavy smoking, rapid onset of symptoms, and evidence of mineralocorticoid excess (hypertension, hypokalemia, and metabolic alkalosis).
- Obtain an imaging study of the BMD, such as a dual-energy x-ray absorptiometry (DEXA) test.

ANALYSIS

Objectives

1. Recognize the diagnostic approach to suspected Cushing syndrome. (EPA 3)
2. Outline the differential diagnosis for Cushing syndrome. (EPA 2)
3. Identify treatment options for Cushing syndrome. (EPA 4)
4. Describe the criteria to diagnose abnormally low BMD, such as osteopenia and osteoporosis. (EPA 1, 3)

Considerations

This 57-year-old man presents with a fragility fracture (bone fracture with minor or no trauma) and radiographic evidence of decreased bone mineralization on x-ray.

He also has many of the stigmata of corticosteroid excess, such as hypertension, central obesity, abdominal striae, hyperglycemia, and likely buffalo hump. Because of the smoking history, the Cushing syndrome may be due to a lung cancer secreting ACTH-like hormone (paraneoplastic syndrome), which stimulates the adrenal gland to produce excess corticosteroids. Another possibility is that there is an autonomous tumor (adenoma) of the adrenal cortex producing corticosteroids. The bony problem is likely due to the high levels of corticosteroids, which is the most common cause of secondary osteoporosis (not aged related); if the patient has an underlying lung cancer, bony metastasis to the arm is also possible. Cigarette smoking also predisposes to osteoporosis. The four most important issues for this patient are (1) suspecting Cushing syndrome based on the history and physical examination, (2) recommending the initial laboratory tests once Cushing syndrome is suspected, (3) determining the etiology of the Cushing syndrome, and (4) understanding other steps in management, including additional diagnostic tests and treatment options.

APPROACH TO:
Osteoporosis, Cushing Syndrome

DEFINITIONS

ACTH-DEPENDENT CUSHING SYNDROME: Cushing syndrome due to an ACTH-secreting pituitary adenoma or ectopic source.

ACTH-INDEPENDENT CUSHING SYNDROME: Cushing syndrome caused by an adrenal disorder.

BISPHOSPHONATES: Synthetic carbon phosphate compounds (alendronate, risedronate, ibandronate) that build bone mass by binding to pyrophosphatase in bone and by inhibiting osteoclast bone resorption.

CUSHING DISEASE: Cushing syndrome caused by an ACTH-secreting pituitary adenoma.

CUSHING SYNDROME: The signs and symptoms that develop when the body is exposed to excess glucocorticoids.

DEXAMETHASONE SUPPRESSION TEST: In normal individuals, supraphysiologic doses of glucocorticoids suppress the secretion of ACTH and cortisol. The low-dose (1-mg) DST is one of three tests obtained to confirm a diagnosis of Cushing syndrome. The high-dose (8-mg) DST is used to confirm the source of ACTH-dependent Cushing syndrome (ACTH-secreting pituitary adenoma or ectopic source).

OSTEOPENIA: BMD that is lower than normal and considered to be a precursor to osteoporosis. Often defined as a BMD T score of between −1 and −2.5.

OSTEOPOROSIS: Progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue and leading to an increase in bone fragility and susceptibility to fracture. Often defined as a BMD T score of less than −2.5.

T SCORE: A BMD comparison against young healthy adults (in standard deviations [SDs] from the mean).

CLINICAL APPROACH TO CUSHING SYNDROME

Pathophysiology

Iatrogenic Cushing syndrome, the most common cause, results from glucocorticoid treatment of inflammatory conditions. **Cushing disease,** which results from an ACTH-secreting pituitary adenoma, is the most common endogenous cause, accounting for 60% to 70% of cases. **Ectopic ACTH syndrome,** which comprises 5% to 10% of cases, refers to nonpituitary tumors that secrete ACTH. Most cases are due to small-cell lung carcinomas or neuroendocrine tumors of the lung, pancreas, or thymus. **Adrenocortical adenomas,** which secrete cortisol, account for 10% to 15% of cases. Other causes of Cushing syndrome include adrenocortical carcinoma, primary pigmented nodular adrenocortical disease (may occur as part of Carney complex), bilateral macronodular adrenal hyperplasia, and tumors that secrete corticotropin-releasing hormone (CRH). Long-term excess corticosteroid exposure (whether endogenous or medications) alters calcium absorption and directly inhibits osteoblast activity and augments osteoclast activity.

Clinical Presentation

Signs and symptoms of Cushing syndrome depend on the degree and duration of cortisol exposure. Some patients may present with obvious features of cortisol excess, while others present with subtle findings. While many features of Cushing syndrome are present in the general population (eg, obesity), some features are more specific for cortisol excess. This includes reddish-purple striae, plethora (ie, red face), proximal muscle weakness, and unexplained bruising. Other symptoms of cortisol excess include menstrual irregularities, decreased libido, and neuropsychiatric manifestations such as depression, sleep disturbances, and cognitive impairment. Associated conditions include hypertension, diabetes, and osteoporosis. On physical examination, the patient may exhibit facial fullness, supraclavicular or dorsocervical fat pads, thin skin, lower extremity edema, acne, or hirsutism.

Step 1: Confirm the Diagnosis of Cushing Syndrome. Once Cushing syndrome is suspected, one of three tests should be obtained: 24-hour UFC, late-night salivary cortisol, or the low-dose (1-mg) overnight DST. Each test has high sensitivity but lacks ideal specificity, so false-positive results may occur. If the initial diagnostic test is positive, one of the remaining tests must be obtained to confirm the diagnosis.

24-hour UFC: Two measurements should be obtained due to variability in cortisol secretion. False-positive results may occur with high fluid intake (> 5 L/d) or conditions associated with hypercortisolism (eg, depression or alcohol dependence). False-negative results may occur in patients with chronic kidney disease. Excreted urine cortisol levels begin to decrease with a creatinine clearance less

than 60 mL/min and decrease markedly with a creatinine clearance less than 20 mL/min.

Late-night salivary cortisol: In healthy individuals, cortisol levels peak in the morning (7-9 am) and fall to very low levels during sleep. Patients with Cushing syndrome typically lose this normal circadian rhythm. Salivary cortisol should be measured between 11 pm and midnight, and like UFC, two measurements should be obtained due to variability in cortisol secretion. **False-positive** results may occur in patients who use tobacco, as tobacco contains 11-beta-hydroxysteroid dehydrogenase type 2 inhibitor glycyrrhizic acid, which inhibits the conversion of cortisol to inactive cortisone. Late-night salivary cortisol may not be appropriate for shift workers or patients with variable sleep patterns.

The low-dose (1-mg) DST: In normal individuals, supraphysiologic doses of glucocorticoids suppress the secretion of ACTH and cortisol. For the low-dose DST, the patient takes 1 mg of dexamethasone between 11 pm and midnight. Cortisol is measured the following morning at 8 am. The Endocrine Society recommends using a diagnostic cutoff value of 1.8 μg/dL to maximize sensitivity (greater than 95%). Using this cutoff, the specificity is 80%, yielding a high false-positive rate. **False-positive** results may occur in women taking oral contraceptive pills, which increase cortisol-binding globulin, leading to higher serum cortisol levels. In addition, false-positive results may occur in patients taking medications (eg, itraconazole, ritonavir) that decrease clearance of dexamethasone by inhibiting CYP (cytochrome P450) 34A. **False-negative** results may occur in patients taking medications (eg, phenobarbital, phenytoin, rifampin) that accelerate the metabolism of dexamethasone by inducing CYP 34A.

Step 2: Determine the Etiology (ACTH-Independent vs ACTH-Dependent Cushing Syndrome). After a diagnosis of Cushing syndrome is confirmed, plasma ACTH should be measured to determine the etiology.

ACTH-independent Cushing syndrome: A suppressed ACTH level (< 10 pg/mL) indicates the presence of an adrenal disorder (eg, adrenal adenoma or adrenal carcinoma). CT or magnetic resonance imaging (MRI) of the adrenal glands should be obtained to determine the type of adrenal lesion.

ACTH-dependent Cushing syndrome: A normal or elevated ACTH level (> 10 pg/mL) indicates the presence of an ACTH-secreting pituitary adenoma (Cushing disease) or ectopic ACTH secretion. Since the majority (80%) of cases are due to Cushing disease, a pituitary-protocol MRI is typically performed as the next diagnostic test. If there is high clinical suspicion for ectopic ACTH secretion, CT or MRI of the neck, chest, or abdomen/pelvis may be obtained to identify the causal tumor. Although there is overlap in ACTH levels and clinical presentation, patients with ectopic ACTH syndrome typically present with more severe hypercortisolism and evidence of mineralocorticoid excess (eg, hypertension, hypokalemia, metabolic alkalosis, or edema).

Step 3: Confirm the Source of ACTH-Dependent Cushing Syndrome. It is often challenging to localize an ACTH-secreting microadenoma on MRI. An adenoma is identified on imaging in only 60% of patients with Cushing disease. A normal MRI does not exclude a diagnosis of Cushing disease. Small pituitary lesions (≤ 6 mm) occur in 10% of the general population, so the presence of a pituitary abnormality

on MRI does not confirm the diagnosis. Additional testing should be obtained to confirm the source of Cushing syndrome prior to surgical resection.

Inferior petrosal sinus sampling (IPSS): The Endocrine Society recommends IPSS for patients without an obvious causal tumor (ie, pituitary adenoma > 6 mm). Blood from the pituitary drains into the inferior petrosal sinuses. During petrosal sinus sampling, blood is sampled from both petrosal sinuses and a peripheral vein simultaneously. The central-to-peripheral ratio of ACTH is greater than 2:1 in patients with Cushing disease. Because ACTH secretion can be intermittent, it is helpful to sample blood at regular intervals (2, 5, and 15 minutes) after CRH is administered. A ratio greater than 3:1 after CRH administration has a sensitivity and specificity of 94% for the diagnosis of Cushing disease.

The high-dose (8-mg) DST: Noninvasive testing may be sufficient to confirm a diagnosis of Cushing disease if a pituitary adenoma greater than 6 mm is identified. In patients with Cushing disease, ACTH secretion is partially resistant to feedback inhibition from glucocorticoids. ACTH and cortisol secretion do not respond to 1 mg of dexamethasone (low-dose DST), whereas secretion is partially suppressed following the administration of 8 mg of dexamethasone (high-dose DST). For the high-dose DST, the patient takes 8 mg of dexamethasone between 11 pm and midnight. Cortisol is measured the following morning at 8 am. A 50% reduction in the cortisol level from baseline indicates a positive result. The high-dose DST yields high sensitivity but low specificity for identifying patients with Cushing disease.

CRH stimulation test: For the CRH stimulation test, ACTH and cortisol are measured at baseline and then every 15 minutes for 1 to 2 hours after CRH is administered. In healthy individuals, CRH produces a 15% to 20% increase in ACTH and cortisol levels. This response is exaggerated in patients with Cushing disease. ACTH typically increases by greater than 50%, and cortisol typically increases by greater than 20%. No response is seen in patients with ectopic ACTH syndrome. The sensitivity and specificity are approximately 90% for the diagnosis of Cushing disease.

Treatment

The first-line approach to treatment is typically surgical resection of the causal tumor. For example, if an adrenal adenoma is found, surgery is usually the best option. Medical management may be considered in the following situations: (1) persistent hypercortisolism following surgery, (2) a tumor that cannot be resected (eg, ACTH-producing small-cell lung carcinoma with metastases), and (3) situations in which cortisol levels need to be rapidly decreased in severely ill patients. The medications listed in Table 35–1 are used to treat patients with **ACTH-independent or ACTH-dependent Cushing syndrome.**

Medications used to treat patients with **ACTH-dependent Cushing syndrome** include **somatostatin receptor agonists and dopamine agonists**. **Pasireotide** is a somatostatin receptor agonist that has a higher affinity for somatostatin receptor subtypes 1 and 5 than octreotide or lanreotide. ACTH-secreting pituitary adenomas have high expression of somatostatin receptor subtype 5. Pasireotide decreases ACTH secretion and may decrease tumor size. **Octreotide** has been used to treat ectopic ACTH syndrome. Some ACTH-secreting tumors express somatostatin receptor subtype 2.

Table 35–1 • MEDICATIONS FOR ACTH-DEPENDENT OR ACTH-INDEPENDENT CUSHING SYNDROME

Class	Medication	Mechanism	Comments
Steroidogenesis inhibitors	**Ketoconazole**	Inhibits adrenal and gonadal steroidogenesis by inhibiting 17,20-lyase and 11-beta-hydroxylase enzymes	Typically causes a rapid decrease in cortisol secretion. Severe hepatic dysfunction is estimated to occur in 1 in 15,000 exposed individuals.
	Metyrapone	Inhibits 11-beta-hydroxylase, rapidly decreasing cortisol secretion by blocking the conversion of 11-deoxycortisol to cortisol	
	Etomidate	Inhibits 11-beta-hydroxylase and cholesterol side-chain cleavage	Often used for anesthesia induction administered as an intravenous infusion. Patients should be monitored in an intensive care unit.
	Mitotane	Adrenal cytotoxic agent	Primarily used to treat adrenal carcinoma.
Glucocorticoid receptor antagonist	**Mifepristone**	Antagonist of glucocorticoid and progesterone receptors	Cortisol levels remain unchanged or increase during treatment, so laboratory testing cannot be used to guide therapy. Approved in the United States to treat patients with diabetes or glucose intolerance due to hypercortisolism.

The **dopamine agonist cabergoline** has high affinity for dopamine receptor subtype 2, which is expressed by most ACTH-secreting pituitary adenomas. It is occasionally used to treat ectopic ACTH syndrome. Cabergoline is typically less effective than other agents for the treatment of Cushing syndrome.

CLINICAL APPROACH TO OSTEOPOROSIS

Epidemiology

Osteoporosis is an important health issue because the resultant bone fractures cause a great deal of morbidity in chronic pain, loss of independence, and loss of function, as well as mortality. Risk factors for the development of osteoporotic fracture include advanced age, previous fracture, glucocorticoid therapy, rheumatoid arthritis, low body weight, loss of steroid hormone production (menopause or hypogonadism), current smoking, excessive alcohol, and parental history of hip fracture. The **Fracture Risk Assessment Tool (FRAX) risk calculator** is available online to assess the 10-year probability of fracture. Approximately 14% of white women and 3% to 5% of white men will develop osteoporosis in their lifetime. The prevalence is lower in African Americans and higher in Asians.

Pathophysiology

Osteoporosis can be either idiopathic or a manifestation of another underlying disease process. Probably the most common form of **secondary osteoporosis** is caused by **glucocorticoid excess**, usually iatrogenic steroid use for an inflammatory disease such as rheumatoid arthritis. Patients, both men and women, with rheumatoid arthritis are susceptible to accelerated bone loss with even low doses of glucocorticoids. **Gonadal deficiency** is another common cause, which is seen physiologically in menopausal women but is seen pathologically in women who are amenorrheic (eg, female athletes such as gymnasts or marathon runners) or as a result of hyperprolactinemia. Men with gonadal failure for any reason also are prone to develop osteoporosis.

Osteoporosis is a common feature of several endocrinopathies. Patients with **hyperparathyroidism** will develop osteoporosis because of increased calcium mobilization from bone. Long-standing **hyperthyroidism**, either naturally occurring, as in Graves disease, or as a result of excessive replacement of levothyroxine in patients with hypothyroidism, will also lead to accelerated bone loss. Malnutrition and nutritional deficiencies are causative and are often seen in patients with malabsorption; for example, most patients, both men and women, with **celiac sprue** have osteoporosis. Certain medications, such as cyclosporine, antiepileptics, heparin, and gonadotropin-releasing hormone inhibitors, among others, may accelerate bone loss.

Peak bone density occurs in young adulthood under the influence of sex steroid hormone production. Other influential factors include **genetics**, which may account for 80% of total bone density, adequate calcium intake, and level of physical activity, especially **weight-bearing activity**. After age 35, bone breakdown begins to exceed bone replacement, and this increases **markedly after menopause** as a consequence of **increased osteoclast activity**.

Treatment

Treatment of osteoporosis takes a multifaceted approach. The first is avoidance of medications or conditions that predispose to bone loss (smoking cessation, reduction of systemic steroid use, and attention to nutrition). Adequate **calcium intake**, 1000 mg/d for premenopausal women and adult men and 1200 mg with 400 to 800 IU of **vitamin D** per day for postmenopausal women, leads to decreased fractures. Steroid estrogen receptor modulators such as raloxifene can increase bone density and reduce fracture risk, as can the use of bisphosphonates, in combination with both calcium and vitamin D. **Bisphosphonates** can lead to **severe esophagitis** and must be used with caution in individuals with gastric reflux disease. Oral bisphosphonates should be taken on an empty stomach, with a large quantity of water, and the patient should remain in the upright position for at least 30 minutes. Intravenous bisphosphonates are now available that can be infused quarterly or annually. There is some concern about long-term effects of bisphosphonates, including risk of osteonecrosis of the jaw and paradoxical bone fragility causing atypical subtrochanteric femur fractures. Many experts recommend a drug holiday after 5 years of treatment for patients with stable BMD.

Weight-bearing physical activity decreases bone loss and improves coordination and muscle strength, which may prevent falls. Ensuring that patients can see adequately, that they use a cane or walker if needed, that throw rugs are removed, that

patients have railings to hold onto in the shower or bath, or that they wear hip protectors can further decrease the risk of life-altering bone fractures.

CASE CORRELATION

- See also Case 6 (Hypertension, Outpatient) and Case 51 (Type 2 Diabetes Diagnosis and Management).

COMPREHENSION QUESTIONS

35.1 A 38-year-old woman is being seen in the office due to concerns about irregular menses and a 15-lb weight gain over the last 2 years. Menarche occurred at age 12. Menses were regular until 2 years ago. Physical examination is notable for a blood pressure of 140/90 mm Hg, facial fullness, hirsutism, and supraclavicular fullness. Which of the following is the best next step?

A. High-dose (8-mg) DST
B. Low-dose (1-mg) DST
C. Measure plasma ACTH
D. Pituitary-protocol MRI

35.2 A 62-year-old man was seen by his primary care provider 2 weeks ago for severe, sudden-onset back pain. On further evaluation, his provider noted new-onset hypertension, dorsocervical fullness, and reddish-purple striae on his abdomen. An x-ray confirmed a T12 compression fracture. Laboratory tests showed an elevated serum cortisol level not suppressed by dexamethasone and two elevated 24-hour UFC values. Which of the following is the best next step?

A. High-dose DST
B. IPSS
C. Measure plasma ACTH
D. Pituitary-protocol MRI

35.3 A 57-year-old woman was seen 3 weeks ago for a health maintenance appointment. She complained about weight gain and difficulty sleeping over the last year. Physical examination revealed new-onset hypertension and centripetal distribution of fat. Laboratory tests show a Hb A_{1c} of 8%, two elevated late-night salivary cortisol values, and two elevated 24-hour UFC values. Plasma ACTH is less than 5 pg/mL (normal 10-60). Which of the following is the best next step?

A. Abdominal CT
B. Chest CT
C. Pituitary-protocol MRI
D. Neck CT

35.4 A 32-year-old man was seen for a 2-year history of decreased libido, weight gain, and anxiety. On further evaluation, he was found to have unexplained bruising and supraclavicular fullness. Laboratory tests show an elevated serum cortisol level not suppressed by dexamethasone and two elevated late-night salivary cortisol values. Plasma ACTH is 38 pg/mL (normal 10-60). Pituitary-protocol MRI is normal. Which of the following is the best next step?

A. Abdominal CT

B. Chest CT

C. Inferior petrosal sinus sampling

D. A 24-hour UFC

35.5 A 60-year-old woman presents to the office for the results of her DEXA scan, which was performed as routine screening. She has no history of fragility fractures. She has a T score of −1.5 SD at the hip and −2.5 at the spine. Which of the following is the most accurate interpretation of these results?

A. She has osteoporosis at the spine and osteopenia at the hip.

B. She has osteoporosis in both areas.

C. This is a normal examination.

D. She has osteoporosis of the hip and osteopenia at the spine.

E. You need to know the Z score.

35.6 A 70-year-old woman is being seen in your office for a routine annual examination, and you order a DEXA scan for BMD screening. The T score returns as −2.5 SD in the spine and −2.6 in the hip. Which of the following statements is most accurate regarding this patient?

A. This patient has osteopenia.

B. Estrogen replacement therapy should be started with an anticipated rebuilding of bone mass to near normal within 1 year.

C. Swimming will help build bone mass.

D. Bisphosphonates would reduce the risk of hip fracture by 30% to 50%.

ANSWERS

35.1 **B.** This patient exhibits several signs and symptoms concerning for Cushing syndrome, including weight gain, hypertension, irregular menses, facial fullness, hirsutism, and supraclavicular fat pads. The low-dose DST is one of three tests performed to confirm the diagnosis of Cushing syndrome. Plasma ACTH (answer C) is obtained to determine the etiology after a diagnosis of Cushing syndrome is established. The high-dose DST (answer A) is one of three diagnostic tests performed to confirm the source of ACTH-dependent Cushing syndrome (ACTH-secreting pituitary adenoma vs ectopic source). A pituitary-protocol MRI (answer D) would not be performed until after the diagnosis of Cushing is established. If Cushing syndrome is ruled out, other

potential causes of the patient's symptoms may include polycystic ovarian syndrome, and pelvic ultrasound may be useful to evaluate for this condition.

35.2 **C.** A diagnosis of Cushing syndrome is confirmed by the positive low-dose DST and two elevated 24-hour UFC values. Plasma ACTH should be measured to determine the etiology (ACTH-independent vs ACTH-dependent Cushing syndrome). A pituitary-protocol MRI (answer D), high-dose DST (answer A), or IPSS (answer B) may be obtained after a diagnosis of ACTH-dependent Cushing syndrome is established.

35.3 **A.** A diagnosis of ACTH-independent Cushing syndrome is established by the suppressed ACTH level. A CT of the adrenal glands should be obtained to determine the type of adrenal lesion. A pituitary-protocol MRI (answer C), chest CT (answer B), or neck CT (answer D) may be obtained to identify the source of ACTH-dependent Cushing syndrome.

35.4 **C.** This young man has clinical findings of corticosteroid excess based on decreased libido, weight gain, bruising, and supraclavicular fullness (fat pad). The elevated serum cortisol not suppressed with dexamethasone and two salivary cortisol levels confirms hypercortisolism. A 24 hour UFC is not necessary since Cushing syndrome has already been established using two tests. The next step is to determine whether this is an ACTH-dependent or independent process. Because of the normal serum ACTH levels, this patient has ACTH-dependent Cushing syndrome; ACTH-independent Cushing syndrome is associated with low levels of serum ACTH. The third step is to determine the source of the ACTH. Most of the time, it will arise from the pituitary gland, but can also result from an ectopic ACTH producing location. This patient has a normal MRI of the pituitary gland; however, this finding does not exclude a diagnosis of Cushing disease (pituitary adenoma) since MRI is only 60% sensitive in these patients; nevertheless, because the MRI is non-invasive, it is the initial test used. If the MRI is negative as in this patient's situation, the more invasive IPSS (answer C) is recommended to distinguish between an ACTH-secreting pituitary adenoma versus a peripheral source of ACTH. IPSS assesses the ACTH levels of the veins draining the pituitary gland. If the IPSS shows low levels of venous ACTH, then an ectopic source of ACTH is responsible, and a CT of the neck, chest, or abdomen/pelvis (answers A and B) may be obtained. If the IPSS is positive for elevated ACTH, then affected patients usually undergo transsphenoidal surgery or medical management if surgery is not possible.

35.5 **A.** The T score is the number of SDs of a patient BMD from the mean of young, adult, white women. It is the standard measurement of BMD used by the World Health Organization. Osteopenia is defined as a T score of 1 to −2.4. A score of −2.5 SD is the definition of osteoporosis. A Z score is the number of standard deviations from the mean BMD of women in the same age group as the patient. Based on this terminology, the patient has osteoporosis of the spine (T score −2.5) and osteopenia of the hip (T score −1.5). The other answer choices (B, C, and D) are inaccurate assessments of the T score.

Answer E (Z score) is age-matched evaluation and not used in the definition of osteoporosis/osteopenia. This patient would benefit from review of her diet, assessment of vitamin D intake and levels, cessation of anything that would compromise bone health, and recommendation of starting pharmacological therapy such as a bisphosphonate.

35.6 **D.** This patient has osteoporosis based on the DEXA scan findings of −2.5 and −2.6. Bisphosphonates would decrease her risk of hip fractures by 30% to 50%. Alendronate and risedronate have been associated with a lower all-cause mortality. Answer A (osteopenia) is defined as a T score between −1 and −2.5. Answer B (estrogen) primarily inhibits loss of bone mass, although not only can it help to build a modest amount of bone mass, but it may also be associated with increased thrombotic and cardiovascular risk; for this reason, osteoporosis is not an indication to start estrogen replacement therapy in postmenopausal women. Answer C (swimming) is not helpful; weight-bearing exercise, not swimming or bicycling, is important in preventing osteoporosis.

CLINICAL PEARLS

- Osteoporosis is a condition of decreased bone mass and microarchitectural abnormalities that predisposes the patient to fragility fractures.
- The T score is a common way of assessing clinical BMD. Osteoporosis is defined as T score of −2.5 or less.
- Osteopenia is defined as a T score of between −1 and −2.5.
- Chronic exposure to excessive corticosteroids is the most common cause of secondary osteoporosis.
- Bisphosphonates are the most common first-line agent for osteoporosis, but they do have some rare but significant side effects.
- Cushing syndrome refers to the signs and symptoms that develop when the body is exposed to excess glucocorticoids.
- Signs of Cushing syndrome include facial fullness, plethora (ie, red face), supraclavicular or dorsocervical fat pads, reddish-purple striae, proximal muscle weakness, and unexplained bruising.
- Once Cushing syndrome is suspected, one of three tests should be obtained: 24-hour UFC, late-night salivary cortisol, or the low-dose (1-mg) overnight DST. If the initial test is positive, one of the remaining tests must be obtained to confirm the diagnosis.
- After a diagnosis of Cushing syndrome is confirmed, plasma ACTH should be measured to determine the etiology (ACTH-independent vs ACTH-dependent Cushing syndrome).

- For ACTH-dependent Cushing syndrome, the source (pituitary vs ectopic ACTH syndrome) can be confirmed with additional testing, including IPSS, the high-dose (8-mg) DST, and the CRH stimulation test.
- The first-line treatment of Cushing syndrome is surgical resection of the causal tumor. Medical management may be considered in certain situations.
- Medications include steroidogenesis inhibitors (ketoconazole, metyrapone, etomidate, mitotane), a glucocorticoid receptor antagonist (mifepristone), somatostatin receptor agonists (pasireotide, octreotide), and a dopamine agonist (cabergoline).

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CASE 36

A 72-year-old man is seen in the emergency department because of the acute onset of a right facial droop, right arm weakness, and some difficulty speaking. These symptoms started 6 hours ago while he was sitting at the breakfast table. He had no headache, no loss of consciousness, and no abnormal involuntary movements. Two weeks ago, he had a transient painless loss of vision in his left eye, which resolved spontaneously within a few hours. His medical history is significant for long-standing hypertension and a myocardial infarction 4 years previously, which was treated with percutaneous angioplasty. His medications include a daily aspirin (81 mg), metoprolol, and simvastatin. He does not smoke. When you see him in the emergency department, his symptoms have nearly resolved. He is afebrile, heart rate is 62 beats per minute (bpm), and blood pressure (BP) is 135/87 mm Hg. The right corner of his mouth droops, with slight flattening of the right nasolabial fold, but he is able to fully elevate his eyebrows. His strength is 4/5 in his right arm and hand, and the rest of his neurologic examination, including cerebellar testing and gait, are normal. He has no carotid bruits; his heart rhythm is regular with no murmur but with an S_4 gallop. The remainder of his physical examination is normal. Laboratory studies, including renal function, liver function, lipid profile, glucose, and complete blood count (CBC), are normal. Within a few hours, all of the patient's symptoms have resolved.

- What is the most likely diagnosis?
- What is your next step in the care of this patient?

ANSWERS TO CASE 36:
Transient Ischemic Attack

Summary: A 72-year-old man presents with

- Acute onset of right facial droop and right arm weakness and some difficulty speaking, which resolves within hours
- No headache, decreased consciousness, or abnormal involuntary movements
- Previous transient painless loss of vision in his left eye that resolved spontaneously within a few hours
- Known atherosclerotic disease but no carotid bruits

Most likely diagnosis: Transient ischemic attack (TIA) most likely caused by atheroembolism from the left internal carotid artery.

Next step: Perform urgent noncontrast computed tomography (CT) of the head.

ANALYSIS

Objectives

1. Describe the most common mechanisms for ischemic stroke: carotid stenosis, cardioembolism, and small-vessel disease. (EPA 2, 10)
2. Understand the evaluation of a stroke patient with the goal of secondary prevention. (EPA 1, 3)
3. Differentiate patients best managed with medical therapy from those who benefit from carotid endarterectomy (CEA). (EPA 4)

Considerations

Patients who present with acute focal neurologic deficits require rapid evaluation for suspected stroke. The saying is, "Time is brain tissue." An efficient but thorough neurologic examination should include cranial nerve testing, somatic motor strength, somatic sensory testing, speech and language assessment, and cerebellar testing, including gait. Neurologic scoring should be done on a standardized manner such as the National Institute of Health Stroke Scale. Emergency laboratory work, such as glucose, CBC, electrolytes, and coagulation profile, and electrocardiography (ECG) are important. **Noncontrast CT of the brain** is necessary to differentiate between ischemic stroke and hemorrhagic stroke, which cannot be definitively distinguished clinically. If CT shows no hemorrhage and no large multilobar infarction (> one-third of the cerebral hemisphere), patients with the clinical diagnosis of acute ischemic attack may receive **thrombolytics** (intravenous recombinant tissue plasminogen activator [tPA]) as long as it can be delivered **within 3 hours** (some patients may be treated with intravenous thrombolytics up to 4.5 hours) of the onset of symptoms; this is associated with a reduction in mortality and disability. Thus, rapid triaging of patients with possible TIA/stroke is critical.

This 72-year-old man presented more than 6 hours after the onset of symptoms and has had resolution of neurologic deficits, consistent with a suspected diagnosis of TIA. He has established atherosclerotic coronary disease but no known carotid artery disease. He denies headache, which is important because migraine headache may be associated with neurologic deficits; it would be rare for an elderly man to have the first presentation of migraine headache. Various neurologic diseases, such as multiple sclerosis, may be characterized by complete resolution of neurologic deficits, but the symptoms usually last longer than 24 hours. He does not have abnormal motor activity, which might suggest seizure disorder.

If the noncontrast CT excludes acute intracranial pathology, the patient should be counseled about secondary prevention of future ischemic events; this includes risk factor reduction through antiplatelet and statin therapy, BP control, smoking cessation, and noninvasive imaging of the carotid arteries to determine the extent of stenosis. With the patient's symptoms, if there is more than 70% stenosis of the left internal carotid artery, the possibility of left CEA should be discussed.

APPROACH TO:

Transient Ischemic Attack and Prevention of Stroke

DEFINITIONS

AMAUROSIS FUGAX: Transient monocular blindness that often is described as a gray shade being pulled down over the eye caused by retinal ischemia, most often due to emboli originating from the carotid artery.

CEREBROVASCULAR ACCIDENT (CVA): Also known as stroke. Acute onset of a focal neurologic deficit due to a cerebral infarction or hemorrhage. CVAs are widely subdivided into ischemic and hemorrhagic.

TRANSIENT ISCHEMIC ATTACK: Transient neurologic deficit caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

CLINICAL APPROACH

Pathophysiology

Transient ischemic attacks, often called "ministrokes," typically refer to the sudden onset of a focal neurologic deficit, with spontaneous resolution within 24 hours (usually within the first hour). However, current definition of TIA focuses on a biological end point (tissue injury) rather than an arbitrary time cutoff. Recent understanding is that there is risk of tissue infarction, even when focal symptoms resolve within less than 24 hours, which may be visualized on brain magnetic resonance imaging (MRI) with diffusion-weighted or perfusion-weighted imaging.

Not all transient focal neurologic events actually represent ischemia, however. The differential diagnosis includes classic migraine, postictal paralysis, seizures,

certain infections, prolonged hypoglycemia, cerebral hemorrhage, or even slow-evolving intracranial processes such as subdural hematoma, abscess, or tumors, which can suddenly produce symptoms because of edema or hemorrhage or can result in seizure activity. However, clinical evaluation and imaging studies of the brain should be sufficient to exclude most or all of these diagnoses.

TIAs are produced by temporary ischemia to a vascular territory, usually caused by thrombosis or embolism and less commonly by vasculitis, hematologic disorders such as sickle cell disease, or vasospasm. By far, the most common causes of stroke or TIA are **carotid atherosclerosis** (large-vessel disease); **cardioembolism,** usually to branches of the middle cerebral artery (medium-size vessel disease); or **lipohyalinosis** affecting the small lenticulostriate arteries (small-vessel disease).

Clinical Presentation

The **focal neurologic symptoms** produced by ischemia depend on the **area of the cerebral circulation** involved and may include (1) amaurosis fugax, (2) hemiparesis, (3) hemianesthesia, (4) aphasia, or (5) dizziness/vertigo as a result of vertebrobasilar insufficiency. The significance of a TIA is not the symptoms it produces because by definition it is self-resolved, but the risk for future events it portends. **The highest-risk patients for stroke are those with previous ischemic events such as TIA**; that is, it can be looked on as a warning sign of recurrent stroke, which may be disabling. Table 36–1 shows the $ABCD^2$ scoring system, which can be used to triage patients with TIA to assess their risk for recurrent events within the first 3 months (most of them occur within the first 2 days).

The workup for a TIA begins with a history and physical examination (see Table 36–2). Pertinent historical factors include time of onset, course, duration

Table 36–1 • $ABCD^2$ SCORE: RISK OF STROKE FOLLOWING TIA

Clinical Factor	Score
A: Age ≥ 60 y	1
B: Blood pressure > 140/90 mm Hg	1
C: Clinical symptoms	
Unilateral weakness	2
Speech disturbance without weakness	1
D: Duration	
≥ 60 min	2
10-59 min	1
D: Diabetes	1
Total Score	**2-Day Stroke Risk**
6-7	High (8%)
4-5	Moderate (4%)
0-3	Low (1%)

Table 36–2 • WORKUP FOR CAUSES OF ISCHEMIC STROKE OR TIA

CT Head and/or MRI • CT is more cost-effective and can quickly rule out bleeding in the brain • MRI is more sensitive for small lacunar infarcts
ECG • Atrial fibrillation
Echocardiography • Dilated cardiomyopathy, mural thrombus • Bacterial endocarditis • Prosthetic valve thrombosis • Paradoxical embolus (atrial septal defect, patent foramen ovale)
MR Angiography or CT Angiography or Carotid Duplex Ultrasonography • Acute thrombosis of large-to-medium arteries (eg, internal carotid, middle cerebral) due to atherosclerotic disease • Carotid stenosis
Basic Blood Tests • CBC, PT, PTT, electrolytes, creatinine, diabetes screening, lipids, ESR
Consider Workup for Other Causes on a Case-by-Case Basis • Hypercoagulable disorders, vasculitis (infectious or autoimmune), sickle cell disease, venous sinus thrombosis, Moyamoya disease, drug-related causes

Abbreviations: ESR, erythrocyte sedimentation rate; PT, prothrombin time; PTT, partial thromboplastin time.

of symptoms, atherosclerotic risk factors, and relevant medical history (ie, atrial fibrillation). Physical examination should begin with BPs in all four extremities and should include a fundoscopic examination. In this patient, the first symptom was amaurosis fugax due to cholesterol emboli, called **Hollenhorst plaques**, which often can be seen lodged in the retinal artery. Auscultation for carotid bruits, cardiac murmurs, assessment of cardiac rhythm, evidence of embolic events to other parts of the body, and a complete neurologic examination should also be performed.

A noncontrast CT scan (or some institutions prefer MRI) of the brain also must be performed initially. Noncontrast CT scans of the brain are very sensitive in detecting acute cerebral hemorrhage but are relatively insensitive to acute ischemic strokes, particularly when the area of the stroke is less than 5 mm in diameter or is located in the region of the brainstem or if the stroke is less than 12 hours old. Further imaging with magnetic resonance may be considered. Laboratory data that should always be obtained include CBC, fasting lipid profile, and serum glucose level. Other laboratory data, such as an **erythrocyte sedimentation rate in elderly populations to evaluate for temporal arteritis**, should be tailored to the patient. Generally, a 12-lead ECG must be obtained to evaluate for atrial fibrillation. An echocardiogram can be useful to evaluate for valvular or mural thrombi, along with a bubble study to assess for a connection between the atria. Finally, imaging of the extracranial vasculature to detect severe **carotid artery stenosis is essential to guide further stroke prevention therapy.** Carotid Doppler ultrasound and magnetic resonance angiography are effective noninvasive imaging studies and are often used as first-line diagnostic tools.

Treatment

Stroke prevention begins with **antiplatelet therapy**, and **aspirin** should be used in all cases unless there is a contraindication to its use. Aspirin should be started within 48 hours of a TIA or stroke. However, if tPA is used, it is best to wait 24 hours after administration of the tPA to start aspirin therapy. Use of **clopidogrel** or combination **aspirin and dipyridamole** may be slightly superior to aspirin for stroke prevention but at a substantially higher cost. Combination therapy with aspirin and clopidogrel has not been shown to provide greater benefit in stroke prevention but does produce a higher rate of bleeding complications.

For patients with **TIA/stroke as a consequence of carotid atherosclerosis**, medical management includes antiplatelet agents and **aggressive risk reduction** via BP control, treatment of hyperlipidemia and diabetes, and smoking cessation. In the acute phase of an ischemic event, when a patient has neurologic symptoms, hypertension is not to be dropped significantly since arterial BP that is too low may underperfuse the brain tissue beyond a blockage (this concept is recognized as *permissive hypertension*). Acute BP management is recommended only when systolic BP > 220 mm Hg, diastolic BP > 120 mm Hg, or tPA will be administered (goal of systolic BP < 185 mm Hg and diastolic BP < 110 mm Hg). Blood glucose should be maintained between 140 and 180 mg/dL during a stroke, as tight glucose control shows a mortality benefit poststroke.

As a part of future stroke risk reduction, after 24 hours, if the patient is stable neurologically, antihypertensive therapy can be restarted in patients with known hypertension. Patients with a TIA who are stable several days after the event and are found to have elevated BP pressure (≥ 140/90 mm Hg) should be treated to a goal BP of < 140 mm Hg systolic and < 90 mm Hg diastolic. **High-intensity statin therapy should be initiated for all TIA patients** to reduce the risk of stroke and other cardiovascular events. These patients should also undergo screening for diabetes with hemoglobin A_{1C}, fasting glucose measurement, or glucose tolerance test, and they should be treated based on the American Diabetic Association guidelines. Patients who are obese (body mass index > 30 kg/m^2) should be encouraged to implement lifestyle modifications to lose weight. While the effect of weight loss on stroke prevention is unclear, weight loss can help control other risk factors. Last, smoking cessation is an extremely important step to take in reducing the risk of a stroke, as primary prevention, as well as after a TIA.

For patients with cardioembolic stroke as a result of **atrial fibrillation**, long-term **anticoagulation with warfarin** (Coumadin) reduces the risk of systemic embolization by approximately 70%. Newer oral anticoagulants (dabigatran, apixaban, rivaroxaban, and edoxaban) have recently been approved for patients with atrial fibrillation and are comparable in efficacy to warfarin with lower risk of cerebral bleeding. The risk of stroke among patients with atrial fibrillation can be predicted using the CHADS2-Vasc score. For patients with small-vessel disease-producing lacunar infarctions, BP control and antiplatelet agents are the mainstays of therapy.

For TIA patients found to have carotid artery stenosis, in addition to medical therapy as described previously, patients should be evaluated for carotid artery endarterectomy (open surgery to remove plaques), carotid artery angioplasty (percutaneous intervention where inflation of a balloon is used to open the artery), or stenting.

Surgical endarterectomy for severe carotid artery stenosis has successfully reduced the long-term risk of stroke in both symptomatic and asymptomatic patients. For patients who suffer a TIA or stroke and have an ipsilateral **carotid artery stenosis** greater than **70%**, CEA reduces the rate of stroke and is highly recommended. For symptomatic patients with stenosis of 50% to 69%, CEA can reduce the future stroke risk, but it is recommended on a case-by-case basis, taking the patient's characteristics into account. For asymptomatic patients with greater than 60% stenoses, endarterectomy reduces the risk of stroke as well, but to a much lesser degree than symptomatic patients. It should be noted that the surgery is not without risk and can actually cause significant morbidity and mortality from a postsurgical stroke; therefore, the surgery should be performed in a center with very low surgical morbidity and mortality.

In asymptomatic patients, carotid surgery should only be performed when there is relatively low comorbidity and a long life expectancy in order to gain the most benefit. **Carotid artery stenting (CAS)** is available for patients with carotid stenosis, but like endarterectomy, it also carries a risk of embolization and stroke. Stenting may be considered as an alternative to surgery for symptomatic patients who are high-risk surgical candidates or for patients with anatomy that would prevent open surgery. In patients over the age of 70 years, endarterectomy is associated with better outcomes. In younger patients, endarterectomy and stenting are considered equal in terms of periprocedural complications. For carotid stenosis of less than 50%, neither CAS nor CEA is recommended.

CASE CORRELATION

- See also Case 8 (Atrial Fibrillation/Mitral Stenosis) and Case 38 (Headache/Temporal Arteritis).

COMPREHENSION QUESTIONS

36.1 A previously healthy 75-year-old man is being seen in the office for an episode of weakness that he reports occurred 2 weeks previously. He states that he had weakness of the left arm and left leg that lasted for 4 hours and slowly resolved over the rest of day. His arm and leg also felt "heavy" and had some numbness. He denies having similar episodes in the past. On physical examination, his BP is 140/90 mm Hg. He is found to have a right carotid bruit on auscultation. A duplex ultrasound demonstrates a 75% stenosis of the right carotid artery. Which of the following is the best therapy for this patient at this time?

A. Aspirin plus clopidogrel
B. Warfarin (Coumadin)
C. Carotid endarterectomy
D. Carotid artery stenting
E. Tissue plasminogen activator

36.2 One year ago, a 24-year-old woman had an episode of diplopia of 2 weeks' duration. The symptoms resolved completely. Currently, she complains of left arm weakness but no headache. Which of the following is the most likely diagnosis?

A. Recurrent TIAs
B. Subarachnoid hemorrhage
C. Complicated migraine
D. Multiple sclerosis

36.3 A 67-year-old woman is being seen in the office for the acute onset of dizziness. She says she was sitting on the couch watching TV when the episode came on, and the room was spinning. She feels nauseous. Her history includes a stroke 2 years ago that left some right-sided weakness. Which of the following arteries is most likely to be affected in today's presentation?

A. Vertebrobasilar
B. Carotid
C. Aorta
D. Middle cerebral

36.4 A 62-year-old man who works at an automobile assembly line has noticed that he feels pain, fatigue, and numbness in his right arm while working for the last several months. This morning at work, he noticed vertigo, then lightheadedness, then lost consciousness for a few seconds. The BP in his right arm is 30 mm Hg lower than that in his left arm. What is the most likely diagnosis?

A. Left middle cerebral artery stroke
B. Lacunar infarction involving right internal capsule
C. Stenosis of right subclavian artery due to atherosclerosis
D. Multiple sclerosis

ANSWERS

36.1 **C.** This patient has symptomatic carotid disease, which includes symptoms such as TIAs and small, nondisabling ischemic strokes. A patient who presents with symptomatic carotid disease and stenosis between 70% and 99% should receive a CEA. It has been found that patients over the age of 70 fare better with a CEA than stenting alone (answer D). When symptomatic patients present with stenosis between 50% and 69%, management depends on gender. Women tend to have better outcomes with optimal medical management, whereas men have improved outcomes with CEA. Medical therapy such as antiplatelet medication (answer A) or anticoagulation (answer B) is not as effective as CEA in this circumstance. Tissue plasminogen activator (tPA) (answer E) is indicated for thromobotic strokes within 4.5 hours of onset of symptoms and not appropriate in this patient's setting.

36.2 **D.** Multiple neurologic deficits separated in space and time in a young patient are suggestive of multiple sclerosis. The symptoms lasting longer than 24 hours as well as the patient's age make TIAs (answer A), even if recurrent, less likely to be the cause of her symptoms. A subarachnoid hemorrhage (answer B) will often present with a "thunder clap headache" or "the worst headache" of the patient's life and is usually an isolated event. A complicated migraine (answer C) can include symptoms such as changes in vision and arm weakness but with or before the onset of the headache.

36.3 **A.** Vertigo and dizziness can be seen in vertebrobasilar insufficiency. Transient monocular blindness or amaurosis fugax is associated with internal carotid (answer B) pathology. Face weakness, dysarthria, and hemiplegia greater in the upper extremity are associated with pathology in the middle cerebral artery (answer D). A problem of the aorta (answer C) would lead to global brain ischemia as well as multiorgan insufficiency.

36.4 **C.** The patient likely has subclavian steal: the phenomenon of flow reversal in the vertebral artery ipsilateral to a hemodynamically significant stenosis of the subclavian artery. The neurologic symptoms can be caused by vertebrobasilar ischemia, hence the problems with vertigo. The difference in BP in both arms strongly suggests this diagnosis. Left middle cerebral artery stroke (answer A) would lead to speech difficulties and right hemiplegia. Lacunar infarcts involving the right internal capsule (answer B) would lead to transient left-sided arm/leg weakness or sensory deficits and not vertigo. Multiple sclerosis (answer D), which is a demyelinating disease affecting the white matter of the brain, can lead to a variety of deficits, including vertigo, weakness, and diplopia; however, there is no difference in BP in the arms with MS.

CLINICAL PEARLS

- The most common causes of cerebral infarction are carotid atherosclerotic stenosis, cardioembolism, and small-vessel disease such as lipohyalinosis.
- Cerebral infarction, TIA, and amaurosis fugax all may be symptoms of carotid stenosis.
- In symptomatic patients with severe stenosis > 70%, CEA is superior to medical therapy in stroke prevention, provided the surgical risk is low (< 6%).
- For other patients, stroke prevention consists mainly of antiplatelet agents (aspirin, clopidogrel) and risk factor modification, for example, lowering BP, controlling hypercholesterolemia, and smoking cessation.

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CASE 37

A 68-year-old woman is noted to have memory loss and confusion. Her daughter relates a history of progressive decline in her mother's cognitive function over the last year. The patient has lived on her own for many years, but recently she has had difficulty taking care of herself. The daughter states that her mother has become withdrawn and has lost interest in her usual activities, such as gardening and reading. The patient was always a fastidious housekeeper; however, recently she has been noted to wear the same clothes for several days, and her house is unkempt and dirty. She seems anxious and confused. She calls her daughter several times a day, worried that the neighbors, who were previously good friends, are now spying on her. She denies bowel or urinary incontinence, and she has had no trouble with headaches or gait instability. Overall, the patient has been very healthy. Her only medication is hydrochlorothiazide for hypertension. She has never smoked cigarettes and rarely drank alcohol. On examination, her vital signs are within normal limits and stable. She is noted to be well developed, but her affect throughout the examination is rather flat. She is oriented to person and place, but she is a little confused regarding the date. Cardiovascular and abdominal examinations are unremarkable. The extremities are without edema, cyanosis, or clubbing. Cranial nerves are intact, and the motor and sensory examinations are within normal limits. Cerebellar examination is unremarkable, and the gait is normal. Mini-Mental State Examination (MMSE) reveals a score of 24 out of 30.

- What is the most likely diagnosis?
- What are the best next diagnostic steps?
- What is the best treatment for the likely condition?

ANSWERS TO CASE 37:
Alzheimer Disease/Dementia

Summary: A 68-year-old woman presents with

- Memory loss, confusion, and fatigue
- Seeming more withdrawn with a flat affect
- Orientation to person and place, but not to time
- Low MMSE score

Most likely diagnosis: Alzheimer dementia.

Next diagnostic steps: Assess for depression and reversible causes of dementia.

Best treatment: Acetylcholinesterase inhibitor.

ANALYSIS

Objectives

1. List some of the common causes and evaluation of dementia. (EPA 1, 2)
2. Understand the presentation and diagnosis of Alzheimer dementia. (EPA 1, 3)
3. Recognize that acetylcholinesterase inhibitors may slow the progression of dementia. (EPA 4)

Considerations

In this elderly patient with slowly progressive decline in memory and cognitive functioning, dementia due to Alzheimer disease (AD) is the most likely diagnosis. As in other cases of major organ system failure (heart and kidney failures), dementia ("brain failure") necessitates investigation into treatable or reversible causes before assigning a diagnosis such as AD, which is progressive and incurable and has no effective treatment. In most studies, AD accounts for about 70% of dementia, and about 10% to 20% is due to vascular disorders such as stroke. However, alcohol use disorder, Parkinson, hypothyroidism, and less common disorders should still be explored. Also, depressive disorder needs to be further evaluated. Depression is more common in older patients and can mimic cognitive decline.

APPROACH TO: Dementia

DEFINITIONS

ALZHEIMER DISEASE: Leading cause of dementia, accounting for half of the cases involving elderly individuals, associated with diffuse cortical and hippocampal atrophy with ventricular enlargement. The pathologic changes in the brains of patients with AD include neurofibrillary tangles and deposition of abnormal amyloid in the brain. Risk factors include advanced age, positive family history, and presence of apolipoprotein E4 allele.

DEMENTIA (also called major neurocognitive disorder): Significant cognitive impairment in more than one of the following cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor function, or social cognition. The impairment represents a decline from previous level of ability, interferes with daily functioning and independent living, and is not occurring exclusively during an episode of delirium.

VASCULAR (MULTI-INFARCT) DEMENTIA: Dementia in the setting of cerebrovascular disease, occurring after multiple cerebral infarctions, whether large or small (lacunar).

CLINICAL APPROACH

Pathophysiology

In assessing the patient with dementia, the clinician should strive to answer three questions: (1) What is the most likely diagnosis? (2) Is there any treatable or reversible condition contributing to the patient's cognitive decline? (3) What interventions are available to preserve the patient's level of function and relieve the burden to caregivers?

To answer the first question, the most important investigation is the history of symptoms. If the patient has an acute or subacute onset of confusion or has a fluctuating level of consciousness, the most likely diagnosis is **delirium,** which can be due to infection, intoxication, adverse medication effects, medication withdrawal, or metabolic derangements such as hyponatremia, hypercalcemia, or hypoglycemia.

Depression and Pseudodementia. If cognitive decline occurs with prominent mood disturbance, then **depression** or **pseudodementia** must be considered. Distinguishing which occurred first is often difficult because many elderly patients with cognitive decline and a declining level of independent functioning suffer from a reactive depression. History provided by involved family members regarding the onset of symptoms or history of prior depression or other psychiatric illness may help establish the diagnosis, and an empiric trial of antidepressants may be considered. An MMSE score of 26 or less suggests mild dementia, with declining scores suggesting more severe dementia. However, a patient should also be screened for depression (eg, Patient Health Questionnaire-9 [PHQ-9]) to rule it out before a diagnosis of dementia is established. Cognitive screenings such as the

MMSE and Montreal Cognitive Assessment (MoCA) have relatively high sensitivity (75%-92%) and specificity (81%-91%) for dementia and should be used in screening.

Vascular Dementia. If the patient has a history of irregular stepwise decline in functioning—especially if the patient has had apparent stroke symptoms or transient ischemic events or has a known cardiovascular disease or atrial fibrillation—then vascular, or **multi-infarct, dementia** is the most likely diagnosis. **Vascular dementia is the second most common cause of dementia in the United States**, comprising 10% to 20% of dementias. Other patients with cerebrovascular disease, especially as a result of long-standing hypertension, may develop diffuse subcortical white matter changes seen on imaging, presenting with an insidious rather than sudden stepwise decline in cognitive function. This condition is often referred to as **Binswanger disease or subcortical arteriosclerotic leukoencephalopathy.**

Other Causes. Other common causes of dementia include long-standing **alcoholism** and **parkinsonism.** Both these conditions may be discovered by the appropriate history or physical findings (eg, resting tremor with bradykinesia and masked faces of parkinsonism). Other dementia syndromes include behavioral changes with intact navigation in **frontotemporal dementia** or rapid progression of dementia with muscular rigidity and myoclonus in **Creutzfeldt-Jakob disease.**

Less common causes of dementia include Wernicke encephalopathy caused from thiamine (vitamin B_1) deficiency, vitamin B_{12} deficiency resulting from pernicious anemia, untreated **hypothyroidism**, or chronic infections such as human immunodeficiency virus (**HIV**) or **neurosyphilis.**

Many primary central nervous system (CNS) diseases can lead to dementia or other cognitive dysfunction, including Huntington disease, multiple sclerosis, neoplastic diseases such as primary or metastatic brain tumors (more likely to produce seizures or focal deficits rather than dementia), or leptomeningeal spread of malignancies. Short-term memory loss, as seen in other dementias, seizures, and psychiatric symptoms, can result from paraneoplastic encephalitis mediated by autoantibodies found in the cerebrospinal fluid (CSF) (eg, limbic encephalitis).

Normal-pressure hydrocephalus is a potentially reversible form of dementia in which the cerebral ventricles slowly enlarge as a result of disturbances to cerebral spinal fluid resorption. The **classic triad is dementia, gait disturbance, and urinary or bowel incontinence (wacky, wobbly, and wet)**. Relief of hydrocephalus through placement of a ventriculoperitoneal shunt may reverse the cognitive decline. Descriptions of the primary neurologic diseases associated with cognitive dysfunction are listed in Table 37–1.

Once likely diagnoses have been established by history and physical examination, investigation should be undertaken to look for treatable or reversible causes. The choice of laboratory or imaging tests is not straightforward because of the numerous, yet uncommon, causes of reversible dementia. Tests that may be considered for the evaluation of dementia are listed in Table 37–2. The American Academy of Neurology recommends routine assessment of **thyroid function tests, a vitamin B_{12} level, and a neuroimaging study,** either with computed tomography (CT) or magnetic resonance imaging (MRI) of the brain.

Table 37–1 • CAUSES OF DEMENTIA

Disease	Clinical Features	Treatment
Alzheimer disease	Slow decline in cognitive and behavioral ability; neurofibrillary tangles, enlarged cerebral ventricles, atrophy	Cholinesterase inhibitors such as donepezil, rivastigmine, galantamine; add memantine for more advanced dementia
Normal-pressure hydrocephalus	Gait disturbance, dementia, incontinence; enlarged ventricles without atrophy	Ventricular shunting process
Vascular (multi-infarct) dementia	Focal deficits, stepwise loss of function; multiple areas of infarct, usually subcortical	Address atherosclerotic risk factors, identify and treat thrombus
Parkinson disease	Extrapyramidal signs (tremor, rigidity), slow onset with motor symptoms occurring before dementia; associated with alpha-synuclein bodies	Dopaminergic agents
HIV infection	Systemic involvement; risk factors for acquisition; positive HIV serology	Antiretroviral therapy
Neurosyphilis	Optic atrophy, Argyll Robertson pupils, gait disturbance; positive cerebrospinal fluid serology	High-dose intravenous penicillin
Frontotemporal dementia (eg, Pick disease)	Behavioral and language deficits with spared memory; frontotemporal atrophy on MRI; intraneuronal inclusions (Pick bodies)	Supportive care, no therapy to slow progression or improve symptoms
Creutzfeldt-Jakob disease (CJD)	Rapidly progressive mental deterioration and myoclonus, death in < 1 y of onset	No effective therapy; prion disease not transmissible, so no special precautions needed
Lewy body dementia	Visual hallucinations, REM sleep disorders, concurrent parkinsonism, cognitive fluctuation	No curative therapy; symptomatic treatment such as with cholinesterase inhibitors, memantine, neuroleptics

Clinical Presentation

For patients with AD, the average life expectancy after diagnosis is 7 to 10 years. The clinical course is characterized by progressive decline of cognitive functions (memory, orientation, attention, and concentration) and the development of psychological and behavioral symptoms (wandering, aggression, anxiety, depression, and psychosis). Table 37–3 outlines the clinical stages of AD.

Treatment

The goals of treatment in AD are to (1) improve cognitive function, (2) reduce behavioral and psychological symptoms, and (3) improve the quality of life. **Donepezil, rivastigmine, and galantamine are *cholinesterase inhibitors* that are effective in improving cognitive function and global clinical state.**

Table 37–2 • INITIAL EVALUATION OF DEMENTIA
Routine Tests:
Complete blood count (CBC)
Electrolytes, blood urea nitrogen (BUN), creatinine, glucose
Thyroid function tests
Liver function tests
Serum vitamin B_{12} level
Computed tomography (CT) or magnetic resonance imaging (MRI) of the head
Optional Tests:
Syphilis (treponemal antibody test)
Human immunodeficiency virus (HIV) assay
Urinalysis, urine toxin screen
Apo E genotyping for Alzheimer dementia
Lumbar puncture
Reversible Causes of Dementia:
Normal-pressure hydrocephalus, alcohol dependence, medication side effects, hypothyroidism, B_{12}, or thiamine deficiency

Antagonists to *N*-methyl-D-aspartate (NMDA) receptors, such as **memantine**, are effective in moderate-to-severe dementia. Antipsychotics such as risperidone can reduce psychotic symptoms and aggression in patients with dementia but must be used with caution. The Beers Criteria list potentially inappropriate medications for older adults that are associated with negative outcomes; this includes medications that could contribute to altered mental status, which could then be confused for or worsen underlying dementia. For this reason, as well as to avoid polypharmacy, routine medication reconciliation should be done by a primary care provider or whenever a patient is admitted to a hospital.

Other issues include wakefulness, night walking and wandering, aggression, incontinence, and depression. A structured environment, with predictability and judicious use of pharmacotherapy, such as a selective serotonin reuptake inhibitor

Table 37–3 • CLINICAL COURSE OF ALZHEIMER DISEASE	
Clinical Stage	**Manifestations**
Early **MMSE 25-26**	Mild forgetfulness, poor concentration, fairly good function, denial, occasional disorientation
Intermediate **MMSE 21-24**	Drastic deficits of recent memory, can travel to familiar locations; suspicious, anxious, aware of confusion
Late **MMSE 10-20**	Cannot remember names of family members or close friends; may have delusions or hallucinations, agitation, aggression, wandering, disoriented to time and place; needs substantial care
Advanced **MMSE < 10**	Totally incapacitated and disoriented, incontinent, personality and emotional changes; eventually all verbal and motor skills deteriorate, leading to need for total care

MMSE 27-30 considered normal.

for depression or trazodone for insomnia, is helpful. The primary caregiver is often overwhelmed and may need support. The Alzheimer Association is a national organization developed to give support to family members and can be contacted through its website (https://www.alz.org).

CASE CORRELATION

- See also Case 36 (Transient Ischemic Attack) and Case 38 (Headache/Temporal Arteritis).

COMPREHENSION QUESTIONS

37.1 A 78-year-old woman is being followed in the office for cognitive decline over the past year. The patient's daughter states that the patient has been forgetting where she is going and has left the stove on for hours. She is otherwise healthy and denies neurologic symptoms. A workup including laboratory work and head imaging has been negative. The patient is diagnosed with early AD. Which of the following agents is most likely to help with the cognitive function?

A. Haloperidol
B. Estrogen replacement therapy
C. Donepezil
D. High-dose vitamin B_{12} injections

37.2 A 74-year-old man was noted to have excellent cognitive and motor skills 12 months ago. His wife noted that 6 months ago his function deteriorated noticeably of somewhat sudden onset, and he seemed to be at this new baseline until he became worse 2 months ago. Which of the following is most likely to reveal the etiology of his functional decline?

A. HIV antibody test
B. Magnetic resonance imaging of the brain
C. Cerebrospinal fluid (CSF) Venereal Disease Research Laboratory (VDRL) test
D. Serum thyroid-stimulating hormone

37.3 A 55-year-old man is noted by his family members to be forgetful and become disoriented. He has difficulty making it to the bathroom in time and complains of feeling as though "he is walking like he was drunk." Which of the following therapies is most likely to improve his condition?

A. Intravenous penicillin for 21 days
B. Rivastigmine
C. Treatment with fluoxetine for 9 to 12 months
D. Ventriculoperitoneal shunt
E. Enrollment into Alcoholics Anonymous

37.4 A 68-year-old man is brought into the clinic due to the patient having difficulty with his memory and with cooking for and shopping for himself. His wife passed away 2 years previously. He often becomes confused about where he is and gets lost when he takes a walk in the neighborhood. He is diagnosed with AD. A CT scan of the brain is performed. Which of the following is most likely to be seen on imaging?

A. Chronic subdural hematoma

B. Cortical atrophy with atrophy of medial temporal structures

C. Ventriculomegaly without cortical atrophy

D. Normal cerebral ventricles and normal brain tissue, acetylcholine deficiency

ANSWERS

37.1 **C.** Cholinesterase inhibitors such as donezepil help with the cognitive function in AD and may slow the progression. Cholinesterase inhibitors are considered first-line therapy. Haloperidol (answer A) is an antipsychotic agent and is used for patients who display psychosis. It is not useful for early AD. Answer B (estrogen replacement therapy) and answer D (vitamin B_{12} injections) are not effective treatments for AD.

37.2 **B.** This is a patient who seems to have a more abrupt staggering or stepwise decline in cognitive function rather than the more gradual decline seen in AD. The stepwise decline in function is typical for multi-infarct dementia, diagnosed by viewing multiple areas of the brain infarct. HIV antibody testing (answer A) can suggest HIV dementia or CNS lymphoma, but this patient does not seem to have risk factors for this infection. CSF for syphilis (answer C) and serum thyroid-stimulating hormone for hypothyroidism (answer D) test for conditions that are usually associated with a gradual decline in cognitive function, versus the stepwise and staggering cognitive decline.

37.3 **D.** The classic triad for normal-pressure hydrocephalus is dementia, incontinence, and gait disturbance; one treatment is shunting the CSF. A favorable response to large volume (30-50 mL) extraction of CSF can predict the usefulness of the shunt. Intravenous penicillin (answer A) is the treatment for neurosyphilis. Rivastigmine (answer B) is a cholinesterase inhibitor and is used for moderate-to-severe AD. Fluoxetine is a selective serotonin reuptake inhibitor used for depressive disorders. Referral to AA (answer E) is not indicated unless medical causes for his condition are ruled out and alcohol abuse disorder is diagnosed.

37.4 **B.** Alzheimer disease has no pathognomonic structural imaging criteria but may include cortical and mesial temporal atrophy. This is in contrast to normal-pressure hydrocephalus, which shows enlarged brain ventricles without significant brain atrophy (answer C). Functional imaging can detect decreased perfusion and decreased metabolism in the temporal, parietal, and prefrontal cortex in patients with AD. Chronic subdural hematomas (answer A) may be

seen in patients who have repeated falls or trauma; this can be due to elder abuse or alcohol abuse. Acetylcholine deficiency without structural problems (answer D) cannot be evaluated on CT imaging since neurotransmitters are not evaluated on this imaging; however, normal neuroimaging may be present with early AD. This patient has moderate-to-severe AD, and there are very likely to be abnormal findings on CT imaging of the head.

CLINICAL PEARLS

- Alzheimer disease is the most common type of dementia, followed by multi-infarct (vascular) dementia.
- Approximately 5% of people older than 65 years and 20% older than 80 years have some form of dementia.
- Depression and reversible causes of dementia should be considered in the evaluation of a patient with memory loss and functional decline.
- Cholinesterase inhibitors are effective in improving cognitive function and global clinical state in patients with AD. An NMDA receptor antagonist is added in more advanced disease.

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CASE 38

A 59-year-old woman comes to your clinic because she is concerned that she might have a brain tumor. She reports a severe headache for the last 3 weeks that she rates as an 8 on a scale of 0-10. She localizes the pain to the right side of her head and reports that it is constant, occasionally throbbing, but mostly a dull ache. She thinks the pain is worse at night, especially when she lies with that side of her head on the pillow. She also has some pain with chewing her food. She denies any nausea, vomiting, photophobia, or other visual disturbances. She has had headaches before, but they were mostly occipital and frontal, relieved by acetaminophen, and she attributed them to "stress." Her medical history is significant for hypertension, which is controlled with hydrochlorothiazide, and "arthritis" of her neck, shoulders, and hips, for which she takes ibuprofen for when she feels stiff and achy. On physical examination, her temperature is 100.4 °F, heart rate is 88 beats per minute (bpm), blood pressure is 126/75 mm Hg, and respiratory rate is 12 breaths per minute. Her visual acuity is normal, visual fields are intact, and her fundoscopic examination is significant for arteriolar narrowing but no papilledema or hemorrhage. She has moderate tenderness over the right side of her head but no obvious scalp lesions. Her chest is clear, and her heart rhythm is regular, with normal S_1 and S_2 but an S_4 gallop. Abdominal examination is benign. She has no focal deficits on neurologic examination. She has no joint swelling or deformity but is tender to palpation over her shoulders, hips, and thighs.

- What is the most likely diagnosis?
- What is the best next step to confirm the diagnosis?

ANSWERS TO CASE 38:
Headache/Temporal Arteritis

Summary: A 59-year-old woman presents with

- A 3-week history of severe right-sided headaches that are worse at night, especially when she lies with that side of her head on the pillow
- History of hypertension and "arthritis" of her neck, shoulders, and hips
- Temperature of 100.4 °F and normal neurologic and eye examinations
- Moderate tenderness over the right side of her head but no obvious scalp lesions
- Pain with chewing food

Most likely diagnosis: Giant cell (temporal) arteritis (GCA).

Best next diagnostic step: Erythrocyte sedimentation rate (ESR).

ANALYSIS

Objectives

1. Describe the clinical features that help to distinguish a benign headache from one representing a serious underlying illness. (EPA 2, 10)
2. Describe the clinical features and diagnostic tests for GCA. (EPA 1, 3)
3. Describe the clinical features of subarachnoid hemorrhage, migraine headache, cluster headache, and tension headache. (EPA 1, 10)

Considerations

Although headaches are a very common complaint, this patient has features that are of greater concern: older age of onset, abrupt onset, severe intensity, and dissimilarity to previous milder headaches. The mnemonic SNOOP can be used as a reminder of red flags of significant underlying pathology and is outlined in Table 38–1. This patient is very concerned that the headaches may indicate a brain tumor. She has no meningeal signs, and her neurologic examination is nonfocal. She has stiffness and achiness of the shoulder and hip girdles. Together, these

Table 38–1 • RED FLAGS FOR SERIOUS HEADACHE DISORDERS

Any of these findings should prompt further investigation, including brain imaging (CT or MRI):

- **S**ystemic symptoms, illness, or condition (fever, cancer, HIV or other immunocompromised state)
- **N**eurologic signs or symptoms (altered mental status, loss of consciousness, focal neurologic signs, seizures, meningismus)
- **O**nset is new (especially age > 40) or sudden (thunderclap headache)
- **O**ther associated conditions or features (head trauma, headache awakens from sleep, worse with Valsalva, exertion, or sexual activity)
- **P**revious headache history with progressive symptoms or change in frequency or severity

factors make the diagnosis of GCA a strong possibility. GCA usually has its onset in patients age 50 or older and occurs in females more often than males. GCA involves inflammation of the medium- or large-size vessels. Her low-grade fever and generalized body aches may represent polymyalgia rheumatica, which is often associated with GCA. Other associated symptoms include jaw claudication and transient vision loss. Although GCA is not a common cause of headache, untreated patients can develop permanent vision loss resulting from ophthalmic artery involvement. Thus, a low index of suspicion is sufficient to begin investigation. The diagnosis could be suggested by an elevated ESR but can only be confirmed by temporal artery biopsy (ESR is a nonspecific marker of inflammation). However, a negative biopsy does not entirely rule out the diagnosis of GCA. Based on the sampled area of the biopsy and due to the discontinuous involvement of arterial pathology, multiple biopsies may be necessary to adequately assess the artery for disease. Indeed, if clinical suspicion is high, high-dose corticosteroids should be administered before the diagnosis is established to prevent irreversible complications.

APPROACH TO: Headache

DEFINITIONS

BERRY ANEURYSM: A small, thin-walled protrusion from the intracranial arteries that has a "berry" appearance on angiographic imaging. They classically occur at the junction where a cerebral artery departs from the circle of Willis. Over time, increased pressure at the aneurysm can compromise the endothelial lining and predispose a rupture to occur, leading to subarachnoid hemorrhage.

C-REACTIVE PROTEIN (CRP): An acute-phase protein of hepatic origin whose concentrations in blood plasma increase in response to inflammation.

ERYTHROCYTE SEDIMENTATION RATE (ESR): The rate at which erythrocytes suspended in plasma fall when placed in a vertical tube. It is an indirect measure of acute-phase response (ie, inflammation).

GIANT CELL ARTERITIS (GCA): Also known as temporal arteritis; a form of systemic vascular inflammation most commonly affecting patients older than 50 years. Medium- and large-size vessels, especially the superficial temporal artery, are affected.

CLINICAL APPROACH

Pathophysiology

Headache is one of the most common complaints of patients in medical practice. As with many common symptoms, a broad range of conditions, from trivial to life threatening, might be responsible. About 90% of all headaches fall under a few main categories of what are called "primary headaches": **tension, migraine, and**

Table 38–2 • CAUSES OF HEADACHE

Disease	Clinical Features	Diagnostic Findings
Meningitis	Nuchal rigidity, headache, photophobia, and prostration; may not be febrile	Lumbar puncture is diagnostic
Intracranial hemorrhage	Nuchal rigidity and headache; may not have clouded consciousness or seizures	Hemorrhage may not be seen on CT scan; lumbar puncture shows "bloody tap" that does not clear by the last tube; a fresh hemorrhage may not be xanthochromic
Brain tumor	May present with positional pounding headaches that are associated with nausea and vomiting; may be associated with focal neurologic deficits or mental status changes	CT or MRI
Temporal arteritis	May present with a unilateral pounding headache; onset generally in older patients (> 50 y) and frequently associated with visual changes	Erythrocyte sedimentation rate is the best screening test and usually is markedly elevated (ie, > 50 mm/h); definitive diagnosis can be made by arterial biopsy
Acute angle-closure glaucoma	Usually consists of severe eye pain; may have nausea and vomiting; the eye usually is painful and red; the pupil may be partially dilated	Elevated intraocular pressure
Migraine headache	Unilateral throbbing headache with preceding aura, photophobia, and nausea, which is relieved with sleep	Headache *with associated features* (photophobia, nausea, aura, unilateral, throbbing, aggravation with movement)
Cluster headache	Male predominance; precipitated by alcohol; occurs with rhinorrhea and lacrimation	
Tension headache	Occipital-frontal headache; constant, "bandlike"; relieved with relaxation	Headache *without* associated features

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cluster headaches. Headache symptoms usually are accompanied by a shortage of associated laboratory findings, leaving the clinician to depend largely on a thorough history with focused neurologic examination as the initial workup. Careful history and physical examination, keeping in mind the red flags of headaches (see Table 38–1), will serve the clinician well. Differentiating serious underlying causes of headache from benign causes may be difficult. Table 38–2 lists some typical features of different causes of headache.

Subarachnoid Hemorrhage

One of the most catastrophic causes of headache is **subarachnoid hemorrhage**, usually secondary to a ruptured intracerebral (berry) aneurysm. A study of alert and oriented patients presenting to the emergency center with a sudden-onset headache peaking in severity within 1 hour revealed 6% of patients had a subarachnoid

hemorrhage. The initial hemorrhage may be fatal, result in severe neurologic impairment, or produce only minor symptoms such as headache. Neurologic findings may not be present initially, and the patient who will benefit the most from intervention will often have mild symptoms; thus, it is important to diagnose subarachnoid hemorrhage early if it is suspected.

The best first diagnostic study is a noncontrast computed tomographic (CT) scan with thin imaging cuts at the brain base. If done within the first 6 hours of symptom onset, this diagnostic test will have nearly 100% sensitivity for subarachnoid hemorrhage, which will then progressively decline over time. If hemorrhage is suspected but the CT is negative, lumbar puncture should be performed as soon as possible to assess for the presence of red cells or xanthochromia (yellowish discoloration of cerebrospinal fluid [CSF]). This finding indicates the presence of bilirubin in the CSF from the breakdown of hemoglobin released from lysed red blood cells and thus differentiates subarachnoid hemorrhage from a traumatic lumbar puncture.

Giant Cell Arteritis and Polymyalgia Rheumatica

GCA, also known as temporal arteritis, is a chronic vasculitis of large- and medium-size vessels usually involving the cranial branches of the arteries arising from the aortic arch. Suggestive signs and symptoms include new headache, abrupt onset of visual disturbances, jaw claudication, fever, anemia, or elevated ESR and/or CRP in a patient aged 50 years or older. GCA is closely related to **polymyalgia rheumatica**, an inflammatory condition characterized by bilateral aching and stiffness of the neck, torso, shoulders, or thighs, with a significantly elevated ESR. Both conditions probably are polygenic diseases in which various environmental and genetic factors influence susceptibility and severity. The most worrisome complication of GCA is permanent vision loss, which can occur as an early manifestation in up to 20% of patients. Temporal artery biopsy is recommended in all patients suspected of having GCA. Long segments (1-2 cm) of the artery may require excision to find the typical areas of segmental inflammation.

Corticosteroids are the drugs of choice to treat both polymyalgia rheumatica and GCA, with daily doses of 10 to 20 mg of prednisone for polymyalgia rheumatica and 40 to 60 mg for GCA. Steroids may prevent, but usually do not reverse, visual loss. Steroid dosage should be gradually tapered when discontinuing therapy; however, relapse is common and should be suspected if symptoms return. It is also important to consider complications of corticosteroid therapy, including hyperglycemia, bone loss, and neutropenia.

Migraine Headache

Migraine headache is the most common cause of clinic visits for headache because of its frequency, disabling qualities, and associated symptoms. Migraine headache is more common in women, and there may be a positive family history. **Migraine headaches present with a throbbing or pulsatile quality, are usually unilateral** (although bilateral presentation does not exclude migraine), and may have a preceding aura. Aura will typically present with temporary visual symptoms like bright shapes but can also present with auditory or somatosensory symptoms. Other associated symptoms include nausea, vomiting, or sensitivity to light or sound. Migraines can

also present with tearing or nasal congestion, which may be confused with sinus infection. Treatment of acute episodes involves the initial use of nonsteroidal anti-inflammatory drugs (NSAIDs), followed by triptans if symptoms persist. Preventive therapies include tricyclic antidepressants, beta-blockers, or anticonvulsants such as valproate or topiramate.

Cluster and Tension Headaches

Episodic **cluster headache** is much less common but is more easily diagnosed by its distinctive pattern. Cluster headaches are more common in men and are characterized by periodic attacks of intense, unilateral, periorbital pain with nasal or ocular watering lasting minutes to hours but recurring daily over several weeks or months. Acute attacks can be treated with oxygen or subcutaneous sumatriptan. Verapamil is used for preventive therapy.

Tension headache is the most common type of headache. It is classically described as a bilateral "band-like" headache that is typically nonthrobbing and does not usually have other associated symptoms like photophobia or phonophobia. Treatment includes NSAIDs or acetaminophen and identifying and preventing headache triggers.

CASE CORRELATION

- See also Case 36 (Transient Ischemic Attack), Case 37 (Alzheimer Disease/Dementia), and Case 43 (Meningitis, Bacterial).

COMPREHENSION QUESTIONS

Match the headache type (A-E) to the clinical presentation described in Questions 38.1 to 38.3.

A. Migraine headache
B. Tension headache
C. Cluster headache
D. Subarachnoid hemorrhage
E. Meningitis

38.1 A 42-year-old man with polycystic kidney disease who complained of a sudden onset of severe headache and then lost consciousness

38.2 A 22-year-old college student with fever, headache, photophobia, and CSF with 25 white blood cells per high-power field, but no red blood cells or xanthochromia

38.3 A 31-year-old woman with a long history of intermittent severe unilateral throbbing headache lasting hours to days associated with nausea and photophobia, but no preceding symptoms and no visual disturbance, occurring once or twice per month

38.4 A 66-year-old man is taken to the emergency department due to new-onset seizures. He reports a severe headache over the past month and morning nausea and vomiting. He also has had some difficulty with walking and balance. On CT imaging, there is a 4-cm mass noted in the right parietal lobe of the brain. Which of the following is the most likely cell type of this brain mass?

A. Glioblastoma multiforme (GBM)
B. Lymphoma
C. Schwannoma
D. Medulloblastoma

ANSWERS

38.1 **D.** The sudden onset of severe headache with diminution in level of consciousness is classic for subarachnoid hemorrhage. This patient likely had rupture of a cerebral artery aneurysm, which is associated with polycystic kidney disease.

38.2 **E.** The presence of white blood cells but no red blood cells in the CSF is indicative of meningeal inflammation, likely due to viral or bacterial infection. This patient would likely be admitted for IV antibiotics pending CSF culture results.

38.3 **A.** The patient's history is strongly suggestive of migraine, given its unilateral and throbbing character, and the associated symptoms of nausea or photophobia. Most patients with disabling headache have migraine. Tension headache should have none of these features.

38.4 **A.** The most common primary brain cancer in adults is GBM. The prognosis unfortunately is not favorable, and a majority of individuals affected die within 18 months. Remember that the histology of GBM shows necrosis and pseudopallisading of cells. Most of these lesions are in the cerebrum (as opposed to in children, where primary lesions are usually in the posterior fossa). Answer B (lymphoma) is usually in HIV-positive patients or others with cell-mediated immunodeficiency. Answer C (schwannoma) is a benign tumor usually at the cerebellopontine angle and often affecting cranial nerve VIII: hearing difficulty and tinnitus. Answer D (medulloblastoma) is of the posterior fossa and usually affects children.

CLINICAL PEARLS

- Temporal arteritis usually involves one or more branches of the carotid artery and almost always occurs in patients older than 50 years. Diagnosis is suggested by an elevated ESR and confirmed by temporal artery biopsy.
- Visual loss is a common complication of temporal arteritis and can be prevented by initiation of high-dose corticosteroids when the diagnosis is suspected.
- Subarachnoid hemorrhage typically presents as a sudden onset of severe headache and is diagnosed by visualization of blood on a CT scan or by finding red blood cells or xanthochromic fluid on a lumbar puncture.
- Migraine is the most common type of headache for which patients seek medical attention in a clinic setting. It is an episodic headache with associated features such as nausea or photophobia.

