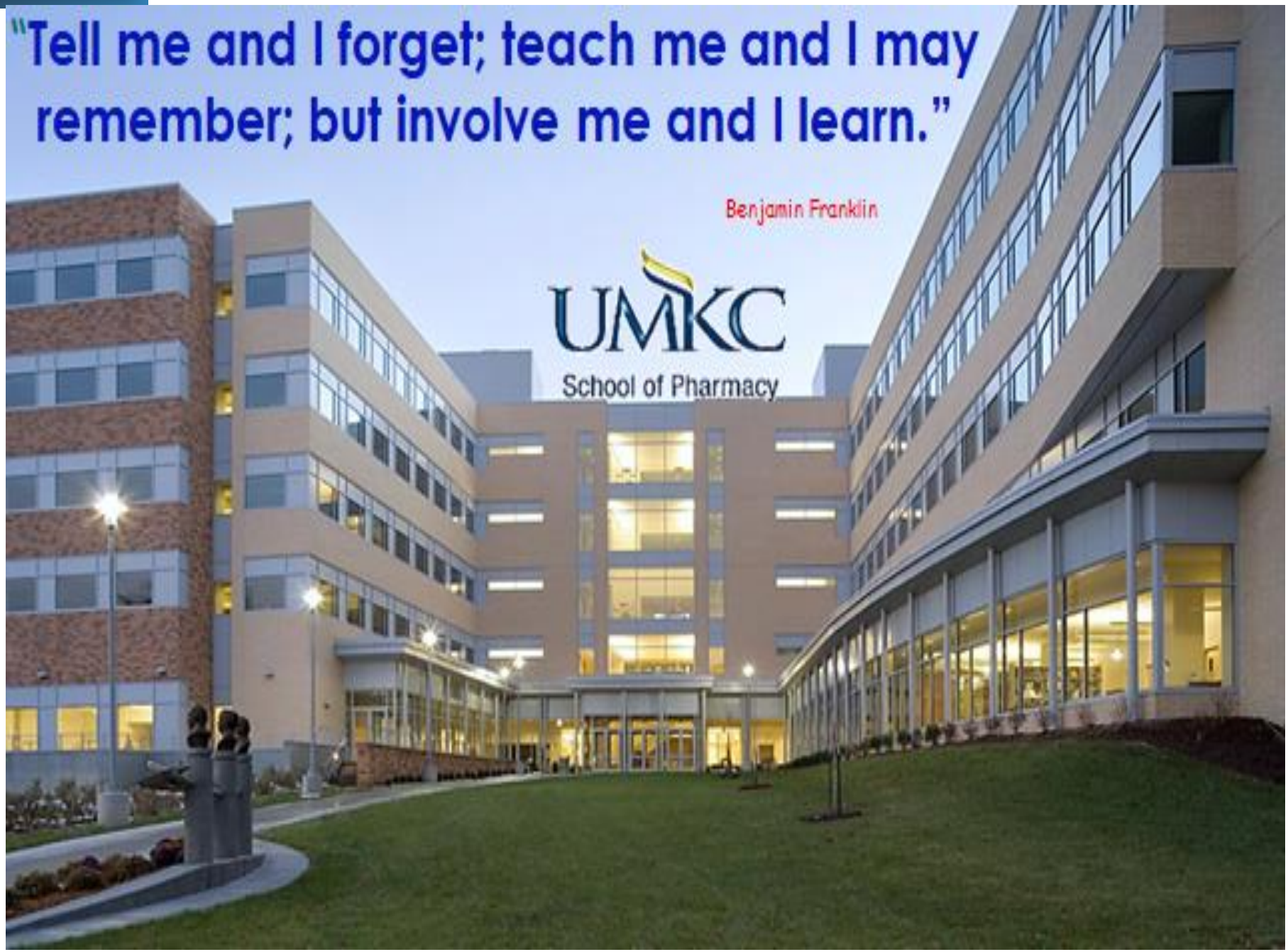
مقدم من فريق أفق الطبي






"Tell me and I forget; teach me and I may remember; but involve me and I learn."
Benjamin Franklin
UMKC
School of Pharmacy

General Pharmacology

"Understanding how drugs work to heal your body"



Esmaa Motawe

Interdisciplinary PhD in Pharmacology and Toxicology/ Pharmaceutical Sciences

Spring 2025 | AUG



Journey of Discovery:

From drug molecules to healing effects

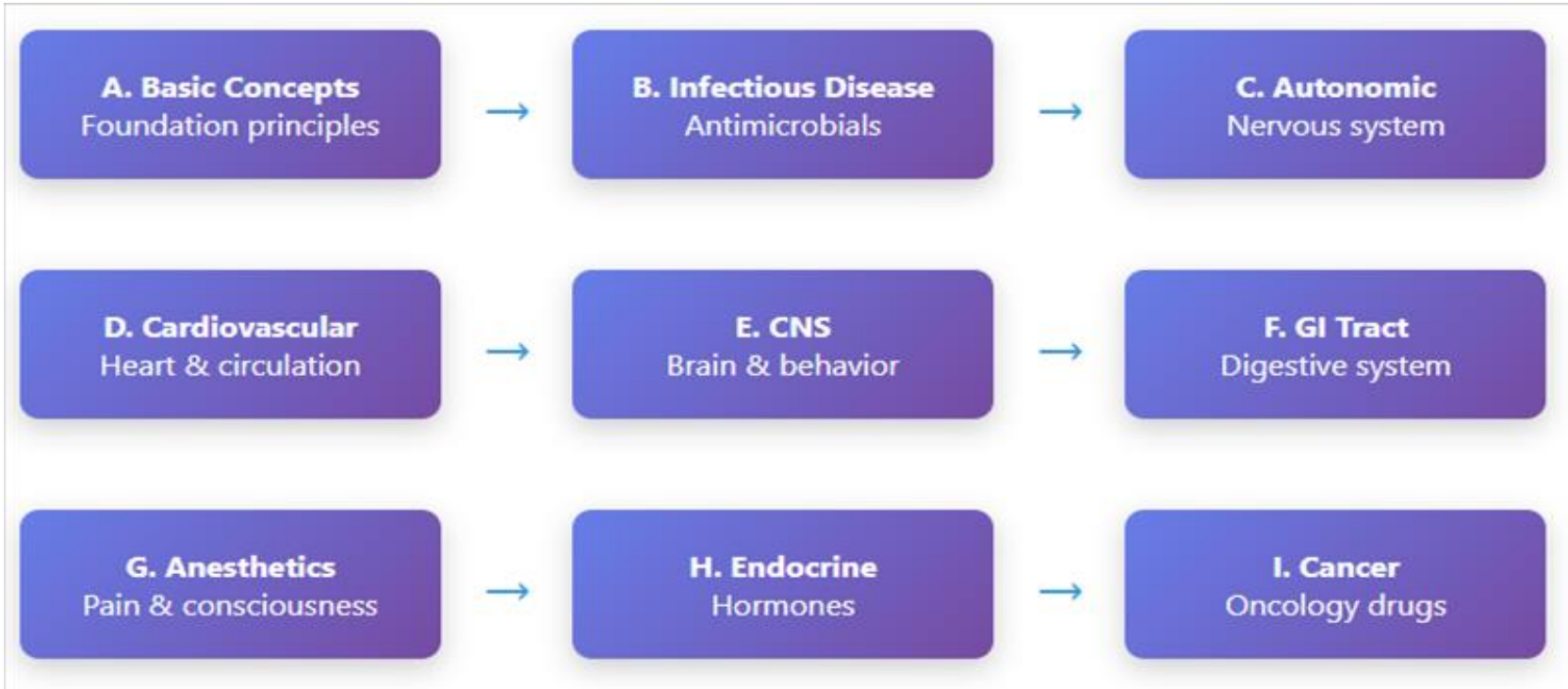


Course Mission: Master the fundamental principles of how drugs interact with the human body to provide safe, effective patient care.

Learning Objectives

- After each specific lecture topics, students are expected to to understand, discuss and explain each of the pharmacological concepts. Where appropriate a list of the relevant drugs is provided for each topic.

- Students should be able to identify which specific drugs belong to each major drug class, as well as have an understanding of the **indications**, **clinical effect**, **mechanism of action** and **adverse effects** of each of the major drug classes.



A.BASIC CONCEPTS IN PHARMACOLOGY

A1. PRINCIPLES OF PHARMACOLOGY

A2. PHARMACODYNAMICS

A3. PHARMACOKINETICS

A4. DRUG METABOLISM AND DRUG INTERACTIONS

A5. DRUG EXCRETION

A7. PHARMACOGENOMICS

A8. TOXICOLOGY

B. THE PHARMACOLOGY OF INFECTIOUS DISEASE (ANTIMICROBIALS PHARMACOLOGY)

B1. GENERAL PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY

B2. CELL WALL INHIBITORS

B3. PROTEIN SYNTHESIS INHIBITORS

B4. ANTIMETABOLITES

B5. ANTIFUNGALS

B6. ANTIVIRALS

B7.ANTIPROTOZOALS

🎯 By the end of this course, you will:

🧠 Understand
Core pharmacological concepts and principles

🔍 Identify
Drug classes and their specific medications

📋 Explain
Mechanisms of action and clinical effects

⚠️ Recognize
Adverse effects and contraindications

💡 ***Remember:*** *Learning drug names is like learning a new language - focus on generic names first, then build your vocabulary!*



What You'll Learn Today:

Master the fundamental principles of how drugs interact with your body, from the moment they enter until they leave!

Pharmacologic Principles

Pharm Logic Plus

What is Pharmacology?

(The study of medicine/drug)

Pharmacology is the study of how drugs/chemicals affect the human body

The Science

Understanding the biological effects of chemicals on living organisms

The Practice

Using this knowledge to prevent, treat, and cure diseases

The word is (from two Greek words, **pharmakon**, which means “drug” or “medicine,” – and logos, which means “study of ”

🤔 **Think About It:** Every time you take a medication, you're applying pharmacology principles. Can you think of a recent example?

Pharm Logic Plus

What is a Drug?

- **Any chemical (substances or compounds) that affects the physiologic processes of a living organism- or the pathological state and used in the prevention, treatment or diagnosis or cure various conditions or diseases**

- **Chemical substance** - Natural or synthetic compound
- **Affects physiology** - Changes how body systems function
- **Therapeutic purpose** - Prevents, treats, or diagnoses disease
- **Dose-dependent** - Effect relates to amount given

Real-World Examples:

- Aspirin → Reduces pain & fever
- Insulin → Controls blood sugar
- Antibiotics → Fight infections
- Vaccines → Prevent diseases

Clinical Pearl: "Drug" and "medication" are used interchangeably in healthcare practice.

The word drug may originate from an old Dutch word,(droog),which means dry, **OR** from an old French term, (drogue)=dry herb.

Pharm Logic Plus

“Where do drugs come from?”

Pharm Logic Plus

Drug Sources, Forms, and Names

- Drugs come from a variety of resources—
  1. Plants
  2. Animal products
  3. Inorganic substances

Plants

- **Digitalis** from foxglove
- **Morphine** from poppy
- **Aspirin** from willow bark
- **Vincristine** from periwinkle

Animals

- **Insulin** from pigs
- **Growth hormone** from pituitary
- **Heparin** from intestines
- **Antivenom** from horses

Synthetic

- **Laboratories**
- **Chemical synthesis**
- **Genetic engineering**
- **Biotechnology**

Biologics - The New Generation

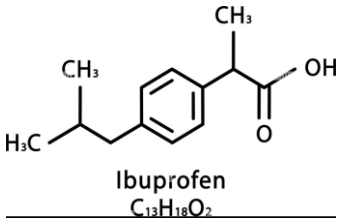
Medications that come from a **living source** and are developed through a combination using biotechnology, immunology, and genetic engineering.

لو رجعت عالصيدلية ما بتقدر تعطيني بديل عنها بالمرة مش زي الدواء

Examples: such as vaccines, antivenins and antitoxins, hormones, and monoclonal antibodies.

Pharm Logic Plus

Drug Names Made Simple



- **Chemical name: Long name** — 2-(4-isobutylphenyl) propanoic acid

Scientific description of molecular structure of the drug's chemical composition

When used: Research & development

- **Generic name** (nonproprietary name): also known as **common names = What it is:** Official medical name — **ibuprofen**
  - Name given by the United States Adopted Names (USAN) Council
  - There is only **one generic name for each drug**, and many organizations worldwide use the generic name for identification.
  - **When used:** Medical practice (learn these)!

https://www.merckmanuals.com/en-ca/home/drugs/brand-name-and-generic-drugs/overview-of-generic-drugs-and-drug-naming

- **Trade name=Brand name=** (proprietary name): when drug is marketed
  - **What they are**: Marketing names by pharmaceutical companies.
  - The drug has a registered trademark; use of the name is restricted by the drug's patent owner (usually the manufacturer).

When used: Consumer marketing

Advil®	Pfizer Inc
Midol®	Bayer Inc
Motrin®	Canada, North Macedonia, USA

Study Tip: Focus on learning generic names - they're used worldwide and on licensing exams!

Here's a table illustrating the difference between chemical, generic, and brand names of some common drugs

Chemical Name	Generic Name/ Non- Proprietary Name	Brand Name/ Proprietary Name
Isobutylphenylpr-opionc acid	Ibuprofen	Trufen, Advil, Ultrafen
Acetaminophen	Paracetamol	Otamol, Acamol, Sedamol,
Aminobenzyl Penicillin	Ampicillin	Ampipharm
7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one	Diazepam	Valium
4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone	Haloperidol	Haldol
N-acetyl-p-aminophenol	Paracetamol, Acetaminophen (US, IP)	Tylenol
(RS)-2-(4-(2-methylpropyl)phenyl)propanoic acid	Ibuprofen	Motrin
2,2-Bis(4-chlorophenyl)ethanol	Chloramphenicol	Chloramphenicol
(S)-1-(4-(2-methoxyphenyl)piperidyl)propan-2-one	Tramadol	Ultram
5-Methoxy-2-(1-propan-2-yl)-1H-indole	Doxapram	Dobutamine
(1S, 3R, 4R, 5S)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-(3-hydroxy-1-adamanty)-4-(hydroxymethyl)-4-(1,1-dimethylethy)-2-oxo-1-pyrrolidinecarboxylic acid	Zopiclone	Zopiclone

Pharm Logic Plus

Drugs are also divided into

1. **Prescription drugs** : require a written or phone order (the prescription), which can only be issued by or under the direction of a licensed physician, dentist, or veterinarian

1. **Nonprescription drugs:** referred to as “over-the-counter” (OTC) drugs (such as aspirin, antacids, cold remedies), can be purchased anywhere and do not require the services of a physician or pharmacist.

The prescription is a legal document that contains instructions for the pharmacist, who is licensed to dispense prescription medications.

OTC drugs follow the same pharmacologic principles as prescription drugs.

Pharm Logic Plus

Pharm Logic Plus

Drug Classifications

Grouped together based on **similar properties**

Drug classifications based on :

- **Structure (ex. Beta Blockers)= Pharmacologic class (or family):** refers to how the drug works in the body—its mechanism of action. Metoprolol pharmacological classification is **beta-adrenergic blocker**
  - Subclass (ex. selective, nonselective)
  - Examples : beta-adrenergic blockers – alpha agonists –ACEi

- **Therapeutic use:** refers to a drug's therapeutic use or clinical indication (ex. Antibiotic)
  - Subclass (ex. penicillins)
  - Examples : Antihypertensive- Antilipidemic – Antivirals– Antifungal drugs

Prototypical drugs ("**class representative**) : first drug in a class of drugs

- Once drugs are sorted into classifications, it is customary to utilize one drug within the class to compare to all the other drugs within that class.