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CASE 39

A 50-year-old man comes into the office complaining of difficulty completing his daily duties due to increasing stiffness on the right side of his body. He states for the last 18 months, he has felt that he had to "command his right arm" to move and perform tasks. In fact, he started using his left arm more often. He denies any tremors. Otherwise, he is healthy. The patient is a former college football player and suffered multiple concussions without neurologic deficits. Both his parents have hypertension, and his older brother was recently diagnosed with Parkinson disease (PD). On examination, the patient appears comfortable sitting in the examination chair. His temperature is 99 °F, heart rate is 88 beats per minute (bpm), and blood pressure is 121/80 mm Hg. His heart and lung examinations are unremarkable. An abdominal examination reveals normal bowel sounds and no masses. On neurologic examination, the patient has decreased sense of smell to lemon and coffee beans. The strength of the four extremities is normal without atrophy or fasciculation. The patient has increased muscle tone (rigidity) throughout, and there is difficulty with repetitive movements of his right hand. While his equilibrium seems normal, he walks slightly bent forward at his waist, and his right arm does not swing. Sensation is intact. Laboratory tests, including cell count, metabolic panel, thyroid tests, rapid plasma reagin, and vitamin B_{12} levels are normal.

- What is the most likely diagnosis?
- What is your next diagnostic step?
- What is the next step in therapy?

ANSWERS TO CASE 39:
Parkinson Disease

Summary: A 50-year-old man presents with

- History of concussions
- Right-sided rigidity and difficult movements, especially repetitive movements
- Hyposmia
- Normal laboratory tests

Most likely diagnosis: Parkinson disease.

Next diagnostic step: Brain magnetic resonance imaging (MRI). Though it does not add to the diagnosis, it is important to rule out other possibilities in the differential diagnosis for this condition.

Next step in therapy: Consider initiation of therapy with amantadine. If no improvement is noted, consider carbidopa/levodopa.

ANALYSIS

Objectives

1. Recognize the clinical features of PD. (EPA 1)
2. Understand its pathophysiology and clinical course. (EPA 1, 12)
3. Outline the differential diagnosis based on presentation. (EPA 2, 3)
4. Describe the therapeutic options. (EPA 4)

Considerations

This is a 50-year-old man who has history of multiple brain concussions and complains of difficulty starting movements of the right arm. He also endorses a history of hyposmia (decreased sense of smell). On examination, there is increased rigidity of the muscle tone throughout. Parkinson disease is a clinical diagnosis and there are no lab biomarkers, or imaging findings that are diagnostic. The classic presentation is a patient aged 55 or older with slowly progressive resting tremor and bradykinesia or ridigity. This condition must be differentiated from essential tremor and multiple sclerosis. Also Wilson disease should be considered in patients below age 40. Because this patient is age 50, a careful history and physical examination should be performed to decide whether further tests should be performed to investigate for secondary causes of PD. While the symptoms and signs are consistent with PD, establishing whether this is primary or secondary is important, especially considering the different response to dopamine agonistic (DA) drugs.

APPROACH TO:
Parkinson Disease

DEFINITIONS

AKINESIA: Difficulty initiating movements.

BRADYKINESIA: Slowness of movements.

EXTRAPYRAMIDAL SYSTEM: The area of the brain including the substantia nigra, striatum (includes caudate and putamen), globus pallidus, subthalamic nucleus, and thalamus (often referred to collectively as the basal ganglia).

PARKINSON DISEASE (PD): A chronic, progressive, neurodegenerative disorder caused by loss of dopaminergic neurons in the substantia nigra pars compacta. It is clinically diagnosed by the presence of classic symptoms, including tremor, rigidity, bradykinesia/akinesia, and postural instability (**TRAP**).

POSTURAL INSTABILITY: Impairment of the central postural reflexes causing a sensation of imbalance and a tendency to fall.

PRIMARY PARKINSON DISEASE: cause of clinical findings without an identifiable cause and accounts for about 80-85% of cases.

SECONDARY PARKINSON: This is also called Parkinsonism and has an underlying etiology such as brain tumors, repeated head trauma, drugs or toxins, or other neurological disorders.

CLINICAL APPROACH

Epidemiology

The etiology of PD is currently unknown. PD is estimated to affect 6.1 million people worldwide (1 million in the United States) and is the fastest growing neurologic disorder causing disability, likely due to the increasing age of the general population. It is estimated that there are 8 to 18.6 people per 100,000 persons diagnosed each year. A family history of the disease and older age are the most commonly associated risk factors. Smoking, caffeine/coffee intake, exercise, ibuprofen, and statins have been shown to decrease overall risk. Depression is also often linked to PD, but it is unclear if depression is a risk factor or a prodromal symptom. **For patients diagnosed prior to age 50, there is increasing evidence to suggest genetic causes of PD.** One out of every four patients with PD reports at least one first-degree relative with the diagnosis.

Pathophysiology

Parkinson disease is caused by depletion of dopamine in the basal ganglia, leading to the development of parkinsonian symptoms. The first three manifestations of PD are **tremor, bradykinesia, and rigidity**. Postural instability is another salient feature that typically develops later in the disease course. The severity of the symptoms is an independent predictor of mortality in patients. The clinical diagnosis is made

by having at least two of the classic symptoms of resting tremor, rigidity, bradykinesia, and postural instability with a benefit from dopaminergic therapy. Diseases that mimic PD include communicating hydrocephalus, lacunar infarcts, progressive supranuclear palsy, and diffuse Lewy body disease. However, these conditions do not respond to extended therapies of dopaminergic drugs.

Three major subtypes of PD exist: tremor dominant, akinetic/rigid dominant, and gait difficulty or postural instability. The postural instability subtype tends to be the most life altering and disabling. These patients tend to exhibit significant tremor and be wheelchair-bound with a slower progression of symptoms. Parkinson subtypes can change as the disease progresses, making the clinical usefulness of the classifications variable and limited.

Clinical Presentation

The **most common** presenting symptom of PD is the **tremor**, which typically begins unilaterally in the hand and spreads contralaterally several years later. The "pill rolling" or resting tremor of PD is 4 to 6 Hz, and is most notable when the patient is not engaged in activities, and tends to be intermittent in the early stages of disease. With purposeful movements, the tremor of PD lessens, distinguishing it from other common conditions, such as essential tremor or multiple sclerosis. As symptoms progress, the tremor may become difficult to distinguish between an action and resting tremor.

Bradykinesia or generalized slowing of movement is present at diagnosis in 80% of patients. Beginning distally, bradykinesia typically decreases manual dexterity, causing difficulty with simple activities of daily living in the upper extremities and difficulty walking in the lower extremities. Patients complain of a shuffling gait and feelings of unsteadiness. Evaluation of limb movements should include finger, heel, and toe tapping; hand gripping; and pronation/supination of the hands.

Increased resistance to passive motion, or rigidity, is due to increased tone. Approximately 90% of patients exhibit some form of rigidity throughout the disease course. Classically, **cogwheel rigidity** can be seen when the patient demonstrates a ratchety pattern of resistance as the limb is examined for range of motion. Additionally, patients can have "lead-pipe" rigidity with constant resistance throughout the entire range of motion.

As PD progresses, patients develop **postural instability,** in which the postural reflexes are impaired and lead to imbalance and falls. Clinicians should evaluate patients for postural instability by standing behind the patient and pulling back on the patient's shoulders. This "pull" test is considered positive if the patient falls or has to take more than one step backward to maintain balance. Early falling and injuries should lead the clinician to consider different diseases than parkinsonian disease, such as supranuclear palsy or multiple-system atrophy (MSA).

In addition to the four cardinal symptoms of PD, there are numerous motor and nonmotor features of the disease. Patients often exhibit hypomimia (masked facial expressions), impaired eye movements, blurry vision, and a shuffling gait. Meyerson sign, or glabellar tap sign, is the inability to suppress eyelid blink in response to the examiner repeatedly tapping on the forehead. Nonmotor symptoms include

Table 39–1 • PHARMACOLOGIC THERAPIES FOR PARKINSON DISEASE

Drug class	Monoamine Oxidase Type B Inhibitors (MAO-B)	Amantadine	Dopamine Agonists (DAs)	Levodopa
Mechanism	Inhibits MAO-B and enzymes that break down dopamine	Unknown	Binds dopamine receptors and stimulates activity of the nerves of the striatum and substantia nigra	Main precursor in dopamine synthesis
Potency	Low	Low	Intermediate	High
Dosing frequency	1-2 times per day	2-3 times per day (IR) Once daily (ER)	3 times per day (IR) Once daily (ER)	3-4 times per day (IR) 2-3 times per day (CR) 3 times per day (ER)
Common side effects	Nausea, headaches	Livedo reticularis, lower extremity edema	Somnolence, hallucinations, impulse control disorders	Nausea, somnolence, dizziness, headache
Special notes		Helpful for tremor-prominent disease	Not well tolerated in older adults with cognitive dysfunction; do not stop abruptly due to withdrawal symptoms	Typically, this agent is formulated together with carbidopa (a decarboxylase inhibitor) to prevent metabolism in the body, allows agent to reach the brain
Examples	Selegiline Rasagiline Safinamide		Pramipexole Ropinirole Rotigotine (transdermal)	Carbidopa-levodopa

Abbreviations: CR, controlled-release formulation; ER, extended-release formulation; IR, intermediate-release formulation.

psychiatric symptoms such as depression, hallucinations, cognitive decline, sleep disturbances, and olfactory dysfunction, which is called hyposmia. In a study of over 1000 patients with PD, 97% of patients reported nonmotor symptoms, averaging eight nonmotor symptoms. Cognitive dysfunction and dementia are independent predictors of mortality in PD.

Currently, there are no diagnostic biomarkers or imaging useful for recognizing PD. To rule out rare parkinsonian syndromes, MRI is typically obtained after PD is suspected. According to the Movement Disorder Society, the true "gold standard" for diagnosis is a postmortem examination of brain tissue, which would show discrete, intensely eosinophilic intracytoplasmic inclusion bodies surrounded by a pale halo, called Lewy bodies.

Treatment

PD has no cure. Compared to other neurodegenerative diseases, PD has more surgical and pharmacologic treatments. Nearly all the available treatments only provide symptom relief and do not appear to influence the progression of the disease. After the establishment of diagnosis, patients and medical professionals need to determine when to start pharmacologic therapy depending on the degree of symptoms and their impact on quality of life. There are four main drug classes used for the treatment of PD (Table 39–1).

Many patients develop levodopa-related complications, including motor fluctuations, after 5 to 10 years of treatment. These complications are most likely due to degenerative progression of the nigrostriatal dopamine terminals, which limits uptake of dopamine as opposed to the initiation of treatment. However, increasing evidence suggests that delaying treatment does not affect long-term outcomes for PD patients. Therefore, clinicians should initiate therapy with the lowest dose of dopaminergic medication that improves the patient's symptoms.

Some patients with mild symptoms opt to avoid medication and its potential side effects in the early stages of disease when the symptoms are not interfering with everyday activities. If a patient with mild disease decides to pursue pharmacologic options, **monotherapy with monoamine oxidase type B inhibitors (MAO-B) or amantadine is typically well tolerated** and can effectively control symptoms.

When a patient's quality of life begins to be affected by the motor symptoms of PD, treatment with **DAs or levodopa** should be considered. The choice of therapy is typically patient specific. Levodopa has been shown to control motor symptoms more effectively compared with DAs but can produce dyskinesia, especially in younger patients. Therefore, the risk and benefits of each therapy should be weighed when considering each patient's symptoms and goals. PD symptoms are highly variable, and there are no signs or symptoms to gauge the future disease burden on the patient. It is estimated that 67% of individuals are disabled after 5 years post-diagnosis, increasing to 80% at 10 years following diagnosis.

Surgical options for PD include **deep-brain stimulation (DBS)**. Since its initial approval in 1997, DBS has been considered when motor symptoms are not adequately controlled on medications. High-frequency electrical stimulation is accomplished by placing thin wires in the thalamus, subthalamus, or globus pallidus interna; an impulse generator battery is implanted under the collarbone or abdomen. DBS has shown improvement of the axial function without influencing behavioral, genitive, or speech symptoms.

CASE CORRELATION

- See also Case 36 (Transient Ischemic Attack) and Case 37 (Alzheimer disease/Dementia).

COMPREHENSION QUESTIONS

39.1 A 57-year-old man is evaluated in the clinic for an 8-month history of right-hand tremor. He has noticed that he has had difficulty signing his checks, but that the tremor is less intense when he brushes his teeth. He denies falls, urinary incontinence, or difficulty with memory. On physical examination, vital signs are normal. His voice is low in volume, and facial expressions are normal. A low-frequency right-hand tremor is noted. Repetitive movements of the right upper and lower extremities slow after 10 seconds. Finger-to-nose testing reveals a bilateral tremor. Muscle tone is increased bilaterally, and you have a difficult time moving the upper extremities passively. Gait is normal, but arm swing is decreased. A presumptive diagnosis of PD is made. What is the best next step to confirm the diagnosis?

A. Dopamine transporter scan

B. *PARK1* genetic testing

C. MRI of the brain

D. No additional testing

39.2 A 59-year-old woman presents with 1 year of right-sided tremor. She reports numerous falls when standing up or turning. She reports urge incontinence and has a history of intermittent constipation. Her husband has begun sleeping on the couch because the patient has been acting out her dreams at night. On physical examination, blood pressure is 120/85 mm Hg and heart rate 66 bpm while sitting; blood pressure is 92/54 mm Hg and heart rate is 76 bpm while standing. She has scattered ecchymosis around her extremities due to numerous falls. A tremor is noted in her right hand with repetitive finger tapping, revealing bradykinetic movements. Mild dysmetria is present with ataxic gait. Pull test confirms postural instability. What is the most likely diagnosis?

A. Alcohol intoxication

B. Progressive supranuclear palsy

C. Parkinson disease

D. Multiple-system atrophy (MSA)

39.3 A 69-year-old man was diagnosed with PD 10 years ago. His symptoms were initially controlled on amantadine. After worsening motor symptoms 7 years ago, carbidopa-levodopa was added, but the patient notes worsening symptoms in the past 2 years. He has tried to increase the dose and has noticed visual hallucinations that frighten his wife. On physical examination, vital signs are within normal limits. He has masked facies and an asymmetric tremor at rest, with marked cogwheel rigidity. Reexamination 1 hour after medication administration shows improvements in his symptoms. Which of the following is the best next treatment option for this patient?

A. Deep-brain stimulation

B. Increased dose of levodopa

C. Addition of MAO-B inhibition

D. Discontinue amantadine

E. No additional interventions needed

39.4 A 45-year-old man is evaluated for depression and suicidal ideation. He reports feelings of general disinterests for the past 5 years that have acutely worsened with the loss of his job. He reports that his wife thinks he is more forgetful, and he walks with small, slow steps. The patient is a former professional football player and is upset that he lacks interests in playing sports with his kids. The patient denies medications. On physical examination, the blood pressure is 132/64 mm Hg. During neurologic examination, he is asked to perform rapid, alternating movements with his hands; and these maneuvers are abnormally slowed bilaterally. He also has a shuffling gait. The patient has a flat affect and appears to think a long time prior to answering a question. He has difficulty with delayed recall. What is the most likely diagnosis?

A. Parkinson disease

B. Lewy body dementia

C. Chronic traumatic encephalopathy

D. Alzheimer disease

ANSWERS

39.1 **D.** This is a 57 year old man who has a straightforward history suggestive of primary PD. There does not seem to be atypical features such as hallucinations, rapid disease progression, supranuclear gaze palsy, or urinary incontinence. Based on the classic symptoms of bradykinesia, rigidity, and resting tremor, this patient most likely has PD. Further testing is not needed in this patient's situation (answers A, B, and C). While PD is a clinical diagnosis, a very careful history and physical exam is required to assess for other potential causes of the presenting symptoms. This can be especially difficult early in the disease course.

39.2 **D.** While this patient has many symptoms of classic PD (answer C), her early postural instability and history of recurrent falls are atypically early in the disease. However, she has ataxia, which is not common with PD. The combination of parkinsonian symptoms with cerebellar ataxic is most consistent with MSA or Shy-Drager syndrome. MSA has also been associated with orthostatic hypotension and dream acting (acting out their dreams), making it the likely diagnosis for this patient. Alcohol intoxication (answer A) should be diagnosed by history and would be associated with slurred speech and bilateral (not unilateral) symptoms. Progressive supranuclear palsy (answer B) is a degenerative disorder of unknown etiology associated with postural instability, falls, and ocular palsy. This patient has no eye findings; also, supranuclear palsy is not associated with acting out dreams.

39.3 **A.** Deep-brain stimulation is appropriate for this patient experiencing symptoms despite pharmacologic therapy. The patient has begun to experience medication-related complications but continues to have benefit until the medication wears off. DBS is likely to provide control of his motor symptoms with possible reduction in medications (not an increase, as in answers B and C), possibly improving the medication side effects. Answer D (amantidine) should be continued and not removed. Answer E (no additional intervention) is not indicated due the patient's severe symptoms.

39.4 **C.** The most likely diagnosis for this patient is chronic traumatic encephalopathy related to repetitive mild head injuries. This disease is often seen in veterans and athletes with history of multiple concussions. This patient's history of playing professional football increases his risk of developing neurologic symptoms. While this patient has features of PD (answer A), he lacks the cardinal symptoms of the disease, making it less likely the diagnosis. Both Lewy body dementia and Alzheimer disease (answers B and D) are associated with cognitive impairment and usually occur in older patients; because of the patient's young age and history of concussions, these dementia conditions are less likely.

CLINICAL PEARLS

- Parkinson disease is a chronic, progressive, neurodegenerative disorder caused by loss of dopaminergic neurons in the substantia nigra pars compacta.
- The diagnosis of PD is clinical and requires no confirmatory testing.
- Mild disease is typically treated without medications, but MAO-B and amantadine monotherapies have been shown to decrease symptoms.
- For moderate-to-severe disease, DA and levodopa can improve symptoms. Potential side effects of the medication should be discussed with the patient.
- Deep-brain stimulation is a surgical option for patients who have had PD for more than 4 years and whose disease is not controlled on medications.
- All therapies for PD only impact symptoms and do not alter the disease progression.

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CASE 40

A 25-year-old man is being seen in the office for a 2-day history of low-grade fever and sore throat. He is otherwise healthy and takes no regular medications. After an evaluation, he is given an injection of intramuscular penicillin for presumed streptococcal pharyngitis. Within a few minutes of the penicillin injection, he begins to complain of swelling of his face and difficulty breathing. He is dyspneic and appears frightened. His heart rate is 130 beats per minute (bpm), blood pressure is 90/47 mm Hg, and respirations are 28 breaths per minute and shallow. His face and lips are edematous, and he can barely open his eyes because of swelling. He is wheezing diffusely, and he has multiple raised urticarial lesions on his skin. Oxygen is given by face mask, and an ambulance has been called.

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 40:
Anaphylaxis/Drug Reactions

Summary: A 25-year-old man presents with

- Facial edema and difficulty breathing minutes after receiving an injection of penicillin
- Tachypnea, tachycardia, and hypotension
- Diffuse wheezing and warm skin with multiple raised urticarial lesions

Most likely diagnosis: Anaphylaxis as a result of penicillin hypersensitivity.

Next step: Immediate administration of intramuscular epinephrine is the first priority; secondary measures include corticosteroids and antihistaminic H_1 and H_2 blockers. Close observation of the patient's airway and oxygenation is also important, with possible endotracheal intubation if these becomes compromised.

ANALYSIS

Objectives

1. Describe the clinical presentation and emergency management of anaphylaxis. (EPA 1, 10)
2. Understand the diagnosis and complications of serum sickness. (EPA 4, 10)
3. Recognize and treat erythema multiforme minor and major. (EPA 1, 4)

Considerations

This young man developed manifestations of immediate hypersensitivity, with urticaria, facial angioedema, and bronchospasm. Penicillin is allergenic and leads to an immunoglobulin E (IgE)–mediated release of histamines and other vasoactive chemicals. **Epinephrine given IM** is the agent of choice in acute anaphylaxis. The route should be **intramuscular** and not subcutaneous because intramuscular injections (best in thigh) have faster and better absorption than the subcutaneous route. Epinephrine improves tissue edema by causing vasoconstriction. Antihistamines may also help. Because the airway is vulnerable to compromise as a result of severe edema, intubation to protect the airway is sometimes indicated. Meanwhile, measures should be taken to calm the patient and help to slow their respirations. Pulse oximetry is important. Because different ambulances have different capabilities, it is important to ask for emergency medical services for possible airway obstruction.

APPROACH TO: Anaphylaxis

DEFINITIONS

ANAPHYLACTOID REACTIONS: Similar clinical picture to anaphylaxis with cutaneous, respiratory, cardiovascular, and gastrointestinal symptoms but not caused by immunologic mechanisms (eg, adverse reaction to iodinated contrast material).

ANAPHYLAXIS: Syndrome with varied mechanisms, clinical presentations, and severity that is an acute life-threatening reaction resulting from a type I hypersensitivity reaction (HSR), which is an **IgE-mediated activation of mast cells. Mast cell degranulation** results in release of histamine, interleukins, and other inflammatory mediators.

ANGIOEDEMA: Swelling of the lips, periorbital region, face, hands, or feet.

ARTHUS REACTION: An example of a type III HSR caused by the development of antigen-antibody immune complexes at the local site of injection of antigens into the skin, which presents with hemorrhage and significant edema.

TYPE I HYPERSENSITIVITY REACTION: IgE-mediated allergic response to environmental antigens.

TYPE II HYPERSENSITIVITY REACTION: IgM- or IgG-mediated damage to cells by either phagocytosis or activation of complement. Examples include autoimmune hemolytic anemia, immune thrombocytopenic purpura, hemolytic disease of the fetus and the newborn, and Goodpasture syndrome.

TYPE III HYPERSENSITIVITY REACTION: IgM- or IgG-mediated reaction with soluble antigens to form antibody-antigen complexes. The complexes activate complement, leading to release of chemotactic factors to attract neutrophils and induce inflammation and subsequent tissue damage. Examples include serum sickness and Arthus reaction.

TYPE IV HYPERSENSITIVITY REACTION: Mediated by T cells and monocytes and/or macrophages. Symptoms take a few days to manifest. Also referred to as delayed-type or cell-mediated HSR. Examples include the tuberculin skin test and poison ivy exposure.

URTICARIA: Heterogeneous, self-resolving skin reaction presenting with pruritic wheals characterized by central swelling and epidermal erythema surrounding the wheals. It usually takes about 24 hours but can take up to 48 hours to resolve without scarring the skin.

CLINICAL APPROACH

Pathophysiology

Common causes of anaphylaxis include drugs, *Hymenoptera* stings (bees, wasps), radiographic contrast media (anaphylactoid), blood products, latex in medical

products, allergen immunotherapy injections, and foods. **The most common cause of drug-related anaphylaxis is beta-lactam antibiotics such as penicillin. The most common cause of food-related anaphylaxis is peanuts**, partly because of the frequency with which peanut products are included in other types of foods. In fact, peanut allergy has doubled in incidence in Western countries. A recent randomized trial suggested that introducing peanut products before the age of 1 seemed to decrease the development of peanut allergy (13.7% control vs 1.9% early exposure). It is important to note that almost any agent that can activate mast cells or basophils can cause an anaphylactic reaction. Approximately one-third of all cases of anaphylaxis are idiopathic.

History of Penicillin Allergy. **Penicillin is the most common medication associated with anaphylaxis**, reported by 10% of patients. Many reported "allergies" are actually adverse effects such as rashes or nausea and not IgE-mediated immediate hypersensitivity. Over time, individuals with true penicillin allergy may no longer have reactions. Careful history taking is important when a patient reports a penicillin allergy, including whether there were hives, throat tightening, swelling of the lips or mouth, or difficulty breathing. When the use of penicillin is critical and the history is unclear, the use of skin testing may be helpful.

When a patient reports a history highly suggestive of anaphylaxis, penicillin and cephalosporins should be avoided. When the history is suggestive of a non-IgE adverse effect, then a beta-lactam may be used, especially cephalosporin (since there is only about 10% cross-reactivity). **When the history is unclear, penicillin skin testing may be helpful.** If skin testing is unavailable, penicillin generally should be avoided, but cephalosporins are probably acceptable given the small cross-reactivity. When penicillin is the only choice in someone with known previous allergic reactions, desensitization protocols administered by pharmacists are viable options. This is the case for pregnant women or patients with AIDS in need of treatment for neurosyphilis.

Differential Diagnosis. Other considerations in the differential diagnosis of anaphylaxis include erythema multiforme major and minor. **Erythema multiforme minor** often occurs after herpes simplex virus (HSV) or other infections. It manifests as urticarial or bullous skin lesions. The pathognomonic finding is a **target lesion**, described as a lesion that is centrally inflamed but is surrounded by an area of less inflamed skin. Treatment includes management of the underlying cause when known, withdrawal of suspected causative drugs, and acyclovir if HSV involvement is suspected. **Erythema multiforme major** (Stevens-Johnson syndrome [SJS]) is similar to erythema multiforme minor but is more severe and involves two or more mucosal surfaces. It is also more likely to be induced by drugs such as sulfonamides or nonsteroidal anti-inflammatory drugs (NSAIDs). Skin findings may include petechiae, vesicles, bullae, and some desquamation of the skin. If the epidermal detachment involves less than 10% of the skin, it is considered SJS. If the epidermal detachment involves more than 30% of the skin, it is considered **toxic epidermal necrolysis** (TEN). Between 10-30% skin affected is considered the SJS/TEN overlap condition. Other symptoms include fever, headache, malaise, arthralgias, corneal ulcerations, arrhythmias, pericarditis, electrolyte abnormalities, seizures, coma, and sepsis.

Treatment involves withdrawal of the suspected offending agent, treatment of concurrent infections, aggressive fluid resuscitation and maintenance, and supportive treatment similar to burn care. Use of corticosteroids is controversial, but they are often prescribed.

Other Types of Drug Reactions. Most drug rashes are maculopapular and occur several days after starting treatment with an offending drug. They usually are not associated with other signs and symptoms, and they resolve several days after removal of the offending agent. **Serum sickness**, on the other hand, is an allergic reaction that occurs 7 to 10 days after primary administration, or 2 to 4 days after secondary administration, of a foreign serum or a drug (ie, a heterologous protein or a nonprotein drug). It is characterized by fever, polyarthralgia, urticaria, lymphadenopathy, and sometimes glomerulonephritis. It is a **type III HSR**, caused by the formation of **immune complexes** of IgG and the offending antigen. Treatment is based on symptomatology, as the disease usually is self-limiting. Treatment may include administration of antihistamines, aspirin, or NSAIDs and therapy for the underlying disease.

Finally, several other types of drug reactions do not fit into the categories discussed. Two of the most important types are iodine allergy and anticonvulsant drug hypersensitivity. "Iodine allergy" is often associated with **radiologic contrast media**. Reactions to contrast media are the result of the hyperosmolar dye causing degranulation of mast cells and basophils rather than a true allergic reaction. These reactions can be prevented by pretreatment with diphenhydramine, H_2 blockers, and corticosteroids beginning 12 hours before the procedure. There is no evidence that a history of seafood allergy is related to adverse events from radiocontrast media. **Phenytoin** and other aromatic **anticonvulsants** have been associated with a **hypersensitivity syndrome** characterized by a severe idiosyncratic reaction, including rash and fever, often with associated hepatitis, arthralgias, lymphadenopathy, or hematologic abnormalities. The skin manifestations can range from skin rash to TEN. This reaction is not IgE mediated, and the exact mechanism remains unclear. Treatment is supportive, with withdrawal of the offending agent.

Clinical Presentation

The clinical presentation of anaphylactic reactions varies greatly, but the following guidelines are a good rule of thumb. Symptoms usually develop within 5 to 60 minutes following exposure, although a delayed reaction is possible. Symptoms and signs are variable and are listed in Table 40–1. The key fact to remember is

Table 40–1 • CLINICAL MANIFESTATIONS OF ANAPHYLAXIS

Cardiovascular: Arrhythmias, bradycardia, cardiac arrest, hypotension, tachycardia
Dermatologic: Angioedema, cyanosis, flushing, pruritis, urticaria
Gastrointestinal: Abdominal cramping, diarrhea, nausea/vomiting
Neurologic: Dizziness, seizures, syncope, weakness
Pulmonary: Bronchorrhea, dizziness, dyspnea, nasal congestion, rhinorrhea, sneezing, stridor, tachypnea, wheezing
Other: Diaphoresis, hoarseness, laryngeal edema, sense of impending doom

that a **true anaphylactic reaction is life threatening.** Angioedema may occur with or without urticaria but is not anaphylaxis unless the reaction is associated with other life threatening processes, such as hypotension or laryngeal edema.

Treatment

Treatment of anaphylaxis begins with first assessing the **ABCs** (**a**irway, **b**reathing, **c**irculation). Intubation, if required, should not be delayed. Second, **epinephrine** should be administered to help control symptoms and blood pressure. **Epinephrine acts on alpha-adrenergic receptors and induces vasoconstriction,** thus reversing peripheral vasodilation induced by inflammatory mediators and alleviating hypotension, angioedema, erythema, and urticaria. Epinephrine also acts on beta-adrenergic receptors, inducing bronchodilation, preventing further mast cell and basophil release of inflammatory mediators, and increasing myocardial contractility and cardiac output. **Intramuscular epinephrine injected in the anterolateral thigh (vastus lateralis)** leads to more rapid and higher peak levels than do subcutaneous or deltoid intramuscular injection. High doses of epinephrine are recommended because low doses can lead to increased release of inflammatory mediators, vasodilation, and hypotension. Intravenous epinephrine is reserved for patients with anaphylaxis unresponsive to intramuscular administration due to risk of myocardial infarction and fatal arrhythmias.

Corticosteroids are also frequently used in the treatment of anaphylaxis. Their role is unclear, but studies have shown that they decrease length of hospitalization, although they do not reduce the number of visits to the emergency department. The benefits of corticosteroids are thought to include inhibition of platelet and neutrophil aggregation and synthesis of inflammatory mediators, as well as increased response to beta-adrenergic agonists.

Additional treatment measures include placing the patient in a recumbent position, elevating the legs, administration of oxygen as needed, normal saline (NS) volume replacement and/or use of vasopressors as required, and administration of diphenhydramine 50 mg orally or intravenously every 4 hours as needed (Table 40–2).

Table 40–2 • SUGGESTED TREATMENT OF ANAPHYLAXIS

1. Address ABCs (airway, breathing, circulation); intubate, if needed
2. Intramuscular epinephrine (1:1000 0.3-0.5 mL every 5 min as needed) or as an intravenous solution (1:1000 0.1-0.3 mL in 10 mL of normal saline over several minutes)
3. Oxygen as needed
4. Place the patient in a recumbent position, elevate the legs
5. Normal saline volume replacement and/or vasopressors as required
6. Diphenhydramine 50 mg orally or intravenously every 4 h as needed
7. Other measures:
   - Ranitidine or other H_2 blockers
   - Albuterol or levalbuterol for bronchospasm
   - Glucagon if the patient is taking beta-blockers
   - Systemic steroids to prevent delayed reactions
   - Atropine for symptomatic bradycardia

CASE CORRELATION

- See also Case 41 (Urinary Tract Infection and Sepsis in the Elderly) and Case 42 (Vascular Catheter Infection in a Patient With Neutropenic Fever).

COMPREHENSION QUESTIONS

40.1 A 55-year-old accountant complains of facial and tongue swelling. He recently started using a new bath soap. His medical problems include osteoarthritis and hypertension, for which he takes acetaminophen and lisinopril, respectively. Which of the following is the most likely etiology?

A. Lisinopril
B. Soap hypersensitivity
C. Hypothyroidism
D. Acetaminophen
E. Food-related allergy

40.2 An 18-year-old man with epilepsy controlled with medication develops fever, lymphadenopathy, a generalized maculopapular rash, elevated transaminases, and arthralgias. He reports having been bitten by ticks while working in the yard outside. Which of the following is the most likely etiology?

A. Severe poison ivy dermatitis
B. Reaction to anticonvulsant medication
C. Acute human immunodeficiency virus (HIV) infection
D. Lyme disease

40.3 A 34-year-old man is brought to the emergency department for a severe allergic reaction caused by fire ant bites. He is treated with intramuscular epinephrine and intravenous corticosteroids. His oxygen saturation falls to 80%, and he becomes apneic. Which of the following is the best next step?

A. Intravenous diphenhydramine
B. Intravenous epinephrine
C. Oxygen by nasal cannula
D. Endotracheal intubation
E. Electrical cardioversion

40.4 A 57-year-old woman with congestive heart failure has a positive cardiac stress test. Cardiac catheterization is required to evaluate for coronary bypass grafting. She states that she has an allergy to iodine. Which of the following is the best next step?

A. Desensitization with increasing doses of oral iodine

B. Infusion of diphenhydramine during the procedure

C. Cancel the procedure and proceed to surgery

D. Diphenhydramine and corticosteroids the night before the procedure

ANSWERS

40.1 **A.** Angiotensin-converting enzyme (ACE) inhibitors are often associated with angioedema. Angioedema secondary to ACE inhibitors can occur at any subsequent point during use, not solely after the initial doses. Reactions to exogenous agents such as soap (answer B) typically result from a type IV HSR and usually present as a skin rash. Causes of anaphylactic reactions include drugs (answer D) and food (answer E). A true anaphylactic reaction is life threatening; it may present with angioedema with or without urticaria, but it also presents with other life threatening processes, such as hypotension. Drug allergies may present as an anaphylactic reaction or a drug rash; most drug rashes are maculopapular and occur several days after starting treatment with an offending drug and resolve with discontinuation of the drug. Hypothyroidism (answer C) is an autoimmune disease process most commonly caused by autoantibodies against thyroid peroxidase, thyroglobulin, and/or TSH receptors.

40.2 **B.** This is a common presentation of hypersensitivity syndrome associated with aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital). Poison ivy (answer A) is not associated with fever and lymphadenopathy. Lyme disease (answer D) is associated with erythema migrans, an erythematous annular rash with a central clearing (target lesion) developing within days of infection. HIV (answer C) is a less likely answer considering that a history of risk factors is not being presented.

40.3 **D.** This patient has developed airway obstruction due to an anaphylactic reaction. He requires intubation and mechanical ventilation to maintain oxygenation. The first step in treating anaphylaxis is assessing the **ABCs**. Intubation, if required, should not be delayed. Second, **epinephrine** (answer B) should be administered to help control symptoms and blood pressure. Additional treatment measures include placing the patient in a recumbent position, elevating the legs, administration of oxygen as needed (answer C), NS volume replacement and/or use of vasopressors as required, and administration of diphenhydramine 50 mg orally or intravenously every 4 hours as needed (answer A). Electrical cardioversion (answer E) is not indicated in the treatment of anaphylaxis.

40.4 **D.** Pretreatment with diphenhydramine, H_2 blockers, and corticosteroids beginning 12 hours before the procedure greatly decreases the reaction to contrast dye. For patients presenting with clinical indication for rapid imaging, premedication should be given at least 5 hours prior to contrast administration (answer B). Therefore, there is no need to cancel the procedure and proceed with surgery (answer C). Desensitization (answer A) is not an appropriate treatment course since radiocontrast allergy is not a true allergic reaction.

CLINICAL PEARLS

- Anaphylaxis is characterized by respiratory distress caused by bronchospasm, cutaneous manifestations such as urticaria or angioedema, and gastrointestinal hypermotility. Patients may die as a consequence of airway compromise or vascular collapse caused by widespread vasodilation.
- Treatment of anaphylaxis is immediate epinephrine, antihistamines, airway protection, and blood pressure support as necessary. Corticosteroids may help prevent late recurrence of symptoms.
- Epinephrine is the immediate drug of choice in treating anaphylaxis.
- Serum sickness is an immune complex-mediated disease that may include fever, cutaneous eruptions, lymphadenopathy, arthritis, and glomerulonephritis. It usually is self-limited, but treatment may be necessary for renal complications.
- Erythema multiforme minor is characterized by urticarial or bullous eruptions, often with target lesions, usually following HSV infections. Erythema multiforme major (SJS) usually is caused by drugs and includes cutaneous and mucosal involvement.

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CASE 41

An 84-year-old woman is brought to the emergency department by ambulance from her long-term care facility for increased confusion, combativeness, and fever. Her medical history is significant for Alzheimer disease and well-controlled hypertension. The patient is "confused" and combative with the staff, which, per her family, is not her baseline mental status. Her temperature is 100.5 °F, heart rate is 130 beats per minute (bpm), blood pressure is 76/32 mm Hg, respiratory rate is 24 breaths per minute, and oxygen saturation is 95% on room air. On examination, she is lethargic but agitated when disturbed, her neck veins are flat, her lung fields are clear, and her heart rhythm is regular and tachycardic without murmur or gallops. Abdominal examination is unremarkable, and her extremities are warm and pink.

After administration of 2 L of normal saline over 60 minutes, her blood pressure is 95/58 mm Hg. The initial laboratory work returns. Her white blood cell count (WBC) is 14,000/mm^3, with 67% neutrophils, 3% bands, and 24% lymphocytes. Serum lactate is 3 mmol/L. No other abnormalities are noted. A chest x-ray obtained in the emergency department is normal. Urinalysis shows 2+ leukocyte esterase, negative nitrites, and trace blood. Microscopy shows 20 to 50 white blood cells per high-power field, 0 to 3 red blood cells, and many bacteria.

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 41:

Urinary Tract Infection With Sepsis in the Elderly

Summary: An 84-year-old woman presents to the emergency department from her nursing home with

- History of Alzheimer disease
- Agitation, confusion, low grade fever, tachycardia, and hypotension
- Flat veins, clear lung fields, no cardiac murmur or gallops, and warm and well-perfused extremities on physical examination
- Improved hemodynamic status with a fluid bolus
- Evidence of urinary tract infection (UTI) on laboratory examination

Most likely diagnosis: Septic shock secondary to a UTI.

Next step: Continued blood pressure support with intravenous (IV) fluids or vasopressors as necessary. Broad-spectrum antibiotics should be started as soon as possible.

ANALYSIS

Objectives

1. Explain how to diagnose a UTI. (EPA 3)
2. List effective treatments for a UTI. (EPA 4)
3. Describe the management of asymptomatic bacteriuria. (EPA 4)
4. Identify and treat septic shock. (EPA 1, 10)
5. Describe goal-oriented therapy of septic shock. (EPA 4, 10)

Considerations

This elderly woman with Alzheimer disease presents with shock, that is, hypotension leading to inadequate tissue perfusion. It is essential to determine the underlying cause and thus initiate appropriate treatment. She has no history or physical examination findings suggestive of hemorrhage or extreme volume losses, so hypovolemic shock is unlikely. She has flat neck veins and clear lung fields, suggesting she does not have right or left heart failure, respectively, so cardiogenic shock (eg, after a myocardial infarction) seems unlikely. Additionally, both hypovolemic and cardiogenic shock typically cause profound peripheral vasoconstriction, resulting in cold, clammy extremities. This patient's extremities are warm and well perfused (inappropriately so) despite serious hypotension, suggesting a distributive form of shock (early septic shock). Older patients may not be able to mount a high fever; importantly, an afebrile patient does not rule out sepsis. With the elevated WBC count with immature forms as well as the urine findings, septic shock as a consequence of UTI seems most likely.

APPROACH TO:
UTI with Sepsis

DEFINITIONS

ASYMPTOMATIC BACTERIURIA: A condition in which urine Gram stain or culture is positive, but no clinical signs or symptoms of infection are present. This condition is rarely requires treatment unless the patient is a pregnant woman or immunocompromised (eg, transplant recipients).

CARDIOGENIC SHOCK: Shock due to intracardiac conditions leading to decreased cardiac output, such as arrhythmias, myocardial infarction, and valvular insufficiencies.

DISTRIBUTIVE SHOCK: Shock characterized by peripheral vasodilation (ie, decreased systemic vascular resistance). It is divided into the following types: anaphylactic shock (caused by a severe type I hypersensitivity reaction); endocrine shock (caused by an underlying endocrine disease, eg, adrenal failure or myxedema); neurogenic shock (caused by trauma to the central nervous system); and septic shock (caused by a dysregulated immune response to infection).

HYPOVOLEMIC SHOCK: Shock due to volume depletion causing decreased intravascular volume, which leads to a compensatory increase in systemic vascular resistance in an attempt to maintain adequate tissue perfusion. Caused by hemorrhagic (eg, gastrointestinal bleeding) and nonhemorrhagic (eg, dehydration, third-spacing) etiologies.

OBSTRUCTIVE SHOCK: Shock due to extracardiac conditions leading to decreased cardiac output, such as pulmonary embolism, tension pneumothorax, and pericardial tamponade.

SEPSIS: A life-threatening multiorgan dysfunction due to dysregulated host response to an infection.

SEPSIS SCORING SYSTEMS: There are various sepsis scoring systems such as SOFA (sequential organ failure assessment) score or simplified qSOFA (quick SOFA) that attempts to estimate morbidity or mortality risk due to sepsis.

SEPTIC SHOCK: Subset of sepsis with circulatory and metabolic/cellular dysfunction that is associated with a higher mortality risk.

SHOCK: A life-threatening condition due to circulatory failure leading to hypotension and thus inadequate oxygen delivery to and utilization by tissues. There are four main categories: cardiogenic, distributive, hypovolemic, and obstructive shock.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS): Criteria that illustrate systemic inflammation that may or may not indicate underlying infection. The criteria include temperature deviation (> 38 °C or < 36 °C), tachypnea (respiratory rate > 20 breaths per minute or $Paco_2$ < 32 mm Hg), tachycardia (heart rate > 90 bpm), and leukocyte shifts with WBC > 12,000/mm^3 or < 4000/mm^3 or > 10% immature forms (bands).

CLINICAL APPROACH TO UTI

Epidemiology

UTIs are a common affliction of the elderly, affecting both debilitated and healthy adults. **UTIs are second only to respiratory infections as the most common infections in patients older than 65 years.** Risk factors that contribute to the high incidence of UTIs in the elderly, as well as in institutionalized patients, include incontinence, a history of prior UTIs, neurologic impairment, immunosuppression, poor nutrition, and comorbid disease states. These conditions may confer functional abnormalities within the urinary tract or altered defenses against infection. Furthermore, frequent hospitalizations expose these patients to nosocomial pathogens and invasive instrumentation, such as indwelling catheters.

Pathophysiology

Most UTIs occur as one of three clinical syndromes: **acute uncomplicated cystitis** (lower tract infection), **acute pyelonephritis** (upper tract infection), or **catheter-associated UTI** (in hospitalized, institutionalized, or neurogenic bladder patients). Symptoms of cystitis reflect bladder irritation and generally include dysuria, increased frequency, urgency, or hematuria. **Pyelonephritis** typically presents with **systemic symptoms such as fever, chills, or nausea**; **flank pain**; and findings of **WBC casts** on urinalysis. **Catheter-associated UTI** can be diagnosed by fever, suprapubic pain, or other symptoms attributable to infection, along with a positive urine culture in patients with permanent or intermittent catheterization of the urinary tract.

Another common situation that deserves mention is **asymptomatic bacteriuria**. Asymptomatic bacteriuria is characterized by positive urine culture without clinical symptoms. Outside of pregnancy or immunocompromised patients such as transplant recipients, no adverse clinical outcomes have been reported as a result of asymptomatic bacteriuria, and no benefits of treatment have been demonstrated.

Diagnostic Criteria. UTIs typically are diagnosed based on a combination of symptoms and urinary findings. In symptomatic patients, bacteria typically are found in high concentrations in the urine, and **10^5 colony-forming units (CFUs)/mL typically are recovered from a clean-catch** specimen. If the specimen is obtained by **catheterization, finding** more than **10^2 CFU/mL** is considered significant. In **women with symptoms of acute cystitis** (such as dysuria, frequency, and urinary tenesmus), urine cultures are often not obtained, but empiric treatment can be initiated based on the **dipstick findings of leukocyte esterase** (used as a marker for pyuria) **or nitrites** (produced by some bacteria that cause UTIs).

Clinical Presentation

Fever, dysuria, urgency, or flank pain may be presenting symptoms for a UTI in younger patients. However, elderly and institutionalized patients often present with less obvious symptoms. These patients may be febrile or hypothermic. Common manifestations include confusion or combativeness. **Mental status or behavioral changes in the elderly** should be considered **strong indicators for serious illness**, and a thorough workup should consider etiologies beyond infections. Even with localizing symptoms suggestive of a UTI, other sources of infection should still

Table 41–1 • ETIOLOGIES OF URINARY TRACT INFECTIONS

Acute uncomplicated cystitis, pyelonephritis
• *Escherichia coli* 75%-90%
• *Staphylococcus saprophyticus* 5%-15%
• *Klebsiella* spp
• *Proteus* spp
• *Enterococcus* spp
Catheter-associated UTI
• *Escherichia coli*
• *Klebsiella* spp
• *Proteus* spp
• *Staphylococcus aureus*
• *Citrobacter* spp
• *Morganella* spp
• *Pseudomonas aeruginosa*
• *Enterococcus* spp
• *Candida* spp

be investigated. Both urine and blood cultures should be obtained in addition to a urinalysis and complete blood count (CBC). The results of the urine and blood cultures may take 2 to 3 days to yield an organism. If the clinical picture suggests a UTI and sepsis, antibiotic treatment should be initiated immediately. Empiric antimicrobial therapy can be directed at the most common pathogens (Table 41–1).

Treatment

For **uncomplicated cystitis**, oral trimethoprim-sulfamethoxazole, fluoroquinolones such as ciprofloxacin, and nitrofurantoin are acceptable first-line therapies and are typically given for 3 days. Empiric therapy should be guided by knowledge of local antibiotic resistance patterns. Similar empiric treatment may be initiated for **pyelonephritis**, but urine and blood cultures should be obtained. Treatment is then guided by culture results and should be continued for 10 to 14 days. Catheter-associated UTI can only be diagnosed with a positive culture (the sample should be obtained from a new catheter, or the catheter port, but not the drainage bag), and antibiotic therapy is tailored to the identified pathogen. If possible, the catheter should be removed or replaced. Bacteria commonly secrete a biofilm in which they embed, making the full sterilization of the urine less likely.

Elderly and institutionalized patients commonly acquire gram-positive and mixed infections, so broad-spectrum antibiotics pending culture results are recommended. In patients presenting with a clinical picture of **sepsis**, broad-spectrum antibiotic coverage against gram-positive and gram-negative organisms, including antipseudomonal activity, is recommended until cultures are available to guide therapy. The duration of therapy should be dictated by the patient's clinical status. In cases where UTIs have progressed to bacteremia, aggressive and prompt treatment is necessary to prevent the onset of septic shock. This life-threatening state may develop with little warning in elderly and institutionalized patients with multiple comorbidities, as it did in the patient in the case, who presented with hypotension and altered mental status because of infection, that is in septic shock.

CLINICAL APPROACH TO SHOCK

Pathophysiology

Shock is the clinical syndrome that results from inadequate tissue perfusion. It can be classified in a variety of ways, but one useful schema divides the causes into hypovolemic shock, cardiogenic shock, or distributive shock, usually caused by sepsis. **Hypovolemic shock** is the most common form. It results from either hemorrhage or profound vomiting or diarrhea, resulting in loss of 20% to 40% of blood volume. **Cardiogenic shock** results from a primary cardiac insult, such as a myocardial infarction, arrhythmia, or end-stage systolic heart failure. Both hypovolemic and cardiogenic shock cause a marked fall in cardiac output and may appear clinically similar with tachycardia, hypotension, and cold, clammy extremities. It is essential to differentiate between the two, however, because the treatments are markedly different. Patients with **hypovolemic shock** should have **flat neck veins** and **clear lung fields**; those with **cardiogenic shock** are more likely to have markedly **elevated jugular venous pressure** and **pulmonary edema**.

Distributive shock, in contrast, is characterized by an **increase in cardiac output** but an inability to maintain systemic vascular resistance, that is, there is **inappropriate vasodilation.** Clinically, it appears different from the other forms of shock in that, despite the hypotension, the **extremities are warm and well perfused**, at least initially. If septic shock continues, cardiac output falls as a consequence of myocardial depression, multiorgan dysfunction ensues, and **intense vasoconstriction** occurs in an attempt to maintain blood pressure, the so-called **cold phase.** These findings portend a poor prognosis; hence, prompt recognition of septic shock in the early (warm) phase is paramount.

Although distributive shock may occur in neurogenic shock as a consequence of spinal cord injury or adrenal crisis, the most common cause is **septic shock, with the most common infectious etiologies of sepsis being UTIs and pneumonia.** Septic shock is associated with high 30-day mortality rates, exceeding 50%. Early diagnosis and prompt treatment are imperative because untreated shock progresses to an irreversible point that is refractory to volume expansion and other medical therapies. The qSOFA score is a rapid, bedside assessment of three variables: Glasgow Coma Score ($\leq$ 14), systolic blood pressure ($\leq$ 100 mm Hg), and respiratory rate ($>$ 22 breaths per minute). The presence of two of those three is associated with high mortality.

New Terminology. In 2016, the International Sepsis Consensus Conference (Sepsis-3) recommended deemphasizing the use of SIRS (nonspecific) and instead adopting SOFA as a more accurate prognostic indicator of the effects of sepsis. Their recommendation is that a total SOFA score of two or more points from baseline represents organ dysfunction; however, the SOFA scores are research tools and have not yet been validated widely in clinical practice.

Treatment

Treatment of hypovolemic shock is aggressive volume resuscitation, either with crystalloid solution or with blood products, as necessary. Treatment of cardiogenic shock focuses on maintaining blood pressure with dopamine or norepinephrine

infusions, relief of pulmonary edema with diuretics, and reducing cardiac afterload, for example, with an intra-aortic balloon pump.

The initial treatment for distributive shock is isotonic fluid resuscitation to maintain adequate intravascular volume. Other cornerstones of therapy include broad-spectrum antibiotics targeted to the underlying infection and removing the source of the infection. Patients often require vasopressor support (norepinephrine is the agent of choice) and mechanical ventilation to optimize tissue oxygenation. Vasopressors increase systemic vascular resistance via vasoconstriction to increase organ perfusion. The three main subtypes are catecholamine–, smooth muscle–, and dopaminergic receptor–targeting vasopressors. Catecholamine vasopressors target the alpha and/or beta receptors and include phenylephrine, norepinephrine, and epinephrine. Vasopressin acts on smooth muscle V-1 receptors and renal V-2 receptors for vasoconstrictive and antidiuretic uses, respectively; it has no inotropic or chronotropic effects. Dopamine acts on dopaminergic, alpha, and beta receptors in a dose-dependent manner. IV hydrocortisone may be administered to patients with hypotension that is refractory to fluid resuscitation and vasopressors.

Surviving Sepsis Campaign. The Surviving Sepsis Campaign is an international collaborative that develops evidence-based guidelines on reducing morbidity and mortality. Some of the key recommendations include

- Hour-1 bundle for expected interventions, therapy, and goals
- Early administration of antibiotics
- Early use of serum lactate and if elevated, measure again
- Vasopressors if hypotension continues despite IV fluids

CASE CORRELATION

- See also Case 40 (Anaphylaxis/Drug Reactions) and Case 42 (Vascular Catheter Infection in a Patient With Neutropenic Fever).

COMPREHENSION QUESTIONS

41.1 Which of the following **asymptomatic** patients would most benefit from treatment of the finding of more than 10^5 CFU/mL of *Escherichia coli* on urine culture?

A. A 23-year-old sexually active woman
B. A 33-year-old pregnant woman
C. A 53-year-old diabetic woman
D. A 73-year-old woman in a nursing home

41.2 Which of the following is the best treatment for a 39-year-old woman with fever of 103 °F, nausea, flank pain, and more than 10^5 CFU/mL of *E. coli* in a urine culture?

A. Oral trimethoprim-sulfamethoxazole for 3 days
B. Single-dose ciprofloxacin
C. Intravenous and then oral levofloxacin for 14 days
D. Oral ampicillin for 21 to 28 days

41.3 A 57-year-old man is brought into the emergency center for shortness of breath and light-headedness. He is found to have a blood pressure of 68/50 mm Hg and heart rate of 140 bpm. His jugular venous pulses are elevated. The lungs have inspiratory crackles on examination. All four extremities are cold and clammy. Which of the following is the most likely etiology for this patient's condition?

A. Septic shock
B. Adrenal crisis
C. Cardiogenic shock
D. Hypovolemic shock

41.4 A 45-year-old man is brought into the emergency center for severe abdominal pain and light-headedness. His wife states that the patient has had lower abdominal pain for 2 days but did not want to see a doctor. He is noted to have a blood pressure of 80/40 mm Hg, heart rate of 142 bpm, and temperature of 102 °F. His abdomen is tender with guarding and rebound, particularly in the right lower quadrant. Acute appendicitis is diagnosed. Three liters of 0.9% saline are infused, and IV antibiotics are administered as he is prepared for surgery. After the saline, his blood pressure is 70/42 mm Hg. Which of the following is the most appropriate next step?

A. Administer a beta-blocker to control his heart rate.
B. Check a cortisol level and administer corticosteroids.
C. Infuse fresh frozen plasma (FFP).
D. Initiate norepinephrine IV infusion.
E. Initiate IV morphine for pain control.

ANSWERS

41.1 **B.** All these patients are asymptomatic, and no benefit from treatment in terms of reduction in hospitalization has been shown for any of the cases mentioned, except for pregnancy. Treatment is undertaken to prevent upper UTI, preterm delivery, and possible fetal loss.

41.2 **C.** The patient in this scenario has symptoms of an upper UTI (eg, pyelonephritis) and is moderately ill with nausea. She will need a 14-day course of treatment and may not be able to take oral antibiotics initially, so hospitalization and treatment with IV antibiotics likely will be necessary. Single-dose (answer B) and 3-day (answer A) regimens are useful only for acute uncomplicated cystitis in women. *E. coli* is frequently resistant to ampicillin (answer D).

41.3 **C.** The patient is a middle-aged man who presents with shortness of breath and light-headedness. He is hypotensive with signs of left and right heart failure, that is, probably cardiogenic shock. The findings of pulmonary crackles and jugular venous distension are consistent with right heart failure; the presence of arterial hypotension and cold and clammy extremities is consistent with left heart failure. The most common cause of acute heart failure would be myocardial infarction, even in the absence of chest pain. Septic shock (answer A) and adrenal crisis (answer B) both are forms of distributive shock that would produce warm extremities. Hypovolemic shock (answer D) would present with flat neck veins, no pulmonary edema, and often a history of trauma, diarrhea, or blood loss.

41.4 **D.** When septic shock is refractory to volume resuscitation with isotonic fluid of at least 30 mL/kg of ideal body weight administration, the next step is adding a vasopressive agent (currently the favored medication is IV norepinephrine). Corticosteroids (answer B) can be administered, empirically if hypotension is refractory to vasopressors; steroids have fallen in and out of favor, but the most current evidence seems to indicate its positive effects. However, steroids are an adjunct and not primary therapy. IV morphine (answer E) might lower his blood pressure further. FFP (answer C) is used when the patient shows evidence of coagulopathy such as disseminated intravascular coagulation. Answer A (beta-blocking agent) is not indicated since this patient's tachycardia is in response to the hypotension and not a primary cardiac arrhythmia.

CLINICAL PEARLS

- UTIs and pneumonia are the most common causes of sepsis in older patients.
- UTIs can be diagnosed by the presence of urinary symptoms and by more than 10^5 CFU/mL of bacteria in a clean-catch specimen or more than 10^2 CFU/mL in a catheterized specimen.
- In healthy women with symptoms of acute uncomplicated cystitis, cultures are not routinely sent, and treatment can be initiated based on symptoms and a urine dipstick finding of leukocyte esterase or nitrites.
- Asymptomatic bacteriuria is a common finding among elderly patients and requires no treatment; it is only routinely treated in pregnancy and in immunocompromised patients.
- Sepsis is a syndrome characterized by fever, tachycardia, tachypnea, leukocytosis, and presence of a known or suspected infection. It requires early and aggressive intervention to prevent clinical deterioration.
- The qSOFA score is a way of assessing organ dysfunction due to septic shock and attempts to estimate morbidity and mortality risks.
- The best treatment for septic shock is IV isotonic fluids, and if the blood pressure is unresponsive, then a vasopressor agent such as norepinephrine.
- Goal-oriented therapy for septic shock, including the early administration of antibiotics and assessment of serum lactate, has been shown to improve outcome.

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CASE 42

A 24-year-old man presents to the emergency department complaining of a fever with shaking chills for the past 12 hours. He is currently being treated for acute lymphoblastic leukemia. His most recent chemotherapy session with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone was 7 days ago. He denies any cough or dyspnea, headache, abdominal pain, or diarrhea. He has had no sick contacts or recent travel. On physical examination, he is febrile to 103 °F and tachycardic with a heart rate of 122 beats per minute (bpm). His blood pressure is 118/65 mm Hg, and respiratory rate is 22 breaths per minute. He is ill appearing; his skin is warm and moist but without any rashes. His chest is clear to auscultation. His heart rate is regular with a soft systolic murmur at the left sternal border. The abdominal examination is benign. The perirectal area is normal. The digital rectal examination is deferred, and his stool is negative for occult blood. He has a tunneled vascular catheter at the right internal jugular vein without erythema overlying the subcutaneous tract or purulent discharge at the catheter exit site. He states he flushes the catheter each day and that yesterday he experienced a 20- to 30-minute episode of shaking chills about 10 minutes after flushing the catheter. Laboratory studies reveal a total white blood cell (WBC) count of 1100 cells/mm^3, with a differential of 10% neutrophils, 16% band forms, 70% lymphocytes, and 4% monocytes (absolute neutrophil count [ANC] 286/mm^3). Chest radiograph and urinalysis exams are normal.

- What is the most likely diagnosis?
- What are your next therapeutic steps?

ANSWERS TO CASE 42:

Vascular Catheter Infection in a Patient With Neutropenic Fever

Summary: A 24-year-old man presents with

- Acute lymphoblastic leukemia
- Fever of 103 °F
- History of immunosuppressive chemotherapy 7 days ago
- ANC of 286/mm^3
- Central venous catheter (CVC) with history suggestive of possible infection

Most likely diagnosis: Neutropenic fever and possible vascular catheter infection; the high suspicion for these diagnoses is due to the symptomatic chills after the flushing of a catheter in a cancer patient with neutropenia.

Next therapeutic step: Blood cultures should be drawn on this patient, ideally simultaneously from the catheter and a peripheral vein. Immediately afterward, the patient should undergo broad-spectrum intravenous antibiotic administration, including coverage for gram-positive organisms such as *Staphylococcus* spp. The vascular catheter should be removed, if possible.

ANALYSIS

Objectives

1. Recognize the possible sources of infection in a neutropenic patient. (EPA 1, 2)
2. Discuss the management of a patient with neutropenic fever. (EPA 4)
3. Explain how to diagnose and treat a catheter-related infection. (EPA 3, 4)
4. Describe the strategies to prevent infection in immunosuppressed patients, including granulocyte colony-stimulating factor (G-CSF) and vaccination of household contacts. (EPA 4, 12)

Considerations

This patient is being treated for a hematologic malignancy with combination chemotherapy, which has a common side effect of leukopenia, especially neutropenia. Generally, the nadir of the white cell count occurs 7 to 14 days after the chemotherapy. This patient has **neutropenia, defined as an ANC less than 1000 cells/mm^3**. The ANC is calculated by neutrophil percent multiplied by total WBC count. Infection in this immunosuppressed condition is life threatening, and immediate antibiotic coverage is paramount. Neutropenic patients are at risk for a variety of bacterial, fungal, or viral infections, but the most common sources of infection are the skin or oral cavity (gram-positive bacteria) and the bowel (gram-negative bacteria). Because of the absence of WBCs, the patient may not manifest the cardinal

inflammatory signs. The spectrum of coverage of empirical antibiotics should include enterobacteria, *Pseudomonas* species, and penicillin-resistant pneumococci. Methicillin-resistant *Staphylococcus aureus* (MRSA) should also be considered in neutropenic patients with skin infections, pneumonia, suspected indwelling catheter infections, or sepsis. Rapid initiation of empiric antibiotic therapy is critical while attempts to find a source of infection are in progress.

APPROACH TO:

Neutropenic Fever

DEFINITIONS

CENTRAL LINE–ASSOCIATED BLOODSTREAM INFECTION (CLABSI): A primary bloodstream infection (ie, there is no apparent infection at another site) that develops in a patient with a central line in place within the 48-hour period before onset of the bloodstream infection that is not related to infection at another site. Culturing the catheter tip or peripheral blood is not a criterion for CLABSI.

CATHETER-RELATED BLOODSTREAM INFECTION (CRBSI): The presence of bacteremia originating from an intravenous catheter.

CENTRAL VENOUS CATHETER: A CVC is a catheter that is inserted into a large vein such as the subclavian, internal jugular, or femoral vein.

FEVER: Single oral temperature measurement greater than or equal to 101 °F (38.3 °C) or a temperature greater than or equal to 100.4 °F (38.0 °C) for 1 hour or more.

MUCOSITIS: Breakdown of skin and mucosal barriers as a result of chemotherapy or radiation. Mucositis can result in bacteremia or fungemia.

NEUTROPENIA: ANC less than 1000 cells/mm^3. It is considered severe when the number is lower than 500 cells/mm^3.

CLINICAL APPROACH

Pathophysiology

Fever in a neutropenic patient with cancer should be considered a medical emergency. Approximately 5% to 10% of cancer patients will die of neutropenia-associated infection. Individuals with a hematologic malignancy (leukemias or lymphomas) are at an even greater risk for sepsis as a result of lymphocyte or granulocyte dysfunction or because of abnormal immunoglobulin production. Chemotherapy often causes further bone marrow suppression and neutropenia. The incidence of an occult infection in a neutropenic patient increases with the **severity and duration of the neutropenia** (high risk if > 7-10 days, and especially if ANC < 100 cells/mm^3). Some neutropenic patients (eg, the elderly or those receiving corticosteroids) may not be able to mount a febrile response to infection; thus, **any neutropenic patient showing signs of clinical deterioration should be suspected of having sepsis.**

CVCs are in widespread use and are common sites of infection in hospitalized patients and patients receiving outpatient infusion therapy. Infection may occur as a consequence of contamination by gram-positive skin flora or by hematogenous seeding, usually by enteric gram-negative organisms or *Candida* spp. Erythema, purulent drainage, and induration are signs of infection.

In the absence of obvious tunnel or exit-site infection, authorities recommend obtaining two or more blood cultures to try to diagnose **catheter-related bacteremia**, with at least one from the CVC. Catheter-related infection is suspected when a patient has two or more positive blood cultures obtained from a peripheral vein; clinical manifestations of infection (eg, fever, chills, and/or hypotension); and no alternative apparent source of bloodstream infection. In some institutions, quantitative blood cultures (counting colony-forming units [CFUs]) are obtained under the assumption that a four-fold higher colony count will be obtained from blood drawn from an infected catheter than blood drawn from a peripheral vein, supporting the diagnosis of catheter-related bacteremia. A blood culture that is drawn from the CVC that becomes positive at least 20 minutes before the peripheral blood cultures is an indication that the CVC is the likely source of infection. If the catheter is removed, the tip of the catheter may be cut off and rolled across a culture plate, using a quantitative culture method.

Clinical Presentation

The typical signs and symptoms of infection noted in immunocompetent patients are the result of the host's inflammatory response. This may be minimal or absent in neutropenic patients. Soft tissue infections may have diminished or absent induration, erythema, or purulence; pneumonia may not show discernible radiologic infiltrates; meningitis may not reveal cerebrospinal fluid (CSF) pleocytosis; and urinary tract infection may be present without pyuria. Infected catheters may manifest as an infection of the subcutaneous tunnel, infection at the exit site, or catheter-related bacteremia and sepsis.

Treatment

Empiric antibiotic therapy should be administered promptly to all neutropenic patients at the onset of fever. Historically, gram-negative bacilli, mainly enteric flora, were the most common pathogens in these patients. Empiric coverage for gram-negative bacteria, including *Pseudomonas aeruginosa*, is almost always indicated for neutropenic fever. Early treatment is associated with reduced mortality. Currently, as a consequence of frequent use of CVCs, gram-positive bacteria account for 60% to 70% of microbiologically documented infections. Another clue that the infection is likely to be a gram-positive organism includes the presence of obvious soft tissue infections, such as cellulitis or oral mucositis. This causes breaks in the mucosal barriers and allows oral flora to enter the bloodstream. If any of these factors is present, an appropriate agent, such as vancomycin, should be added to the regimen. If patients continue to be febrile despite antibacterial therapy, empiric antifungal therapy should be considered. Figure 42–1 shows a useful algorithm for patient management.

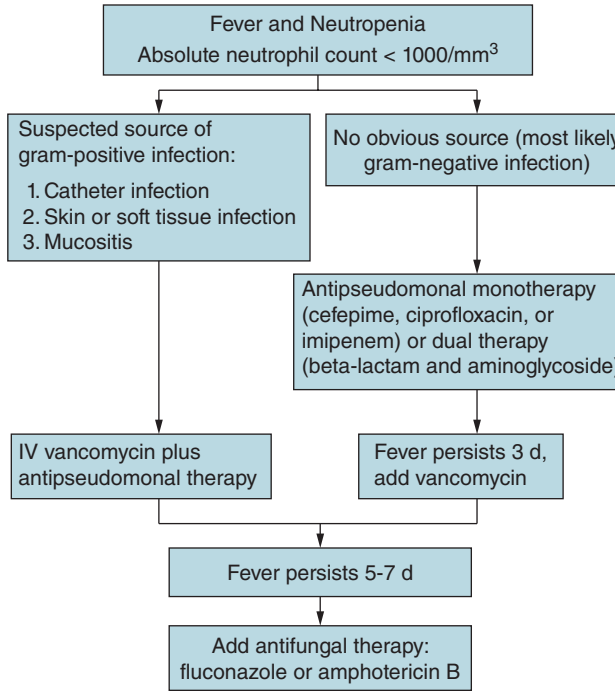


Figure 42–1. Algorithm of a suggested approach to neutropenic fever.

Catheter-Related Infection. The two main decisions impacting suspected catheter-related infection are (1) whether the catheter is really the source of infection and, if it is, and (2) must the catheter be removed or can the infection be cleared with antibiotic therapy alone? **Most nontunneled or implanted catheters** should be **removed**. For more permanent catheters, the decision to remove the catheter depends on the patient's clinical state, identification of the organism, and the presence of complications, such as endocarditis or septic venous thrombosis.

S. aureus* and coagulase-negative *Staphylococcus* are the most common causes of catheter-associated infections**. For **coagulase-negative *Staphylococcus bacteremia, response to **antibiotic therapy without catheter removal** is possible up to 80% of the time. Generally, **erythema overlying the subcutaneous tract** of a tunneled catheter necessitates catheter removal. Leaving the catheter in place may result in severe cellulitis and soft tissue necrosis. If there is only erythema at the exit site, it may be possible to salvage the line using antibiotics, usually vancomycin, through the CVC.

Considerations for removal would be those infections caused by **fungi** or **nontuberculous mycobacteria** or if there is **persistent bacteremia after 48 to 72 hours** of appropriate antimicrobial treatment. Keeping the catheter in place is also usually not advisable in critically ill or hemodynamically unstable patients. Bacteremia as a consequence of ***S. aureus*, gram-negative organisms, and fungemia caused by *Candida* spp responds poorly to antimicrobial therapy** alone. Therefore, **prompt removal of the catheter is recommended.**

Prevention. Because of the serious complications associated with neutropenia, preventive measures are critical in cancer patients who are receiving chemotherapy. Patients should be **immunized against pneumococcus and influenza.** Administration of live virus vaccines, such as measles-mumps-rubella or varicella zoster, is generally contraindicated. **G-CSF**, which stimulates the bone marrow to produce neutrophils, is frequently used prophylactically in patients receiving chemotherapy to shorten the duration and depth of neutropenia, thereby reducing the risk of infection. It is sometimes used after a neutropenic patient develops a fever, but its use at this point is controversial and may result in more harm than benefit.

Prophylactic use of oral quinolones to prevent gram-negative infection or the use of antifungal agents to prevent *Candida* infection may reduce certain types of infection, but it may also lead to the emergence of resistant organisms. Thus, this is recommended for patients who are anticipated to have an ANC < 100 cells/mm^3 for more than 7 days; antiviral agents are also recommended to reduce the risk of herpes simplex virus and varicella zoster reactivation in this setting. Other recommendations include avoiding sick contacts and overcrowded areas, as well as proper handwashing and cough etiquette. Slight trauma to mucosal surfaces can cause bacteremia, so careful oral hygiene, avoidance of rectal thermometers or rectal examinations, and skin care are also important.

CASE CORRELATION

- See also Case 40 (Anaphylaxis/Drug Reactions) and Case 41 (Urinary Tract Infection and Sepsis in the Elderly).

COMPREHENSION QUESTIONS

42.1 A 64-year-old man has been hospitalized for intravenous antibiotics due to osteomyelitis. A CVC was placed to infuse antibiotics. After 5 days, he developed a fever, and 48-hour blood cultures were positive for growth. The clinician suspects that an infected CVC is responsible. Which of the following is the most likely offending organism?

A. *Candida albicans*
B. Coagulase-negative *Staphylococcus*
C. *Klebsiella pneumoniae*
D. *Pseudomonas aeruginosa*
E. *Streptococcus pyogenes*

42.2 A 32-year-old man with acute myelogenous leukemia is undergoing chemotherapy. He was hospitalized 7 days ago for fever to 102 °F with an ANC of 100 cells/mm^3, and he has been placed on intravenous imipenem and vancomycin. He continues to have fever to 103 °F without an obvious source. Which of the following is the best next step?

A. Add an aminoglycoside antibiotic.

B. Add an antifungal agent.

C. Continue present therapy.

D. Perform lumbar puncture to assess CSF.

E. Stop all antibiotics because he likely has drug fever.

42.3 A 68-year-old woman is diagnosed with acute leukemia and is undergoing induction chemotherapy. Last cycle, she developed neutropenia with an ANC of 350 cells/mm^3, which has now resolved. Which of the following is the most appropriate therapy?

A. Immunization against mumps

B. Immunization against varicella

C. Use of G-CSF after the next cycle of chemotherapy

D. Use of recombinant erythropoietin before the next cycle of chemotherapy

ANSWERS

42.1 **B.** Coagulase-negative staphylococci, such as *Staphylococcus epidermidis*, along with *S. aureus* are the most common etiology of catheter-related infections because they are part of the skin flora. The other bacteria are isolated at a much lower frequency, such as *Klebsiella* species and *Pseudomonas* species (answers C and D), and even less common is *C. albicans* (answer A).

42.2 **B.** Antifungal therapy should be added when the fever is persistent for 5 to 7 days despite broad-spectrum antibacterial agents. Patients with neutropenia, defined as an ANC less than 1000 cells/μL, are at greater risk for bacterial (gram-positive and gram-negative) and fungal infections such as caused by *C. albicans* and *Aspergillus*. Answer A (aminoglycoside) would not add much coverage to imipenem, which already has excellent gram-negative coverage. Answer C (continue present therapy) is not wise with the persistent fever. Answer D (lumbar puncture) is not indicated since there is no sign of meningeal irritation. Answer E (stop all antibiotics) is not prudent in this immunosuppressed patient.

42.3 **C.** Granulocyte colony-stimulating factor administered after chemotherapy may decrease the duration and severity of neutropenia and the subsequent risk of sepsis in these patients. Live vaccines, such as varicella (answer B) and mumps (answer A), are contraindicated in immunosuppressed individuals. Erythropoietin (answer D) is not indicated since the patient is not anemic.

CLINICAL PEARLS

- Fever in a neutropenic patient should be considered a medical emergency and is associated with a high mortality rate.
- The usual sources of bacterial infection in neutropenic patients are the skin and mouth (gram-positive organisms) and the intestine (gram-negative enteric flora, including *Pseudomonas*.
- Antibiotics should be started within 60 minutes of presentation of neutropenic fever.
- Antifungal therapy should be started in neutropenic patients who have persistent fever despite broad-spectrum antibiotic therapy and who have no obvious source of infection.
- Vascular catheters should be removed if there is apparent evidence of a purulent infection or subcutaneous tract at the catheter site, there is an infection caused by a nontuberculous mycobacteria or fungi, or the infection is not properly controlled after 48 to 72 hours of appropriate antibiotic therapy.
- If a catheter is deemed necessary but is infected with coagulase-negative staphylococci, antibiotic treatment may sterilize the catheter, allowing it to remain in place.

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CASE 43

A 20-year-old college student is the next patient in the emergency department. When you walk into the room, he is lying on the examination table on his side with his arm covering his eyes. The light in the room is turned off. His temperature is 102.3 °F, heart rate is 110 beats per minute (bpm), and blood pressure is 120/80 mm Hg. When you gently ask how he has been feeling, he says that for the past 3 days he has had fever, body aches, and a progressively worsening headache. The light hurts his eyes, and he is nauseated. He has not had any episodes of emesis. He has experienced rhinorrhea but denies diarrhea, cough, or nasal congestion. He has no known ill contacts. On examination, he has no skin rash, and his pupils are difficult to assess due to photophobia. Ears and oropharynx are normal. Heart, lung, and abdominal examinations are normal. Neurologic examination reveals no focal neurologic deficits. Passive flexion of his neck worsens his headache, and he is unable to touch his chin to his chest without pain.

- What condition concerns you the most?
- What diagnostic test would confirm this diagnosis?

ANSWERS TO CASE 43:
Meningitis, Bacterial

Summary: A 20-year-old college student presents with

- A 3-day history of fever, body aches, and headache
- Fever to 102.3 °F
- Photophobia and nausea
- Nuchal rigidity suggesting meningeal irritation

Most concerning condition: Meningitis (especially bacterial).

Diagnostic test to confirm diagnosis: Lumbar puncture (LP) for evaluation of the cerebrospinal fluid (CSF), in some cases (not this one) preceded by a computed tomographic (CT) scan of the head.

ANALYSIS

Objectives

1. Identify the clinical presentations of viral and bacterial meningitis. (EPA 1)
2. Discuss LP as the diagnostic test of choice for meningitis. (EPA 3)
3. Describe the CSF findings in different forms of meningitis. (EPA 3)
4. Recall the treatment for meningitis. (EPA 4)

Considerations

This 20-year-old college student has headache, nausea, photophobia, fever, and neck pain and stiffness, all suggestive of meningitis, which could be caused by different organisms. Prompt LP and analysis of CSF are essential to establish the diagnosis. Prior to the LP, a CT scan should be obtained if the patient is immunocompromised or has new-onset seizures, papilledema, altered mental status, or a focal neurologic deficit. In the event that an LP cannot be performed prior to antibiotic administration, blood cultures can be obtained; they are positive in 50% to 90% of patients with meningococcal meningitis. Two sets of blood cultures should be collected before the start of antibiotic therapy. In a patient without these signs and symptoms, a preceding CT scan may be unnecessary. A purpuric skin rash increases suspicion for *Neisseria meningitidis*. Antibiotic administration should not be delayed in suspected meningococcal infection because progression of the disease is rapid, and the mortality and morbidity are extremely high even when antibiotics are given in a timely manner. This seemingly immunocompetent patient does not have risk factors for fungal or parasitic organisms, and therefore empiric therapy with intravenous antibiotics such as vancomycin with cefotaxime or ceftriaxone should be initiated. However, patients at higher risk for opportunistic or unusual organisms should be managed differently; these patients include those with human immunodeficiency virus (HIV) and low CD4 counts, immunosuppression from

chemotherapy or transplant antirejection agents, chronic antibiotic therapy, and status post brain/spinal surgery.

APPROACH TO: Meningitis

DEFINITIONS

ENCEPHALITIS: Brain parenchymal injury and inflammation most often secondary to a viral etiology. When focal brain parenchymal infection is secondary to bacterial infection, it is usually termed *cerebritis* or *abscess*.

INFECTIOUS MENINGITIS: Inflammation of the subarachnoid space and meninges caused by bacteria, viruses, fungi, or protozoa; infection is the most common etiology of meningitis.

PAPILLEDEMA: Swelling of the optic nerve caused by increased intracranial pressure. On fundoscopic examination, the optic disc margin may appear hazy.

CLINICAL APPROACH

Epidemiology

Infections of the central nervous system involve either the meninges (meningitis) or the brain parenchyma (encephalitis). The incidence is dropping due to the more widespread administration of pneumococcal and *Haemophilus influenzae* vaccines. However, bacterial meningitis is still dangerous, with a case fatality rate of approximately 10% to 20% with treatment, and nearly 100% without any treatment. Serious sequelae, such as seizures, hearing loss, or brain damage, may occur despite adequate treatment. College students are at risk due to living in close quarters with other students.

Bacterial meningitis is the most common pus-forming intracranial infection, with an incidence of 1.38 per 100,000 persons. The microbiology of the disease has changed somewhat since the introduction of the *H. influenzae* type b vaccine in the 1980s. Now ***Streptococcus pneumoniae* is the most common bacterial isolate**, with ***N. meningitidis* as a close second. Group B *Streptococcus*** or *Streptococcus agalactiae* occurs in approximately 10% of cases, more frequently in neonates, patients older than 50 years, and those with chronic illnesses such as diabetes or liver disease. ***Listeria monocytogenes*** accounts for approximately 10% of cases and must be considered in pregnant women, the elderly, and patients with impaired cell-mediated immunity such as with acquired immunodeficiency syndrome (AIDS). *H. influenzae* is responsible for less than 10% of meningitis cases. Resistance to penicillin and some cephalosporins is currently a concern in the treatment of *S. pneumoniae*.

Pathophysiology

Bacteria usually seed the meninges hematogenously after colonizing and invading the nasal or oropharyngeal mucosa. Occasionally, bacteria directly invade the

intracranial space from a site of abscess formation in the middle ear or sinuses. The gravity and rapidity of progression of disease depend on characteristics of both the host defense system and organism virulence. For example, patients with defects in the complement cascade are more susceptible to invasive meningococcal disease. Patients with CSF rhinorrhea caused by trauma or postsurgical changes may also be more susceptible to bacterial invasion.

Staphylococcus aureus* and *Staphylococcus epidermidis are common causes of meningitis in patients following **neurologic procedures** such as placement of **ventriculoperitoneal shunts**. The brisk host inflammatory response in the subarachnoid space may cause edema, vasculitis, and coagulation of vessels, leading to severe neurologic complications, including seizures, increased intracranial pressure, and stroke. Acute bacterial meningitis can progress over a matter of hours to days. **Typical symptoms include fever, nuchal rigidity, and headache**. Patients may also complain of photophobia, nausea and vomiting, as well as other nonspecific constitutional symptoms. Approximately 75% of patients will experience some confusion or altered level of consciousness. Less than 40% may experience seizures during the course of their illness.

Differential Diagnosis. The differential diagnosis of bacterial meningitis is fairly limited and can be narrowed down depending on the patient's age, exposure history, and course of illness. Various viral infections may also cause meningitis. The most common include **enteroviruses**, which tend to be more common in the summer and fall. Patients may present with severe headache accompanied by symptoms of gastroenteritis. The **CSF white blood cell (WBC) count will be elevated** with a **predominance of lymphocytes**, and **glucose and protein levels are usually normal**. Herpes simplex virus (HSV) 1 or HSV-2 may cause a viral meningitis. The CSF of these patients will also have a normal glucose level, whereas protein and WBC counts will be elevated with a predominance of lymphocytes. Typically, these patients have a high CSF red blood cell (RBC) count, which is not seen in bacterial meningitis in the absence of a traumatic LP. In a patient with HIV infection, fungal meningitis, specifically *Cryptococcus*, should be considered. Tuberculous meningitis presents subacutely; it is more common in older, debilitated patients and patients with HIV. Rickettsial disease, specifically Rocky Mountain spotted fever, may also present with meningitis. Intracranial empyema, or brain or epidural abscess, should be considered if the patient has focal neurologic findings. The one nonsuppurative diagnosis in the differential is **subarachnoid hemorrhage** from bleeding intracranial aneurysms. These patients present with sudden onset of the "worst headache of their lives" in the absence of other symptoms of infection. They may have photophobia, and the CSF will be grossly bloody; the supernatant will be xanthochromic, reflecting the breakdown of blood into bilirubin.

Clinical Presentation

Some physical examination findings may be useful in the evaluation of a patient with suspected meningitis. **Nuchal rigidity** is demonstrated when passive or active flexion of the neck results in an inability to touch the chin to the chest. Classic tests include Kernig and Brudzinski signs. **Kernig sign** can be elicited with the patient on his or her back with the hip and knees flexed. The knee is then passively extended.

Table 43–1 • CSF CHARACTERISTICS OF MENINGITIS

Causative Organism	Opening Pressure	WBC Count/ Type	Glucose	Protein	RBC Count	Special Stains/Tests
Bacteria	High	Elevated, predominantly neutrophilic	Low, < 40 mg/dL	Elevated	None	Gram stain
Viral	Normal	Elevated, predominantly lymphocytic	Normal	Normal	None	Cell culture or PCR
Herpes simplex	Normal to high	As in other viral meningitis	Normal	Normal to high	**High**	PCR
Tuberculosis	Normal to high	Elevated, monocytes may be elevated	Very low	Very high	None	PCR, AFB smear (usually negative), and culture
Fungal	Variable	Elevated, predominantly lymphocytes	Low	Elevated	None	Fungal stains

Abbreviations: AFB, acid-fast bacillus; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RBC, red blood cell; WBC, white blood cell.

If passive extension of the knee elicits pain, the test is positive. **Brudzinski sign** is positive if the supine patient flexes the knees and hips when the neck is passively flexed. Neither sign is very sensitive for the presence of meningeal irritation. However, if present, both are highly specific. **Papilledema**, if present, would indicate **increased intracranial pressure.** Focal neurologic signs, altered level of consciousness, or seizures may reflect ischemia of the cerebral vasculature or focal suppuration.

Laboratory Evaluation. Blood cultures should be obtained in all patients with suspected meningitis. LP and CSF evaluation are critical to the diagnosis. Table 43–1 lists typical findings in the CSF from various etiologies of meningitis. The **necessity of imaging of the head and brain prior to performing an LP should be individualized**. CT scans are most useful in the initial presentation to exclude intracranial mass or bleeding or to evaluate for other signs of increased intracranial pressure. Performing an LP without a preceding imaging study in a patient with signs of increased intracranial pressure poses the risk for brain herniation following the LP procedure. However, studies have shown that in the patient with suspected meningitis who does not have papilledema, focal neurologic signs, or altered level of consciousness, an LP may be safely performed without preceding imaging. Furthermore, in instances in which performance of the LP may be delayed, antibiotics should be administered *after* blood cultures are obtained while awaiting the radiologic studies.

Ideally, the CSF should be examined within 30 minutes of antibiotics, but it has been shown that it takes up to 4 to 10 hours for the CSF to become sterile in a patient with pneumococcal meningitis. One exception is meningococcal meningitis, in which cultures convert to negative within 1 hour of antibiotic administration. If CSF is obtained, then a culture and Gram stain should be studied. CSF cell

count, glucose, and protein levels should be measured. Though not very sensitive, latex agglutination tests for *S. pneumoniae* and *H. influenzae* are highly specific and can be useful in diagnosing the infectious agent in patients pretreated with antibiotics. If positive, they can establish the etiology. Polymerase chain reaction (PCR) testing is available for some bacteria; however, it may be more useful in the diagnosis of herpes simplex and tuberculous meningitis. In all, no more than 3.5 to 4 mL of CSF is necessary. **The most critical issue in a patient with suspected bacterial meningitis is the initiation of antibiotics.** The CSF examination and imaging studies can be deferred in this medical emergency.

Imaging. When **HSV meningoencephalitis** is suspected, magnetic resonance imaging (MRI) may demonstrate **enhancement of the temporal lobes.** In tuberculous meningitis, enhancement of the basal region may be seen. An electroencephalogram (EEG) may be helpful in patients suspected of HSV meningitis. Within 2 to 15 days after the start of the illness, periodic sharp and slow wave complexes originating within the temporal lobes can be demonstrated at 2- to 3-second intervals. On the other hand, if purpuric skin lesions are present, a skin biopsy may demonstrate *N. meningitidis* and can be helpful in confirming the diagnosis. The patient's age may also provide clues regarding the etiology of the meningitis (Table 43–2).

Treatment

Treatment of meningitis often is empiric until specific culture data are available. Because of the growing incidence of antibiotic-resistant pneumococci and meningococci, the recommended empiric therapy in most regions is a **high-dose**

Table 43–2 • ETIOLOGIES OF BACTERIAL MENINGITIS BY AGE

Age of Patient	Bacteria	Empiric Treatment	Comments
Neonate	1. Gram-negative enteric bacteria (*Escherichia coli*) and group B *Streptococcus* 2. *Listeria monocytogenes*	Ampicillin + cefotaxime	Vaginal organisms common
1-23 mo	1. *Streptococcus. pneumoniae* 2. *Neisseria meningitidis* 3. *Haemophilus influenzae* type b (less common since vaccine)	Cefotaxime (or ceftriaxone) + vancomycin	Previous to vaccine, *H influenzae* caused 70% of meningitis in children
2-18 y	1. *N. meningitidis* 2. *S. pneumoniae* 3. *H. influenzae* type b (less common since vaccine)	Vancomycin + ceftriaxone	Ampicillin in immunocompromised patients
19-59 y	1. *S. pneumoniae* 2. *N. meningitidis* 3. *H. influenzae* type b	Vancomycin + ceftriaxone	Ampicillin in immunocompromised patients
60+ y	1. *S. pneumoniae* 2. *L. monocytogenes* 3. Group B *Streptococcus*	Ampicillin + vancomycin + ceftriaxone (or cefotaxime)	*Listeria* more common

third-generation cephalosporin given concurrently with vancomycin. In some cases, if the disease presentation is typical for meningococcus (with the characteristic rash), third-generation cephalosporins are sufficient. If the organism is proven to be susceptible to penicillin, therapy with high-dose penicillin G may be started. **Ampicillin is added when there is a concern for listeriosis. Acyclovir should be started for suspicion of HSV**, and antituberculosis therapy should be considered if the presentation is suspicious for tuberculous meningitis.

Glucocorticoids, when indicated, should be administered just before or concurrent with the first dose of antibiotics to reduce central nervous system inflammation and further neurologic deficits. One study in adults demonstrated decreased mortality in patients with *S. pneumoniae* meningitis who were also given glucocorticoids. There are stronger data supporting steroids for *H. influenzae* and *S. pneumoniae* meningitis in children. There is also some evidence for the benefit of steroids in severe tuberculous meningitis. A Cochrane database review in 2015 concluded that corticosteroids may help reduce the incidence of hearing loss and neurologic sequelae, but do not affect mortality.

Prevention. Prevention of meningitis can be achieved through the administration of **vaccines and chemoprophylaxis** to close contacts of the infected. **Specific vaccinations are available for *H. influenzae* type b and some strains of *S. pneumoniae*** and are now routinely administered to **children. Meningococcal vaccination** is recommended for those living in dormitories or close living quarters, such as college students and military recruits, but not for the general population. **Rifampin given twice daily for 2 days** or a **single dose of ciprofloxacin** is recommended for **household and close contacts** of an index case of **meningococcemia or meningococcal meningitis.**

CASE CORRELATION

- See also Case 38 (Headache/Temporal Arteritis), Case 41 (Urinary Tract Infection and Sepsis in the Elderly), Case 42 (Vascular Catheter Infection in a Patient With Neutropenic Fever), and Case 45 (Syphilis).

COMPREHENSION QUESTIONS

43.1 An 18-year-old young man with a 3-day history of fever, headache, increasing confusion, and lethargy presents to the emergency department. His physical examination is normal, and he has no focal neurologic signs. The CT scan of his head is negative. An LP reveals a WBC count of 250/mm^3, with 78% lymphocytes, and RBCs were 500/mm^3 in tube 1 and 630/mm^3 in tube 2, respectively. No organisms are seen on Gram stain. Which of the following is the best next step?

A. Careful observation with no antibiotics

B. Intravenous azithromycin

C. Intravenous ceftriaxone, acyclovir, and vancomycin

D. Intravenous fluconazole

43.2 A 55-year-old man with a long history of alcohol abuse has been hospitalized for 2 days. He was initially brought in by emergency medical services to the emergency center with a 3-week history of progressive confusion and stupor. On examination, he was afebrile, with heart rate 100 bpm and blood pressure 130/70 mm Hg. He was confused and drowsy but would open his eyes to verbal stimuli. On examination, he had a new right sixth cranial nerve palsy and tremulousness of all four extremities. An LP was performed, and his CSF showed 250 WBCs/mm^3 (68% lymphocytes), 300 RBCs/mm^3, protein level of 1070 mg/dL, and glucose 10 mg/dL. The serum glucose was 90 mg/dL. He was started on intravenous ceftriaxone, vancomycin, and acyclovir as empiric therapy. A purified protein derivative (PPD) placed on admission is positive today (48 hours), and bacterial cultures are negative at 48 hours. Which of the following would best help to confirm this patient's probable diagnosis?

A. CT of the head with contrast
B. Gram stain of throat scrapings
C. Herpes simplex virus PCR
D. MRI of the head
E. Repeat LP after 48 hours of therapy

43.3 A 65-year-old man was diagnosed with stage III colon cancer, and after surgical staging, he was placed on a regimen of irinotecan, infusional fluorouracil, and leucovorin. His last course was 2 weeks previously. Today, he presents to the emergency center with a fever and severe headache of 3 days' duration. His temperature is 101 °F. There is no papilledema or focal neurologic findings present. An LP is performed, and the Gram stain reveals gram-positive rods. Which of the following therapies is most appropriate for this patient?

A. Ampicillin
B. Ceftriaxone
C. Gentamicin
D. Metronidazole
E. Vancomycin

ANSWERS

43.1 **C.** This young man most likely has viral meningitis, given the modest CSF pleocytosis count with predominant lymphocytes. Given the high RBC count, the etiology might be HSV, so acyclovir should be instituted until more specific testing can be performed. However, because bacterial meningitis cannot be excluded based on the CSF analysis alone, empiric antibiotics should be given until culture results are known; culture results usually return within 48 hours. Moreover, the early CSF findings in bacterial meningitis may resemble those of viral meningitis. If in doubt, a second LP 24 to 48 hours later may be advisable. This patient does not exhibit signs of immunosuppression, so

fluconazole (answer D) is not necessary to treat fungal meningitis. Careful observation without antibiotics (answer A) is inappropriate since untreated bacterial meningitis is associated with severe morbidity or mortality. Intravenous azithromycin (answer B) is a standard treatment for community-acquired pneumonia but has a very limited role in meningitis.

43.2 **E.** Tuberculous meningitis is extremely difficult to diagnose, and the index of suspicion should be high in susceptible individuals. Certain clinical findings, such as nerve palsies and CSF findings, including an extremely low glucose and high protein levels with a fairly low WBC count, are highly suggestive but not diagnostic. This patient has an elevated CSF protein level and low CSF glucose level. Mortality is high and correlates with the delay in instituting therapy. The only definitive test is acid-fast bacillus culture, but it can take 6 to 8 weeks to grow. PCR test for *Mycobacterium tuberculosis* is diagnostic if positive; however, the sensitivity is low, so a negative test does not rule out the disease. Findings such as a positive PPD or CSF cell counts and protein levels that do not change with standard antimicrobial or antiviral therapies can also suggest the diagnosis. **Low CSF glucose is a hallmark of tuberculosis (TB) meningitis;** if the glucose level falls at 48 hours, it is highly suggestive of TB. A CT scan (answer A) and MRI (answer D) may demonstrate basilar meningitis in TB, but this finding is not specific. TB meningitis is an extrapulmonary form of TB; as such, pulmonary involvement occurs concomitantly in 50% of patients. A chest x-ray can provide further data. Gram stain of the throat (answer B) would not have a role in this case. HSV PCR (answer C) should be performed on this patient since HSV can present atypically; however, the typical HSV meningoencephalitis usually yields CSF of mildly increased white cells (eg, 100 cells/mm^3), glucose levels that are normal or mildly decreased (40 mg/dL), and protein levels in the range of 100 to 600 mg/dL.

43.3 **A.** This patient should be placed on ampicillin as a minimum, and depending on his absolute neutrophil count, a broader antimicrobial regimen may be prudent. The organism identified by Gram stain is likely *L. monocytogenes*, a gram-positive rod that causes approximately 10% of all cases of meningitis. This infection is more common in the elderly and in other patients with impaired cell-mediated immunity, such as patients on chemotherapy. It is also more common in neonates. It is not sensitive to cephalosporins or aminoglycosides, and specific therapy with ampicillin must be instituted if the suspicion for this disease is high. Ceftriaxone (answer B) is a third-generation cephalosporin and is often chosen as a first-line agent for most community-acquired meningitis pending cultures; however, because this patient has likely *Listeria* meningitis, this agent would not be sufficient. Gentamicin (answer C) is an adjuvant antibiotic and offers some synergistic effect when used with another medication, such as a cephalosporin; gentamicin has no efficacy against *Listeria*. Vancomycin (answer E) is used as part of the empiric antibiotics covering staphylococcal infections. Metronidazole (answer D) covers for anaerobes and has little use in the therapy of meningitis.

CLINICAL PEARLS

- Generally, an LP should not be delayed in a patient who is suspected of having meningitis. If LP is contraindicated or impossible because of hemodynamic instability, empiric therapy should be started immediately after blood cultures are drawn.
- CT imaging of the brain prior to LP is not necessary in most cases, but it should be considered when the risk of brain herniation is high. These findings include new-onset seizures, signs suspicious for space-occupying lesions (eg, **papilledema and focal neurologic signs**), and moderate-to-severe impairment in consciousness.
- The most common cause of bacterial meningitis in adults is *S. pneumoniae*, followed by *N. meningitidis*. *L. monocytogenes* meningitis may occur in neonates and immunocompromised and older patients.
- Patients who have undergone neurosurgical procedures or who have been subject to skull trauma are at risk for staphylococcal meningitis.
- Hemorrhagic CSF with evidence of temporal lobe involvement by imaging or EEG suggests HSV meningoencephalitis; acyclovir is the treatment of choice.
- Corticosteroid use does not affect mortality but seems to reduce hearing loss and neurologic sequelae. It should be used just before or concurrent with antibiotic therapy.

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CASE 44

A 62-year-old man is brought to the clinic for a 3-month history of unintentional weight loss (12 lb). His appetite has diminished, but he reports no vomiting or diarrhea. He does report some depressive symptoms since the death of his wife a year ago, at which time he moved from Cambodia to the United States to live with his daughter. He denies a smoking history. He complains of a 3-month history of productive cough with greenish sputum. He has not felt feverish. He takes no medications regularly. On examination, his temperature is 100.4 °F and respiratory rate is 16 breaths per minute. His neck examination shows a normal thyroid gland and no cervical or supraclavicular lymphadenopathy. His chest has scattered crackles in the left midlung fields and a faint expiratory wheeze on the right. His heart rhythm is regular with no gallops or murmurs. His abdominal examination is benign, his rectal examination shows no masses, and his stool is negative for occult blood. His chest x-ray is shown in Figure 44–1.

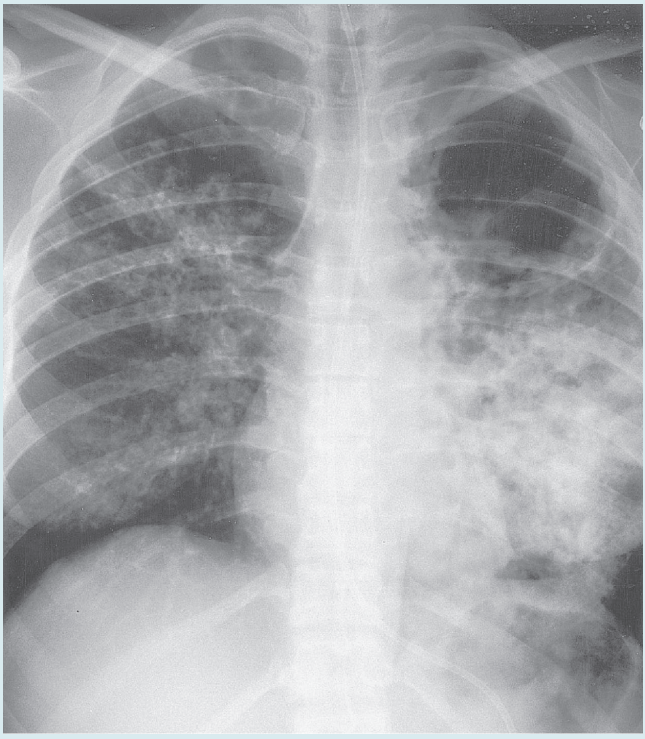


Figure 44–1. Chest x-ray. (Reproduced with permission, from Fishman AP. *Fishman's Pulmonary Diseases and Disorders*. 3rd ed. 1998. Copyright © McGraw Hill LLC. All rights reserved.)

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 44:
Tuberculosis (Pulmonary), Cavitary Lung Lesions

Summary: A 62-year-old man from Cambodia presents with

- A 12-lb unintentional weight loss over 3 months
- Diminished appetite
- A low-grade fever and productive cough
- A chest x-ray with right upper lobe reticulonodular pattern and a left lung cavitary lesion

Most likely diagnosis: Pulmonary tuberculosis (TB).

Next step: Serial sputum samples for identification of the organism and for culture and sensitivities to guide antimicrobial therapy.

ANALYSIS

Objectives

1. Recognize the natural history, clinical manifestations, and radiographic findings of primary, secondary, and latent TB infection. (EPA 1, 3)
2. Understand the methods of diagnosis of TB. (EPA 1, 3)
3. Describe treatment strategies for TB. (EPA 4)
4. List the common extrapulmonary sites of TB infection, including the pleura, lymph nodes, meninges, genitourinary tract, skeletal system, adrenal glands, and miliary TB. (EPA 12)

Considerations

This elderly Asian man has symptoms suggestive of TB, including low-grade fever, weight loss, and productive cough. A chest radiograph is essential to establish the diagnosis. His chest x-ray shows findings consistent with TB, but many other diseases may cause cavitary lung lesions, including other infections and malignancies. If the sputum samples do not reveal acid-fast organisms, then further testing, such as bronchoscopy, may be needed.

APPROACH TO:
Tuberculosis

DEFINITIONS

LATENT TB: Asymptomatic infection with *Mycobacterium tuberculosis*.

PRIMARY TB: Development of clinical illness immediately after infection with *M. tuberculosis*.

REACTIVATION TB: Clinical illness that occurs when latent TB becomes active and infectious after a period of dormancy. The dormant period can last years after the initial infection.

CLINICAL APPROACH

Pathophysiology

Pulmonary TB. TB is a bacterial infection caused by the acid-fast bacillus (AFB) *M. tuberculosis*, which is usually transmitted through **airborne spread of droplets** from infected patients with pulmonary TB. Most cases occur in developing countries, but a resurgence of cases in the United States occurred during the mid-1980s as a consequence of various factors, including human immunodeficiency virus (HIV) infection. Untreated disease can have a 1-year mortality rate of 33% and a 5-year mortality rate as high as 50%.

Often seen in children, primary pulmonary TB usually affects the middle and lower lobes. Lesions form in the periphery with hilar and paratracheal lymphadenopathy. Granulomatous lesions are caused by the inflammatory response of lymphocytes and macrophages with cytokines such as tumor necrosis factor alpha (TNF alpha). The center of the lesion may become necrotic (caseous necrosis) and liquefied, forming a cavity. **Healed lesions are called Ghon lesions.** Most patients exposed to *M. tuberculosis* do not manifest clinical symptoms, but they may have a latent infection. Years later, TB may reactivate and become symptomatic. Reactivation TB usually involves the apical and posterior segments of the upper lobes or the superior segments of the lower lobes of the lungs. The course may be rapid (weeks to months), chronic and slowly progressive ("consumption"), or spontaneously remit.

Signs and symptoms are nonspecific and subacute, including fever, night sweats, malaise, weight loss, and anorexia. The cough usually is productive of purulent sputum and sometimes is streaked with blood. A Rasmussen aneurysm sometimes develops in proximity to a cavitary lesion as the inflammatory reaction causes thinning of the wall of an adjacent bronchial artery. Rupture of the aneurysm can lead to massive hemoptysis. Physical findings are nonspecific and can include fever, wasting, crackles and rhonchi, pallor, or finger clubbing. Possible laboratory abnormalities are leukocytosis, anemia, and hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone.

Extrapulmonary TB. The sites of extrapulmonary spread of TB, in order of decreasing frequency of occurrence, are the lymph nodes, pleura, genitourinary

tract, bones and joints, meninges, and peritoneum. **TB lymphadenitis is common in HIV-infected patients, children, and nonwhite women, and it generally manifests as painless adenopathy.** Pleural disease can have an exudative effusion but may require pleural biopsy for diagnosis. TB meningitis is usually diagnosed by finding cerebrospinal fluid with high protein, lymphocyte predominance (or neutrophils in early infection), and low glucose level. Adjunctive glucocorticoids may improve the treatment response in TB meningitis. Genitourinary TB can be asymptomatic or have local symptoms such as dysuria, hematuria, and urinary frequency. It is characterized by the finding of leukocytes in the urine but negative bacterial cultures—termed **"sterile pyuria."** Skeletal TB affects weight-bearing joints, whereas Pott disease involves the spine. Miliary TB refers to hematogenously disseminated TB and describes the radiographic or pathologic finding of 1- to 2-mm granulomas that resemble millet seeds (hence the name). Adrenal involvement is common in miliary TB and may cause adrenal insufficiency.

Diagnosis. The diagnosis of TB is made by combining the history and clinical picture with AFB stains or culture of a specimen (smear or tissue biopsy). When pulmonary TB is suspected, three sputum samples should be obtained while the patient is on isolation if hospitalized. At least one of these should be collected in the early morning. Biopsy material should not be put in formaldehyde. Culture results may take from 4 to 8 weeks on ordinary solid media or 2 to 3 weeks on liquid media.

Nucleic acid amplification testing (NAAT) should also be performed on patients with signs of active pulmonary TB disease. This is done through a sputum sample as well, typically on the first respiratory specimen sent for AFB stains. Although NAAT can help confirm the diagnosis of TB and may prompt earlier initiation of treatment, it should not be used as a substitution for AFB testing. Confirmed TB cases should be reported to the local public health department.

Purified protein derivative (PPD), or tuberculin, skin testing is useful for screening for latent TB infection but has a limited role in diagnosing active infection because of frequent false-negative results in this setting. A positive PPD is defined by induration of at least 5 mm after 48 to 72 hours, **although this can vary based on the risk group** (Table 44–1).

Interferon-gamma release assays (IGRAs) are new diagnostic tools for latent TB. They are in vitro blood tests of cell-mediated immune response to *M. tuberculosis* and measure T-cell release of interferon-gamma (IFN-gamma) following stimulation by TB antigens. The Centers for Disease Control and Prevention (CDC) recommends that such tests can be used in place of tuberculin skin testing. IGRAs are preferred for patients with a history of bacille Calmette-Guérin (BCG) vaccination (it is not affected by BCG). It requires only one visit (PPD requires a second visit to read the result 2 days after its intradermal administration). The most commonly used IGRAs are the QuantiFERON™-TB Gold assay and the T-SPOT™ TB assay.

Treatment

The probable resistance pattern of the TB organism, based on the country of origin, may help to guide treatment. For individuals from areas with low drug resistance, therapy generally starts with a 2-month course of four-drug treatment with

Table 44–1 • TUBERCULIN REACTION SIZE AND DIAGNOSIS OF LATENT *M. TUBERCULOSIS* INFECTION

Risk Group	Tuberculin Reaction Size, mm
HIV-infected persons or persons receiving immunosuppressive therapy	≥ 5
Close contacts of tuberculosis patients	≥ 5
Persons with fibrotic lesions on chest radiography	≥ 5
Recently infected persons (≤ 2 y)	≥ 10
Persons with high-risk medical conditions	≥ 10
Low-risk persons	≥ 15

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isoniazid (INH), rifampin, pyrazinamide, and ethambutol, followed by 4 months of INH and rifampin. Multiple drugs are used to avoid development of resistance. Directly observed treatment (watching patients take the medication) should be instituted in all patients in this phase to ensure compliance. Pyridoxine is frequently added to the regimen to prevent peripheral neuropathy caused by INH.

Drug resistance or intolerable side effects may require alternate therapy. Patients should be monitored for hepatitis, hyperuricemia, and cytopenias—especially thrombocytopenia—as these can indicate drug toxicity. The World Health Organization defines treatment failure as a positive smear or culture after 5 months of therapy. Latent TB infection is usually treated with INH for 9 months or rifampin for 4 months, with the goal of preventing reactivation TB later in life. Extrapulmonary TB sometimes requires longer therapy, which varies depending on the affected organ.

CASE CORRELATION

- See also Case 15 (Chronic Obstructive Pulmonary Disease), Case 16 (Chronic Cough/Asthma), Case 18 (Hemoptysis/Lung Cancer), and Case 19 (Community-Acquired Pneumonia).

COMPREHENSION QUESTIONS

44.1 A 42-year-old woman from Pakistan is being treated with infliximab, a TNF alpha blocker, for rheumatoid arthritis. After 6 months of therapy, she develops persistent fever, weight loss, and night sweats, and TB is suspected. Which of the following is the most likely location of the TB?

A. Middle and lower lung zones

B. Pleural space

C. Apical segment of the upper lung lobes

D. Cervical or supraclavicular lymph nodes

44.2 A 24-year-old man is being seen in the office for his monthly follow-up for treatment with INH, rifampin, and pyrazinamide for active pulmonary TB. He has been taking his medications for 3 months. While his cough and fever are now resolved, he states that he is having numbness and tingling of both feet but no back pain. He denies taking other medications. Which of the following is the most appropriate next step?

A. Perform a computed tomography (CT) scan of the lumbar spine.

B. Initiate pyridoxine.

C. Continue the TB agents and monitor for further neurologic problems.

D. Initiate a workup for TB adenopathy compression on the femoral nerve.

44.3 A 25-year-old woman is seen in the clinic because her father, who recently emigrated from South America, was diagnosed with and has been treated for TB. She denies a cough, and her chest radiograph is normal. A PPD test shows 10 mm of induration. Her only medication is an oral contraceptive. Which of the following is the best next step?

A. Isoniazid

B. Combination therapy, including INH, rifampin, and pyrazinamide

C. Observation

D. Induce three sputum samples

44.4 A 56-year-old woman is being seen at a pulmonary clinic for a chronic cough and weight loss. She is diagnosed with pulmonary TB. She denies having medical problems. The planned therapy includes INH and rifampin. Which of the following tests are the most important to follow for a patient receiving these agents for her TB treatment?

A. Renal function tests

B. Liver function tests

C. Slit-lamp examinations

D. Amylase and lipase tests

ANSWERS

44.1 **C.** Reactivation TB (in this case, likely triggered by infliximab) usually involves the apical aspects of the lungs. Primary pulmonary TB infection most often affects the middle and lower lobes (answer A). Lymphadenitis (answer D) and pleural disease (answer B) are the most common extrapulmonary TB infections, but they are less common than pulmonary TB.

44.2 **B.** Pyridoxine (vitamin B_6) is important for preventing the peripheral neuropathy that can complicate INH therapy. Assuming that his neurologic examination is normal other than some minimal decreased sensation, initiation of pyridoxine and careful monitoring is the best course of action. If the physical examination shows weakness, abnormal deep tendon reflexes, or dermatomal distribution, then imaging of the lumbar spine such as CT scan (answer A)

would be indicated. If the numbness were caused by Pott disease, he would be expected to have back pain and other neurologic findings, such as lower extremity weakness. Continuing therapy without pyridoxime is inappropriate (answer C), and vitamin B_6 should have been started at the onset of his therapy. Workup for femoral nerve impingement (answer D) is not indicated unless the physical examination points to a pure femoral nerve palsy.

44.3 **A.** Because this woman is a household contact of a patient with active TB, she is in the highest risk group. Her skin test would be considered positive with 5-mm induration. Therefore, observation (answer C) would be inappropriate, and inducing three sputum samples (answer D) would not be required. She has latent TB infection and should be offered treatment to prevent reactivation TB later in life. INH is the treatment of choice for exposure prophylaxis. Rifampin offers a safe alternative for a shorter duration. Triple therapy (answer B) is indicated for an active TB infection, but not for a contact asymptomatic situation.

44.4 **B.** Drug-induced liver injury is a complication of treatment with INH, pyrazinamide, and rifampin; therefore, liver enzyme levels are the most important parameters to monitor. Baseline liver tests are obtained in all patients, and monthly monitoring of hepatic enzymes is recommended for patients at increased risk of liver toxicity. Alcohol use, prior liver disease, pregnancy, and the first 3 months postpartum are risk factors for liver injury. Renal (answer A) and pancreatic (answer D) functions are not as much of a concern with drugs used to treat TB. Slit-lamp examinations assess the anterior chamber of the eye (answer C) and are indicated for medications such as amiodarone, which can cause corneal deposits; the TB drug that can lead to blindness is ethambutol, but this would be an optic neuritis and not detected on slit-lamp examination.

CLINICAL PEARLS

- Reactivation pulmonary TB most commonly presents radiographically with opacities in the apical and posterior segments of the upper lobes.
- Tuberculin skin testing is not a diagnostic test but is a useful screening test for potential contacts of infected persons; the response cutoff for a positive test depends on the patient's level of risk. IGRAs such as QuantiFERON®-TB Gold are also useful to diagnose latent TB.
- Patients with a positive tuberculin skin test and no clinical or radiographic evidence of active disease are said to have latent TB infection; they can be treated with INH or rifampin to reduce their lifetime risk of developing reactivation TB.
- Individuals with active TB should be initiated on multidrug therapy, such as INH, rifampin, pyrazinamide, and ethambutol.
- Pyridoxine (vitamin B_6) is usually added to antituberculosis medications to prevent peripheral neuropathy.

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CASE 45

A 23-year-old man comes to the clinic. In the chart, the chief complaint is listed as, "Wants a general checkup." You enter the room and greet a generally healthy-appearing young man who seems nervous. He finally admits that he has been worried about a lesion on his penis. He denies pain or dysuria. He has never had any sexually transmitted infections (STIs) and has an otherwise unremarkable medical history. He is afebrile, and his examination is notable for a shallow, clean ulcer without exudates or erythema on the shaft of his penis, which is nontender to palpation and has a cartilaginous consistency. There are some small, nontender, inguinal lymph nodes bilaterally.

- What is the most likely diagnosis?
- What is the likely treatment?

ANSWERS TO CASE 45:
Syphilis

Summary: A 23-year-old healthy man presents with

- A firm nontender penile ulcer
- Nontender inguinal lymph nodes bilaterally

Most likely diagnosis: Chancre of primary syphilis.

Likely treatment: Single intramuscular injection of benzathine penicillin G.

ANALYSIS

Objectives

1. Understand the pathogenesis and natural history of *Treponema pallidum* infection. (EPA 1, 12)
2. Name the differential diagnosis of genital ulceration and STIs. (EPA 2)
3. Explain how to diagnose syphilis. (EPA 3)
4. Describe the treatment of syphilis. (EPA 4)

Considerations

This 23-year-old man reluctantly reveals his concern about a nontender ulcer of the penis. Although he has no history of STIs, the most common cause of a painless ulcer of the genital area in a young, immunocompetent person is syphilis. The STIs often present together, so he should be evaluated for other STIs, such as *Chlamydia*, gonorrhea, and human immunodeficiency virus (HIV). Other causes of genital ulcers should also be considered, including chancroid and herpes virus (both usually painful), and a superficially infected skin lesion. Compliance with therapy and follow-up are crucial because syphilitic infections can become chronic and lead to cardiovascular and neurologic disease. Additionally, he could transmit the disease to others, including women of childbearing age, who, if infected during pregnancy, could pass the infection to their newborns.

APPROACH TO:
Syphilis

DEFINITIONS

LATENT SYPHILIS: Asymptomatic period between secondary and tertiary syphilis. It is classified as early (up to 1-year duration), late (after 1 year), or of unknown duration.

PRIMARY SYPHILIS: Initial lesion of *T. pallidum* infection, usually in the form of a firm, nontender ulcer (the chancre).

SECONDARY SYPHILIS: Disseminated infection manifesting in a pruritic, maculopapular diffuse rash that classically involves the **palms and soles**, or the flat moist lesion of **condyloma lata.**

TERTIARY (LATE) SYPHILIS: Symptomatic infection involving the central nervous system (CNS), cardiovascular system, or the skin and subcutaneous tissues (gummas).

CLINICAL APPROACH

Epidemiology

Syphilis is classically called one of the "great imitators" for its multifaceted manifestations. After a decline in cases over the prior decades, the incidence of syphilis has been skyrocketing since the 1980s. The public health consequences of late-stage or undiagnosed syphilis can be devastating, so recognizing and correctly treating this disease is of great importance. In 2017, new syphilis cases increased by 10.5% from the previous year, resulting in 30,644 cases of reported primary and secondary disease in the United States. The largest growing demographics include men who have sex with men (MSM) and women (possibly secondary to increased drug use). Other patterns seen were high primary and secondary cases seen in association with HIV coinfection MSM, men living in the western United States, black males, and men aged 20 to 34. Late-stage syphilis also saw increased rates that were associated with the use of screening and confirmatory testing.

Clinical Presentation

Caused by the spirochete *T. pallidum*, the organism penetrates abraded skin or mucous membranes in order to disseminate through the lymphatics and bloodstream to later involve almost every organ. The most common form of transmission is via sexual exposure through open lesions that are extremely infectious (above 30% transmission rate); on the other hand, cutaneous inoculation has lower risk of transmission. Within 1 week to 3 months of inoculation, a painless papule develops that eventually ulcerates into a chancre, which usually forms at the site of entrance. Multiple ulcers may form in addition with regional lymphadenopathy, but some patients may not notice the ulceration at all. The **chancre** of syphilis is typically **nonerythematous, with rolled borders and a clean base, with a very firm consistency on palpation**. It usually is **painless**, although it may be mildly tender if touched.

The appearance of the chancre represents primary syphilis. Other diseases that present with ulcerations include **chancroid caused by Haemophilus ducreyi** and herpes simplex infection. Chancroid ulcers are usually **painful and exudative, with ragged borders and a necrotic base** that bleeds easily. Lymph nodes can also suppurate in chancroid, unlike in syphilis. The ulcers in **herpes simplex infections typically are painful, grouped vesicles on an erythematous base** that eventually ulcerate.

If untreated, the syphilitic chancre disappears within 2 to 6 weeks, and the disease progresses to a **second stage** and disseminates widely; characteristically, the patient may present with a **pruritic, maculopapular diffuse rash that classically involves the palms and soles.** Constitutional symptoms such as fever, myalgias, headache, and weight loss can develop in untreated patients in addition to dermatologic findings such as **condyloma lata**, a gray papillomatous lesion found in intertriginous areas, and patchy hair loss. Secondary syphilis can also affect the following: the liver, skeletal muscle, kidneys, and CNS.

If still left untreated, the patient will transition into a quiescent, or **latent**, stage. Although relapses of symptoms of secondary syphilis can occur during this time, they become less frequent over years. Between 25% and 40% of patients will go on to develop **late-stage syphilis**, which can occur 1 to 30 years after initial infection. The symptoms of this stage result from infiltration and destruction of various tissues as a result of chronic infection. The most frequent clinical presentations involve the CNS (neurosyphilis), cardiovascular system, and diffuse organ involvement. The immune reaction to *T. pallidum* causes a proliferative, obliterative endarteritis, which involves the vasa vasorum, leading to necrosis of the tunica media and arterial wall. This progressive weakness of the walls leads to the formation of **saccular aneurysmal dilations of the aorta.** In some organs, such as the skin, liver, and bone, these lesions organize into **granulomas** with an amorphous or coagulated center called **gummas.** While benign, gummas create organ dysfunction through their progressive destruction of normal tissue. The phase known as latent syphilis involves the period where the patient fails to show clinical manifestations but has positive serologic testing. This distinction matters when treatment is being considered.

Neurosyphilis is another form of tertiary disease that may occur after secondary disease or from the latent stage. *T. pallidum* disseminates within the cerebrospinal fluid (CSF), before spreading to the vasculature and meninges in the early phase and later the brain and spinal cord in advanced stages. In the CNS, it may cause progressive vasculitis associated with local ischemia, stroke, and gradual focal neurologic deficits. Some patients may exhibit personality changes or even dementia. *T. pallidum* causes demyelination of the posterior spinal column, leading to a wide-based gait, ataxia, and loss of proprioception (**tabes dorsalis**); other cranial nerve impairments include the development of the Argyll Robertson, small bilateral pupils that do not constrict when exposed to bright light but do constrict when focused on a nearby object. Lumbar puncture should be performed to exclude neurosyphilis in any patient with previous syphilis diagnosis who develops neurologic or ocular symptoms; evaluation of the CSF should strongly be considered in asymptomatic HIV-infected patients with syphilis with CD4 < 350 cells/mm^3 or with a high rapid plasma reagin (RPR) titer (> 1:32) since these conditions greatly increase the risk of CNS infection.

Laboratory Findings. The diagnosis of syphilis is always made indirectly, as the organism has not yet been cultured. Diagnostic tests for *T. pallidum* are divided into two categories: nontreponemal (**nonspecific**) and treponemal. Nonspecific serologic tests, such as the RPR and Venereal Disease Research Laboratory (VDRL) tests, examine the reactivity of serum antibodies against lipid antigens in response to the host reaction to *T. pallidum*. Despite its sensitivity, the likelihood for false positives is higher at low titers. Therefore, **confirmatory testing** in the form of **specific** antibody testing for *T. pallidum*, such as the **fluorescent treponemal antibody absorption (FTA-ABS) or microhemagglutination assay for *T. pallidum* (MHA-TP) test**, is the next step. Traditionally, treponemal tests were not utilized until initial screening returned positive; however, technological advances have allowed for them to now serve as initial screening tests for syphilis (known as **reverse screening**). FTA-ABS and MHA-TP tests determine current serum antibodies against treponemal antigens. **Dark-field microscopy**, in which scrapings from an ulcer are placed under a phase contrast lens to identify the organisms, remains the classic method of diagnosis but is rarely performed today. Lesion biopsy, such as those performed in secondary syphilis with special stains, also can identify the organisms. A positive CSF VDRL or RPR test in the setting of increased CSF leukocytosis, elevated protein levels, and sometimes with low glucose levels, is suggestive of CNS involvement. False-negative results for the VDRL test in CSF are common; however, clinical suspicion remains crucial for an accurate diagnosis.

Treatment

The treatment of choice for syphilis is penicillin, specifically parenteral penicillin G, in all stages. Treatment recommendations vary based on the stage of syphilis (Table 45–1). Individuals with early disease, specifically primary, secondary, or

Table 45–1 • TREATMENT OF SYPHILIS BASED ON STAGE

Stage	Clinical Manifestations	Treatment[a]
Primary disease	Chancre	Single dose of intramuscular penicillin G 2.4 mU
Secondary disease	Maculopapular rash involving palms and soles, condyloma lata	Single dose of intramuscular penicillin G 2.4 mU
Early latent (< 1 y—no symptoms)	None	Single dose of intramuscular penicillin G 2.4 mU
Late latent (> 1 y—no symptoms) or **latent of unknown duration**	None	Intramuscular penicillin G 2.4 mU at 1-wk intervals for total of **three** doses
Tertiary syphilis, neurosyphilis	Various: dementia, focal neurologic deficits, cranial nerve palsies, gummas, aortitis	Intravenous penicillin for 10-14 d

[a]*For penicillin-allergic patients with primary, secondary, and latent syphilis, oral tetracycline or doxycycline for 2 weeks is an acceptable treatment. For penicillin-allergic patients with neurosyphilis or syphilis in pregnancy, desensitization and treatment with penicillin are required.*

early latent syphilis, may be treated with a single intramuscular injection of benzathine penicillin, a long-lasting intramuscular injection. Alternative therapies include doxycycline or, tetracycline, or for up to 14 days. Ceftriazone IM or IV for 10-14 days has been used but the optimal dosage has not been established. For patients with late latent disease or unknown duration of the latent phase (presumed to be > 1 year), those with cardiovascular manifestations, or those with gummas, treatment consists of three weekly intramuscular injections of benzathine penicillin. Alternative therapies include doxycycline or tetracycline for various time frames.

Neurosyphilis is notoriously difficult to treat. Those with known CNS disease require high doses of intravenous penicillin G for 10 to 14 days; an alternative but inferior therapy is daily IV ceftriaxone for 10 to 14 days. All patients should be followed closely to ensure that their titers fall over the year after treatment. Pregnant women who are allergic to penicillin should be desensitized and then receive penicillin, as this is the only treatment known to prevent congenital infection. The sequelae of congenital syphilis can be devastating; this is why the World Health Organization has developed initiatives to increase prenatal screening and treatment of syphilis.

Prognosis. ***T. pallidum*** infection usually leads to a **positive specific serologic test** (FTA-ABS or MHA-TP) for **life**, whereas an adequately treated infection will lead to a fall in RPR serology. A **normal response** is considered a **four-fold drop in titers within 3 months** and a **negative or near-negative titer after 1 year**. A suboptimal response may mean inadequate treatment, undiagnosed tertiary disease, or reinfection. In some persons, nontreponemal antibodies can persist, usually in low titers, for a long period of time, a response referred to as the "**serofast reaction**." Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity.

Nontreponemal titers should be collected prior to treatment initiation, as they can increase shortly after starting therapy. Shortly after starting treatment, a patient can experience constitutional symptoms such as fevers, myalgia, rigors, rash, headache, hypotension, and sometimes even seizures or alterations in mental status. While not completely understood, it is believed that the lysis of infected cells can cause a massive inflammatory response. This phenomenon is referred to as a **Jarisch-Herxheimer** reaction and should not result in stopping treatment.

Prevention. In any patient diagnosed with an STI, the possibility of coinfection with other STIs should be considered. HIV is often asymptomatic early in the course of infection, and screening should be recommended to those persons who have histories of high-risk behaviors or who have evidence of other STIs. Because HIV takes months to undergo seroconversion, the screening strategy should last for that long.

Chlamydia trachomatis is the most common bacterial STI in the United States, and the majority of newly diagnosed patients report being asymptomatic, especially women. In women, it characteristically causes cervicitis (vaginal discharge, postcoital bleeding) and urethritis (dysuria or urinary tract infection symptoms).

If untreated, *C. trachomatis* can ascend the female reproductive tract, leading to severe abdominal and pelvic pain, adnexal tenderness, worsening cervicitis, vaginal discharge, and dysuria, collectively known as **pelvic inflammatory disease.** Repeated episodes can result in tubal scarring and increased risk of infertility. Men with symptoms typically present with urethritis (dysuria and urethral discharge), but they may also experience fever, epididymitis, or proctitis with rectal pain or diarrhea. Diagnosis is usually made by antigen detection or gene probe directly from the urethra or cervix. Treatment consists of a single dose of 1000 mg of azithromycin (often given under direct observation) or a 7-day course of doxycycline.

Neisseria gonorrheae, a gram-negative diplococcus, can present with similar clinical syndromes as *Chlamydia* (in fact, up to 30% of patients are coinfected with both organisms), but patients are more likely to be symptomatic, especially men. Historically, *N. gonorrhoeae* can initially present as **disseminated infection** characterized by fever, migratory polyarthritis, tenosynovitis of hands and feet, a rash on the distal extremities, and rare incidences of endocarditis or meningitis. Unlike primary *N. gonorrhoeae* management, disseminated infection requires hospitalization and intravenous ceftriaxone. Outpatients with genitourinary symptoms are often treated with a single intramuscular injection of ceftriaxone, along with a single dose of azithromycin 1000 mg or doxycycline for a 7-day course for likely *Chlamydia* coinfection.

CASE CORRELATION

- See also Case 41 (Urinary Tract Infection With Sepsis in the Elderly), Case 42 (Vascular Catheter Infection in a Patient With Neutropenic Fever), Case 43 (Meningitis, Bacterial), and Case 46 (HIV/AIDS and *Pneumocystis* Pneumonia).

COMPREHENSION QUESTIONS

45.1 A 25-year-old HIV-negative man presents to your office after being treated for syphilis 1 year ago. He continues to have unprotected sex with multiple partners but denies any symptoms of penile discharge, rash, or fevers. What is the next best step in avoiding transmission of STIs?

A. Empiric treatment of syphilis, gonorrhea, and chlamydia

B. Encouraging use of barrier contraception (ie, condoms)

C. Frequent STI screening, including HIV, syphilis, gonorrhea, and chlamydia

D. Encouraging abstinence

E. Prescribing this patient PrEP (preexposure prophylaxis)

45.2 As part of normal screening during pregnancy, a 28-year-old patient (gravida 2, para 1) has a positive RPR test with a titer of 1:64 and a positive MHA-TP and is treated with intramuscular penicillin. She returns to your office 3 months later with an RPR titer of 1:8. Which of the following treatments do you offer?

A. Repeat single injection of intramuscular penicillin
B. No treatment is necessary
C. Three injections of intramuscular penicillin weekly
D. Doxycycline

45.3 A 23-year-old man is found to have late latent syphilis (RPR 1:64) as part of a workup following his diagnosis with HIV. He is asymptomatic, has a CD4 count of 150 cells/mm^3, and does not remember having lesions or rashes in the past. Prior to starting therapy with penicillin for the syphilis, the patient should undergo which of the following procedures?

A. Lumbar puncture to exclude neurosyphilis
B. Skin biopsy to confirm the diagnosis of syphilis
C. Magnetic resonance imaging (MRI) of his brain and an electroencephalogram (EEG)
D. Skin testing to exclude penicillin allergy
E. Adjustment of his HIV medications to optimize his CD4 count prior to treatment for syphilis

45.4 A 28-year-old woman is seen in the office for "sores" on her vulva area. She denies a recent change in sexual partners and is not aware of any STI. On examination, she is found to have a nontender 1-cm ulcer of the right labia majus. A herpes culture is taken of the ulcer scraping, which is negative. A serum RPR titer is also negative. Which of the following is the next best step?

A. Empiric treatment with doxycycline for *C. trachomatis*
B. Empiric treatment with acyclovir for herpes simplex virus
C. Empiric treatment with azithromycin for *Haemophilus ducreyi*
D. Dark-field microscopy/empiric treatment with intramuscular penicillin
E. Biopsy for possible vulvar cancer

ANSWERS

45.1 **C.** According to the Centers for Disease Control and Prevention (CDC) guidelines, men with high-risk sexual behaviors should be screened at least annually or more frequently for HIV, gonorrhea, chlamydia, and syphilis, and treated if they have a positive result. There are no data to support empirically treating for all STIs (answer A). This patient has a history of not using barrier contraception; thus, encouraging abstinence (answer D) and condom use (answer B) are insufficient. There are data to support starting individuals with high-risk sexual practices on PrEP (tenofovir and emtricitabine)

to avoid infection with HIV (answer E); however, this will not reduce the patient's transmission of other STIs at this time.

45.2 **B.** A four-fold change in titer, equivalent to a change of two dilutions (eg, from 1:16 to 1:4 or from 1:8 to 1:32) is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results obtained using the same serologic test. This patient's titer has dropped more than four-fold and thus can be considered successfully treated. Therefore, repeat treatment with penicillin is not necessary (answers A and C). Failure of nontreponemal test titers to decline four-fold within 6 to 12 months after therapy for primary or secondary syphilis might be indicative of treatment failure (per the CDC guideline). Doxycycline (answer D) should only be used in a patient who has a true allergy to penicillin and cannot undergo desensitization.

45.3 **A.** Lumbar puncture to exclude neurosyphilis is generally indicated when any patient with syphilis develops neurologic or ocular symptoms; it is also considered if HIV-infected patients with syphilis have a CD4 count less than 350 cells/mm^3 or an RPR titer exceeding 1:32. Skin biopsy (answer B) is not the way to diagnose syphilis; rather, diagnostic procedures include serology or, if very early, scraping with dark-field analysis. MRI and EEG (answer C) are not indicated in an asymptomatic patient and would not diagnose CNS syphilis. Skin testing for penicillin allergy (answer D) is not indicated unless the patient had a history of severe allergic reactions. Adjustment of HIV medications prior to penicillin (answer E) is not indicated, and once the stage of syphilis is ascertained, treatment should be started.

45.4 **D.** Approximately one-third of patients who have the primary lesion of the chancre will have negative serology. They will require either dark-field microscopy or biopsy with special stains to identify the spirochetes; the organism is too thin to be visualized by conventional light microscopy. Empiric treatment with penicillin is reasonable if dark-field microscopy is not available. Chancroid (answer C) is much less likely due to the epidemiologic considerations, and usually this condition is painful. Genital herpes (answer B) and chancroid should produce painful genital ulcers, and *Chlamydia* (answer A) should cause nonulcerative cervicitis or urethritis. Biopsy for vulvar cancer (answer E) is indicated for an older patient or a persistent ulcer, but it is not indicated in this patient.

CLINICAL PEARLS

- Syphilitic chancres are generally clean, painless, ulcerative lesions that resolve in 2 to 6 weeks if untreated; the eruption of a maculopapular rash on the palms and soles signifies secondary syphilis.
- Elevated RPR and VDRL tests are nonspecific and may be falsely positive in several normal conditions (pregnancy) and disease states (systemic lupus erythematosus).

- Specific treponemal antibody tests, such as the MHA-TP and the FTA-ABS test, should be performed for confirmation of a syphilis diagnosis, but once positive, they usually stay positive for life.
- The reverse testing algorithm has advantages over traditional testing in that *T. pallidum* antibodies (1) are specific to syphilis, (2) are more sensitive than VDRL testing or RPR titer for detecting both primary and late syphilis, (3) can be tested using automated instruments, and (4) can provide a more rapid time to result. The biggest clinical impact of the reverse algorithm is the recognition of untreated late latent syphilis.
- Current screening now is utilizes the specific treponemal antibody tests first (reverse screening) due to their higher specificity for syphilis infection.
- A declining RPR titer can be followed to test the efficacy of therapy, and if levels fail to decline or increase, it can point at incomplete treatment, failed therapy, or possible reinfection.
- Central nervous system involvement can be excluded only through testing of the CSF.
- Treatment of syphilis is based on stage: Early syphilis can be treated with a single intramuscular injection of penicillin; late latent syphilis can be treated with three weekly injections; and neurosyphilis or tertiary syphilis can be treated with intravenous penicillin for 10 to 14 days.
- If a patient presents with a positive titer and has reported past treatment, it is important to confirm with the state health department to avoid re-treating.

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CASE 46

A 27-year-old man infected with human immunodeficiency virus (HIV) presents to the emergency department (ED) with a fever of 39.2 °C (102.5 °F). His last CD4 count is unknown. The patient was diagnosed as HIV positive approximately 3 years ago when he presented to his primary care provider with oral thrush. At that time, he was immediately started on highly active antiretroviral therapy (HAART). Approximately 10 months ago, the patient discontinued all treatment due to inability to pay for his medications after losing his job and health insurance. He reports feeling more fatigued recently. For the last 3 to 4 weeks, the patient endorses subjective fevers, a nonproductive cough, and shortness of breath with mild exertion, such as when walking upstairs in his house. The patient noticed unintentional weight loss of approximately 5 pounds over the last 2 months. The patient's blood pressure (BP) is 134/82 mm Hg, pulse is 110 beats per minute (bpm), and respirations are 28 breaths per minute. Oxygen saturation is 89% on room air but drops to 80% with minimal exertion, and his breathing becomes quite labored. Physical examination shows a cachectic male in mild respiratory distress seated upright in bed. The patient is tachypneic with clear lung fields and white, painless plaques covering his oral mucosa; these plaques are easily scraped off with a tongue depressor. He denies dysphagia. The remaining physical examination is unremarkable. Laboratory testing shows a leukocyte count of 2800 cells/mm^3. Serum lactic dehydrogenase (LDH) is 540 U/L (normal 140-280 IU/L). Chest radiograph is shown in Figure 46–1.

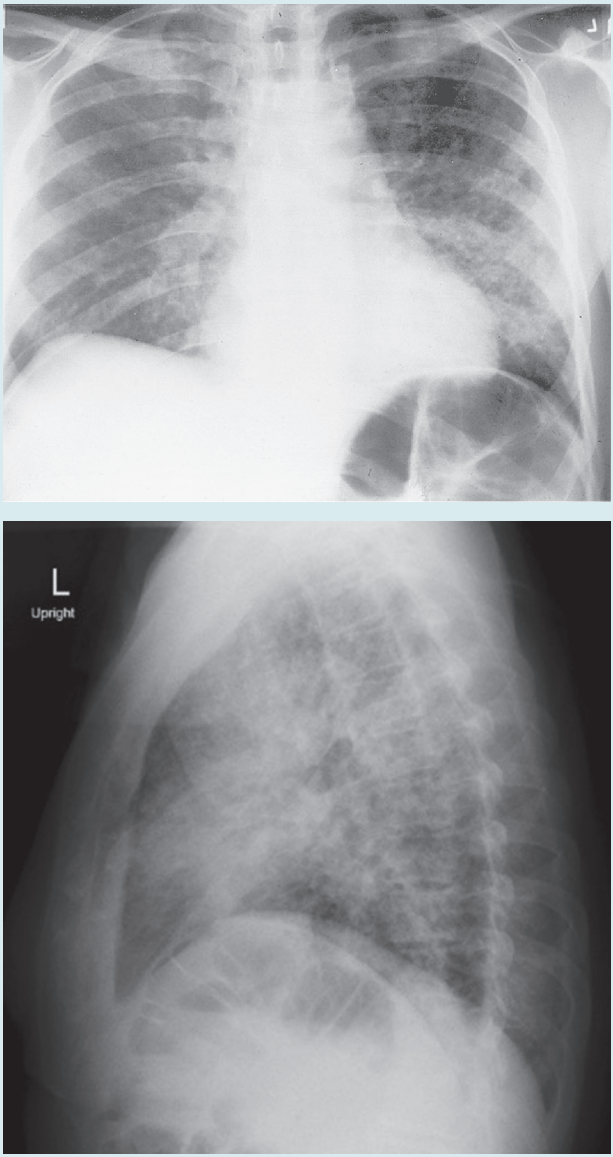


Figure 46–1. Chest radiograph: (A) posteroanterior view; (B) lateral view. (Part A, Reproduced with permission, from Braunwald E, Fauci AS, Kasper DL, et al., eds. *Harrison's Principles of Internal Medicine*, 15th ed. 2001. Copyright © McGraw Hill LLC. All rights reserved. Part B, Courtesy of Dr. Gabriel Aisenberg.)

- What is the most likely diagnosis?
- What is your next diagnostic step?
- What preventive measure could have significantly reduced the likelihood of developing this disease?
- What is the most appropriate next step in management?

ANSWERS TO CASE 46:
HIV/AIDS and *Pneumocystis* Pneumonia

Summary: A 27-year-old man presents with

- A known HIV infection but unknown CD4 count
- Ten months without antiretroviral therapy or prophylactic medications
- 3 to 4 weeks of fevers, dry cough, weight loss, and worsening dyspnea on exertion
- Febrile temperature of 39 °C, tachycardia, tachypnea
- Oxygen saturation 89% on room air and 80% with minimal exertion
- Painless, white oral plaques that can be scraped
- Chest x-ray showing bilateral, interstitial lung opacities
- Leukocyte count < 3500 cells/mm^3, LDH elevated

Most likely diagnosis: *Pneumocystis jiroveci* pneumonia (PJP); the history, presumed low CD4 count (based on the presence of oral thrush), chest film appearance, and elevated serum LDH make this diagnosis highly suggestive.

Next diagnostic step: Obtain sputum samples for microbiological analysis (specify what you are looking for). Consider a bronchoalveolar lavage if the sputum analysis yields no diagnosis.

Preventive measures: Aside from HAART, prophylactic administration of trimethoprim-sulfamethoxazole (TMP-SMX) could have reduced his likelihood of acquiring PJP once his CD4 count dropped below 200 cells/mm^3. The most recent guidelines no longer recommend TMP-SMX if the patient takes HAART and has undetectable HIV viral load (not applicable to this patient), regardless of the CD4 count.

Next step in management: The next step is to stabilize the patient. Although hemodynamically stable, he remains tachypneic, hypoxic, and in mild distress. The hypoxemia should be treated with supplemental oxygen or, if needed, endotracheal intubation and mechanical ventilation. An arterial blood gas (ABG) measurement should be obtained to quantify his degree of hypoxemia and initiate proper treatment.

ANALYSIS

Objectives

1. Describe the natural history of HIV infection. (EPA 1, 12)
2. Define the types of opportunistic infections that typically affect HIV-infected patients at various levels of immunocompromise. (EPA 3)
3. Recognize respiratory infections in patients with AIDS. (EPA 1, 10)
4. Identify indications for HAART and for prophylactic medications against opportunistic infections. (EPA 4)

Considerations

This individual with HIV, currently not taking antiviral medications or any antibiotic prophylaxis, presents with subacute dyspnea and cough. His lack of sputum production, hypoxia, and **elevated LDH** level are suggestive of PJP. The protracted course makes *Streptococcus pneumoniae*, *Mycoplasma*, or influenza infection less likely. *Mycobacterium tuberculosis* can present with atypical radiologic features in severely immunocompromised patients. Other mycobacteria, like *Mycobacterium avium-intracellulare* complex (MAC); certain fungi, such as *Cryptococcus neoformans*, *Coccidioides immitis*, or *Aspergillus* species; and *Nocardia* species; and Kaposi sarcoma are only a few examples of a broad differential diagnosis for the patient with AIDS and pulmonary infiltrates. The presence of oral thrush strongly suggests a CD4 count less than 200 cells/mm^3; however, oral candidiasis can be present regardless of CD4 count. If laboratory findings reveal a CD4 count lower than 200 cells/mm^3, then PJP seems the most likely explanation for his symptoms and chest x-ray findings. Obtaining an ABG measurement will provide additional information about prognosis and guide therapy to determine the utility of corticosteroid administration. Arterial oxygen concentration less than 70 mm Hg on room air or alveolar-arterial gradient (A-a gradient) greater than or equal to 35 mm Hg suggests more severe disease. Treatment with corticosteroids may be helpful when given concurrently with antibiotic therapy, such as TMP-SMX.

APPROACH TO:

HIV/AIDS and *Pneumocystis* Pneumonia

DEFINITIONS

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS): An advanced stage of HIV infection in which the CD4 count is lower than 200 cells/mm^3 or in which an AIDS-defining illness is diagnosed, regardless of the CD4 count.

***PNEUMOCYSTIS JIROVECI* (FORMERLY *PNEUMOCYSTIS CARINII*):** A unicellular fungus that causes pneumonia in immunocompromised patients, especially those infected with AIDS.

CLINICAL APPROACH

Pathophysiology

When evaluating a patient with HIV infection and suspected opportunistic infections, determining the level of immunodeficiency via the CD4 count is of clinical significance. Normal CD4 levels in adults range from 600 to 1500 cells/mm^3. As levels decline to fewer than 500 cells/mm^3, immune function decreases, and patients become increasingly more susceptible to opportunistic infections and/or malignancies.

As many as 40% of patients at the time of initial HIV infection will develop an **acute HIV syndrome** characterized by sudden onset of a mononucleosis-like illness

with fever, headaches, nontender lymphadenopathy, pharyngitis, myalgias, diarrhea, weight loss, and sometimes a macular rash. The most common symptoms are fever, myalgias, and generalized fatigue. The rest of the patients remain asymptomatic and have a clinically **latent period** of 8 to 10 years, on average, before the clinical manifestations of immunocompromise appear. As CD4 levels decline, the risk of contracting opportunistic infections or reactivation of dormant illnesses increases.

At CD4 levels **less than 500 cells/mm^3**, patients are susceptible to infections, such as recurrent pneumonias, tuberculosis (TB), vaginal candidiasis, and herpes zoster.

At CD4 levels **less than 200 cells/mm^3**, patients are diagnosed with AIDS and are considered significantly immunocompromised. Patients with AIDS can easily contract infections by organisms that rarely cause significant illness in immunocompetent hosts, such as PJP, toxoplasmosis, cryptococcosis, histoplasmosis, and cryptosporidiosis.

At CD4 levels **less than 50 cells/mm^3**, patients are severely immunocompromised and are susceptible to disseminated infection with MAC, cytomegalovirus (CMV) retinitis, colitis, and esophagitis and malignancies such as primary central nervous system (CNS) lymphoma. The Centers for Disease Control and Prevention has published a list of AIDS-defining conditions, which are clinical conditions that define progression from HIV to AIDS (Table 46–1).

Differential Diagnosis. Many other respiratory infections are possible and should be considered in patients with AIDS. Chest radiography helps to narrow down possible diagnoses. Diffuse interstitial lung opacities present in PJP, *M. tuberculosis*, other mycobacterial infections (such as MAC). Patchy alveolar and nodular lung opacities are also described in the former infections as well as in viral infections, such as CMV. Pleural-based opacities are commonly described in TB and cryptococcal lung disease. Cavitary lesions are seen in TB, PJP, and coccidiomycosis.

In addition to imaging, remember the importance of obtaining a clinical and travel history. Since the **most common causes of bacterial pneumonia in AIDS patients are the same organisms that cause pneumonia in immunocompetent hosts**, acute onset of fever, and productive cough, along with pulmonary opacities, should suggest **community-acquired pneumonia**.

A more indolent or chronic history of cough (productive or nonproductive) with weight loss and/or persistent night sweats, especially in high-risk patients (ie, recent exposures, previous incarceration, homelessness or association with shelters, recent emigrant from highly endemic countries, or health care workers), should raise the question of **TB**. In patients with CD4 count more than 200 cells/mm^3, the radiographic appearance of TB is likely to be similar to that of immunocompetent hosts. However, **in those with CD4 count lower than 200 cells/mm3, the radiographic appearance is extremely variable;** this population often presents with noncavitary pulmonary lesions, lymphadenopathy, and more diffuse presentation of TB (miliary or cutaneous findings). Patients with suspected pulmonary TB should be placed in respiratory isolation until their airborne infectiveness is ruled out. A negative purified protein derivative (tuberculin skin test) or interferon-gamma release assay does not rule out TB in immunocompromised hosts, as they might not be able to mount an immunologic response. Diagnosis and treatment of TB

Table 46–1 • AIDS-DEFINING ILLNESSES

Bacterial infections, multiple or recurrent
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (> 1-mo duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age > 1 mo
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related
Herpes simplex: chronic ulcers (> 1-mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 mo)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (> 1-mo duration)
Kaposi sarcoma
Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age > 1 mo
Wasting syndrome attributed to HIV

is discussed in Case 44, but it should be noted that TB in AIDS patients primarily spreads hematogenously and produces extrapulmonary manifestations. In HIV patients, ***Mycobacterium kansasii*** also causes pulmonary disease and radiographic findings identical to those of *M. tuberculosis*.

Several other opportunistic infections in AIDS deserve mention. **Cerebral toxoplasmosis** is the **most common central nervous system (CNS) space-occupying lesion in AIDS patients** presenting with headache, seizures, or focal neurologic deficits. Contrasted computed tomography (CT) or magnetic resonance imaging (MRI) scans reveal multiple ring-enhancing lesions, often located in the basal ganglia. Presumptive diagnosis often is made based on the radiologic appearance, supported by serologic evidence of infection. Treatment consists of 2 weeks of empiric toxoplasmosis therapy with sulfadiazine and pyrimethamine; the most likely alternative diagnosis is **CNS lymphoma.** CNS lymphoma usually presents with a single mass lesion but is suspected when presumed lesions of toxoplasmosis do not regress after 2 weeks of specific therapy. If this is the case, historically, the next diagnostic step has been

stereotactic brain biopsy. However, recent evidence indicates a next step of examining cerebrospinal fluid (CSF) for **Epstein-Barr virus DNA** to find malignant lymphocytes that are more likely to be present in immunocompromised patients with **CNS lymphoma.** Treatment includes starting high-dose methotrexate because of its CNS penetration, glucocorticoids to decrease mass effect, and restarting antiretroviral therapy.

Another CNS complication that requires a high index of suspicion is **cryptococcal meningitis.** This is a chronic, indolent fungal infection due to *C. neoformans*, which often presents with vague symptoms, including fever, headaches, fatigue, personality and vision disturbances, and sometimes vomiting or nuchal rigidity; keep in mind that some patients can present with sepsis and in a coma. If the diagnosis is considered, the patient should be screened for evidence of cryptococcal infection by testing for cryptococcal antigen in the serum and via lumbar puncture (LP) for culture.

Imaging (CT or MRI) needs to be performed prior to LP to prevent possible cerebral herniation. The CSF frequently shows mild inflammatory response (ie, low, mostly lymphocytic, white blood cell count; increased CSF protein; and low glucose levels), but the patient often presents with elevated intracranial pressures. Diagnosis can be confirmed by identifying the yeast using, fungal culture or measuring the level of cryptococcal antigen from CSF or serum. Treatment of cryptococcal meningitis requires induction with intravenous amphotericin B plus flucytosine, followed by chronic suppression (consolidation and maintenance) with oral fluconazole. At times, frequent LPs with removal of large volumes of CSF are required to treat the intracranial hypertension, and CSF shunts may be required.

At very low CD4 counts (< 50 cells/mm^3), patients with AIDS are also susceptible to **CMV** infections. This can manifest as viremia with persistent fever, abdominal pain, diarrhea, and other symptoms, including retinitis, which can lead to blindness, esophagitis with severe odynophagia; colitis, and necrotizing adrenalitis, occasionally leading to adrenal insufficiency. Therapy for severe CMV infections includes intravenous ganciclovir, valganciclovir, cidofovir, or foscarnet.

One of the most frequent opportunistic infections occurring in patients with **very low CD4 counts** (< 50 cells/mm^3) is **MAC.** The most frequent presentations include disseminated infection with persistent constitutional symptoms such as fevers, weight loss, lymphadenopathy, and gastrointestinal symptoms, such as abdominal pain or chronic watery diarrhea. Diagnosis requires a mycobacterial blood culture, which can take up to 10 days for positive results; respiratory or stool cultures have significantly lower sensitivity and specificity. Treatment involves combination therapy, usually beginning with a macrolide (azithromycin or clarithromycin) and ethambutol. The decision to include rifabutin depends on whether the patient is currently doing well on antiretroviral therapy or has a more severe infection. Either way, therapy is continued for a **minimum of 12 months.**

Clinical Presentation

***P. jiroveci* pneumonia** remains the **most common opportunistic infection affecting AIDS patients** but often is very difficult to diagnose. The clinical presentation ranges from mild to severe, typically involving fever, dyspnea, nonproductive cough for weeks, significant hypoxemia with respiratory compromise, and worsening fatigue. Some patients experience subjective chills, pleuritic chest pain, and mild

weight loss. As many as 5% to 10% of patients are asymptomatic. In addition, the radiographic presentation can be highly variable, ranging from a near-normal chest film to diffuse bilateral interstitial lung opacities. Lung opacities can progress to severe alveolar lung infiltrates, acute respiratory distress syndrome (ARDS) type. Additionally, lung cysts and pleural effusions are occasionally seen. Lung cysts can rupture, causing spontaneous pneumothorax. Suspect PJP in patients presenting with subacute onset of fever, dyspnea, nonproductive cough, and HIV/AIDS without PJP prophylaxis.

Laboratory Findings. **Definitive diagnosis can be established by use of Giemsa, direct fluorescence antibody, silver stain, or polymerase chain reaction of sputum or bronchoalveolar lavage.** Sputum induction using aerosolized hypertonic saline increases sensitivity. **Elevated serum LDH** levels may be used as an indirect marker for PJP, although it is nonspecific and may also be elevated in disseminated histoplasmosis or lymphoma. Increasing LDH in the setting of therapy predicts poor prognosis. However, an **LDH level** less than **220 IU/L is a negative predictor of having PJP.** Similarly, in patients with a CD4 count greater than 250 cells/mm^3 or those currently taking PJP prophylaxis with TMP-SMX, the diagnosis of PJP should be considered highly unlikely.

Determining the oxygenation levels of patients with PJP via ABG significantly affects prognosis and therapy. Patients with arterial PO_2 less than **70 mm Hg or A-a gradient more than 35 mm Hg** have significant disease and benefit from the simultaneous use of **corticosteroids and antimicrobial therapy**.

Treatment

The usual treatment for PJP is TMP-SMX. Alternative therapies for those with sulfa allergies include inhaled pentamidine, clindamycin with primaquine, dapsone, or atovaquone.

HAART includes a combination of at least three drugs, often consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) along with either a nonnucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor, or integrase inhibitor. HAART is very potent and has dramatically revolutionized the treatment of HIV, producing suppression of viral replication and allowing a patient's CD4 count to recover. Initiation of HAART is usually indicated for all HIV-infected patients at their diagnosis, regardless of being asymptomatic or current immune status.

However, initiation of HAART is not always possible in acutely ill patients because the medications often cause side effects that can be confused with the underlying disease process. Additionally, within 1 to 2 months of starting HAART, worsening of clinical symptoms can occur despite increasing CD4 count, termed **immune reconstitution inflammatory syndrome (IRIS),** as a result of newly awakened host responses. Therefore, it may be preferable to initiate antiretroviral therapy within 2 weeks of presentation, while consulting an infectious disease expert and establishing reliable follow-up. Guidelines indicate that HAART should be restarted in all AIDS patients within 2 weeks except in cases of cryptococcal meningitis, which requires a delay.

Prevention. Because of the frequency and severity of common opportunistic infections, **antimicrobial prophylaxis** is routinely given as a patient's immune status

declines. With CD4 counts less than 200 cells/mm^3 and a detectable viral load, PJP prophylaxis with either daily or three times a week TMP-SMX is recommended. When CD4 counts fall under 100 cells/mm^3 and patients have a positive *Toxoplasma* serology, toxoplasmosis should be prevented with daily dosing of TMP-SMX. If CD4 levels are less than 50 cells/mm^3, a MAC prophylactic regimen with clarithromycin 500 mg twice daily or azithromycin 1200 mg weekly should be started; the current guidelines do not recommend prophylaxis against MAC if the patients take HAART.

CASE CORRELATION

- See also Case 15 (Chronic Obstructive Pulmonary Disease), Case 16 (Chronic Cough/Asthma), Case 18 (Hemoptysis/Lung Cancer), Case 19 (Community-Acquired Pneumonia), Case 44 (Tuberculosis (Pulmonary), Cavitary Lung Lesions), and Case 45 (Syphilis).

COMPREHENSION QUESTIONS

46.1 A 32-year-old woman with a medical history of hypertension, hypothyroidism (treated with levothyroxine), and 5-year history of HIV infection (not adherent to HAART, with most recent CD4 count 87 cells/mm^3) is admitted to the hospital with a 2-week history of subjective fever and chills, worsening fatigue, new shortness of breath, and a persistent dry cough. On presentation, her vital signs were the following: 38.3 °C, BP 132/76 mm Hg, heart rate (HR) 105 bpm, respiratory rate (RR) 30 breaths/min, and SpO_2 (oxygen saturation as measured by pulse oximetry) 86% on room air. Which of the following diagnostic tests would most likely confirm the diagnosis?

A. Acid-fast smear of the sputum
B. Gram stain of the sputum showing gram-positive diplococci
C. Serum cryptococcal antigen
D. Silver stain or direct fluorescence assay (DFA) of the sputum

46.2 A 67-year-old man with a medical history of hypertension, diabetes mellitus (controlled with insulin), atrial fibrillation (on warfarin), and HIV (restarted on HAART 4 weeks ago) presents to the hospital for 2 days of fever, productive, nonbloody cough, and worsening shortness of breath. His vital signs are the following: temperature 38.3 °C, BP 140/82 mm Hg, HR 109 bpm, RR 26 breaths/min, and SpO_2 95% on room air. His current CD4 count is 190 cells/mm^3. Which of the following is the most likely organism to cause pneumonia in this patient?

A. *Histoplasmosis capsulatum*
B. *Mycobacterium tuberculosis*
C. *Pneumocystis jiroveci*
D. *Streptococcus pneumoniae*

46.3 A 44-year-old woman with a medical history of diabetes mellitus (on insulin), chronic kidney disease stage III, and HIV (not adherent to HAART) is noted to have a CD4 count of 180 cells/mm^3 during a visit to her primary care provider. Multiple attempts at starting HAART have failed in the past, but she states that she is now ready to start. She is hemodynamically stable with vital signs showing temperature 37 °C, BP 127/73 mm Hg, HR 86 bpm, RR 16 breaths/min, and SpO_2 97% on room air. Which of the following is the best therapy to start in this patient?

A. One NRTI, one NNRTI, one protease inhibitor, and TMP-SMX
B. One NRTI, two NNRTI, one protease inhibitor, and TMP-SMX
C. Two NRTI, one integrase inhibitor, and TMP-SMX
D. Two NRTI, one NNRTI, one protease inhibitor, and TMP-SMX
E. Two NRTI, two NNRTI, and TMP-SMX

46.4 A 36-year-old man with a medical history of HIV (not on HAART; CD4 count of 120 cells/mm^3) presents with a worsening headache rated 8 on a scale of 0 to 10 and a fever for the last 1 day. His vital signs on presentation are the following: temperature 38 °C, BP 110/58 mm Hg, HR 101 bpm, RR 16 breaths/min, and SpO_2 97% on room air. A CT of his brain is performed and reveals multiple 2-cm solitary lesions. He is started on TMP-SMX with clinical improvement and discharged home with scheduled follow-up in 1 week. Instead, he presents 4 weeks later, brought in by his family after collapsing with a seizure at dinner. The patient is hemodynamically stable. A repeat CT is performed showing the same 2-cm solitary lesions. His wife states that he has been adherent with medications. Which of the following is the next best step?

A. Change therapy to sulfadiazine with pyrimethamine
B. Initiate high-dose methotrexate and glucocorticoids and restart HAART
C. Initiate high-dose methotrexate and glucocorticoids, but delay HAART to avoid IRIS
D. Perform a stereotactic biopsy of the lesion to determine etiology

ANSWERS

46.1 **D.** The fever, dry cough, and dyspnea are consistent with PJP, which is diagnosed by silver stain or DFA of the sputum. Sometimes, bronchoalveolar lavage is necessary to obtain adequate samples. Sputum Gram stain (answer B) is useful when there is suspicion for a lobar community-acquired pneumonia most commonly caused by *Streptococcus pneumoniae*, which is more likely to have an acute onset. Acid-fast smear of the sputum (answer A) would help diagnose TB; the absence of clinical clues such as unintentional weight loss, chronic night sweats, and sometimes blood-tinged sputum makes this diagnosis less likely. *Cryptococcus* (answer C) is more likely to present with CNS involvement (ie, meningitis).

46.2 **D.** The same organisms that cause community-acquired pneumonia in immunocompetent individuals can cause pneumonia in patients living with HIV. Since *Streptococcus pneumoniae* is the most common isolate in adult patients with community-acquired pneumonia, it is therefore the most likely etiology. Additionally, HIV patients may be more susceptible to encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. The fact that symptoms started 2 days ago makes *M. tuberculosis* (answer B) less likely since it is more of an indolent illness. Disseminated histoplasmosis (answer A) may affect HIV-infected patients as an opportunistic infection and usually manifests as fever, fatigue, chest pain, and respiratory distress; this organism, while found in HIV-infected patients, is not as common as pneumococcal pneumonia. Last, PJP (answer C) tends to present with nonproductive cough and hypoxia, which is not described in this patient.

46.3 **C.** All HIV-positive patients should be recommended HAART therapy at the time of diagnosis, except in the case of current cryptococcal meningitis. The three-drug therapy consists of two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) and either one integrase inhibitor, one NNRTI, or one protease inhibitor (thus eliminating answer choices A, B, D, and E). In addition to starting HAART, this patient should receive PJP prophylaxis since her CD4 count is less than 200 cells/mm^3. The most common treatment for patients who can tolerate sulfa drugs is TMP-SMX.

46.4 **D.** This patient should have a biopsy; this is indicated when there is nonresponse to empiric therapy after 14 days. The most common cause of a mass lesion of the brain in an HIV patient is toxoplasmosis, which is treated with TMP-SMX or sulfadiazine and pyrimethamine. However, since this patient failed to show clinical improvement after treatment and still possesses 2-cm brain lesions, primary CNS lymphoma should escalate to the top of the differential diagnosis list. A brain biopsy is diagnostic in that case. Answer A (changing to sulfadiazine with pyrimethamine) would be inappropriate without first ensuring there is no CNS lymphoma. Methotrexate, glucocorticoids, and HAART (answer B) may be a consideration for treating CNS lymphoma, although therapy should not be started without tissue diagnosis. Answer C (methotrexate and steroids without HAART to avoid IRIS) is not indicated. Note that IRIS is a worsening of the neurologic function during the first 60 days of antiretroviral therapy thought to be due to enhanced immune function.

CLINICAL PEARLS

- *Pneumocystis* pneumonia typically has a subacute presentation with fever, a dry cough, and new shortness of breath in HIV patients with a CD4 count lower than 200 cells/mm^3 who are not on PJP prophylaxis (TMP-SMX).
- Patients with PJP can present with a normal chest x-ray, discrete bilateral interstitial lung opacities, or diffuse severe alveolar lung opacities (ARDS type) and typically have an elevated serum lactic acid dehydrogenase level.
- Pulmonary TB should always be considered in AIDS patients with respiratory symptoms and suggestive history; its radiographic presentation may be atypical, and signs and symptoms of dissemination are more common than in immunocompetent patients.
- The most frequent isolate in bacterial pneumonia in AIDS patients is *S. pneumoniae.*
- In patients with CD4 counts less than 200 cells/mm^3, TMP-SMX prophylaxis is effective in preventing *Pneumocystis* pneumonia and in preventing toxoplasmosis when the CD4 count is less than 100 cells/mm^3.
- When the CD4 is less than 50 cells/mm^3, clarithromycin or azithromycin are indicated to prevent MAC infection in patients not taking HAART.
- HAART is effective in reducing viral replication, increasing CD4 counts, and restoring immunocompetence. With the exception of *C. neoformans* meningitis, it should not be delayed.
- HAART consists of a three-drug treatment: two NRTIs plus one integrase inhibitor, one NNRTI, or one protease inhibitor.