أول دواء تم تصنيعه حيث بعدها بدأوا يقارنوا الأدوية التي تم تصنيعها

Pharm Logic Plus

Pharm Logic Plus

Common Classes of Medications Examples

therapeutic use ↓ comp

Class Of Medication	Examples	Common Suffixes	Common Roots
Local Anesthetics	Lidocaine, Procaine, Benzocaine, Novocaine, Bupivacaine, Articaine, Mepivacaine	**-caine**	*From "cocaine" - originally derived from coca leaves*
Antacids	Omeprazole, Pantoprazole, Esomeprazole, Lansoprazole, Rabeprazole	**-azole**	*Proton pump inhibitors - "praz" indicates gastric acid suppression*
Anticoagulants	Warfarin, Heparin, Rivaroxaban, Apixaban, Dabigatran	**-arin**	*"Coagul" = clotting; these prevent blood clots*
Antihistamines	Diphenhydramine, Loratadine, Cetirizine, Fexofenadine, Chlorpheniramine	**-amine**	*"Hist" = tissue; blocks histamine reactions*
Beta-Blockers	Esmolol, Metoprolol, Propranolol, Atenolol, Carvedilol	**-olol**	*Block beta-adrenergic receptors in heart*
Bronchodilators	Salmeterol, Formoterol, Albuterol, Terbutaline, Levalbuterol	**-terol**	*"Bronch" = airways; dilate breathing passages*
ACE Inhibitors	Lisinopril, Enalapril, Captopril, Ramipril, Benazepril	**-pril**	*Block angiotensin-converting enzyme for blood pressure*
Antibiotics (Penicillins)	Amoxicillin, Ampicillin, Penicillin, Methicillin, Nafcillin	**-cillin**	*From Penicillium mold; destroys bacterial cell walls*
Antibiotics (Cephalosporins)	Cephalexin, Cefazolin, Ceftriaxone, Cefuroxime, Cefdinir	**Cef-, Ceph-**	*From Cephalosporium fungus; similar to penicillins*
Statins	Atorvastatin, Simvastatin, Rosuvastatin, Pravastatin, Lovastatin	**-statin**	*"Stat" = stop; inhibit cholesterol synthesis*

Pharm Logic Plus

Class Of Medication	Examples	Common Suffixes	Common Roots
Benzodiazepines	Lorazepam, Diazepam, Alprazolam, Clonazepam, Midazolam	**-azepam, -azolam**	*"Benzo" ring structure; enhance GABA neurotransmitter*
Calcium Channel Blockers	Amlodipine, Nifedipine, Verapamil, Diltiazem, Felodipine	**-dipine**	*Block calcium channels in heart and blood vessels*
Diuretics	Furosemide, Hydrochlorothiazide, Spironolactone, Amiloride, Bumetanide	**-ide, -thiazide**	*"Diur" = urine; increase fluid elimination*
NSAIDs	Ibuprofen, Naproxen, Aspirin, Celecoxib, Indomethacin	**-profen**	*Non-steroidal anti-inflammatory drugs*
Opioids	Morphine, Codeine, Oxycodone, Hydrocodone, Fentanyl	**-codone, -morphine**	*From opium poppy; bind to opioid receptors for pain relief*
Antidepressants (SSRIs)	Fluoxetine, Sertraline, Paroxetine, Citalopram, Escitalopram	**-tine, -pram**	*Selective serotonin reuptake inhibitors*
Antifungals	Fluconazole, Ketoconazole, Itraconazole, Terbinafine, Nystatin	**-conazole**	*"Azole" compounds disrupt fungal cell membranes*
Antiarrhythmics	Amiodarone, Lidocaine, Procainamide, Quinidine, Flecainide	**-arone, -caine**	*Regulate heart rhythm abnormalities*
Thyroid Hormones	Levothyroxine, Liothyronine, Desiccated thyroid, Methimazole	**-thyroxine**	*"Thyro" = thyroid gland; replace or regulate thyroid hormones*
Corticosteroids	Prednisone, Hydrocortisone, Dexamethasone, Methylprednisolone, Betamethasone	**-sone, -lone**	*Synthetic versions of cortisol; reduce inflammation*

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Question #1

A drug that has the potential for abuse and is regulated by the Drug Enforcement Agency is classified as a

A. Poison

B. OTC drug

C. Prescription drug

D. Controlled substance

E. Nonproprietary drug



What You'll Learn Today:
Master Drug schedules and learn what are different types of controlled drugs !!!!

Controlled Substances

Drug Schedules Defined in the Federal Comprehensive Drug Abuse Prevention and Control Act

Schedule	Definition	Controlled drugs
I	Drugs with high abuse potential and no accepted medical use	Heroin, hallucinogens, marijuana, these drugs are not to be prescribed
II	Drugs with high abuse potential and accepted medical use	Narcotics (morphine and pure codeine), cocaine, amphetamines, short-acting barbiturates (*Amobarbital, Secobarbital*), nabilone; no refills without a new written prescription from the physician
III	Drugs with moderate abuse potential and accepted medical use	Moderate- and intermediate-acting barbiturates, dronabinol, anabolic steroids, preparations containing codeine plus another drug; prescription required, may be refilled five times in 6 months when authorized by the physician
IV	Drugs with low abuse potential and accepted medical use	Phenobarbital, chloral hydrate, zolpidem (*Ambien*), antianxiety drugs (*Librium, Valium*); prescription required, may be refilled five times in 6 months when authorized by the physician
V	Drugs with limited abuse potential and accepted medical use	Narcotic drugs used in limited quantities for antitussive (codeine) and antidiarrheal purposes (diphenoxylate, *Lomotil*); drugs can be sold only by a registered pharmacist; buyer must be 18 years old and show identification. Some states require a prescription for this class of drugs



حالياً محكمة بستخدموها للأشخاص اللي عندهم cancer ومي وجع

Pharm Logic Plus

NAPRA(CANADA)

Schedule I Drugs: **require a prescription** for sale and are provided to the public by the pharmacist following the diagnosis and **professional intervention** of a practitioner.

تحتاج إلى وصفة طبية لازم

Schedule II Drugs: less strictly regulated, do **require professional intervention** from the pharmacist at the point of sale and possibly referral to a practitioner. While a **prescription is not required**, the drugs are available only from the pharmacist and must be retained within an area of the pharmacy where there is **no public access and no opportunity for patient self-selection**

لا تحتاج إلى وصفة طبية بس لازم الصيدلي يوصف للمريض الدواء وبكون الدواء بعيدًا عن الناس حيث لا تشكي من هون ما تشوفه وتختاره أنت الصيدلي هو يختار بس

Schedule III Drugs : may present risks to certain populations in self-selection. Available **without a prescription**, sold from the **self-selection area of the pharmacy** which is operated under the direct supervision of the pharmacist, subject to any local professional discretionary requirements which may increase the degree of control. Such an environment **is accessible to the patient and clearly identified as the "professional services area" of the pharmacy**. The pharmacist is available, accessible and approachable to assist the patient in making an appropriate self-medication selection.

لا تحتاج لوصفة ولا اختيار صيدلي في محكمة المريض يطلب طلبه زي أكامول وعادي يتم وصفه على المكشوف

Unscheduled Drugs: can be sold **without professional supervision**. Adequate information is available for the patient to make a safe and effective choice and labeling is deemed sufficient to ensure the appropriate use of the drug. These drugs are not included in Schedules I, II or III and may be **sold from any retail outlet.**

تبيعوا بأي مكان ومحكمة صيدلية ماركت
لا يحتاجوا إلى طبيب أو صيدلي

Pharm Logic Plus

Question #2

The medical situation when a particular drug should not be administered is referred to as

A. Side effect
B. Adverse effect
C. Drug allergy
D. Contraindication
E. Antagonism

يعني المريض بكون بحاجة لهذا الدواء
وكذلك يقدر أعطيه اياه لأنواع وقد
عليه سبباً ، مثلاً النساء الحامل يصير
عندهم تشوه بالأجنة



What You'll Learn Today:
Master Terminology related to drugs !!

Pharm Logic Plus

TERMINOLOGY RELATED TO DRUG

Therapeutic effect: The intended effect الأثر المطلوب من الدواء

بعد البحث والتجارب عليه، سيقدم الدواء

Drug indication: The therapeutic use(s) of any drug- meaning indications for use

معلومة يشتغل على أكثر من receptor فيعطي أكثر من

Contraindication: Situations or circumstances when a drug should not be used.

renal failer, Pregnancy

Side Effects: more of a nuisance than harmful. The dry mouth and sedation caused by some antihistamine

تأثير مزعج ليس مؤذي (نوم، فم جاف)

Adverse Effects: undesired effects, may be **harmful** (persistent diarrhea, vomiting, or central nervous system [CNS] disturbances such as confusion) or that **with prolonged treatment may cause conditions** affect the function of vital organs such as the liver or kidney

تأثير مزعج ومؤذي (يؤثر على الجهاز العصبي، تقيؤ) ولو تم استخدامه بشكل طويل يوقف

Toxic Effects: drug poisoning, the consequences of which can be extremely harmful and may be life-threatening

بجرعة سام ومهدد للحياة - بعد ما يقدر الـ maximum therapeutic effect

The site of action: The location within the body where the drug exerts its therapeutic effect- **Aspirin**

هو خافض للحرارة فيؤثر على الـ hypothalamus عشان يخفض الحرارة فهو مكان طلاء الفعال

Mechanism of action: how a drug produces its effects

Pharm Logic Plus

Pharmacologic Principles

Encompasses a variety of principles

- Pharmaceutics
- Pharmacokinetics
- Pharmacodynamics
- Pharmacogenomics (pharmacogenetics)
- Pharmacotherapeutics
- Pharmacognosy
- Pharmacoeconomics
- Toxicology

Pharm Logic Plus

علم الصيدلانيات (طلاب الصيدلة)

Pharmaceutics

- The study of how various **drug forms** influence the way in which the drug affects the body. دراسة كل أشكال الدواء وكيف يأثروا على الجسم
- Dissolution—dissolving of solid dosage forms and their absorption
- Different drug dosage forms have different pharmaceutical properties.
- Dosage form determines drug dissolution rate.

Pharm Logic Plus

Question #3

A patient is prescribed ibuprofen 200 mg PO every 4 hours as needed for pain. The pharmacy sends up enteric-coated tablets, but the patient refuses the tablets, stating that she cannot swallow pills. What will you do?

A. Crush the tablets and mix them with applesauce or pudding.
B. Call the pharmacy and ask for the liquid form of the medication.
C. Call the pharmacy and ask for the IV form of the medication.
D. Encourage the patient to try to swallow the tablets.

ANS: B

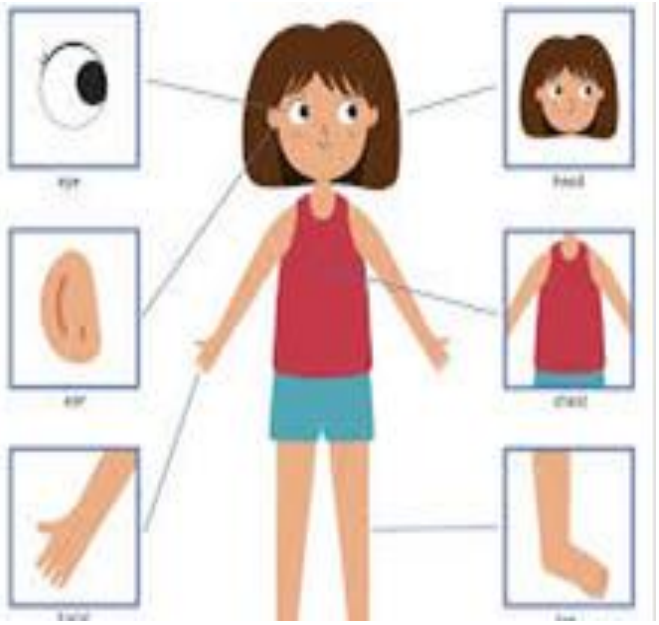
The liquid form is appropriate because it is also given via the oral route.
Enteric-coated tablets should not be crushed, and the patient should not be forced to take the tablets. This medication does not have an IV form, but even if it did, the routes cannot be changed without a health care provider's order.



“ What the ? does to the ? ”

“ What the **Body** does to the **Drug** ”

“ What the **Drug** does to the **Body** ”

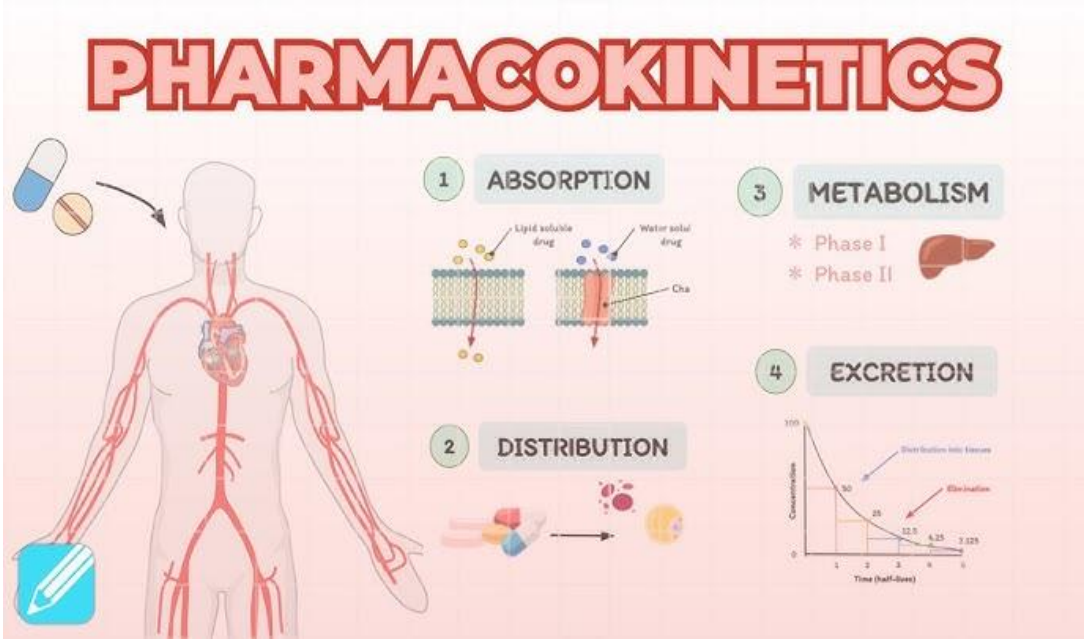


Pharmacokinetics PK

يعني الدواء وهو بتحرك جوا الجسم شو الجسم بعمل فيه (رحلة الدواء)

" What **the body** does to **the drug**"

Absorption → Distribution → Metabolism → Excretion



- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

T (transport) وأحيانًا

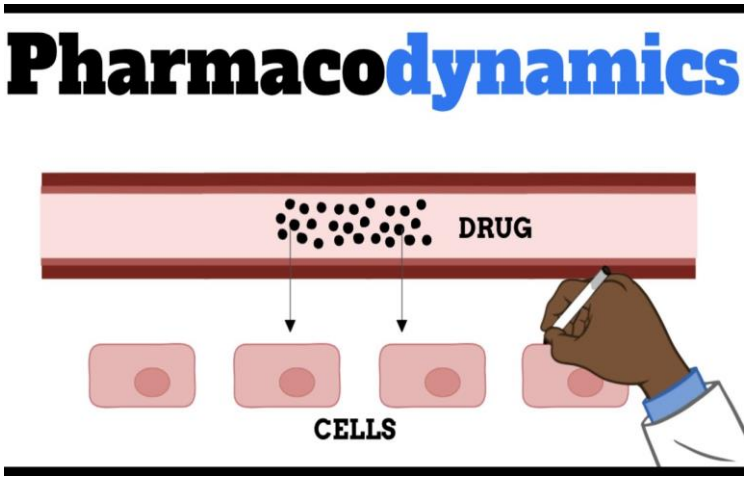
- Study of (ADME) of drugs
- **A**ll **D**rugs **M**ust **E**xit"

Pharm Logic Plus

Pharmacodynamics PD

شو بعمل الدواء فيا

"What **the drug** does to **the body**" = The study of the biological and therapeutic effects of drugs





- How drugs produce their effects
- Drug-receptor interactions
- Therapeutic responses
- Side effects & toxicity
- Drug/Drug and Drug/food interactions

شو بعمل في الخلايا
وشو الـ receptors اللي بيرتبط فيها

Pharm Logic Plus



What You'll Learn Today:

Master the fundamental principles of how drugs interact with your body, from the moment they enter until they leave!

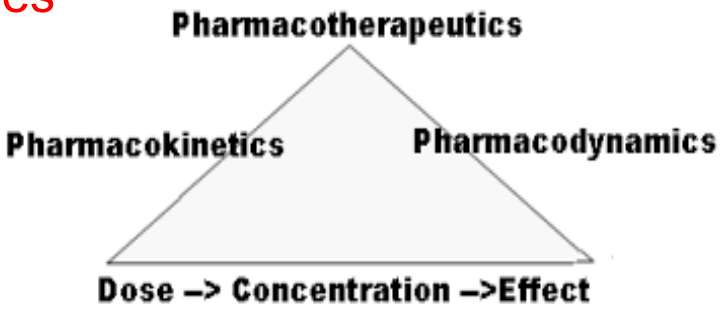
Pharmacologic Principles

Pharm Logic Plus

Pharmacotherapeutics

The clinical use of drugs to prevent and treat diseases

It's the bridge between pharmacology knowledge and patient care!



Proper Drug Selection→Correct Dosing→Patient Safety→Therapeutic Success

Real-World Example: Patient with Hypertension:

✓ Select appropriate antihypertensive (ACE inhibitor vs Beta-blocker)

✓ Consider patient's age, comorbidities, and contraindications

✓ Monitor effectiveness and side effects

✓ Adjust therapy as needed

Think About It

Why can't we just use the same drug for every patient with the same condition?

Pharm Logic Plus



Pharmacognosy

"Nature's Pharmacy: From Plants to Pills"

What is Pharmacognosy?

The study of natural (versus synthetic) drug sources (i.e., plant, animals, minerals)

Famous Plant-Derived Drugs

Aspirin → Willow bark (Salix species)
Morphine→ Opium poppy (Papaver somniferum)
Digoxin → Foxglove plant (Digitalis purpurea)
Paclitaxel (Taxol) → Pacific yew tree

Important Note:Just because something is "natural" doesn't mean it's automatically safe!
Many natural compounds are highly toxic (e.g., poison ivy, deadly nightshade)

Memory Tip: "Pharmacognosy = Pharma + Gnosis (knowledge)“
Knowledge of where drugs come from in nature!

Pharm Logic Plus

Pharmacoeconomics

"Healthcare Dollars & Sense"

What is Pharmacoeconomics?

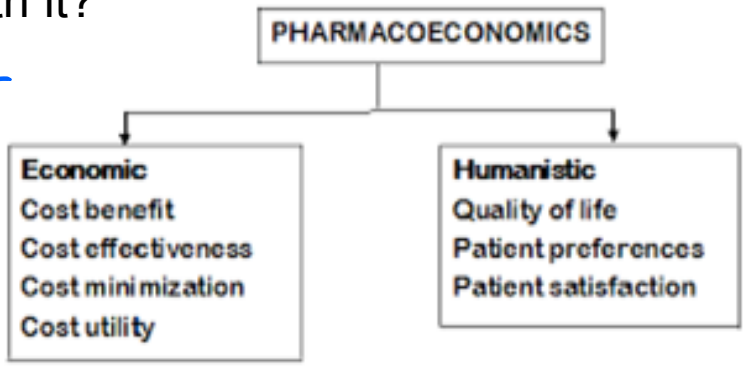
Study of the economic factors influencing drug therapy costs

Helps answer: "Is this expensive treatment worth it?“

بكون في الدواء اكتر من واحد بدي احكي عن الدواء اللي بدي اختاره

Key Analysis Types: حساب التكلفة لكل دواء بدي استخدمه

مثلاً: هل هذا الدواء الغالي رح يوصل لل therapeutic effect وبرضه رح يكون غالي عالمريض



Real-World Scenario: Expensive Cancer Drug

Drug cost: $100,000 per year

Extends life by 6 months on average

Reduces hospitalizations by 50%

Is it cost-effective?

How do you put a price on human life? What factors should influence these decisions?

Pharm Logic Plus

Toxicology

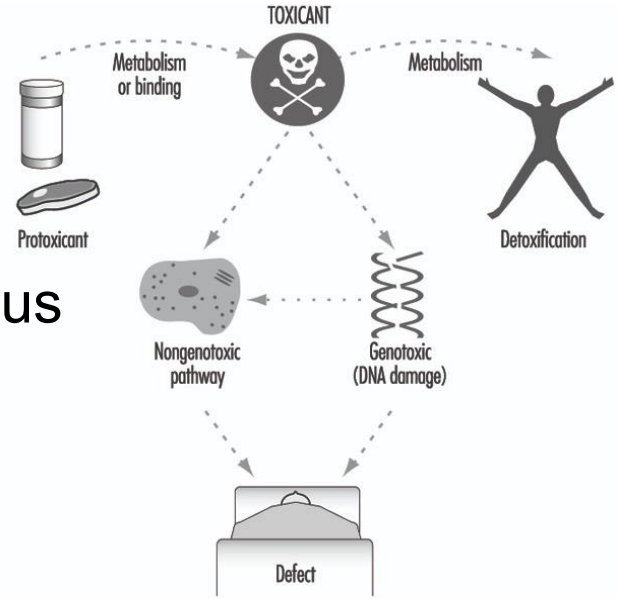
"The Dark Side of Pharmacology"

What is Toxicology?

The science of adverse effects of chemicals on living organisms

Remember!

it is a Branch of pharmacology



"The dose makes the poison" - Paracelsus

Key Concept: Therapeutic Index (TI)

KEY POINTS

- High TI= Safer drug (e.g., penicillin)
- Low TI= Dangerous drug (e.g., warfarin, digoxin)

Pharm Logic Plus

Types of Toxicity

ACUTE	CHRONIC	ORGAN SPECIFIC
Single dose High dose	Repeated exposure	Liver Kidney Heart

يتخلص من ال toxicity إما عن طريق ال anti-dot أو عن طريق غسيل المعدة

Clinical Toxicology Examples:

Acetaminophen overdose→ Liver damage

Aspirin toxicity→ Ringing in ears, confusion

Chemotherapy→ Hair loss, nausea, bone marrow suppression

Remember: "Any substance can be toxic - it's all about the DOSE!

Pharm Logic Plus

✓ The "Rights" of Medication Administration

The Traditional "5 Rights“

- ✅ Right PATIENT
- ✅ Right DRUG
- ✅ Right DOSE
- ✅ Right ROUTE
- ✅ Right TIME

Additional Modern "Rights

Documentation & Legal

- ✅ Right Documentation
- ✅ Right Reason/Indication
- ✅ Right to Refuse

Safety & Quality

- ✅ Right Response
- ✅ Right Education
- ✅ Right Evaluation

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Never Skip These Checks!

Medication errors are a leading cause of preventable patient harm

Check patient ID bands

Verify allergies

Double-check calculations

Know what you're giving and why



: "PATIENT"

P-atient
A-ccurate drug,
T-iming,
I-ndication,
E-ducation,
N-ote everything,
T-hink safety!

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Principles of Prescription Writing

"Your License to Heal (Responsibly)"

What is a Prescription?

A legal document containing instructions for a pharmacist to dispense medication to a specific patient

A prescription is a **written, verbal, or electronic order** from a (practitioner or designated agent) to a pharmacist

Who can prescribe medications?

Medical Doctors (Physicians)- Veterinarians (for animals)- Dentists (for dental conditions)
Pharmacists (limited conditions)of minor ailments - Nurse Practitioners (NPs)
Other Professionals: like chiropodists/podiatrists, midwives, naturopaths, optometrists, and physiotherapists may have prescribing authority under certain conditions.

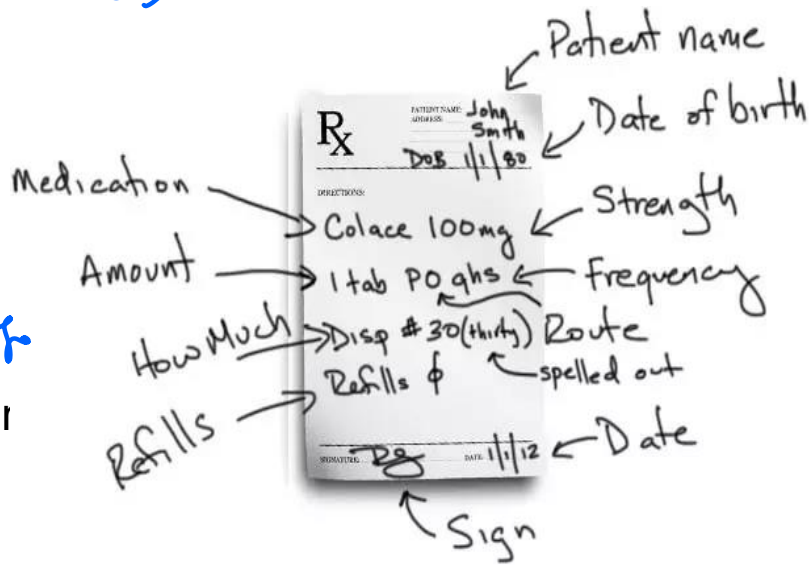
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Content of Prescriptions

- Physicians **must** ensure that written prescriptions are legible.
- Physicians **must** ensure that the following information is included on every written or electronic prescription

Legal Requirements - Every Prescription Must Include

- ❑ **Patient: name + another identifier (date of birth or address)**
- ❑ **Drug/Medication: name and strength, form, amount (**in numbers AND words :e.g. #45 forty-five) **, directions for use (route, frequency) , number of refills.**
- ❑ **The prescribing physician's printed name, signature (or electronic signature), and registration number, the prescribing physician's practice address**
- ❑ The full **date the prescription** was issued (day, month, and year); antibiotic, controlled
Written out in letters not numeric (e.g. July 10, 2004,



tenth of July, two thousand and four

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Prescription for Safety

Before Prescribing

Physicians **must** only prescribe a drug if they have the knowledge, skill, and judgment to do so safely and effectively.



Before Before You Prescribe a drug, **MUST DO**:

- Proper Clinical assessment of the patient
- Make accurate diagnosis or differential diagnosis
- Consider the risks and benefits of prescribing the chosen drug
- Check for drug interactions
- Obtain valid Patient consent

إنه يكون المريض جاي إله و محتاج لعلاج

لازم نعمل حساب هل في طعام معين بأثر على الدواء أحيانا المريض بأخذ أدوية أخرى food drug interaction

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Prescription Safety Tips

"Preventing Deadly Mistakes"

- All prescriptions must be **legible** and written in **black ink**.
- **Avoid abbreviations and dangerous dose expressions**
- All prescriptions should include a brief notation of purpose, unless deemed inappropriate (e.g. for nausea, for blood pressure, etc.).
- Always use a **leading zero** before a number (e.g. 0.5 mg) (NOT .5 mg)
- Never use a terminal zero 5 mg and (NOT 5.0 mg)
- No abbreviations for drug names
- Write quantities in numbers AND words.
- Do not make any changes or cross-outs.
- Never loan your prescription pads to anyone and contact the pharmacy immediately if they are misplaced or stolen.
- Medication safety and error avoidance organizations such as the Institute for Safe Medication Practices (ISMP) and JCAHO have recommended that abbreviations and dangerous dose expressions be avoided when prescribing medications because of the increased risk of medication errors.

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Do Not Use

Dangerous Abbreviations, Symbols and Dose Designations

The abbreviations, symbols, and dose designations found in this table have been reported as being frequently misinterpreted and involved in harmful medication errors. They should NEVER be used when communicating medication information.

Abbreviation	Intended Meaning	Problem	Correction
U	unit	Mistaken for "0" (zero), "4" (four), or cc.	Use "unit".
IU	international unit	Mistaken for "IV" (intravenous) or "10" (ten).	Use "unit".
Abbreviations for drug names		Misinterpreted because of similar abbreviations for multiple drugs; e.g., MS, MSO_4 (morphine sulphate), $MgSO_4$ (magnesium sulphate) may be confused for one another.	Do not abbreviate drug names.
QD QOD	Every day Every other day	QD and QOD have been mistaken for each other, or as 'qid'. The Q has also been misinterpreted as "2" (two).	Use "daily" and "every other day".
OD	Every day	Mistaken for "right eye" (OD = oculus dexter).	Use "daily".
OS, OD, OU	Left eye, right eye, both eyes	May be confused with one another.	Use "left eye", "right eye" or "both eyes".
D/C	Discharge	Interpreted as "discontinue whatever medications follow" (typically discharge medications).	Use "discharge".
cc	cubic centimetre	Mistaken for "u" (units).	Use "mL" or "millilitre".
µg	microgram	Mistaken for "mg" (milligram) resulting in one thousand-fold overdose.	Use "mcg".
Symbol	**Intended Meaning**	**Potential Problem**	**Correction**
@	at	Mistaken for "2" (two) or "5" (five).	Use "at".
> <	Greater than Less than	Mistaken for "7"(seven) or the letter "L". Confused with each other.	Use "greater than"/"more than" or "less than"/"lower than".
Dose Designation	**Intended Meaning**	**Potential Problem**	**Correction**
Trailing zero	x.0 mg	Decimal point is overlooked resulting in 10-fold dose error.	Never use a zero by itself after a decimal point. Use "x mg".
Lack of leading zero	.x mg	Decimal point is overlooked resulting in 10-fold dose error.	Always use a zero before a decimal point. Use "0.x mg".

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Adapted from ISMP's List of *Error-Prone Abbreviations, Symbols, and Dose Designations 2006*

Report actual and potential medication errors to ISMP Canada at https://www.ismp-canada.org/err_report.htm **or by calling** 1-866-54-ISMPC.

ismp CANADA — Institute for Safe Medication Practices Canada / Institut pour la sécurité des médicaments aux patients du Canada

Permission is granted to reproduce material for internal communications with proper attribution. Download from: www.ismp-canada.org/dangerousabbreviations.htm

DON'T USE

SAFE TO USE

Common frequencies abbreviations for prescription writing

- daily (no abbreviation)
- every other day (no abbreviation)
- BID/b.i.d. (twice a day)
- TID/t.id. (three times a day)
- QID/q.i.d. (four times a day)
- QHS (every bedtime)
- Q4h (every 4 hours)
- Q4-6h (every 4 to 6 hours)
- QWK (every week)

https://www.ismp-canada.org/dangerousabbreviations.htm

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A Well-Written Prescription Contains:

All required elements clearly written to prevent medication errors

Good Prescription Example

Patient: John Smith, DOB: January 15, 1985
Address: 123 Main St, Toronto, ON

Rx: Amoxicillin 500 mg capsules
Quantity: #21 (twenty-one)
Directions: Take one capsule by mouth three times daily for 7 days
Indication: For bacterial infection
Refills: 0 (zero)

Dr. Sarah Johnson, MD
License #: 12345
Date: June fourth, 2025
Signature: Dr. S. Johnson



SAFE TO USE

- Tablets - tab
- Capsule – cap
- Syrup – syr
- Suspension – susp
- Injection – Inj
- Metered dose inhaler – as such

asthma ya ajibu.

- Lotion – as such



Remember: **"When in doubt, write it out!"**

Clear, complete prescriptions prevent medication errors and save lives. Every missing detail is a potential safety risk.!

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Routes of Administration: Your GPS for Drug Delivery

What Are Routes of Administration?

Different pathways to get medications into your body - each with unique destinations and travel times!

ENTERAL ROUTES

"Enter through GI tract"

- **Oral (PO)** - Swallow pills/liquids
- **Sublingual (SL)** - Under tongue
- **Buccal** - Inside cheek
- **Rectal (PR)** - Suppository

sub pao zuh taw rel

PARENTERAL ROUTES

"Parent gives injection (bypass GI)"

- **Intravenous (IV)** - Into vein
- **Intramuscular (IM)** - Into muscle
- **Subcutaneous (SC)** - Under skin
- **Intradermal (ID)** - Into skin

TOPICAL

Applied to body surfaces

- Skin patches
- Eye drops
- Nasal sprays
- Inhalation

Example: Nicotine patch

Memory Trick:
Enteral = **Enter** through GI tract
Parenteral = **Parent** gives injection (bypass GI)

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Route Selection: The Clinical Decision Tree?