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CASE 47

A 65-year-old woman is brought to the emergency department (ED) by her family for increasing confusion and lethargy over the past week. She was recently diagnosed with limited-stage small-cell lung cancer but has not begun cancer treatment. She has been afebrile and has not had any illnesses. She is not taking any medications. Her blood pressure is 136/82 mm Hg, heart rate is 84 beats per minute (bpm), and respiratory rate is 14 breaths per minute and unlabored. On examination, she is an elderly woman who is difficult to arouse and reacts only to painful stimuli. She is able to move her extremities without apparent motor deficits, and her deep tendon reflexes are decreased symmetrically. The remainder of her examination is normal, with normal jugular venous pressure and no extremity edema. You order some laboratory tests, which reveal a serum sodium level of 108 mmol/L, potassium 3.8 mmol/L, bicarbonate 24 mEq/L, blood urea nitrogen (BUN) 5 mg/dL, and creatinine 0.5 mg/dL. Serum osmolality is 220 mOsm/kg, and urine osmolality is 400 mOsm/kg. Urine sodium concentration is 50 mEq/L. A computed tomography (CT) scan of the brain shows no masses or hydrocephalus.

- What is the most likely diagnosis?
- What is your next step in therapy?
- What is the most serious complication of this therapy?

ANSWERS TO CASE 47:

Hyponatremia, Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Summary: A 65-year-old woman with small-cell lung cancer presents with

- Increasing confusion and lethargy over the past week, but no focal deficit
- Normal temperature and blood pressure
- No edema or jugular venous distention
- Symmetrically decreased deep tendon reflexes
- Significant hyponatremia and low serum osmolality, with unexpectedly high urine osmolality
- No masses or hydrocephalus on brain CT scan

Most likely diagnosis: Coma/lethargy secondary to severe hyponatremia, which is most likely caused by a paraneoplastic syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

Next therapeutic step: Treat the hyponatremia with hypertonic saline.

Most serious complication of this therapy: Osmotic demyelination syndrome, formerly referred to as central pontine myelinolysis.

ANALYSIS

Objectives

1. List the causes of hyponatremia. (EPA 1, 2)
2. Understand the use of laboratory testing in the diagnosis of hyponatremia. (EPA 3)
3. Describe the treatment of hyponatremia and some of the potential complications of therapy. (EPA 4, 10)

Considerations

This 65-year-old woman with small-cell lung cancer presents in a stuporous state with hypotonic hyponatremia. She appears euvolemic, as she does not have findings suggestive of either volume overload (jugular venous distention or peripheral edema) or volume depletion (diminished skin turgor). Of note, the term *volemia* refers to intravascular volume. In this chapter, we use volemia to represent total body sodium (in this case, both variables are not coincident all the time). She has no focal neurologic deficits or apparent masses on CT scan of the brain suggesting cerebral metastases. The most likely cause of her altered mental status is hyponatremia. The patient does not take medications. Thus, in the situation of hypotonic hyponatremia in a euvolemic state and with inappropriately concentrated urine, the most likely etiology is inappropriate antidiuretic hormone (ADH) produced by the lung cancer. Therapy is guided by the severity of the hyponatremia and the

symptoms. Because this individual is stuporous and the sodium level is severely decreased, hypertonic saline is required with fairly rapid partial correction. This therapy is not benign and requires monitoring in the intensive care unit. Also, the goal is not correction of the sodium level to normal (135 mmol/L) but rather an increase in serum sodium concentration by 4 to 6 mmol/L in 24 hours.

APPROACH TO: Hyponatremia

DEFINITIONS

ANTIDIURETIC HORMONE: The posterior pituitary hormone that controls excretion of free water and thus, indirectly, sodium concentration and serum tonicity. Also referred to as arginine vasopressin.

OSMOLALITY: Concentration of osmotically active particles, which draw water into a compartment; the normal range for serum osmolality is 280 to 300 mOsm/kg.

SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE: Nonphysiologic elevation of ADH levels as a consequence of ectopic production, as in malignancy, or stimulation of excess pituitary production by various pulmonary or central nervous system (CNS) diseases.

CLINICAL APPROACH

Pathophysiology

Hyponatremia is defined as a serum sodium level < 135 mmol/L and is, by far, the **most common electrolyte disturbance among hospitalized patients.** Patients are often asymptomatic, especially if the hyponatremia develops slowly. Depending on how rapidly the hyponatremia develops, most patients do not have symptoms until the serum sodium level is in the low 120 mmol/L range. Note: since sodium is a monovalent cation, 1 mmol/L = 1 mEq/L.

Serum sodium concentrations are important because they almost always reflect tonicity, the effect of extracellular fluid on cells that will cause the cells (eg, brain cells) to swell (hypotonicity) or to shrink (hypertonicity). For purposes of this discussion, we use serum osmolality as an indicator of tonicity.

Hypotonic hyponatremia *always* occurs because there is water gain, that is, impairment of free water excretion. If one considers that the normal kidney capacity to excrete free water is approximately 18 to 20 L/d, it becomes apparent that it is very difficult to overwhelm this capacity solely through excessive water intake, as in psychogenic polydipsia. Therefore, when hyponatremia develops, the kidney is usually holding on to free water, either pathologically, as in SIADH, or physiologically, as an attempt to maintain effective circulating volume when patients are significantly volume depleted. Hyponatremia can also occur in cases of sodium loss, for example, as a consequence of diuretic use or because of aldosterone deficiency. However, in those cases, there is then a secondary gain of free water.

To determine the cause of the hypotonic hyponatremia, the health care provider must clinically **assess the volume status** of the patient by history and physical examination. A useful algorithm for assessment of patients with hyponatremia is seen in Figure 47–1. Please note that the figure uses the term *volemia*. Though less commonly used, the "volume status" we refer to is actually "total body sodium." A more comfortable way to name the issue at stake is "interstitial volume status."

A history of vomiting, diarrhea, or other losses, such as profuse sweating, suggests **hypovolemia**, as do flat neck veins, dry oral mucous membranes, and diminished urine output. In cases of significant hypovolemia, there is a physiologic increase in ADH in an attempt to retain free water to maintain circulating volume, even at the expense of hypotonicity. In these cases, the excess ADH is not "inappropriate" as in SIADH, but extremely appropriate. At this point, one can **check the urinary sodium levels**. In hypovolemia, the kidney should be avidly retaining sodium, so the urine sodium level should be less than 20 mmol/L. If the patient is hypovolemic, yet the urine sodium level is more than 20 mmol/L, then the kidneys do not have the ability to retain sodium normally. In this case, kidney function is impaired by the use of diuretics, the kidney is lacking necessary hormonal stimulation as in adrenal insufficiency, or there is a primary renal problem, such as tubular damage from acute tubular necrosis. When patients are **hypovolemic**, treatment of the hyponatremia requires **correction of the volume status, usually replacement with isotonic (0.9%) saline.**

Hypervolemia is usually apparent as edema or elevated jugular venous pressure. It commonly occurs as a result of **heart failure, cirrhosis of the liver, or nephrotic syndrome.** In these edematous disorders, there is usually a total body excess of both sodium and water, yet arterial baroreceptors perceive hypoperfusion or a decrease in intravascular volume, which leads to an increase in the level of ADH and, therefore, retention of free water by the kidneys. Renal failure itself can lead to hypotonic hyponatremia because of an inability to excrete dilute urine. In any of these cases, the usual initial treatment of hyponatremia is administration of diuretics to reduce excess salt and water.

Thus, hypovolemic or hypervolemic hyponatremia is often apparent clinically and often does not present a diagnostic challenge. **Euvolemic hyponatremia**, however, is a frequent problem that is not so easily diagnosed. Once the clinician has diagnosed the patient with euvolemic hypotonic hyponatremia, the next step is to measure the urine osmolality. This measurement is taken to determine whether the kidney is actually capable of excreting the free water normally (urine osmolality should be maximally dilute, < 100 mOsm/kg) or whether the free water excretion is impaired (urine not maximally diluted, > 100 mOsm/kg). If the urine is maximally diluted, it is handling free water normally, but its capacity for excretion has been overwhelmed, as in central polydipsia. More commonly, free water excretion is impaired, and the urine is not maximally diluted as it should be.

Two important diagnoses must be considered at this point: **hypothyroidism** and **adrenal insufficiency. Thyroid hormone and cortisol both are permissive for free water excretion, so their deficiency causes water retention.** Cortisol deficiency in secondary (pituitary) adrenal insufficiency can mimic SIADH. In contrast, patients with primary adrenal insufficiency (Addison disease) may also lack aldosterone, so they

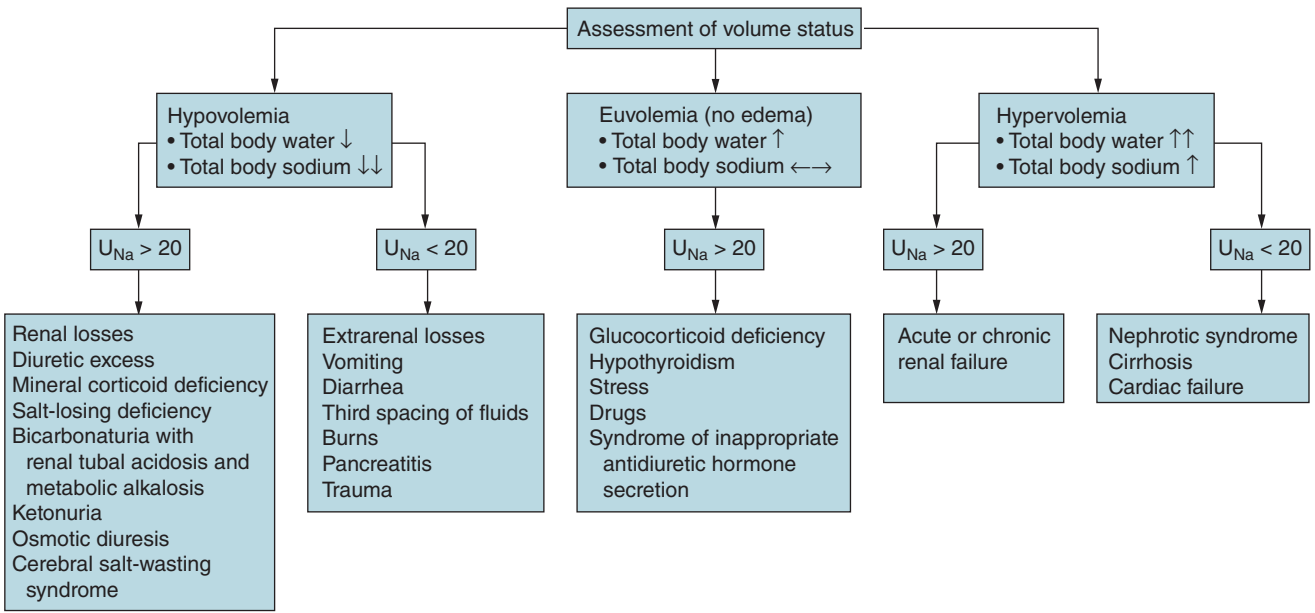


Figure 47–1. Assessment of hyponatremia. (Reproduced with permission, from Longo DL, Fauci AS, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine.* 18th ed. 2012. Copyright © McGraw Hill LLC. All rights reserved.)

have impaired ability to retain sodium and often appear hypovolemic and may even present in shock.

Euvolemic hyponatremia is most commonly caused by **SIADH.** However, as mentioned, Addison disease and hypothyroidism should also be considered as potential causes of euvolemic hyponatremia (it should be noted that forms of Addison disease that impair both cortisol and aldosterone production will present with hypovolemia, while those that affect only cortisol production will present with euvolemia).

Clinical Presentation

Nonphysiologic, nonosmotically mediated (therefore "inappropriate") secretion can occur in the setting of pulmonary disease, CNS disease, pain, in the postoperative period, or as part of a paraneoplastic syndrome. Because of retention of free water, patients actually have mild (although clinically insignificant) volume expansion. Additionally, if they have a normal dietary sodium intake, the kidneys do not retain sodium avidly. Therefore, modest natriuresis occurs so that the urine sodium level is elevated > 40 mmol/L.

SIADH is a diagnosis of exclusion: The patient must be hypoosmolar but euvolemic, with urine that is not maximally dilute (osmolality > 100 mOsm/L), urine sodium more than 40 mmol/L, and normal adrenal and thyroid function. Some laboratory clues to SIADH are low blood urea nitrogen (BUN) and low uric acid levels.

The clinical manifestations are related to osmotic water shifts leading to cerebral edema; thus, the symptoms are mainly neurologic. Early symptoms include headache, nausea, and vomiting; later symptoms may progress to lethargy, confusion, seizures, or coma.

Treatment

Unless the patient has severe neurologic symptoms, the **usual initial treatment of SIADH is free water restriction.** Patients with **severe neurologic symptoms**, such as seizures or coma, require **rapid** partial correction of the sodium level. The treatment of choice is hypertonic (eg, 3%) saline. When there is concern that the saline infusion might cause volume overload, the infusion can be administered with a loop diuretic such as furosemide. The diuretic will cause the excretion of hypotonic urine that is essentially "half-normal saline," so a greater portion of sodium than water will be retained, helping to correct the serum sodium level.

For patients with chronic hypervolemic hyponatremia, as in heart failure or cirrhosis, vasopressin antagonists (tolvaptan and conivaptan are approved for use in the United States) are now available and are very effective in increasing free water excretion and raising serum sodium concentrations. Therapy with these agents is initiated in the hospital with close monitoring of sodium concentration.

Complications

When hyponatremia occurs for any reason, especially when it occurs slowly, the brain adapts to prevent cerebral edema. Solutes leave the intracellular compartment of the brain over hours to days, so patients may have few neurologic symptoms despite very low serum sodium levels. If the serum sodium level is corrected rapidly, the brain does not have time to readjust, and it may shrink rapidly as it loses fluid to

the extracellular space. It is believed that this rapid shrinkage may trigger demyelination of the cerebellar and pontine neurons. This osmotic demyelination syndrome may cause **quadriplegia, pseudobulbar palsies, a "locked-in" syndrome, coma, or death.** Demyelination can occur even when fluid restriction is the treatment used to correct the serum sodium level. For any patient with hyponatremia, the general rule is that chronic hyponatremia should be corrected slowly, and acutely developing hyponatremia can be corrected more quickly. In chronic hyponatremia, the serum sodium concentration should be corrected no faster than 4 to 6 mEq/L in the first 24 hours.

CASE CORRELATION

- See also Case 18 (Hemoptysis/Lung Cancer), Case 37 (Alzheimer Disease/Dementia), Case 49 (Adrenal Insufficiency), and Case 50 (Hypercalcemia/Multiple Myeloma).

COMPREHENSION QUESTIONS

47.1 A 24-year-old man developed seizures 12 hours after an emergent splenectomy, which he required after a motor vehicle collision. After a search for etiology, he was found to have a serum sodium level of 116 mEq/L. He was treated with intravenous hypertonic saline; after 3 hours, the serum sodium level was 120 mEq/L. Which of the following factors most likely led to his hyponatremia?

A. Postoperatively inappropriate elevation of serum vasopressin
B. Administration of hypertonic solutions
C. Acute kidney injury
D. Seizure-induced hyponatremia

47.2 A 56-year-old man presents to the doctor for the first time complaining of fatigue and weight loss. He has never had any health problems, but he has smoked one pack of cigarettes per day for about 35 years. He is a day laborer and is currently homeless and living in a shelter. His physical examination is notable for a low-to-normal blood pressure, skin hyperpigmentation, and digital clubbing. He appears euvolemic. You tell him you are not sure of the problem as yet, but you will draw some blood tests and schedule him for follow-up in a week. The laboratory calls you that night and informs you that the patient's sodium level is 126 mEq/L, potassium level is 6.7 mEq/L, creatinine level is normal, and bicarbonate and chloride levels are low. Which of the following is the likely cause of his hyponatremia given his presentation?

A. SIADH
B. Hypothyroidism
C. Gastrointestinal losses
D. Adrenal insufficiency
E. Renal insufficiency

47.3 An 83-year-old woman comes to your clinic complaining of a headache and mild confusion. Her medical history is remarkable only for hypertension, which is well controlled with hydrochlorothiazide. Her examination and laboratory tests show no signs of infection, but her serum sodium level is 119 mEq/L, and plasma osmolality is 245 mOsm/kg. She confides that she has been drinking and eating less since her husband passed away 4 months ago. She appears to be clinically hypovolemic. Which of the following is the best initial therapy?

A. Fluid restriction

B. Infusion of 0.9% saline

C. Infusion of 3% saline

D. Infusion of 3% saline with furosemide

47.4 A 58-year-old man has undergone a lengthy colon cancer surgery. On the first postoperative day, he is noted to have hyponatremia with a sodium level of 128 mEq/L. You suspect that the hyponatremia is due to the intravenous infusion of hypotonic solution. Which of the following laboratory findings best supports your diagnosis?

A. Urine sodium > 20 mmol/L

B. Urine osmolality > 200 mOsm/L

C. Serum osmolality < 280 mOsm/kg

D. Serum potassium > 5 mmol/L

ANSWERS

47.1 **A.** In the postoperative state or in situations where the patient is in pain, the serum vasopressin level may rise, leading to inappropriate retention of free water, which leads to dilution of the serum. Concomitant administration of hypotonic fluids (not hypertonic, as in answer B) may exacerbate the situation. Acute kidney injury (answer C) may lead to mild hyponatremia due to inability to excrete free water; usually, the sodium level will be > 125 mmol/L. Seizures (answer D) are likely a result of this patient's hyponatremia, rather than causing the low sodium; in fact, seizures are more likely to lead to hypernatremia.

47.2 **D.** Hyponatremia in the setting of hyperkalemia and acidosis (low bicarbonate level) is suspicious for adrenal insufficiency. This patient's examination is also suggestive of the diagnosis, given his complaints of fatigue, weight loss, low blood pressure, and hyperpigmentation. The diagnosis is made by an early morning cortisol test or by measuring the response to adrenocorticotropic hormone (ACTH) stimulation, showing low cortisol levels. In this case, the cause of the adrenal gland destruction is probably due to either tuberculosis or metastatic lung cancer. As a reminder, some forms of Addison disease can cause reduced production of cortisol and aldosterone, which can present as a hyponatremic hypovolemia, while

forms that affect cortisol production only will present with hyponatremic euvolemia. SIADH (answer A) and hypothyroidism (answer B) do not lead to hyperpigmentation, low blood pressure, hyperkalemia, or acidosis. Gastrointestinal fluid losses (answer C) also would not lead to hyperpigmentation; furthermore, the electrolyte derangements would be hypokalemia and alkalosis with diarrhea. Renal insufficiency (answer E) would not be associated with hyperpigmentation or digital clubbing.

47.3 **B.** Because the patient is hypovolemic, probably as a result of the use of diuretics, volume replacement with isotonic saline is the best initial therapy. Hyponatremia caused by thiazide diuretics can occur by several mechanisms, including volume depletion. It is most common in elderly women. Volume replacement takes precedence over sodium correction (answers C and D). A fluid restriction (answer A) would be inappropriate at this time.

47.4 **C.** In a patient with hyponatremia due to the infusion of excessive hypotonic solution, the serum osmolarity should be low. When responding normally, the kidneys should attempt to retain sodium and excrete water; hence, the urine sodium concentration should be low, and the urine osmolality should be low (not high, as in answer B). When the infusion of hypotonic solution is used, the serum potassium level will also be low. This is in contrast to a situation of mineralocorticoid deficiency, in which the serum sodium level will be decreased (answer A) and potassium level may be elevated (answer D). Similarly, hyperaldosteronism can lead to hypertension and hypokalemia (Conn syndrome). In summary, while a low serum osmolality is common to many possible diagnoses, the alternative answers are clearly wrong, because in essence, the kidneys will be excreting free water.

CLINICAL PEARLS

- Hyponatremia almost always occurs by impairment of free water excretion.
- SIADH is a diagnosis of exclusion. Criteria include a euvolemic patient, urine that is not maximally dilute (osmolality > 150-200 mmol/L), urine sodium > 20 mmol/L, and normal adrenal and thyroid function.
- Hypovolemic patients with hyponatremia should be treated with volume replacement, typically with isotonic (0.9%) saline.
- Euvolemic patients with asymptomatic hyponatremia can be treated with fluid restriction. Patients with severe symptoms, such as coma or seizures, can be treated with hypertonic (3%) saline.
- The rate of sodium correction generally should not exceed 4-6 mmol/L per day; otherwise, central pontine myelinolysis (osmotic demyelination) can occur.

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CASE 48

A 38-year-old woman presents to your clinic for evaluation of menstrual irregularity. She states that her periods started when she was 12 years old, and they have been fairly regular ever since, coming once every 28 to 30 days. She has had three previous uncomplicated pregnancies and deliveries. However, approximately 9 months ago, her cycles seemed to lengthen, and for the last 3 months she has not had a period at all. She stopped breastfeeding 3 years ago, but over the last 3 months she noticed that she could express a small amount of milky fluid from her breasts. She had a bilateral tubal ligation after her last pregnancy, and she has no other medical or surgical history. She takes no medications except multivitamins. Over the last year or so, she thinks she has gained about 10 lb, and she feels as if she has no energy despite adequate sleep. She has noticed some mild thinning of her hair and slightly more coarse skin texture. She denies headaches or visual changes. Her physical examination, including pelvic and breast examinations, are normal. She is not obese or hirsute. Slight whitish nipple discharge is elicited from her breasts. Her pregnancy test is negative.

- What is the most likely diagnosis?
- What is the most likely etiology for the condition?

ANSWERS TO CASE 48:

Oligomenorrhea Caused by Hypothyroidism and Hyperprolactinemia

Summary: A 38-year-old woman presents with

- Oligomenorrhea and now secondary amenorrhea, along with galactorrhea
- Weight gain, fatigue, mild thinning of her hair, and slightly more coarse skin
- No headaches or visual changes, which might suggest a pituitary adenoma
- Normal pelvic and breast examinations
- No obesity or hirsutism; last pregnancy 3 years ago and not breast-feeding
- Slight whitish nipple discharge

Most likely diagnosis: Oligomenorrhea and galactorrhea due to hypothyroidism.

Most likely etiology: Primary hypothyroidism is the most likely diagnosis, most often due to autoimmune (Hashimoto) thyroiditis.

ANALYSIS

Objectives

1. Understand the differential diagnosis of secondary amenorrhea and the approach to the investigation of possible hormonal causes. (EPA 2, 3)
2. Understand the interactions of the hormones involved in the hypothalamic-pituitary-gonadal axis. (EPA 12)
3. Recognize the clinical features and diagnostic evaluation of hypothyroidism. (EPA 1, 3)
4. Describe the treatment of hypothyroidism. (EPA 4)

Considerations

This 38-year-old woman presents with secondary amenorrhea, weight gain, fatigue, and galactorrhea despite having previously normal menses and discontinuing breastfeeding 3 years ago. Her history of fatigue, weight gain, and hair loss suggests a systemic cause of her symptoms, possibly hypothyroidism. However, her normal physical examination with lack of myxedema or bradycardia, normal reflexes, normal cognition, and nondisplaced point of maximal impulse suggest mild hypothyroidism. Lack of virilization or obesity does not exclude polycystic ovary syndrome (PCOS), but their absence makes this diagnosis less likely. Hypothyroidism alone could be the cause of the galactorrhea because elevated thryoid releasing hormone can lead to hyperprolactinemia. Prolactinomas can also cause galactorrhea as well as secondary amenorrhea, however, and should be excluded.

APPROACH TO:
Oligomenorrhea and Hypothyroidism

DEFINITIONS

AMENORRHEA: *Primary*—Absence of menarche by the age of 15 regardless of the presence or absence of secondary sex characteristics. *Secondary*—Absence of menstruation for 3 or more months in women with normal past menses.

GALACTORRHEA: Any discharge of milk-containing fluid from the breast; may be unilateral or bilateral and may appear clear, milky, or bloody.

OLIGOMENORRHEA: Menses occurring at infrequent intervals of more than 35 days or fewer than nine menses per year.

POLYCYSTIC OVARY SYNDROME: Syndrome characterized by infertility, hirsutism, obesity, and amenorrhea or oligomenorrhea and often clinically significant insulin resistance.

CLINICAL APPROACH TO OLIGOMENORRHEA

Pathophysiology

The assessment of oligomenorrhea is similar to the workup for secondary amenorrhea, with the understanding that secondary amenorrhea is present when a normally menstruating woman stops having periods for 3 consecutive months or more. **The most common cause of both symptoms, and the easiest to exclude in the clinic, is pregnancy.** A negative in-clinic pregnancy test should be confirmed with a serum beta-human chorionic gonadotropin (hCG). Primary amenorrhea is present when the first menses has not appeared in a girl by the age of 15 and is generally caused by a variety of genetic or congenital defects. It is commonly associated with disorders of puberty. Given this patient's age and history, primary amenorrhea is not a consideration; thus, a diagnostic pathway for secondary amenorrhea/oligomenorrhea should be undertaken (Figure 48–1).

Problems of the Hypothalamic-Pituitary-Ovarian Axis. Excluding pregnancy and problems in the genital outflow tract, disorders of the hypothalamic-pituitary-ovarian axis account for the largest number of cases of oligomenorrhea and amenorrhea. Disorders of the hypothalamus account for the largest percentage of abnormality (> 45%); these include problems of nutrition (rapid weight loss/anorexia), excessive exercise, stress, and infiltrative diseases (eg, craniopharyngioma, sarcoidosis, histiocytosis).

PCOS. The largest single cause of oligomenorrhea is PCOS, accounting for 30% of all cases. PCOS was once thought to be a disease originating in the ovary; however, it now is known that **PCOS is a much more complicated neuroendocrine disorder** with evidence of **estrogenization**, as well as **insulin resistance.** The diagnosis is a clinical one (anovulation, hyperandrogenism, and small follicles on the ovary on ultrasound) after ruling out other causes. These women often have glucose intolerance and may develop metabolic syndrome. They are at risk for cardiovascular

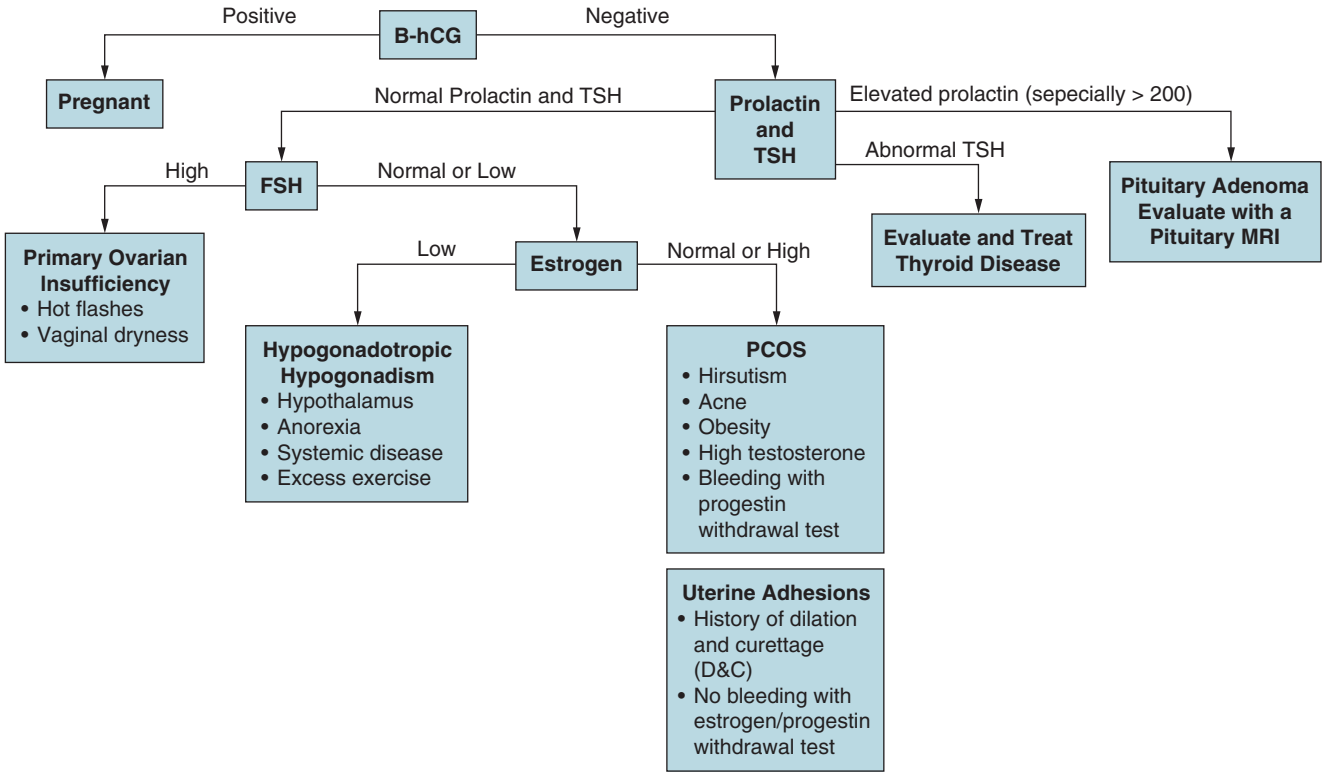


Figure 48–1. Algorithm for diagnosis of secondary amenorrhea.

disease and endometrial cancer. Treatment for PCOS includes weight loss (via diet and exercise), oral contraceptives, androgen blockers such as spironolactone, and metformin. Clomiphene citrate or letrozole can be used as a fertility treatment to induce ovulation in patients looking to get pregnant.

Other Causes. Other important causes of amenorrhea include diseases of the pituitary, specifically neoplasms (eg, prolactinomas, functioning or nonfunctioning adenomas), which account for 18% of cases. Empty sella syndrome, caused by cerebrospinal fluid herniation into the pituitary fossa, and Sheehan syndrome, caused by severe obstetric hemorrhage and/or maternal hypotension at delivery, are important causes of atrophy and ischemia of the pituitary. If suspected, they should be investigated by magnetic resonance imaging (MRI). Finally, disorders such as premature ovarian failure (loss of all functional ovarian follicles before the age of 40), diseases of the thyroid, and adult-onset adrenal hyperplasia should be considered and investigated if supported by history and physical examination with the appropriate laboratory studies (Table 48–1).

Hypothyroidism. The history and physical examination will narrow the range of possible causes. In this patient, the history of fatigue, weight gain, and galactorrhea, along with previously normal menses and a normal physical examination, place **hypothyroidism** at the top of the list. In primary hypothyroidism, the hypothalamus increases thyrotropin-releasing hormone, which also stimulates prolactin secretion. Measurement of both thyroid hormone and prolactin levels would be indicated in this case. **Prolactinomas** are the most common functional pituitary tumors in both men and women and should be suspected if the prolactin level is markedly elevated, > 200 μg/L. If prolactin levels are markedly elevated, pituitary

Table 48–1 • DIFFERENTIAL DIAGNOSIS OF OLIGOMENORRHEA[a]

	History	Laboratory	Therapy
Polycystic ovarian syndrome	Irregular menses since menarche, obesity, hirsutism	Slightly elevated testosterone, elevated LH/FSH	Weight loss, OCP, spironolactone, and/or metformin
Hypothyroidism	Fatigue, cold intolerance	Elevated TSH	Thyroxine replacement
Prolactinoma	Headache, bitemporal hemianopsia, galactorrhea, medications especially psychiatric meds, hypothyroidism	Elevated prolactin level	Dopamine agonist
Ovarian failure	Hot flushes, vaginal dryness, other menopausal symptoms	Elevated FSH and LH	Estrogen +/- progesterone
Sheehan syndrome	Postpartum hemorrhage, unable to breastfeed	Low pituitary hormones (FSH, TSH, ACTH)	Replacement of pituitary hormones

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; OCP, oral contraceptive pill; TSH, thyroid-stimulating hormone.

[a]*Pregnancy must always be suspected with oligomenorrhea or amenorrhea.*

imaging with MRI is indicated. Hyperprolactinemia from any cause inhibits hypothalamic gonadotropin-releasing hormone (GnRH) secretion, leading to amenorrhea in women and infertility and diminished libido in men. In the workup of secondary amenorrhea, these two diagnoses are the easiest to start with because the tests are noninvasive and relatively inexpensive.

CLINICAL APPROACH TO HYPOTHYROIDISM

Pathophysiology

Hypothyroidism is defined as the insufficient production of thyroid hormone. Secondary hypothyroidism as a result of dysfunction of hypothalamic and pituitary hormone secretion is much less common but should be suspected in a patient with a history suggestive of Sheehan syndrome or with symptoms or signs of a tumor in the region of the sella. **Ninety-five percent of cases of hypothyroidism** are caused by **primary thyroid gland failure**, resulting in insufficient thyroid hormone production. In the United States, **the most common cause of hypothyroidism is autoimmune (Hashimoto) thyroiditis**, in which cytotoxic antibodies are produced, leading to thyroid atrophy and fibrosis. The next most common cause is surgical or radioactive iodine treatment for hyperthyroidism, or Graves disease. **Worldwide, iodine deficiency** is the **most common cause of goitrous (enlarged thyroid) hypothyroidism**, but in the United States, this is rare.

Clinical Presentation

Most hypothyroid patients present with vague and nonspecific symptoms. **Elderly** individuals may be suspected of having **dementia or depression** when the cause is really hypothyroidism. In general, symptoms of fatigue, weight gain, muscle cramping, cold intolerance, hair thinning, menstrual changes, or carpal tunnel syndrome are common and should prompt an investigation of thyroid function.

Laboratory Values. When testing outpatients for hypothyroidism, measurement of the **serum thyroid-stimulating hormone (TSH)** level is the most sensitive and useful test. Because most cases of hypothyroidism are caused by thyroid gland failure, the normal pituitary response is to markedly increase the TSH levels in an attempt to stimulate the failing gland. Falling levels of thyroid hormone lead to an increase in the TSH concentration. **Measurement of TSH alone would be insufficient in suspected cases of pituitary disease**, so measurement of the thyroid hormone level can also be performed. One should remember that almost all thyroxine (T_4) circulates bound to protein, but it is the free or unbound fraction that is able to diffuse into cells and become active. Most laboratories can now measure **free T_4** directly, or it can be estimated by using the **free thyroxine index (FTI)**. The FTI is calculated from measurements of total T_4 and the triiodothyronine (T_3) resin uptake test. When there is excess thyroid-binding globulin (TBG), as in pregnancy or oral contraceptive use, T_4 levels will be high (as a consequence of the large amount of carrier protein), but T_3 uptake will be low (value varies inversely with amount of TBG present). Conversely, when there is a low level of TBG, as in a hypoproteinemic patient with nephrotic syndrome, the T_4 level will necessarily also be low (not

much carrier protein), but the T_3 uptake will be high. If both total T_4 and T_3 uptake are low, the FTI is low, and the patient is hypothyroid.

In mild cases, or **subclinical hypothyroidism**, the TSH level is mildly elevated, but the free T_4 or FTI is within the normal range. Patients may be asymptomatic or report the vague and subtle symptoms of hypothyroidism, such as fatigue. About half of such patients will progress to overt hypothyroidism within 5 years. They often have some **derangement of cholesterol metabolism, such as elevated total and low-density lipoprotein cholesterol.** Thyroid hormone replacement can be prescribed in the cases of TSH > 10 mU/L, pregnancy, infertility, and/or strongly convincing symptoms of hypothyroidism. In clinical hypothyroidism, the TSH level is markedly elevated, and the free T_4 or FTI is low.

Treatment

The overwhelming majority of patients with hypothyroidism can be treated with once-daily dosing of synthetic levothyroxine, which is biochemically identical to the natural hormone. **Levothyroxine is relatively inexpensive; has a long half-life (6–7 days), which allows once-daily** dosing; and gives a predictable response. Older thyroid preparations, such as desiccated thyroid extract, are available but are not favored because of the variable content of T_3 and T_4 in each tablet.

If there is no residual thyroid function, the daily replacement dose of levothyroxine is 1.6 μg/kg, which usually calculates to 100 to 150 μg. However, in **older patients and in those with known cardiovascular disease, dosing should start at a lower level**, such as 25 to 50 μg/d, and be increased at similar increments once **every 4 to 6 weeks** until the patient achieves a euthyroid state. Overly rapid replacement with the sudden increase in metabolic rate can overwhelm the coronary or cardiac reserve. The goal of treatment is normalized TSH, ideally in the lower half of the reference range. Patients may not experience full relief of symptoms until 3 to 6 months after normal TSH is achieved.

Complications

In severe, prolonged hypothyroidism, a syndrome termed **myxedema** may develop. These patients present with hypothermia, hypotension, hypoventilation, altered mental status, hyponatremia, and/or hypoglycemia. They may also have underlying adrenal insufficiency. This is a life-threatening emergency with a high mortality, even when managed aggressively with intravenous hydrocortisone (in case of underlying adrenal insufficiency) followed by intravenous levothyroxine.

CASE CORRELATION

- See also Case 49 (Adrenal Insufficiency), Case 50 (Hypercalcemia/Multiple Myeloma), Case 51 (Type 2 Diabetes Diagnosis and Management), and Case 53 (Thyrotoxicosis/Graves Disease).

COMPREHENSION QUESTIONS

48.1 A 42-year-old woman presents to your clinic for her annual physical examination. On examination, you note neck fullness. When you palpate her thyroid, it is enlarged, smooth, rubbery, and nontender. The patient is asymptomatic. You send her for thyroid function testing. Her T_4, free T_4, and T_3 are normal, but her TSH is slightly elevated. Which of the following is the most likely diagnosis?

A. Iodine deficiency
B. Thyroid cancer
C. Hashimoto thyroiditis
D. Graves disease
E. Multinodular goiter

48.2 Which of the following laboratory tests is most appropriate to be performed to confirm your diagnosis of the patient in Question 48.1?

A. Repeat thyroid function tests
B. Thyroid ultrasound
C. Nuclear thyroid scan
D. Antithyroperoxidase (anti-TPO) antibody tests
E. Complete blood count with differential

48.3 A 19-year-old gymnast active in national competition is brought to your clinic by her mother because the daughter's menses have ceased for the last 3 months. Prior to this, she was always regular. She denies excess dieting, although she does work out with her team 3 hours daily. Her physical examination is normal except for her body mass index of 20 kg/m^2. Which of the following laboratory tests should be ordered first?

A. Thyroid function tests
B. Complete blood count
C. Luteinizing hormone (LH)/follicle-stimulating hormone (FSH)
D. Prolactin
E. Beta-human chorionic gonadotropin (beta-hCG)

48.4 A 35-year-old woman who was diagnosed with hypothyroidism 4 weeks ago presents to your clinic complaining of persistent feelings of fatigue and sluggishness. After confirming your diagnosis with a measurement of the TSH, you started her on levothyroxine 50 μg daily. She has been reading about her diagnosis on the Internet and wants to try desiccated thyroid extract instead of the medicine you gave her. On examination, she weighs 175 lb, her heart rate is 64 beats per minute (bpm) at rest, and her blood pressure is normal. Which of the following is the best explanation to be conveyed to the patient?

A. The delay in resolution of symptoms is to be expected.

B. Thyroid extract is approved by the Food and Drug Administration (FDA) but inconsistent in activity.

C. Her dose of levothyroxine should be increased.

D. She should take a multivitamin with iron for her symptoms.

ANSWERS

48.1 **C.** Hashimoto thyroiditis is the most common cause of hypothyroidism with goiter in the United States. It is most commonly found in middle-aged women, although it can be seen in all age groups. Iodine deficiency (answer A) is exceedingly uncommon in the United States because of iodized salt. Graves disease (answer D) is a hyperthyroid condition. Patients with multinodular goiter (answer E) usually are euthyroid. Patients with thyroid cancer (answer B) usually are also euthyroid.

48.2 **D.** Hashimoto thyroiditis is an autoimmune disease of the thyroid. Several different autoantibodies directed toward components of the thyroid gland will be present in the patient's serum; however, of these, anti-TPO antibody almost always is detectable. These antibodies are the markers, not the cause, of gland destruction. On thyroid biopsy, lymphocytic infiltration and fibrosis of the gland are pathognomonic. The presence of these autoantibodies predicts progressive gland failure and the need for hormone replacement. None of the other tests (answer A, repeat thyroid function tests; answer B, thyroid ultrasound; answer C, nuclear thyroid scan; answer E, complete blood cell count with differential) will be helpful.

48.3 **E.** In a young woman with oligomenorrhea, pregnancy should always be the first diagnosis considered. Urine pregnancy tests are easily performed in the clinic and are highly sensitive. Serum beta-hCG can be measured to confirm a negative test. In this patient, the next most likely diagnosis is hypothalamic hypogonadism, secondary to her strenuous exercise regimen. These young women are at risk for osteoporosis and should be counseled on adequate nutrition and offered combined oral contraceptives if the amenorrhea persists. If the pregnancy test is negative, then evaluation of oligomenorrhea includes TSH (answer A), serum prolactin level (answer D), and serum LH and FSH (answer C); this patient likely has a hypothalamic dysfunction with lack of pulsatile GnRH from the excessive exercise and low body weight. Answer B (complete blood count) is not indicated in this case.

48.4 **C.** This patient's thyroid replacement should be increased. She has been on thyroid replacement therapy for 4 weeks which is sufficient time for a clinical effect (answer A). The symptoms point to continued hypothyroidism. Levothyroxine is the preferred replacement hormone for hypothyroidism. The amount of hormone batch to batch and the patient dose response are believed to be more predictable than with other forms of hormone replacement, such as thyroid extract (answer B), which is made from desiccated beef or pork thyroid glands; this preparation is not FDA approved. There is no evidence that the natural hormone replacement is superior to the synthetic form. The dose of levothyroxine should be titrated to relief of symptoms, as well as to normalization of the TSH. Other medications, especially iron-containing vitamins (answer D), should be taken at different times than levothyroxine because they may interfere with absorption.

CLINICAL PEARLS

- The most common causes of oligomenorrhea are disorders of the hypothalamic-pituitary-gonadal axis, such as PCOS and hypothyroidism.
- Hypothyroidism may cause hyperprolactinemia. Hyperprolactinemia from any cause induces hypothalamic dysfunction, leading to menstrual irregularities in women and diminished libido and infertility in men.
- The most common cause of hypothyroidism is primary thyroid gland failure as a result of Hashimoto thyroiditis.
- A low free T_4 or FTI and a high TSH characterize primary hypothyroidism.
- Synthetic levothyroxine (T_4) replacement is the treatment of choice for hypothyroidism; in older patients, you need to "start low and go slow."
- The goal of therapy is to normalize the TSH level in primary hypothyroidism and to relieve symptoms.

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CASE 49

A 58-year-old woman comes to the office after she experienced a near-fainting spell 1 day ago. She was outside playing tennis when she vomited and felt lightheaded. She spent the rest of the day lying down with mild, diffuse abdominal pain and nausea. She had no fever or diarrhea. She reports several months of worsening fatigue; mild, intermittent, generalized abdominal pain; and loss of appetite with a 10- to 15-lb unintentional weight loss. Her medical history is significant for hypothyroidism, for which she takes levothyroxine. She takes no other medications. On examination, her temperature is 99.8 °F, heart rate is 90 beats per minute (bpm), blood pressure is 89/62 mm Hg, and respiratory rate is 14 breaths per minute. Upon standing, she becomes lightheaded, her pulse increases to 112 bpm, and her systolic blood pressure drops to 70 mm Hg. She is alert and tanned, with hyperpigmented creases in her hands. Her lungs are clear, and her heart rhythm (after standing) is tachycardic but regular. On abdominal examination, she has normal bowel sounds and mild diffuse tenderness without guarding. Her pulses are rapid and thready. She has no peripheral edema. Initial laboratory studies are significant for sodium 121 mEq/L, potassium 5.8 mEq/L, bicarbonate 16 mEq/L, glucose 52 mg/dL, and creatinine 2 mg/dL.

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 49:
Adrenal Insufficiency

Summary: A 58-year-old woman presents with

- Near-fainting episode 1 day ago with vomiting, feeling lightheaded, and abdominal pain
- Orthostatic hypotension
- Intermittent chronic abdominal pain
- Constitutional symptoms such as fatigue and unintentional weight loss
- Hyponatremia, hyperkalemia, acidosis, and hypoglycemia
- Hyperpigmented creases in her hands along with darker skin

Most likely diagnosis: Primary adrenal insufficiency. The most common cause of primary adrenal insufficiency in adults is autoimmune adrenalitis. Her presentation was likely exacerbated by levothyroxine use.

Next step: After drawing a cortisol level, immediate administration of intravenous saline with glucose and an intravenous stress dose of corticosteroids.

ANALYSIS

Objectives

1. Recognize the presentation of primary and secondary adrenal insufficiency and of adrenal crisis. (EPA 1, 10)
2. Recognize the most common causes of primary and secondary adrenal insufficiency. (EPA 2)
3. Describe the treatment of adrenal insufficiency. (EPA 4)

Considerations

This patient has a low-grade fever, which may be a feature of adrenal insufficiency or may signify infection, which can precipitate an adrenal crisis or produce a similar clinical picture. It is important to diagnose and treat any underlying infection. Because of the adrenal insufficiency and the aldosterone deficiency, she has volume depletion, hypoglycemia, and hypotension. Additionally, she has an acute kidney injury secondary to hypovolemia, as evidenced by her elevated creatinine. Furthermore, she began thyroid hormone replacement (for hypothyroidism) prior to her office visit; this likely exacerbated the adrenal crisis. Thus, immediate intravenous replacement with normal saline with 5% glucose is critical. A low serum cortisol level with the patient's clinical presentation and without other explanation confirms the diagnosis of adrenal insufficiency.

APPROACH TO:
Adrenal Insufficiency

DEFINITIONS

ACTH STIMULATION TEST: An examination to evaluate the cortisol level after an intravenous (IV) injection of adrenocorticotropic hormone (ACTH; corticotropin). A normal individual should have a sufficient increase in cortisol, whereas a patient with adrenal insufficiency will have either an insufficient or no cortisol increase.

ADDISON DISEASE: Failure of the adrenal cortex leading to underproduction of corticosteroids.

CLINICAL APPROACH

Pathophysiology

Primary adrenal insufficiency (**Addison disease**) refers to adrenal failure or destruction or infiltration of the adrenal glands. The **most common cause worldwide is autoimmune destruction** of the **adrenal glands**. Tuberculosis adrenalitis remains a frequent cause in the developing world. Among children, the most common cause is congenital adrenal hyperplasia. Other causes include chronic granulomatous infections (histoplasmosis, coccidiomycosis), bilateral adrenal hemorrhage (usually in the setting of sepsis with disseminated intravascular coagulation), adrenal metastases (commonly from lung, breast, or stomach cancers), or X-linked adrenoleukodystrophy, a genetic disorder with adrenal and neurologic manifestations. Patients with acquired immunodeficiency syndrome (AIDS) often develop adrenal involvement as a result of infection with cytomegalovirus or *Mycobacterium avium-intracellulare*.

In **primary adrenal insufficiency**, the glands themselves are destroyed so that the patient becomes deficient in cortisol and aldosterone. Primary adrenal insufficiency is a relatively uncommon disease seen in clinical practice. A **high level of suspicion**, particularly in individuals who have suggestive signs or symptoms or who are susceptible by virtue of associated autoimmune disorders or malignancies, must be maintained. The nonspecific symptoms might otherwise be missed for many years until a stressful event leads to crisis and death.

Secondary and tertiary adrenal insufficiency are types of central adrenal insufficiency. Secondary adrenal insufficiency is adrenal failure caused by a lack of ACTH stimulation from the **pituitary gland**. Any disease of the pituitary can cause this, including infectious, malignant, traumatic, or autoimmune etiologies. **Tertiary adrenal insufficiency** is adrenal failure from lack of corticotropin-releasing hormone (CRH) secretion from the **hypothalamus**. Chronic exogenous administration of corticosteroids preferentially suppresses the hypothalamic CRH secretion. Because of the widespread use of corticosteroids, tertiary adrenal insufficiency is relatively common. In both secondary and tertiary adrenal insufficiencies, the

renin-angiotensin system usually is able to maintain near-normal levels of aldosterone so that the patient is deficient only in cortisol.

Clinical Presentation

The clinical presentation of primary adrenal insufficiency depends on the relative deficiency of glucocorticoids and mineralocorticoids, ACTH excess, and other associated disorders. An adrenal crisis may present with fatigue, reduced strength, weight loss, **nausea, vomiting, abdominal pain, and hypotension.** Laboratory findings may **include hyponatremia, hyperkalemia, metabolic acidosis**, and azotemia because of aldosterone deficiency, as well as hypoglycemia and eosinophilia resulting from cortisol deficiency.

Patients with adrenal insufficiency may go into crisis when stressed by infection, trauma, or surgery. The **clinical features may appear identical to those of septic shock**; the only clues that the cause is adrenal disease may be the hypoglycemia (blood sugar is often elevated in sepsis) and profound **hypotension that is refractory to administration of pressors** but is reversed almost immediately when intravenous fluids and steroids (preferentially hydrocortisone, which has both glucocorticoid and mineralocorticoid activity) are given.

Chronic adrenal insufficiency has nonspecific clinical features, such as **malaise, weight loss, chronic fatigue, and gastrointestinal symptoms such as anorexia, nausea, and vomiting.** A patient may have hypoglycemia and postural hypotension as a result of volume depletion. **Hyperpigmentation** is seen over time in primary adrenal insufficiency; this is caused by elevated melanocyte-stimulating hormone production from the pituitary as a by-product of high ACTH levels. It is typically seen as generalized hyperpigmentation of the skin and mucous membranes. It is increased in sun-exposed areas or over pressure areas, such as elbows and knees, and may be noted in skin folds. In contrast, patients with secondary adrenal insufficiency may be pale due to lack of ACTH and its by-products. Additionally, these patients maintain aldosterone production due to the renin-angiotensin system, despite the lack of cortisol production. Therefore, volume depletion and hyperkalemia are not present.

Diagnosis. Cortisol levels show a diurnal variation. Cortisol levels are high in the morning and low as the day progresses, and levels should be elevated in stressful situations such as acute medical illness, surgery, or trauma. A **morning plasma cortisol level less than or equal to 5 μg/dL in an acutely ill patient is definitive evidence of adrenal insufficiency.** Conversely, a random cortisol level more than 18 μg/dL usually is interpreted as evidence of intact adrenal function. As in other endocrine deficiency states, the diagnostic test in this case is a stimulation test (conversely, in endocrine excess states, the diagnostic test is often a suppression test). **The ACTH stimulation test** is used to confirm adrenal insufficiency. Synthetic ACTH (cosyntropin) 250 μg is administered intravenously, and serum cortisol levels are measured at baseline and then at 30- and 60-minute intervals. A maximal stimulated level of more than 18 μg/dL is considered normal and indicates intact adrenal function. If cosyntropin stimulation testing indicates probable adrenal insufficiency, ACTH levels can then be measured to distinguish between primary adrenal insufficiency (high ACTH) and secondary/tertiary adrenal insufficiency (low ACTH).

The insulin-glucose tolerance test is the gold standard for testing the entire hypothalamic-pituitary axis. It is based on the principle that if a stressful situation is induced (in this case, hypoglycemia), the ACTH level should rise with a consequent increase in cortisol levels. Computed tomography and magnetic resonance imaging are helpful in evaluating adrenal and pituitary disease after biochemical confirmation.

Treatment

Treatment of **Addisonian crisis** includes **intravenous 5% glucose with normal saline** to correct volume depletion and hypoglycemia and administration of **corticosteroid therapy**. Hydrocortisone usually is given intravenously at doses of 100 mg every 6 to 8 hours, or it can be given as a bolus followed by a continuous infusion. At high doses, the hydrocortisone provides both glucocorticoid and mineralocorticoid activity. A cortisol level should be drawn before treatment to confirm the diagnosis. Causes of the acute crisis should be identified and treated; in particular, there should be a **search for infection**.

Long-term treatment of patients with primary adrenal insufficiency includes replacement doses of **glucocorticoids** (eg, hydrocortisone 15–25 mg/d) and **mineralocorticoids** (eg, fludrocortisone 0.1–0.2 mg/d). Patients with secondary adrenal insufficiency still produce aldosterone, as mentioned previously, so only glucocorticoids must be replaced. In both cases, to prevent the long-term complications of glucocorticoid excess (diabetes, hypertension, obesity, osteoporosis, cataracts), patients should not be overtreated. Stress doses of steroids should be given for intercurrent illnesses. Patients should wear a medical alert bracelet.

Stress Dose Steroids. When a patient has adrenal insufficiency or adrenal suppression due to chronic supraphysiologic corticosteroid use (equivalent of prednisone 15 mg/d for 3 weeks or longer during the prior 12 months), then stress dose steroids are needed for events such as surgery or acute illness. Hydrocortisone 100 mg IV every 6 to 8 hours is the standard dose.

Thyroid Hormone and Adrenal Insufficiency. Many patients with adrenal insufficiency also have hypothyroidism. As the administration of thyroid hormone treatment increases the overall metabolic rate, the rate of urinary cortisol secretion is increased. This can exacerbate existing adrenal insufficiency. It is ideal to begin steroid therapy first, then add thyroid hormone replacement. The situation may be challenging, as adrenal insufficiency is a much less common disease than hypothyroidism, and its development can occur over a period of several years.

CASE CORRELATION

- See also Case 47 (Hyponatremia, Syndrome of Inappropriate Secretion of Antidiuretic Hormone), Case 48 (Oligomenorrhea Caused by Hypothyroidism and Hyperprolactinemia), Case 52 (Diabetic Ketoacidosis, Type 1 Diabetes), and Case 53 (Thyrotoxicosis/Graves Disease).

COMPREHENSION QUESTIONS

49.1 A 40-year-old man with rheumatoid arthritis presents to the postop unit after an irrigation and debridement of a methicillin-resistant *Staphylococcus aureus* (MRSA)–positive septic joint. His blood pressure is 84/60 mm Hg, rectal temperature is 101.5 °F, and his heart rate is 95 bpm. Total blood loss from the surgery was 500 mL. The anesthesia staff give him a bolus 2 L of normal saline with dopamine and norepinephrine for pressors. His blood pressure elevates to 89/61 mm Hg. You are called to the postop unit to assess the situation. Which of the following is the best decision?

A. Start broad vancomycin to combat MRSA infection from septic joint.

B. Administer 1 unit of packed red blood cells due to blood loss.

C. Bolus hydrocortisone due to possible steroid dependence.

D. Order a cosyntropin stimulation test to assess for adrenal insufficiency.

49.2 A 30-year-old woman takes oral prednisone 15 mg/d for systemic lupus erythematosus, which is largely in remission. She is admitted to the hospital for a cholecystectomy. Which of the following is the most important intervention for her?

A. Hydrocortisone intravenously before surgery and every 6 hours for 24 hours

B. Double the prednisone the night before and hold her steroids the day of the surgery

C. Use of cyclophosphamide in lieu of corticosteroids for 2 weeks following surgery to promote wound healing

D. Cancel the surgery and use lithotripsy to break up the stones

49.3 A 30-year-old woman who is 12 weeks' postpartum is noted to have adrenal insufficiency and a very distinct tan, although she hardly ventures outside. Which of the following is the most likely etiology?

A. Long-term steroid use

B. Sheehan syndrome (pituitary insufficiency)

C. Brain tumor

D. Autoimmune adrenal destruction

ANSWERS

49.1 **C.** This patient is experiencing adrenal insufficiency in the setting of chronic steroid dependence. His history of rheumatoid arthritis points to this dependence, and his steroids may have been prematurely discontinued. Septic shock (answer A) should react to the bolus and pressor therapy. Half a liter of blood loss (answer B) is not sufficient to cause this profound hypotension. Additionally, the emergent situation makes the cosyntropin test (answer D) inadequate.

49.2 **A.** A stress dose of corticosteroids (hydrocortisone) is important to prevent adrenal insufficiency before surgery, which is a physiologically stressful event. Doubling the prednisone the night before and holding the steroids on the day of surgery (answer B) would not supply the sufficient stress dose of steroids needed. Using cyclophosphamide instead of steroids (answer C) would likely lead to a flare-up of the lupus; also, corticosteroids need to be discontinued at least 1 to 2 months prior to surgery so that wound healing is not affected. Lithotripsy (answer D) would also likely require stress dose steroids and can lead to sepsis; this modality has limited utility, and patients need to be carefully selected (eg, patients with small stones).

49.3 **D.** Hyperpigmentation occurs as a result of increased melanocyte-stimulating factor, a byproduct of ACTH, and occurs in primary adrenal insufficiency. Secondary causes of adrenal insufficiency such as Sheehan syndrome (answer B) result in low ACTH levels and do not cause the "tanned" appearance. A brain tumor (answer C), such as an ACTH-producing pituitary adenoma, would cause overactivation of the adrenal glands, resulting in a Cushingoid appearance and hyperpigmentation due to the excess ACTH. There is no history of long-term steroid use (answer A) or the discussion of a disease process for which long-term steroid use would be indicated.

CLINICAL PEARLS

- Primary adrenal insufficiency presents with weakness, fatigue, abdominal pain with vomiting, hyperpigmentation, and hyponatremia with hypotension refractory to pressors.
- Treatment of adrenal crisis is immediate administration of salt (saline), sugar (glucose if patient is hypoglycemic), and steroids (hydrocortisone).
- The most common cause of primary adrenal insufficiency worldwide is autoimmune destruction. Tuberculosis remains a common cause in the developing world.
- Tertiary adrenal insufficiency is a common presentation of adrenal insufficiency due to suppression of the hypothalamic-pituitary axis by exogenous corticosteroids.

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CASE 50

A 63-year-old woman is brought to the emergency center for upper arm pain and swelling following a fall at home. The family has noted that for approximately the past 2 months, the patient has become progressively fatigued and absentminded, and she has developed loss of appetite and weight loss. She has been getting up to urinate several times per night and complains of thirst; a glucose test for diabetes mellitus in her doctor's office was negative. This morning, she lost her balance because she felt "light-headed" and fell, landing on her left arm. Physical examination is notable for an older, thin woman in mild distress as a result of pain. She is afebrile, and her blood pressure is 110/70 mm Hg, and heart rate is 80 beats per minute (bpm). Her thyroid gland is normal to palpation. Her mucous membranes are dry and sticky. Heart and lung examinations are normal, and carotid auscultation reveals no bruits. Examination of her extremities is significant only for deformity of the left midhumerus with swelling. The left radial pulse is 2+ and symmetric. The radiologist calls you to confirm the fracture of the midleft humerus but also states that there is suspicion for some lytic lesions of the proximal humerus and recommends a skull film (Figure 50–1). Serum creatinine level is 2.1 mg/dL, with normal electrolyte and glucose concentrations, but serum calcium level is 13 mg/dL, and hemoglobin level is 9.2 g/dL.



Figure 50–1. X-ray of skull.

- What is the most likely diagnosis?
- What is the most likely underlying etiology in this patient?
- What is your next therapeutic step?

ANSWERS TO CASE 50:
Hypercalcemia/Multiple Myeloma

Summary: A 63-year-old woman presents with

- A humeral fracture sustained during a fall because of light-headedness
- A 2-month history of fatigue, absentmindedness, loss of appetite and weight, and nocturia
- Normal vital signs, but appearance of dehydration
- Lytic lesions of the skull, proximal humerus, renal insufficiency, anemia, and hypercalcemia

Most likely diagnosis: Hypercalcemia with pathologic fracture of the left humerus.

Most likely underlying etiology: Multiple myeloma.

Next therapeutic step: Initial therapy of the hypercalcemia with intravenous (IV) fluids could be started in the emergency department.

ANALYSIS

Objectives

1. Describe the clinical presentation and differential diagnosis of hypercalcemia. (EPA 1, 2)
2. Outline the treatment of symptomatic hypercalcemia. (EPA 4, 10)

Considerations

The patient presents with acute confusion, fatigue, and lethargy, all symptoms of hypercalcemia, consistent with the calcium level of 13 mg/dL. The first step in therapy should be IV saline to restore volume status and facilitate urinary calcium excretion. Given the rapidity of onset of symptoms, weight loss, age, and presence of lytic bone lesions, the first concern should be for malignancy, such as multiple myeloma or bony metastases from an undiagnosed cancer. Both serum and urine electrophoresis would help to identify the presence of a monoclonal gammopathy. Low serum parathyroid hormone (PTH) and absent PTH-related protein (PTHrP) levels would exclude other causes of hypercalcemia.

APPROACH TO:
Hypercalcemia and Multiple Myeloma

DEFINITIONS

CORRECTED CALCIUM LEVEL: Add 0.8 mg/dL to the serum total calcium for every 1 g/dL of albumin level below 4 g/dL. Example: If the serum calcium level is 9 mg/dL and the albumin level is 2 g/dL, the corrected calcium level is 10.6 mg/dL.

HYPERCALCEMIA: Elevated serum calcium levels after correction for albumin concentration (normal range approximately 8.8-10.4 mg/dL).

CLINICAL APPROACH TO HYPERCALCEMIA

Pathophysiology

The most common causes of hypercalcemia include malignancies or hyperparathyroidism, accounting for 90% of cases. Other causes include granulomatous disorders such as sarcoidosis and tuberculosis; less commonly, hypercalcemia may be the presentation of intoxication with vitamin A, vitamin D, or calcium-containing antacids or may occur as a side effect of drugs such as lithium or thiazide diuretics. Genetic conditions such as familial hypocalciuric hypercalcemia and hyperparathyroidism as part of a multiple endocrine neoplasia syndrome are less common causes. Causes of hypercalcemia are listed in Table 50–1.

The differential diagnosis can be narrowed based on the chronicity of the patient's presentation and the presence or absence of other symptoms and signs (Figure 50–2). **Primary hyperparathyroidism**, usually caused by a **solitary parathyroid adenoma**, is the most likely cause when hypercalcemia is discovered in an otherwise **asymptomatic** patient on routine laboratory screening.

However, a patient presenting with acute onset of **symptomatic hypercalcemia** is more likely to have a **malignancy**. Multiple myeloma, lymphoma, and leukemia all can present with hypercalcemia, as can solid tumors such as breast, lung, and kidney cancers. Some of these cancers cause elevated calcium levels by **stimulating osteoclast activity** through direct bone marrow invasion (multiple myeloma, leukemia, and breast cancer). Others produce **excess 1,25-vitamin D** (lymphomas), and still others secrete a **PTHrP** that binds the PTH receptor (kidney and lung). Cancer-related hypercalcemia can be differentiated from primary hyperparathyroidism by finding a suppressed PTH level.

Clinical Presentation

Most patients have no symptoms with mild hypercalcemia (less than 12 mg/dL), except perhaps some polyuria and dehydration. When calcium exceeds 13 mg/dL, patients begin developing increasingly severe symptoms, including central nervous system symptoms (lethargy, stupor, coma, mental status changes, psychosis), gastrointestinal symptoms (anorexia, nausea, constipation, peptic ulcer disease), kidney problems (polyuria, nephrolithiasis, prerenal azotemia), and musculoskeletal complaints (arthralgias, myalgias, weakness).

The **symptoms of hyperparathyroidism** can be remembered as **stones** (kidney), **moans** (abdominal pain), **groans** (myalgias), **bones** (bone pain), and **psychiatric overtones** (mental status changes). Diagnosis can be established by finding hypercalcemia, hypophosphatemia, and inappropriately elevated PTH levels. Patients with primary hyperparathyroidism are generally treated surgically with parathyroidectomy if any of the following conditions are met: the patient is symptomatic, the calcium is greater than 1 mg/dL above upper limit of normal, the patient is less than 50 years old, or if there is significantly decreased bone mineral density (T score < -2.5). Patients younger than 50 tend to have a lower morbidity and mortality risk.

Table 50–1 • CAUSES OF HYPERCALCEMIA

Disease Process	Mechanism	Clinical Presentation	Diagnostic Evaluation	Treatment
Primary hyperparathyroidism	Elevated PTH leading to increased turnover of bone	Solitary adenoma or part of multiple endocrine neoplasia (MEN); nephrolithiasis, peptic ulcers, and mental status changes (stones, bones, groans, etc)	Hypercalcemia, hypophosphatemia, elevated PTH	Medical therapy for mild symptoms; surgery for symptoms of hypercalciuria or osteoporosis
Malignancy	Local destruction of bone (multiple myeloma or leukemia or lymphoma) or humoral release of PTHrP (solid tumors, eg, breast, renal, or lung cancer)	Symptoms of hypercalcemia and of the particular cancer	Imaging of bones (either plain film or bone scan), PTHrP levels, serum protein electrophoresis, bone marrow biopsy	Treatment of the tumor and control of cancer, bisphosphonates, calcitonin
Sarcoidosis (and other granulomatous disorders)	Excess $1,25(OH)_2D$ synthesized in macrophages and lymphocytes	Pulmonary symptoms, lymphadenopathy, erythema nodosum	Low PTH levels and elevated $1,25(OH)_2D$ levels. Elevated ACE level, biopsy showing granulomas	Bisphosphonates or calcitonin; glucocorticoids for sarcoidosis
Excessive vitamin D intake	Increased calcium intestinal absorption and, if severe, bone resorption	Symptoms of hypercalcemia	Low PTH levels, markedly elevated levels of 25(OH)D, and normal $1,25(OH)_2D$ levels	Decrease vitamin D and calcium intake
Renal insufficiency	Secondary hyperparathyroidism as a result of partial resistance to PTH effects	Bone pain, pruritus, ectopic calcification, osteomalacia	Elevated renal function tests	Limit dietary phosphate intravenous calcitriol

Abbreviations: ACE, angiotensin-converting enzyme; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein.

Laboratory Tests and Imaging. In this case scenario, checking electrolytes to assess acid-base status and renal function are important tests to consider. A normal complete blood count (CBC) and peripheral smear would make leukemia a less likely cause. Levels of PTH and specific assays for PTHrP are generally measured. If multiple myeloma is suspected, serum and urine electrophoresis for

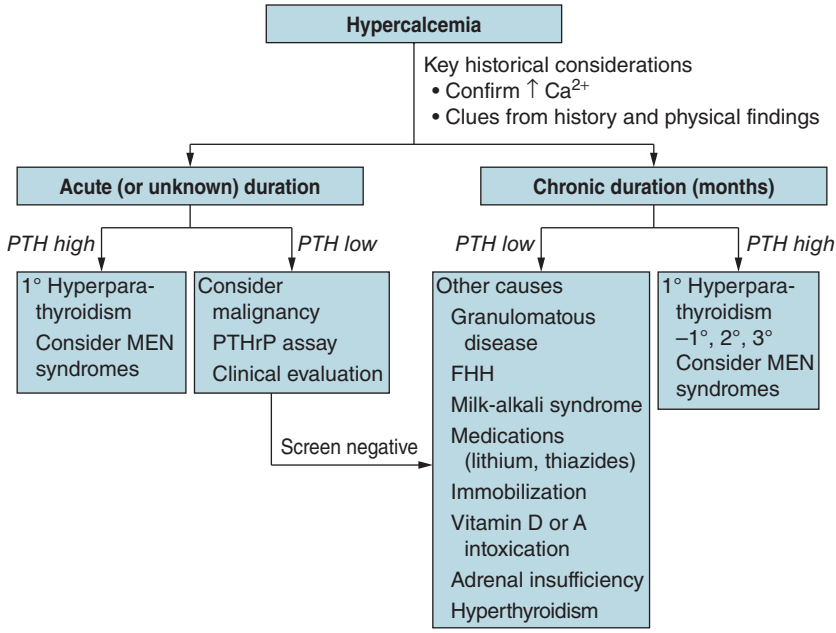


Figure 50–2. Algorithm for evaluation of patients with hypercalcemia. FHH, familial hypocalciuric hypercalcemia; MEN, multiple endocrine neoplasia; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein. (Reproduced with permission, from Braunwald E, Fauci AS, Kasper KL, et al. *Harrison's Principles of Internal Medicine*. 16th ed. 2005. Copyright © McGraw Hill LLC. All rights reserved.)

monoclonal antibody spikes should be examined. Radiographs showing lytic or blastic lesions may be helpful. Finally, a bone marrow biopsy may be considered to confirm the diagnosis. Treatment then can be aimed at the underlying cause (Table 50–2).

Table 50–2 • TREATMENT OF SEVERE HYPERCALCEMIA

Treatment	Onset	Adverse Effects
Hydration ± loop diuretic	Acute (effect seen in hours)	Volume overload, electrolyte disturbances
Bisphosphonates	Subacute (1-2 d)	Hypophosphatemia, hypomagnesemia, hypocalcemia, osteonecrosis of jaw
Calcitonin	Acute (hours)	Efficacy short-lived (tachyphylaxis)
Glucocorticoids (effective in cancer-induced hypercalcemia)	Lengthy (days)	Hyperglycemia, osteoporosis, immune suppression
Dialysis (renal insufficiency)	Acute (hours)	Volume shifts, electrolyte disorders, complicated procedure

CLINICAL APPROACH TO MULTIPLE MYELOMA

Pathophysiology

Multiple myeloma is a neoplastic proliferation of plasma cells that usually produce monoclonal immunoglobulins. Patients typically present with **lytic bone lesions, hypercalcemia, renal insufficiency, anemia**, and an elevated globulin fraction on serum chemistries, which, if separated by electrophoresis and identified by immunofixation, shows a **monoclonal proliferation** (M-spike). The **diagnosis** of multiple myeloma requires laboratory and clinical criteria: a **monoclonal antibody spike** in the serum, or light chains in the urine; more than **10% clonal plasma cells in the bone marrow; and end-organ damage such as lytic bone lesions.**

Patients with lower level monoclonal immunoglobulin (Ig) A or IgG antibody production without the signs or symptoms of multiple myeloma have what is termed a *monoclonal gammopathy of undetermined significance* (**MGUS**). MGUS is much more common than myeloma, affecting up to 1% of the population older than 50 years or up to 10% of people older than age 75. Long-term studies demonstrated that approximately 1% per year of these patients with MGUS will progress to develop multiple myeloma.

Treatment

Patients with MGUS typically require no therapy. Some patients with myeloma with no bone lesions or other end-organ damage have an indolent course (**"smoldering myeloma"**) and can be **observed without treatment** for many years if asymptomatic. **Therapy for symptomatic multiple myeloma** includes evaluation for autologous stem cell transplant and induction chemotherapy with high-dose pulsed **dexamethasone**, in combination with thalidomide or lenalidomide, and bortezomib.

CASE CORRELATION

- See also Case 31 (Osteoarthritis/Degenerative Joint Disease) and Case 32 (Low Back Pain).

COMPREHENSION QUESTIONS

50.1 On routine blood work performed for a life insurance application, a 48-year-old premenopausal woman was found to have a calcium level of 12 mg/dL (normal 8.8-10.4 mg/dL) and a phosphate level of 2 mg/dL (normal 3.0-4.5 mg/dL). She is not anemic and has no symptoms. Her medical history is significant for osteoporosis, which was discovered on a dual-energy x-ray absorptiometry (DEXA) scan performed last year. Which of the following is the most likely cause of her hypercalcemia?

A. Multiple myeloma
B. Parathyroid adenoma
C. Familial hypocalciuric hypercalcemia
D. Sarcoidosis
E. Undiagnosed breast cancer

50.2 A 62-year-old asymptomatic woman is noted to have multiple myeloma and hypercalcemia but no bone lesions or end-organ damage. Which of the following therapies is useful for immediate treatment of the hypercalcemia?

A. Bisphosphonates
B. Erythropoietin
C. Dexamethasone plus thalidomide
D. Interferon-alpha
E. Observe without treatment since she is asymptomatic

50.3 A 22-year-old woman presents with a worsening cough over 6 weeks that did not improve with a course of antibiotics or antitussives. Her serum calcium level is found to be 12.5 mg/dL, and a chest x-ray reveals bilateral hilar lymphadenopathy. She has erythema nodosum on her legs. Which of the following is the most likely diagnosis?

A. Sarcoidosis
B. Mycoplasma pneumonia
C. Acute lymphoblastic leukemia
D. Squamous cell carcinoma of the lung
E. Pulmonary embolism

50.4 A 66-year-old man with known metastatic squamous cell carcinoma of the esophagus is brought to the emergency department for increasing lethargy and confusion. He is clinically dehydrated, his serum calcium level is 14 mg/dL, and his creatinine level is 2.5 mg/dL, though 1 month ago it was 0.9 mg/dL. Which therapy for his hypercalcemia should be instituted first?

A. Intravenous bisphosphonate
B. Intravenous furosemide
C. Glucocorticoids
D. Intravenous normal saline
E. Chemotherapy for squamous cell carcinoma

ANSWERS

50.1 **B.** This patient has an elevated serum calcium level and low phosphate level, which are likely due to an elevated parathyroid level. An asymptomatic and likely chronically elevated calcium level is most likely caused by primary hyperparathyroidism due to a parathyroid adenoma. The hypercalcemia is presumed to be chronic because she has osteoporosis and is premenopausal.

Multiple myeloma (answer A) usually leads to elevated calcium and phosphate levels and lytic lesions of the bones. Familial hypocalciuric hypercalcemia (answer C) can also lead to elevated serum calcium and low serum phosphate levels, but it is usually asymptomatic and is far rarer than primary hyperparathyroidism. Sarcoidosis (answer D) is a granulomatous disease that is associated with an elevated calcitriol production leading to increased serum calcium and phosphate as well as increased $1,25(OH)_2$ vitamin D; osteoporosis is not seen. Undiagnosed breast cancer (answer E) with metastases to the bones can lead to elevated serum calcium and phosphate levels; this is less likely.

50.2 **A.** Bisphosphonates are helpful in controlling hypercalcemia through inhibition of osteoclastic bone reabsorption. Dexamethasone, in combination with thalidomide (answer C), is useful in treatment of the myeloma, with a slower effect on the calcium level. Erythropoietin (answer B) is inappropriate and is used to increase synthesis of red blood cells in those with renal failure. Interferon-alpha (answer D) is also not a treatment for hypercalcemia but is used for some cancers such as kidney, melanoma, carcinoid, and some lymphomas. Though the patient has no symptoms, observing alone (answer E) is not appropriate in presence of hypercalcemia.

50.3 **A.** Both sarcoidosis and lymphoma can present with cough, dyspnea, and hilar adenopathy on chest x-ray. In approximately 10% of cases, sarcoidosis can cause elevated calcium levels through the production of 1,25-vitamin D that occurs in the macrophages of the granulomas. This can also be seen in granulomas caused by tuberculosis and in lymphoma. Leukemia (answer C) usually does not present in this manner, although it can cause hypercalcemia. Squamous cell carcinoma of the lung (answer D) would be unusual in a patient of this age, and the radiographic presentation is atypical. The case scenario is consistent with Lofgren syndrome, an acute presentation of sarcoidosis, which includes hilar adenopathy, erythema nodosum, migratory polyarthralgia, and fever, seen most often in women. Neither pneumonia (answer B) nor pulmonary embolism (answer E) is associated with hypercalcemia.

50.4 **D.** Although all of the other therapies listed may be helpful in the treatment of hypercalcemia, given the clinical findings of dehydration and elevated creatinine level with a history of previously normal renal function, volume expansion with normal saline would correct the dehydration and presumed prerenal azotemia, allowing the kidneys to more efficiently excrete calcium. Other therapies (answers A, B, C, E) can be added if the response to normal saline alone is insufficient.

CLINICAL PEARLS

- Hypercalcemia that is acutely symptomatic is most likely caused by cancer.
- Asymptomatic hypercalcemia is most likely caused by primary hyperparathyroidism.
- In primary hyperparathyroidism, serum PTH and calcium levels are elevated, and phosphate levels are decreased. In malignancy-related hypercalcemia, the calcium level is high and PTH levels are suppressed.
- Symptoms of hyperparathyroidism can be remembered as "stones, moans, groans, bones, and psychiatric overtones."
- MGUS and symptomatic multiple myeloma are on opposite ends of a spectrum of neoplastic disease of plasma cells.
- The classic triad of multiple myeloma consists of bone pain due to lytic lesions, anemia, and renal insufficiency.

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CASE 51

A 52-year-old woman who presents for her yearly physical examination. She has been doing well and has no complaints today. Her medical history is notable only for borderline hypertension and moderate obesity. Last year, her fasting lipid profile was acceptable for someone without known risk factors for coronary artery disease. Her mother and older brother have diabetes and hypertension. At prior visits, you see that your preceptor has counseled her on a low-calorie, low-fat diet and recommended that she start an exercise program. However, the patient says she has not made any of these recommended changes. With her full-time job and three children, she finds it difficult to exercise, and she admits that her family eats out frequently. Today, her blood pressure is 140/92 mm Hg. Her body mass index (BMI) is 29 kg/m^2. Her examination is notable for acanthosis nigricans at the neck but otherwise is normal. A Papanicolaou (Pap) smear is performed, and a mammogram is offered. The patient has not eaten yet today, so on your preceptor's recommendation, a fasting plasma glucose test is performed, and the result is 140 mg/dL.

- What is the most likely diagnosis?
- What is your next step?

ANSWERS TO CASE 51:
Type 2 Diabetes Diagnosis and Management

Summary: A 52-year-old woman presents for her yearly physical examination with

- Medical history notable only for borderline hypertension and moderate obesity
- Family history of diabetes and hypertension
- Poor adherence to the recommended lifestyle changes
- Blood pressure of 140/92 mm Hg and BMI of 29 kg/m^2
- Acanthosis nigricans at the neck, suggesting insulin resistance
- Fasting plasma glucose level of 140 mg/dL, consistent with diabetes mellitus

Most likely diagnosis: Given her obesity, family history, and the finding of acanthosis nigricans, this patient most likely has type 2 diabetes. Diagnostic criteria for diabetes as defined by the American Diabetes Association (ADA) include (1) hemoglobin A_{1C} greater than 6.5%, (2) fasting plasma glucose of 126 mg/dL or greater, (3) 2-hour plasma glucose of 200 mg/dL or greater during oral glucose tolerance test, or (4) a random plasma glucose of 200 mg/dL in the setting of hyperglycemic symptoms.

Next step: Dietary counseling, assess for end-organ disease, and check hemoglobin A_{1C} (Hb A_{1C}).

ANALYSIS

Objectives

1. Recognize the diagnostic criteria for type 2 diabetes. (EPA 3)
2. Describe the initial medical management of diabetes. (EPA 4)
3. Understand cardiovascular risk modification in diabetic patients. (EPA 4, 12)
4. Understand the prevention of microvascular complications of diabetes. (EPA 12)

Considerations

This patient has a diagnosis of diabetes mellitus unless there was a laboratory error (patient not truly fasting). If this patient's diagnosis of diabetes is confirmed, she will require patient education, lifestyle modification, and medical therapy to prevent acute and chronic complications of diabetes. Strict glycemic control can reduce the incidence of microvascular complications such as retinopathy and nephropathy. In addition, patients with diabetes are among the highest at risk for cardiovascular disease, so risk factor modifications, such as smoking cessation and lowering of cholesterol, are essential. **Diabetes confers the same level of risk for coronary events, such as heart attack, as in patients with established coronary artery disease and no prior diabetes.** In patients with diabetes, the target blood pressure is generally less than 130/80 mm Hg, and the percentage of low-density lipoprotein (LDL)

cholesterol lowering should be based on the calculated atherosclerotic cardiovascular disease risk.

APPROACH TO: Diabetes Mellitus

DEFINITIONS

TYPE 1 DIABETES: Autoimmune destruction of the pancreatic beta cells and complete loss of endogenous insulin production. The presentation of this type of diabetes usually is acute, with hyperglycemia and metabolic acidosis. These patients are dependent on exogenous insulin delivery.