The ROA is determined by the

1. Patient status
2. The speed which the drug is absorbed and/ or released
3. Physical characteristics of the drug
4. The need to bypass hepatic metabolism and achieve high conc. at particular sites

Drug-related factors

1. Properties of the drug(physical and chemical properties)- water or lipid solubility, ionization, effect of gastric pH, digestive enzymes, first pass metabolism
2. Therapeutic objectives
3. Onset of action/ duration of treatment (emergency/ routine use)

يعني لو المريض عنده مرض مزمن ما يقدر آخذ
أعطيه إلا طول العمر

Patient-related factors

1. Site of action (local / systemic).
2. Condition of the patient (unconscious, vomiting, diarrhea)
3. Age of the patient
4. Patient`s/doctor`s choice



Emergency Scenarios

Unconscious Patient

Available routes:

- ✅ IV (fastest)
- ✅ IM (if no IV access)
- ✅ Rectal (some drugs)
- ❌ Oral (choking risk)

Nausea/Vomiting

Avoid oral route:

- ✅ IV/IM injection
- ✅ Rectal suppository
- ✅ Sublingual tablet
- ❌ Oral medications

Asthma Attack

Direct to lungs:

- ✅ Inhalation (best)
- ✅ IV (severe cases)
- ❌ Oral (too slow)
- ❌ IM (not direct)

Speed Comparison

IV: Seconds | **Sublingual:** 1-3 minutes | **IM:** 10-30 minutes | **Oral:** 30-60 minutes

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Routes of Drug Administration(ROA)

💊 Getting Drugs Where They Need to Go! 💊

By the end of this presentation, you will be able to:

🔍 Identify and describe all major routes of drug administration

⚖️ Compare advantages and disadvantages of each route

🏥 Select appropriate routes for different clinical situations

☐ Understand onset times and bioavailability differences

🎯 Apply route selection principles in patient care scenarios



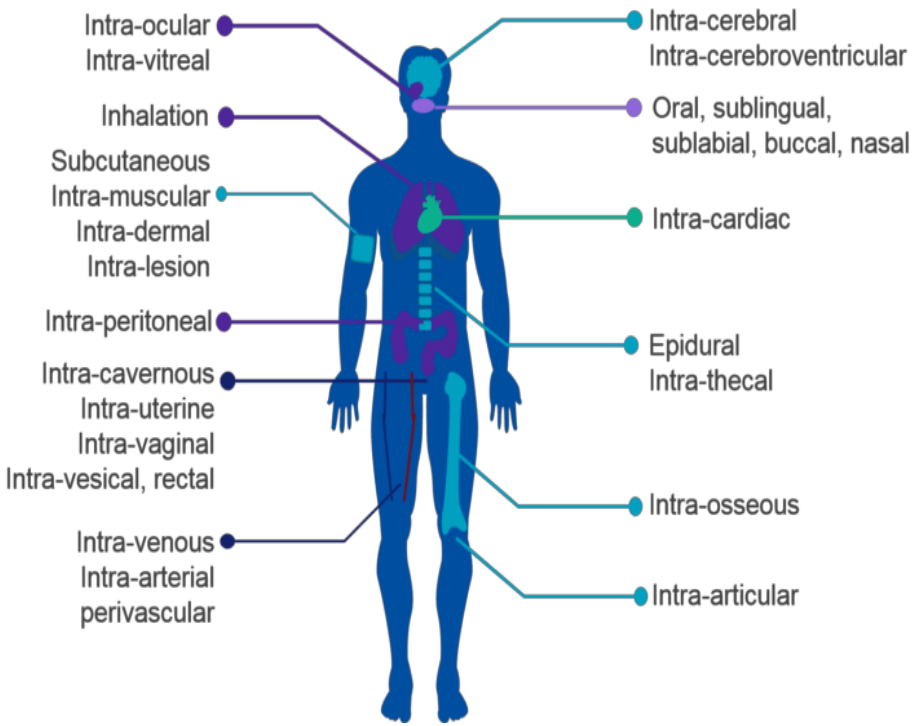
💡 *Memory Tip: "Routes are like roads - each gets you to your destination differently!"*

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ROA

TOPICAL

rectal



SYSTEMIC

Oral
Sublingual
Buccal
Rectal

inter GI

- (Enteral)
- Parenteral
  - Injections
    - Intradermal
    - Subcutaneous
    - Intramuscular
    - Intravenous
    - Intraperitoneal
    - Intra-arterial
    - Intrathecal
    - Intra-articular
    - Intramedullary
  - Inhalation
    - Adhesive unit
    - Inunction
    - Iontophoresis
    - Jet injection
  - Transdermal
  - Transmucosal
    - Sublingual
    - Nasal
    - Rectal

Rectal (can also be topical)

What it is ? How it works? When to use it? pros/cons? and a real example.

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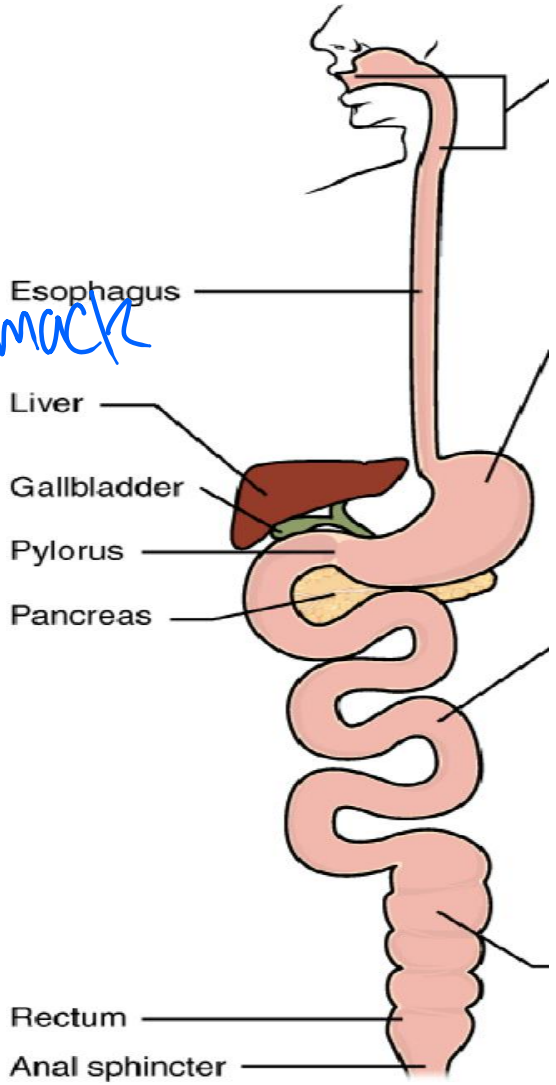
Enteral Route Of Administration

GIT

- The drug is absorbed into the systemic circulation through the oral or gastric mucosa or the small intestine.
  - Oral
  - Sublingual
  - Buccal
  - Rectal

mouth stomach

80-90 %



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Oral Route: The Patient's Favorite

"PO = Per Os = By Mouth" (Latin origin)

What is the Oral Route?

Medications taken by mouth and absorbed through the GI tract - the most common and convenient route!



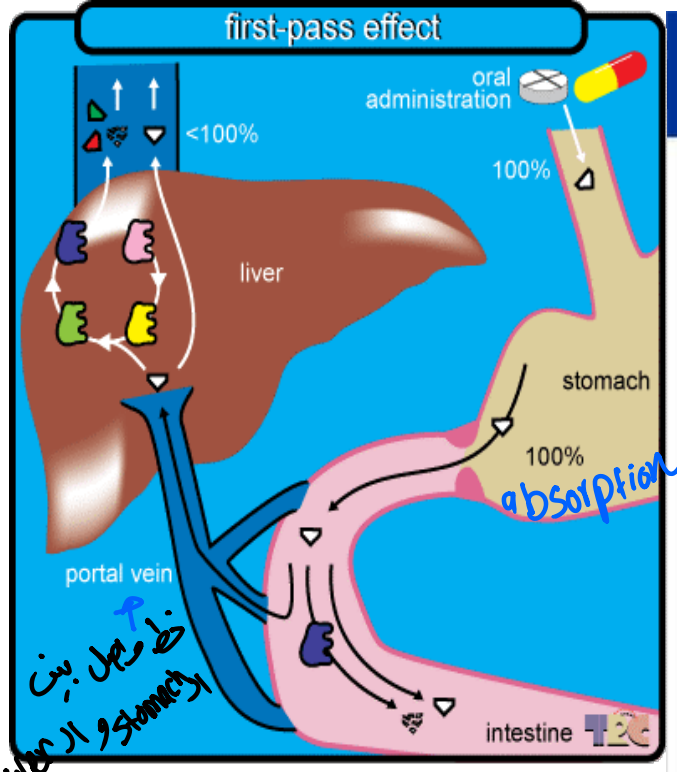
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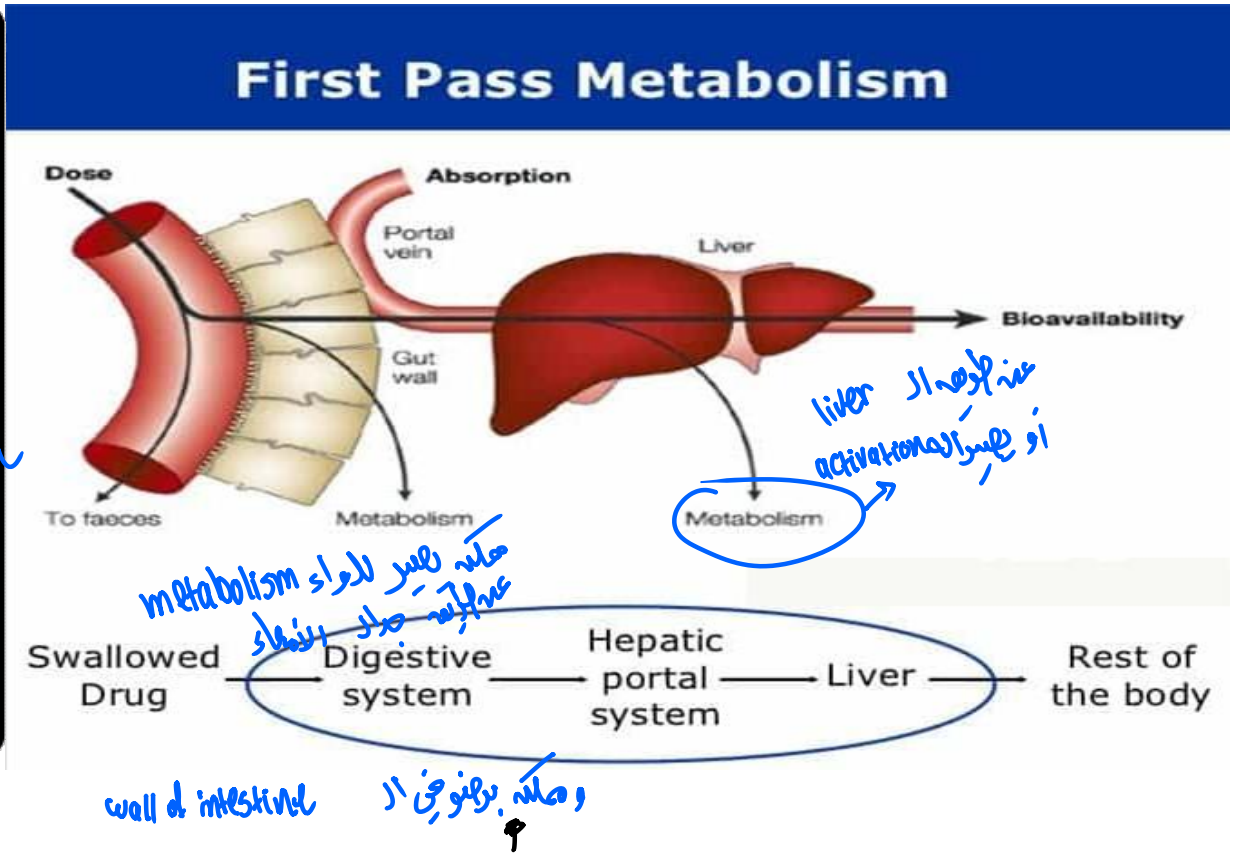
Convenient - Ease of administration- Cost-effective - Widespread acceptance by the patients (most commonly used medication administration route).

The primary site of drug absorption is usually the **small intestine**, and the bioavailability of the medication is influenced by the amount of drug ab d across the intestinal epithelium.

The first-pass effect is an important consideration for orally administered medications.

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After oral absorption, drugs must pass through the liver before reaching the body.

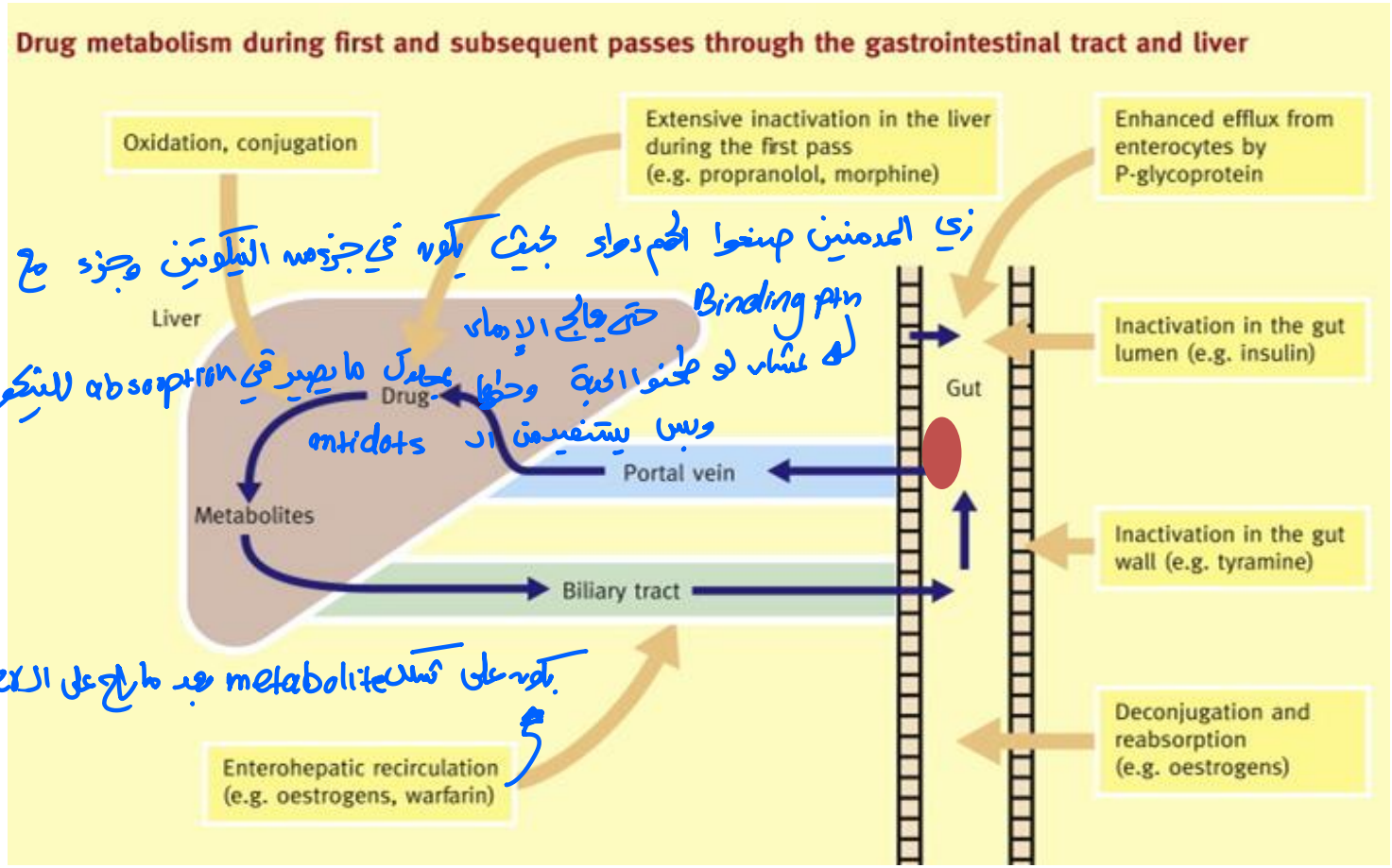
The liver can metabolize up to 90% of some drugs, requiring higher oral doses!

The first-pass effect after oral absorption is the result of uptake and metabolism of compounds by the intestinal and hepatic degradation/alteration of a drug after oral administration resulting in decreased drug concentration significantly before it reaches the systemic circulation.

The greater the first-pass effect, the less the agent will reach the systemic circulation when the agent is administered orally

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A drug is inactivated in the gastrointestinal tract or metabolized in the **gut wall** or **liver** before it enters the systemic circulation, the amount reaching the site of action is reduced



Advantages Vs Disadvantages of Oral administration



- Variable absorption rates
- Degradation of some drugs before reaching the site of absorption into the bloodstream
- The inability of many compounds to effectively be absorbed to reach the bloodstream.
- The insolubility of many drugs at low pH levels is prevalent in the digestive tract.
- The inactivation of the drug in the liver on its way to the systemic circulation
- Irritation of the mucous lining of the gastrointestinal tract. This can be prevented to some extent by coating.

⏰ **Onset Time: 30-60 minutes**

🎯 **Bioavailability: Variable (affected by first-pass metabolism)**

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Dosage form



The physical form in which a drug is manufactured or administered= the physical state in which pharmaceuticals are available for administration, such as solid, liquid, or gas, including semi-solid forms)

1. The **active pharmaceutical ingredient** (API) is mixed with
2. non-APIs called **excipients**. The excipients play a very important role in formulating different dosage forms.

لي مواد غير فعّالة تساعد على تشكيل الدواء وعطوه (كبسولة ، سائل ، حبة)

Vehicles : Medium in which ingredients of a formulation are dissolved, suspended m or dispersed.

Vehicles can be (oil- aquaes- solid-semisolid)

لازم يكونوا بنفس الـ active الدواء

Ideal Properties

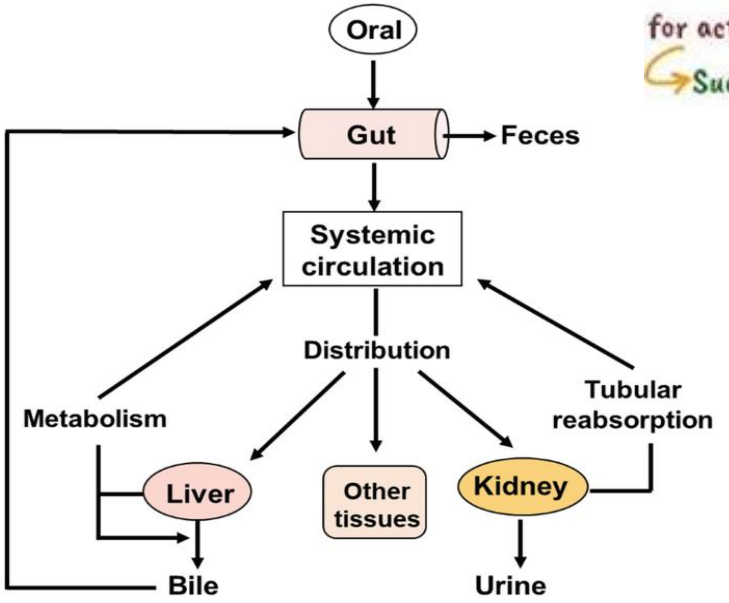
- Physiologically inert
- Physiologically stable
- Do not impart any undesired taste , colour, and odour.
- Non toxic , Non irritant , Non sensitizing
- Effective in low concentration
- Free from microorganism
- Not interfere with bioavailability of the drug
- Accepted by regulatory authorities

Oral Preparations(PO)



Wide range of oral preparations including:

- Tablets
- Capsules
- Powders
- Oral Suspension
- Emulsions
- Troches and Lozenges
- Liquid and lyophilized vials for injection
- Aqueous Preparations(Syrups)
- Alcoholic Preparations(Elixirs, spirits, tinctures, and fluid extracts)



Real-World Examples

Acetaminophen (Tylenol): Headache relief in 30-60 minutes

Antibiotics: Amoxicillin for infections

Vitamin supplements: Daily multivitamins

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Tablets

Effervescent tablet: A tablet that produces gas (CO_2) when placed in water. vitamin C

Chewable tablet: A tablet consumed by chewing. These tablets are usually formulated to avoid leaving a bitter taste in the mouth.

Sublingual tablet: A tablet placed under the tongue.

Buccal tablet: A tablet placed on the inside of the cheek.

Lozenge tablet: Used by sucking it inside the mouth.

Vaginal tablet (ovule): A tablet inserted into the vagina.

Special Oral Preparations: Engineering Better Pills

Enteric-Coated

Acid-resistant coating

- Protects stomach from irritation
- Protects drug from stomach acid
- Dissolves in intestine (pH > 7)

Example: Aspirin EC, Omeprazole

Extended-Release (XR/ER)

Slow, controlled release

- Releases drug over 8-24 hours
- Less frequent dosing
- Better compliance

Example: Metformin XR, Diltiazem ER

Orally Disintegrating (ODT)

Dissolves on tongue

- No water needed
- Great for swallowing difficulties
- Fast onset

Example: Zofran ODT, Zyprexa Zydis

(ER) (EC) عشان نحافظ على التركيز بالدم ثابت و ما يكون في حرجان دواء كثيرة

Extended-release tablet: A tablet formulated to make the active ingredient available for a specific period after administration.

Enteric-coated tablet: A tablet formulated with an enteric coating to delay the drug's release until the tablet has passed the stomach.

ODT (orally disintegrating tablet): A tablet formulated to rapidly disintegrate upon contact with saliva

Sugar-coated/film-coated tablet: A tablet coated with sugar or film to protect the drug from air, moisture, or light, mask the unpleasant odor and taste of the drug, and improve the tablet's appearance.

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🚨 Critical Safety Alert

NEVER crush or break:

- Enteric-coated tablets (causes stomach irritation)
- Extended-release preparations (causes drug overdose)
- Sublingual/buccal tablets (changes absorption)

🔍 How to Identify Special Preparations

Look for these suffixes:

- **EC** = Enteric Coated
- **XR/ER/SR/LA** = Extended/Sustained/Long-Acting Release
- **ODT** = Orally Disintegrating Tablet
- **SL** = Sublingual

💎 ***Clinical Pearl:*** *Most medications are designed for oral use - it's the gold standard when patient can swallow safely*

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Question #4

Quick Check: Can you crush this tablet?

A) Tylenol Regular

B) Aspirin EC

C) Metformin XR

D) Zofran ODT

Answer A: Only (Tylenol Regular) can be safely crushed!

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Sublingual & Buccal: The Express Lane



"SUB-lingual = SUB-marine = UNDER the tongue!"

"BUCCal = Between cheek and gum like a BUCCaneer hiding treasure!"

What's the Difference?

Sublingual: Under the tongue | **Buccal:** Inside the cheek

Both bypass the liver's first-pass effect!



SUBLINGUAL

Under the tongue

- Rich blood supply
- Rapid absorption (1-3 min)
- Highly permeable mucosa

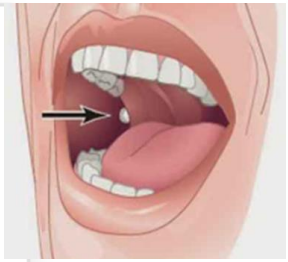
Example: Nitroglycerin for chest pain

BUCCAL

Inside the cheek

- Less permeable than sublingual
- Slower absorption (5-10 min)
- Longer contact time

Example: Testosterone buccal tablet



- The medication undergoes a passive diffusion through the venous blood in the oral cavity, which bypasses the hepatic portal vein and flows into the superior vena cava.



Real-World Scenario: Heart Attack : Patient experiencing chest pain (angina):

- **Step 1:** Place nitroglycerin tablet under tongue
- **Step 2:** Let it dissolve (don't swallow!)
- **Step 3:** Relief in 1-3 minutes
- **Why sublingual?** Bypasses liver, works immediately

Real-World Example: Testosterone buccal tablets for hormone replacement therapy

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✅ ADVANTAGES

- Rapid onset (1-10 minutes)
- Bypasses first-pass metabolism
- Can remove if needed
- Good for swallowing difficulties
- No GI irritation

❌ DISADVANTAGES

- Must not be swallowed
- Excessive saliva affects absorption
- Unpleasant taste
- Limited drug options
- Patient cooperation needed

- Convenience
- Low risk of infection
- Rapid absorption is due to the abundant mucosal network of systemic veins and lymphatics, leading to a rapid onset of action.
- A tablet can be kept for a long time in the buccal cavity, which helps develop formulations with a sustained-release effect.

- Neither chewed nor swallowed.

👩‍⚕️ Patient Education Points

- 📍 **Placement:** Right spot for absorption
- ⏰ **Time:** Let it dissolve completely
- 💧 **Saliva:** Don't generate too much
- 🚫 **Don't:** Chew, swallow, or drink water

💎 ***Clinical Pearl:*** *Perfect for cardiac emergencies - nitroglycerin SL can save lives by rapidly dilating coronary arteries*

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Rectal Route (PR)

- **A rectal route** allows for rapid and effective absorption of medications via the highly vascularized rectal mucosa (**Drug administration through the rectum via suppositories, enemas, or solutions**).

How it Works?



- Drug absorbed through rectal mucosa
- Partial first-pass metabolism (lower rectum bypasses liver initially)
- Rich blood supply allows good absorption



When to Use?

- Patient is vomiting or nauseous
- Unconscious or uncooperative patients
- NPO (nothing by mouth) orders
- Local treatment (hemorrhoids, constipation)

- rectally administered medications undergo passive diffusion and partially bypass the first-pass metabolism (50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration.

- Only about half of the drug absorbed in the rectum directly goes to the live

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PROS:

- Avoids first-pass metabolism (partially)
- Good when oral route unavailable
- Self-administration possible
- Local and systemic effects

CONS:

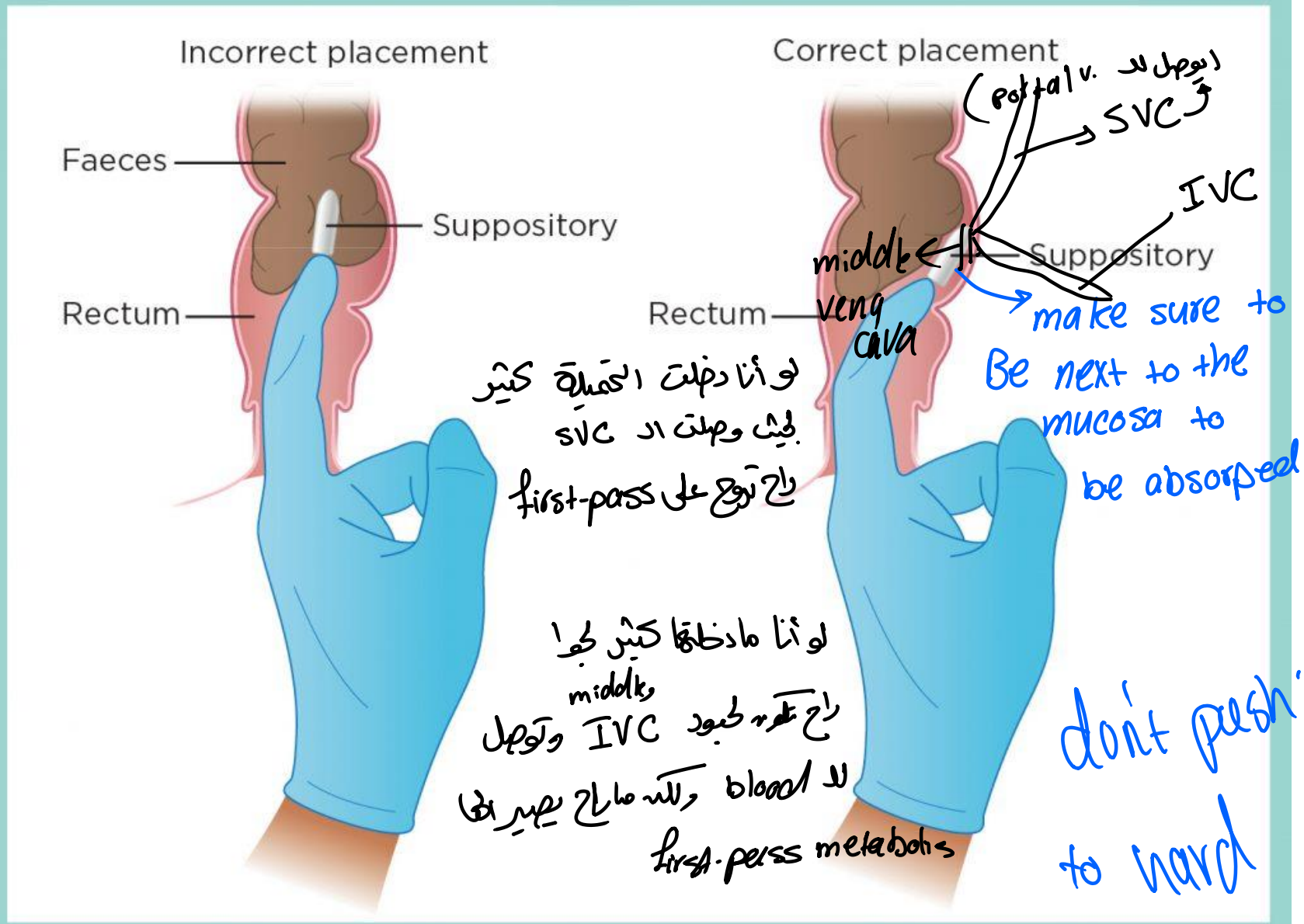
- Patient embarrassment/discomfort
- Unpredictable absorption
- Limited drug formulations
- Retention issues

- A relatively large amount of the drug can be administered.
- Safe and convenient for infants and the elderly in emergency situations, such as in infants having seizures when the intravenous route is unavailable.
- For drugs destroyed by the **acidic medium** in the stomach or metabolized by **pancreatic enzymes** (preventing destruction of the drug in the GI environment.)
- Absorption is not influenced by the ingestion of food or the rate of gastric emptying.
- Easy to terminate exposure
- Good for drugs affecting the bowel such as laxatives

- Some hydrophilic drugs like antibiotics and peptide drugs are unsuitable for rectal administration as they are not readily absorbed.
- Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. (Some drugs can cause rectal irritation and proclitic, leading to ulceration and bleeding).
- Absorption may be variable

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Fig 1. **Correct placement of suppositories**

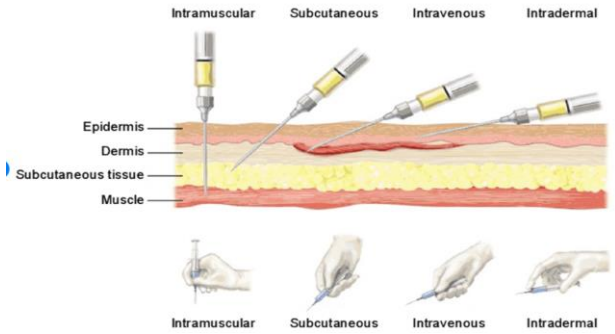


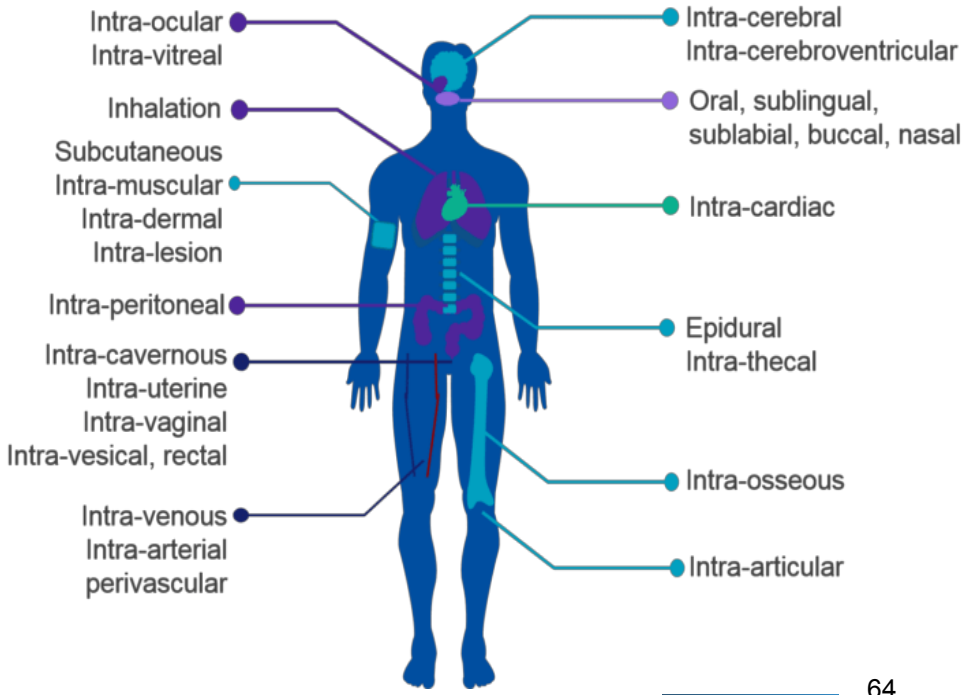
Parenteral Route

Parenteral (para = around; enteral = related to the GI tract) literally means around the GI tract. أي بس ماعدا الـ GIT

Introduces drugs directly across the body's barrier defenses into systemic circulation

- Intravenous (fastest delivery into the blood circulation)
- Intramuscular
- Subcutaneous
- Intradermal
- Intra-arterial
- Intrathecal
- Intraarticular





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Uses:

– Drugs that are **poorly absorbed** from GI tract (e.g. heparin).