TYPE 2 DIABETES: Heterogeneous syndrome consisting of insulin resistance, progressively decreased insulin secretion, increased hepatic gluconeogenesis, and multiple other defects; it is exacerbated by genetic factors, obesity, and/or lack of physical activity. Oral medications and injectable incretin mimetic drugs that address specific defects of type 2 diabetes are useful. Exogenous insulin may be used when oral drugs and incretin mimetic medications are no longer sufficient for adequate glycemic control.

CLINICAL APPROACH

Epidemiology

As the prevalence of obesity increases in the American population, so does the prevalence of type 2 diabetes. Ninety percent of all new cases of diabetes diagnosed in the United States are type 2, and it is estimated that this disease affects approximately 30.3 million people in the United States. **Diabetes is the leading cause of blindness, renal failure, and nontraumatic amputations of the lower extremities.** It is a major risk factor in patients with coronary artery disease, peripheral vascular disease, and stroke.

In contrast to type 1 diabetics, patients with type 2 diabetes usually have a **prolonged asymptomatic phase**. During these years of asymptomatic hyperglycemia, however, organ damage begins to occur.

Screening. The ADA recommends screening overweight and obese adults with one of the following risk factors: hypertension, HDL level below 35 mg/dL, hypertriglyceridemia above 250 mg/dL, first-degree relative with diabetes, being a member of a high-risk ethnic/race group (ie, African Americans, Hispanics, American Indians, Asian Americans, or Pacific Islanders), prediabetes, physical inactivity, history of gestational diabetes, history of cardiovascular disease, history of polycystic ovarian syndrome, or other insulin-resistant condition (eg, acanthosis nigricans, severe obesity).

Repeat screening should be done at least yearly for prediabetes and at least every 3 years for a history of gestational diabetes. For all other adult patients, the ADA recommends screening start at age 45 with a minimum of 3-year intervals between tests.

Older children and adolescents who are overweight/obese and exhibit an aforementioned risk factor should also be screened.

Pathophysiology

Most patients with type 2 diabetes mellitus are insulin resistant and hyperinsulinemic for years before developing overt diabetes. They are able to maintain normoglycemia for a long time, then develop postprandial hyperglycemia and later both postprandial and fasting hyperglycemia (eg, hyperglycemia all the time). Thus, a **glucose tolerance test** to detect postprandial hyperglycemia would be the most sensitive test for diabetes mellitus, but it is time consuming and difficult to perform in a clinical practice. The **fasting plasma glucose** is a more specific test. **Hemoglobin A_{1C}** > 6.5% has now also been recognized as an acceptable diagnostic criterion (Table 51–1). In the setting of hyperglycemia symptoms, a random plasma glucose above 200 mg/dL is enough for diagnosis. If there are no clear symptoms of hyperglycemia, the diagnosis of diabetes should be confirmed on a subsequent day by repeat measurement, repeating the same test for confirmation. However, if two different tests (eg, fasting glucose and A_{1C}) are available and are concordant for the diagnosis of diabetes, additional testing is not needed.

By using these tests, patients can be classified into one of three categories: (1) normal, (2) impaired glucose tolerance/impaired fasting glucose (eg, "prediabetic"), or (3) diabetic. Increased risk for microvascular complications of hyperglycemia is seen at a fasting glucose more than 126 mg/dL or Hb A_{1C} > 6.5%. Once diabetes is diagnosed, therapy is instituted with three major goals, which are listed below.

1. Prevention of acute complications of hyperglycemia (eg, diabetic ketoacidosis [DKA] or nonketotic hyperosmolar hyperglycemia) or hypoglycemia
2. Prevention of long-term complications of hyperglycemia, for example, microvascular disease such as retinopathy or nephropathy
3. Prevention of long-term complications of macrovascular disease, for example, cardiovascular or cerebrovascular disease

Treatment

The foundation of diabetes therapy is **dietary and lifestyle modifications**. Exercise and even small amounts of weight loss can lower blood pressure and improve

Table 51–1 • TESTS FOR DIAGNOSING DIABETES

Test	Normal	Impaired Fasting Glucose/Impaired Glucose Tolerance ("Prediabetes")	Diabetes
Fasting plasma glucose	< 100 mg/dL	100-125 mg/dL	> 126 mg/dL
Hemoglobin A_{1C}	< 5.6%	5.75%-6.4%	> 6.5%
2-h glucose tolerance test (75-g load)	< 140 mg/dL	140-199 mg/dL	> 200 mg/dL

glucose control. Patients should be given instruction in nutrition and encouraged to change sedentary lifestyles.

However, most people with diabetes will eventually require medical therapy, and many patients will eventually require a combination of at least two medications. Because of the difficulty in achieving and sustaining glycemic targets and achieving significant weight loss, the ADA recommends that **metformin** should be initiated concurrently with lifestyle intervention at the time of diagnosis.

The **glycemic goal is individualized based on multiple factors (eg, hypoglycemia risk, life expectancy, other disease comorbidities) but is generally a hemoglobin A_{1C} < 7%.** If patients fail to achieve the glycemic goal with initial therapy, including lifestyle modification and metformin, therapeutic options include adding a second oral or injectable agent, including insulin, or switching to insulin monotherapy. A list of therapeutic agents for diabetes is included in Table 51–2.

Table 51–2 • MEDICATIONS AVAILABLE IN THE UNITED STATES FOR TREATMENT OF TYPE 2 DIABETES

Medication	Mechanism of Action/ Indications	Special Considerations	Relative Cost
Insulin	↑ glucose utilization, ↓ hepatic glucose production	Weight gain, risk of hypoglycemia, need for frequent home glucose monitoring	$-$$$
Sulfonylureas (glimepiride, glipizide, glyburide)	Augment patient's own insulin production, work at the pancreatic beta cells	Can cause hypoglycemia; can accumulate in renal insufficiency and cause prolonged hypoglycemia; best for young patients with fasting plasma glucose < 300 mg/dL	$-$$
Metformin	Decreases gluconeogenesis in the liver; decreases insulin resistance	Risk of lactic acidosis in patients with renal insufficiency or liver dysfunction	$
alpha-Glucosidase inhibitors (acarbose)	Inhibit breakdown of complex carbohydrates in the GI tract, reduce postprandial hyperglycemia	Can cause GI distress, flatulence, dose-dependent hepatotoxicity	$$
Thiazolidinediones (pioglitazone, rosiglitazone)	Promote skeletal muscle glucose uptake and decrease insulin resistance	Hepatotoxicity; edema, increased HF risk	$$-$$$
GLP-1 agonists (exenatide, liraglutide)	↑ insulin, ↓ glucagon, slow gastric emptying	Requires injection, nausea, risk of pancreatitis	$$$$
DPP-4 inhibitors (saxagliptin, sitagliptin)	Prolong endogenous GLP-1 action preventing its breakdown	No hypoglycemia or weight gain, reduce dose in renal insufficiency	$$$$
SGLT2 inhibitors (canagliflozin, empagliflozin)	Promote urinary loss of glucose, reduce cardiovascular risk	Reportedly increase urinary infections and risk for diabetic ketoacidosis	$$$$

Abbreviation: HF, heart failure; GI, gastrointestinal.

When diabetes is diagnosed, other cardiovascular risk factors should be assessed. Blood pressure and lipid levels should be measured. The cardiovascular risk in those with diabetes is equivalent to those with known coronary artery disease. Statins are the preferred LDL reduction medication, with goal reduction depending on the intensity of the regimen. Moderate-dose statins should aim to reduce LDL by 30% to 50%, while high-intensity statins should aim for 50% reduction or more.

The desired **blood pressure goal in an individual with diabetes and hypertension is < 140/90 mm Hg if the 10-year atherosclerotic cardiovascular risk is less than 15%; otherwise, one should pursue a lower target of < 130/80 mm Hg** if it can be safely attained. Several randomized trials have demonstrated a **benefit for angiotensin-converting enzyme (ACE) inhibitors** and **angiotensin receptor blockers** in preventing the progression of proteinuria and kidney disease.

Other routine care in diabetic patients includes frequent primary care provider visits, at least every 3 to 6 months depending on the patient's glucose control, at least **yearly ophthalmologic examinations** to screen for retinopathy, yearly urine screens to detect microalbuminuria, and **yearly foot examinations** to detect peripheral neuropathy (if patient has no prior neuropathy). **Hemoglobin A_{1C}** should be checked at least **every 3 to 6 months**, depending on the patient's glucose control. This test allows the clinician to know the general glucose control over the preceding 2 to 3 months.

Patients with established neuropathy should be examined at every visit and be instructed on daily self-examination and prevention of injury. In fact, neuropathy is the main risk factor for the development of a foot ulcer and subsequent development of a wound; this can progress into a nonhealing ulcer that sometimes requires surgical amputation. Thus, careful foot care and daily examination are the most important preventive steps.

CASE CORRELATION

- See also Case 48 (Oligomenorrhea Caused by Hypothyroidism and Hyperprolactinemia), Case 52 (Diabetic Ketoacidosis, Type 1 Diabetes), and Case 53 (Thyrotoxicosis/Graves Disease).

COMPREHENSION QUESTIONS

51.1 A 45-year-old man comes in for counseling about his fasting plasma glucose test after a routine health maintenance examination. On two separate occasions, the result has been 115 mg/dL and 120 mg/dL. Which of the following is the most appropriate next step at this time?

A. Reassurance that these are normal blood sugars.

B. Recommend weight loss, an ADA diet, and exercise.

C. Diagnose diabetes mellitus and start on a sulfonylurea.

D. Recommend cardiac stress testing.

E. Obtain stat arterial blood gas and serum ketone levels.

51.2 A 45-year-old obese woman presents for follow-up for her diabetes. She currently takes metformin 1000 mg twice per day, and her fasting morning glucose runs approximately 170 to 200 mg/dL. Her last serum Hb A_{1C} level was 7.9%. She states that she conscientiously follows her diet and walks 30 minutes to 1 hour daily. Which of the following is the best next step in her care?

A. Refer to an endocrinologist for an insulin pump.

B. Stop metformin and start on glimepiride.

C. Add a second agent for the treatment of her diabetes.

D. Hospitalize her urgently.

51.3 A 75-year-old woman with type 2 diabetes for approximately 20 years, diabetic retinopathy, and diabetic nephropathy is brought into the clinic by her daughter for follow-up. The patient's last serum creatinine level was 2.2 mg/dL. The patient currently takes a glyburide for her diabetes and lisinopril for her proteinuria. Her daughter reports that on three occasions in the past 2 weeks, her mother became sweaty, shaky, and confused, which resolved when she was given some orange juice. Which of the following conditions is most likely to be contributing to these episodes?

A. Excess caloric oral intake

B. Interaction between the ACE inhibitor and the sulfonylurea agents

C. Worsening renal function

D. Hyperglycemic amnesia

51.4 A 42-year-old woman with a past medical history of gestational diabetes during her last pregnancy 6 years previously usually has screening for type 2 diabetes every year. Which of the following screening methods has the highest sensitivity for diagnosing type 2 diabetes?

A. Fasting serum glucose

B. 2-hour glucose tolerance test

C. Hemoglobin A_{1C}

D. Random glucose

51.5 A 36-year-old man has been recently diagnosed with type 2 diabetes. If not vaccinated previously, which of the following immunizations is most important to administer?

A. Toxoplasmosis

B. Human papilloma virus (HPV)

C. Hepatitis B

D. Rubella

ANSWERS

51.1 **B.** By diagnostic criteria, this patient falls into the definition of impaired fasting glucose, which is between 100 and 125 mg/dL. A normal fasting glucose level is < 100 mg/dL; diabetes can be diagnosed by a fasting glucose level of 126 mg/dL or higher. Although she does not yet meet the criteria for diabetes (answer C), she is at greater risk for developing diabetes in the future and for macrovascular disease. Intensive lifestyle changes (diet and exercise for 30 minutes per day, 5 days per week) can prevent or delay the development of diabetes. Patients should be monitored annually to screen for progression to diabetes. Cardiac stress testing (answer D) is indicated if there is chest pain or other suspicion of coronary heart disease. This patient does not have normal blood sugars (answer A) or DKA (answer E).

51.2 **C.** When patients fail to achieve glycemic goal (Hb A_{1C} < 7%) using metformin and lifestyle modifications, the next step is to add a second agent (not discontinue metformin, as in answer B). Among the choices are glucagon-like peptide 1 (GLP-1) receptor agonists (eg, liraglutide), dipeptidyl peptidase 4 (DPP-4) inhibitors (eg, sitagliptin), sodium-glucose co-transporter-2 (SGLT-2) inhibitors (eg, empagliflozin), thiazolidinediones (eg, pioglitazone), sulfonylureas (eg, glipizide), and once-daily basal insulin injection (a long-acting insulin such as NPH, glargine, or detemir). If a patient has known atherosclerotic cardiovascular disease, a GLP-1 receptor agonist or SGLT-2 is preferred. If patient has heart failure or chronic kidney disease, consider an SGLT-2 inhibitor (answer B). An endocrine consultation and an insulin pump (answer A) in a type 2 diabetic are mainly needed because of failure to achieve glycemic control with multiple injections of insulin. Hospitalization for an urgent condition (answer D) is indicated if there is suspicion of a serious complication, such as HHNS.

51.3 **C.** Sulfonylureas have long half-lives and can cause prolonged hypoglycemia in elderly patients as well in those with **renal insufficiency; glyburide is notorious for this complication.** For these reasons, many practitioners will avoid sulfonylurea agents (even newer ones) in elderly patients. Another hypoglycemic agent, such as insulin, may be more appropriate in this patient, as well as less-intensive control, aiming for an Hb A_{1C} of 8% instead of 7%. If a sulfonylurea agent must be used for some reason, then glipizide and glimepiride are the agents of choice with chronic kidney disease. Excess caloric intake (answer A) would not lead to hypoglycemia, but rather hyperglycemia. ACE inhibitors and sulfonylurea agents (answer B) may lead to a temporary sensitization of the sulfonylurea agent, but this usually resolves after a short time. Hyperglycemic amnesia (answer D) presents a cognitive decline due to hyperglycemia; this patient's symptoms are much more consistent with hypoglycemia.

51.4 **B.** The 2-hour oral glucose tolerance test is used as the reference standard and has the highest sensitivity for the diagnosis of type 2 diabetes. Even with this "gold standard," there are undiagnosed diabetics. Fasting glucose

(answer A) is a fairly good test with a sensitivity of about 82% and has the advantage of reproducibility. Hemoglobin A_{1C} (answer C) is also an acceptable test; however, the sensitivity is around 60% in patients with a hemoglobin A_{1C} above 6.5%. The hemoglobin A_{1C} is additionally advantageous because serum levels correlate with long-term outcomes. A random glucose (answer D) is only about 50% sensitive and is seldom used as a screening test.

51.5 **C.** A patient who is diagnosed with diabetes should receive the hepatitis B vaccine as soon as feasible if not vaccinated previously. The Centers for Disease Control and Prevention recommends hepatitis B vaccination for diabetics aged 18 to 59, and consideration for those > 60 years due to the increased risk of hepatitis B case fatality rate in diabetics. Diabetes confers a 60% higher infection rate versus nondiabetics. Diabetics should receive an annual influenza vaccination as well as the pneumococcal vaccine after the age of 65 if the first dose was administered prior to the age of 65. HPV vaccine (answer B) is recommended for patients between the ages of 11 and 26 years. Rubella vaccine (answer D) is routinely recommended in men; however, women in the childbearing age who are nonimmune should also be vaccinated. Toxoplasmosis vaccine (answer A) does not exist. In summary, diabetics should receive five vaccines: annual influenza vaccine, Tdap (tetanus, diphtheria, acellular pertussis) vaccine, zoster vaccine, pneumococcal vaccine, and the hepatitis B vaccine.

CLINICAL PEARLS

- Type 2 diabetes has a prolonged asymptomatic stage during which microvascular disease (retinopathy, nephropathy, or neuropathy) can occur. Clinicians should have a high index of suspicion and screen patients with risk factors.
- Lifestyle modification and metformin are the initial therapy for most patients when they are diagnosed with type 2 diabetes.
- The major cause of morbidity and mortality in patients with type 2 diabetes mellitus is macrovascular disease, such as coronary artery disease, stroke, and peripheral vascular disease, so aggressive cardiovascular risk factor reduction is essential.
- Glycemic goals are individualized for each patient but generally include Hb $A_{1C} < 7\%$.
- Blood pressure target should be < 140/90 or < 130/80 mm Hg (depending on cardiovascular risk), and LDL cholesterol should be lowered (usually by 30% to 50%) with a statin, based on the patient's atherosclerotic cardiovascular disease risk.

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CASE 52

An 18-year-old woman is brought to the emergency department by her mother because the daughter seems confused and is behaving strangely. The mother reports the patient has always been healthy and has no significant medical history, but she has lost 20 lb recently without trying and has been complaining of fatigue for 2 or 3 weeks. The patient had attributed the fatigue to sleep disturbance, as recently she has been getting up several times at night to urinate. This morning, the mother found the patient in her room, complaining of abdominal pain and vomiting. She appeared confused and did not know that today was a school day.

On examination, the patient is slender and lying on a stretcher with her eyes closed, but she is responsive to questions. She is afebrile and has a heart rate (HR) of 118 beats per minute (bpm), blood pressure (BP) of 125/84 mm Hg, and deep and rapid respirations at the rate of 24 breaths per minute. Upon standing, her HR rises to 145 bpm, and her BP falls to 110/80 mm Hg. Her fundoscopic examination is normal, her oral mucosa is dry, and her neck veins are flat. Her chest is clear to auscultation, and her heart is tachycardic with a regular rhythm and no murmur. Her abdomen is soft with active bowel sounds and mild diffuse tenderness, but no guarding or rebound. Her neurologic examination reveals no focal deficits.

Laboratory study results include serum Na^+ 131 mEq/L, K^+ 5.3 mEq/L, Cl^- 95 mEq/L, HCO_3 9 mEq/L, blood urea nitrogen (BUN) 35 mg/dL, creatinine 1.3 mg/dL, and glucose 475 mg/dL. Arterial blood gas (ABG) reveals pH 7.12 with PCO_2 24 mm Hg and PO_2 95 mm Hg. Urine drug screen and urine pregnancy test are negative, and urinalysis shows no hematuria or pyuria, but 3+ glucose and 3+ ketones. A chest radiograph is normal, and plain film of the abdomen has a nonspecific gas pattern but no signs of obstruction.

- What is the most likely diagnosis?
- What is the underlying pathophysiology of this diagnosis?
- What are some known precipitating factors associated with this diagnosis?
- What is your next step in medical management?

ANSWERS TO CASE 52:
Diabetic Ketoacidosis, Type 1 Diabetes

Summary: An 18-year-old woman presents with

- A few weeks of unintentional weight loss, nocturia, and polyuria
- Hyperglycemia that likely represents new-onset diabetes mellitus, probably type 1
- Hypovolemia due to osmotic diuresis
- An anion gap metabolic acidosis due to an increase in ketoacid production
- Acute altered mental status (confusion)
- Abdominal pain, vomiting, and labored breathing

Most likely diagnosis: Diabetic ketoacidosis (DKA).

Underlying pathophysiology: Absolute insulin deficiency favors glycogenolysis, gluconeogenesis, and ketosis, resulting in hyperglycemia, osmotic diuresis, and an anion gap metabolic acidosis.

Known precipitating factors: New-onset diabetes mellitus (typically type 1), inadequate insulin treatment or nonadherence, poor socioeconomic status, infection, pancreatitis, volume depletion, cocaine use, pregnancy, myocardial infarction, or cerebrovascular accident.

Next step in medical management: Aggressive hydration to improve her volume status and insulin therapy to resolve the ketoacidosis.

ANALYSIS

Objectives

1. Differentiate causes of anion gap metabolic acidosis. (EPA 2)
2. Differentiate DKA from nonketotic hyperosmolar hyperglycemia and alcoholic ketoacidosis. (EPA 2, 3)
3. Manage DKA by restoring volume, replacing electrolyte, and treating ketosis and hyperglycemia. (EPA 4, 10)
4. List the complications of DKA and of improper management. (EPA 12)

Considerations

DKA occurs as a result of severe insulin deficiency and may be the initial presentation of diabetes mellitus, as in this patient. In all patients with DKA, one must be alert for precipitating factors, such as infection, pregnancy, or severe physiologic stressors, such as myocardial infarction. The diagnostic criteria include arterial pH < 7.3, low serum bicarbonate with an anion gap, glucose > 250 mg/dL, elevated serum ketones (> 5 mEq/L), and elevated beta-hydroxybutyrate (> 3 mmol/L). The patient in this scenario has significant DKA based on the pH of 7.11. The bicarbonate of 9 mEq/L and anion gap of 27 mEq/L confirm metabolic

acidosis from accumulation of organic acids. This patient needs immediate fluid repletion with normal saline (NS) and insulin infusion. Initial testing should include serum glucose, serum electrolytes, magnesium, phosphorus, amylase and lipase, urine dipstick, serum ketones, ABG, complete blood count (CBC), BUN and creatinine, urine and/or blood cultures, and an electrocardiogram (ECG).

APPROACH TO: Diabetic Ketoacidosis

DEFINITIONS

DIABETIC KETOACIDOSIS: A syndrome of hyperglycemia, anion gap metabolic acidosis, and ketone bodies in the serum, caused by insufficient insulin levels.

KUSSMAUL RESPIRATIONS: Deep and rapid breathing that represents hyperventilation in an attempt to generate a respiratory alkalosis to compensate for the metabolic acidosis.

CLINICAL APPROACH

Pathophysiology

DKA is a hyperglycemic complication of diabetes mellitus caused by a significant insulin deficiency and characterized by **anion gap metabolic acidosis, hyperglycemia, and ketosis.** It is a medical emergency, with an overall mortality rate less than 5% if patients receive prompt and appropriate medical treatment. Most episodes are preventable, and many deaths are avoidable with proper attention to detail during management.

Normal Physiology. In the normal physiologic state, there is a fine balance between anabolic and catabolic hormones. In the fed state, anabolic actions of insulin predominate. Glycogenesis, lipogenesis, and protein synthesis all are increased. This results in storage of energy reserves in the form of triglycerides and glycogen.

In the fasting state, insulin serves to inhibit lipolysis, ketogenesis, gluconeogenesis, glycogenolysis, and proteolysis. These effects are critical in controlling the rate of breakdown of energy stores under the influence of catabolic hormones. **Glucagon is the most important catabolic hormone.** In the fasting state, it maintains normal glucose levels by stimulating hepatic gluconeogenesis and glycogenolysis.

Diabetic Ketoacidosis. Diabetes mellitus is the condition of relative or absolute insulin deficiency. When there is a severe insulin deficiency and a relative excess of glucagon, lipolysis is enhanced, causing release of free fatty acids. Oxidation of the fatty acids produces ketones, such as acetoacetate and beta-hydroxybutyrate, which are organic acids often referred to as **ketoacids.** The excess of these ketoacids can produce a life-threatening metabolic acidosis. In addition, hyperglycemia produces an osmotic diuresis, which causes severe volume depletion and electrolyte deficiencies by washing extracellular sodium, potassium, magnesium, phosphate,

and water out of the body. The combination of acidosis, hypovolemia, and electrolyte deficiencies can lead to **cardiovascular collapse, the most common cause of death in DKA.**

Patients with diabetes have an underlying impairment in glucose metabolism and, when challenged by a stressor, an increase in insulin requirements. If they are unable to meet these insulin requirements, DKA may result. It is important to correct precipitating factors in order to restore metabolic balance. Identifiable sources of infection should be treated aggressively. Possible presence of ischemia and infarction should be evaluated and treated appropriately with help from specialists as needed. **The most common precipitating events are infections** such as **pneumonia or urinary tract infection, vascular disorders such as myocardial infarction, or other stressors such as trauma.**

DKA may be the presentation of new-onset diabetes; it may also occur in patients with established diabetes because of failure to use insulin or because of the use of other medications (eg, glucocorticoids) that interfere with insulin action.

Clinical Presentation

An episode of DKA evolves over a short period of time, typically in less than 24 hours. The patient with DKA has the signs and symptoms of hyperglycemia, acidosis, and dehydration. Polyuria, polydipsia, weight loss, visual blurring, and alteration in mental status are related to hyperglycemia and osmotic diuresis. Nausea, vomiting, abdominal pain, fatigue, malaise, and shortness of breath may be related to the acidosis.

Typical signs include decreased skin turgor, dry mucous membranes, hypotension, and tachycardia related to volume depletion. **Kussmaul respirations**, deep and rapid breathing, represent hyperventilation in an attempt to generate a respiratory alkalosis to compensate for the metabolic acidosis. One may also note the **fruity breath odor** typical of ketosis.

Laboratory Values. Laboratory values show hyperglycemia (usually > 250 mg/dL), acidosis (pH < 7.3), anion gap (usually > 15 mmol/L), and ketonemia. The most important laboratory parameters are the degree of acidosis, the anion gap, and the serum potassium level. Beta-hydroxybutyrate assay may be obtained in order to quantify the severity of the ketonemia present. Patients with a very low pH (< 7.0) are severely acidotic and have a worse prognosis. The lower pH is a result of the higher concentration of ketoacids, which are estimated using the anion gap.

Anion Gap. The first step in evaluating any patient with metabolic acidosis should be calculation of the **anion gap.** This concept is based on the principle of electrical neutrality, that is, all the cations must equal all the anions. The anion gap estimates those negatively charged particles that are not routinely measured and can be calculated using the following calculation:

$$\text{Anion Gap} = [\text{Na}] - [\text{Cl} + \text{HCO}_3]$$

The normal anion gap is 10 to 12 mmol/L. When it is elevated, there is an excess of unmeasured anions, which typically occurs because of one of the four causes (Table 52–1).

Table 52–1 • CAUSES OF HIGH ANION GAP METABOLIC ACIDOSIS

Lactic acidosis
Ketoacidosis • Diabetic • Alcoholic • Starvation
Toxins • Ethylene glycol • Methanol • Salicylates
Renal failure (acute or chronic)

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Lactic acidosis results from severe tissue hypoxia, as in septic shock or carbon monoxide poisoning, or from hepatic failure and subsequent inability to metabolize lactate. Ketoacidosis most commonly occurs as an acute complication of uncontrolled diabetes, but it also can be seen in starvation and alcoholism. The ingested toxins may be organic acids themselves, such as salicylic acid, or have acidic metabolites, such as formic acid from methanol. Renal failure leads to an inability to excrete organic acids as well as inorganic acids such as phosphates (often without an anion gap).

In patients with DKA, total body potassium stores are depleted because of urinary losses, and potassium replacement will always be necessary. Initially, the measured serum potassium levels may be high despite the total body potassium deficit because of acidosis resulting in movement of potassium from the intracellular to the extracellular compartment. With the correction of the acidosis and the administration of insulin, which drives potassium intracellularly, **serum potassium levels will fall rapidly**.

The serum sodium level can be variable. Hyperglycemia causes water to move extracellularly, which can lead to hyponatremia. Similarly, phosphate levels can be variable in the presence of body store deficits, with the extracellular movement of phosphate caused by catabolic state. BUN and creatinine levels are elevated, reflecting hypovolemia. Serum acetoacetate may cause a false elevation in the serum creatinine level because of interference with the assay.

Treatment

The goal of treatment is restoration of metabolic homeostasis with correction of precipitating events and biochemical deficits, which consists of the following:

1. Replacement of fluid losses with improvement of circulatory volume
2. Correction of hyperglycemia and, in turn, plasma osmolality
3. Replacement of electrolyte losses
4. Clearance of serum ketones
5. Identification and treatment of precipitating cause and complications

Close monitoring of the patient is important. A flow sheet recording vital signs, fluid input and output, insulin dosage, and metabolic progress is important. Serum glucose concentration should be measured every 1 hour, and levels of serum electrolytes and phosphate must be assessed every 3 to 5 hours. Common ketone assays, blood, urine, and/or sputum cultures should be obtained if urine analysis or chest radiography indicates infection. Electrocardiography (ECG) should be checked to look for evidence of a cardiovascular event or arrhythmias due to metabolic derangement. Other investigations should be pursued as symptoms and signs warrant.

Fluids. **All patients with DKA are volume depleted** as a consequence of osmotic diuresis as well as from other ongoing losses, such as vomiting. Hydration improves renal perfusion and cardiac output, facilitating glucose excretion. Rehydration may also diminish insulin resistance by decreasing levels of counterregulatory hormones and hyperglycemia. Sudden reduction in hyperglycemia can lead to vascular collapse with a shift of water intracellularly. To avoid this, initial replacement fluid should be isotonic NS to correct circulatory volume deficit. **Over the first hour, 1 to 2 L of NS should be infused.** Following this, total body water deficit is corrected at the rate of 250 to 500 mL/h, depending on the state of hydration. The composition of fluid should be tailored according to serum sodium and chloride measurements. Hydration should be gentler in patients with heart failure or end-stage renal disease because such patients can easily be affected by fluid overload.

Insulin. The goal of therapy is a glucose reduction of 80 to 100 mg/dL/h. Use of continuous low-dose intravenous infusion of insulin is recommended because it reduces episodes of hypoglycemia and hypokalemia, and it allows for a more controlled reduction of serum glucose and osmolality. Intramuscular and subcutaneous routes can be used if tissue perfusion is adequate.

Insulin treatment may be initiated as an **intravenous bolus** of 0.1 to 0.15 U/kg. This should be followed by a **continuous infusion of 0.1 U/kg/h with hourly serum glucose determinations**. If blood glucose fails to decline at the desired rate, volume status should be reassessed, and the insulin infusion should be titrated accordingly. The rate of infusion should be decreased to 0.05 U/kg/h when the blood glucose level decreases to 250 to 300 mg/dL (if the acidosis is corrected). **Glucose levels fall more quickly than ketosis resolves.** Insulin is necessary for resolution of the ketoacidosis and can be coadministered with a glucose infusion until the anion gap is resolved. A 5% to 10% dextrose solution should be added to the hydrating solution when plasma glucose is less than 300 mg/dL.

One can judge the resolution of ketoacidosis when the bicarbonate is more than 18 mEq/L, the anion gap is less than 12, the patient feels better, and the vital signs are stabilized. **Serial determination of serum ketone levels is not clinically useful** in measuring response to therapy. Common ketone assays utilize nitroprusside, measuring acetoacetate and acetone, but not beta-hydroxybutyrate. Administration of insulin will induce oxidation of beta-hydroxybutyrate to acetoacetate, resulting in an increase in ketone levels despite effective therapy. When available, beta-hydroxybutyrate assay can be helpful, as a level greater than 3 mmol/L is shown to be highly sensitive and specific for DKA.

In the event serum ketone measurements are not available, one should be guided by normalizing the anion gap when making decisions about the rate of insulin infusion. Subcutaneous insulin should be given approximately 30 minutes before stopping insulin infusion to avoid rebound acidosis.

Bicarbonate. Bicarbonate therapy is controversial and should not be given to ketoacidotic patients unless their **arterial pH is less than 7.00** or other indications, such as cardiac instability or severe hyperkalemia, are present. Bicarbonate therapy can cause worsening hypokalemia, paradoxical central nervous system acidosis, and delay in ketone clearance.

Electrolytes. In DKA, there is a **deficit of total body potassium, phosphate, and magnesium**. Patients frequently have hyperkalemia as a result of acidosis, insulin deficiency, and hypertonicity that cause a shift of potassium extracellularly. During treatment, the plasma potassium concentration will fall as the metabolic abnormalities are corrected. Potassium should be added to initial intravenous fluids once the concentration is less than 5 mEq/L. Once adequate urine output is established, 20 to 40 mEq of potassium should be added to each liter of fluid. The goal is to maintain potassium in the range of 4 to 5 mEq/L. Cardiac monitoring is recommended in the presence of hypokalemia or hyperkalemia.

Other Electrolytes. Phosphate replacement should be given to patients with serum phosphate concentrations less than 1 mg/dL and to patients with moderate hypophosphatemia with concomitant hypoxia, anemia, or cardiorespiratory compromise. Careful monitoring of the serum calcium level is necessary with phosphate administration. Magnesium and calcium can be supplemented as needed.

Prevention. The major precipitating factors in the development of DKA are inadequate insulin treatment and infection. These events can be prevented by patient education and effective communication with a health care team. Sick-day management regarding dosing of insulin, blood glucose monitoring, avoiding prolonged fasting, and preventing dehydration should be addressed. Socioeconomic barriers contribute to the high rates of admission for DKA. Appropriate allocation of health care resources toward preventive strategies is needed.

Complications

Cerebral edema secondary to hyperglycemia and osmotic diuresis, acute respiratory distress syndrome, thromboembolism secondary to coagulation cascade and fibrinolysis derangement, fluid overload, and acute gastric dilation are rare, but serious, complications of DKA.

Other metabolic complications of deranged carbohydrate metabolism deserve mention at this point. The first is **hyperosmolar nonketotic diabetic coma**. This condition occurs mainly in patients with type 2 diabetes who become profoundly dehydrated because of osmotic diuresis. However, these patients have sufficient insulin action to prevent the development of ketoacidosis. They may present with glucose levels more than 1000 mg/dL, serum osmolarity more than 320 to 370 Osm/L, and neurologic symptoms ranging from confusion to seizures to coma. Compared to patients with DKA, they have a much larger fluid deficit, and therapy is primarily volume resuscitation with NS. Insulin is also used to reverse hyperglycemia but usually is given in lesser doses than is required for clearance of ketosis in DKA.

Alcoholic ketoacidosis develops in chronic alcoholics who are malnourished and have depleted glycogen stores. It is often seen in the setting of binge drinking, which may shift the ratio of the reduced form of nicotinamide adenine dinucleotide (NADH) to nicotinamide adenine dinucleotide (NAD), inhibiting gluconeogenesis. These patients develop an anion gap metabolic acidosis as a result of ketoacidosis and lactic acidosis. They present with the same symptoms of acidosis as do DKA patients, for example, abdominal pain, nausea, and vomiting, but with low, normal, or slightly elevated glucose levels (in contrast to DKA, in which the glucose level usually is markedly elevated). Treatment is administration of volume in the form of NS and glucose solution. Insulin administration is typically unnecessary. Thiamine may need to be coadministered.

CASE CORRELATION

- See also Case 41 (Urinary Tract Infection With Sepsis in the Elderly), Case 53 (Thyrotoxicosis/Graves Disease), and Case 59 (Delirium/Alcohol Withdrawal).

COMPREHENSION QUESTIONS

52.1 A 36-year-old woman is brought into the emergency department for lethargy. She is unable to respond to commands but does open her eyes to painful stimuli. On examination, her HR is 110 bpm, BP is 90/60 mm Hg, and respiratory rate (RR) is 24 breaths/min. An arterial blood gas reveals a pH of 7.28, pco_2 of 28 mm Hg, po_2 of 90 mm Hg, and HCO_3 of 22 mEq/L. Serum electrolytes reveal Na^+ 138 mEq/L, K^+ 3.8 mEq/L, Cl^- 105 mEq/L, and HCO_3 of 23 mEq/L. Which of the following is the most likely diagnosis that led to this patient's condition?

A. Diarrhea

B. Lactic acidosis

C. Diabetic ketoacidosis

D. Ethylene glycol ingestion

52.2 An 18-year-old man is being seen the emergency center for nausea, vomiting, lightheadedness, and fatigue. He is a known type 1 diabetic and states that he has been taking his insulin as scheduled. On examination, his BP is 80/40 mm Hg, temperature is 101 °F, HR is 120 bpm, and RR is 30 breaths/min. He has some adenopathy of the cervical area. Laboratory test values show an arterial pH of 7.20, po_2 of 100 mm Hg, pco_2 of 28 mm Hg, and HCO_3 of 12 mEq/L. His serum glucose level is 400 mg/dL. Which of the following is the most accurate statement regarding this patient's likely potassium status?

A. Likely to have a serum potassium level less than 3 mEq/L.

B. Likely to have a serum potassium level more than 7 mEq/L.

C. Likely to have a total body potassium deficit regardless of the serum level.

D. Serum level is likely to increase with correction of the acidosis.

52.3 An 11-year-old girl is being seen in the pediatric emergency department for near syncope. She is being followed for type 1 diabetes and is not very adherent to her medications or diet. Her current BP is 90/60 mm Hg, HR is 120 bpm, RR is 26 breaths/min, and temperature is afebrile. Based on an arterial blood gas with a pH of 7.23 and a serum glucose level of 550 mg/dL, she is diagnosed with DKA. Which of the following is the most important first step in the treatment of this patient?

A. Replacement of potassium

B. Intravenous fluid replacement

C. Replacement of phosphorus

D. Antibiotic therapy

52.4 A 59-year-old man with a long history of diabetes with chronic renal insufficiency due to diabetic nephropathy is seen in clinic for routine laboratory work. He is asymptomatic, but his glucose is elevated at 258 mg/dL. His other chemistries are as follows: sodium 135 mEq/L, potassium 5.4 mEq/L, chloride 108 mEq/L, and bicarbonate 18 mEq/L. His creatinine is stable at 2.1 mg/dL. Which of the following is the most likely cause of this patient's acidemia?

A. Diabetic ketoacidosis

B. Lactic acidosis

C. Type 4 renal tubular acidosis (RTA)

D. Accidental salicylate overdose

ANSWERS

52.1 **A.** This patient has a metabolic acidosis based on the low pH and the low pco_2 (partial respiratory compensation). The anion gap is calculated by the following formula: Anion Gap = $[Na^+] - [Cl^- + HCO_3]$. In this case, the patient's anion gap = 138 – (105 + 23) = 10, which is normal (recall

normal anion gap is 10-12). Diarrhea leads to bicarbonate loss and usually does not affect the anion gap. All other choices (answer B, lactic acidosis; answer C, DKA; and answer D, ethylene glycol ingestion) are causes of a high anion gap metabolic acidosis. Common causes can be remembered with the MUDPILES mnemonic (methanol, uremia, DKA, propylene glycol, iron/isoniazid/infection, lactic acidosis, ethylene glycol, salicylates).

52.2 **C.** Total body potassium usually is depleted regardless of the serum level due to urinary loss; an extracellular shift of potassium in the setting of acidosis may explain high serum potassium levels (answer B) upon diagnosis of DKA. Answer A (serum potassium < 3 mEq/L) would be unusual in light of the acidosis; the typical level would be normal. Answer D (serum potassium > 7 mEq/L) would be highly unusual, since this level of elevation would often lead to cardiac arrhythmias and possibly death; a mildly elevated or normal serum potassium level would be more commonly encountered.

52.3 **B.** The basic tenets of treating DKA include intravenous fluid, insulin to control the glucose level, correction of metabolic disturbances (eg, repletion of potassium), and identification of the underlying etiology. Intravenous fluids to support the circulatory status (BP) are the most important first step in this patient. Lowering the blood sugar would be the next important step. Correction of metabolic abnormalities such as of potassium (answer A) and phosphorus (answer C) are next considered, although the potassium level is more dangerous and a higher priority. Answer D (antibiotics) should be given if a patient is thought to have an infection leading to the DKA; in this patient, there is no fever or symptom suggestive of infection. Even with the presence of infection, intravenous fluids would be the first priority.

52.4 **C.** The patient likely has type 4 RTA. RTA leads to electrolyte abnormalities due to abnormal renal tubular transport.

- Type 1 = impaired renal hydrogen ion excretion in the distal tubule
- Type 2 = impaired bicarbonate resorption in the proximal tubule
- Type 4 = abnormal aldosterone production or response (usually hyperkalemia and non–anion gap acidosis)

NOTE: Type 3 RTA is combined proximal and distal tubule and very rare.

The laboratories are consistent with a non–anion gap metabolic acidosis. The anion gap = 135 – (108 + 18) = 9 (normal is 10-12). Patients with chronic kidney disease due to diabetes are prone to subtle volume expansion and low plasma renin activity, leading to hypoaldosteronism. Since aldosterone is the major hormone that promotes potassium excretion, hyperkalemia is the primary electrolyte abnormality. The disorder is typically associated with a type 4 RTA and a mild metabolic acidosis (bicarbonate usually > 17 mEq/L). The other illnesses (answer A, DKA; answer B, lactic acidosis; and answer D, accidental salicylate overdose) cause anion gap acidosis.

CLINICAL PEARLS

- All patients with DKA are volume depleted and require significant replacement of salt solution and, later, free water in the form of glucose solutions.
- Despite sometimes elevated initial potassium concentrations, all patients with DKA have a total body potassium deficit and will require substantial potassium replacement.
- Patients with DKA develop an anion gap metabolic acidosis. This acidemia prompts respiratory compensation, resulting in deep and rapid breathing to ventilate carbon dioxide. This is known as Kussmaul breathing.
- Glucose levels fall more quickly than ketones resolve. Continuous insulin therapy is necessary for resolution of the ketoacidosis and can be coadministered with a glucose infusion until the anion gap is resolved.
- Cerebral edema can result from overly rapid correction of hyperglycemia or possibly from rapid administration of hypotonic fluids.
- DKA can be precipitated by either insulin deficiency or a physiologic stressor such as infection.

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CASE 53

A 37-year-old, previously healthy woman presents to the clinic for unintentional weight loss. Over the past 3 months, she has lost approximately 15 lb without changing her diet or activity level, but she otherwise feels great. She has an excellent appetite, no gastrointestinal complaints except for occasional loose stools, and no complaints of fatigue. She denies heat or cold intolerance. On examination, her heart rate (HR) is 108 beats per minute (bpm) and blood pressure (BP) is 142/82 mm Hg, and she is afebrile. When she looks at you, she seems to stare, and her eyes are somewhat protuberant. You note a large, smooth, nontender thyroid gland and a 2/6 systolic ejection murmur on cardiac examination. Her skin is warm and dry. There is a fine resting tremor when she spreads her fingers.

- What is the most likely diagnosis?
- How could you confirm the diagnosis?
- What are the options for treatment?
- How might treatment differ if the patient were pregnant?

ANSWERS TO CASE 53:
Thyrotoxicosis/Graves Disease

Summary: A 37-year-old woman presents with

- Three months of unintentional weight loss without anorexia or increased activity level
- Tachycardia and borderline hypertension
- Exophthalmos
- A smooth, nontender goiter

Most likely diagnosis: Thyrotoxicosis/Graves disease.

Confirming the diagnosis: A low serum thyroid-stimulating hormone (TSH) level and an increased free thyroxine (T_4) level with this clinical presentation would confirm the diagnosis of hyperthyroidism. However, other tests to define the etiology include thyroid-stimulating immunoglobulins (TSIs) or diffusely elevated uptake of radioactive iodine on thyroid scan.

Treatment options: Antithyroid drugs, radioactive iodine ablation, or less commonly, surgical removal of the thyroid.

Considerations in a pregnant patient: Radioactive iodine can cause spontaneous miscarriage or birth defects during pregnancy and is thus contraindicated. Methimazole (antithyroid drug) is also contraindicated in the first trimester of pregnancy.

ANALYSIS

Objectives

1. Describe the clinical presentation of thyrotoxicosis. (EPA 1)
2. Discuss the causes of hyperthyroidism, including Graves disease and toxic nodule. (EPA 1, 2)
3. List the complications of thyrotoxicosis, including thyroid storm. (EPA 10)
4. Describe the evaluation of a patient with a thyroid nodule. (EPA 1, 3)
5. Recognize the available treatment options for Graves disease and outcomes of treatment. (EPA 4)
6. Understand the considerations in management of a pregnant patient with thyrotoxicosis. (EPA 4, 10)

Considerations

This 37-year-old woman has unintentional weight loss, loose stools, and warm skin, which are all symptoms of hyperthyroidism. Her thyroid gland is diffusely enlarged and nontender, and she has exophthalmos (protuberant eyes), which is consistent with Graves disease. This is a systemic disease with many complications

that affect the entire body, including osteoporosis and heart failure. Symptomatic treatments aim to eliminate the excessive thyroid hormone with antithyroid medication. Definitive therapy consists of radioactive ablative therapy or, less frequently, surgical excision.

APPROACH TO: Hyperthyroidism

DEFINITIONS

HYPERTHYROIDISM: Hypermetabolic condition that results from the effect of excessive amounts of thyroid hormones produced by the thyroid gland itself. Because almost all cases of thyrotoxicosis are caused by thyroid overproduction, these terms are often used synonymously.

THYROID STORM: Rare but life-threatening condition caused by untreated hyperthyroidism. Can cause severe symptoms of thyrotoxicosis, such as tachycardia, fever, agitation, weakness, delirium, and most fatally, coma or death.

THYROTOXICOSIS: Usually used as a general term for the state of thyroid hormone excess from any source, for example, exogenous ingestion of thyroid hormone (factitious or iatrogenic).

CLINICAL APPROACH

Pathophysiology

Graves disease is the most common cause of hyperthyroidism (80%) and usually is seen in women, especially between the ages of 30 and 50 years. It is an autoimmune disease caused by autoantibodies that activate the TSH receptor of the thyroid follicular cell, stimulating thyroid hormone synthesis and secretion as well as thyroid gland growth. In the pregnant patient, these antibodies cross the placenta and can cause neonatal thyrotoxicosis. The disease might follow a relapsing and remitting course.

A low serum TSH will confirm the diagnosis. The degree of elevation of serum-free T_4 and free T_3 (triiodothyronine) levels can give an estimate of the severity of the disease. Tests that might be helpful in determining the etiology of thyrotoxicosis include the levels of TSI, which is elevated in Graves disease; thyroid peroxidase antibodies, which are markers of autoimmunity in both Graves disease and Hashimoto thyroiditis; and a **thyroid uptake and scan, which will reveal diffusely elevated iodine uptake in our patient.** Less common causes of thyrotoxicosis include the following:

Toxic multinodular goiter: Found mainly in elderly and middle-aged patients. Treatment consists of radioactive iodine or surgery. Radioactive iodine uptake is normal to increased, and the scan reveals irregular thyroid lobes and a heterogeneous pattern.

Autonomous hyperfunctioning adenoma ("hot nodule" or Plummer disease): Hyperthyroidism usually is not present unless the nodule is more than 3 cm. The iodine scan looks like the flag of Japan: It demonstrates the hot nodule as having increased uptake (dark) and the rest of the gland with suppressed uptake (white). **Hot nodules are almost never malignant.**

Thyroiditis: Caused by destruction of thyroid tissue and release of preformed hormone from the colloid space. Subacute (de Quervain) thyroiditis is an inflammatory viral illness with thyroid pain and tenderness. The hyperthyroid phase lasts for several weeks to months, followed by recovery, but some patients will then develop hypothyroidism. Treatment with nonsteroidal anti-inflammatory medications and beta-blockers usually is sufficient, but in severe cases, glucocorticoids might be used. Other forms include postradiation, postpartum, subacute (painless thyroiditis), and amiodarone-induced thyroiditis. In thyroiditis, the radioactive iodine uptake is decreased.

Pregnancy: The beta subunits of human chorionic gonadotropic (hCG) and TSH share considerable homology, and thus hCG has weak thyroid-stimulating effects. This can cause transient hyperthyroidism during peak hCG concentrations. Likewise, during normal pregnancy, there are changes in thyroid physiology to meet the increased metabolic demands. Rises in thyroid hormone-binding globulin can cause increased total T_4 and total T_3 concentrations without increased free T_4 or free T_3 concentrations.

Medications: Excessive ingestion of thyroid hormone (factitious or iatrogenic), amiodarone, and iodine load.

Diagnosis. Thyroid function tests indicating low TSH levels and increased free T_4 or T_3 levels are confirmatory for hyperthyroidism. Once the diagnosis has been established, the etiology should be determined. Tests to distinguish the cause of hyperthyroidism include measurement of thyrotropin (TSH) receptor antibodies, thyroid scan of radioactive iodine uptake, and measurement of thyroidal blood flow on ultrasound.

Positive thyrotropin receptor antibodies would indicate Graves disease as the most likely etiology. Thyroid scans of radioactive iodine uptake measure areas of thyroid activity. Hot nodules (areas of increased thyroid activity) are likely secondary to hyperfunctioning adenoma and are almost never malignant. **Cold nodules (no demonstration of local uptake) have a 5% to 10% risk of malignancy.** Fine-needle aspiration, surgical removal, or ultrasonographic follow-up is needed for these nodules.

Clinical Presentation

Hyperthyroidism is a multisystemic condition that can affect numerous body systems (Table 53–1). Weight loss is a common finding, especially in older patients who develop anorexia. Many patients develop an aversion to heat and a preference for cold temperatures. In **apathetic hyperthyroidism,** older patients may lack typical adrenergic features and present instead with depression or apathy, weight loss, atrial fibrillation, worsening angina pectoris, or heart failure.

Table 53–1 • SIGNS AND SYMPTOMS OF HYPERTHYROIDISM

System	Signs and Symptoms	Comments
Cardiac	• Wide pulse pressure • Flow heart murmurs • Tachycardia • Atrial fibrillation (10%-20% of patients)	Long-standing thyrotoxicosis can cause cardiomegaly and result in high-output heart failure.
Dermatologic	• Warm, moist, and velvety skin • Fine hair texture • Alopecia • Sweating	Vasodilation and sweating occur to dissipate heat.
Eyes	• Retraction of the upper eyelid, resulting in a wide-eyed stare • Lid lag (sclera can be seen above the iris as the patient looks downward)	Exophthalmos occurs as a consequence of increased sympathetic tone.
Gastrointestinal	• Weight loss despite increased food intake • Hyperdefecation as a result of increased motility	Diarrhea is rare.
Neuromuscular	• Nervousness • Tremors • Brisk reflexes • Inability to concentrate • Proximal muscle weakness • Emotional lability • Insomnia	
Reproductive	• Impaired fertility in women • Oligomenorrhea • Reduced sperm count in men • Impotence • Gynecomastia	

Graves disease is marked by **goiter** (enlarged thyroid gland), thyroid bruit, **hyperthyroidism**, **ophthalmopathy, and dermopathy**. These features are variably present. Ophthalmopathy is characterized by inflammation of extraocular muscles, orbital fat, and connective tissue, resulting in proptosis (exophthalmos), sometimes with impairment of eye muscle function (diplopia), and periorbital edema. Ophthalmopathy, caused directly by the TSH receptor–directed antibodies, can progress even after treatment of thyrotoxicosis with antithyroid drugs or radioiodine ablation. Graves dermopathy is characterized by raised hyperpigmented orange peel texture papules. The most common site is the skin overlying the shins (pretibial myxedema).

Treatment

Treatment options for hyperthyroidism are medications, radioactive iodine, or surgery. Medications include **beta-blockers** such as propranolol (which are used for symptom relief) and **antithyroid drugs** such as **methimazole** and **propylthiouracil (PTU)**.

The antithyroid drugs work mainly by decreasing the production of thyroid hormone. They can be used for short-term (prior to treatment with radioactive iodine or surgery) or long-term (1-2 years) treatment, after which the chance for remission is 20% to 30%. Possible side effects are rash, allergic reactions, arthritis, hepatitis, and agranulocytosis.

For nonpregnant patients, **radioactive iodine** is usually the treatment of choice in the United States. It is administered as an oral solution of sodium ^{131}I that is rapidly concentrated in thyroid tissue, inducing damage that results in ablation of the thyroid within 6 to 18 weeks. At least 30% of patients will have hypothyroidism in the first year after treatment and 3% each year after that, requiring thyroid hormone supplementation. Radioactive iodine is contraindicated in pregnancy due to the risk of miscarriage or birth defects, and women of reproductive age are advised to postpone pregnancy for 6 to 12 months after treatment. Methimazole is contraindicated in the first trimester, but pregnant women with Graves disease can be managed with PTU, as it has a low transplacental transfer. Graves ophthalmopathy might be exacerbated by radioactive iodine treatment, so glucocorticoids can be used to prevent this in selected patients.

Subtotal thyroidectomy usually is reserved for large goiters with obstructive symptoms (dyspnea, dysphagia). Possible complications include recurrent laryngeal nerve injury and hypoparathyroidism (due to removal of the parathyroid glands or compromise of their vascular supply).

For our patient, treatment with radioactive iodine or antithyroid medications seems the most reasonable way to proceed, and a discussion regarding her options and our recommendations should take place after the diagnosis is confirmed and nonpregnant status is confirmed.

Complications

Thyroid storm is a dangerous condition of decompensated thyrotoxicosis. Symptoms include severe signs of hyperthyroidism such as **tachycardia** (> 140 bpm), **fever** (104 °F to 106 °F), **agitation, delirium, restlessness or psychosis, vomiting, and/or diarrhea**. Thyroid storms are usually due to untreated hyperthyroidism complicated by an intercurrent illness such as infection, surgery, or trauma. Treatment includes supportive care with fluids, beta-blockers to control symptoms of increased adrenergic tone, antibiotics if needed, and specific treatment directed at the hyperthyroidism.

CASE CORRELATION

- See also Case 41 (Urinary Tract Infection With Sepsis in the Elderly), Case 52 (Diabetic Ketoacidosis, Type 1 Diabetes), and Case 59 (Delirium/Alcohol Withdrawal).

COMPREHENSION QUESTIONS

53.1 A 44-year-old woman is being seen in the office for a 2-month history of progressive anxiety, nervousness, and tremor. She also says she has heat intolerance. On exam, her HR is 110 bpm and BP is 130/80 mm Hg. Her thyroid gland is diffusely enlarged and nontender, and an audible bruit is present. Her serum TSH level is 0.01 mIU/L (normal 0.35-5.0). Which of the following is the most likely diagnosis?

A. Lymphocytic thyroiditis
B. Hashimoto thyroiditis
C. Graves disease
D. Multinodular toxic goiter

53.2 A 34-year-old woman is being seen in the urgent care center for "feeling ill." She was diagnosed with hyperthyroidism 6 months ago, but she has not taken her medications for 5 days. After the history and physical examination, the provider is suspicious of possible thyroid storm. Which of the following features would best distinguish hyperthyroidism from thyroid storm?

A. Heart rate of 120 bpm
B. Weight loss
C. Fever and delirium
D. Large goiter

53.3 A 58-year-old woman is being seen in the office for her first evaluation of hyperthyroidism. On examination, she is found to have a diffusely slightly enlarged thyroid gland that is nontender. She has exophthalmos, tremor, and brisk deep tendon reflexes. Serum TSH is 0.03 mIU/L (normal 0.35-5.0). Which of the following is the best therapy for this patient?

A. Long-term oral propranolol
B. Lifelong oral PTU
C. Radioactive iodine ablation
D. Surgical thyroidectomy

ANSWERS

53.1 **C.** Graves disease is the most common cause of hyperthyroidism in the United States. It often includes the thyroid gland features described (diffusely enlarged and nontender), as well as the distinctive eye findings. The patient in this question does not have exophthalmos described, but its absence does not rule out Graves disease. The other answer choices (answer A, lymphocytic thyroiditis; answer B, Hashimoto thyroiditis; and answer D, multinodular toxic goiter) are less common causes of hyperthyroidism. Patients with multinodular toxic goiter usually have multiple irregular and variable sized nodules

on thyroid palpation, and usually do not present with exophthalmos. The patient in this scenario does not have exophthalmos (thyroid stare). Only about 20-30% of patients with Graves disease have these eye findings, and therefore, their absence does not rule out Graves disease.

53.2 **C.** Thyroid storm is an exaggeration of hyperthyroid features with autonomic dysfunction manifesting in fever and/or central nervous system dysfunction, such as confusion or coma. It is a medical emergency with a high mortality. Although some patients may have tachycardia (answer A), mild tachycardia is very common in straightforward hyperthyroidism and not an indicator of thyroid storm. Weight loss (answer B) and a large goiter (answer D) can occur with hyperthyroidism and are not distinguishing factors. Other findings of thyroid storm include heart failure and a markedly elevated BP.

53.3 **C.** This patient most likely has Graves disease based on the symptoms of hyperthyroidism, mildly enlarged goiter, eye findings, and low TSH level. Radioactive iodine is a definitive treatment for Graves disease. Surgery (answer D) is indicated for obstructive symptoms or for women during pregnancy. Propranolol (answer A) is a good initial option to control tachycardia but not a long-term option. PTU (answer B) is a second-line option due to the risk of hepatocellular necrosis; long-term medical therapy with methimazole is the preferred agent in the United States and is used in many cases.

CLINICAL PEARLS

- The most common cause of thyrotoxicosis is Graves disease. No other diagnosis is likely if the patient has bilateral proptosis and a goiter.
- In patients with Graves disease, thyrotoxic symptoms may be treated with antithyroid medication or by thyroid gland ablation with radioactive iodine or surgery, but the ophthalmopathy may not improve.
- Graves disease may remit and relapse; in patients treated medically, one-third to half will become asymptomatic within 1–2 years.
- After radioactive iodine ablation, most patients with Graves disease will have hypothyroidism and require thyroid hormone supplementation.
- Hyperfunctioning thyroid nodules (excessive thyroid hormone production, suppressed TSH, "hot" on radionuclide scan) almost never are malignant.
- Most "cold" thyroid nodules are not malignant, but fine-needle aspiration should be used to evaluate the need for surgical excision.

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CASE 54

A healthy 52-year-old man presents to the office complaining of increasing fatigue for the past 4 to 5 months. He exercises every day, and lately he has noticed becoming short of breath while jogging. He denies orthopnea, paroxysmal nocturnal dyspnea, or swelling in his ankles. The patient reports occasional joint pain, for which he frequently uses over-the-counter ibuprofen. He denies bowel changes, melena, or bright red blood per rectum, but he reports vague left-sided abdominal pain for a few months off and on unrelated to food intake. The patient denies fever, chills, nausea, or vomiting. He has lost a few pounds intentionally with diet and exercise.

On examination, the patient weighs 205 lb and is afebrile. There is slight pallor of the conjunctiva, skin, and palms. No lymphadenopathy is noted. Chest is clear to auscultation bilaterally. Examination of the cardiovascular system reveals a regular rate and rhythm, with no rub or gallop. There is a systolic ejection murmur. His abdomen is soft and nontender, with no hepatosplenomegaly. Bowel sounds are present. He has no extremity edema, cyanosis, or clubbing. His peripheral pulses are palpable and symmetric. His hemoglobin level is 8.2 g/dL.

- What is the most likely diagnosis?
- What is your next diagnostic step?
- What are the risk factors for this condition?

ANSWERS TO CASE 54:
Iron-Deficiency Anemia

Summary: A 52-year-old man presents with

- A 4- to 5-month history of increasing exercise intolerance
- Regular nonsteroidal anti-inflammatory drug (NSAID) use
- Systolic ejection murmur and pallor on examination
- Hemoglobin of 8.2 g/dL

Most likely diagnosis: Chronic blood loss and iron-deficiency anemia, possibly due to regular NSAID use.

Next diagnostic step: Analyze the complete blood count (CBC), particularly the mean corpuscular volume (MCV), to determine if the anemia is microcytic, normocytic, or macrocytic; assess the leukocyte count and platelet count.

Risk factors: NSAID or anticoagulant use, iron-poor intake, gastrointestinal (GI) disorder (eg, celiac disease, autoimmune gastritis), or menses.

ANALYSIS

Objectives

1. Recognize iron-deficiency anemia as the most common cause of anemia. (EPA 1, 2)
2. Describe the diagnostic approach to anemia. (EPA 3)
3. Identify the treatment of iron-deficiency anemia. (EPA 4)

Considerations

This 52-year-old man presents to the office with complaints of fatigue and dyspnea on exertion for the few months prior to the office visit. His physical examination is significant only for pallor. The serum hemoglobin level confirms anemia. The next step would be to characterize the anemia; if it is microcytic, which would be consistent with iron deficiency, confirmation should be performed with further testing for total iron-binding capacity (TIBC) and ferritin. In the postmenopausal female or adult male, **iron-deficiency anemia indicates GI tract blood loss until proven otherwise,** with colon cancer being the most serious possibility. This patient is using an NSAID, which may predispose to erosive gastritis. Once iron-deficiency anemia is confirmed, a thorough evaluation, including upper and lower endoscopy of the GI tract, is needed.

APPROACH TO:
Iron-Deficiency Anemia

DEFINITIONS

ANEMIA: Decreased red blood cell (RBC) mass, leading to less oxygen-carrying capacity. Anemia is defined as a hemoglobin level less than 13 g/dL in men and less than 12 g/dL in women.

IRON STUDIES: Ferritin is a marker of iron stores and is decreased in cases of iron deficiency. It is also an acute-phase reactant and therefore increases with inflammatory chronic diseases. The TIBC is an indirect measure of transferrin saturation levels and increases in iron deficiency.

MEAN CORPUSCULAR VOLUME: MCV is the average of RBC volume. Based on RBC size, anemia is categorized as microcytic (MCV < 80 fL), normocytic (MCV 80-100 fL), and macrocytic (MCV > 100 fL).

RETICULOCYTE: An immature RBC that usually is 1 to 1.5 days old.

RETICULOCYTE COUNT: A fraction of RBCs consisting of reticulocytes that indirectly indicates the bone marrow activity of the erythrocyte line. It is usually expressed as a percentage, with a normal value of 0.5% to 2% in nonanemic adults; the reticulocyte index adjusts the count for the level of anemia.

CLINICAL APPROACH

Pathophysiology

Iron-deficiency anemia is the **most common** cause of anemia in the United States, affecting all ages and both genders. Iron is essential to the synthesis of hemoglobin. The normal daily intake of elemental iron is approximately 15 mg, of which only 1 to 2 mg are absorbed. The daily iron losses are about the same, and menstruation adds approximately 30 mg of iron lost each month.

When iron loss exceeds intake, iron deposits are gradually depleted. Hemoglobin and serum iron levels may remain normal in the initial stages, and decreasing **serum ferritin (iron stores)** levels can be one of the first changes seen. This leads to a progressive decrease in iron available for RBC formation. The liver tries to compensate for this change by increasing transferrin production and maximizing the use of available iron. Transferrin levels are indirectly measured by TIBC. Due to increased transferrin production, **TIBC is high in patients with iron-deficiency anemia**. As a result, **transferrin saturation (serum iron divided by TIBC) is low**. Initially anemia will have normal-appearing RBCs, but as anemia becomes more severe, microcytosis and hypochromia will develop. Later in the disease process, iron deficiency will affect other tissues, resulting in a variety of symptoms and signs.

Etiologies. The primary etiology for iron-deficiency anemia is blood loss (Table 54–1). **In men, the most frequent cause is chronic GI tract occult bleeding; gastroenterology referral and endoscopic study of potential blood losses should be considered**. In women, menstrual loss may be the main mechanism,

Table 54–1 • COMMON CAUSES OF IRON-DEFICIENCY ANEMIA

BLOOD LOSS
Gastrointestinal blood loss
• Esophageal varices
• Peptic ulcer disease
• Gastritis (eg, NSAID induced)
• Small bowel polyp or carcinoma
• Colonic angiodysplasia
• Colon cancer
• Inflammatory bowel disease (eg, ulcerative colitis)
• Hookworm infestation
Uterine blood loss
• Menstruation/menorrhagia
• Uterine fibroids
Other blood loss
• Chronic hemodialysis
• Surgical blood loss
• Repeated blood donation or phlebotomy
• Paroxysmal nocturnal hemoglobinuria
MALABSORPTION
• Gastrectomy
• Celiac disease
• Inflammatory bowel disease (eg, Crohn disease)
INADEQUATE DIETARY INTAKE/INCREASED PHYSIOLOGIC DEMANDS
• Infancy/adolescence
• Pregnancy
• Vegetarian diet

but other causes must be considered. During pregnancy, iron transfer from the mother to the developing fetus makes supplemental iron especially important. Iron deficiency may also be a result of increased iron requirements, diminished iron absorption, or both. Iron deficiency can develop during the first 2 years of life if dietary iron is insufficient for the demands of rapid growth. Adolescent girls may become iron deficient from inadequate oral intake in addition to the loss from menstruation. The growth spurt in adolescent boys may also produce a significant increase in demands for iron. Less common than blood loss are other possible causes of anemia, such as decreased iron absorption after gastrectomy or malabsorption syndromes such as celiac disease.

Sideroblastic anemia is a disease in which the bone marrow produces abnormal RBCs, commonly microcytic and hypochromic. It can be both acquired and congenital, with X-lined sideroblastic anemia and **isoniazid** being some of the more common etiologies of microcytic sideroblastic anemia. The iron studies in **sideroblastic anemia** include **increases in serum iron, serum ferritin concentration, and saturation of transferrin.** Iron stain of the bone marrow (Prussian blue) reveals the pathognomonic feature of engorged mitochondria in the developing RBCs, called **ringed sideroblasts** (Figure 54–1). Another important clue to the presence of sideroblastic anemia is the presence of **stippled RBCs** in the peripheral blood smear (Figure 54–2); this is also seen in heavy lead exposure.

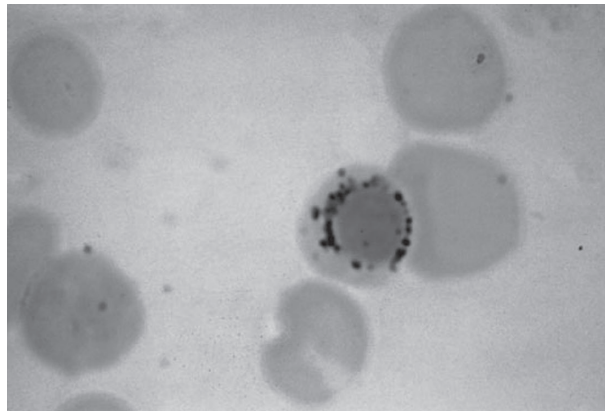


Figure 54–1. Ringed sideroblasts. (Reproduced with permission, from Jameson J, Fauci AS, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 20th ed. 2018. Copyright © McGraw Hill LLC. All rights reserved.)

Categorizing Anemias by MCV. A CBC with differential, platelets, and RBC indices is helpful in narrowing the differential diagnosis of anemia. The first step is to look at the **MCV** to categorize the anemia (Table 54–2). Iron deficiency usually leads to a microcytic anemia. The **RBC distribution width (RDW)** is a calculated index that quantitates the anisocytosis (variation in the RBC size) and helps to distinguish uncomplicated iron deficiencies from uncomplicated thalassemia. Microcytic anemia with an increased RDW is suggestive of iron-deficiency anemia because the bone marrow produces new erythrocytes of various sizes. A normal RDW in the presence of microcytic anemia is more suggestive of chronic disease, thalassemia, or even iron deficiency with concomitant anemia of chronic disease.

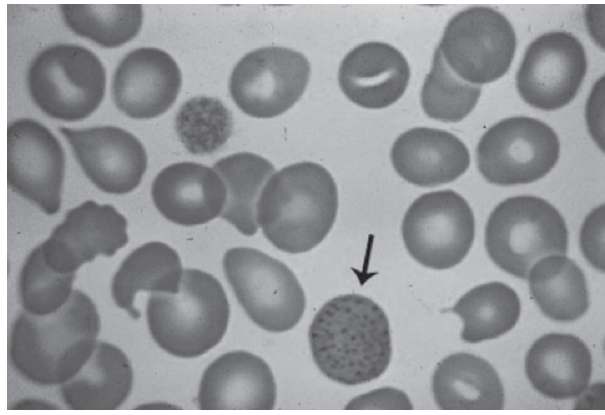


Figure 54–2. Basophilic stippling (arrow). (Reproduced with permission, from Litchman MA, Shafer MS, Felgar RE, et al, eds. *Lichtman's Atlas of Hematology. 2016.* 2017. Copyright © McGraw Hill LLC. All rights reserved.)

Table 54–2 • CLASSIFICATION OF ANEMIA BY MCV

Microcytic (low MCV) • Iron deficiency • Thalassemia • Sideroblastic anemia • Lead poisoning • Anemia of chronic disease
Normocytic (normal MCV) • Acute blood loss • Hemolysis • Anemia of chronic disease • Anemia of renal failure • Myelodysplastic syndromes
Macrocytic anemia (high MCV) • Folate deficiency • Vitamin B_{12} deficiency • Drug toxicity (eg, zidovudine) • Alcoholism/chronic liver disease

A detailed history, physical examination, and further laboratory data may be necessary to achieve a final diagnosis.

Reticulocyte Count. The **reticulocyte count** is another important parameter to help in the differential diagnosis of anemia. A new RBC can be stained as a reticulocyte for 24 to 36 hours, after which the RBC circulates for approximately 120 days. The blood normally contains about 1 reticulocyte per 100 RBCs. The reticulocyte count is the percentage of reticulocytes per 100 RBCs, and it may be falsely elevated in the presence of anemia. Therefore, a corrected reticulocyte count (CRC) is calculated by multiplying the reported reticulocyte count by the patient's hematocrit divided by 45 (normal hematocrit), or hemoglobin divided by 15.

Reticulocyte Production Index. Another calculated measure to assess anemia is to look at the bone marrow response using the **reticulocyte production index** (RPI). The RPI accounts for prematurely released reticulocytes, or shift cells, as they have a longer life span and can lead to overestimation of daily RBC production. RPI can be calculated by dividing the CRC by 2.

For example, if the patient's reticulocyte count is 6% and hematocrit 18, then

$$\text{RPI} = \frac{\textbf{CRC}}{\textbf{2}} = \frac{6 * (^{18}/_{45})}{\textbf{2}} = \textbf{1.2}$$

An RPI less than 2 indicates that the patient's bone marrow is not responding to the anemia and not making enough reticulocytes; therefore, a **hypoproliferative bone marrow** disorder should be suspected. A normal or **high reticulocyte count** (RPI > 3) indicates that the marrow is responding appropriately to the anemia, suggestive of **acute blood loss, hemolysis**, or a response to therapy for anemia.

Iron Studies. Iron studies are very helpful to confirm a diagnosis of iron-deficiency anemia and to help in the differential diagnosis of other types of anemia, such as anemia of chronic disease and sideroblastic anemia (Table 54–3). These studies include serum iron levels, serum TIBC, and calculation of percentage saturation

Table 54–3 • CHARACTERISTICS OF MICROCYTIC ANEMIAS

Tests	Iron Deficiency	Chronic Disease	Thalassemia	Sideroblastic Anemia
Smear	Microcytic/ hypochromic	Normal microcytic/ hypochromic	Microcytic/hypochromic with targeting	Variable
SI (µg/dL)	< 30	< 50	Normal to high	Normal to high
TIBC (µg/dL)	> 360	< 300	Normal	Normal
Saturation (%)	< 10	10-20	30-80	30-80
Ferritin (µg/L)	< 15	30-200	50-300	50-300
Hemoglobin electrophoresis	Normal	Normal	Abnormal with beta-thalassemia; can be normal with alpha-thalassemia	Normal

Abbreviations: SI, serum iron; TIBC, total iron-binding capacity.
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of transferrin. Low **serum ferritin concentration is a reliable indication of iron deficiency.** Serum **ferritin values are increased with chronic inflammatory disease,** malignancy, or liver injury; therefore, serum ferritin concentration may be above normal when iron deficiency exists with chronic diseases, such as rheumatoid arthritis, Hodgkin disease, or hepatitis, among many other disorders.

Peripheral Blood Smear. Evaluating the peripheral blood smear for specific abnormalities in RBC morphology may be very useful for determining the etiology of anemia. In iron-deficiency anemia, the peripheral blood smear shows RBCs smaller than normal (microcytes) and hypochromia (Figure 54–3).

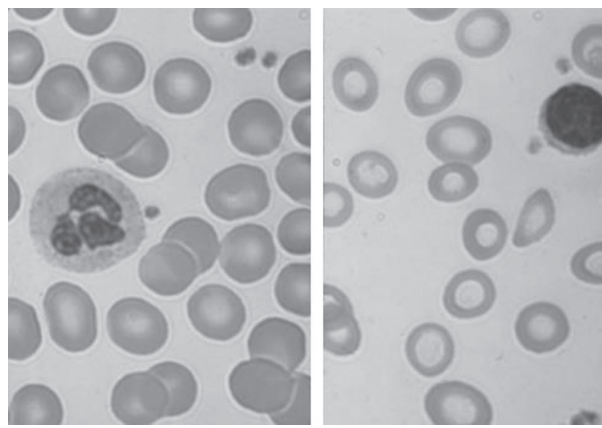


Figure 54–3. Hypochromic, microcytic RBCs (right side) are smaller than normal (left panel). (Reproduced with permission, from Jameson J, Fauci AS, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine.* 20th ed. 2018. Copyright © McGraw Hill LLC. All rights reserved.)

Clinical Presentation

Anemia is most commonly diagnosed by a routine laboratory test, and patients are often asymptomatic. The lack of symptoms reflects the very slow development of iron deficiency and the ability of the body to adapt to lower iron reserves and anemia. More severe anemia may produce symptoms such as fatigue, shortness of breath, dizziness, headache, palpitations, and impaired concentration. Additionally, patients with chronic severe iron deficiency may develop **pica**, which involves **cravings for nonfood objects such as dirt, paint, and ice. It is also linked to restless legs syndrome. Glossitis**, cheilosis, or koilonychia may develop, and in rare cases, dysphagia associated with a postcricoid **esophageal web (also known as Plummer-Vinson syndrome**) may occur.

Treatment

Although the treatment of iron deficiency is straightforward, finding the underlying etiology is paramount. Treatment of iron-deficiency anemia consists of iron replacement therapy, typically with **oral ferrous sulfate 325 mg two or three times daily**, which provides 130 to 195 mg of elemental iron. Other iron preparations, such as ferrous fumarate or ferrous gluconate, can also be used and are equally effective. Correction of anemia usually occurs **within 6 weeks**, but therapy should continue for at least 6 months to replenish the iron stores. Oral iron therapy may cause GI side effects, such as constipation, nausea, and abdominal cramping. Taking the iron with meals may help with tolerance but can reduce absorption. Failure of iron-deficiency anemia to improve with oral iron supplementation suggests nonadherence to therapy, possible coexisting disease interfering with marrow response (eg, coexisting folate or B_{12} deficiency), or malabsorption of iron (eg, celiac sprue, atrophic gastritis). Parenteral iron therapy is indicated in patients with a poor absorption state (occurs in celiac disease, chronic kidney disease) or with excessive intolerance to oral therapy. **Caution must be taken with parenteral high-molecular-weight iron dextran because anaphylaxis may occur.** Newer parenteral iron compounds are now available with lower rates of adverse events.

It should be emphasized once again that after the diagnosis of iron deficiency is established, the cause of the iron loss should be identified. Except in menstruating women, the most common site of blood loss is the GI tract, and **most patients will require endoscopic evaluation.** Gastritis, peptic ulcers, and angiodysplasia are all common sources of blood loss, but the most serious diagnosis to exclude would be the possibility of an occult GI malignancy. Fecal occult blood testing (FOBT), such as a stool guaiac test, should not be used as a substitute for endoscopic evaluation, as even high-sensitivity FOBT has only 50% to 80% sensitivity for colorectal cancer.

CASE CORRELATION

- See Case 55 (Symptomatic Anemia and Transfusion Medicine), Case 56 (Immune Thrombocytopenic Purpura/Abnormal Bleeding), and Case 58 (Sickle Cell Crisis).

COMPREHENSION QUESTIONS

54.1 A 25-year-old man with a history of a duodenal ulcer is being seen in the office for follow-up. He does not complain of abdominal pain and does not report any bloody stool or melena. His blood pressure (BP) is 120/80 mm Hg, heart rate (HR) is 80 beats per minute, and respiratory rate (RR) is 12 breaths/min. His hemoglobin level is 10 g/dL. Which of the following most likely will be seen on laboratory investigation?

A. Elevated TIBC
B. Mean corpuscular volume of 105 fL
C. Normal serum ferritin
D. Reticulocyte count of 4%

54.2 A 22-year-old woman is pregnant at 14 weeks' gestation. She denies vaginal bleeding or prior medical problems. Her BP is 100/60 mm Hg, HR is 90 beats per minute, and RR is 14 breaths/min. Her hemoglobin level is 9 g/dL. She is counseled that the most likely cause of the low hemoglobin level is due to iron deficiency. She asks why she could have iron deficiency when she is no longer menstruating. Which of the following is the best explanation?

A. Expanded blood volume and transport to the fetus
B. Hemolysis
C. Iron losses as a result of relative alkalosis of pregnancy
D. Occult GI blood loss

54.3 A 35-year-old man who is mildly obese has undertaken a strict fad diet for 3 months. He previously had been healthy but now complains of fatigue. His hemoglobin level is 10 g/dL, and his MCV is 105 fL. Which of the following is the most likely etiology of his anemia?

A. Folate deficiency
B. Iron deficiency
C. Sideroblastic anemia
D. Thalassemia
E. Vitamin B_{12} deficiency

54.4 A 20-year-old woman is found to be anemic (10 g/dL) on routine laboratory tests. She is otherwise healthy, with review of systems notable only for heavy menses. Iron studies are as follows: decreased MCV, decreased ferritin, increased TIBC, and increased RDW. Which of the following is the best next step?

A. Transfuse one unit of packed RBCs
B. Start oral ferrous sulfate 325 mg twice daily
C. Refer for colonoscopy
D. Start oral folic acid 1 mg daily
E. Treat with intravenous iron dextran 100 mg

54.5 A 34-year-old woman of Mediterranean descent is found to have mild anemia on prenatal screening CBC. She denies any shortness of breath, fatigue, or blood in stool. Family history is notable for a brother who requires frequent blood transfusions. A CBC demonstrates microcytic, hypochromic anemia with high serum iron, normal RDW, normal ferritin, and low reticulocytes. Hemoglobin electrophoresis is normal. Which of the following is the best next diagnostic step?

A. Check lead levels

B. Repeat hemoglobin electrophoresis for improved sensitivity

C. Bone marrow biopsy

D. DNA testing

E. Start ferrous sulfate 325 mg daily and recheck CBC in 6 weeks

54.6 A 50-year-old man is being seen in the office for follow-up of severe rheumatoid arthritis. He declines taking medications except for a daily multivitamin with iron. His laboratory examination results include a hemoglobin level of 9.8 g/dL. The colonoscopy this year was normal. Which of the following lab findings would most likely to be seen on laboratory workup of his anemia?

	Mean Corpuscular Volume (normal 80-96 fL)	Serum Ferritin (nl 12-300 µg/L)	Total Iron-Binding Capacity (nl 240-450 µg/dL)	Serum Iron Levels (nl 46-132 µg/dL)
A	105	300	330	100
B	80	300	330	120
C	80	100	200	40
D	65	10	500	40
E	95	500	40	200

ANSWERS

54.1 **A.** Chronic GI blood loss leads to low ferritin levels, reflecting diminished iron stores; elevated TIBC; and low iron saturation. There is a microcytic anemia (low MCV) with a low reticulocyte count. The reticulocyte count would be elevated (answer D) with acute blood loss, but the patient has not experienced this. An elevated MCV of 105 fL (answer B) would be indicative of macrocytic anemia such as folate or vitamin B_{12} deficiency, whereas iron deficiency is suggestive of microcytic anemia. Serum ferritin levels (answer C) would be decreased in iron deficiency.

54.2 **A.** Iron deficiency occurs in pregnancy as a result of the expanded blood volume and active transport of iron to the fetus. Hemolysis (answer B) and occult GI blood loss (answer D) would not be normal findings in pregnancy and would warrant further workup. Iron loss does not occur due to alkalosis (answer C).