– Drugs that are **unstable** in the GI tract (e.g. insulin)

– In **patients unable** to take oral medication (e.g. unconscious patients)

– Circumstances that require a **rapid onset** of action

- **Advantages:**

– Avoid first-pass metabolism or harsh GI environments.

– provides the most control over the actual dose of drug delivered to the body.

– Good bioavailability

– More rapid and more predictable than is administration by other routes.

– Advantageous in emergency therapy or if a patient is unconscious, uncooperative, or unable to retain anything given by mouth.

- **Disadvantages:**

– Irreversible

– Low convenience, may cause pain, fear

– local tissue damage, and infections.

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Intravenous (IV)



No absorption

"IV = Instant Victory over disease!"

Direct injection into a vein - the fastest route to systemic circulation

Real-World Example: Emergency epinephrine IV for severe allergic reaction - works in seconds!

Onset Time: IMMEDIATE (seconds)

Bioavailability: 100% (by definition)

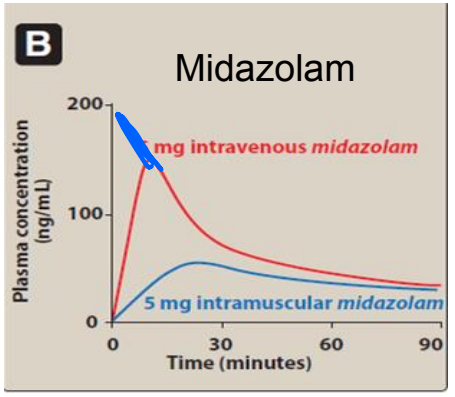
one dose ← جرعة واحدة أعطيتني الصف وخلص

- If the dose is administered over a few minutes, it is a **bolus** dose administered through a set directly into a vein.
- If administered over hours from a hanging bag, it is termed an **IV drip or infusion**.

مثلاً الـ antibiotics زي vancomycin — بطيئة – IV وبتاخد وقت عشان لو سريعة بتعمل reaction like allergy

Why ? To maintain effect of short-acting drugs (usually with an IV pump to control and help monitor the drip).

- IV injections: administered directly into the venous circulation, and highly vascular organs, such as the heart, lungs, liver, and kidney (rapidly perfused with the drug).
- Adverse reactions because of high concentrations of drug are attained rapidly in both plasma and tissues.
- To prevent reactions give a slow IV bolus injection or controlling an IV drip.
- Drugs with poor aqueous solubility may precipitate from solution and produce adverse reactions, including embolism.



خدرة

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✅ PROS:

- Immediate onset
- 100% bioavailability
- Precise dosing control
- For unconscious patients
- Large volumes possible

❌ CONS:

- Risk of infection
- Phlebitis/extravasation
- Requires skilled personnel
- More expensive
- Irreversible (can't "take back")

💎 ***Clinical Pearl:*** *The route of choice for emergencies, critical care, and when you need immediate, reliable drug effects*

⚠️ **DANGER:** Always check for air bubbles! Air embolism can be fatal. Double-check drug compatibility!

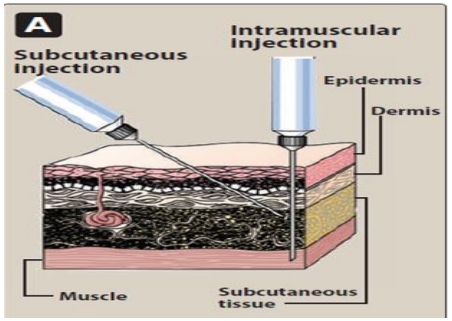
Pharm Logic Plus

Intramuscular (IM)

زاوية قائمة 90°

"IM = Into Muscle = Better than SC, not as fast as IV!"

Injection into muscle tissue for absorption into svstemic circulation



- Onset Time: 10-30 minutes
- Common Sites: Deltoid, vastus lateralis, ventrogluteal

مسافة كف يد تحت الكتف arm thigh من فوق hip

The deltoid muscle of **the upper arm** or the vastus lateralis muscle in the anterolateral aspect of the **middle or upper thigh** (1 or 2 mL).

The Gluteus muscles used for a hip injection(usually up to 5 mL). (Extreme caution to avoid injury to the sciatic nerve). عصب خرج النسا

Real-World Example: أكثر عصب بصير له damage

- Flu vaccine in deltoid muscle, or emergency epinephrine auto-injector in thigh
- Penicillin suspensions (procaine or benzathine penicillin G), are sometimes administered IM . Procaine penicillin G blood levels last for several days but benzathine penicillin G may last for a week.

mechanism يعني إيش الي بتعلم فيها في ج + هي نوع عالج في الدواء

Pharm Logic Plus

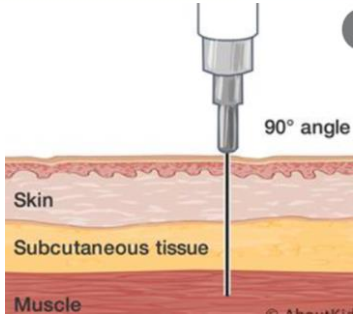
✅ PROS:

- Faster than oral/SC
- Good for depot preparations
- Bypasses first-pass metabolism
- Larger volumes than SC
- For uncooperative patients

❌ CONS:

- Painful injection
- Risk of nerve/vessel damage
- Requires trained personnel
- Variable absorption
- Not reversible

Very slow, sustained release with constant absorption from the IM site results if the drug is injected in a **solution in oil** or is **suspended** in various other repository vehicles rather than as a true aqueous solution= **Depot preparations**



💎 ***Clinical Pearl:*** *Perfect for vaccines and long-acting medications. Z-track technique prevents medication leakage and staining*

Pharm Logic Plus

Subcutaneous (SC/SQ)

🧠 "SUBcutaneous = SUB the skin = Slow and Steady!"

Injection into fatty tissue beneath the skin for slow, sustained absorption

⏰ **Onset Time: 15-60 minutes**

🎯 **Volume Limit: Usually ≤2 mL**

💡 **Real-World Example:** Daily **insulin** injections for diabetes management - predictable and steady absorption -**human growth hormone, heparin** .

✅ **PROS:**

- Self-administration possible
- Sustained absorption
- Less painful than IM
- Bypasses first-pass metabolism
- Suitable for frequent dosing

❌ **CONS:**

- Limited injection volume
- Slower onset than IM/IV
- Local irritation possible
- Variable absorption
- Not for emergency situations

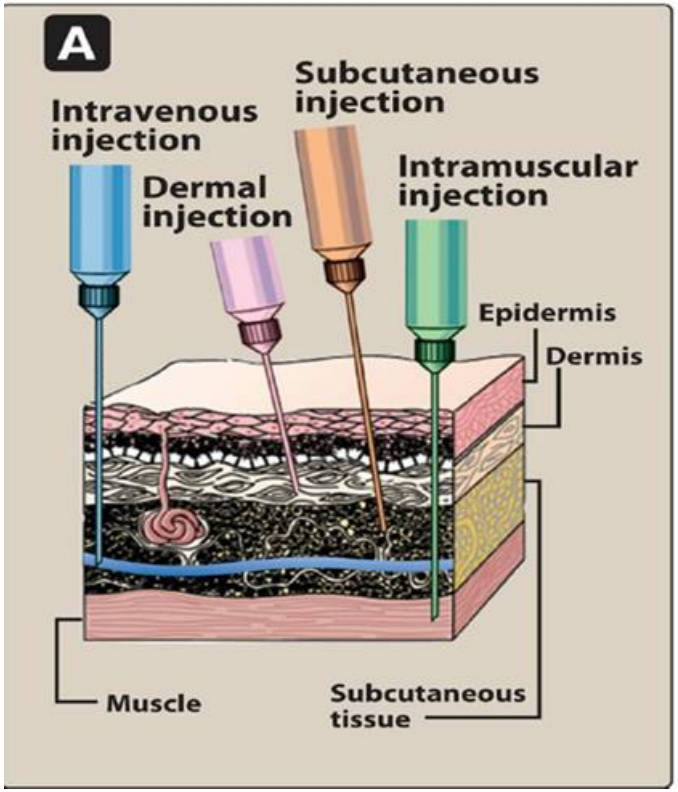
- Only for not irritating drugs; otherwise, severe pain, necrosis, and sloughing of tissue occur-SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection
- SC absorption of a drug (via simple diffusion) is sufficiently continuous and slow to provide a sustained input over a period of 4–12 h
- The incorporation of a vasoconstrictor agent in a solution of a drug to be injected SC delays absorption and prolongs the local effect (e.g., lidocaine with epinephrine injection).

💎 ***Clinical Pearl:*** *The diabetic's best friend! Rotate injection sites to prevent lipodystrophy (fatty tissue changes)*

Question #5

Which route has 100% bioavailability?

A) Oral
B) IM
C) IV
D) SC

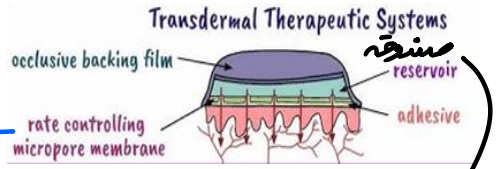


Answer: C) IV - Direct into bloodstream!

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Transdermal Route



هو نظام لخروج جرعة من الـ patch خلال وقت معين

موجود فيه المادة الفعالة زي النيكوتين

"TRANSdermal = TRANSport across the skin barrier!"

Drug delivery through intact skin for systemic absorption via patches or gels

Onset Time: 30 minutes - several hours (2 h)

microneedle يتوجد على الـ release بتعدد

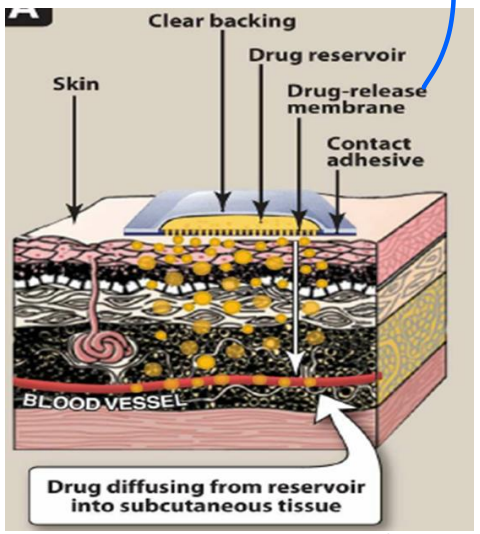
Duration: 12-72+ hours (depending on patch)

Real-World Example:

Nicotine patch for smoking cessation - steady delivery over 24 hours



مادة النيكوتين توصل للدم بمعدل ثابت لمدة 24 ساعة



لأن أشخاص المدخنين كانوا يتم معالجتهم على أساس أنهم مدمنين Nicotine patch فحاولوا يقلل من الجرعة شوية شوية ويعطوه الـ

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✅ PROS:

- Sustained drug delivery
- Avoids first-pass metabolism
- Improved patient compliance
- Easy to discontinue
- Non-invasive (no pain)

❌ CONS:

- Slow onset
- Skin irritation/sensitization
- Limited to potent drugs
- Variable absorption
- Expensive technology

I. Stable blood levels
III. Drug must be potent or patch becomes to large

* يستخدم للأدوية اللي عندها t½ طويلة نسبياً عشان يتم إعطاء الدواء بأكثر من مرة خلال اليوم في ال patch حل مناسب

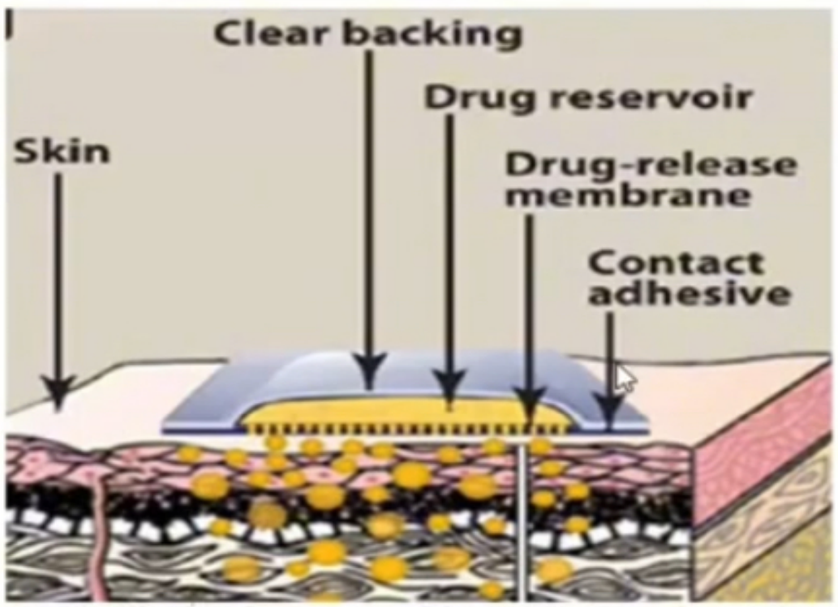
دواء قوي وعنده قدرة إنه يعمل therapeutic effect حتى لو تم تغيير ال patch

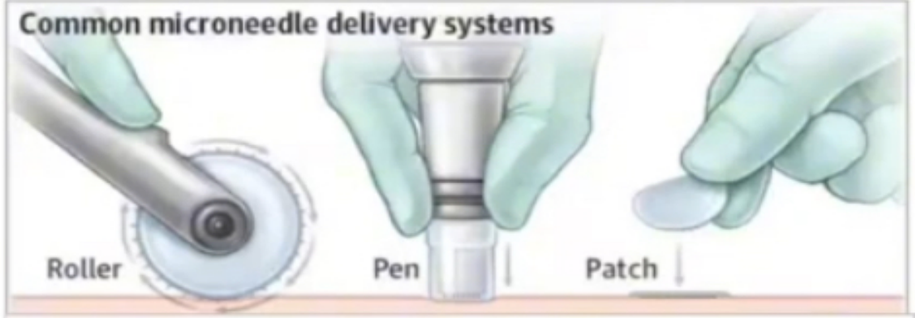
💎 **Clinical Pearl:** *Rotate patch sites to prevent skin irritation. Never cut patches - it disrupts controlled release!*

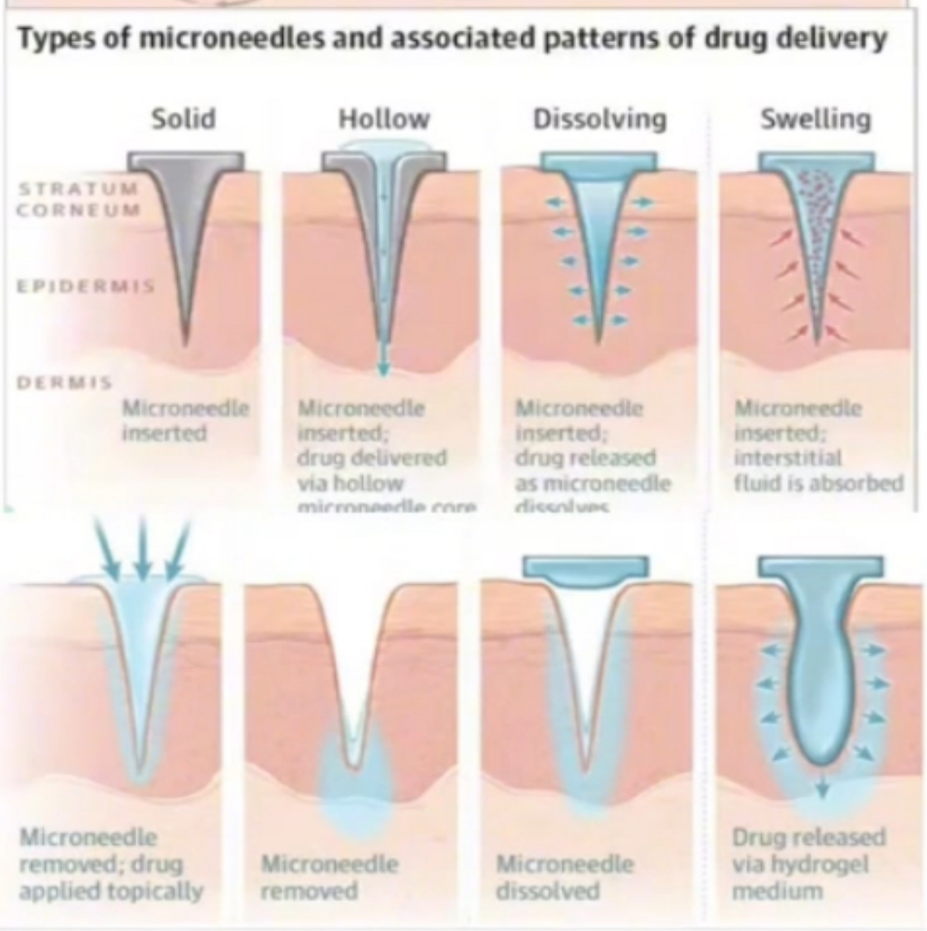
⚠️ **Remember:** Remove old patch before applying new one to avoid overdose!