54.3 **A.** Macrocytic anemia is usually a result of folate or vitamin B_{12} deficiency. Vitamin B_{12} stores last for nearly 10 years; therefore, **a dietary change of several months would more likely cause folate deficiency.** Folate is found in green leafy vegetables. Vitamin B_{12} deficiency (answer E) can also lead to neurologic symptoms. Iron deficiency (answer B), thalassemias (answer D), and sideroblastic anemias (answer C) will likely be microcytic with an MCV < 80 fL.

54.4 **B.** This patient has ongoing blood loss from heavy menses leading to iron-deficiency anemia, with characteristic laboratory test values (low MCV, low ferritin, high TIBC, high RDW). Treatment of choice is oral iron supplementation. Intravenous iron formulations (answer E) are indicated only in specific situations, such as inability to tolerate oral iron and malabsorption. Demonstration of a failure of oral therapy is often needed prior to intravenous iron treatment. Iron dextran is rarely used due to concern for anaphylaxis. In addition, the patient has a clear etiology for iron loss, so endoscopy (answer C) is not indicated. Transfusion (answer A) is reserved for patients with hemoglobin < 7 g/dL or hemoglobin < 8 g/dL if symptomatic. Oral folic acid supplementation (answer D) would not be contraindicated in this case but is not as important as iron supplementation. Typically, vitamin C is also provided in addition to the oral iron to enhance intestinal absorption.

54.5 **D.** Thalassemia usually leads to a microcytic anemia with uniform red cell size (normal RDW) and excess iron stores. The patient's asymptomatic anemia, ethnicity, and family member with transfusion-dependent anemia are consistent with alpha-thalassemia minor. **Alpha-thalassemia minor can have normal hemoglobin electrophoresis**, and diagnosis requires DNA sequencing. Checking lead levels (answer A) would be indicated if there is suggestive history, such as occupational exposure or living in an old house with lead-based paint. Repeating hemoglobin electrophoresis (answer B) does not increase sensitivity for the diagnosis of thalassemia. A bone marrow biopsy (answer C) is indicated when there is suggestion of a bone marrow process such as compromise of more than one cell line (eg, anemia and/or leukopenia and/or thrombocytopenia). Iron sulfate supplementation (answer E) is not indicated since serum iron stores are in excess and supplementation may lead to iron toxicity.

54.6 **C.** The patient has an inflammatory condition (rheumatoid arthritis) that would cause an anemia of chronic disease. The typical parameters with chronic inflammation would be a normocytic (normal to slightly low MCV), normal to high serum ferritin level (due to inability to mobilize iron), and low serum iron levels (due to lack of iron in circulation). Although a microcytic anemia can be seen, normocytic anemia with elevated ferritin (acute-phase reactant) is more common in chronic disease. Answer A (high MCV, normal to elevated ferritin, normal TIBC, and normal serum iron levels) is consistent with a folate or vitamin B_{12} deficiency. Answer B (borderline low MCV, high/normal ferritin, TIBC normal, and normal serum iron level) is consistent with sideroblastic anemia. Answer D (low MCV, low ferritin, high TIBC,

and low iron levels) is consistent with iron-deficiency anemia. Answer E (normal/high MCV, normal ferritin, low TIBC, normal serum iron) is consistent with hemochromatosis (iron overload).

CLINICAL PEARLS

- The values for MCV, RDW, and RPI are important parameters in the evaluation of anemia.
- Reticulocyte production index < 2 in an anemic patient is indicative of hypoproliferative bone marrow disorder.
- Think of iron deficiency in an anemic patient with low MCV, low ferritin, and low RPI.
- Iron-deficiency anemia in men or postmenopausal women is primarily a result of GI blood losses; therefore, iron-deficiency anemia in this patient population warrants a thorough GI workup.
- Iron-deficiency anemia in reproductive age women is most often caused by menstrual blood loss.
- Fecal occult blood testing is negative in approximately 20% to 50% of patients with colorectal cancer. Therefore, a negative fecal occult blood test in the presence of iron-deficiency anemia should not discourage you from pursuing a thorough GI workup if clinically indicated.

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CASE 55

A 62-year-old man presents to the emergency department with the sudden onset of abdominal discomfort and passage of several large, black, tarry stools. The patient states he has chest pain similar to that of his recent non–ST-segment elevation myocardial infarction (NSTEMI) 3 weeks ago, with coronary angiography performed prior to discharge revealing no significant coronary artery stenosis. He was discharged with aspirin, clopidogrel, atorvastatin, and metoprolol. On present examination, his temperature is 99 °F, blood pressure (BP) is 124/92 mm Hg lying down and 95/70 mm Hg upon standing, heart rate (HR) is 104 beats per minute (bpm), respiratory rate (RR) is 14 breaths per minute, and oxygen saturation is 96% on room air. On physical examination, he appears pale and diaphoretic. His neck veins are flat, his chest is clear to auscultation, and his heart rhythm is tachycardic but regular, with a soft systolic murmur at the right sternal border and an S_4 gallop. His apical impulse is focal and nondisplaced. His abdominal examination is positive for mild epigastric tenderness. Rectal examination shows black, sticky stool and is positive for occult blood. His hemoglobin level is 5.9 g/dL. Prothrombin time (PT) and partial thromboplastin time (PTT) are both normal, as are his renal and liver function tests. An electrocardiogram (ECG) reveals sinus tachycardia with no ST-segment changes, T-wave inversion in the anterior precordial leads, and no ventricular ectopy. Creatine kinase (CK) is 127 U/L with a normal creatine kinase myocardial band (CK-MB) fraction, and troponin I levels are normal.

- What is the most likely diagnosis?
- What is the next step?
- What are some possible complications from the intervention?

ANSWERS TO CASE 55:
Symptomatic Anemia and Transfusion Medicine

Summary: A 62-year-old man presents with

- A recent NSTEMI without major blockage
- Angina at rest without electrocardiographic changes
- Tachycardia with orthostatic hypotension, which indicates major hypovolemia from blood loss
- Melena and hemoglobin 5.9 g/dL, suggesting upper gastrointestinal (GI) hemorrhage, possibly from antiplatelet agents

Most likely diagnosis: Unstable angina, which has been precipitated by anemia secondary to acute GI blood loss.

Next step: Transfusion with packed red blood cells (PRBCs).

Possible complications: There are a multitude of transfusion complications, ranging from transmission of infections (hepatitis C, hepatitis B, human immunodeficiency virus [HIV], etc) to reactions such as acute hemolytic transfusion reaction, febrile nonhemolytic transfusion reaction, transfusion-related acute lung injury (TRALI), and anaphylaxis.

ANALYSIS

Objectives

1. Understand the indications for transfusion of red blood cells. (EPA 1, 4)
2. Recognize the indications for transfusion of platelets and of fresh frozen plasma (FFP). (EPA 1, 4)
3. Describe the complications of transfusions. (EPA 10)
4. Be aware of alternatives to transfusion. (EPA 4, 12)

Considerations

This 62 year old patient has two urgent problems, the upper GI hemorrhage and acute coronary syndrome, which is most likely unstable angina. The first set of cardiac enzymes are negative, but another set is important to obtain to definitely rule out acute MI. The patient had a recent coronary angiography which did not show blockage; thus, the severe anemia likely is causing the chest pain and ECG findings, consistent with unstable angina. The unstable angina may be the result of decreased oxygen supply to the heart due to blood loss. Thus, replacing blood volume treats both problems. Importantly, restoration of oxygen delivery to the heart is critical to avoid myocardial necrosis. The hemoglobin level of 5.9 g/dL may not be reflective of the true severity of anemia. Acutely, because patients bleed whole blood, the ratio of red cells to plasma volume does not change. It is only after volume repletion and restoration of the intravascular volume that we may see the

true hemoglobin level. Meanwhile, another consideration is that transfusion that is too rapid may lead to volume overload, if the patient has any degree of heart failure. Thus, this patient is very complex and fragile, and should be monitored carefully in the critical care area.

APPROACH TO: Transfusion Medicine

DEFINITIONS

ACUTE HEMOLYTIC REACTION: Transfusion reaction due to antibody lysis of transfused red blood cells.

NON–ST-ELEVATION MYOCARDIAL INFARCTION: Clinical features of unstable angina, but with evidence of myocardial necrosis such as elevated cardiac biomarkers.

TRANSFUSION-RELATED ACUTE LUNG INJURY: Immune-mediated lung injury in reaction to any blood product. Characterized by acute respiratory distress occurring during or within 6 hours of the transfusion.

UNSTABLE ANGINA: Angina pectoris or equivalent ischemic discomfort occurring at rest, or severe and new onset, or in a crescendo pattern. Unstable angina, unlike NSTEMI or STEMI (ST-segment elevation myocardial infarction), does not cause elevated levels of cardiac biomarkers or ST-segment elevation on ECG.

CLINICAL APPROACH

Anemia

Anemia occurs when the hemoglobin level is less than 12 g/dL in women or less than 13 g/dL in men. Symptoms attributable to anemia are manifold and depend primarily on the patient's underlying cardiopulmonary status and the chronicity with which the anemia developed. For a slowly developing, chronic anemia in patients with good cardiopulmonary reserve, symptoms may not present until hemoglobin levels are as low as 3 or 4 g/dL. Patients with serious underlying cardiopulmonary disease who depend on adequate oxygen-carrying capacity may become symptomatic with smaller drops in hemoglobin.

Packed Red Blood Cells

Indications for transfusion of PRBCs are acute surgical or nonsurgical blood loss; anemia with end-organ effects (eg, syncope, angina pectoris) or hemodynamic compromise; and critical illness to improve oxygen-carrying capacity or delivery to tissues. There are no absolute guidelines or thresholds for transfusion. Many believe that a hemoglobin level of 7 g/dL is adequate in the absence of a clearly defined increased need, such as cardiac ischemia, for which a hematocrit level of at least 30% may be desired. In the absence of ongoing bleeding or destruction of red cells, we typically expect that **each unit of PRBCs will result in an increase of 1 g/dL in**

the hemoglobin level or 3% in the hematocrit level. In addition to PRBCs, there are other components of whole blood, including platelets, FFP, cryoprecipitate, and intravenous immunoglobulin (IVIg).

Platelets and Fresh Frozen Plasma

Thrombocytopenia can frequently be treated with platelet transfusion. When a patient has a platelet count of less than 50,000/mm^3 and has significant bleeding, or when a patient is at risk for spontaneous bleeding with a level of less than 10,000/mm^3, platelets can be transfused. Each unit increases the platelet count from 5000 to 10,000/mm^3. Transfusion is generally not helpful in cases of platelet destruction, such as immune thrombocytopenic purpura (ITP), unless active, severe bleeding occurs. Platelet transfusion is contraindicated in patients with thrombotic thrombocytopenic purpura (TTP), as it may worsen microvascular thrombosis and cause worsening neurologic symptoms or renal failure.

Fresh Frozen Plasma. FFP replaces clotting factors and is often given to reverse **warfarin (Coumadin) anticoagulation.** Cryoprecipitate from FFP replaces fibrinogen and some clotting factors, making it useful in patients with hemophilia A and von Willebrand disease.

Alternatives to Transfusions

Erythropoietin, a hormone that promotes red cell production, is often used in the treatment of **renal failure–related anemia** or in patients who are banking a presurgical autologous transfusion to encourage quicker recovery of their hemoglobin levels prior to surgery. Cell savers salvage some intraoperative blood losses, which are then transfused back into the patient. Some patients may not wish to have foreign blood products transfused. In these cases, we can increase the baseline hemoglobin level by using erythropoietin and iron before planned surgery, minimize phlebotomy for laboratory testing, and use cell savers during surgery.

Complications

Infection. Viruses that are screened for but can still be transmitted include hepatitis C virus (1 in 103,000 units), human T-cell lymphocyte virus types I and II, HIV (1 in 700,000), hepatitis B virus (1 in 66,000), and parvovirus B19. Rarely, bacterial contamination (eg, *Yersinia enterocolitica*) causes fevers, sepsis, and even death during or soon after transfusion. Parasites (eg, malaria) are screened for by questioning a donor's medical and travel history.

Immune-Mediated Complications. With respect to immune mechanisms, it is possible that a recipient has preformed natural antibodies that lyse foreign donor erythrocytes, which can be associated with the major A and/or B or O blood types or with other antigens (eg, D, Duffy, Kidd). To avoid hemolysis, a "type and cross" is first performed, in which blood samples are tested for compatibility prior to transfusion.

An **acute hemolytic transfusion** reaction, which is caused by ABO incompatibility due to clerical error, typically occurs within 1 hour of the transfusion being started. It may be associated with **hypotension, fever, chills, hemoglobinuria, flank pain, disseminated intravascular coagulation (DIC)**, and **renal failure.** This is **a medical emergency**, so transfusion must be halted immediately, and fluids, specifically

normal saline, should be started urgently to prevent progression into renal failure. Lactated Ringer's solution and fluids with dextrose should be avoided; the calcium content in lactated Ringer's may cause clotting of blood in the intravenous line, and dextrose can cause hemolysis of red blood cells in the intravenous line. Diuretics may be used in those with volume overload if the patient is not hypotensive; in severe cases, dialysis may be initiated to protect from kidney failure via immune-complex deposits. Laboratory tests for intravascular hemolysis should be checked (lactate dehydrogenase [LDH], indirect bilirubin, haptoglobin), as well as coagulation tests for DIC.

Delayed hemolytic reactions are less predictable and usually milder; these reactions involve amnestic responses from the recipient. They range from urticaria treated with diphenhydramine and transfusion interruption to anaphylaxis, in which case the transfusion must be stopped and epinephrine and steroids given. Febrile nonhemolytic transfusion reactions, thought to result from production of leukocyte cytokines during storage, can be treated by antipyretics and prevented by leukoreduction. Sometimes TRALI occurs, in which case the appearance of bilateral interstitial infiltrates in the lung represents noncardiogenic pulmonary edema.

Nonimmune Complications. Considering nonimmune consequences, the transfusion itself supplies 300 mL of fluid per unit of PRBCs intravascularly, so patients can easily become volume overloaded. Adjusting the volume and rate and using diuretics will prevent this complication. Each unit of blood also provides 250 mg of iron. Multiple and frequent transfusions can cause iron overload and deposition (hemosiderosis), leading to cirrhosis, cardiac problems (eg, arrhythmia, heart failure), or diabetes.

CASE CORRELATION

- See also Case 3 (Acute Coronary Syndrome), Case 54 (Iron-Deficiency Anemia), Case 56 (Immune Thrombocytopenia Purpura/Abnormal Bleeding), and Case 58 (Sickle Cell Crisis).

COMPREHENSION QUESTIONS

55.1 A 32-year-old man with no significant past medical history is brought into the emergency department after a motor vehicle accident. On examination, he is actively bleeding from a femur fracture. He is found to be in hypovolemic shock with a BP of 60/40 mm Hg, HR of 120 bpm, and RR of 20 breaths/min. Laboratory tests show a hemoglobin level of 6 g/dL. His wife is absolutely sure that the patient's blood type is A positive. Which of the following is the most appropriate type of blood to be transfused?

A. Await crossmatched A-positive blood.

B. Give AB-positive blood, uncrossmatched.

C. Give O-negative blood, uncrossmatched.

D. Give type-specific A-positive blood, uncrossmatched.

55.2 A 45-year-old woman presents to the emergency department for 6 months of severe menorrhagia. Initial vital signs reveal a temperature of 98.2 °F, BP of 105/82 mm Hg, HR of 102 bpm, RR of 14 breaths/min, and oxygen saturation 95% on room air. Laboratory tests showed a hemoglobin level of 6 g/dL. She feels dizzy, weak, and fatigued. She receives 3 units of packed erythrocytes intravenously. Two hours into the transfusion, she develops fever to 103 °F and shaking chills. Which of the following laboratory tests would most likely confirm an acute transfusion reaction?

A. Direct bilirubin level

B. Glucose level

C. LDH level

D. Leukocyte count

55.3 A 57-year-old man on warfarin with a past medical history of hypertension and aortic stenosis with prosthetic aortic valve replacement is brought to the emergency department by his wife. He is noted to have an international normalized ratio (INR) of 7 and is actively bleeding large clots from his gums and rectum and when urinating. Which of the following is the best next step in management?

A. Administer IVIg.

B. Administer vitamin D.

C. Discontinue the warfarin and observe.

D. Transfuse FFP.

55.4 A 34-year-old woman presents to the emergency department complaining of weakness, dizziness, and fatigue. Her menstrual period started 4 days ago, and she has been having heavier than normal bleeding, soaking through four or five pads a day. She appears pale on physical examination. On initial vitals, she is afebrile and hemodynamically stable. Hemoglobin level is 6.6 g/dL. One unit of red blood cells is ordered. One hour into the transfusion, she complains of chills and flank pain. Vitals reveal a temperature of 101.5 °F, BP of 95/70 mm Hg, HR of 110 bpm, RR of 18 breaths/min, and O_2 saturation of 95% on room air. The blood transfusion is immediately stopped. Which of the following is the best next step in management?

A. Antibiotics

B. Furosemide

C. Methylprednisolone

D. Normal saline

ANSWERS

55.1 **C.** This patient needs a blood transfusion immediately, as evidenced by his dangerously low BP. He does not have the 45 minutes required for crossmatching his blood (answer A). Even though the patient's wife is "absolutely sure" about the blood type being type A (answer D), history is not completely reliable.

In an emergent situation such that uncrossmatched blood must be given, O-negative blood (universal donor) (answer C) usually is administered. Giving AB-positive blood, uncrossmatched (answer B), is not the best treatment for this patient in any circumstance.

55.2 **C.** This patient is suffering from acute hemolytic transfusion reaction characterized by fever, hypotension, and hemolysis. Elevated LDH and **indirect** bilirubin levels or decreased haptoglobin levels would be consistent with hemolysis. Glucose (answer B), direct bilirubin (answer A), and leukocyte count (answer D) are not direct markers of hemolysis.

55.3 **D.** This patient has active bleeding, so watching and observing (answer C) is not an option. When life-threatening acute bleeding occurs in the face of coagulopathy due to warfarin use, the treatment is FFP. The INR is extremely high, consistent with a severe coagulopathy. IVIg (answer A) is not treatment for bleeding secondary to supratherapeutic INR; IVIg is used in the treatment of immune thrombocytopenia. Vitamin D (answer B) does not have a primary role in coagulation, whereas vitamin K does have a primary role.

55.4 **D.** This patient is likely experiencing an acute hemolytic transfusion reaction, as evidenced by his fever, hypotension, and flank pain an hour after red blood cell transfusion. Treatment includes immediately stopping the transfusion and starting normal saline to prevent the progression to renal failure. Diuretics (answer B) can be used to prevent oliguric renal failure, but this patient is hypotensive, so that would not be the next step. This patient spiked a fever, but this is likely a result of a transfusion reaction rather than sepsis at this point. Therefore, antibiotics (answer A) are not yet warranted. Methylprednisolone (answer C), which is a potent corticosteroid, has not been shown to be effective in treating acute transfusion reactions but is sometimes used as an adjunct medication for anaphylactic reactions following transfusions.

CLINICAL PEARLS

- The symptoms of anemia are related to the onset time with which the anemia developed as well as the patients' underlying cardiopulmonary status.
- Myocardial ischemia or infarction may be precipitated by factors related to loss of oxygen-carrying capacity.
- Transfusion of blood carries certain risks, such as hemolytic reaction, infection (ie, HIV and hepatitis C), and transfusion-related lung injury.
- Platelet transfusions are indicated for severe thrombocytopenia with bleeding symptoms, but they have limited benefit in ITP and are definitely contraindicated in TTP.
- Fresh frozen plasma is used to correct coagulopathy by providing clotting factors.

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CASE 56

A 26-year-old woman presents to the emergency department complaining of bleeding from her nose and mouth that started last night. She also noticed small, reddish spots on her lower extremities when she got out of the bed this morning. She denies fever, chills, nausea, vomiting, abdominal pain, or joint pain. The patient reports she had developed an upper respiratory infection 2 weeks prior to the emergency department visit, but the infection resolved. She has no current medical problems. Her menses have been normal, and her last menstrual period was approximately 2 weeks ago. She denies excessive bleeding in the past. Prior to this episode, she never had epistaxis, easy bruising, or bleeding into her joints. There is no family history of abnormal bleeding. The patient does not take any medications.

On examination, she is alert, oriented, and somewhat anxious. Her blood pressure (BP) is 110/70 mm Hg, her heart rate (HR) is 90 beats per minute (bpm), and she is afebrile. No pallor or jaundice is noted. There is bright red blood oozing from the nose and the gingiva. Skin examination reveals multiple 1-mm flat reddish spots on her lower extremities. The rest of the examination is normal. No lymphadenopathy or hepatosplenomegaly is noted. Her complete blood count (CBC) is normal, with the exception of a platelet count of 18,000/mm^3. Prothrombin time (PT) and partial thromboplastin time (PTT) are normal.

- What is the most likely diagnosis?
- What is the next diagnostic step?
- What is the best initial treatment?

ANSWERS TO CASE 56:
Immune Thrombocytopenic Purpura/Abnormal Bleeding

Summary: A 26-year-old woman presents with

- Persistent epistaxis
- Petechiae on legs
- No past medical history and no personal or family history of excessive bleeding or easy bruising
- No lymphadenopathy or hepatosplenomegaly
- Other than thrombocytopenia (18,000/μL), CBC normal
- Prothrombin time and PTT normal

Most likely diagnosis: Immune thrombocytopenic purpura (ITP).

Next diagnostic step: Peripheral smear to rule out other causes of thrombocytopenia.

Best initial treatment: Oral corticosteroids.

ANALYSIS

Objectives

1. Recognize causes of bleeding disorders, including those affecting platelets and coagulation factors. (EPA 1, 2)
2. Differentiate causes of thrombocytopenia, specifically thrombocytopenic purpura versus other platelet disorders, such as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC). (EPA 2, 3)
3. Describe the treatment of ITP. (EPA 4)

Considerations

This patient presents with mucosal bleeding, petechiae, and thrombocytopenia. She has no other history, symptoms, or physical examination findings of any systemic disease; thus, her problem appears to an isolated hematologic problem. A CBC is important to ensure that other cell lines are normal; if abnormal, conditions such as acute leukemia or a bone marrow infiltrative process must be considered and cannot be ruled out. A peripheral smear would also be helpful in teasing out the etiology of her thrombocytopenia. Her coagulation studies (PT and PTT) are also normal; if they were deranged, we would suspect a consumptive coagulopathy causing the thrombocytopenia and a serious underlying disorder. Her current platelet count does not pose a risk for spontaneous hemorrhage, but counts lower than 10,000/μL might place her at risk for serious or life-threatening bleeding.

APPROACH TO: Abnormal Bleeding

DEFINITIONS

HEMOLYTIC UREMIC SYNDROME: A clinical complex consisting of progressive renal failure that is associated with microangiopathic hemolytic anemia and thrombocytopenia.

IMMUNE THROMBOCYTOPENIC PURPURA: A hematologic disorder characterized by the destruction of blood platelets due to the presence of antiplatelet autoantibodies.

THROMBOCYTOPENIA: Platelet count of less than 150,000/μL.

THROMBOTIC THROMBOCYTOPENIC PURPURA: A life-threatening syndrome characterized by a pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, fever, and renal dysfunction.

CLINICAL APPROACH

Pathophysiology

Background. For a patient with abnormal bleeding, it is important to screen for previous episodes of bleeding, even if it affected other bodily areas. It is necessary to ask about a history of recurrent epistaxis, menorrhagia, excessive prolonged bleeding from minor cuts, dental extraction, major surgery, obstetric delivery, or trauma. Excessive mucosal bleeding (eg, gum and nose bleeding) and petechiae are suggestive of thrombocytopenia or abnormal platelet function such as von Willebrand disease (vWD). On the other hand, more severe bleeds such as hemarthrosis, deep hematomas, and retroperitoneal bleeding are more likely signs of a severe coagulation abnormality, such as hemophilia due to factor VIII or IX deficiencies.

Definition and Causes. Thrombocytopenia is defined as a platelet count of less than 150,000/μL, although spontaneous bleeding usually occurs at much lower platelet counts. The causes of thrombocytopenia can be divided into (1) decreased platelet production, (2) decreased platelet survival, (3) sequestration (hypersplenism), and (4) dilutional.

Impaired platelet production is caused by **bone marrow abnormalities.** Examples include marrow infiltration by malignancy or myelofibrosis and marrow suppression resulting from exposure to chemicals, drugs, radiation, or viruses. In bone marrow diseases, thrombocytopenia is often accompanied by abnormalities in the other cell lines.

Decreased platelet survival is another cause of thrombocytopenia. Hemolytic reactions represent a prime example. They can be caused by infection, medications, autoimmune diseases (eg, systemic lupus erythematosus), HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, and other etiologies. Decreased platelet survival can also be due to **splenic sequestration** in patients with splenomegaly due to various reasons (eg, portal hypertension, myelofibrosis).

When a patient presents with thrombocytopenia, **any drug that the patient is using should be considered a possible cause.** Common drugs known to cause thrombocytopenia include H_2 blockers, quinine, and sulfonamides. In general, the diagnosis is made by clinical observation of the response to drug withdrawal. Discontinuation of the offending medication should lead to improvement in the platelet count within a time frame consistent with the drug's metabolism, almost always within 7 to 10 days.

Immune Thrombocytopenic Purpura

Acute ITP is most common in early childhood, **often following an upper respiratory infection**; it is usually self-limiting. ITP in children has a higher likelihood of spontaneous remission. **ITP in adults**, commonly presenting in women ages 20 to 40, is more likely to have an insidious or subacute presentation that can persist for months to years, with **uncommon spontaneous remission.** The patient presents with the clinical manifestations of thrombocytopenia (petechiae and mucosal bleeding) without systemic toxicity, lymphadenopathy, or splenomegaly.

Laboratory values show normal white and red blood cell counts, and normal peripheral blood smear except for thrombocytopenia. Laboratory testing is usually focused on a search for secondary causes of thrombocytopenia such as human immunodeficiency virus (HIV), hepatitis C, antinuclear antibody (ANA), and a direct Coombs test to evaluate for autoimmune hemolytic anemia with ITP (Evans syndrome). Bone marrow biopsy, although seldom recommended, reveals increased megakaryocytes but otherwise normal findings. In patients older than 60 years, bone marrow examination may be needed in order to exclude myelodysplastic syndrome.

Adults with ITP and platelet count > 30,000/μL and no bleeding may be observed without treatment. Those with lower platelet counts or bleeding can be treated with **oral glucocorticoids**, such as prednisone. Platelet transfusions are usually unnecessary and should be reserved for rare life-threatening situations. The survival of transfused platelets in ITP may be as short as a few minutes. **Intravenous immunoglobulin (IVIg)** is often used when platelet counts are less than 10,000/mm^3 and can raise platelet counts rapidly. Anti-D is an anti-Rh(D) immune globulin for patients who have an Rh+ blood type, but it may be ineffective in patients who have had a splenectomy. Rituximab is an anti-CD20 monoclonal antibody that targets autoantibody-producing lymphocytes and is a second-line therapy for patients with chronic ITP.

Because the spleen removes the antibody-bound platelets, patients with chronic ITP who do not respond to medical therapy may be candidates for **splenectomy**. Patients being considered for splenectomy should receive immunizations for encapsulated organisms such as *Pneumococcus* prior to surgery.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an immune-mediated disorder caused by the formation of antibodies against the heparin-platelet factor 4 complex, with the **fall in platelet count usually occurring 5 to 10 days after heparin begins or sooner if the patient had been sensitized by prior heparin use.** HIT can cause

serious consequences. HIT differs from other drug-induced causes of thrombocytopenia in that it is **not associated with bleeding, but rather with increased risk of thrombosis.** The four Ts are a useful mnemonic of the diagnostic criteria for HIT:

- **T**hrombocytopenia (nadir rarely < 20,000/μL).
- **T**iming of platelet count drop (usually 5–10 days).
- New **T**hrombosis of skin necrosis.
- Other causes of **T**hrombocytopenia are not likely.

Diagnosis depends on clinical suspicion and utilization of an enzyme-linked immunosorbent assay (ELISA) for the HIT antibodies. Treatment includes discontinuing heparin (one cannot switch from unfractionated heparin to low-molecular-weight heparin because HIT antibodies will cross-react), and using a nonheparin anticoagulant with a different mechanism of action such as argatroban, fondaparinux, or bivalirudin to treat thrombosis.

Disseminated Intravascular Coagulation

Thrombocytopenia may also be caused by consumptive coagulopathy, the most common of which is **DIC**. DIC usually is triggered by serious underlying conditions, such as bacterial sepsis; malignancy, such as acute promyelocytic leukemia; or obstetric catastrophes, such as abruptio placentae. Any of these disease processes can produce pathologic levels of tissue factor, triggering uncontrolled thrombin generation with systemic fibrin deposition in the microcirculation. This uncontrolled activation of coagulation results in consumption of platelets and clotting factors, leading to secondary bleeding. Laboratory findings include thrombocytopenia, elevated PT and PTT (consumptive coagulopathy), decreased fibrinogen, and **elevated fibrin-split products and D-dimer** (uncontrolled fibrin deposition). Treatment should be directed toward correcting the underlying cause, as well as replacement of platelets and coagulation factors if there is clinically significant bleeding.

Thrombotic Thrombocytopenic Purpura

TTP may be triggered by infection such as HIV or medications such as clopidogrel, or it may be idiopathic. TTP is caused by autoantibody-mediated deficiency of the ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) protease, which cleaves ultra-large von Willebrand factor (vWF) multimers on the endothelial surface. TTP is remembered by a pentad of findings: **(1) thrombocytopenia**, **(2) microangiopathic hemolytic** anemia with elevated lactate dehydrogenase (LDH) level and schistocytosis in the peripheral blood smear, **(3) fever**, **(4) fluctuating central nervous system (CNS) deficits with altered mental status**, and **(5) renal failure**. Patients may be acutely ill, and differentiation from DIC may be challenging except that the PT and PTT are typically normal in TTP, but elevated in DIC. Plasma exchange is the standard treatment and has reduced the mortality of this condition greatly. Table 56–1 compares DIC, TTP, and ITP.

Table 56–1 • COMPARISON OF DIC, TTP, AND ITP

Condition	Etiology	Clinical Course	Treatment
Disseminated intravascular coagulopathy (DIC)	Secondary to some other process, such as sepsis, trauma, metastatic malignancy, and obstetric causes.	Can be relatively mild indolent course or severe life-threatening process; ongoing coagulation and fibrinolysis can cause thrombosis or hemorrhage; consumption of coagulation factors is seen as prolonged PT and PTT.	Treatment aimed at underlying cause. No proven specific treatment for the coagulation problem. If bleeding, replace factors and fibrinogen with fresh frozen plasma (FFP) or cryoprecipitate; if clotting, consider anticoagulating with heparin.
Thrombocytopenic thrombotic purpura (TTP)	Autoantibody with inhibition of ADAMTS13 protease (< 10% activity) release of von Willebrand factor (vWF), triggering formation of microvascular thrombi.	May present as septic-appearing patient with fever, altered mental status, thrombocytopenia, microangiopathic hemolytic anemia, and renal failure. Normal PT and PTT. Mortality mainly due to CNS involvement.	Plasmapheresis (removal of the excess/abnormal vWF), after which most patients recover. Corticosteroids.
Immune thrombocytopenic purpura (ITP)	Antiplatelet antibody leading to platelet destruction.	Children: occurs following a viral illness with resolution; in adults, a more indolent course with progression and rarely spontaneous resolution. Isolated thrombocytopenia, normal PT, PTT.	Oral corticosteroids; intravenous immunoglobulin (IVIg); splenectomy if refractory.

Hemolytic Uremic Syndrome

HUS presents very similarly to TTP, with acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. Clinically, it may appear to be "TTP limited to the kidney," but the mechanism and treatment differ from TTP. HUS occurs most often in children after a diarrheal illness, often with the **hemorrhagic strain of *Escherichia coli* O157:H7**. Treatment is supportive, and plasma exchange for HUS has not been shown to be useful.

von Willebrand Disease

Patients with vWD present clinically with impaired primary hemostasis (ie, petechiae, easy bruising, mucosal bleeding, menorrhagia) with normal platelet counts but impaired platelet function. vWD is the **most common inherited bleeding**

disorder. It may occur as often as 1 in 1000 individuals. It may be acquired, or it may be inherited as an **autosomal dominant disorder;** however, it is often not recognized because of relatively mild bleeding symptoms. von Willebrand factor is a large, complex multimeric protein that has two major functions: It allows for platelet adhesion to endothelium at sites of vascular injury, and it is the carrier protein for coagulation factor VIII, which stabilizes the molecule. vWD is a heterogeneous group of disorders, but a common feature is **deficiency in the amount** or **function of vWF.** Clinical features are those of primary hemostatic defects as discussed. Typical laboratory features are reduced levels of vWF, reduced vWF activity as measured by ristocetin cofactor assay, and reduced factor VIII activity. The platelet count is usually normal, bleeding time is increased, and PTT may or may not be prolonged. Treatment is **desmopressin acetate**, which causes release of vWF from endothelial stores, or use of factor VIII concentrate, which contains a large amount of vWF.

CASE CORRELATION

- See also Case 54 (Iron-Deficiency Anemia) and Case 58 (Sickle Cell Crisis).

COMPREHENSION QUESTIONS

56.1 A 28-year-old woman presents to the emergency department with complaints of excessive bleeding from her gums and petechiae. She is otherwise healthy and takes no medications. She smokes half a pack of cigarettes daily and occasionally drinks beer. Her temperature is 99.1 °F, BP is 110/81 mm Hg, HR is 85 bpm, and respiratory rate (RR) is 12 breaths/min. On physical examination, she has bleeding from her gums and petechiae on her bilateral lower extremities. Her CBC shows a white blood cell (WBC) count of 87,000/mm^3, a hemoglobin of 8.9 g/dL, and a platelet count of 22,000/mm^3. Which of the following is the most likely etiology of her low platelet count?

A. Acute leukemia

B. Drug-induced thrombocytopenia

C. Immune thrombocytopenia purpura

D. Systemic lupus erythematosus

56.2 A 50-year-old man has been treated for rheumatoid arthritis for many years. He currently is taking corticosteroids for the disease. On examination, he has stigmata of rheumatoid arthritis and some fullness on his left upper abdomen. His platelet count is slightly low at 105,000/mm^3. His WBC count is 3100/mm^3 with neutropenia, and hemoglobin level is 9 g/dL. Which of the following is the most likely etiology of the thrombocytopenia?

A. Autoimmune destruction
B. Prior gold therapy
C. Splenic sequestration
D. Steroid induced

56.3 A 30-year-old woman with ITP comes to her outpatient hematology office for a routine follow-up. She reports that despite taking maximum corticosteroid doses, she still has a platelet count of 20,000/mm^3 and frequent bleeding episodes. Which of the following should she receive before her splenectomy?

A. Bone marrow radiotherapy
B. Intravenous interferon therapy
C. Pneumococcal vaccine
D. Washed leukocyte transfusion

56.4 A 65-year-old man with a history of prosthetic aortic valve, hypertension, and osteoarthritis is hospitalized for an elective knee replacement surgery. The patient is a nonsmoker but drinks one or two glasses of wine on the weekends. His admission CBC shows a WBC count of 8000/mm^3, hemoglobin of 9.2 g/dL, and a platelet count of 250,000/mm^3. Medications started on admission include acetaminophen, heparin prophylaxis, lisinopril, and pantoprazole. The patient's hospital course was complicated by acute kidney injury and postsurgery ileus. Five days after his knee surgery, laboratory tests are significant for a platelet count of 62,000/mm^3. Which of the following is the most likely cause of the thrombocytopenia?

A. Acetaminophen
B. Alcohol intake
C. Heparin
D. Prosthetic heart valve

ANSWERS

56.1 **A.** The thrombocytopenia is seen with other hematologic abnormalities, the most abnormal of which is a markedly elevated WBC count, suggesting acute leukemia, which should be further worked up with a peripheral smear. The patient is not on any known medication to cause thrombocytopenia (answer B). ITP is often a diagnosis of exclusion in the setting of low platelets without additional hematologic abnormalities (answer C). The patient is not showing any additional symptoms pointing to lupus, such as discoid or malar rashes, oral ulcers, arthralgia, glomerulonephritis, and hypocomplementemia (answer D).

56.2 **C.** This patient is likely suffering from Felty syndrome, characterized by rheumatoid arthritis, neutropenia, and splenomegaly. Splenomegaly from any etiology may cause sequestration of platelets, leading to thrombocytopenia. An acronym for Felty syndrome is SANTA: splenomegaly, anemia, neutropenia, thrombocytopenia, and arthritis (rheumatoid). The other answer choices (answer A, autoimmune destruction; answer B, prior gold therapy; and answer D, steroid induced) can also cause thrombocytopenia, but splenic sequestration is the most likely with this patient's constellation of symptoms.

56.3 **C.** This patient should undergo splenectomy for refractory ITP. Thus, she will be at risk for infections by encapsulated organisms such as *Streptococcus pneumoniae* and will benefit from the pneumococcal vaccine. Usually, it is given at least 2 weeks prior to splenectomy so that the spleen can help in forming a better immune response. The other choices (answer A, bone marrow radiotherapy; answer B, intravenous interferon therapy; and answer D, washed leukocyte transfusion) would not provide the protective immune response prior to splenectomy like the pneumococcal vaccine would.

56.4 **C.** The patient likely has HIT, which may be confirmed by assay for HIT antibodies, including immunoglobulin G against platelet factor 4. The timing after the exposure to heparin, the new platelet count, and the absence of a possible alternative cause support the suspicion. Treatment consists of stopping the heparin and starting a direct Xa inhibitor such as argatroban or bivalirudin. Acetaminophen is more commonly associated with hepatotoxicity than thrombocytopenia (answer A). Chronic alcohol intake (answer B) may lead to thrombocytopenia through toxicity to the bone marrow, though we would not likely see such an acute manifestation in the hospital setting. Prosthetic heart valves (answer D) can lead to an increased risk of thrombosis and embolization, especially in the setting of HIT.

CLINICAL PEARLS

- Disorders of primary hemostasis are characterized by mucosal bleeding and the appearance of petechiae or superficial ecchymoses.
- Disorders of secondary hemostasis are characterized by the development of superficial ecchymoses as well as deep hematomas and hemarthroses.
- Immune thrombocytopenic purpura is a diagnosis of exclusion.
- Spontaneous hemorrhage may occur with platelet counts of less than 10,000/mm^3.
- Platelet transfusion in ITP is often ineffective.
- Corticosteroids are the initial treatment of ITP. Patients with more severe disease can be treated with IVIg; chronic refractory cases are treated with rituximab or splenectomy.

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CASE 57

A 55-year-old woman comes to the clinic complaining of 6 months of progressive dull headaches and dizziness. She also endorses occasional blurred vision. She has a history of hypertension treated with metoprolol and is otherwise healthy. Her temperature is 99 °F, heart rate is 80 beats per minute (bpm), blood pressure is 110/70 mm Hg, and O_2 saturation is 95%. On examination, the patient looks flushed. Her mucous membranes are normal. Her heart and lung examinations are unremarkable, but the liver is palpable 3 cm below the costal margin, and dullness to percussion is noted at the lowest intercostal space in the left axillary line. Though the patient did not notice this, the right leg is swollen compared to the left one. The neurologic examination is nonfocal; no nystagmus is appreciated. The fundoscopic examination shows bilateral plethora of the retinal veins. The complete blood count reveals a white blood cell (WBC) count of 11,500/mm^3, hemoglobin level of 17 g/dL with a hematocrit of 51%, and platelet count of 350,000/mm^3.

- What is the most likely diagnosis?
- What is your next diagnostic step?
- What is the next step in therapy?

ANSWERS TO CASE 57:
Polycythemia Vera

Summary: A 55-year-old woman presents with

- Headaches, dizziness, blurred vision
- Congested retinal veins, flushed face, and hepatosplenomegaly
- Right leg swelling
- No hypoxemia
- Hemoglobin level of 17 g/dL with a hematocrit of 51%, all cell lines increased

Most likely diagnosis: Polycythemia vera (PV), with elevated hemoglobin and hematocrit and clinical symptoms of hyperviscosity. Additionally, a deep vein thrombosis (DVT) of the right leg is likely.

Next diagnostic step: Serum erythropoietin (EPO) level, *JAK2* mutation testing, peripheral smear to look for blasts, lower extremity duplex scan, and bone marrow biopsy.

Next step in therapy: Low-dose aspirin and therapeutic phlebotomy for PV. Due to thrombus history, can consider hydroxyurea if symptoms not controlled by phlebotomy. Therapeutic anticoagulation for DVT is also important.

ANALYSIS

Objectives

1. Recognize the diagnostic criteria for PV. (EPA 1, 3)
2. Enumerate basic characteristics of myeloproliferative disorders. (EPA 1)
3. Understand alternative reasons for expansion of all lineages of blood cells. (EPA 1, 2)
4. Outline the treatment options for PV. (EPA 4)

Considerations

This 55-year-old woman with 6 months of **headache, dizziness, and blurry vision** is admitted with a DVT of the right leg. Physical examination consists of several signs of hyperviscosity commonly seen in polycythemia, including **congested retinal veins, flushed face, hepatosplenomegaly, and right leg swelling.** Together with an elevated hemoglobin > 16 g/dL and hematocrit > 49% (criteria for women) with normal oxygen saturation, this scenario points toward one of the myeloproliferative neoplasms (MPNs), namely, PV. Peripheral smear, EPO, and *JAK2* mutation should be obtained. A low EPO level would point toward a primary polycythemia as opposed to a secondary polycythemia. *JAK2* mutation is positive in nearly all PV patients. A bone marrow biopsy would likely show hypercellularity with trilineage growth. According to the World Health Organization guidelines, the diagnosis

of PV requires meeting either all three major criteria (hemoglobin/hematocrit, bone marrow, and *JAK2* mutation) or two major criteria and one minor criteria (low EPO). PV is a chronic condition and will require low-dose aspirin and therapeutic phlebotomy to keep hematocrit levels < 45% in men and < 42% in women. A cytoreductive agent such as hydroxyurea can be considered if the patient continues to be symptomatic despite phlebotomy due to her thrombus.

APPROACH TO: Polycythemia Vera

DEFINITIONS

ERYTHROPOIETIN: Hormone produced by the kidneys that is stimulated by low oxygen levels to produce more RBCs in the bone marrow.

HYPERVISCOSITY SYNDROME: Constellation of symptoms arising from increased blood cellularity, including headache, blurry vision, transient loss of vision, chest pain, abdominal pain, and muscle pain.

MYELOPROLIFERATIVE DISEASE: Group of hematologic disorders characterized by overgrowth of bone marrow cell lines. Includes essential thrombocythemia (ET), PV, and primary myelofibrosis (MF).

POLYCYTHEMIA VERA: Disorder of the bone marrow resulting in overproduction of red blood cells (RBCs).

CLINICAL APPROACH

Pathophysiology

MPNs are a collection of disorders that are caused by the overproliferation of stem cells of the bone marrow, including ET, primary MF, and PV. All three may share the *JAK2* mutation, present in about 50% of cases of ET and MF, but in over 95% of PV (Table 57–1). All have increased risk of leukemia. ET is defined by thrombocytosis, which is overproduction of platelets. MF is the replacement of bone marrow by fibrosis. It has characteristic findings on peripheral smear, described as a leukoerythroblastic picture, and commonly associated with teardrop-shaped RBCs, nucleated erythrocytes, and precursors of granulocytes. PV is defined by

Table 57–1 • TYPES OF MYELOPROLIFERATIVE NEOPLASMS

Essential Thrombocythemia	Myelofibrosis	Polycythemia Vera
Overproduction of platelets > 450,000/mm^3	Teardrop cells Leukoerythroblastic	Overproduction of RBCs
JAK2+ in about 50%	*JAK2*+ in about 50%	*JAK2*+ in > 95%

Abbreviations: JAK2+, JAK2 V517F mutation positve; RBCs, red blood cells.

Table 57–2 • CLASSIFICATION OF POLYCYTHEMIA

Primary PV	Secondary PV	
Mutations [*JAK2*]	Hypoxia related • COPD • OSA/OHS • Heavy smoking • Carbon monoxide poisoning • Right-to-left shunt • High altitude	Other causes • Performance-enhancing drugs (testosterone) • EPO-producing tumor (hepatocellular carcinoma, renal cell carcinoma, pheochromocytoma)

Abbreviations: COPD, chronic obstructive pulmonary disease; EPO, erythropoietin; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea.

erythrocytosis, which is overproduction of RBCs, which we explore in more depth in the following sections.

Etiology. PV, the most common of the myelodysplastic disorders, is seen with an elevated hemoglobin and/or hematocrit; it can be initially differentiated as relative polycythemia or absolute polycythemia. When plasma volume is decreased secondary to diuretics or GI losses such as vomiting and diarrhea, hemoglobin and hematocrit (which represent the concentration of RBCs in blood) can be artificially elevated, commonly referred to as hemoconcentration or **relative polycythemia**. In these cases, once a patient is appropriately fluid resuscitated, hemoglobin and hematocrit are expected to normalize on a repeat CBC. If there is no normalization of hemoglobin/hematocrit or if the clinical picture is suggestive of PV, then absolute polycythemia, characterized by an increase in RBC mass, is suspected.

Absolute polycythemia can then further be divided into two categories, primary or secondary (Table 57–2). **Primary polycythemia**, caused most commonly by the *JAK2* mutation, results in increased RBC mass. **Secondary polycythemia** is driven by elevated levels of EPO, which is secreted in response to low levels of oxygen, to stimulate RBC production by the bone marrow. Most commonly, secondary polycythemia stems from chronic hypoxia from a cardiac or pulmonary origin, namely, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), obesity hypoventilation syndrome (OHS), right-to-left cardiac shunt, high altitude, or even heavy smoking. Performance-enhancing drugs such as anabolic steroids/testosterone, growth hormone, and EPO have started to become a more common cause of polycythemia. Additional causes include EPO-producing tumors, such as hepatocellular carcinoma, renal cell carcinoma, uterine leiomyoma, and adrenal sources such as pheochromocytoma.

Diagnosis. If patient has elevated hemoglobin/hematocrit on complete blood count in the context of normovolemia and normal O_2 saturation along with signs and symptoms of PV, then further evaluation with serum EPO level and/or *JAK2 V617F* mutation is warranted. If the EPO is elevated, then it is secondary polycythemia, most commonly associated with hypoxia. If the EPO is low to normal or if signs/symptoms of PV are seen, then a positive *JAK2* mutation is helpful in confirming its diagnosis. A bone marrow biopsy shows hypercellularity with trilineage growth. Diagnostic criteria are shown in Table 57–3.

Table 57–3 • POLYCYTHEMIA VERA DIAGNOSTIC CRITERIA

Major Criteria	Minor Criterion
1. Hb > 16.5 g/dL in men, > 16 g/dL in women, or Hct > 49% in men, > 48% in women, or increased RBC mass > 25% above mean normal predicted value 2. Bone marrow biopsy shows hypercellularity with trilineage growth (erythroid, granulocytic, and megakaryocytic proliferation) 3. *JAK2* V617F mutation positive	1. Low to low-normal EPO level
Diagnosis requires all three major criteria or two major and one minor criteria	

Abbreviations: EPO, erythropoietin; Hct, hematocrit; Hb, hemoglobin; RBC, red blood cell.

Clinical Presentation

Many times, patients are asymptomatic, and polycythemia is suspected from an elevated hemoglobin and hematocrit. Other times, patients present with a constellation of symptoms, many of which may be nonspecific. **Symptoms commonly associated with PV include night sweats, weight loss, early satiety, gout, pruritis, and erythromelalgia.** Pruritis, described by many as itchiness, tingling, or burning after a warm or hot shower, is often one of the chief complaints of a PV patient. Erythromelalgia, which consists of a burning pain, redness, and increased temperature in the hands and feet, is also a classic finding. Patients with PV are known to have an increased risk of thrombosis, whether a DVT, pulmonary embolism (PE), stroke, or arterial thrombus. Physical examination of a PV patient may include a plethora of the retinal veins and face, hepatomegaly, splenomegaly, thrombosis, easy bleeding or bruising, and tophi. If hyperviscosity develops, patients may have fatigue, headache, blurry vision, stroke, and paresthesias.

Treatment

PV is a slowly progressive disease that can develop over decades, so treatment may be indefinite. Overall, there are two main goals: (1) to reduce microvascular symptoms, such as pruritis, erythromelgia, and bleeding; and (2) to reduce thrombotic events.

Low-dose aspirin is recommended for all PV patients unless contraindications are present. Aspirin is particularly useful in reducing pruritis and erythromelalgia. **Therapeutic phlebotomy,** which decreases risk of thrombotic events by reducing hematocrit and expanding plasma volume, is the centerpiece of PV treatment. Phlebotomy aims to keep hematocrit levels < 45% in men and < 42% in women.

High-risk PV patients are those who are > 60 years old and/or have a history of thrombosis. In these patients, cytoreductive treatment might be useful. Furthermore, treatment may be indicated in low-risk patients with uncontrolled symptoms, increasing platelet counts (especially over 1,000,000/μL) or persistently elevated hematocrit despite phlebotomy. **Hydroxyurea**, a ribonucleotide reductase inhibitor that disrupts DNA repair to reduce the number of RBCs made by bone marrow, is the first-line cytoreductive agent. Side effects include cytopenia, oral ulcers, and diarrhea. In patients who fail hydroxyurea, **ruxolitinib** (Jakafi), a *JAK* inhibitor, is

becoming a mainstay in PV treatment. Other cytoreductive agents include interferon alfa or busulfan. Interferon alfa is often used in patients < 40 years and in pregnant patients. **Busulfan,** an alkylating agent, is tied to many side effects, including cytopenias, pulmonary fibrosis, skin discoloration, and/or leukemia.

Prognosis. **All of the MPNs (PV, MF, and ET) can spontaneously progress to acute myeloid leukemia or myelodysplastic syndrome.** Of the three, ET is the least likely to progress, while primary MF is the most likely to transform. The 10-year transformation rate is roughly 2% to 5% in ET, 5% to 8% in PV, and 8% to 20% in MF. The median survival times also follow a similar pattern, with average survival being 20 years for ET, 14 years for PV, and 6 years for MF. In PV patients, risk factors that increase risk of transformation to leukemia include age > 60, history of thrombosis, and leukocytosis. In ET, increased age and anemia correlate with risk of fibrotic transformation. Once progression to leukemia and/or blast phase has occurred, treatment includes induction chemotherapy followed by allogenic hematopoietic cell transplantation.

CASE CORRELATION

- See also Case 14 (Pulmonary Embolism) and Case 58 (Sickle Cell Crisis).

COMPREHENSION QUESTIONS

57.1 A 52-year-old man with diabetes and COPD presents to the emergency department for 2 days of poor oral intake due to nausea, vomiting, and diarrhea. Over the past few months, the patient reports worsening fatigue, headaches, shortness of breath, and insomnia. His temperature is 98.7 °F, blood pressure is 130/81 mm Hg, heart rate is 88 bpm, respiratory rate is 12 breaths/min, and oxygen saturation is 94% on room air. His body mass index (BMI) is 40 kg/m^2. On physical examination, he is obese, but he has normal cardiac, respiratory, and abdominal examinations. On his CBC, WBC count is 8500/mm^3, hemoglobin is 19 g/dL, hematocrit is 54%, and platelet count is 327,000/mm^3. Chest x-ray is unremarkable. Which of the following is the next best step in management?

A. Bone marrow biopsy

B. Computed tomography (CT) of the chest

C. Erythropoietin level

D. Phlebotomy

57.2 The patient in Question 57.1 receives 1 L of normal saline and on repeat laboratory work, the WBC count is 7500/mm^3, hemoglobin is 19 g/dL, hematocrit is 53%, and platelet count is 315,000/mm^3. EPO is elevated. The patient is sent home from the emergency department and returns to his primary care provider's office for a posthospitalization follow-up. Which of the following is the next best step in management?

A. Bone marrow biopsy
B. *JAK2* mutation evaluation
C. Phlebotomy
D. Pulmonary function test

57.3 A 67-year-old woman with a history of asthma and hypertension presents to her primary care provider's office for 6 months of fatigue, headache, and blurry vision. She reports smoking 1 pack of cigarettes daily and drinking two or three beers each week. She denies use of illicit drugs. Her temperature is 98.3 °F, blood pressure is 140/75 mm Hg, heart rate is 92 bpm, respiratory rate is 13 breaths/min, and oxygen saturation is 95% on room air. The WBC count is 11,500/mm^3, hemoglobin is 17 g/dL, hematocrit is 50%, and platelet count is 600,000/mm^3. EPO is low. *JAK2* mutation is positive. Bone marrow biopsy shows hypercellularity with trilineage growth. Which of the following is the most likely diagnosis?

A. Chronic myelogenous leukemia
B. Essential thrombocythemia
C. Polycythemia vera
D. Primary MF

57.4 A 67-year-old man with a history of systolic heart failure, pulmonary hypertension, left lower extremity DVT, and PV comes to his primary care provider for an annual checkup. The patient is on aspirin, atorvastatin, metoprolol, lisinopril, and therapeutic phlebotomy. He continues to report fatigue, blurry vision, and headache. The physical examination is unremarkable. The WBC count is 11,000/mm^3, hemoglobin is 17 g/dL, hematocrit is 48%, and platelet count is 325,000/mm^3. Which of the following is the best next step in management?

A. Continue current regimen
B. Start busulfan
C. Start hydroxyurea
D. Start induction chemotherapy

ANSWERS

57.1 **C.** This male patient's hemoglobin is > 16.5 g/dL and hematocrit is > 49%, so he meets the criteria for polycythemia. Polycythemia could be primary or secondary due to COPD or volume depletion. The best next step would be to test the EPO levels, as a low level would point to PV and a high level would point to a secondary polycythemia due to hypoxia or volume depletion, especially in the setting of his COPD history. *JAK2* mutation is also another test that is performed as part of the diagnostic approach prior to biopsy. Bone marrow biopsy (answer A) and *JAK2* evaluation can be obtained later if EPO is low, but a high EPO makes PV unlikely. CT scan of the chest (answer B) would be indicated if the patient had a pulmonary complaint such as chronic cough, but it would not be high yield in this case. Phlebotomy (answer D) can improve the hyperviscosity symptoms of polycythemia, but treatment should be aimed toward finding and treating the underlying cause.

57.2 **D.** An elevated EPO level points toward a secondary polycythemia, likely due to chronic hypoxia from a pulmonary or cardiac source, so *JAK2* mutation (answer B) and bone marrow biopsy (answer A) are not warranted at this time. Due to the patient's BMI of 40 kg/m^2, shortness of breath, and insomnia, pulmonary function tests may reveal the underlying cause of his polycythemia. Phlebotomy (answer C) can improve the hyperviscosity symptoms of polycythemia, but treatment should be aimed toward finding and treating the underlying cause.

57.3 **C.** This female patient has hemoglobin > 16 g/dL, low EPO, *JAK2* mutation, and bone marrow findings suggestive of PV, so she meets not only all three major criteria, but also the minor criteria. Though her platelets are over 450,000/mm^3 and *JAK2* mutation is positive, which can also be seen in ET, she has classic bone marrow biopsy findings of PV, and ET (answer B) is considered a diagnosis of exclusion. Chronic myelogenous leukemia (answer A) would typically lead to bone marrow infiltration of cancer cells and cause anemia rather than polycythemia. Similarly, primary MF (answer D) is a disorder where fibrous tissue forms in the bone marrow, leading to abnormally shaped RBCs and anemia.

57.4 **C.** This patient is over the age of 60 and has a history of DVT, so he is considered a high-risk PV patient. Despite being on both aspirin and therapeutic phlebotomy, the patient continues to have a hematocrit > 45%, so adding a cytoreductive agent is recommended. Hydroxyurea is considered first-line treatment. Busulfan (answer B) is another option, but it can cause pulmonary fibrosis and would not be a good option in this patient with pulmonary hypertension. Induction chemotherapy (answer D) would not be needed unless we have confirmed progression to leukemia. Continuing the current regimen (answer A) is not appropriate for this patient, who continues to have an increased hematocrit.

CLINICAL PEARLS

- Myeloproliferative neoplasms include ET, primary MF, and PV.
- Classic PV findings include pruritis and erythromelalgia.
- Hyperviscosity syndrome is characterized by fatigue, headache, blurry vision, transient vision loss, paresthesias, and thrombosis.
- Patients with primary polycythemia have low EPO and positive *JAK2* mutation.
- Those with secondary polycythemia have elevated EPO.
- In PV, hemoglobin is > 16.5 g/dL or hematocrit > 49% in men, hemoglobin > 16 g/dL or hematocrit > 48% in women.
- Essential thrombocythemia is associated with overproduction of platelets and is a diagnosis of exclusion.
- Teardrop cells are commonly seen on peripheral smear of MF.
- Mainstays of PV treatment include low-dose aspirin, therapeutic phlebotomy, and addition of cytoreductive agent in higher risk patients.
- Ruxolitinib (Jakafi) is a JAK inhibitor.

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CASE 58

A 25-year-old African American man is admitted to your service with the diagnosis of a sickle cell pain episode. He was admitted to the hospital six times last year with the same diagnosis, and he was last discharged 2 months ago. This time, he presented to the emergency department complaining of abdominal and bilateral lower extremity pain, his usual sites of pain. When you examine him, you note his temperature is 101 °F, blood pressure is 110/81 mm Hg, heart rate is 100 beats per minute (bpm), and respiratory rate is 25 breaths per minute. Lung examination reveals bronchial breath sounds and egophony in the right lung base. His oxygen saturation on 2 L/min nasal cannula is 92%. Besides the usual abdominal and leg pain, he is now complaining of chest pain, which is worse on inspiration. Although he has tenderness on palpation of his extremities, the remainder of his examination is normal. His laboratory examinations reveal elevated white blood cell and reticulocyte counts and a hemoglobin and hematocrit that are slightly lower than baseline. Sickle and target cells are seen on the peripheral smear.

- What is the most likely diagnosis?
- What is the most appropriate next step in management?
- What are the potential complications of this condition?
- What are the best treatment options for the probable condition?

ANSWERS TO CASE 58:
Sickle Cell Crisis

Summary: A 25-year-old African American man presents with

- A history of numerous pain crises
- Fever, tachypnea, oxygen saturation of 92% on 2 L via nasal cannula, and slight tachycardia
- Abdominal pain, lower extremity pain, and chest pain that is worse on inspiration
- Bronchial breath sounds and egophony in the right lung base
- Leukocytosis, elevated reticulocyte count, and lower than baseline hemoglobin and hematocrit
- Sickle and target cells on the peripheral blood smear

Most likely diagnosis: Acute chest syndrome (ACS) since the patient has fever and chest pain with respiratory symptoms.

Next step in management: Chest radiograph and empiric antibiotic therapy.

Potential complications: Respiratory failure, possible death.

Best treatment options: Aside from empiric antibiotic therapy, oxygen, pain control, incentive spirometry, and blood transfusion (simple if mild symptoms or exchange transfusion if severe).

ANALYSIS

Objectives

1. Understand the pathophysiology of sickle cell anemia and acute painful episodes. (EPA 12)
2. List the acute and chronic complications of sickle cell anemia. (EPA 10, 12)
3. Describe the treatment options available for the complications of sickle cell anemia. (EPA 4)

Considerations

The patient in this case, a 25-year-old man with known sickle cell disease and a history of numerous pain crises, is admitted with abdominal pain and bilateral leg pain. He also **has the acute onset of chest pain, cough, fever, and abnormal findings on pulmonary auscultation**. His **oxygen saturation is only 92% on 2 L oxygen via nasal cannula**, which is concerning. Pulmonary embolism, pneumonia, and **ACS** should be considered as possible diagnoses. **ACS** is a constellation of symptoms that includes chest pain and tachypnea. It can result from infection or from noninfectious causes such as pulmonary infarction or fat embolism. It usually presents with some combination of **chest pain, fever, hypoxia, and a new pulmonary infiltrate on chest radiography**. Often, ACS and pneumonia cannot be initially distinguished.

Therefore, it is prudent to treat these patients with antibiotics, obtain a Gram stain and culture of the sputum, and admit them to the hospital. The treatment for ACS is supportive and includes oxygen, intravenous fluid hydration, broad-spectrum antibiotics, analgesia, and transfusion. With significant disease, an exchange transfusion may be necessary. These patients should be carefully evaluated because significant morbidity or mortality can result.

APPROACH TO: Sickle Cell Anemia

DEFINITIONS

ACUTE CHEST SYNDROME: A condition found in individuals with sickle cell disease; the condition is characterized by **fever, tachycardia, chest pain, leukocytosis, and pulmonary infiltrates**.

SICKLE CELL ANEMIA: A congenital defect in hemoglobin formation such that both genes code for hemoglobin S, leading to hemolysis and an abnormal shape of the red blood cell. Affected individuals have numerous complications, including pain crises.

CLINICAL APPROACH

Pathophysiology

Sickle cell anemia is the most common autosomal recessive disorder and the most common cause of hemolytic anemia in African Americans. Approximately 8% of African Americans carry the gene (ie, sickle cell trait), with 1 in 625 affected by the disease.

The molecular structure of a normal hemoglobin molecule consists of two alpha-globin chains and two beta-globin chains. Sickle cell anemia is an autosomal recessive disorder resulting from a substitution of valine for glutamine in the sixth amino acid position of the beta-globin chain. Individuals in whom only half of their beta chains are affected are heterozygous, a state referred to as sickle cell trait. When both beta chains are affected, the patient is homozygous and has sickle cell anemia. In patients with sickle cell disease, the altered quaternary structure of the hemoglobin molecule causes polymerization of the molecules under conditions of deoxygenation. These rigid polymers distort the red blood cell into a sickle shape, which is characteristic of the disease. **Sickling** is promoted by **hypoxia, acidosis, dehydration, or variations in body temperature**.

Pain Crises. These are also called acute painful episodes and result from **microvascular occlusion of bones by sickled cells.** The most common sites are the long bones of the arms and legs, the vertebral column, and the sternum. Acute painful episodes are precipitated by infection, hypoxia (ie, at high altitude), cold exposure, dehydration, venous stasis, or acidosis. They usually last 2 to 7 days.

Infections. Patients with sickle cell disease are at greater risk for infections, especially with encapsulated bacterial organisms. **Infarction of the spleen** occurs during early childhood secondary to microvascular obstruction by sickled red blood cells. The spleen gradually regresses in size and by age 4 is no longer palpable. As a consequence of infarction and fibrosis, the immunologic capacity of the spleen is diminished. Patients with sickle cell disease are at greater risk for pneumonia, sepsis, and meningitis by encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. For the same reason, patients with sickle cell disease are at greater risk for **osteomyelitis with *Salmonella* spp.**

Acute Chest Syndrome. This a vaso-occlusive crisis in the lungs and may be associated with infection or pulmonary infarction. It is characterized by the presence of the following signs and symptoms: **new pulmonary infiltrate, chest pain, fever, and respiratory symptoms such as tachypnea, wheezing, or cough**. These episodes may be precipitated by pneumonia causing sickling in the infected lung segments or, in the absence of infection, intrapulmonary sickling can occur as a primary event. It is virtually impossible to clinically distinguish whether or not infection is present; thus, empiric antibiotic therapy is recommended.

Aplastic Crisis. This occurs secondary to viral suppression of red blood cell precursors, most often by **parvovirus B19**. It occurs because of the very short half-life of sickled red blood cells and consequent need for brisk erythropoiesis. If red blood cell production is inhibited, even for a short time, profound anemia may result. The process is acute and usually reversible, with spontaneous recovery.

Other Complications. Other complications include hemorrhagic or ischemic stroke as a result of thrombosis, pigmented gallstones, papillary necrosis of the kidney, priapism, pulmonary hypertension, and heart failure.

Treatment

Patients admitted with sickle cell crises should have a complete blood cell count and reticulocyte count upon admission. While this intervention does not change management substantially, it helps determine baseline values, risk stratify patients with suspected concomitant infection, and rule out aplastic crisis. To protect against encapsulated organisms, all patients with sickle cell disease should receive **penicillin prophylaxis** and a **vaccination against pneumococcus.**

The mainstays of treatment of a pain crisis are hydration and pain control with nonsteroidal anti-inflammatory agents and narcotics. It is important to also provide adequate oxygenation to reduce sickling. One must search diligently for any underlying infection and start empirical treatment with antibiotics when infection is suspected. **ACS** is treated with **oxygen, analgesia, and antibiotics.**

In general, blood **transfusions** may be required for aplastic crisis, for severe hypoxia in ACS, or to decrease viscosity and cerebral thrombosis in patients with stroke. Transfusion does not shorten the duration of a pain crisis. In severe disease, especially when simple transfusions do not control the severity, **exchange transfusions** have shown benefit.

Hydroxyurea is often used to reduce the occurrence of painful crises or ACS. This medication works by stimulating hemoglobin F production and thus decreasing hemoglobin S concentration. The antineoplastic agent 5-deoxyazacytidine (**decitabine**) may also elevate levels of hemoglobin F without excessive side effects.

Phosphodiesterase type 5 inhibitors such as sildenafil promote smooth muscle relaxation in the lungs and can treat pulmonary hypertension. **Endothelin receptor agonists** such as bosentan can improve pulmonary hypertension caused by sickle cell disease. The mechanism of this agent is competitive binding to endothelin 1 (ET-1) receptors A and B in the pulmonary vascular endothelium. Because of the numerous transfusions, sometimes iron chelators are needed to prevent iron overload (which may lead to heart or liver failure).

Emerging Concepts. Research is being concentrated on allogeneic hematopoietic stem cell transplantation, which can be curative. In children with severe disease, myeloablative stem cell transplantation has been effective if there is a sufficiently matched donor such as a sibling. There are side effects in approximately 10% of patients. Adults usually have more complications. Gene therapy is only in its initial stages of research but holds promise.

CASE CORRELATION

- See also Case 54 (Iron-Deficiency Anemia), Case 55 (Symptomatic Anemia and Transfusion Medicine), and Case 56 (Immune Thrombocytopenia Purpura/Abnormal Bleeding).

COMPREHENSION QUESTIONS

58.1 A 32-year-old woman with a known history of sickle cell anemia presents to the emergency department for the fifth time this year, complaining of diffuse abdominal pain and severe bilateral lower extremity pain typical of her previous pain crises. Normally, she takes hydrocodone/acetaminophen every 8 hours, but for the past day she has required doses every 4 hours without relief. Which of the following therapies would most likely decrease her number of sickle cell crises?

A. Hydroxyurea

B. Folate supplementation

C. Prophylactic penicillin

D. Pneumococcal vaccination

58.2 A 31-year-old man with a history of diabetes mellitus and sickle cell anemia presents to the emergency department with 2 days of cough, chest pain, and difficulty breathing. His temperature is 100.7 °F, blood pressure is 112/65 mm Hg, heart rate is 117 bpm, respiratory rate is 22 breaths/min, and pulse oximetry shows 94% on room air. White blood cell count is 13,000/mm^3, and hemoglobin is 9.9 g/dL (baseline of 10.1 g/dL). Chest x-ray reveals a right lower lobe opacity. Blood and sputum cultures are collected. Which of the following is the most appropriate empiric antibiotic therapy for this patient?

A. Vancomycin
B. Ceftriaxone
C. Cefotaxime and azithromycin
D. Penicillin

58.3 A 6-year-old boy with a history of sickle cell anemia is brought to the emergency department by his parents because of the boy's 4 days of fatigue. The patient is up to date on all his immunizations. His home medications include penicillin and folic acid. His temperature is 99.3 °F, blood pressure is 102/70 mm Hg, heart rate is 116 bpm, respiratory rate is 22 breaths/min, and oxygen saturation shows 96% on room air. On physical examination, he appears pale, but he has normal chest, respiratory, and abdominal examinations. His white blood cell count is 7000/mm^3, hemoglobin is 6.5 g/dL, platelet count is 27,000/mm^3, and reticulocyte count is 0.2%. Which of the following is the most likely diagnosis?

A. Acute chest syndrome
B. Splenic sequestration
C. Aplastic anemia
D. Aplastic crisis

58.4 Which of the following is the most likely organism responsible in Question 58.3?

A. *Streptococcus pneumoniae*
B. *Salmonella* spp
C. Parvovirus B19
D. *Staphylococcus aureus*

ANSWERS

58.1 **A.** Hydroxyurea and decitabine may decrease the incidence of sickle cell crises by increasing levels of hemoglobin F. Penicillin prophylaxis (answer C) and pneumococcal vaccine (answer D) protect against encapsulated organisms. While folate supplementation (answer B) is needed for hematopoiesis, it has no effect on the number of sickle cell crises.

58.2 **C.** In patients with suspected ACS and/or pneumonia, the third-generation cephalosporin cefotaxime, together with a macrolide such as azithromycin, is optimal to provide coverage for the most common pathogens, such as *S. pneumoniae* and *Moraxella*, respectively. Azithromycin or erythromycin provides coverage for atypical organisms, such as *Mycoplasma* and *Chlamydia*. Although a cephalosporin such as ceftriaxone (answer B) is appropriate to cover for common gram-positive and gram-negative etiologies of pneumonia, this patient with likely autosplenectomy requires broader coverage. In very ill patients or if a large and/or increasing infiltrate concerning for methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected, vancomycin (answer A) can be added, but it is not routinely used as an initial stand-alone agent. Answer D (penicillin) is insufficient coverage for pneumonia due to high resistance.

58.3 **D.** In sickle cell patients, aplastic crisis can result from a temporary stop in red blood cell production, characterized by a very low hemoglobin and reticulocyte count less than 1%. In contrast, aplastic anemia (answer C) is defined as pancytopenia in patients without sickle cell disease. Splenic sequestration (answer B) is associated with abdominal pain, increased reticulocytes, and an acute drop in hemoglobin due to vaso-occlusion and pooling of red blood cells in the spleen. In ACS (answer A), chest pain and respiratory symptoms are commonly seen.

58.4 **C.** In children with sickle cell anemia, aplastic crisis is most commonly associated with parvovirus B19. *Staphylococcus aureus* (answer D) and *Salmonella* (answer B) are the most common causes of osteomyelitis in sickle cell patients. It is important to remember the association between sickle cell anemia and *Salmonella* osteomyelitis. *S. pneumoniae* (answer A) is the most common causative agent for pneumonia in sickle cell patients.

CLINICAL PEARLS

- Treatment of an acute painful episode in sickle cell anemia includes hydration, narcotic analgesia, adequate oxygenation, and the search for an underlying infection.
- Acute chest syndrome is characterized by chest pain, fever, new radiographic pulmonary infiltrate, and respiratory symptoms; it can be caused by pneumonia, vaso-occlusion, or pulmonary embolism.
- Blood transfusion may be required for aplastic crisis, for severe hypoxemia in ACS, or to decrease viscosity and cerebral thrombosis in patients with stroke.
- In sickle cell patients, parvovirus B19 is commonly associated with aplastic crisis, and *Salmonella* is commonly associated with osteomyelitis.
- Hydroxyurea and decitabine increase hemoglobin F production (decreasing hemoglobin S concentration) and thus reduce the frequency of pain crises and other complications.

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CASE 59

A 57-year-old man was admitted to the hospital 2 days ago following a motor vehicle accident. He suffered multiple contusions and a femur fracture that was surgically repaired 24 hours ago. He also had a laceration on his forehead; a computed tomography (CT) scan of his head on admission showed no intracranial bleeding. His hospital course has been uncomplicated, and he currently is taking morphine as needed for pain and subcutaneous enoxaparin for prophylaxis of deep venous thrombosis. This evening he has been agitated and combative and pulled out his intravenous (IV) line. He is cursing at the nurses and is trying to get out of bed to leave the hospital. When you see him, he is febrile with a temperature of 100.8 °F, heart rate of 122 beats per minute, blood pressure of 168/110 mm Hg, respiratory rate of 28 breaths per minute, and oxygen saturations of 98% on room air. He is awake and fidgety, staring around the room nervously. He is disoriented to place and time; he seems to be having auditory hallucinations and is brushing off unseen objects from his arms. On examination, his forehead wound is bandaged, his pupils are dilated but reactive, and he is mildly diaphoretic. His lung sounds are clear to auscultation, his heart rhythm is tachycardic but regular, his abdomen is benign, and he is tremulous. You are able to contact family members by phone. They confirm that prior to his car accident, the patient had no medical problems, had no dementia or psychiatric illness, and was employed as an attorney. They report that he took no medications at home, did not smoke or use illicit drugs, and drank three to four mixed drinks every day after work, sometimes more on the weekends.

- What is the most likely diagnosis?
- What should be your next step?

ANSWERS TO CASE 59:
Delirium/Alcohol Withdrawal

Summary: A 57-year-old man hospitalized for 2 days for multiple contusions presents with

- Surgery performed 24 hours ago for a femur fracture sustained in a motor vehicle accident
- Report from family members that the patient had no medical problems, dementia, or psychiatric illness; no medications; no history of smoking or illicit drugs; alcohol intake of three to four mixed drinks every day after work
- Sudden onset of agitation and combativeness
- Normal CT scan of the head
- Current medications of morphine and subcutaneous enoxaparin
- Tachycardia, hypertension, and temperature of 100.8 °F
- Fidgeting, disorientation, and suspected auditory and tactile hallucinations
- Dilated pupils, mild diaphoresis, and tremors

Most likely diagnosis: Delirium as a result of an acute medical illness or possibly alcohol withdrawal.

Next step: Look for serious or reversible underlying medical causes for the delirium. If no other medical problems are identified, based on the patient's daily alcohol use, a possible diagnosis is alcohol withdrawal syndrome.

ANALYSIS

Objectives

1. Recognize delirium in a hospitalized patient. (EPA 1)
2. List the most common causes of delirium. (EPA 2)
3. Understand the management of an agitated, delirious patient. (EPA 4)
4. Recognize the special considerations applicable to an older demented patient with delirium. (EPA 1, 3)
5. Describe the stages, treatment, and complications of alcohol withdrawal syndrome. (EPA 1, 4)

Considerations

This 57-year-old man had been in a normal physical and mental state prior to hospitalization. He then developed an acute change in mental status, with fluctuating consciousness and orientation, the hallmark of delirium. There are many possible causes for his delirium: hypoxia, pulmonary embolism, acute electrolyte disturbances, hypoglycemia, occult infection, central nervous system hemorrhage or infection, or drug intoxication or withdrawal. These conditions require

investigation before ascribing the symptoms to alcohol withdrawal because they are potentially very serious or even fatal. In addition, further investigation to quantify his alcohol intake is necessary. Rapid diagnosis and treatment are vital since this patient has findings of significant autonomic instability based on the hyperthermia, tachycardia, and high blood pressure. Mortality if untreated can approach 20%. The use of a benzodiazepine such as lorazepam is a fundamental part of the treatment regimen.

APPROACH TO:
Delirium and Alcohol Withdrawal

DEFINITIONS

DELIRIUM: An **acute, fluctuating** confusional state that is one of the most common mental disorders encountered in hospitalized or otherwise medically ill patients.

DEMENTIA: Significant loss of intellectual abilities, such as memory capacity, severe enough to interfere with social or occupational functioning, usually **over a long period of time.**

CLINICAL APPROACH TO DELIRIUM

Pathophysiology

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* defines delirium as a clinical diagnosis. It has the following features:

- Disturbance in attention (eg, reduced ability to direct, focus, sustain, and shift attention) and awareness.
- Change in cognition (eg, memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a preexisting, established, or evolving dementia.
- The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.
- Evidence that the aforementioned features are caused by a medical condition, medications, or intoxicants.

Delirium can be a manifestation of an underlying medical disorder. Sometimes, the underlying condition is apparent. At other times, especially in elderly demented patients, delirium may be the first or the only sign of an acute illness, or it may be a serious decompensation or complication of a stable medical condition. Table 59–1 lists conditions that should be considered as causes of delirium. Of these conditions, the most common are **drug toxicity** (especially anticholinergics, sedatives, or narcotics in elderly patients), **infection**, **electrolyte disturbances** (most commonly hyponatremia or hypoglycemia), and withdrawal from **alcohol** or other sedatives.

Table 59–1 • MEDICAL CAUSES OF DELIRIUM

Discrete CNS Lesion Present	No Discrete CNS Lesion	
Head injury: stroke or intracranial bleed CNS infection: meningitis, meningoencephalitis, brain abscess Mass lesion: hematoma, tumor Seizure, postictal	*Metabolic encephalopathy* • Anoxia: heart or respiratory failure, pulmonary embolus, sleep apnea • Hepatic encephalopathy • Uremic encephalopathy • Hypo-, hyperglycemia • Hyponatremia/ hypercalcemia • Hypo-, hyperthermia	*Toxic encephalopathy* • Drug withdrawal, especially alcohol and benzodiazepines, SSRIs • Drug toxicity, eg, phenytoin • Substance abuse • Infections: pneumonia, urinary tract infections, intra-abdominal infection, bacteremia (all more frequent in the elderly)

Abbreviations: CNS, central nervous system; SSRI, selective serotonin reuptake inhibitor.

Delirium in the Geriatric Population. Delirium in the geriatric population can be the presenting manifestation of any acute illness, with an incidence of up to 10% on admission and up to 30% during an acute hospitalization. Causes of delirium in the elderly include pneumonia, urinary tract infection, myocardial infarction, gastrointestinal hemorrhage, traumatic injury, or virtually anything else that precipitates an acute hospitalization. This is even more of a problem after major surgery; nearly half of individuals (usually elderly) who suffer hip fractures develop delirium postoperatively. Urinary retention and constipation may also precipitate delirium and must be evaluated in all patients, especially given its high incidence in the elderly population.

Persons at any stage of dementia may develop delirium during an acute illness or injury or with additional pharmaceutical agent(s). Additionally, an acute delirium may "unmask" an early underlying, undetected dementia. The confused and disoriented geriatric patient cannot be dismissed as having one or the other, and the history should concentrate on any changes in the behavioral status of the patient since the acute event.

Clinical Presentation

Regardless of etiology, delirium produces a profound disturbance of brain function, and all etiologies are serious and potentially fatal illnesses. **Delirium must be approached as an acute medical emergency.** A detailed history, aggressively pursued, is mandatory, and because the responses from these patients cannot be relied upon, information from family, friends, or other caregivers is essential. A thorough physical examination with emphasis on neurologic status, clarity of speech, level of awareness, attention span, facial droop, and weakness of an extremity must be established because such changes must be carefully and frequently assessed. Basic laboratory studies should focus on chemical abnormalities (glucose, creatinine, bilirubin, serum sodium levels), drug intoxication, and evidence of hypoxia. The two threatening and potentially easily reversible conditions—**hypoxia and hypoglycemia**—should be immediately investigated and treated.

One of the earliest signs of a disturbance of consciousness is an inability to focus or sustain attention, which may be evident as distractibility in conversation.

Usually, there also is disturbance of the sleep-wake cycle. In alcohol withdrawal, signs of autonomic hyperactivity predominate, and patients may become hypervigilant and agitated. As symptoms progress, patients may become lethargic or even stuporous (arousable only to painful stimuli). Determining the time of the patient's last drink is key to diagnosing withdrawal delirium, as symptoms of delirium typically present 72 to 96 hours after the patient's last alcoholic beverage.

To diagnose and monitor a delirious patient, it is important to utilize the **Confusion Assessment Method (or CAM) score.** The CAM is a four-part screening tool used to differentiate delirium and other causes of altered mental status and is described as follows:

1. Acute onset and fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

The patient must have features 1 and 2 PLUS either 3 or 4 in order to meet criteria for delirium. Questions concerning the patient's mental state should be directed to either the family or the nursing staff to assess for changes. Specifically, it is important to ascertain from family members whether these impairments were chronic, as in dementia, or developed acutely over hours to days and whether their symptoms are fluctuating throughout the day. Not uncommonly, hospitalized patients appear relatively lucid on morning rounds, especially if mental status is only superficially assessed, but then the night staff reports severe confusion and agitation. Delirious patients may hallucinate or have vague delusions of harm, but hallucinations are not a mandatory feature of the condition. Delirium more commonly manifests with hypoactive symptoms such as lethargy and inactivity and often goes unrecognized by medical staff.

Treatment

The management of delirium needs first and foremost the identification and treatment of the acute underlying illness. Adequate hydration, oxygenation, good nursing care, and around-the-clock careful supervision are always the initial measures. Management of agitation and disruptive behavior is the most challenging aspect of care of the delirious patient. Nonpharmacologic interventions should be attempted first, including frequent reassurance and orientation from familiar persons or constant supervision. A delirious patient is reoriented by sensory input, so it is important that they be provided with glasses and/or hearing aids if required. **Agitation with psychotic symptoms (hallucinations and delusions) can be treated with a neuroleptic such as low-dose haloperidol.** However, older patients are more likely to experience extrapyramidal side effects, so newer atypical antipsychotics such as **risperidone** may be used. **Benzodiazepines** have a rapid onset of action but may worsen confusion and sedation. Physical restraint should be used as a last resort. Restraints are often important and necessary in delirious patients to prevent removal of IV lines, nasogastric tubes, and the like.

There is limited evidence that antipsychotics improve delirium, and recent studies have shown that use of antipsychotics does not shorten the amount of time a patient is delirious when compared to placebo. Therefore, antipsychotics in delirious patients should be used cautiously and in the right circumstance because of variable efficacy and potential side effects.

CLINICAL APPROACH TO ALCOHOL WITHDRAWAL

Epidemiology

It is estimated that 5% to 10% of the population has alcoholism, and a fair proportion will have withdrawal symptoms upon cessation. Excessive alcohol use is defined in men as 15 or more drinks per week and 5 or more drinks on a single occasion. In women, this is reduced to 8 drinks or more per week and 4 or more drinks on any single occasion. It is difficult to predict who specifically will suffer from alcohol withdrawal, but excessive, daily drinkers are more likely to experience symptoms. Many Americans are also habituated to benzodiazepines, and the withdrawal syndrome is similar to alcohol withdrawal.

Pathophysiology

The withdrawal findings of alcohol or benzodiazepine cessation are complex and can be explained largely due to the **interaction of ethanol to the postsynaptic gamma-aminobutyric acid (GABA) A receptors**, which are inhibitory neurons. Long-term alcohol use leads to downregulation of the GABA-A receptors; the brain compensates for this chronic loss of excitatory neurotransmission by increasing excitatory neurotransmitters such as norepinephrine, serotonin, and dopamine. Thus, with the sudden cessation of alcohol, these excitatory neurotransmitters are unopposed, leading to profound effects.

Clinical Presentation

Alcohol withdrawal manifests as a spectrum of symptoms, ranging from minor tremulousness and insomnia to the most severe form, **delirium tremens (DT)**, characterized by delirium, tremor, and autonomic hyperactivity. The severity of withdrawal can be assessed using a validated assessment tool, the Clinical Institute Withdrawal Assessment (CIWA) scale. However, the CIWA is labor intensive for caregivers and especially tedious for nursing staff to conduct, so shorter assessments can be used.

Risk factors for the development of **DTs** include a history of sustained drinking, prior withdrawal symptoms, age older than 30, and a concurrent medical illness. Withdrawal can coexist with or mimic other conditions, such as infection, intracranial bleeding, hepatic failure, gastrointestinal bleeding, or drug overdose. DT is a diagnosis of exclusion; other serious diagnoses must be excluded before the patient's mental status and autonomic signs are attributed to withdrawal.

It is important to understand the temporal course of the spectrum of alcohol withdrawal syndromes (Table 59–2). A key component of assessing alcohol withdrawal is therefore determining the time of the patient's last drink.

Table 59–2 • ALCOHOL WITHDRAWAL SYMPTOMS

Stage	Symptoms
Tremulousness	Earliest symptom occurring within 6 h of abstinence, caused by CNS and sympathetic hyperactivity, often referred to as the "shakes" or "jitters," and can occur even when patients still have a significant blood alcohol level. In addition to the typical 6- to 8-Hz tremor, which can be violent or subtle, insomnia, anxiety, gastrointestinal upset, diaphoresis, and palpitations can occur. Tremor typically diminishes over 48-72 h, but anxiety and easy startling can persist for 2 wk.
Withdrawal seizures	Also called "rum fits." Typically generalized tonic-clonic seizures, often occurring in clusters of two to six episodes, and almost always within 6-48 h of abstinence. Seen in patients with a long history of chronic alcoholism.
Alcoholic hallucinosis	Typically develops within 12 h of abstinence and resolves within 48 h. Hallucinations are most often visual (eg, bugs, pink elephants) but can be auditory or tactile. When auditory, they are often maligning or reproachful human voices. Despite the hallucinations, patients maintain a relatively intact sensorium.
Delirium tremens (DT)	Most dramatic and serious form of alcohol withdrawal but occurs in only 5% of patients with withdrawal symptoms. DT typically begins within 48-72 h after the last drink and can last several days, often with a resolution as abrupt as its onset. Characterized by hallucinations, agitation, tremor, and sleeplessness, as well as signs of sympathetic hyperactivity: dilated pupils, low-grade fever, tachycardia, hypertension, diaphoresis, and hyperventilation. Delirium tremens is a serious condition with an in-hospital mortality of 5% to 10%, usually from arrhythmias or infection, which is often unsuspected.

Treatment

In contrast to other causes of delirium, **benzodiazepines are the drugs of choice in alcohol withdrawal.** They can be given on a fixed schedule in high-risk patients (previous history of DT or withdrawal seizures) to prevent withdrawal symptoms. If symptoms have already developed, benzodiazepines can be given according to one of two strategies. **Long-acting benzodiazepines such as diazepam or chlordiazepoxide** can be given in high doses until withdrawal symptoms cease, and then the slow clearance of the drug is allowed to prevent further withdrawal symptoms. However, these medications are metabolized by the liver and should be used with caution in cirrhotic patients since many alcoholics have some form of impaired liver function. Alternatively, benzodiazepines not metabolized in the liver, such as lorazepam, oxazepam, and temazepam may be used in these patients. These are shorter acting medications and must be given as needed when the patient has symptoms. Both strategies are effective.

In either case, the key to successful management is initially aggressive upward titration of dosage until the patient is heavily sedated but responsive, followed by rapid downward titration as agitation decreases, usually over 48 to 72 hours. Supportive measures are also important, such as adequate hydration, replacement of electrolytes (eg, magnesium and phosphate), and early supplementation with **thiamine** and other B vitamins in malnourished, chronic alcoholics to prevent the development of Wernicke encephalopathy.

CASE CORRELATION

- See also Case 53 (Thyrotoxicosis/Graves Disease).

COMPREHENSION QUESTIONS

59.1 A 35-year-old man is brought into the emergency department after a motor vehicle collision. He is intoxicated due to alcohol. In assessing the effect of alcohol on cognitive function, the emergency physician notes some similarities to the effects of an other substance use. Which of the following agents most closely resembles the action of alcohol in the brain?

A. Amphetamines
B. Marijuana
C. Cocaine
D. Benzodiazepine
E. Acetaminophen

59.2 A 56-year-old man is brought into the emergency center for being disoriented and combative. He looks around the room with a wild look in his eyes and does not follow directions. His wife states that his baseline is alert and oriented with intact memory. He is diagnosed to have delirium. Compared with dementia, which of the following is a characteristic of delirium?

A. A fluctuating level of consciousness
B. Slow onset
C. Can be due to deficiencies of thiamine or cyanocobalamin
D. Decreased memory ability

59.3 A 34-year-old man is brought to the emergency department by his friends for "freaking out." They state that he is usually in good health and has had no head trauma or injuries but that he does drink a lot of alcohol each day. He is noted to have marked tremors of his extremities and states that he is seeing large scorpions skittering across the walls of the room and hearing the scorpions talking to him. Which of the following statements is the most accurate description related to this patient?

A. Auditory hallucinations are unique to alcohol withdrawal and cannot be caused by a brain tumor.
B. If the serum blood alcohol level is higher than the legal limits of intoxication, these symptoms cannot be alcohol withdrawal.
C. This patient should immediately receive glucose intravenously for possible hypoglycemia.
D. If the patient also has hypertension, fever, and tachycardia, he has a 5% to 10% chance of mortality.

ANSWERS

59.1 **D.** Alcohol and benzodiazepines both interact with the GABA system; thus, benzodiazepines are the drugs of choice for treatment of acute alcohol withdrawal. Answer C (cocaine) and answer A (amphetamines) both act as stimulants in the brain, increasing levels of dopamine. Answer B (marijuana) acts on the cannabinoid receptor in the brain, a typical G protein-coupled receptor.

59.2 **A.** Fluctuating levels of alertness and consciousness are typical of delirium. Remember that delirium is usually acute in onset and fluctuates, whereas dementia (the other answers) is slower and more gradual in onset and consistent in alteration of cognition, such as memory issues.

59.3 **D.** This patient likely is suffering from alcohol withdrawal. DT with autonomic instability and sympathetic overactivity is associated with a 5% to 10% mortality. Auditory hallucinations (answer A) can occur from a number of illicit agents or even brain tumors. The fall in serum blood alcohol level and not the absolute level may induce symptoms of withdrawal. Thus, even if the patient's serum alcohol level is elevated, he can still have withdrawal (answer B). An individual who abuses alcohol should first be given thiamine before glucose (answer C) is administered to prevent acute Wernicke encephalopathy.

CLINICAL PEARLS

- Delirium is characterized by acute onset of impaired attention and cognition and fluctuating levels of consciousness, often with psychomotor and autonomic hyperactivity.
- Delirium requires urgent investigation to search for serious underlying systemic or metabolic causes.
- Frequent reassurance and orientation and constant observation are useful in managing the agitated delirious patient. Low-dose haloperidol can be used to control agitation or psychotic symptoms. Physical restraint is used as a last resort.
- Delirium tremens is the most severe and dramatic form of alcohol withdrawal, with abrupt onset from 2 to 4 days after cessation of drinking and sudden resolution several days later, and is associated with a mortality rate of 5% to 10%.
- Therapy for alcohol withdrawal syndromes includes benzodiazepines, hydration, electrolyte replacement, and B vitamins to prevent Wernicke encephalopathy.
- The mechanism of alcohol withdrawal is due to excitatory neurotransmitters due to sudden cessation of alcohol, which binds to GABA-A (inhibitory) receptors.

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CASE 60

A 21-year-old woman is brought into the emergency department by her college roommate. The patient has been unconscious for at least 30 minutes. The patient's roommate is unaware of any health condition but states that the patient has attended several college parties over the last weeks, and though she is uncertain of this fact, she believes her roommate "has been doing drugs." On examination, the patient is somewhat pale. Her mucous membranes are dry. Her temperature is 98 °F, heart rate is 80 beats per minute (bpm), respiratory rate is 8 breaths per minute, and blood pressure is 90/60 mm Hg. The skin has no lesions suggestive of intravenous injections. Her heart and lung examinations are unremarkable. The abdominal examination reveals hypoactive bowel sounds, and the abdomen is nontender. The patient barely opens her eyes upon painful stimulus. There is no evident focal deficit. Pupils are miotic and sluggish. There is a normal gag reflex. Routine laboratory tests are normal. The pregnancy test is negative. A urine drug screen is positive for opiates.

- What is the most likely diagnosis?
- What is the next step in therapy?

ANSWERS TO CASE 60:
Opioid Overdose

Summary: A 21-year-old woman presents with

- A history of possible drug misuse
- Stupor
- Normal gag reflex, cardiac and pulmonary examinations, and routine laboratory tests
- Hypoactive bowel sounds
- Bradypnea, hypotension, dry mucosa, and sluggish miotic pupils
- Positive urine drug screening for opiates

Most likely diagnosis: Opiate overdose.

Next step in therapy: Ensure airway, breathing, and circulation (ABC); administer naloxone, the antidote for opiates.

ANALYSIS

Objectives

1. Recognize the clinical characteristics of opiate overdose. (EPA 1)
2. Outline the differential diagnosis of stupor and coma. (EPA 2)
3. Compare the effect of opiates over the central nervous system with that of other drugs with potential for abuse. (EPA 1, 2)
4. Describe the sequence of interventions in the management of an emergent intoxication. (EPA 4, 10)

Considerations

This young woman presents stuporous with the reassuring presence of a gag reflex, which ensures that she is able to protect her airway. Her examination is nonspecific and shows sluggish miotic pupils. Her blood pressure is low, and her respiratory rate is slow. Her roommate says the patient "has been doing drugs," and the drug screen is positive for opiates. While the differential diagnosis of stupor is broad, many signs point toward an acute opiate intoxication. Sadly, this patient's presentation is all too common, since opioid use disorder has become an epidemic and is associated with a large number of deaths. The most important immediate intervention is respiratory support, since respiratory depression is the most common cause of death. Her oxygen saturation should be assessed, and ventilation should be provided using bag/mask for hypoxemia and/or a respiratory rate below 12/minute. Nalaxone, a competitive mu opioid receptor antagonist should be administered parenterally.

APPROACH TO:
Opiate Overdose

DEFINITIONS

COMA: A state in which an individual is unarousable and unresponsive.

DRUG ADDICTION: Neuropsychiatric disorder characterized by a recurring desire to continue taking the drug despite harmful consequences, or engagement in illegal or criminal activities in order to obtain access to such a drug.

OPIATE: A drug containing or derived from opium. It can be natural, semisynthetic, or synthetic.

STUPOR: A state between alertness and comatose, with an alert patient being arousable.

SUBSTANCE DEPENDENCE: Physiopharmacologic term that implies that the body has adapted to a substance, so its absence leads to some form of withdrawal syndrome.

SUBSTANCE USE DISORDER: According to the fifth edition of the *Diagnostic Manual of Mental Disorders* (*DSM-5*), it is defined as a problematic pattern of use of a substance leading to clinically significant impairment or distress, manifested within a 12-month period. The manifestations can include the following: strong urges; preoccupation with use; a reduction in social, occupational, or recreational activities; and more. Depending on the number of the diagnostic criteria met, a severity of mild, moderate, or severe is assigned.

CLINICAL APPROACH

Pathophysiology

Substance use disorder is a significant source of morbidity and mortality in the United States and throughout the world. Opioids continue to rise as a cause of drug overdoses, and an increasing amount of prescription opioids are involved. Due to this phenomenon, chronic opioid dependence to acute opioid toxicity as in this case are all part of the spectrum of pathology that can result from opioid use.

Opioids have central nervous system depressant and analgesic effects and can create a feeling of euphoria as well. The receptors for opioids are located in the central and peripheral nervous systems and include mu, kappa, and delta. **Stimulation of mu receptors in the central nervous system results in responses such as respiratory depression, analgesia, euphoria, and miosis.** Cough suppression and constipation can result from activation of peripheral mu-opioid receptors located in the smooth muscle of the bronchi and intestines, respectively.

Diagnosis. The history, physical examination, and routine and toxicologic laboratory evaluations are used to establish and confirm acute opioid toxicity. When

approaching a stuporous patient, it is important to be methodical: **Think first of the conditions for which an early diagnosis modifies the outcome.** Such is the case for hypoglycemia, meningoencephalitis (needing a lumbar puncture), and some types of cerebrovascular accidents. As a rule of thumb, any other diagnosis allows clinicians to select tests appropriate to historical and exam-based features.

As soon as the patient presents, particularly if altered from an unknown drug, a rapid screening examination should be completed to determine if any immediate steps are needed to stabilize the patient. Vital signs should be measured, mental status should be assessed, and pupil size should be measured. Skin moisture should be assessed, and a thorough skin examination should be conducted to identify any stigmata of drug use (eg, needle tracks or presence of skin-based drug delivery such as a fentanyl patch). Pulse oximetry, continuous cardiac monitoring, and an electrocardiogram should be obtained. Intravenous access with large-bore catheters and a finger-stick blood glucose measurement should be obtained as well.

If unable to obtain a history from the patient, any information about known current medications or possible ingestion or substance consumed from a bystander or someone familiar with the patient would be helpful.

Differential Diagnosis. Table 60–1 offers a nonexhaustive differential diagnosis of stupor. A plethora of drugs that can result in stupor or coma need to be considered. Some of them cause distinct physical examination findings supporting alternative diagnoses. Antihistamines, antipsychotics, barbiturates, beta-adrenergic antagonists, carbon monoxide, cholinergics, clonidine, cyclic antidepressants, ethanol, toxic alcohols such as methanol or ethylene glycol, **organophosphates** and sympatholytics represent some examples of drugs that can impair the brain function.

Laboratory Tests. A finger-stick serum glucose concentration should be quickly obtained since hypoglycemia, which can be rapidly detected and corrected, may otherwise obfuscate the differential of opioid toxicity. All patients should have a urinalysis and serum chemistries evaluated, including electrolytes, blood urea nitrogen (BUN), creatinine, and glucose. Serum creatine kinase, liver function tests, lipase, ionized calcium, magnesium, arterial blood gas, serum osmolality, and serum lactate can also be tested. Urine pregnancy testing should always be obtained in any woman of childbearing age.

Some drug levels can be measured; such is the case of acetaminophen, alcohol, aspirin, and lithium. Salicylate concentration need not be obtained in the absence of elevated respiratory rate or high anion gap metabolic acidosis.

Other Tests. Other studies should be based on the known history and tailored to each patient's presentation. This includes thyroid function tests, blood cultures, a chest x-ray, and brain imaging studies. An electrocardiogram may provide useful information, such as the duration of the QRS and QTc intervals, which could be modified by loperamide or methadone, respectively.

Special Considerations. A urine toxicologic screen is not always necessary but may be helpful. Acute opioid toxicity is a clinical diagnosis; importantly, if the clinical characteristics are present, the management of a patient with an opioid toxicity would not change if a urine opioid screen is negative. A positive test demonstrates

Table 60–1 • CAUSES OF STUPOR

Space-Occupying Lesions
- Vascular
  - Cerebral hematoma
  - Extracerebral hematoma (trauma or spontaneous)
- Tumors
  - Metastatic
  - Primary
- Infections
  - Abscess and cerebritis
  - Echinococcosis
  - Toxoplasmosis

Cerebral Infarction
- Thrombotic
- Embolic
- Venous occlusion

Diffuse or Metabolic
- Infection
  - Brain dysfunction in sepsis
  - Meningoencephalitis
- Status epilepticus
- Anoxia
- Hypoglycemia
- Selective hypovitaminosis
- Hepatic encephalopathy
- Uremia
- Dialysis disequilibrium syndrome
- Hypothyroidism
- Hypercarbia
- Hypothermia
- Hyponatremia
- Hypercalcemia

Psychiatric Causes
- Schizophrenia with stupor
- Affective disorder with stupor
- Dissociative stupor
- Hysterical stupor

recent use but does not confirm toxicity. Many opioids, especially the synthetic formulations, will produce a false-negative result in several available urine drug screens.

Clinical Presentation

The physical examination findings of opioid toxicity can include the following changes in vital signs: bradypnea, bradycardia, hypotension, and hypothermia. A **common finding in opioid toxicity is respiratory depression.** Hypoactive bowel sounds may be noted, and the patient may present comatose or with seizure. While miosis is characteristic, its absence or even the presence of mydriasis does not

preclude opiate toxicity but could instead suggest co-ingestion of other drugs. The mental status of a patient presenting with opioid toxicity can range from euphoric to comatose.

Persistent immobility in the patient with stupor can lead to compressed fascia-bound muscle groups, resulting in compartment syndrome and rhabdomyolysis; the myoglobin released from injured muscle can precipitate in the renal tubules, leading to acute kidney injury.

Treatment

The initial management is focused on addressing the patient's **airway, breathing, and circulation** and providing support to these systems if needed. Pulse oximetry may measure oxygenation but cannot determine the presence of hypercapnia. An arterial blood gas measurement may be needed.

The most significant therapeutic decision to make is the administration of **naloxone**; the success of this intervention also confirms the diagnosis of opioid toxicity. Naloxone is a short-acting opioid antagonist. It can be dosed starting at 0.04 mg intravenously; for patients presenting with apnea or cardiopulmonary arrest, at least 2 mg are usually necessary. Bradypneic patients should be ventilated by a bag valve mask attached to supplemental oxygen before and after naloxone administration to reduce the risk of acute respiratory distress syndrome. The dose should be increased every few minutes until the respiratory rate is 12 breaths/min or greater. The goal is to achieve adequate ventilation and not necessarily to normalize consciousness.

Naloxone can also be given intramuscularly, subcutaneously, or even intranasally if intravenous access cannot be obtained, but with these routes absorption is delayed and titration is difficult. As long as symptoms of opioid withdrawal are not present, more naloxone can be given, but after administration of 5 to 10 mg without a clinical response, the diagnosis should be reconsidered.

If opioid withdrawal occurs, the patient should be managed symptomatically and not by administration of more opioids. One important consideration in opioid toxicity as opposed to other drug toxicities is that **activated charcoal and gastric emptying are never an appropriate management decision** and are only considered if there is a strong suspicion for co-ingestion of other drugs.

Prevention. Most patients with acute opioid toxicity can be cared for in the emergency department without hospital admission, assuming there is no other medical issue of concern. Psychiatric evaluation can be done once respirations and mental status are normal. For patients with features consistent with addiction, rehabilitation is indicated. Teaching opioid users, family members, and friends how to recognize opioid toxicity and prescribing them naloxone reduces mortality.

Detoxification or supervised opioid withdrawal is the first step in treatment and reduces withdrawal symptoms. Medication is typically needed to prevent relapse. Naltrexone, which is an opioid antagonist, is a possible treatment, but it should be started after opioid withdrawal is thoroughly completed. Other treatments, such as methadone and buprenorphine, which are opioid agonists, can be started while a patient is still using opioids.

CASE CORRELATION

- See also Case 36 (Transient Ischemic Attack), Case 41 (Urinary Tract Infection With Sepsis in the Elderly), Case 43 (Meningitis, Bacterial), and Case 59 (Delirium/Alcohol Withdrawal).

COMPREHENSION QUESTIONS

60.1 A 59-year-old man with past medical history significant for long-standing hip and knee pain secondary to osteoarthritis is seen in clinic. The pain mildly improves with heat and relaxation, but he also has several acute exacerbations of pain daily that cause his "legs to freeze" and prevent him from working. These episodes do not respond to nonpharmacologic therapy, such as acupuncture. He has tried multiple nonopioid analgesic drugs but stopped them due to minimal improvement in pain or gastrointestinal side effects. Opioid therapy is considered. Which of the following is also recommended before prescribing opioid therapy to this patient?

A. Psychiatry referral
B. Current Opioid Misuse Measure survey
C. Naloxone prescription and education
D. Nonsteroidal anti-inflammatory therapies
E. Opioid-related harm risk factor assessment

60.2 A 29-year-old man with past medical history significant for heroin use is evaluated in the emergency department for stupor. On arrival, he was minimally responsive with miotic and sluggish pupils. He had needle tracks on his arms. His respiration rate was 8 breaths/min, but 5 minutes after administration of two doses of intravenous naloxone, his respiration rate is 16 breaths/min, and he is alert but not completely oriented. He does not remember what happened before the admission but is able to answer some questions. His vital signs have normalized. Which of the following is the best next step?

A. Discharge now with outpatient follow-up
B. Administer regular doses of naloxone starting now
C. Continue to observe for several hours
D. Elective endotracheal tube placement now
E. Gastric lavage now

60.3 A 37-year-old woman is brought into the emergency department by emergency medical services. The patient has been unconscious for at least 30 minutes and was found in a park. On examination, the patient is pale. Her mucous membranes are dry. Her temperature is 98 °F, heart rate 100 bpm, respiratory rate 10 breaths/min, and blood pressure 95/65 mm Hg. The skin has no lesions suggestive of intravenous injections. Her heart and lung examinations are unremarkable. The abdominal examination reveals hypoactive bowel sounds, and the abdomen is nontender. The patient barely opens her eyes upon painful stimulus. There is no evident focal deficit. Pupils are normal. There is a normal gag reflex. Routine laboratory tests are normal. The pregnancy test is negative. A urine drug screening is negative for opiates. What is the next best step in management?

A. Evaluate serum chemistries to evaluate anion gap
B. Assess serum osmolarity
C. Draw an ethanol level
D. Evaluate carboxyhemoglobin
E. Perform gastric lavage
F. Administer naloxone

60.4 A 34-year-old man with past medical history significant for the use of multiple illicit drugs is evaluated in the emergency department for impaired mentation. On arrival, he was minimally responsive with miotic and sluggish pupils. His respiration rate on arrival was 8 breaths/min, but 10 minutes after administration of three doses of intravenous naloxone, his respiration rate is 16 breaths/min, and he is alert and oriented and completely conversant. His vital signs are normal now, and his pulse oximetry demonstrates 99% on room air. He says that he would like to go home today, and he wants to completely stay away from drugs and be rid of this addiction. Which of the following is the best step in management?

A. Refer to psychiatry
B. Admit to the hospital
C. Discharge and refer to an opioid detoxification program
D. Administer naloxone

ANSWERS

60.1 **E.** Opioid therapy is reasonable in a patient with pain unresponsive to nonpharmacologic and nonopioid therapies. A treatment plan may include other therapies, such as cognitive behavioral therapy or physical therapy. If the risks outweigh the benefits and yet opiates are indicated, providers can offer a prescription for naloxone (answer C). Factors that increase risk for opioid overdose are history of overdose, history of substance use disorder, higher opioid dosages, and concomitant use of benzodiazepines. The presence of

chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea should also encourage naloxone prescription. However, this would only be done after risk factor assessment. If the patient does not have an apparent mental health diagnosis, psychiatry referral (answer A) is not necessary before prescribing opioid therapy. Nonsteroidal therapies (answer D) have been ineffective in the past, and prescribing them again does not address the patient's concerns. The Current Opioid Misuse Measure (answer B) is a self-report survey of current drug-related behavior meant for patients currently receiving long-term opioid therapy with possible misuse.

60.2 **C.** In the treatment of opioid overdose, naloxone therapy should be titrated to respiratory rate and not normalized mentation. This patient's respiratory rate has recovered to greater than 12 breaths/min, but his mentation has not fully recovered. The antidote effects of naloxone will usually wear off before the opioid effects are eliminated. Thus, observation and repeated dosing depending on the clinical status may be necessary. The most crucial aspect to be wary of is respiratory depression. Discharging the patient now (answer A) would be inappropriate. Serial escalating doses of naloxone (answer B) may be necessary in some patients, and those patients may require a continuous naloxone infusion. However, it is not indicated in this patient at this time. Since breathing has normalized and the patient is protecting his airway, there is no indication for intubation (answer D). Gastric lavage (answer E) is never indicated in these patients unless there is a strong suspicion for co-ingestion of a substance for which such intervention has been proven useful.

60.3 **F.** When comparing the effects of opiates with that of other drugs with potential for abuse, it is helpful to begin the approach with whether the patient is in a state of physiologic excitation versus depression. There is more evidence here of physiologic depression. Physiologic depression can manifest as central nervous system depression, hypotension, bradycardia, bradypnea, and hypothermia; these symptoms are associated with opiates, ethanol cholinergics, sympatholytics, and toxic alcohols. Mixed effects can occur in many patients, and considerations of physical examination findings outside the central nervous system and vital signs can be helpful to elicit the diagnosis. They include body odors, pupillary findings, skin findings, and neuromuscular aberrations.

Normal pupillary findings do not rule out opiate toxicity. Urine toxicology screen may also be negative, particularly with synthetic opioids, and does not rule out the diagnosis. The most specific finding in this patient for possible opiate toxicity is the respiratory rate depression, and the quickest therapeutic decision that can be made here is administration of naloxone. Obtaining serum chemistries (answer A) or osmolarity (answer B) would be appropriate only after naloxone administration. Gastric lavage (answer E) is not indicated unless evaluation suggests another toxic ingestion and naloxone is ineffective. The ethanol level (answer C) may be checked but neither rules in nor excludes ethanol-related toxicity. Evaluation of carboxyhemoglobin (answer D) may be warranted due to unknown history, but it should be measured only after naloxone administration.

60.4 **C.** Opioid use disorder is a significant source of morbidity and mortality in the United States and throughout the world. The patient's recognition of the drug burden on his life and desire to get over this drug use disorder should not be taken lightly. Detoxification or supervised opioid withdrawal is the first step in treatment and reduces withdrawal symptoms. Most patients with opioid toxicity can be cared for in the emergency department without hospital admission (answer B), assuming there is no other medical issue of sufficient concern. Psychiatric evaluation (answer A) may be needed if the patient's history and presentation are consistent with indication for referral, but there is no such indicator in this patient. Teaching opioid users how to recognize opioid toxicity and giving them naloxone reduces mortality and may be beneficial to give to the patient upon discharge, but naloxone administration (answer D) does not need to be repeated now. Medication is typically needed to prevent relapse.

CLINICAL PEARLS

- The typical signs of acute opioid intoxication are central nervous system depression, bradypnea (especially < 12 breaths/minute), bradycardia, hypotension, decreased bowel sounds, and miotic pupils.
- A normal pupil examination does NOT exclude opioid toxicity.
- In stuporous patients, a finger-stick serum glucose concentration should be quickly obtained, as hypoglycemia can be rapidly detected and corrected.
- Electrocardiographic findings may provide useful information; the duration of the QRS and QTc intervals should be carefully noted.
- The initial management when opioid toxicity is suspected is addressing the patient's airway, breathing, and circulation.
- If opioid toxicity is suspected, treat with the short-acting opioid antagonist naloxone, preferably intravenously.
- Normal mentation is not the goal, but rather a respiratory rate of 12 breaths/min or greater. Titrate the naloxone dose up and frequently until this goal is achieved.
- Opioid withdrawal symptoms should be managed symptomatically and not with more opioids.
- Activated charcoal and gastric emptying are not appropriate in acute opioid intoxication unless there is a strong suspicion for co-ingestion of other drugs for which these measures are indicated.

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SECTION III

Review Questions

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REVIEW QUESTIONS

R1. A 55-year-old man with a history of end-stage renal disease (ESRD) secondary to chronic uncontrolled hypertension (HTN) presents to the emergency department (ED) after sustaining a fall in his bathroom onto his right hip. He complains of pain with passive motion of the hip, and on physical examination the hip has limited range of motion upon internal rotation. An x-ray of the right hip shows a fracture. Which of the series of serum laboratory values are consistent with the underlying condition predisposing to this patient's fracture?

	Serum Ca	Serum Po_3	Serum PTH
A.	Increased	Decreased	Increased
B.	Increased	Increased	Decreased
C.	Decreased	Increased	Decreased
D.	Decreased	Increased	Increased
E.	Decreased	Decreased	Increased

R2. A 24-year-old African American man comes into clinic as a referral after having significant bleeding following a wisdom tooth extraction 1 week ago. He has no significant medical history and took aspirin 1 week ago for a headache. However, he reports getting nosebleeds that persisted longer than 10 minutes when he was a child. He reports no family history of diagnosed bleeding disorders but endorses that his mother easily bruises and has heavy menstrual bleeding. Laboratory values include a normal platelet count, an increased bleeding time, a normal prothrombin time (PT), and an increased partial prothrombin time (PTT). Which of the following is the most likely diagnosis?

A. Aspirin overdose
B. Bernard-Soulier syndrome
C. Hemophilia A
D. Vitamin K deficiency
E. von Willebrand disease (vWD)

R3. A 40-year-old woman who is infected with human immunodeficiency syndrome (HIV) presents to the clinic with complaints of difficulty and pain with swallowing. She has been experiencing substernal, burning chest pain for the past 2 weeks. Her most recent CD4+ count was 80 cells/mm^3, and her medications include trimethoprim/sulfamethoxazole (TMP-SMX) and highly active antiretroviral therapy (HAART). On physical examination, there are white plaques visible in the oral cavity and posterior pharynx that are easily removed with a tongue blade. No vesicular lesions are visible in the posterior pharynx. An endoscopy is performed that demonstrates additional white plaques in the proximal esophagus. Biopsies are significant for pseudohyphae. What is the best pharmacotherapy for this patient's condition?

A. Acyclovir
B. Azithromycin
C. Fluconazole
D. Ganciclovir
E. Sulfadiazine-pyrimethamine

R4. A 55-year-old man with known alcoholic cirrhosis presents to the ED with the recent onset of confusion and diffuse abdominal pain. Blood pressure is 98/68 mm Hg, temperature is 100.4 °F, and pulse is 102 beats per minute. The abdomen is distended, and a fluid wave is present on physical examination. In the past, his ascites was controlled with furosemide and spironolactone. Paracentesis is performed, and the fluid is found to have an absolute polymorphonuclear (PMN) count of 280 cells/mm^3 and an albumin of 1 g/dL, with cultures pending. Serum albumin is 2.6 g/dL. Which of the following is the best next step in the management of this patient?

A. Administer oral lactulose
B. Empiric intravenous (IV) ceftriaxone
C. Empiric IV octreotide
D. Liver transplant
E. Protein-restricted diet

R5. A 30-year-old woman was admitted to the shock trauma intensive care unit (ICU) after sustaining a motor vehicle collision. She has required multiple major surgeries as well as mechanical ventilation for the past week. Vital signs have been stable during this time, and her chest x-rays have been clear. On hospital day 8, she develops a temperature of 102.2 °F. Blood pressure is 110/70 mm Hg, heart rate is 104 beats per minute, Spo_2 (oxygen saturation by pulse oximetry) is 92%, and new purulent secretions from the endotracheal tube are identified and sent for Gram stain and culture. A chest x-ray is found to have a new infiltrate in the right lower lobe. Initial antibiotic therapy should include coverage for which of the following organisms?

A. *Chlamydia pneumoniae*

B. *Haemophilus influenzae*

C. *Legionella pneumophila*

D. *Pseudomonas aeruginosa*

E. Methicillin-sensitive *Staphylococcus aureus* (MRSA)

R6. A 60-year-old man presents to the office with a report of nonbloody, watery diarrhea for over 1 year. He has a history of hyperlipidemia controlled on simvastatin and well-controlled hypertension. He complains of episodes of wheezing and increased redness and heat in his face, neck, and upper chest that last up to 5 minutes. On physical examination, there is hepatomegaly, and a 2/6 holosystolic murmur is auscultated on the left lower sternal border that is accentuated with inspiration. Blood pressure is 135/85 mm Hg, heart rate is 85 beats per minute, and respiratory rate is 16 breaths per minute. Which of the following is the best next diagnostic test?

A. 24-hour urine 5-hydroxyindoleacetic acid

B. 24-hour urine metanephrines

C. Endoscopy with colonoscopy

D. Methacholine challenge

E. Secretin injection test

R7. A 37-year-old woman with a history of IV drug use and sex work presents with complaints of fatigue and increased swelling around her eyes, hands, and feet. She has also noticed increased abdominal girth. She is not on any medications. Physical examination shows a temperature of 98.9 °F, blood pressure of 125/80 mm Hg, heart rate of 76 beats per minute, respiratory rate of 14 breaths per minute, periorbital edema, and shifting dullness on abdominal examination. Laboratory values include serum albumin 2.4 g/dL, negative rapid plasma reagin (RPR), positive hepatitis B surface antigen (HBsAg), positive HBeAg, and negative anti-HIV antibody. Urinalysis is negative for red blood cells (RBCs) and positive for waxy casts. The 24-hour urine protein excretion is 3.7 g/d. Which of the following is the most likely diagnosis?

A. Diabetic nephropathy
B. Focal segmental glomerulosclerosis
C. Immunoglobulin A (IgA) nephropathy
D. Membranous nephropathy
E. Minimal change disease

R8. The patient in Question R7 suddenly develops redness, swelling, and pain in her left calf. On physical examination, there is pain with dorsiflexion of the foot. Which of the following is the most likely pathophysiology of her current condition?

A. Increase in clotting factor VIII
B. Decrease in antithrombin III
C. Increase in protein C
D. Inactivation of protein S
E. A mutation in clotting factor V

R9. A 61-year-old man presents to the ED complaining of substernal chest pain and malaise. He was previously hospitalized 3 weeks ago for a myocardial infarction (MI). He reports increased pain when taking deep breaths but denies shortness of breath or palpitations. His chest pain improves when he is sitting upright and leaning forward. An electrocardiogram (ECG) is performed and shows ST elevation in all of the leads including anterior, lateral, inferior ones; also, his erythrocyte sedimentation rate (ESR) is elevated at 35 mm/h. Which of the following is the best treatment for this patient's condition?

A. Nitroglycerin and metoprolol
B. Morphine and supplemental oxygen
C. High-dose aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)
D. IV heparin and clopidogrel
E. IV vancomycin and ceftriaxone

R10. A 45-year-old man with a history of seizure disorder and alcohol use disorder is hospitalized after a 30-minute tonic-clonic seizure. At 24 hours after the seizure, he is found on physical examination to have a blood pressure of 157/90 mm Hg; heart rate is 110 beats per minute, and temperature is 98.6 °F. Urine draining from the Foley catheter is dark and sent for analysis. Laboratory values include the following: serum sodium 143 mEq/L, serum potassium 5.1 mEq/L, serum bicarbonate 19 mEq/L, serum creatinine (Cr) 3.0 mg/dL, and blood urea nitrogen (BUN) 32 mg/dL. Urinalysis reveals negative protein, negative leukocytes, negative nitrites, 4+ blood with microscopy 2 to 5 RBCs, 0 to 1 white blood cells (WBCs). Which of the following is the most likely underlying pathophysiology concerning this patient's condition?

A. Vascular inflammation

B. Outflow tract obstruction

C. Poor renal perfusion

D. Toxic injury to renal tubules

R11. A 65-year-old man with a 30-year history of smoking 2 packs per day complains of increased swelling in both of his legs, increased dyspnea, and fatigue on exertion. He denies having to use extra pillows at night to help him breathe. He also notes an increase in number of times he urinates during the night. On physical examination, there is distention of the right jugular vein when firm pressure is applied over the liver and the presence of a parasternal heave; there are diffuse expiratory wheezes heard on auscultation of the lungs. Which of the following is most likely to be found on his chest x-ray?

A. Bilateral pulmonary infiltrates

B. Depressed diaphragm with prominent pulmonary artery

C. Unilateral lobar consolidation

D. Widened mediastinum

E. Multiple pulmonary nodules

R12. A 40-year-old woman comes into clinic complaining of a 15-lb weight gain over the past 6 months despite a decrease in appetite. She states she is more bothered by cold temperatures, her hair is thinner, and recently she has had more difficulty passing bowel movements. She states that 8 months ago, she was experiencing diarrhea, felt like her heart was beating quickly, and was always hot. Today, her blood pressure is 125/85 mm Hg, heart rate is 70 beats per minute, and she is afebrile. On physical examination, there is no exophthalmos, the thyroid is nontender and diffusely enlarged with a rubbery texture without any isolated nodules, and her skin is dry to the touch. Laboratory values include elevated thyroid-stimulating hormone (TSH), decreased free triiodothyronine (T_3) and thyroxine (T_4), and positive antithyroid peroxidase (anti-TPO) antibodies. This patient is now at risk for which of the following complications?

A. Anaplastic carcinoma of the thyroid
B. Follicular carcinoma of the thyroid
C. Lymphoma of the thyroid
D. Medullary carcinoma of the thyroid
E. Papillary carcinoma of the thyroid

ANSWERS

R1. **D. This patient suffered a hip fracture with minimal trauma.** He has secondary hyperparathyroidism with low calcium, high phosphate, and high PTH levels. ESRD patients can be at risk for bone fractures due to a decrease in bone mineral density, described as osteitis fibrosa cystica. Individuals with ESRD are unable to activate vitamin D in the kidney, thus creating hypovitaminosis D, which impairs the absorption of calcium from the gastrointestinal (GI) tract. Decreased serum calcium then impairs regulation of parathyroid hormone (PTH) production, causing a secondary hyperparathyroidism (high PTH). Furthermore, decreased kidney function impairs the excretion of phosphate, causing serum phosphate levels to become elevated, sometimes requiring treatment with phosphate binders. Thus, this patient should have decreased serum calcium, increased serum phosphate, and increased serum PTH. It is called secondary hyperparathyroidism since the low calcium drives the body to increase PTH levels. Answer A (increased Ca, decreased Po_3, increased PTH) is consistent with **primary** hyperparathyroidism where increased PTH (usually due to a parathyroid adenoma) causes an increase in calcium release from the bone, as well as increased excretion of phosphate by the kidney. The patient in this question instead has **secondary** hyperparathyroidism in response to the low calcium level. Answer B (increased Ca, increased Po_3, decreased PTH) is consistent with hypervitaminosis D, which is caused by excessive vitamin supplementation or granulomatous disease such as sarcoidosis. In sarcoidosis, immune cells in the granulomas outside of the kidney synthesize the active form of vitamin D. Excess vitamin D will stimulate intestinal absorption of calcium and phosphate; additionally, the

elevated calcium will inhibit PTH secretion. Thus, the driving force is the hypercalcemia which causes the low PTH level. Hip fractures secondary to osteoporosis are unlikely to demonstrate abnormal laboratory values, where those that are secondary to Paget disease will show an isolated elevated alkaline phosphatase (see Case 35 [Osteoporosis, Cushing Syndrome] and Case 50 [Hypercalcemia/Multiple Myeloma]).

R2. **E. This man has both platelet and clotting factor dysfunction inherited in an autosomal dominant fashion, most consistent with** vWD. This condition is caused by a deficiency of von Willebrand factor (vWF), which plays a role in primary (platelet-driven) and secondary (clotting factors) hemostasis. In primary hemostasis, vWF is released by damaged endothelium and binds to the platelet glycoprotein Ib (GpIb) receptor. If vWF is decreased or absent, platelets are unable to bind to the damaged endothelium, which causes manifestations of platelet dysfunction (increased bleeding time) such as petechiae, epistaxis, and increased bruising without affecting the number of platelets. Also, vWF is responsible for protecting clotting factor VIII from rapid breakdown in the blood; therefore, a deficiency of vWF can cause a deficiency of factor VIII, elevating the aPTT without affecting the PT. Answer A (aspirin overdose) causes platelet dysfunction without decreasing the number of platelets by irreversibly inhibiting thromboxane A2 (TXA2), making platelet aggregation ineffective in primary hemostasis; however, aspirin does not affect secondary hemostasis laboratory values (PT/PTT). Answer B (Bernard-Soulier syndrome) is also an isolated dysfunction of platelets, whereby there is a deficiency of the GpIb receptor, preventing platelet adhesion to the vWF expressed by the damaged epithelium. This syndrome produces the same effect as vWD in primary hemostasis; however, there is no dysfunction of clotting factors and no elevation in PT or PTT. Answer C (hemophilia A) is an X-linked inherited disorder characterized by a deficiency in factor VIII that causes dysfunction in secondary hemostasis alone, which is clinically manifested by an elevated PTT, normal bleeding time and PT, and increased deep bleeding, such as hemarthrosis (bleeding into joints). Answer D (vitamin K deficiency) would manifest as an elevated PT, mildly increased PTT, and no effect on bleeding time or platelet number from the inability to activate clotting factors II, VII, IX, and X through gamma-carboxylation (see Case 56 [Immune Thrombocytopenia Purpura/Abnormal Bleeding]).

R3. **C. This patient needs an antifungal treatment such as fluconazole for *Candida esophagitis*.** When the CD4+ counts fall below 100 cells/mm^3, patients infected with HIV are at risk for developing esophagitis. Esophagitis presents with primary complaints of odynophagia (painful swallowing), dysphagia, and a substernal burning chest pain. White plaques that are easily removed with a tongue blade are consistent with oral thrush caused by the opportunistic fungus *Candida*, which can result in esophagitis when it extends beyond the oral cavity to the proximal esophagus. C. *esophagitis* is the most likely diagnosis in patients presenting with oral thrush. Endoscopy

and biopsy are not necessary before initiating treatment with oral fluconazole. However, if patients show no improvement and have no signs of oral thrush, endoscopy with biopsy is warranted. Answer A (acyclovir) would be appropriate treatment for herpes simplex virus (HSV) esophagitis, which would present with multiple small vesicles and round/ovoid ulcers on endoscopy. Cells on biopsy would contain eosinophilic intranuclear inclusions. Answer B (azithromycin) is appropriate for *Mycobacterium avium* complex (MAC) prophylaxis when the CD4 count is < 100 cells/mm^3. Answer D (ganciclovir) is appropriate for treating cytomegalovirus (CMV) esophagitis, which demonstrates large linear ulcerations likely in the distal esophagus. Biopsy would be positive for intranuclear and intracytoplasmic inclusions. Answer E (sulfadiazine-pyrimethamine) is appropriate treatment for toxoplasmosis, which usually presents as **multiple** ring-enhancing lesions in the brain when the CD4 count is < 100 cells/mm^3 (see Case 46 [HIV/AIDS and *Pneumocystis* Pneumonia]).

R4. **B. This patient is most likely suffering from spontaneous bacterial peritonitis, which is best treated with IV antibiotics.** This patient is likely in end-stage liver failure due to known alcoholic cirrhosis. One of the many complications of cirrhosis is spontaneous bacterial peritonitis, an infection of the ascitic fluid most often caused by flora of the GI tract, such as *Escherichia coli* or *Klebsiella*. It is associated with a high mortality rate (20%-30%) and is likely to recur. Clinical presentation is subtle, and there should be a high index of suspicion in order to initiate treatment as soon as possible. Common symptoms include fever, diffuse abdominal pain, and altered mental status in a patient with known cirrhosis. Diagnosis is confirmed with a diagnostic paracentesis evaluating fluid for WBCs, in particular PMN cells, Gram stain, and culture. There will be a serum ascites-albumin gradient (SAAG) ≥ 1.1 g/dL, the fluid will have a PMN count ≥ 250 cells/μL, and there will be a positive culture. However, empiric treatment should be initiated with a third-generation cephalosporin (ceftriaxone, cefotaxime) while awaiting culture results since the most common cause is gram-negative organisms. Answer A (oral lactulose) would be the appropriate treatment for hepatic encephalopathy to prevent reabsorption of the toxic metabolite ammonia. Clinical presentation would include an altered mental status; however, this diagnosis is less likely given the patient's fever and diffuse abdominal pain. Answer C (empiric IV octreotide) would be appropriate during the treatment of bleeding esophageal varices, which usually present in a patient with liver failure and massive hematemesis. Octreotide acts as a vasoconstrictor to the splanchnic vessels, helping to reduce portal pressure and therefore decreasing variceal bleeding. Answers D (liver transplant) and E (protein-restricted diet) would not be appropriate initial treatments for this patient presenting with an active infection (see Case 24 [Liver Cirrhosis]).

R5. **D. This patient has developed a ventilator-associated pneumonia (VAP), and empiric antibiotics should include antipseudomonal coverage.** VAP is a pneumonia that occurs in the patient who has been mechanically ventilated for

more than 2 days. It should be suspected when there is an acute change in the intubated patient, including a new fever, decrease in oxygen saturation, and new purulent secretions. A chest x-ray should be obtained, and VAP should be suspected if there is an acute change in a previously clear chest x-ray (showing new infiltrates). A lower respiratory tract endotracheal sample should be sampled and cultured. Pending cultures, empiric antibiotics optimally would include gram-positive coverage, as well as anti-*Pseudomonas* and gram-negative coverage; additionally, coverage for MRSA should be considered in settings of higher prevalence. Once bacteriological sensitivities come back, the antibiotic regimen can be narrowed to the specific organism. Answer A (*C. pneumoniae*) is a cause of community-acquired atypical pneumonia where the patient presents with an insidious onset of various symptoms, such as headache and fatigue with dry cough and fever—"walking pneumonia." Chest x-ray will most likely demonstrate interstitial infiltrates. Answer B (*H. influenzae*) is the organism associated with pneumonias found in patients with other comorbidities, such as chronic obstructive pulmonary disease (COPD), diabetes, or alcoholism. Clinical presentation will be similar to patients with community-acquired pneumonia, such as fever, cough, and shortness of breath. Answer C (*L. pneumophila*) is the causal organism associated with pneumonia named "Legionnaires' disease," usually in patients who are heavy smokers and have been exposed to a contaminated water source. A urine antigen test can confirm this diagnosis. Answer E (MRSA) would be incorrect because in a hospitalized patient, MRSA would be a more likely cause of VAP (see Case 19 [Community-Acquired Pneumonia] and Case 42 [Neutropenic Fever, Vascular Catheter Infection]).

R6. **A. This patient's symptoms are consistent with carcinoid syndrome caused by a neuroendocrine serotonin-secreting tumor.** Carcinoid tumors are neuroendocrine tumors, usually arising in the appendix, that secrete serotonin. The serotonin excretion is usually asymptomatic when the tumor arises in the GI tract due to liver detoxification of the serotonin into inactive metabolites. However, when there are **metastases** to the liver, serotonin excretion becomes symptomatic. Clinical manifestations often include profuse watery diarrhea, episodes of flushing and bronchospasm, and valvular lesions affecting the right side of the heart, such as tricuspid regurgitation. This patient's 2/6 holosystolic murmur is consistent with this complication. Niacin deficiency is a potential complication due to increased conversion of tryptophan to serotonin, manifesting as dermatitis, diarrhea, and dementia. The next best test would be 24-hour urine 5-hydroxyindoleacetic acid levels, which would be elevated in someone suffering from carcinoid syndrome. Answer B (24-hour urine metanephrines) is a screening test for pheochromocytoma, which would present as a patient suffering from persistently high blood pressure and episodes of severe HTN and headache. Answer C (endoscopy with colonoscopy) would be the next appropriate test to diagnose various GI disorders such as Crohn disease, an inflammatory bowel disease that presents with chronic diarrhea (usually not grossly bloody but may test occult

blood positive), weight loss, possible anemia from diseased ileum, and other manifestations, such as uveitis, arthritis, and skin lesions. Answer D (methacholine challenge) is the appropriate diagnostic test to evaluate for asthma, which is characterized by bronchospasm and wheezing. Notably, asthma is usually diagnosed as a child and presents **without** long-standing diarrhea. Answer E (secretin injection test) is the diagnostic test of choice to evaluate for Zollinger-Ellison syndrome (ZES), a gastrinoma that is a pancreatic islet cell tumor. Clinical manifestations include side effects related to excessive gastrin production, such as gastric ulcers, abdominal pain, and diarrhea. Secretin usually suppresses gastrin; however, patients with ZES would demonstrate high gastrin levels after the secretin injection test (see Case 47 [Hyponatremia, Syndrome of Inappropriate Secretion of Antidiuretic Hormone]).

R7. **D. This patient most likely has a nephrotic syndrome due to membranous nephropathy secondary to hepatitis B infection.** Nephrotic syndrome is defined as an abnormal glomerular permeability and may be due to many causes. It results in urine protein excretion > 3.5 g/24 h, hypoalbuminemia, hyperlipidemia, edema, a hypercoagulable state, and an increased risk for infection. Membranous nephropathy is the most common cause of primary nephrotic syndrome in Caucasian adults, and the most common secondary cause is hepatitis B. Histologic examination will demonstrate diffuse capillary and glomerular basement membrane thickening. Answer A (diabetic nephropathy) presents as a nephrotic syndrome from nonenzymatic glycosylation of the basement membrane in a patient with long-standing uncontrolled diabetes. Histologic examination of diabetic nephropathy will demonstrate mesangial expansion and eosinophilic nodular glomerulosclerosis, also known as Kimmelstiel-Wilson lesions. There is nothing in this patient's history to suggest diabetes. Answer B (focal segmental glomerulosclerosis) is a nephrotic syndrome associated with African Americans and Hispanics and can be secondary to conditions such as HIV and sickle cell disease. Answer C (IgA nephropathy) usually presents as a nephritic syndrome characterized by HTN, azotemia, oliguria, and hematuria following an upper respiratory infection or gastroenteritis. Answer E (minimal change disease) is the most common cause of nephrotic syndrome in children; it is caused by T-cell dysfunction (see Case 24 [Liver Cirrhosis] and Case 29 [Nephrotic Syndrome and Diabetic Nephropathy]).

R8. **B. This patient is suffering a deep venous thrombosis (DVT) secondary to a hypercoagulable state.** Those with nephrotic syndrome are in a hypercoagulable state primarily due to a loss of antithrombin III in the urine. Other fibrinolytic proteins, such as proteins S and C (answers C and D), are also contributory but are not thought to be the major factor. Renal vein thrombosis is often seen in this setting (see Case 29 [Nephrotic Syndrome and Diabetic Nephropathy]).

R9. **C. This patient is most likely suffering from Dressler syndrome, which is an autoimmune reaction to the pericardium usually occurring 2 to 10 weeks**

after an MI, associated with fibrinous pericarditis. Appropriate treatment is NSAIDs and high-dose aspirin. The typical clinical presentation is fever, malaise, and pericarditis (chest pain with a friction rub that improves when leaning forward) occurring weeks to months after an MI. Answers A (nitroglycerin and metoprolol) and B (morphine and supplemental oxygen) are appropriate treatments during the acute phase of an MI; only nitroglycerin and metoprolol should be initiated as maintenance therapy after the MI. Answers D (IV heparin and clopidogrel) are appropriate treatments for anticoagulation during another MI or for a left ventricular mural thrombus. Answers E (IV vancomycin and ceftriaxone) is appropriate treatment for bacterial endocarditis, which would most likely present with fever and a new murmur (see Case 3 [Myocardial Infarction, Acute]).

R10. **D. This patient developed acute kidney injury after a 30-minute tonic-clonic seizure. A urine dipstick that is positive for blood and a urinalysis with few microscopic RBCs is highly suggestive of myoglobinuria.** The seizure activity likely led to muscle injury. Rhabdomyolysis is caused by excessive, rapid muscle breakdown as a result of crush injury, trauma, seizures (in this patient), prolonged immobility, or snakebites. As muscle breaks down, myoglobin is released into the bloodstream and filtered by the kidneys. Myoglobin is toxic to the renal tubules (precipitates) and can cause an acute kidney injury via acute tubular necrosis. Typically, the creatine kinase (CK) levels are markedly elevated. Given that the injury to the kidney is intrinsic and impairs renal function, the BUN:Cr ratio will usually be < 20, and the kidney will be unable to conserve sodium and concentrate the urine. Answer A (vascular inflammation) is more consistent with the pathophysiology of nephritic syndrome, which is characterized by HTN, azotemia, oliguria, and hematuria. Answer B (outflow obstruction) is more consistent with a postrenal kidney injury secondary to obstruction of the ureter, bladder, or urethra. Diagnosis would be made by physical examination, ultrasound imaging, and catheterization. Renal failure is present when kidneys are obstructed bilaterally, but when the obstruction is removed (provided this is not a chronic condition), renal function is restored. Answer C (poor renal perfusion) is the pathophysiology behind prerenal failure usually secondary to decreased cardiac output, hypotension, or volume loss/sequestration. Laboratory values will include a BUN:Cr of > 20 and preserved function of the kidney to concentrate urine and reabsorb sodium (see Case 30 [Acute Kidney Injury]).

R11. **B. This patient is suffering from cor pulmonale, right-sided heart failure secondary to a COPD.** On chest x-ray, the lungs would be clear, and there would be evidence of hyperinflation with depression of the diaphragm. Clinical signs suggestive of cor pulmonale in this patient include jugular venous distention, hepatojugular reflex, and no crackles on lung auscultation. Differentiating between left and right heart failure can be difficult, especially when left ventricular failure can often lead to right ventricular dysfunction. However, given this patient's long-standing smoking history and no evidence of left ventricular dysfunction, such as orthopnea or pulmonary edema, the

cause of his heart failure is most likely due to right ventricular dysfunction (as evidenced by the parasternal heave) secondary to long-standing pulmonary disease. The pulmonary artery would also be prominent from increased pulmonary pressures over time. Answer A (bilateral pulmonary infiltrates) is more consistent with pulmonary edema and the transduction of fluid into the lungs from increased pulmonary venous pressure via left ventricular dysfunction. These findings would be seen with left heart failure. Answer C (unilateral lobar consolidation) is consistent with a lobar pneumonia, which presents as a patient with fever, cough, shortness of breath with or without secretions, and crackles on auscultation of the lobe with consolidation. Answer D (widened mediastinum) is consistent with an aortic dissection, which usually presents as a patient with tearing chest pain radiating to the back who has long-standing hypertension or a collagen-vascular disease such as Marfan syndrome. Answer E (multiple pulmonary nodules) would be consistent with pulmonary cancer. Affected individuals usually have hemoptysis, weight loss, dyspnea, and night sweats (see Case 4 [Heart Failure due to Critical Aortic Stenosis]).

R12. **C. This woman most likely has Hashimoto thyroiditis based on the symptoms and positive anti-TPO antibodies. She is at an increased risk for lymphoma of the thyroid.** Hashimoto thyroiditis is an autoimmune condition common in middle-aged women characterized by antibodies toward components of the thyroid gland. Initially, patients may present with a transient period of hyperthyroidism due to release of thyroid hormone from follicle rupture. Eventually, patients will present with symptoms of hypothyroidism such as weight gain, fatigue, cold intolerance, constipation, dry cool skin, and thin, brittle hair. Hashimoto thyroiditis is diagnosed clinically by physical examination of a diffusely enlarged thyroid with a possibly rubbery texture, symptoms of hypothyroidism, and an elevated TSH with positive anti-TPO antibodies. Histologic confirmation can be established with thyroid fine-needle aspiration biopsy. These patients are at a 40- to 80-fold increased risk for primary lymphoma of the thyroid gland, thought to be due to somatic hypermutation. Other neoplasms of the thyroid are associated with different disease processes. Answer A (anaplastic carcinoma of the thyroid) is associated with an older patient population, usually with history of long-standing follicular or papillary carcinoma, and is highly malignant. Answer B (follicular carcinoma of the thyroid) may be associated with iodine deficiency and is more malignant than papillary cancer. Biopsy would be the only way to differentiate follicular carcinoma from a benign adenoma, by assessing whether there is extension into surrounding vasculature or through the capsule. Answer D (medullary carcinoma of the thyroid) is associated with multiple endocrine neoplasia type 2A (MEN2A) and MEN2B syndromes arising from the parafollicular cells (C cells), which produce calcitonin. Answer E (papillary carcinoma of the thyroid) is associated with a history of radiation of the head and neck during childhood, and histologic examination would demonstrate empty-appearing nuclei with central clearing (see Case 53 [Thyrotoxicosis/Graves Disease]).

Page numbers followed by *f* or *t* indicate figures or tables, respectively.

A
abatacept, 359
ABCD^2 score, stroke risk, 380*t*
abdominal aortic aneurysm (AAA), 67, 71, 72*t*, 73
abdominal pain
  in acute pancreatitis, 268
  in adrenal insufficiency, 510
  in diverticulitis, 234
  in peptic ulcer disease, 216
ABGs (arterial blood gases), 164, 166, 478, 482
ABI (ankle-brachial index), 145, 146
abnormal bleeding, 577–579
abruptio placentae, 581
abscess
  in diverticulitis, 236*t*
  pancreatic, 269
acarbose, 529*t*
accelerated idioventricular rhythm, 47
ACE inhibitors. *See* angiotensin-converting enzyme inhibitors
acetaminophen
  hepatotoxicity, 277, 277*f*, 282, 284
  for low back pain, 339
  for osteoarthritis, 327, 329
acid-fast bacillus (AFB) culture, 447*t*
acidosis
  diabetic. *See* diabetic ketoacidosis (DKA)
  lactic, 539
  metabolic. *See* metabolic acidosis
  non–anion gap, 544
  renal tubular, 544
acquired immunodeficiency syndrome (AIDS), 480, 480*t*. *See also* HIV infection
ACTH (adrenocorticotropic hormone), 198, 198*t*, 366, 494. *See also* Cushing syndrome
ACTH stimulation test, 509, 510
acute angle-closure glaucoma, 400*t*
acute arterial occlusion, 145, 146, 151
acute calcium pyrophosphate (CPP) crystal arthritis, 343–345, 347*f*, 348, 350
acute chest syndrome, 599, 600, 603
acute coronary syndromes, 40–52. *See also* ST-segment elevation myocardial infarction (STEMI); unstable angina
  clinical presentation, 42, 42*t*
  definition, 40–41
  diagnostic criteria, 42–44, 43*f*
  differential diagnosis, 44
  history, 39–40, 39*f*
  pathophysiology, 41, 41*t*
  treatment, 44–46
acute cough, 175
acute diarrhea, 243–244
acute diverticulitis, 232. *See also* diverticulitis
acute endocarditis, 135. *See also* endocarditis
acute glomerulonephritis, 296–297, 299*f*
acute heart failure, 57. *See also* heart failure (HF)
acute hemolytic transfusion reaction, 571, 572, 575
acute hepatitis, 278. *See also* viral hepatitis
acute hepatocellular necrosis, 291*t*
acute HIV syndrome, 478
acute kidney injury (AKI), 313–322
  clinical presentation, 316–317
  definition, 315
  diagnosis, 317–319, 318*t*
  in opiate overdose, 620
  pathophysiology, 300, 315–316, 316*t*, 317*t*, 639
  treatment, 319
acute leukemia, 578, 584
acute lymphoblastic leukemia (ALL), 435–436
acute pancreatitis, 265–272
  alcohol use and, 14, 267, 271
  clinical presentation, 14, 265–266, 268–269, 272
  complications, 269, 271–272
  differential diagnosis, 268
  gallstones and, 267, 272
  pathophysiology and etiology, 14, 266–267, 267*t*
  pleural effusion in, 188*t*
  SIRS criteria, 267*t*
  treatment, 269
acute pericarditis, 117–124
  clinical presentation, 120–121, 129*t*
  definition, 120
  differential diagnosis, 44
  etiology, 120, 120*t*
  vs. myocardial infarction, 121, 121*t*
  pathophysiology, 129*t*
  treatment, 121
acute promyelocytic leukemia, 581
acute renal failure. *See* acute kidney injury (AKI)
acute respiratory distress syndrome (ARDS), 168*t*, 269, 482
acute tubular necrosis, 317*t*, 318*t*
acyclovir, 418, 449, 450, 636
AD. *See* Alzheimer disease
adalimumab, 359
ADAMTS13, 581
Addison disease, 490, 509. *See also* adrenal insufficiency
addisonian crisis, 511
adenocarcinoma, 21, 197, 201
adenovirus, 175, 205
ADH (antidiuretic hormone), 489
adhesins, 325
adolescence, iron deficiency in, 560
ADPKD (autosomal dominant polycystic kidney disease), 68*t*
adrenal crisis, 430, 433
adrenal hyperplasia, 366

adrenal insufficiency, 507–513
clinical presentation, 508–509, 510
diagnosis, 510–511
etiology, 509–510, 513
hyponatremia in, 490, 494
hypothyroidism and, 511
treatment, 511, 513
adrenal metastases, 509
adrenocortical adenoma, 365, 366, 368
adrenocorticotropic hormone (ACTH), 198, 198*t*, 366, 494. *See also* Cushing syndrome
adrenoleukodystrophy, 509
Advisory Committee on Immunization Practices (ACIP), 27
AF. *See* atrial fibrillation
AFB (acid-fast bacillus) culture, 447*t*
AIDS. *See* acquired immunodeficiency syndrome (AIDS)
AKI. *See* acute kidney injury
akinesia, 407
albuterol, 171, 420*t*
alcohol use
acetaminophen hepatitis and, 282
cirrhosis and, 257, 258–259. *See also* cirrhosis
dementia and, 390
pancreatitis and, 14, 267, 271
alcohol withdrawal
clinical presentation, 609, 610, 611*t*, 613
delirium in, 607
epidemiology, 610
pathophysiology, 610
treatment, 611, 613
alcoholic cirrhosis, 636
alcoholic hallucinosis, 611*t*
alcoholic ketoacidosis, 542
aldosterone, 544
aldosterone antagonists, 49, 59, 60*t*, 64
aldosterone deficiency, 510
alendronate, 374
ALL (acute lymphoblastic leukemia), 435–436
allergic rhinitis, 176
allergies, 4
allopurinol, 348
alpha$_1$-antitrypsin deficiency, 257*t*
alpha-beta blockers, 81*t*
alpha-blockers, 80, 81*t*, 94
alpha-glucosidase inhibitors, 529*t*
alpha-thalassemia minor, 567
Alzheimer Association, 393
Alzheimer disease (AD)
clinical presentation, 391, 391*t*, 392*t*
definition, 389
functional imaging of, 394–395
treatment, 391–393, 391*t*
amantadine, 409*t*, 410
amaurosis fugax, 379, 381, 385
ambulatory blood pressure monitoring, 77
amenorrhea, 499, 500*f*. *See also* oligomenorrhea
American Cancer Society, 24
American Heart Association (AHA), 138
amiodarone, 462, 550
amlodipine, 82*t*
amoxicillin, 138, 209, 211, 215
amphotericin B, 439*f*, 481
ampicillin, 448*t*, 449, 451
ampicillin-clavulanate, 209, 211
ampicillin-sulbactam, 209, 211, 259*t*, 260
ampullary cancer, 290
amylase, serum, 268, 271
amyloidosis, 129, 132
ANA. *See* antinuclear antibody
anabolic steroids, 590
anakinra, 359
anaphylactoid reactions, 417
anaphylaxis, 415–423
clinical presentation, 415–416, 419–420, 419*t*
definition, 417
differential diagnosis, 418
pathophysiology, 417–418
treatment, 419, 420, 420*t*
anemia
of chronic disease, 563*t*, 567
classification by MCV, 561, 562*t*
clinical presentation, 564, 571
definition, 559, 571
diagnosis, 561–563, 561*f*
iron deficiency. *See* iron-deficiency anemia
macrocytic, 559, 562*t*, 567
microcytic, 559, 560–561, 562*t*, 563*f*, 563*t*, 566
normocytic, 559, 562*t*, 567
pernicious, 390
renal failure–related, 572
sickle cell. *See* sickle cell disease
sideroblastic, 560, 563*t*
aneurysm
abdominal aortic. *See* abdominal aortic aneurysm (AAA)
berry, 399, 400
cerebral artery, 403
left ventricular, 43*f*, 46*t*, 51
Rasmussen, 458
angina pectoris, 8–9, 42, 51. *See also* unstable angina
in aortic stenosis, 56, 61, 63
angioedema, 82*t*, 201, 417, 420
angiography, 8, 15, 147
angiotensin receptor blockers (ARBs)
in diabetes, 530
for heart failure, 59, 63
for hypertension, 79, 80, 82*t*
for metabolic syndrome, 34
for nephrotic syndrome, 308
angiotensin-converting enzyme (ACE) inhibitors
acute kidney injury and, 315–316
angioedema from, 422
cough from, 180
in diabetes, 530
in heart failure management, 13, 59, 60*t*, 97
in hypertension management, 79, 80, 82*t*, 85, 97
for metabolic syndrome, 34
in nephrotic syndrome management, 308
in post-STEMI patient management, 49, 52
anion gap metabolic acidosis, 537, 538, 539*t*, 543–544
ankle-brachial index (ABI), 145, 146
ankylosing spondylitis, 226*t*, 361
anterior wall infarction, 51
antiadrenergics, 81*t*
antibiotics. *See specific antibiotics*
anti-CCP antibodies, 355, 356, 362
anti-CD20 monoclonal antibody. *See* rituximab
anticoagulation
in atrial fibrillation, 101, 102, 382
contraindications, 161
for disseminated intravascular coagulation, 582*t*
for pulmonary embolism, 159
reversing, 572

anti-D, 580
antidepressants, 618
antidiuretic hormone (ADH), 489
antiepileptics, 370, 419, 422
antifungal therapy, 440, 441
antihistamines, 419, 618
antihypertensive agents, 81*t*–82*t*, 113
antimicrobial prophylaxis, 138
antinuclear antibody (ANA), 122*t*, 124, 257*t*, 297*t*
antiplatelet therapy, 382, 384
antipsychotics, 609–610, 618
antithrombin III, 308
antithyroid drugs, 551–552
anuria, 315
aortic aneurysm. *See* abdominal aortic aneurysm (AAA)
aortic dissection, 65–70
  classification, 69–70, 70*f*
  clinical presentation, 66, 69, 69*t*, 640
  definition, 67
  differential diagnosis, 44
  epidemiology, 67
  genetic syndromes associated with, 68*t*
  hypertension and, 67
  pathophysiology, 67, 640
  risk factors, 68*t*
  treatment, 70
aortic regurgitation, 69, 69*t*
aortic stenosis
  clinical presentation, 61
  heart failure and, 56
  pathophysiology, 61
  syncope and, 113, 115
  treatment, 61–62, 62*t*
aortic valve replacement, 61, 62*t*, 63
aortography, 69
apathetic hyperthyroidism, 550
apixaban, 159, 382
aplastic crisis, 600, 603
appendicitis, 239
ARBs. *See* angiotensin receptor blockers
ARDS (acute respiratory distress syndrome), 168*t*, 269, 482
Argyll Robertson pupils, 468
arrhythmias
  bradyarrhythmias, 47, 113
  syncope and, 113–114
  tachyarrhythmias, 47, 113–114
  ventricular, 46–47, 46*t*
arterial blood gases (ABGs), 164, 166, 478, 482
arteriography, 147
arthritis, monoarticular. *See* monoarticular arthritis
arthrocentesis, 345, 351
arthroplasty, 328
arthroscopy, 328
Arthus reaction, 417
asbestos exposure, 188*t*
ascites
  definition, 257
  differential diagnosis, 258, 260*t*
  in heart failure, 58
  in hepatocellular disease, 259*t*, 293
  pleural effusion and, 187*t*
L-asparaginase, 268*t*
Aspergillus, 210, 441
aspiration pneumonia, 208, 211
aspirin
  for myocardial infarction, 44, 49, 51, 639
  overdose, 635
  for peripheral vascular disease, 150
  for polycythemia vera, 591
  for stroke prevention, 382
asthma, 173–181
  classification, 178*t*
  cough-variant, 176
  definition, 175
  diagnosis, 638
  drug contraindications in, 81*t*
  as obstructive lung disease, 166, 168*t*
  pathophysiology, 175–178, 177*f*
  treatment, 178*t*, 180–181
asymptomatic bacteriuria, 427, 428, 433
atenolol, 81*t*
atherosclerosis
  atrial fibrillation and, 101
  carotid, 380, 382
  in extremities, 145, *See also* peripheral vascular disease
  heart failure and, 63
atherosclerotic vascular disease (ASCVD) risk calculator, 30–31, 31*t*
atrial fibrillation (AF), 100–107
  after carotid massage, 116
  chronic, 102, 102*t*, 103*t*
  definition, 100
  epidemiology, 101
  etiology, 101, 101*t*
  pathophysiology, 101
  rheumatic heart disease and, 103–104
  stroke and, 382
  syncope and, 113
  treatment, 101–103, 382
  in Wolff-Parkinson-White syndrome and, 104–105, 104*f*, 107
atrial tachyarrhythmia, 47
atrioventricular (AV) blocks
  first-degree, 47, 114
  Mobitz I second-degree, 47, 114
  Mobitz II second-degree, 47, 114
  third-degree, 47, 114, 116
atrioventricular (AV) conduction disturbances, 47
atropine, 45*f*, 47, 110, 420*t*
autoimmune hepatitis, 257*t*
autoimmune (Hashimoto) thyroiditis, 502, 505. *See also* hypothyroidism
autonomic neuropathy, 115
autonomous hyperfunctioning adenoma, 550
autosomal dominant polycystic kidney disease (ADPKD), 68*t*
azathioprine, 225, 268*t*
azithromycin
  for *C. trachomatis*, 471
  for MAC infection, 481, 636
  for PJP prophylaxis, 483
  for pneumonia, 208, 211, 224
  for pneumonia prophylaxis, 603

B

Bacillus Calmette-Guérin vaccine (BCG), 459
bacteremia
  catheter-related, 437, 438
  in endocarditis, 136
  transient, 140
  in urinary tract infection, 429
bacterial meningitis, 445. *See also* meningitis
barbiturates, 618
bariatric surgery, 34

baricitinib, 360
basic information, 3
basophilic stippling, 560, 561*f*
Beck's triad, 127
Beers Criteria, 392
behavioral counseling, 23
benzathine penicillin G, 470
benzodiazepines, 2, 609, 611, 613
Bernard-Soulier syndrome, 635
berry aneurysm, 399, 400
beta-2 agonists, 178*t*, 180
beta-blockers
  in aortic dissection management, 70, 73
  in atrial fibrillation management, 101–103
  avoidance in Wolff-Parkinson-White syndrome, 105
  in chest pain assessment, 45*f*
  in heart failure management, 13, 59, 60*t*, 63
  in hypertension management, 80, 81*t*, 97
  in hypertensive emergency, 93
  for hyperthyroidism, 551
  for myocardial infarction, 44, 52, 93
  overdose, 618
  for secondary prevention of heart disease, 49
beta-hCG, 505
beta-lactam antibiotics, 418, 439*f*
bicarbonate therapy, for diabetic ketoacidosis, 541
bicuspid aortic valve, 67
bilevel positive airway pressure (BiPAP), 168
biliary colic, 216, 219, 270
biliary obstruction, 288, 290
bilirubin, 289
Binswanger disease, 390
bismuth subsalicylate, 244
bisoprolol, 59
bisphosphonates, 365, 370, 374, 520*t*, 523
blood cultures, in endocarditis, 136
blood transfusions. *See* transfusions
BNP (B-type natriuretic peptide), 57
body mass index (BMI), 31, 33
bone density, 370
bone marrow abnormality, 579
bone marrow biopsy, 590, 591*t*
bone mineral density (BMD), 365, 366, 518, 634
bortezomib, 521
bosentan, 601
Bouchard nodes, 325, 326
boutonnière deformity, 329, 356, 358*f*
bowel sounds, hypoactive, 619
bradyarrhythmias, 47, 112*t*, 113. *See also* sinus bradycardia
bradykinesia, 407, 408
brain tumors, 390, 400*t*, 403
bronchiectasis, 195
bronchitis, 165, 166, 195
bronchodilators, 167, 169, 169*t*, 171
bronchogenic carcinoma, 175
bronchoscopy, 207–208, 211
Brudzinski sign, 447
bruits, 146
budesonide, 225
Buerger disease (thromboangiitis obliterans), 145, 150
bullous myringitis, 210
buprenorphine, 620
bursitis, 325, 345
busulfan, 592