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Compound	MW	Log $K_{o/w}$	mp (C)	
Estradiol	272.38	4.01	178.5	
Fentanyl	336.47	4.05	83	
Lidocaine	234.34	2.26	68	
Nicotine	162.23	1.17	− 79	
Nitroglycerine	227.09	1.62	13.5	
Scopolamine	303.35	0.98	59	
Testosterone	288.42	3.32	155	
Methotrexate	454	−2.200	195	100 %
Etanercept	150,000	−0.529	-	76%
Adalimumab	148,000	−0.441	-	64%







The controlled-release matrix or reservoir system in patches is engineered to maintain consistent drug flux across the skin, providing therapeutic advantages particularly for drugs with short half-lives or narrow therapeutic indices, such as fentanyl, nicotine, or hormone replacement therapies

الـ patches بتحل هذه المشكلة
وهي ما بتوصل للـ toxicity

في جرعة بالدواء تعطي الـ therapeutic level وجرعة أخرى
من نفس الدواء راح تسبب الـ toxicity الفرق
بين الجرعتين اسمه therapeutic indices و في أدوية الفرق
بين الجرعتين كثير قليل جيش أي زيادة في الجرعة راح تعمل
narrow therapeutic index يسبب toxicity

Q. When administering drugs via transdermal patches, we aim to avoid several types of fluctuations, What are they?

Plasma concentration fluctuations : primary concern. Transdermal patches designed to provide steady, continuous drug delivery over extended periods (typically 12-72 hours), avoiding the peaks seen with oral medications. This steady-state delivery helps maintain therapeutic drug levels within the narrow therapeutic window.

زي دواء scopolamine يستخدم ضد القيء بسبب السفر او الجو ويظل عدة ٣ أيام

Absorption rate fluctuations due to factors like skin temperature, moisture, application site characteristics, and patch adhesion quality. To minimize these, patches are designed with **rate-controlling membranes** and patients are instructed on proper application techniques, site rotation, and environmental considerations.

This ROA avoided

- **First-pass metabolism fluctuations** are completely avoided : transdermal delivery bypasses the gastrointestinal tract and liver
- **Dosing interval fluctuations** are eliminated : the patch provides continuous release, unlike oral medications that require multiple daily doses with potential timing variations.
- **Patient compliance fluctuations** are reduced: patches typically need changing only every few days rather than multiple daily doses

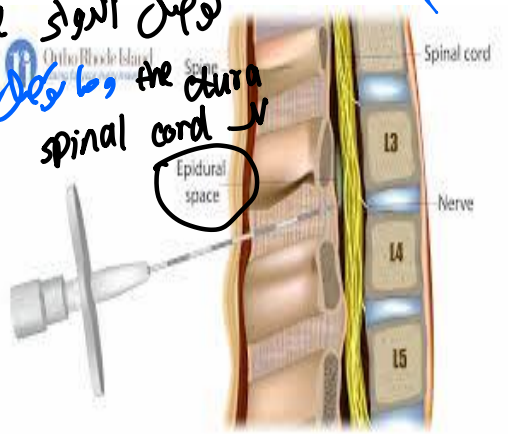
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Intraspinal injections

Administration of drugs directly into the vertebral column. It includes epidural and intrathecal injections.

Epidural injection

- Administered on or over the dura mater, and drug is delivered to the outside of the dura and not into the cerebrospinal fluid. Thus, the clinical effects are more localized to the spinal cord.
- Drugs can be delivered by a single bolus injection or as a continuous infusion.
- For example, morphine sulfate extended-release liposome injection (DepoDur) is a special liposomal dosage formulation injected into the epidural space.



DEPODUR® (morphine sulfate extended-release liposome injection) CII

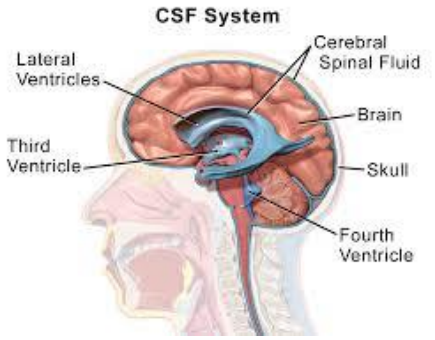
- DepoDur injection is a sterile, preservative-free suspension of multivesicular liposomes containing morphine sulfate present as a suspension in 0.9% sodium chloride solution.
- On epidural injection, the multivesicular liposomes release morphine systemically and into the intrathecal space through the meninges at a slow rate over a prolonged period.
- When given as a single dose 30 minutes pre operatively, DepoDur has produced persistent analgesia **for 48 hours postoperatively**.
- Its distribution, metabolism, and elimination is similar to that after delivery of other parenteral morphine formulations.

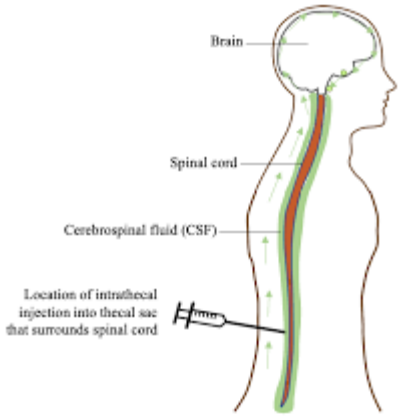
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Intrathecal/intraventricular IC

INTRATHECAL: Into spinal fluid

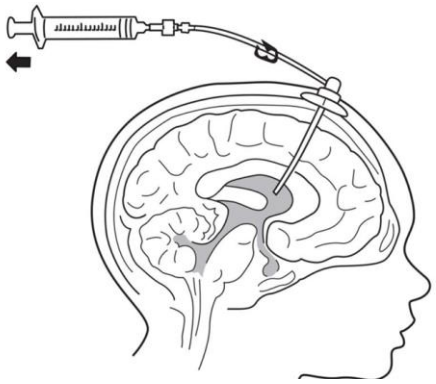
Example: Spinal anesthesia for surgery





- **Intrathecal injection** is the administration of drugs within the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles.

- When **lipid-insoluble drugs -**to treat some neurologic disorders- necessary to bypass the blood–brain barrier (BBB) and deliver drugs directly into the brain. This achieved by intrathecal administration, in which drugs are injected into the cerebrospinal fluid surrounding the spinal cord, or by direct injection of drugs into the brain by intra cerebroventricular injection, which is an invasive approach.



- Advanced primary or metastatic cancer pain, thoracic and lumbar pain, nerve root injuries, and neuropathic pain are treated with intrathecal injections and infusions of opioids, local anesthetics, clonidine, baclofen, and other drugs used for the treatment of chronic pain, cancer pain, and intractable spasticity.

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Inhalation Routes

🧠 "INhalation = IN the lungs = Instant help for breathing!"

Drug delivery through breathing - directly to lungs or systemic absorption

⏰ Onset Time: 1-5 minutes (local), 5-30 minutes (systemic)

🎯 Huge Surface Area: Lungs = size of tennis court!

تسعف المريض



💡 **Real-World Example**: Rescue inhaler (albuterol) and corticosteroids, such as fluticasone.

↳ Bronchodilation

for asthma attack - rapid bronchodilation in minutes!

بأي عداد IV

ممكن يستخدم للتخدير للأسنان للأطفال

✅ PROS: (Nitrous oxide) laughing gas

- Rapid onset for lung conditions
- Direct delivery to target organ
- Lower systemic side effects
- Large absorption surface
- Self-administration possible

❌ CONS:

- Requires proper technique
- Particle size critical
- Not suitable for all drugs
- Device dependence
- Respiratory irritation possible

- Drug effects are almost as rapid as those with IV bolus.
- Gases Drugs (some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation.
- This route is effective and convenient for patients with respiratory disorders (such as asthma or COPD), because the drug is delivered directly to the site of action, thereby minimizing systemic side effects.
- Include : Oral and Nasal

💎 ***Clinical Pearl:*** *"Shake, breathe out, seal lips, breathe in slowly and deeply, hold 10 seconds" - proper MDI technique saves lives!*

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Oral inhalation

- Delivery of drugs (the airways and the lungs) for local or systemic action



- Optimal route to manage asthma and COPD and for drugs to treat pulmonary diseases such as chronic bronchitis, respiratory infections, and cystic fibrosis. (mutation in chloride channel)
  مسؤولة عن secretion لـ mucus فبتتجمع في الـ lung
- Represents targeted drug delivery to the site of action- faster pharmacologic effects and reduced side effects.
- Noninvasive drug administration for the treatment of systemic diseases such as diabetes mellitus (e.g., inhaled insulin).
- The interest in the pulmonary delivery of drugs is due to the development of new inhalation devices that make possible the delivery of larger drug doses (milligram compared with microgram dosing) to achieve greater deposition efficiency than did older devices.

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Topical/Local Route



"TOPical = TOP of skin = Local action where you put it!"

Drug application to skin or mucous membranes for LOCAL effects

Onset Time: Minutes to hours (local effects)

لأنه الـ Blood supply في skin مختلف يقوم في ج

Goal: LOCAL treatment, minimal systemic absorption

Real-World Example: Applying sunscreen, antibiotic ointment on cuts, or steroid cream for eczema

- Eyes
- Ears
- Nose
- Lungs (inhalation)
- Rectum
- Vagina

PROS:

- Direct application to affected area
- Minimal systemic side effects
- Easy self-administration
- Non-invasive
- Wide variety of formulations

CONS:

- Limited to surface conditions
- Messy application
- Skin irritation possible
- Patient compliance issues
- Variable absorption



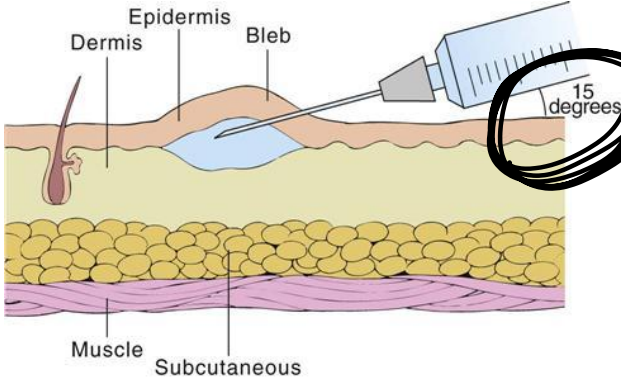
كمية الدواء اللي منبسحقها للبشرة الجافة

Clinical Pearl: *"Wet-on-wet, dry-on-dry" - use ointments for dry skin, lotions for moist conditions*

كمية الدواء فيه أكثر ∴ بلزم أكثر wet

Pharm Logic Plus

Intradermal (ID)



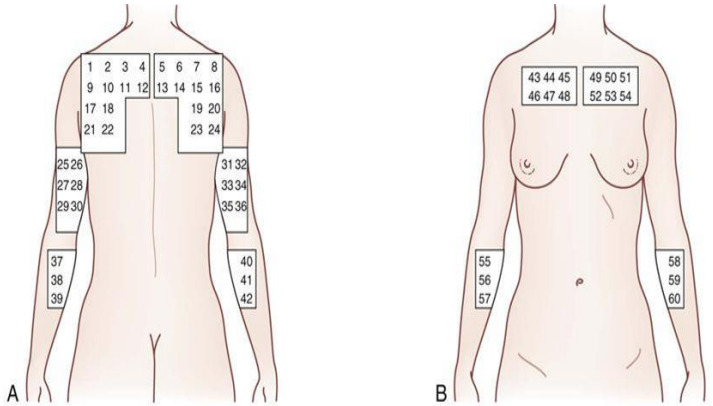
administered within the dermis layer of the skin (i.e., the upper layer of the skin just below the epidermis).

- ID injections are very small volume injections (0.1 mL) and are used to deliver drugs to produce local effects.

- ID injections may prolong the drug release sometimes for days.

- Examples of uses of ID delivery are injections for skin testing, antigen delivery to evaluate for allergic reactions, and sometimes administration of vaccines (e.g., influenza vaccine).

- ID injections may be made on any skin surface, but the site should be hairless and receive little friction from clothing.
- The upper chest, the scapular areas of the back, and the in of the forearms are the most commonly used areas



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Intra-articular injection

Administration of a drug into a joint.

Intra-articular administration of local anesthetics and adjuvants is an alternative method for postoperative analgesia.



Patients who have undergone ligament reconstruction and experience moderate to severe postoperative pain can benefit from intraarticular injection of ropivacaine and morphine through a catheter in the knee joint.

This approach decreases the need for supplemental IV morphine.

For the first few hours after intrasynovial or intraarticular injection, local discomfort in the joint may occur, but such discomfort is rapidly followed by effective relief of pain and improvement of local function.

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Nasal inhalation(Intranasal)



Administration of drugs directly into the nose.

NASAL: Through nasal mucosa (local or systemic)

Example: Nasal spray decongestants, flu vaccine nasal spray

local and systemic

مرضى السكري الآزب هرمون



diabetes insipidus

↑ نفس ↑ العراقي السكري

↓ Polyuria





- **Real-World Examples** include :
  - Nasal decongestants, such as oxymetazoline,
  - Corticosteroids, such as mometasone furoate.
  - Desmopressin is administered intranasally

in the treatment of diabetes insipidus.

Pharm Logic Plus

Question #6

The nurse is preparing to administer a transdermal patch to a patient and finds that the patient already has a medication patch on his right upper chest. What will the nurse do?

A. Remove the old medication patch and notify the health care provider.
B. Apply the new patch without removing the old one.
C. Remove the old patch and apply the new patch in the same spot.
D. Remove the old patch and apply the new patch to a different, clean area.

ANS: D

Transdermal drugs should be placed on alternating sites, on a clean and non irritating area, and only after the previously applied patch has been removed.