C
cabergoline, 369
CAD. *See* coronary artery disease
CAGE questionnaire, 259–260
calcitonin, 520*t*
calcium channel blockers, 79, 82*t*, 101
calcium intake, 370
calcium pyrophosphate dihydrate (CPPD), 343, 345, 347*f*
Campylobacter, 224
canagliflozin, 529*t*
cancer. *See also specific cancers*
  hypercalcemia in, 518
  joint pain in, 325
  low back pain and, 335
  pleural effusion in, 186*t*, 187, 188*t*, 190
  screening for, 22, 24–25, 25*t*
  staging, 12
  tissue diagnosis, 201
candesartan, 82*t*
Candida esophagitis, 635–636
Candida spp, 137*t*, 140, 440, 441
CAP. *See* community-acquired pneumonia
capsaicin, 327
captopril, 82*t*
carbamazepine, 422
carbidopa-levodopa, 409*t*
carbon monoxide, 618
carcinoid tumors, 245, 637
cardiac biomarkers, 43–44
cardiac index, 48
cardiac pump failure, 47
cardiac remodeling, 57
cardiac resynchronization therapy, 60, 64
cardiac tamponade, 125–132
  clinical presentation, 119, 127–128, 129*t*, 131
  definition, 127
  pathophysiology, 127
  in pericarditis, 121
  treatment, 128–129, 131
cardiac-specific troponin I (cTnI), 44
cardiac-specific troponin T (cTcT), 44
cardioembolism, 380
cardiogenic shock, 47–48, 427, 430–431, 433
cardiogenic syncope, 111, 113
cardiomyopathy
  ischemic, 57, 62
  restrictive, 129, 129*t*, 131
cardiorenal syndrome, 60
cardiovascular disease, 22
  diabetes and, 530
  risk factors, 78
  screenings for, 25*t*
cardioversion. *See* direct current (DC) cardioversion
Carney complex, 366
carotid artery angioplasty, 382
carotid artery stenosis, 381, 382–383
carotid artery stenting, 383
carotid atherosclerosis, 380, 382
carotid endarterectomy, 382–383, 384
carotid massage, 116
carotid sinus hypersensitivity, 113, 115, 116
carvedilol, 59, 81*t*
catecholamine vasopressors, 431
catecholamines, 94
catheter-associated UTI, 428, 429*t*
catheter-related bacteremia, 437, 438

catheter-related bloodstream infection (CRBSI), 437, 439
cauda equina syndrome, 333, 339
cavitary lung lesions, 457, 458
cavitation, 207
CBC (complete blood count), 7, 15
cefepime, 208, 211
cefotaxime, 259*t*, 260, 448*t*, 603, 636
ceftriaxone
  for endocarditis, 137, 639
  for gonococcal arthritis, 345, 350
  for gonorrhea, 471
  for meningitis, 448*t*, 451
  for peritonitis, 636
  for syphilis, 470
celecoxib, 359
celiac disease
  clinical presentation, 242–243
  diagnosis, 248–249, 251
  iron absorption and, 560, 564
  osteoporosis and, 370
  pathophysiology, 248
central line–associated bloodstream infection (CLABSI), 437
central nervous system (CNS) lymphoma, 480, 485
central pontine myelinolysis. *See* osmotic demyelination syndrome
central venous catheter (CVC), 437, 439
cephalosporins
  anaphylaxis history and, 418
  for endocarditis prophylaxis, 138
  for pneumonia, 208
  resistance to, 449
  for spontaneous bacterial peritonitis, 260, 636
cerebral artery aneurysm, 403
cerebral blood flow autoregulation, 92, 92*f*
cerebral infarction, 93, 379. *See also* stroke
cerebral toxoplasmosis, 480, 483
cerebrospinal fluid (CSF), in meningitis, 447–448, 447*t*
cerebrovascular accident (CVA), 379. *See also* stroke
certolizumab, 359
cervical cancer, 25*t*, 27, 161, 321
cervical cytology, 27
CFUs (colony-forming units), 428, 438
CHA_2DS_2-VASc Score, 102, 102*t*, 103*t*, 106
chancres, 467, 473
chancroid, 468, 473
cheilosis, 564
chemical pneumonitis, 208
chemoprevention, 23
chemotherapy, 436, 437, 440
chest pain
  in acute pericarditis, 119, 124
  in aortic dissection, 69
  assessment and treatment algorithm, 45*f*
  in gastroesophageal reflux, 51
  in lung cancer, 197
chest radiography
  indications, 7, 180
  normal, in nonsmoker, 175
  in pulmonary embolism, 156
chief complaint, 3
Child-Turcotte-Pugh system, liver disease classification, 259
Chlamydia psittaci, 205
Chlamydia trachomatis, 470–471
Chlamydophila pneumoniae, 205, 210, 637
chlordiazepoxide, 611
chlorthalidone, 81*t*, 85
cholangiocarcinoma, 290
cholangitis, 270, 272. *See also* primary sclerosing cholangitis
cholecystectomy, 270
cholecystitis, 270, 272
cholelithiasis. *See* gallstones (cholelithiasis)
cholestasis, 289, 290, 291*t*
cholesterol, 308, 503
cholesterol embolisms, 150
cholinergics, 618
cholinesterase inhibitors, 391, 394
chondrocalcinosis, 345, 347*f*
chondroitin, 327
chronic airway obstruction, 171
chronic bronchitis, 165, 166. *See also* chronic obstructive pulmonary disease (COPD)
chronic cough, 175–176, 177*f*. *See also* asthma
chronic diarrhea, 241–252
  in bowel motility disorders, 245*t*, 247–248
  clinical presentation, 241–242
  definition, 243
  diagnostic approach, 246*f*
  inflammatory, 245*t*, 247. *See also* Crohn disease; ulcerative colitis
  in malabsorption syndromes, 248–249
  osmotic, 245*t*, 247
  secretory, 245–246, 245*t*
chronic heart failure. *See* heart failure (HF)
chronic hepatitis, 257, 257*t*, 278
chronic hepatocellular disease, 291*t*
chronic hypertension, complications of, 16–17
chronic myelogenous leukemia, 594
chronic obstructive pulmonary disease (COPD), 163–172
  classification, 165*t*
  complications, 170, 590, 637, 639
  definition, 165
  diagnosis, 166, 167*f*
  pathophysiology, 166, 167*f*, 168*f*
  smoking and, 166, 171
  treatment, 167–170, 169*t*
chronic pancreatitis, 248
chronic traumatic encephalopathy, 413
chylothorax, 188*t*
cidofovir, 481
cilostazol, 147, 150
ciprofloxacin, 224, 429, 449
cirrhosis, 255–263
  alcoholic, 636
  clinical presentation, 255–256, 258
  compensated, 258
  complications, 259*t*
  decompensated, 258
  definition, 257, 278
  diagnosis, 257–258, 260*t*
  hypervolemia in, 490
  pathophysiology and etiology, 257, 257*t*
  pleural effusion in, 187*t*
  prevention, 259–260
  primary biliary, 290, 292*t*
  treatment, 258–260
CK (creatine phosphokinase), 43
CK-MB (creatine kinase myocardial band), 41, 43, 51
clarithromycin, 215, 217, 483
claudication, 144, 145, 146

clindamycin, 138, 209
Clinical Institute Withdrawal Assessment scale (CIWA), 610
clinical problem solving, approach to, 10–13
  diagnosis, 10–12
  disease severity assessment, 12
  patient response to treatment, 13
  treatment based on disease stage, 12–13
clinical state, 15
clinical thinking, 13
clonidine, 81*t*, 85, 90
clopidogrel, 49, 382, 639
Clostridium difficile, 223, 224, 244
clubbing, finger, 194, 196
cluster headache, 400*t*, 402
CMV (cytomegalovirus), 479, 481, 509, 636
coagulase-negative staphylococci, 137*t*, 439, 441
coagulopathy, 581
coarctation of the aorta, 83
coccidioidomycosis, 205, 210, 509
cogwheel rigidity, 408
colchicine, 121, 348, 350
colectomy, 225, 226
colitis, 223–224, 239. *See also* ulcerative colitis
colon cancer, 25*t*, 27, 139, 226
colonic diverticulum, 233
colonoscopy, 139, 637
colony-forming units (CFUs), 428, 438
coma, 617
community-acquired pneumonia (CAP), 203–211
  atypical, 206
  clinical presentation, 175, 181, 203–204, 206, 640
  definition, 205
  diagnosis, 207–208
  pathophysiology, 204, 205–206
  pleural effusion in, 188*t*
  risk stratification, 206–207
  treatment, 208, 210–211
compartment syndrome, 620
complete blood count (CBC), 7, 15
computed tomography (CT), 8
  in acute pancreatitis, 269
  in aortic dissection, 66
  in diverticulitis, 234, 239
  in meningitis, 447
  in pancreatic cancer, 290
  in pulmonary embolism, 157
  in subarachnoid hemorrhage, 401
  in transient ischemic attack, 378, 381
  in VIPoma, 251
conduction disturbances, 47
condyloma lata, 468
Confusion Assessment Method (CAM) score, 609
congenital adrenal hyperplasia, 509
congestive heart failure (CHF). *See* heart failure (HF)
conivaptan, 492
conjugated bilirubin, 289
conjugated (direct) hyperbilirubinemia, 289–290, 293
Conn syndrome, 495
connective tissue disease, pleural effusion in, 188*t*
constrictive pericarditis, 128, 129*t*
consumptive coagulopathy, 581
continuous positive airway pressure (CPAP), 168
contrast media, 419, 423
COPD. *See* chronic obstructive pulmonary disease
cor pulmonale, 639
coronary artery bypass surgery, 49
coronary artery disease (CAD), 8–9, 42*t*, 314
calcium level, corrected 517
corticosteroids
  for acute joint pain, 348
  for adrenal insufficiency, 511, 513
  for anaphylaxis, 420
  for asthma, 178*t*, 180, 181
  for COPD, 169*t*, 171
  for Crohn disease, 225
  for giant cell arteritis, 401
  for gout, 342
  for Graves ophthalmopathy, 552
  for hypercalcemia, 520*t*
  for meningitis, 449
  for osteoarthritis, 328
  for pericarditis, 121
  for prevention of contrast dye reaction, 423
  for rheumatoid arthritis, 359, 361
  for septic shock, 433
  for thrombocytopenia, 580, 582*t*
  for thyroiditis, 550
  for tuberculous meningitis, 459
  for ulcerative colitis, 225
corticotropin-releasing hormone (CRH) stimulation test, 368
cortisol, 490, 494–495, 510–511
cough
  acute, 175
  in acute chest syndrome, 600
  in asthma, 176. *See also* asthma
  chronic, 175–176
  in HIV infection, 479
  subacute, 175
Coumadin. *See* warfarin
COX-2 inhibitors, 327, 359
CPAP (continuous positive airway pressure), 168
CPPD (calcium pyrophosphate dihydrate), 343, 345, 347*f*
crackles (rales), 161, 196
C-reactive protein (CRP), 399
creatine kinase myocardial band (CK-MB), 41, 43, 51
creatine phosphokinase (CK), 43
crepitus, 325
Creutzfeldt-Jakob disease, 390, 391*t*
critical leg ischemia, 146, 147. *See also* peripheral vascular disease
Crohn disease
  clinical presentation, 637–638
  complications, 226–227
  definition, 223
  extraintestinal manifestations, 226*t*
  pathophysiology, 224–225
  treatment, 225
  vs. ulcerative colitis, 225*t*
"crypt abscesses," 224
cryptococcal meningitis, 481
Cryptococcus, 446
crystal arthritis. *See* acute calcium pyrophosphate (CPP) crystal arthritis; gout
cTcT (cardiac-specific troponin T), 44
cTnI (cardiac-specific troponin I), 44
Cullen sign, 71, 268
CURB-65 score, in pneumonia, 206–207, 211
Cushing disease, 365, 366

Cushing syndrome, 363–369
ACTH-dependent, 365, 367
ACTH-independent, 365, 367, 373
clinical presentation, 363–365, 366, 372
definition, 365
diagnosis, 366–368, 372–373, 374
iatrogenic, 366
pathophysiology, 366
secondary hypertension in, 78*t*, 83, 85
treatment, 368–369, 369*t*
cyanide toxicity, 93
cyclosporine, 370
cystic degeneration, 67
cystitis, acute uncomplicated, 428, 429*t*, 433
cytochrome P450 enzyme system, 282, 367
cytomegalovirus (CMV), 479, 481, 509, 636

D
dabigatran, 159, 382
dactylitis, 356
daptomycin, 348
dark-field microscopy, 469, 473
DASH diet, 77
DC cardioversion. *See* direct current (DC) cardioversion
D-dimer, 135, 155, 156
de Quervain (subacute) thyroiditis, 550
decitabine (5-deoxyazacytidine), 601, 602
deep venous thrombosis (DVT). *See also* pulmonary embolism (PE)
definition, 155
pathophysiology, 638
in polycythemia vera, 591
risk factors, 16
treatment, 159, 160
deep-brain stimulation, 410, 413
defibrillation, 47
delirium, 605–610
clinical presentation, 389, 605–609, 613
definition, 607
diagnosis, 608–609
etiology, 607, 608*t*
in geriatric population, 608
in thyroid storm, 552
treatment, 609–610
delirium tremens (DT), 610, 611*t*
dementia, 387–395
alcoholism and, 390
Alzheimer. *See* Alzheimer disease (AD)
clinical presentation, 387–388
definition, 389, 607
delirium and, 608
depression and, 389–390
etiology, 389–390, 391*t*
frontotemporal, 390
in HIV infection, 390, 391*t*
hypothyroidism and, 502
initial evaluation of, 392*t*
vascular (multi-infarct), 389, 390, 391*t*, 394
5-deoxyazacytidine (decitabine), 601, 602
deoxyribonuclease (DNase), 189
Department of Health and Human Services, 24
depression
cognitive decline and, 389–390
hypothyroidism and, 502
joint pain in, 355
in Parkinson disease, 407
screening after MI, 49
desmopressin acetate, 583
DEXA (dual-energy x-ray absorptiometry), 26, 364
dexamethasone, 521, 523
dexamethasone suppression test (DST), 365, 367, 368
diabetes mellitus, 525–533
antihypertensive agents in, 85
cardiovascular disease risk evaluation in, 530
clinical presentation, 525–526
complications, 527, 637. *See also* diabetic ketoacidosis (DKA)
coronary artery disease and, 311
diagnosis, 526, 528, 528*t*, 532–533
epidemiology, 527
gestational, 527
immunizations in, 533
myocardial infarction/ischemia in, 51
nephrotic syndrome and, 307, 638. *See also* diabetic nephropathy
new-onset, 36
orthostatic hypertension in, 115
pathophysiology, 528
peripheral vascular disease and, 145
screening, 25*t*, 527–528, 532
treatment, 528–530, 529*t*, 532
type 1, 527
type 2, 305–306, 311, 527
diabetic ketoacidosis (DKA), 535–545
clinical presentation, 538
complications, 541–542
definition, 537
diagnosis, 538–539
pathophysiology, 537–538
prevention, 541
treatment, 539–541, 544
diabetic nephropathy
clinical presentation, 307
complications, 309
diagnosis, 540, 638
treatment, 310–311, 532
diabetic neuropathy, 530
diabetic retinopathy, 530
diagnosis
confirming, 17
making, 10–12
diagnostic reasoning, 11
dialysis, 319, 321, 520*t*
diarrhea
acute, 243–244
chronic. *See* chronic diarrhea
definition, 243
watery, 223
diastolic dysfunction, 57, 63
diazepam, 611
diclofenac, 327
didanosine, 268*t*
differential diagnosis, 11
digoxin, 59, 60*t*, 101
dihydropyridines, 82*t*
diltiazem, 82*t*
diphenhydramine, 420, 420*t*, 422
dipyridamole, 382
direct current (DC) cardioversion, 100, 101–102, 106
direct thrombin inhibitors, 159
direct-reacting bilirubin, 289
discriminating features, 11
disease severity assessment, 12

disease-modifying antirheumatic drugs (DMARDs), 359–360, 361
disseminated intravascular coagulation (DIC)
  in adrenal insufficiency, 509
  clinical presentation, 582*t*
  diagnosis, 581
  etiology, 581, 582*t*
  treatment, 572, 581, 582*t*
distributive shock, 427, 430, 431
diuretics
  for acute hemolytic transfusion reaction, 573, 575
  for acute kidney injury, 319
  adverse effects, 489, 490, 495
  for ascites, 258
  for heart failure, 60*t*
  for hypertension, 79, 81*t*, 85
  for hypervolemia, 490
  for nephrotic syndrome, 308
diverticular hemorrhage, 236–237
diverticulitis, 231–240
  clinical presentation, 234, 234*t*
  complications, 236–237, 236*t*, 239
  definition, 233
  diagnosis, 234
  pathophysiology, 233–234
  prevention, 235–236
  recurrent, 236, 239
  treatment, 235
diverticulosis, 233, 235, 236
dizziness, 380
DKA. *See* diabetic ketoacidosis
DMARDs. *See* disease-modifying antirheumatic drugs
DNase (deoxyribonuclease), 189
donepezil, 391, 394
dopamine, 407, 431
dopamine agonists, 368–368, 409*t*, 410
doxycycline, 208, 470, 471
DPP-4 inhibitors, 529*t*
Dressler syndrome, 46*t*, 638–639
drug addiction, 617
drug reactions, 419. *See also* anaphylaxis
drug-induced liver injury, 281, 462. *See also* acetaminophen, hepatotoxicity
DT (delirium tremens), 610, 611*t*
dual-energy x-ray absorptiometry (DEXA), 26, 364
Duke criteria, endocarditis, 136, 137*t*
duloxetine, 327
duodenal ulcers, 215, 216, 217. *See also* peptic ulcer disease (PUD)
duplex ultrasound, 150
DVT. *See* deep venous thrombosis
dysentery, 223, 224
dysmorphic red blood cells, 298, 301
dysmotility, 247–248
dyspepsia, 181, 215, 216
dyspnea
  in COPD, 166, 169
  exertional, 56
  in pulmonary embolism, 154, 156, 195

E
EBV (Epstein-Barr virus), 481
echocardiography, 8, 136, 140, 158
ECMO (extracorporeal membrane oxygenation), 48, 158–159
ectopic ACTH syndrome, 366
edoxaban, 159, 382
EHEC (enterohemorrhagic *Escherichia coli*), 244, 251
Ehlers-Danlos syndrome, 68*t*
electrocardiogram (ECG)
  in acute coronary syndrome, 40
  in acute kidney injury, 319
  in acute pericarditis, 44, 121*t*
  in aortic stenosis, 61
  in atrial fibrillation, 381
  in health screening, 8
  in myocardial infarction, 42–43, 43*f*, 121*t*
  in opiate overdose, 618
electrolytes
  in diabetic ketoacidosis, 541
  urinary, 318–319
ELISA. *See* enzyme-linked immunosorbent assay
embolectomy, 158
embolism
  cardiogenic, 80, 145
  cholesterol, 150
  peripheral vascular disease and, 145
  pulmonary. *See* pulmonary embolism (PE)
  septic, 135, 137
empagliflozin, 529*t*
emphysema, 165. *See also* chronic obstructive pulmonary disease (COPD)
empty sell syndrome, 501
empyema, 186, 189
enalapril, 82*t*
encephalitis, 445
encephalopathy
  hepatic, 259*t*, 261, 636
  hypertensive, 90–91, 93
  metabolic, 608*t*
  subcortical arteriosclerotic leukoencephalopathy, 390
  toxic, 608*t*
  Wernicke, 390, 611, 613
endarterectomy. *See* carotid endarterectomy
endarterectomy, carotid, 382–383, 384
endocarditis, 133–140
  acute, 135
  antimicrobial prophylaxis guidelines, 138
  clinical presentation, 135–136
  complications, 138
  culture-negative, 137, 140
  Duke criteria, 136, 137*t*
  fungal, 140
  infective, 135, 140
  left-sided native valve, 140
  pathophysiology, 135–136, 137*t*
  prophylaxis, 138*t*
  right-sided, 136, 140
  subacute, 135
  treatment, 136–137, 138*t*
endomyocardial biopsy, 129
endomyocardial fibrosis, 129, 131
endoscopic retrograde pancreatography (ERCP), 267
endothelin receptor agonists, 601
end-stage renal disease (ESRD), 122, 186, 309, 634
enoxaparin, 159
Entamoeba histolytica, 224
Enterococci, 137*t*
enterohemorrhagic *Escherichia coli* (EHEC), 244, 251
enterovaginal fistula, 228
enteroviruses, 446
entrapment neuropathy, 359

enzyme-linked immunosorbent assay (ELISA)
D-dimer, 135, 155, 156
for HIT antibodies, 581
eosinophilic nodular glomerulosclerosis, 638
epinephrine, 416, 420, 420*t*, 422
epistaxis, 577–578
eplerenone, 81*t*
Epstein-Barr virus (EBV), 481
erosive gastritis, 558
erythema multiforme major, 418, 423
erythema multiforme minor, 418, 423
erythema nodosum, 180, 226*t*
erythrocyte sedimentation rate (ESR), 399, 401
erythromelalgia, 591
erythropoietin (EPO), 523, 572, 589, 590, 594
Escherichia coli
ampicillin resistance in, 433
bloody diarrhea and, 244, 582
enterohemorrhagic, 244, 251
in gallbladder, 270
infectious colitis and, 224
in peritonitis, 636
esmolol, 70, 74
esophageal pH monitoring, 181
esophageal varices, 260, 262, 636
esophageal web, 564
esophagogastroduodenoscopy (EGD), 217
ESRD (end-stage renal disease), 122, 186, 309, 634
essential hypertension, 77, 84
essential thrombocytopenia, 589, 589*t*, 592, 594
estrogens, 374
etanercept, 359
ethambutol, 460, 462, 481
ethylene glycol, 618
etomidate, 369*t*
euvolemic hyponatremia, 490, 492
Evans syndrome, 580
exchange transfusion, 600
exenatide, 529*t*
exercise stress tests, 8, 49, 51
exertional dyspnea, 56
exophthalmos, 551, 551*t*, 552, 554
extracorporeal membrane oxygenation (ECMO), 48, 158–159
extrahepatic cholestasis, 291ty
extrahepatic dilation, 290
extrapulmonary tuberculosis, 458–459
extrapyramidal system, 407
exudate, 186, 187, 188*t*

F

factor V Leiden mutation, 155, 161
familial hypocalciuric hypercalcemia, 518, 523
family history, 4
fasting plasma glucose, 528, 528*t*, 532
fatty liver, 263
febuxostat, 348
fecal occult blood testing (FOBT), 25*t*, 564
fecaliths, 234
felodipine, 82*t*
Felty syndrome, 359, 585
FE_{Na} (fractional excretion of sodium), 318, 318*t*
ferritin, 559, 563, 563*t*
ferrous sulfate, 564
FEV_1/FVC
in asthma, 176
in COPD, 165, 165*t*, 166, 167*f*, 169*t*
fever, 437. *See also* neutropenic fever
FFP (fresh frozen plasma), 572, 575, 582*t*
fibrinogen, 581
fibrinolytic therapy, 147
fibrinous pericarditis, 639
fibromuscular dysplasia, 145, 150
fibromyalgia, 355
finger clubbing, 194, 196
first-degree AV block, 47, 114
fistula, 226–227, 228, 236*t*
Fleischner Society, 199
flexion abduction external rotation (FABER) test, 336
flow-volume loops, 167*f*, 169*f*
fluconazole, 439*f*, 481, 635
flucytosine, 481
fludrocortisone, 511
fluid replacement, for diabetic ketoacidosis, 540
fluorescent treponemal antibody absorption (FTA-ABS), 469
fluoroquinolones, 67, 208, 260, 429
FOBT (fecal occult blood testing), 25*t*, 564
focal segmental glomerulosclerosis, 307, 638
folate deficiency, 567
fondaparinux, 159
food poisoning, 244
forced expiratory volume in one second (FEV_1), 165, 165*t*. *See also* FEV_1/FVC
forced vital capacity (FVC), 165
foscarnet, 481
fractional excretion of sodium (FE_{Na}), 318, 318*t*
Fracture Risk Assessment Tool (FRAX), 369
free fatty acids (FFAs), 32
free thyroxine index (FTI), 502
fresh frozen plasma (FFP), 572, 575, 582*t*
frontotemporal dementia (Pick disease), 390, 391*t*
fruity breath odor, 538
fulminant hepatic failure, 278, 281
functional (nonulcer) dyspepsia, 215
fungal endocarditis, 140
fungal meningitis, 446, 447*t*
furosemide, 268*t*

G

galactorrhea, 498, 499
galantamine, 391
gallstones (cholelithiasis)
acute pancreatitis and. *See* acute pancreatitis
clinical presentation, 14, 265–266
in Crohn disease, 226*t*, 228
diagnosis, 290, 293
pathophysiology, 270
risk factors, 219, 293
treatment, 270
ganciclovir, 481, 636
gastric cancers, 217–218
gastric MALT lymphoma, 217
gastric outlet obstruction, 217
gastric ulcers, 217. *See also* peptic ulcer disease (PUD)
gastric varices, 260
gastrinomas, 216, 245, 638
gastritis, 558
gastroesophageal reflux disease (GERD), 51, 178–179, 181, 216
gastrointestinal bleeding, 558, 559, 564, 566, 569–570
gastrointestinal ischemia, 268
G-CSF. *See* granulocyte colony-stimulating factor
genitourinary tuberculosis, 459
gentamicin, 137, 321

gestational diabetes, 527
Ghon lesions, 458
giant cell (temporal) arteritis
  clinical presentation, 397–398, 400*t*, 401
  definition, 399
  diagnosis, 381, 398–399, 400*t*
  treatment, 401
giardiasis, 244
Gilbert syndrome, 289, 294
glabellar tap sign, 408
glaucoma, acute angle-closure, 400*t*
gliadin, 251
glimepiride, 529*t*, 532
glioblastoma multiforme, 403
glipizide, 529*t*, 532
glomerulonephritis, 295–303
  acute, 296–297, 299*f*
  acute kidney injury in, 317*t*
  classification, 301*t*
  clinical presentation, 300–301
  diagnostic approach, 297–298, 299*f*, 318*t*
  differential diagnosis, 298, 300
  membranoproliferative, 307
  pathophysiology, 297–298
  postinfectious/poststreptococcal, 300, 303, 311
  serologic markers, 297*t*
  treatment, 301
glomerulosclerosis
  eosinophilic nodular, 638
  focal segmental, 307
glossitis, 564
GLP-1 agonists, 34, 529*t*
glucagon, 420*t*, 537
glucocorticoid excess states, 83, 365, 370, 373
glucocorticoids. *See* corticosteroids
glucosamine, 327
glucose, for adrenal insufficiency, 511
glucose tolerance test, 528, 528*t*, 532
glutathione, 282
gluten-free diet, 249
glyburide, 309, 529*t*, 532
goiter, 549, 551
golimumab, 359
gonadal deficiency, 370
gonadotropic-releasing hormone inhibitors, osteoporosis and, 370
gonococcal arthritis, 330, 344–345, 350
gonorrhea, 471
Goodpasture disease, 303
gout
  clinical presentation, 341–342, 344
  definition, 343
  prognosis and prevention, 348
  stages, 343, 344*t*
  treatment, 348
gouty arthritis, 330, 343, 344*t*
Gram stain, in pneumonia, 207
granulocyte colony-stimulating factor (G-CSF), 440, 441
granulomas, 468
granulomata, 291*t*
Graves disease. *See also* hyperthyroidism
  clinical presentation, 547–548, 550–551, 551*t*, 553
  complications, 552
  diagnosis, 550
  osteoporosis in, 370
  pathophysiology, 549
  treatment, 551–552
Grey Turner sign, 71, 268
gross hematuria, 297, 303
Group B *Streptococcus*, 445
gummas, 468

H
H_2 blockers, 419, 420*t*, 423, 580
HAART (highly active antiretroviral therapy), 482, 485
HACEK organisms, 136, 137
Haemophilus ducreyi, 468
Haemophilus influenzae
  in HIV infection, 485
  in meningitis, 445, 448, 449
  in pneumonia, 205, 209, 637
  in sickle cell disease, 600
haloperidol, 394, 609
Hampton hump, 156
Hashimoto thyroiditis, 502, 505, 640. *See also* hypothyroidism
headaches, 397–404
  cluster, 400, 400*t*, 402
  etiology, 399–400, 400*t*
  migraine, 400*t*, 401–402, 403
  red flags, 398, 398*t*
  tension, 400*t*, 402
health care-associated pneumonia (HCAP), 205, 206, 211
health maintenance, 22–28
heart block, 110, 114
heart failure (HF), 55–64
  acute, 57, 60
  acute cough from, 175
  aortic stenosis and, 56
  chronic, 57, 58–59, 64
  clinical pearls, 64
  clinical presentation, 57–58, 63
  endocarditis and, 138
  functional classification, 58, 58*t*
  hypervolemia in, 490
  pathophysiology, 57, 639–640
  pleural effusion in, 186, 187*t*, 190
  pulmonary embolism and, 156
  treatment, 13, 58–60, 59*t*, 63
heart sounds, 61
heat exhaustion, 302
Heberden nodes, 325, 326*f*, 356, 357*f*
Helicobacter pylori, 215, 217, 219
HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, 579
hemarthrosis, 579
hematemesis, 217
hematochezia, 223
hematopoietic stem cell transplantation, 601
hematuria, 297, 298*t*, 303
hemochromatosis, 257*t*, 258
hemoglobin A_{1C}, 528, 528*t*, 529, 533
hemoglobin levels, 571
hemolysis, 289, 291*t*, 293
hemolytic reactions, 572–573
hemolytic uremic syndrome (HUS), 244, 251, 579, 582
hemophilia A, 635
hemoptysis
  clinical presentation, 195–196
  definition, 195
  in Goodpasture syndrome, 303
  massive, 195
  pathophysiology, 195

in pulmonary embolism, 195
treatment, 196
hemorrhage
diverticular, 236–237
gastrointestinal, 217, 219
intracranial, 400*t*
pericardial, 121
splinter, 135
subarachnoid, 385, 400–401, 403, 446
hemosiderosis, 573
heparin
low-molecular-weight, 135, 155, 159
for myocardial infarction, 44, 639
osteoporosis and, 370
unfractionated, 159
heparin-induced thrombocytopenia (HIT), 580–581, 585
hepatic encephalopathy, 259*t*, 261, 636
hepatic failure, fulminant, 278, 281
hepatitis
acetaminophen. *See* acetaminophen, hepatotoxicity
acute, 278
autoimmune, 257*t*
chronic, 257, 257*t*, 278
iron deficiency in, 563
viral. *See* viral hepatitis
hepatitis A, 278, 279. *See also* viral hepatitis
hepatitis A vaccine, 281
hepatitis B. *See also* viral hepatitis
clinical presentation, 278
diagnosis, 257*t*, 280*f*
immunity to, 284
nephrotic syndrome and, 638
pathophysiology, 279
hepatitis B vaccine, 281, 283, 533
hepatitis C, 25*t*, 257*t*, 278–281, 572. *See also* viral hepatitis
hepatitis D, 278, 279. *See also* viral hepatitis
hepatitis E, 278, 279. *See also* viral hepatitis
hepatobiliary disorders, 291*t*, 292*t*
hepatobiliary iminodiacetic acid (HIDA) scan, 270
hepatocellular carcinoma, 279
hepatocellular disease, 291*t*, 293
hepatorenal syndrome, 261, 263
herniated disk (nucleus pulposus), 333
herpes simplex virus (HSV) infections
erythema multiforme minor, 418
esophagitis, 636
genital ulcers, 468
meningitis, 446, 447*t*, 448
neutropenia and, 440
herpes zoster vaccine, 26
HF. *See* heart failure
highly active antiretroviral therapy (HAART), 482, 485
hilar mass, 201
hip fracture, 634–635
histoplasmosis, 206, 482, 485, 509
history, 3–5
HIT (heparin-induced thrombocytopenia), 580–581, 585
HIV infection, 475–485
acetaminophen hepatitis and, 282
acute syndrome, 478–479
adrenal involvement in, 509
AIDS-defining illnesses in, 479–481, 480*t*
dementia in, 390, 391*t*
fungal meningitis in, 446
meningitis in, 445
nephrotic syndrome in, 638
opportunistic infections in, 479–481, 635–636
pneumonia in, 205, 479, 485. *See also Pneumocystis jirovecii* pneumonia (PJP)
screening, 25*t*
stages, 478–479
syphilis in, 467, 468, 470
thrombocytopenia in, 580
hoarseness, 201
Hodgkin disease, 563
Hollenhorst plaques, 381
homocystinuria, 68*t*
Horner syndrome, 195, 197
hot nodules, 550
HSV. *See* herpes simplex virus
HTN. *See* hypertension
human immunodeficiency virus (HIV), 572
human immunodeficiency virus infection. *See* HIV infection
human papilloma virus (HPV) vaccine, 27, 533
human T-cell lymphocyte virus, 572
Huntington disease, 390
Hurler syndrome, 68*t*
HUS (hemolytic uremic syndrome), 244, 251, 579, 582
hydralazine, 59, 60*t*, 81*t*
hydrochlorothiazide, 81*t*
hydrocortisone, 431, 511, 513. *See also* corticosteroids
hydronephrosis, 316, 321
hydroxychloroquine, 359, 361
hydroxyurea, 589, 591, 601, 602
β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, 150
hyperacute T waves, 42
hyperaldosteronism, 83, 495
hyperbilirubinemia, 289, 293
hypercalcemia, 518–524
clinical presentation, 518
definition, 518
diagnosis, 519–520, 520*f*
differential diagnosis, 518
etiology, 518, 519*t*
in sarcoidosis, 523, 634–635
treatment, 520*t*
hypercholesterolemia, 147
hypercoagulable state, 638
hyperglycemia, 537, 538
hyperkalemia, 319, 495, 510, 541
hyperlipidemia, 25*t*
hyperosmolar nonketotic diabetic coma, 541
hyperparathyroidism
clinical presentation, 370, 518, 519*t*, 522, 640
diagnosis, 519*t*
hypercalcemia and, 518, 522, 634
treatment, 518, 519*t*
hyperphosphatemia, 319
hyperpigmentation, 511, 513
hyperprolactinemia, 501–502, 506
hypersensitivity reactions, 417, 419
hypertension (HTN)
aortic dissection and, 67, 640
atrial fibrillation and, 101
classification, 77
crises in. *See* hypertensive crises
management after stroke, 382

hypertension (HTN) (*Cont.*):
in metabolic syndrome, 31–32
in outpatient, 76–86
cardiac risk factors, 79
clinical presentation, 78–79
epidemiology, 77–78
evaluation, 78–79, 79*t*, 86
pathophysiology, 78
prognosis in, 85
treatment, 79–80, 81*t*–82*t*
pheochromocytoma and, 637
postoperative pain and, 97
pulmonary, 600, 601
screening, 25*t*
secondary causes, 77, 78*t*, 80, 83, 85
stroke risk and, 106
hypertensive crises, 91–98
hypertensive emergency, 91
hypertensive encephalopathy, 90–91, 93
hypertensive urgency, 91, 96–97
pathophysiology, 92, 92*f*
treatment, 93
hypertensive retinopathy, 76
hyperthyroidism. *See also* Graves disease
apathetic, 550
atrial fibrillation and, 107
clinical presentation, 550–551, 551*t*
complications, 552
osteoporosis and, 370
secondary hypertension in, 83
treatment, 551–552
hypertriglyceridemia, 267
hyperuricemia, 342, 344*t*, 348. *See also* gout
hyperviscosity syndrome, 589
hypervolemia, 490
hypoalbuminemia, 293
hypoglycemia, 608, 618
hypokalemia, 495
hyponatremia, 487–495
in adrenal insufficiency, 510
assessment, 490, 491*f*
clinical presentation, 487–489
complications, 492–493
definition, 489
in diabetic ketoacidosis, 539
etiology, 490–492
pathophysiology, 489–490
hyposmia, 409
hypotension, 48, 510
hypothalamic-pituitary-ovarian axis disorders, 499
hypothalamus, 509
hypothyroidism
adrenal insufficiency and, 511
bone loss in, 370
clinical presentation, 497–498, 501, 502
complications, 503
dementia and, 390
diagnosis, 501–503
differential diagnosis, 501*t*
hyponatremia in, 490, 492
joint pain in, 355
pathophysiology, 502
subclinical, 503
treatment, 503, 506
hypovolemia, 490, 492
hypovolemic shock, 427, 430
hypoxia, 608
hysterectomy, 27

I
IBD. *See* inflammatory bowel disease
IBS. *See* irritable bowel syndrome
icterus. *See* jaundice
idiopathic dysautonomia, 111
idiopathic thrombocytopenic purpura (ITP), 16
IgA nephropathy, 300, 638
IGRAs (interferon-gamma release assays), 459, 463, 479
imaging procedures, 7–8
imipenem, 208, 441
immune complexes, 417, 419
immune reconstitution inflammatory syndrome (IRIS), 482, 485
immune thrombocytopenic purpura (ITP), 577–585
clinical presentation, 577–578, 580, 582*t*, 584
diagnosis, 580
etiology, 582*t*
treatment, 572, 582*t*, 585
immunizations, 22, 23, 26, 533. *See also specific diseases*
impaired glucose tolerance (IGT), 34
implanted cardiac defibrillator (ICD), 60, 64
in situ thrombosis, 41, 145
indirect-reacting bilirubin, 289
indomethacin, 121, 348, 350
infections, 7
catheter-related, 437, 438
in sickle cell anemia, 600
staging, 12
urinary tract. *See* urinary tract infection (UTI)
infectious arthritis. *See* septic arthritis
infectious colitis, 223
infectious diseases, screening for, 25*t*
infectious meningitis. *See* meningitis
infective endocarditis. *See* endocarditis
inferior petrosal sinus sampling, 368, 373
inferior vena cava filters, 159, 161
inflammatory arthritis, 325. *See also* rheumatoid arthritis (RA)
inflammatory bowel disease (IBD), 223, 224, 293. *See also* Crohn disease; ulcerative colitis
inflammatory diarrhea, 243, 247
infliximab, 225, 359, 461
influenza, 175, 205
influenza vaccine, 26, 208, 440, 533
insulin, 319, 529*t*, 540
insulin-glucose tolerance test, 511
interferon-alpha, 523
interferon-gamma release assays (IGRAs), 459, 463, 479
international normalized ratio (INR), 159
interstitial lung disease, 359
interstitial nephritis, 318*t*
intracranial hemorrhage, 400*t*
intracranial pressure, increased, 447
intravascular hemolysis, 573
intravenous immunoglobulin (IVIg), 575, 580
intrinsic renal failure, 316, 317*t*. *See also* acute kidney injury (AKI)
invasive diarrhea, 243
iodine deficiency, 502
irbesartan, 82*t*
IRIS (immune reconstitution inflammatory syndrome), 482, 485
iron-deficiency anemia, 557–567
as alarm symptom in dyspepsia, 218
in celiac disease, 248, 252
clinical presentation, 557–558, 564

diagnosis, 562–563, 563*t*
etiology, 559–560, 560*t*, 567
in nephrotic syndrome, 309
pathophysiology, 559
in pregnancy, 560, 566
treatment, 564, 567
iron dextran, 564
iron overload, 573
iron studies, 559, 563–564, 563*t*
irritable bowel syndrome (IBS), 216, 229, 247–248, 251
ischemia
gastrointestinal, 268
limb. *See* peripheral vascular disease
myocardial, 8–9
vertebrobasilar, 385
ischemic cardiomyopathy, 57, 62
ischemic colitis, 223, 239
ischemic heart disease. *See* acute coronary syndromes
ischemic stroke. *See* stroke
isoniazid (INH), 460, 461, 462, 560
ITP. *See* idiopathic thrombocytopenic purpura; immune thrombocytopenic purpura
itraconazole, 367
IVIg (intravenous immunoglobulin), 575, 580

J
JAK2 mutation, 588, 589, 589*t*, 594
Janeway lesions, 135, 137*t*
Jarisch-Herxheimer reaction, 470
jaundice (icterus)
in acute cholangitis, 272
definition, 289
obstructive, 291*t*
painless, 289–290
in pancreatitis, 268
joint mouse, 328
joint stiffness, 325
jugular venous pressure (JVP), 48, 56

K
keratoconjunctivitis sicca, 359
Kernig sign, 446
ketoacidosis
alcoholic, 542
diabetic. *See* diabetic ketoacidosis (DKA)
ketoacids, 537
ketoconazole, 369*t*
ketones, 539, 540
ketosis, 537
Kimmelstiel-Wilson lesions, 638
Klebsiella pneumoniae, 207, 270, 636
koilonychia, 564
Kussmaul respirations, 537, 538
Kussmaul sign, 128, 129, 131

L
labetalol, 70, 74, 85
laboratory assessment, 7
lactate dehydrogenase (LDL), 478, 482
lactic acidosis, 539
lactose intolerance, 247
lactulose, 636
lamivudine, 281
large cell lung cancer, 197–198, 198*t*
latent syphilis, 467, 468, 469*t*, 470
latent tuberculosis, 458, 459, 460, 460*t*, 462
LDL cholesterol, 308
"lead pipe colon," 224
"lead-pipe" rigidity, 408
leflunomide, 362
left anterior descending coronary artery (LAD), 43
left bundle branch block (LBBB), 43, 47
left ventricular aneurysm, 43*f*, 46*t*, 51
left ventricular ejection fraction (LVEF), 57, 58
left ventricular function/dysfunction, 49
Legionella, 207, 210, 637
lenalidomide, 521
leukemia, 523
acute, 578, 584
acute promyelocytic, 581
myeloproliferative disease and, 589, 592
leukocyte esterase, 428
leukocytosis, 235
levalbuterol, 420*t*
levodopa, 409*t*, 410
levofloxacin, 208
levothyroxine, 370, 503, 506
Lewy body dementia, 391*t*
lidocaine, 327
lifestyle modification
for diabetes, 532
for hypertension, 77, 79, 86
for ischemic heart disease prevention, 62
for metabolic syndrome, 33–34, 36
Light criteria, pleural effusion, 187
likelihood ratio, 9, 10*f*
limb ischemia, 143–144. *See also* peripheral vascular disease
linezolid, 348
lipid panel, 7
lipohyalinosis, 380
liraglutide, 529*t*
lisinopril, 82*t*, 85
Listeria monocytogenes, 445, 449, 451
livedo reticularis, 150
liver failure, fulminant, 278, 281
liver transplant, 259
lobectomy, 199
"locked-in" syndrome, 493
Loeys-Dietz syndrome, 68*t*
Lofgren syndrome, 523
loop diuretics, 13, 258, 321, 520*t*
loperamide, 224, 244, 618
lorazepam, 611
losartan, 82*t*
low back pain, 331–339
clinical presentation, 331–332
diagnosis, 335–336
epidemiology, 333
etiology, 333–335, 334*t*
"red flag" signs and symptoms, 335, 335*t*, 338, 339
treatment, 336, 338
low-molecular-weight heparin (LMWH), 135, 155, 159
lumbar puncture
in cryptococcal meningitis, 481
in meningitis, 447, 447*t*
in neurosyphilis, 468, 473
in subarachnoid hemorrhage, 401
lung cancer, 193–202
classification, 197–198, 198*t*
clinical presentation, 194, 197–198, 640
diagnosis, 201
pathophysiology, 196–197
screening, 25*t*, 197
treatment, 198–199

lymphadenitis, in tuberculosis, 459, 461
lymphadenopathy, 125
lymphoma
  central nervous system, 480–481
  clinical presentation, 523
  hypercalcemia in, 518
  non-Hodgkin, 125
  thyroid, 640

M
MAC (*Mycobacterium avium*-intracellulare complex), 479, 481, 483, 509, 636
macrocytic anemia, 559, 562*t*, 567
macrolide antibiotics, 208
magnetic resonance angiography (MRA), 66
magnetic resonance imaging (MRI), 8, 158
malabsorption, 227, 248–249, 252
malignancy. *See* cancer
malnutrition
  acetaminophen hepatitis and, 282
  osteoporosis and, 370
Marfan syndrome, 66, 67, 68*t*, 640
masked hypertension, 77
mast cell degranulation, 417, 419
mean corpuscular volume (MCV), 559, 561, 562*t*, 566
medications, 4
MELD (Model for End-stage Liver Disease) score, 259
melena, 217, 223
memantine, 392
membranoproliferative glomerulonephritis (MPGN), 298, 301*t*
membranous nephropathy, 638
MEN (multiple endocrine neoplasia) syndromes, 216, 640
meningitis, 443–452
  bacterial, 445, 447*t*, 448*t*
  clinical presentation, 400*t*, 444–445, 446–447
  cryptococcal, 481
  diagnosis, 400*t*, 403, 447–448, 447*t*
  differential diagnosis, 446, 448
  epidemiology, 445
  fungal, 446, 447*t*
  herpes simplex, 446, 448
  in HIV infection, 446
  pathophysiology, 445–446
  prevention, 449
  treatment, 448–449, 448*t*
  tuberculous, 446, 447*t*, 448, 451, 459
  viral, 446, 447*t*, 450
meningococcal vaccine, 449
meningoencephalitis, 618
menopause, osteoporosis and, 370
6-mercaptopurine, 225
meropenem, 208
mesalamine, 225
metabolic acidosis
  in adrenal insufficiency, 510
  anion gap, 537, 538, 539*t*, 543–544
  non–anion gap, 544
metabolic encephalopathy, 608*t*
metabolic syndrome, 29–37
  clinical pearls, 37
  clinical presentation, 32–33
  diagnostic criteria, 32*t*
  epidemiology, 31–32
  pathophysiology, 32
  in polycystic ovary syndrome, 499
  treatment, 33–34, 36
metanephrines, 94
metformin, 34, 529, 529*t*, 532
methacholine challenge, 638
methadone, 618, 620
methanol, 618
methimazole, 551, 552
methotrexate, 225, 359, 361
metoprolol
  after myocardial infarction, 639
  for aortic dissection, 59, 70, 74
  for hypertension, 81*t*, 85, 89
metronidazole, 209, 211, 215, 235, 244
metyrapone, 369*t*
Meyerson sign, 408
MHA-TP (microhemagglutination assay for *T. pallidum*), 469, 470
MI. *See* myocardial infarction
microalbuminuria, 309
microcytic anemia, 560–561, 562*t*, 563*f*, 563*t*, 566
microhemagglutination assay for *T. pallidum* (MHA-TP), 469, 470
microscopic hematuria, 297
mifepristone, 369*t*
migraine headache, 400*t*, 401–402, 403
migratory arthritis, 330
miliary tuberculosis, 459
mineralocorticoids, 511
minimal change disease, 638
minocycline, 359
mitotane, 369*t*
mitral regurgitation, 46*t*, 48
mitral stenosis, 100, 103–104, 106
Mobitz I second-degree AV block, 47, 114
Mobitz II second-degree AV block, 47, 114
Model for End-stage Liver Disease (MELD) score, 259
monoamine oxidase type B inhibitors (MAO-B), 409*t*, 410
monoarticular arthritis, 341–351
  clinical presentation, 341–343
  crystalline. *See* acute calcium pyrophosphate (CPP) crystal arthritis
  diagnosis, 343, 344–345, 346*f*, 347*f*, 351
  infectious, 325, 343, 344, 345, 350. *See also* gonococcal arthritis
  pathophysiology, 343
  prognosis and prevention, 348
  treatment, 345, 348
monoclonal antibodies, 359–360
monoclonal gammopathy of undetermined significance (MGUS), 521
monoclonal proliferation (M-spike), 521
monosodium urate crystals, 345, 348
morning stiffness, 356
moxifloxacin, 208
MPGN (membranoproliferative glomerulonephritis), 298, 301*t*
MR angiography (MRA), 8
MRI (magnetic resonance imaging), 8, 158
MRSA (methicillin-resistant *S. aureus*), 137, 208, 437, 637
mu receptors, 617
mucositis, 437
multi-infarct (vascular) dementia, 389, 390, 391*t*, 394
multiple endocrine neoplasia (MEN) syndromes, 216, 640

multiple myeloma
back pain in, 335
clinical presentation, 338, 515–517, 523
diagnosis, 516*f*, 521
hypercalcemia in, 517, 518
pathophysiology, 521
treatment, 521
multiple sclerosis, 385, 390
multiple-system atrophy (MSA), 408, 413
multivessel atherosclerotic stenosis, 49
murmurs, 61
Mycobacterium avium-intracellulare complex (MAC), 479, 481, 483, 509, 636
Mycobacterium kansasii, 480
Mycobacterium tuberculosis, 451, 458, 459, 479
mycoplasma, 175
Mycoplasma pneumoniae, 205, 206, 210
mycotic aneurysm, 140
myelofibrosis, 589, 589*t*, 592
myeloproliferative disease, 589–590, 589*t*, 592
myocardial infarction (MI), 49, 116. *See also* ST-segment elevation myocardial infarction (STEMI)
vs. acute pericarditis, 121*t*
fibrinous pericarditis and, 638–639
myocardial ischemia, 8–9
myoglobinuria, 298, 302, 639
myxedema, 187*t*, 503

N
N-acetylcysteine (NAC), 77, 282
nafcillin, 137, 350
naloxone, 620, 623
naltrexone, 620
National Lung Screening Trial (NLST), 197
Neisseria gonorrhoeae, 471
Neisseria meningitidis, 444, 445, 448
neomycin, 261
nephritic syndrome, 300–301, 311, 638, 639
nephritis, 300, 317, 317*t*. *See also* glomerulonephritis
nephrolithiasis, 226*t*
nephropathy
diabetic. *See* diabetic nephropathy
membranous, 638
overt, 309
nephrosis, 300
nephrotic syndrome, 306–312
clinical presentation, 300, 307
complications, 308–309
in diabetes mellitus, 307
diagnosis, 307–308
in hepatitis B infection, 638
hypervolemia in, 490
vs. nephritic syndrome, 311
pathophysiology, 307
pleural effusion in, 187*t*
treatment, 308
neuropathic pain, 355
neuropathy, diabetic, 530
neurosyphilis
clinical presentation, 468
dementia in, 390, 391*t*
diagnosis, 468, 473
pathophysiology, 468
treatment, 391*t*, 469*t*, 470
neutropenia, 437
neutropenic fever, 437–440, 439*f*
New York Heart Association (NYHA), 57, 57*t*
niacin deficiency, 637
nifedipine, 82*t*
nitrates, 44, 60, 60*t*, 121
nitrites, 60*t*, 428
nitrofurantoin, 429
nitroglycerin, 45*f*, 48, 51, 639
NLST (National Lung Screening Trial), 197
NMDA receptor antagonists, 392
non–anion gap acidosis, 544
non-Hodgkin lymphoma, 125
noninflammatory diarrhea, 244
non–small cell lung cancer (NSCLC), 197, 198, 198*t*
nonsteroidal anti-inflammatory drugs (NSAIDs)
for crystalline arthritis, 347
duodenal and gastric ulcers from, 216, 217
erosive gastritis and, 558
for gout, 342, 348
for low back pain, 338, 339
for osteoarthritis, 327, 329
for pericarditis, 121, 123, 639
for rheumatoid arthritis, 359, 361
non-ST-segment elevation myocardial infarction (NSTEMI), 41, 41*t*, 52, 569, 571. *See also* acute coronary syndromes
Noonan syndrome, 68*t*
norepinephrine, 431
normal pressure hydrocephalus, 390, 391*t*, 394
normocytic anemia, 559, 562*t*, 567
nuchal rigidity, 400*t*, 446
nucleic acid amplification testing (NAAT), 459
nucleus pulposus (herniated disk), 333
nutritional deficiencies, osteoporosis and, 370

O
OA. *See* osteoarthritis
obesity hypoventilation syndrome, 590
obstructive jaundice, 291*t*
obstructive lung disease, 165–166, 168*f*, 168*t*, 172
obstructive shock, 427
obstructive sleep apnea, 83, 590
octreotide, 260, 262, 368, 636
oligomenorrhea
definition, 499
diagnosis, 500*f*, 505
differential diagnosis, 501*t*
pathophysiology, 499–502
oliguria, 315
omeprazole, 181
ophthalmopathy, in Graves disease, 551, 551*t*, 552, 554
opiate/opioid overdose, 615–624
clinical presentation, 615–616, 619–620
diagnosis, 617–618
differential diagnosis, 618, 623
prevention, 620, 624
risk factors, 622–623
treatment, 620, 623
opiate/opioid withdrawal, 620, 624
opiates/opioids, 617
oral contraceptives, 27
oral thrush, 635
organophosphates, 618
orthostatic hypotension, 94, 97, 113
orthostatic syncope, 111
Osler nodes, 135, 137*t*
osmolality, 489
osmotic demyelination syndrome, 493

osmotic diarrhea, 243, 247
osteitis fibrosa cystica, 634
osteoarthritis (OA), 323–330
  clinical presentation, 325–326
  diagnosis, 326–327
  differential diagnosis, 325, 355
  epidemiology, 325
  joint involvement in, 326*f*, 329, 357*f*
  treatment, 327–328, 329
osteogenesis imperfecta, 68*t*
osteomyelitis, 338–339, 601, 603
osteopenia, 248, 251, 365, 373
osteophytes, 327
osteoporosis, 369–371
  definition, 366
  diagnosis, 374
  epidemiology, 369
  hip fracture and, 635
  pathophysiology, 370
  risk factors, 370
  secondary, 370
  treatment, 370–371, 374
ovarian failure, 501*t*

P
pacemakers, 47
packed red blood cells, 571–572
Paget disease, 635
pain crises, sickle cell, 599, 600–601
painless jaundice, 289–290
Palla sign, 156
Pancoast tumor, 197
pancreatic abscess, 269
pancreatic cancer, 288, 290, 294
pancreatic necrosis, 269
pancreatic pseudocyst, 267, 269, 272
pancreatitis
  acute. *See* acute pancreatitis
  chronic, 248
Pap smear, 27
papillary muscle dysfunction, 48
papillary muscle rupture, 48
papilledema, 445, 447, 452
paraneoplastic syndrome, 365
parapneumonic effusion, 186, 190. *See also* pleural effusion
parasites, 244
parathyroid adenoma, 518, 522
parathyroid hormone, 634
parenchymal restrictive disease, 168*f*
parenteral iron therapy, 564
Parkinson disease, 405–414
  clinical presentation, 113, 405–406, 408–409, 412
  definition, 407
  dementia in, 390, 391*t*
  diagnosis, 409
  differential diagnosis, 406
  epidemiology, 407
  pathophysiology, 407–408
  primary, 407
  risk factors, 407
  subtypes, 408
  treatment, 409*t*, 410
parkinsonism, 407
partial thromboplastin time (PTT), 581, 582*t*, 635
parvovirus, 361, 572, 600, 603
pasireotide, 368
patient, approach to, 3–10
  history, 3–5
  imaging procedures, 7–8
  laboratory assessment, 7
  physical examination, 5–7
  test result interpretation, 8–9, 10*f*
Patrick maneuver, 336
pattern recognition, 10–11
PCOS (polycystic ovary syndrome), 373, 499, 501, 501*t*
PCR (polymerase chain reaction), 448
PDE5 (phosphodiesterase type 5) inhibitors, 601
peanut allergy, 418
pegloticase, 348
pelvic inflammatory disease, 471
penicillin
  anaphylaxis from, 415–417, 418
  in sickle cell crisis, 600
  for syphilis, 17, 469, 469*t*
penicillin G
  for aspiration pneumonia, 209
  for endocarditis, 136–137
  for meningitis, 449
  for syphilis, 469, 469*t*
pentamidine, 268*t*
pentoxifylline, 147
peptic ulcer disease (PUD), 213–220
  alarm symptoms, 218, 219
  clinical presentation, 214, 216–217
  complications, 217–218
  definition, 215
  pathophysiology, 215–216
  treatment, 217
percutaneous coronary intervention (PCI), 44, 49, 52
perianal disease, 227
pericardial effusion, 127, 131. *See also* cardiac tamponade
pericardial friction rub, 119, 120, 124
pericardial hemorrhage, 121
pericardial knock, 128
pericardial tamponade, 124. *See also* cardiac tamponade
pericardiocentesis, 124, 126, 128
pericarditis
  acute. *See* acute pericarditis
  constrictive, 129, 129*t*
  fibrinous, 639
  uremic, 321
peripheral blood smear, 563, 563*f*
peripheral neuropathy, 460, 461
peripheral pulses, 146
peripheral vascular disease, 143–151
  clinical presentation, 146
  diagnosis, 146
  pathophysiology, 145
  treatment, 146–147, 148*f*
peritonitis
  in diverticulitis, 235
  from perforated peptic ulcer, 217
  secondary, 260
  spontaneous bacterial, 257, 259*t*, 260, 636
  in ulcerative colitis, 226
permissive hypertension, 382
pernicious anemia, 390
pertussis, 175
PFT (pulmonary function test), 166
phenobarbital, 282, 367, 422
phenoxybenzamine, 94

phenytoin, 367, 419, 422
pheochromocytoma
  clinical presentation, 90, 94
  diagnosis, 637
  epidemiology, 93–94
  pathophysiology, 94
  secondary hypertension in, 83, 90
  treatment, 94, 95*f*
phlebotomy, 591, 594
phlegmon, 269
phosphodiesterase type 5 (PDE5) inhibitors, 601
photophobia, 444, 446
physical activity, 370
physical examination, 5–7
physical therapy, 327
physiologic depression, 623
pica, 564
Pick disease (frontotemporal dementia), 390, 391*t*
"pill rolling" tremor, 408
pioglitazone, 529*t*
piperacillin-tazobactam, 208
pituitary gland, 509
plasmapheresis, 582*t*
platelet counts, 15
platelet production, 579
platelet survival, 579
platelet transfusion, 572, 580
pleural effusion, 183–191
  clinical presentation, 183, 184*f*, 185
  definition, 186
  diagnostic criteria, 187
  differential diagnosis, 186*t*
  in lung cancer, 197, 201
  pathophysiology, 186–187, 190
  transudative vs. exudative, 187, 187*t*, 188*t*, 190
  treatment, 188–189, 190
Plummer disease, 550
Plummer-Vinson syndrome, 564
pneumococcal vaccines
  after community-acquired pneumonia, 208
  in cancer patients, 440
  in diabetics, 533
  recommendations, 26
  in sickle cell disease, 600
  before splenectomy, 580, 585
  types, 27
Pneumocystis jirovecii, 205, 207, 478
Pneumocystis jirovecii pneumonia (PJP)
  clinical presentation, 475–477, 481–482, 484
  diagnosis, 476*f*, 477, 478, 482
  differential diagnosis, 478, 479–480
  prophylaxis, 482–483
pneumonectomy, 199
pneumonia
  aspiration, 208
  atypical, 637
  community-acquired. *See* community-acquired pneumonia
  definition, 205
  lobar, 640
  Pneumocystis jirovecii. *See Pneumocystis jirovecii* pneumonia (PJP)
  PSI (Pneumonia Severity Index), 206
  sepsis from, 430
  ventilator-associated, 205, 636–637
Pneumonia Severity Index (PSI), 206
pneumonitis, chemical, 208–209
podagra, 343, 344. *See also* gout
polyarthritis, 355
polyarticular arthritis, 355–356
polycystic kidney disease, 86, 403
polycystic ovary syndrome (PCOS), 373, 499, 501, 501*t*
polycythemia vera, 587–595
  clinical presentation, 587–588, 591, 594
  definition, 589
  diagnosis, 590, 591*t*, 594
  etiology, 590
  pathophysiology, 589*t*, 590
  primary, 590, 590*t*
  prognosis, 592
  secondary, 590, 590*t*
  treatment, 591–592, 594
polymerase chain reaction (PCR), 448
polymyalgia rheumatica, 325, 401
portal hypertension, 255, 258, 259*t*, 260*t*
postrenal kidney failure, 316, 318*t*, 639. *See also* acute kidney injury (AKI)
poststreptococcal glomerulonephritis, 297*t*, 300
posttest probability, 10*f*
postural instability, 407, 408
potassium levels, in diabetic ketoacidosis, 539, 541, 544
potassium-sparing diuretics, 79
Pott disease, 338, 459, 462
PPD (purified protein derivative) test, 459, 460*t*, 462, 479
pramipexole, 409*t*
prednisone, 225, 513
pregnancy, 550, 560, 566
prerenal kidney failure, 315, 316*t*, 317, 318*t*, 639. *See also* acute kidney injury (AKI)
present illness history, 3–4
pretest probability, 8–9, 10*f*
primary biliary cirrhosis, 290, 292*t*
primary hyperaldosteronism, 80, 83
primary sclerosing cholangitis (PSC), 228, 290, 292*t*, 293
primary syphilis, 467, 469*t*
primary tuberculosis, 458
probenecid, 348
procainamide, 105, 107
prolactinomas, 501–502, 501*t*
propranolol, 551, 554
propylthiouracil (PTU), 551, 554
prostaglandins, 216
prostate-specific antigen (PSA), 13, 25*t*
proteinuria, 307, 310, 317
prothrombin gene mutations, 155
prothrombin time (PT), 581, 582*t*, 635
proton pump inhibitors (PPIs), 51
pruritis, 591
pseudobulbar palsies, 493
pseudodementia, 389
pseudodiverticula, 233
pseudogout. *See* acute calcium pyrophosphate (CPP) crystal arthritis
Pseudomonas aeruginosa, 206, 207, 437, 438
Pseudoxanthoma elasticum, 68*t*
PSI (Pneumonia Severity Index), 206
psoriatic arthritis, 355–356
PTT (partial thromboplastin time), 581, 582*t*, 635
PUD. *See* peptic ulcer disease
pulmonary cancer. *See* lung cancer
pulmonary edema, 430
pulmonary embolism (PE), 153–161
  clinical prediction score, 157*t*
  clinical presentation, 156, 195
  D-dimer test, 156

pulmonary embolism (PE) (*Cont.*):
definition, 155
epidemiology, 155
hemoptysis and, 195
imaging, 156–158
pathophysiology, 155–156
pleural effusion in, 187*t*, 190
risk factors, 16, 154
septic, 135, 137
treatment, 158–159
pulmonary function test (PFT), 166
pulmonary hypertension, 600, 601
pulmonary tuberculosis, 458. *See also* tuberculosis
pulsus paradoxus, 126, 127–128, 129*t*, 131
purified protein derivative (PPD) test, 459, 460*t*, 462, 479
pyelonephritis, 428, 429, 433
pyrazinamide, 460, 462
pyridoxine, 460, 461
pyrimethamine, 480, 485, 636

Q
Q waves, 42, 43*f*
qSOFA score, septic shock, 430
quadruple therapy, for peptic ulcer disease, 215, 217, 220
quality-adjusted life-year (QALY), 24
QuantiFERON TB Gold assay, 459, 463
quantitative reasoning, 12
quinine, 580
quinolones, 244, 440

R
R waves, 42, 43*f*
RA. *See* rheumatoid arthritis
radiation enteritis, 223
radiation therapy, restrictive cardiomyopathy from, 125–126, 128
radioactive iodine, 502, 552, 554
rales (crackles), 161, 196
ramipril, 82*t*
ranitidine, 420*t*
rapid plasma reagent (RPR), 13, 17
rasagiline, 409*t*
rash, in syphilis, 468
Rasmussen aneurysm, 458
Raynaud phenomenon, 145
RBBB (right bundle branch block), 47
RCA (right coronary artery), 43
reactivation tuberculosis, 359, 361, 458, 460, 462
reactive arthritis, 356
reading, approach to, 13–17
best therapy, 17
complications with disease process, 16–17
diagnosis confirmation, 17
most likely diagnosis, 14
most likely mechanism for process, 15–16
next step, 14–15
risk factors for process, 16
recombinant plasminogen activator (r-PA), 41
red blood cell distribution width (RDW), 561, 567
red blood cells, 560, 561*f*, 563, 563*f*
red cell casts, 298, 299*f*, 301
relative polycythemia, 590
renal artery stenosis, 80
renal biopsy, 307
renal disease
anemia in, 572
in diabetes. *See* diabetic nephropathy
hypercalcemia in, 519*t*
secondary hypertension in, 80, 83
renal failure
acute. *See* acute kidney injury (AKI)
in hemolytic uremic syndrome, 579, 582
in thrombotic thrombocytopenic purpura, 581, 582*t*
renal tubular acidosis, 544
reperfusion therapy, 44, 52
respiratory depression, 619, 623
respiratory syncytial virus (RSV), 175
rest pain, 144, 146
restless legs syndrome, 564
restrictive cardiomyopathy, 129, 129*t*, 131
restrictive lung disease, 166, 168*f*, 168*t*, 172
reteplase, 41
reticulocyte, 559
reticulocyte count, 559, 562
reticulocyte production index, 562
revascularization, 147, 151
reverse screening, for syphilis, 469
rhabdomyolysis, 302, 620, 639
rheumatic fever, 355
rheumatic heart disease, 103
rheumatoid arthritis (RA), 353–362
anemia in, 567
classification criteria, 358*t*
clinical presentation, 353–355, 356–359, 361, 370
diagnosis, 356–359
differential diagnosis, 355–366
joint involvement in, 326*f*, 329, 356, 357*f*, 358*f*
thrombocytopenia in, 585
treatment of, 359–360
rheumatoid factors (RFs), 356
rheumatoid nodules, 356
rhinorrhea, CSF, 446
ribavirin, 261
Rickettsial disease, 446
rifabutin, 481
rifampin, 367, 449, 460, 462
right bundle branch block (RBBB), 47
right coronary artery (RCA), 43
right ventricular infarction, 48
ringed sideroblasts, 560, 561*f*
risedronate, 374
risk factors, 16
risperidone, 392, 609
ritonavir, 367
rituximab, 359, 580
rivaroxaban, 159, 382
rivastigmine, 94, 391
Rocky Mountain spotted fever, 446
ropinirole, 409*t*
rosiglitazone, 529*t*
Roth spots, 135
rotigotine, 409*t*
r-PA (recombinant plasminogen activator), 41
RPR (rapid plasma reagent), 13, 17
RSV (respiratory syncytial virus), 175
rubella vaccine, 533
ruxolitinib, 591–592

S
SAAG (serum ascites-albumin gradient), 260*t*, 636
safinamide, 409*t*
salivary cortisol, 367
Salmonella spp., 600, 603

sarcoidosis
clinical presentation, 180, 228, 518, 519*t*, 523
diagnosis, 180–181, 519*t*
pathophysiology, 522, 634
treatment, 519*t*
saxagliptin, 529*t*
sciatic nerve root compression, 334
sciatica, 333
SCLC (small cell lung cancer), 197–199, 198*t*, 487–488
sclerodactyly, 124
scleroderma, 124
screening, 23–24
colon cancer, 27
lung cancer, 197
USPSTF recommendations, 25, 25*t*
secondary hypertension, 77, 78*t*, 80, 83, 85
secondary syphilis, 467, 469*t*, 473
secretin stimulation test, 216
secretory diarrhea, 243, 245, 245*t*, 247
seizure, 619, 639
selective serotonin reuptake inhibitors (SSRIs), 51, 392
selegiline, 409*t*
sepsis, 427
sepsis scoring systems, 427
septic arthritis, 325, 343, 344, 345, 350
septic pulmonary emboli, 134, 135. *See also* pulmonary embolism (PE)
septic shock
definition, 427
diagnosis, 430
in elderly patient, 425–426
treatment, 429, 430, 433
serofast reaction, 470
serology, 17
serum chemistry, 7
serum lipase, 268
serum sickness, 417, 419
SGLT2 inhibitors, 34, 529*t*
Sheehan syndrome, 501, 501*t*, 513
Shiga toxin, 223–224
shock
classification, 427, 430
definition, 427, 430
pathophysiology, 430
treatment, 430–431
Shy-Drager syndrome, 413
SIADH. *See* syndrome of inappropriate secretion of antidiuretic hormone
sick sinus syndrome (SSS), 81*t*, 113, 116
sickle cell crisis, 597–599, 600–601
sickle cell disease, 597–603, 638
Sickle Cell Disease Pathophysiology, 599
Sickle Cell Disease Treatment, 600
sideroblastic anemia, 560, 563*t*
sildenafil, 601
simeprevir, 281
sinus bradycardia, 47, 51, 113
SIRS (systemic inflammatory response syndrome), 267, 267*t*, 427
sitagliptin, 529*t*
Sjögren syndrome, 359
SJS (Stevens-Johnson syndrome), 418, 421
skeletal tuberculosis, 459
SLE. *See* systemic lupus erythematosus
small cell lung cancer (SCLC), 197–199, 198*t*, 487–488
smoking
abdominal aortic aneurysm and, 71, 73
chronic cough and, 175
COPD and, 166, 171
heart failure and, 639
lung cancer and, 196–197, 201
peripheral vascular disease and, 145, 147
smoking cessation
after pneumonia treatment, 208
for COPD, 170
for ischemic heart disease prevention, 36, 49, 52
for peripheral vascular disease, 147, 150
smoldering diverticulitis, 236. *See also* diverticulitis
smoldering myeloma, 521
SNOOP mnemonic, for headaches, 398, 398*t*
social history, 4–5
sodium nitroprusside, 70, 93
sofosbuvir, 281
solitary pulmonary nodule, 199
somatostatin receptor agonists, 368
spinal cord compression, 334, 336
spinal stenosis, 333
spirometry, 166, 176
spironolactone, 59, 81*t*, 85, 258
splenectomy, 580, 585
splenic infarction, 600
splenic sequestration, 579, 585, 603
splenomegaly, 585
splinter hemorrhages, 135
spondylolisthesis, 333
spondylosis, 333
spontaneous bacterial peritonitis, 258, 259*t*, 260, 636
SPRINT trial, 79
squamous cell carcinoma, lung, 198*t*, 523
SSRIs (selective serotonin reuptake inhibitors), 51, 392
SSS (sick sinus syndrome), 81*t*, 113, 116
staging, 12
Staphylococci, coagulase-negative, 137*t*
Staphylococcus aureus
in catheter-related infections, 439, 441
in endocarditis, 133, 137, 137*t*, 138*t*
in food poisoning, 244
in meningitis, 446
methicillin-resistant, 137, 208, 437, 637
in nongonococcal septic arthritis, 344, 348
in osteomyelitis, 338
in pneumonia, 207
Staphylococcus epidermidis, 441, 446
statins, 49, 52, 308, 382
steatorrhea, 243, 248–249
steroids. *See* corticosteroids
Stevens-Johnson syndrome (SJS), 418, 421
stool culture, 244
straight leg raise testing, 336
Streptococcus agalactiae, 445
Streptococcus bovis, 137*t*, 139
Streptococcus pneumoniae
in community-acquired pneumonia, 204–206, 208
in HIV infection, 484–485
in meningitis, 445, 448, 448*t*, 449
in sickle cell disease, 600
vaccine. *See* pneumococcal vaccines
Streptococcus species, 135, 137*t*, 140
Streptococcus viridans, 137*t*
streptokinase, 41
stress dose steroids, 511, 513

stress treadmill tests, 8
strictures, 236*t*
stroke
  chronic atrial fibrillation and, 102–103, 106
  endocarditis and, 138
  evaluation for cause, 380–381, 381*t*
  prevention, 382
  risk following transient ischemic attack, 380*t*
ST-segment depression, 9, 43
ST-segment elevation, 121
ST-segment elevation myocardial infarction (STEMI)
  complications, 46–49, 46*t*
  definition, 41. *See also* acute coronary syndromes
  diagnostic criteria, 41*t*, 43, 43*f*
  differential diagnosis, 44
  pathophysiology, 41
  risk stratification after, 49
  treatment, 44, 46
stupor, 617–618, 619*t*
subacute cough, 175
subacute endocarditis, 135. *See also* endocarditis
subacute (de Quervain) thyroiditis, 550
subarachnoid hemorrhage, 385, 400–401, 403, 446
subclavian steal, 385
subcortical arteriosclerotic leukoencephalopathy, 390
submaximal exercise stress testing, 49
substance dependence, 617
substance use disorder, 617, 623, 624. *See also* opiate/opioid overdose
subtotal thyroidectomy, 552
sulfadiazine, 480, 485, 636
sulfasalazine, 225, 359, 361
sulfonamides, 268*t*, 580
sulfonylureas, 529*t*, 532
superior vena cava (SVC) syndrome, 195, 197, 201
supplemental oxygen therapy, 166, 170
supraventricular tachyarrhythmia, 47, 113
surgical embolectomy, 158
Surviving Sepsis Campaign, 431
swan-neck deformity, 326*f*, 329, 356, 357*f*, 358*f*
syncope, 109–116
  in aortic stenosis, 61, 63
  cardiogenic, 113–114
  definition, 111
  in diabetes mellitus, 115
  epidemiology, 111
  etiology, 112*t*
  in heart failure, 61
  neurogenic, 111–112
  pathophysiology, 111
syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
  clinical presentation, 492
  complications, 492–493
  definition, 489
  diagnosis, 490
  hyponatremia in, 492
  in small-cell lung cancer, 198, 198*t*, 487–488
  treatment, 492
synovial fluid analysis, 345, 347*f*, 350
synovitis, 325, 355
syphilis, 465–473
  clinical presentation, 17, 465–466, 467–468
  coinfections, 470–471
  diagnosis, 469, 473
  epidemiology, 467
  latent, 467, 468, 469*t*, 470
  neurosyphilis. *See* neurosyphilis
  prevention, 470, 472
  prognosis, 470
  treatment, 17, 469–470, 469*t*
systemic inflammatory response syndrome (SIRS), 267, 267*t*, 427
systemic lupus erythematosus (SLE)
  clinical presentation, 124, 228, 355
  complications, 119, 122
  diagnostic criteria, 122*t*, 297*t*
  nephrotic syndrome and, 307
  pathophysiology, 122
  platelet survival in, 579
  pleural effusion in, 188*t*
  preoperative management, 513
systolic dysfunction, 57
systolic murmur, 48

T
T score, 365, 366, 373, 374
tabes dorsalis, 468
tachyarrhythmias
  after myocardial infarction, 47
  syncope and, 112*t*, 113
  treatment, 80, 81*t*
  in Wolff-Parkinson-White syndrome, 104
tachypnea
  in acute chest syndrome, 600
  in COPD, 169
  in pulmonary embolism, 156, 160
Takayasu arteritis, 145, 150
TAVR (transcatheter aortic valve replacement), 61
TBG (thyroid-binding globulin), 502
Tdap vaccine, 533
temporal arteritis. *See* giant cell (temporal) arteritis (GCA)
TEN (toxic epidermal necrolysis), 418
tendonitis, 325
tenesmus, 223
tension headache, 402
tension-type headache, 400*t*
tertiary (late) syphilis, 467, 469*t*, 473
test result interpretation, 8–9, 10*f*
tetracycline, 215, 470
thalassemia, 561, 563*t*, 567
thalidomide, 521, 523
thiamine, 611, 613
thiamine deficiency, 390
thiazide diuretics
  adverse effects, 268*t*, 348, 495
  for hypertension, 79, 81*t*, 85
thiazolidinediones, 34, 60, 529*t*
thiocyanate toxicity, 93
third-degree AV block, 47, 110, 114
thoracentesis, 188
thoracostomy, 188, 190
thromboangiitis obliterans (Buerger disease), 145, 150
thrombocytopenia. *See also* immune thrombocytopenic purpura; thrombotic thrombocytopenic purpura (TTP)
  definition, 579
  disseminated intravascular coagulation and, 581. *See also* disseminated intravascular coagulation (DIC)
  drug-induced, 580
  etiology, 579–580
  heparin-induced, 580–581, 585
  pathophysiology, 16, 579

thrombolytics
adverse effects, 121, 158
for MI treatment, 41, 44–46
for peripheral vascular disease, 147
for pulmonary embolism, 158–159
for transient ischemic attack, 378
thrombotic thrombocytopenic purpura (TTP)
clinical presentation, 581, 582*t*
definition, 579
diagnosis, 581
etiology, 581, 582*t*
treatment, 572, 581, 582*t*
thyroid carcinoma, 640
thyroid lymphoma, 640
thyroid peroxidase (TPO), 549
thyroid storm, 549, 552, 554
thyroid-binding globulin (TBG), 502
thyroiditis, 550
thyroid-stimulating hormone (TSH)
in hyperthyroidism, 83, 549, 550, 640
in hypothyroidism, 502, 505
thyroid-stimulating immunoglobulin (TSI), 549
thyrotoxicosis, 549–550
thyroxine (T_4), 502
TIA. *See* transient ischemic attack
tinzaparin, 159
tiotropium, 171
TIPS (transjugular intrahepatic portal-systemic shunt), 260
tissue plasminogen activator (tPA), 41, 158, 189
TMP-SMX. *See* trimethoprim-sulfamethoxazole
tocilizumab, 360
tofacitinib, 360
tolvaptan, 492
tonic-clonic seizure, 639
total iron-binding capacity (TIBC), 559, 563*t*, 567
toxic encephalopathy, 608*t*
toxic epidermal necrolysis (TEN), 418
toxic megacolon, 226, 229
toxic multinodular goiter, 549
toxicologic screen, 618–619
toxoplasmosis, 480, 483, 485, 636
TPO (thyroid peroxidase), 549
transcatheter aortic valve replacement (TAVR), 61
transferrin saturation, 559
transfusion-related acute lung injury (TRALI), 571, 573
transfusions
alternatives, 572
complications, 572–573, 575
emergency, 574–575
fresh frozen plasma, 572
for gastrointestinal bleeding, 219, 570–571
infection screening, 572
packed red blood cells, 571–572
platelets, 572
for sickle cell crises, 600
transient ischemic attack (TIA), 377–380
clinical presentation, 377–378, 380
evaluation, 380–381, 381*t*
pathophysiology, 379–380
stroke risk following, 380*t*
transjugular intrahepatic portal-systemic shunt (TIPS), 260
transudate, 186, 187, 187*t*, 191
trazodone, 393
tremor, 408
tremulousness, 611*t*
Treponema pallidum, 466, 467, 469
tricuspid valve, endocarditis and, 136
tricyclic antidepressants, 618
trimethoprim-sulfamethoxazole (TMP-SMX), 429, 478, 482, 483, 485
triple therapy, for peptic ulcer disease, 215, 217, 220
TSH. *See* thyroid-stimulating hormone
T-SPOT TB assay, 459
TTP. *See* thrombotic thrombocytopenic purpura
tube thoracostomy, 188, 190
tuberculin skin test, 459, 460*t*, 462, 479
tuberculosis, 455–463
adrenal insufficiency in, 509
clinical presentation, 455–457, 458
diagnosis, 456*f*, 459, 460*t*
extrapulmonary, 458–459
in HIV infection, 479, 485
hypercalcemia in, 518
latent, 458, 459, 460, 460*t*, 462
miliary, 459
pathophysiology, 458–459
pleural effusion in, 188*t*
primary, 458
pulmonary, 458, 461
reactivation, 359, 361, 458, 460, 462
risk factors, 205–206
skeletal, 459
treatment, 459–460
tuberculous meningitis, 446, 447*t*, 448, 451, 459
tuberculous osteomyelitis, 338
tubulointerstitial nephritis, 317
tumor necrosis factor (TNF) antagonists, 359, 361
Turner syndrome, 68*t*
T-wave inversion, 42, 43*f*, 569
type 1 diabetes, 527
type 2 diabetes. *See* diabetes mellitus

U

ulcerative colitis
clinical presentation, 221–222, 247
complications, 226
vs. Crohn disease, 225*t*
definition, 223
extraintestinal manifestations, 226*t*
pathophysiology, 224
treatment, 225
ultrasonography, 7, 8
for aortic aneurysm monitoring, 74
in cholestasis, 290
in gallstones, 270
in pulmonary embolism, 157
in renal injury, 321
unconjugated bilirubin, 289
unconjugated (indirect) hyperbilirubinemia, 289, 293
unfractionated heparin (UFH), 159
unstable angina, 41, 41*t*, 569–570, 571. *See also* acute coronary syndromes
upper airway cough syndrome (UACS), 176
urea breath test, 217
urease, 215
uremia, 129*t*, 131, 315
uremic pericarditis, 321
urethritis, 356, 471
urinalysis, 7, 317–318
urinary electrolytes, 318–319

urinary tract infection (UTI), 425–430
  catheter-associated, 428, 429*t*
  clinical presentation, 428–249
  diagnosis, 428
  epidemiology, 428
  etiology, 429*t*
  pathophysiology, 428
  sepsis from, in elderly, 425–426
  treatment, 429, 433
urine-free cortisol (UFC), 366–367
urticaria, 417, 573
US Preventive Services Task Force (USPSTF), screening recommendations, 25, 25*t*
uveitis, 226*t*, 356

V
vacA gene, 215
valganciclovir, 481
valsartan, 82*t*
valve replacement, 140
vancomycin
  for bacterial meningitis, 448*t*, 451
  for *C. difficile* infection, 224
  for endocarditis, 137, 639
  for neutropenic fever, 438, 439*f*
  for nongonococcal septic arthritis, 348
variceal bleeding, 260
varicella zoster, 440
varicella zoster vaccine, 27
vascular catheter infection. *See* catheter-related bloodstream infection (CRBSI)
vascular (multi-infarct) dementia, 389, 390, 391*t*, 394
vasoconstriction, cerebral, 92
vasodilation, cerebral, 92
vasopressin, 431, 494
vasopressors, 431
vasovagal syncope, 110, 111, 112–113, 115
Venereal Disease Research Laboratory (VDRL), 17, 124, 469, 474
ventilator-associated pneumonia (VAP), 205, 636–637
ventricular arrhythmias, post-MI, 46–47, 46*t*
ventricular fibrillation (VF), 48, 114
ventricular free wall rupture, 48
ventricular septal rupture, 48
ventricular tachycardia (VT), 48, 104, 107, 114
verapamil, 82*t*
vertebrobasilar insufficiency, 380, 385
vertebrobasilar ischemia, 385
vertigo, 380, 385
VIPoma, 247, 251
viral arthritis, 355
viral hepatitis
  clinical presentation, 279–280
  complications, 281
  diagnosis, 280–281, 280*f*
  differential diagnosis, 278
  epidemiology, 278
  pathophysiology, 279
  prevention, 281
  treatment, 281
viral meningitis, 446, 447*t*, 450. *See also* meningitis
Virchow triad, 155
vital signs, 5
vitamin B_{12} deficiency, 390, 564
vitamin D
  excess, 518, 519*t*, 523, 634
  for osteoporosis, 370
vitamin K deficiency, 640
volume depletion, 537, 538
volume overload, 315
volume resuscitation, 219, 430
von Willebrand disease (vWD), 579, 582–583, 635
V/Q scan, 157
VT (ventricular tachycardia), 48, 104, 107, 114

W
waist-to-hip ratio, 31
warfarin
  in atrial fibrillation, 103, 106–107, 382
  for pulmonary embolism, 159
  reversal, 572, 575
Wells score, 156, 157*t*
Wernicke encephalopathy, 390, 611, 613
Westermark sign, 156
wheezing, 160, 600
Whipple procedure, 292
white coat hypertension, 77
Wilson disease, 257*t*, 258
withdrawal seizures, 611*t*
Wolff-Parkinson-White (WPW) syndrome, 104–105, 104*f*, 107
World Health Organization, 24

X
Xa inhibitors, 159
X-linked adrenoleukodystrophy, 509

Y
Yersinia enterocolitica, 572

Z
Z score, 373, 374
Zollinger-Ellison syndrome (ZES), 216, 638