Additional Important Routes

OPHTHALMIC: Eye drops/ointments for local eye treatment

Example: Antibiotic drops for conjunctivitis

OTIC: Ear drops for local ear treatment

Example: Antibiotic drops for ear infection

INTRAOSSEOUS (IO): Into bone marrow for emergency access

Example: Emergency IV access when veins can't be found

Pharm Logic Plus

Route Comparison

Route	Bioavailability	Onset	First-Pass Effect	Main Uses
Oral	Variable	30-60 min	Yes	Most medications
IV	100%	Immediate	No	Emergency, precise dosing
IM	High	10-30 min	No	Vaccines, depot forms
SC	High	15-30 min	No	Insulin, heparin
Sublingual	High	1-5 min	No	Nitroglycerin

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Route Selection Decision Tree

🚨 EMERGENCY SITUATION?

→ YES: IV (fastest) or IM (if no IV access)

→ NO: Continue below ↓

💊 CAN PATIENT SWALLOW SAFELY?

→ YES: Oral route (most convenient)

→ NO: Consider IV, IM, SC, rectal, or transdermal

🎯 LOCAL vs SYSTEMIC EFFECT NEEDED?

→ LOCAL: Topical, ophthalmic, otic, nasal

→ SYSTEMIC: IV, IM, SC, oral, transdermal

⏰ HOW QUICKLY DO YOU NEED IT TO WORK?

→ IMMEDIATELY: IV (seconds)

→ QUICKLY: Sublingual (1-3 min), IM (10-30 min)

→ MODERATELY: SC (15-60 min), Oral (30-60 min)

→ SUSTAINED: Transdermal (hours to days)

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Question #7

What is the Best route for unconscious patient?

A) Oral

B) Sublingual

C) IV

D) Topical

Answer: C) IV - Patient can't swallow!

Pharm Logic Plus

Question #8

Fastest onset for chest pain?

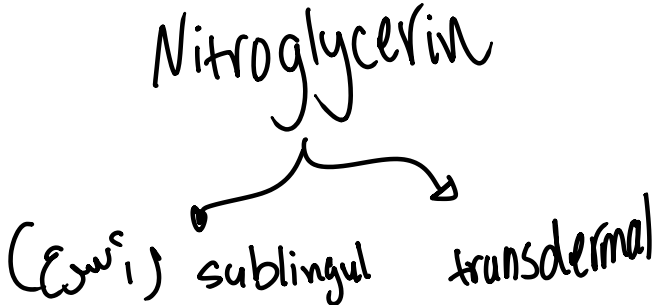
A) Oral

B) Sublingual

C) IM

D) Transdermal

Answer: B) Sublingual - Under tongue, 1-3 minutes!



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ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high molecular weight proteins and peptide drugs	• Unsuitable for oily substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self-administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)

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Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic and have poor oral bioavailability • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route
Inhalation	• Systemic absorption may occur; this is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs: lower doses used compared to that with oral or parenteral administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed

Figure 1.5
The absorption pattern, advantages, and disadvantages of the most common routes of administration.

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Contraindications of ROA

Each medication administration route has unique contraindications:

An oral medication route is contraindicated for patients who cannot tolerate oral drugs, such as those who have altered mental status or have nausea or vomiting

عند المريض مشاكل عقلية أو صرع

A rectal route is contraindicated in patients with active rectal bleeding or diarrhea or after a recent rectal or bowel surgery.

An intramuscular route is contraindicated in an active infection or inflammation at the site of drug administration, myopathies, muscular atrophy, thrombocytopenia, or coagulopathy.

A subcutaneous route is contraindicated in an actively infectious or inflamed site. Doses that require to be injected more than 1.5 mL at once should be avoided.

An intranasal medication is contraindicated in patients with nasal trauma, anatomic obstruction, the presence of a foreign body, or copious mucous or bleeding.

Inhaled drug is contraindicated in patients with airflow obstruction.

لو الهدف كان من الدواء لو كان systemic والغرض منه Local

فتح الشعيبات

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Clinical Scenarios - Route Detective!

Determine the Best Possible Route and Why?

Scenario 1: 65-year-old patient having chest pain

Scenario 2: Unconscious trauma patient

Scenario 3: Child with severe asthma attack

Scenario 4: Post-surgical patient with nausea/vomiting

Scenario 1: 65-year-old patient having chest pain
Best Route: Sublingual nitroglycerin
Why: Rapid onset, bypasses first-pass metabolism

Scenario 2: Unconscious trauma patient
Best Route: IV or intraosseous
Why: Immediate access, 100% bioavailability

Scenario 3: Child with severe asthma attack
Best Route: Inhalation (nebulizer/inhaler)
Why: Direct delivery to lungs, rapid bronchodilation

Scenario 4: Post-surgical patient with nausea/vomiting
Best Route: IV, IM, or rectal
Why: Patient can't keep oral medications down

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Summary

- Thorough understanding of pharmacologic principles is essential for safe, quality practice.
- Application of principles enables the practitioner to provide safe and effective drug therapy.

💎 Clinical Pearls to Remember

⚡ ***Speed Ranking:*** *IV (seconds) > Sublingual (1-3 min) > IM (10-30 min) > SC (15-60 min) > Oral (30-60 min)*

🎯 ***Bioavailability:*** *IV (100%) > IM/SC > Sublingual > Oral (variable due to first-pass)*

🆘 ***Emergency Routes:*** *IV first choice, then IM, then intraosseous if no IV access*

🤢 ***Nausea/Vomiting:*** *Skip oral route! Use IV, IM, SC, rectal, or transdermal*

👶 ***Pediatric Tips:*** *Rectal good for kids, smaller volumes for IM/SC, taste matters for oral*

📱 ***Patient Education:*** *Proper technique is CRITICAL for inhalers, eye drops, and self-injections*

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🎯 Take-Home Messages

1. 🎪 **Right Route for Right Situation**
   Match the route to patient needs, not convenience!

1. ⚡ **Speed vs Safety Balance**
   Faster isn't always better - consider risks!

3.🎓 Patient Education is KEY
Proper technique = therapeutic success!

4.⚠️ Always Have a Backup Plan
What if your first choice doesn't work?

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"Drug Journey“ Assignment

Follow one **single drug** (like acetaminophen)with one **dosage form (tablets)** through its entire journey. From mouth to bloodstream (PK). Make sure your Journey has the minimum required rubric information

Meet Acetaminophen (Tylenol)!
Our hero needs to stop a terrible headache...

Route 1 - ORAL Journey:
Mouth → Stomach → Small intestine → Portal circulation → Liver (first-pass) → Systemic circulation → Brain
Time: 30-60 minutes, Some drug lost in liver

Route 2 - IV Journey:
Vein → Heart → Systemic circulation → Brain
Time: Seconds, 100% reaches target!

Route 3 - Transdermal Journey:
Skin surface → Through skin layers → Capillaries → Systemic circulation → Brain
Time: Hours, but steady and sustained!

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Build Your Route Memory Palace

🧠 **Picture a HOUSE with different rooms for different routes!**

🚪 **FRONT DOOR (Oral):** Most common entrance - everyone comes through here first!

🪟 **WINDOWS (Transdermal):** Slow but steady entry through the "skin" of the house

🚨 **EMERGENCY ENTRANCE (IV):** Direct, immediate access when seconds count!

💨 **VENTILATION (Inhalation):** Air ducts bring medication directly to where needed

🚪 **BACK DOOR (Rectal):** Alternative entrance when front door is blocked!

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Formative Assessment Opportunities

- **Exit tickets**: "One thing you learned,
- one question you have"

- **Peer teaching**: "Explain first-pass effect to your neighbor"

- **Quick sketches**: "Draw how a drug gets from mouth to bloodstream"

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Questions??
Thoughts?



Remember: The best route is the one that gets the right drug to the right place at the right time safely! 🎯

💊 → 🎯 → 😊

Thank you



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General Pharmacology

"Understanding how drugs work to heal your body"



Esmaa Motawe

Interdisciplinary PhD in Pharmacology and Toxicology/ Pharmaceutical Sciences

Spring 2025 | AUG

Pharm Logic Plus

Learning Objectives



Journey of Discovery:

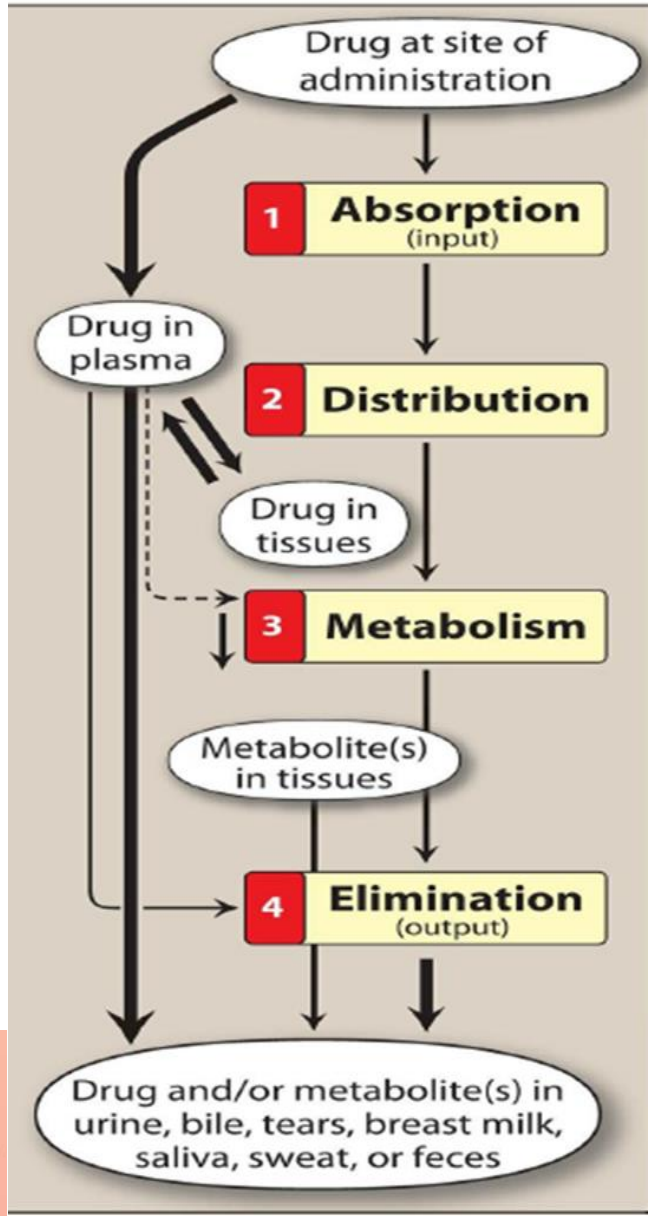
From drug molecules to healing effects

- Understand the four ADME processes and their clinical significance
- Master key pharmacokinetic equations and their applications
- Master CYP450 enzyme system and drug interactions
- Analyze drug metabolism pathways and enzyme systems
- Apply pharmacokinetic principles to clinical scenarios
- Calculate dosing regimens and steady-state concentrations based on ADME parameters

PHARMACOKINETICS



Course Mission: Master the journey of drugs through your body: from administration



Key Concept

ADME determines how drugs move through the body from administration to elimination, affecting efficacy and safety.

Pharmacokinetics PK

What the Body Does to the Drug

Pharmaco (drug) + **Kinesis** (movement) = Study of drug movement through the body

🎯 Clinical Relevance:

- ❖ Design optimal dosing regimens
- ❖ Predict drug interactions
- ❖ Adjust doses for patients
- ❖ Understand drug safety profiles

تحديد هل لازم أعطي المريض الدواء كل ٨ ساعات
ولا كل ٩ ساعات

What is Pharmacokinetics?

Pharmacokinetics describes **what the body does to the drug** from administration to elimination

PK determines:

- **Onset** of drug action
- **Intensity** of drug effect
- **Duration** of drug action

Helps clinicians decide:

- Route of administration
- Dose and frequency
- Duration of treatment

- "**Why does** your grandmother's heart medication **work** perfectly at 8 AM but barely touch her chest pain by evening—even though she takes the exact same dose?“

أخذت حبة دواء وانفتح عيناي

حبة دواء لم تؤثر

- **"The difference between a life-saving drug and expensive urine often comes down to a few millimeters of intestinal wall and the right pH.“**

- "That morning coffee you grabbed before taking your antibiotic didn't just wake you up—it might have just turned your medication into a very expensive placebo.“

- "**Two identical pills, same drug, same dose—one saves a patient's life while the other does absolutely nothing. The only difference? What they ate for breakfast**.“

- "**Your patient's genetics can turn a standard dose into either a toxic overdose or a therapeutic failure, and you won't know which until you understand the hidden journey every drug takes through the human body."**

The ADME Journey

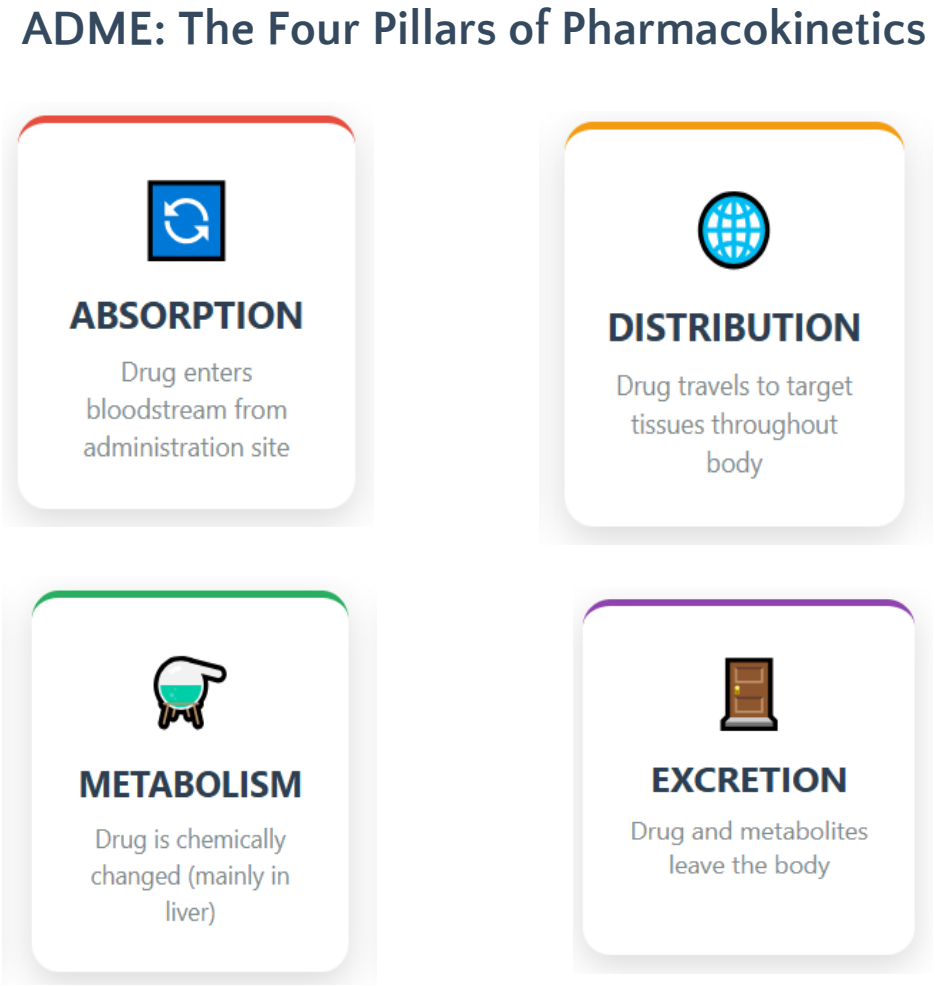
Memory Trick: "All Drugs Must Exit"

Absorption
- Drug enters systemic circulation
- Affected by route of administration
- First-pass metabolism consideration

Distribution
- Drug spreads throughout body
- Volume of distribution (Vd)
- Protein binding effects

Metabolism
- Chemical modification of drug
- Phase I & II reactions
- CYP450 enzyme system

Excretion/Elimination
- Drug removal from body
- Primarily via kidneys
- Half-life and clearance



Why Study ADME?

Understanding ADME is crucial for:

- Predicting drug efficacy and safety
- Designing optimal dosing regimens
- Understanding drug interactions
- Personalizing medicine for patients
- Developing new pharmaceutical compounds

كل مريض حسب كيف ظروف جسمه
يتم وصف الدواء له

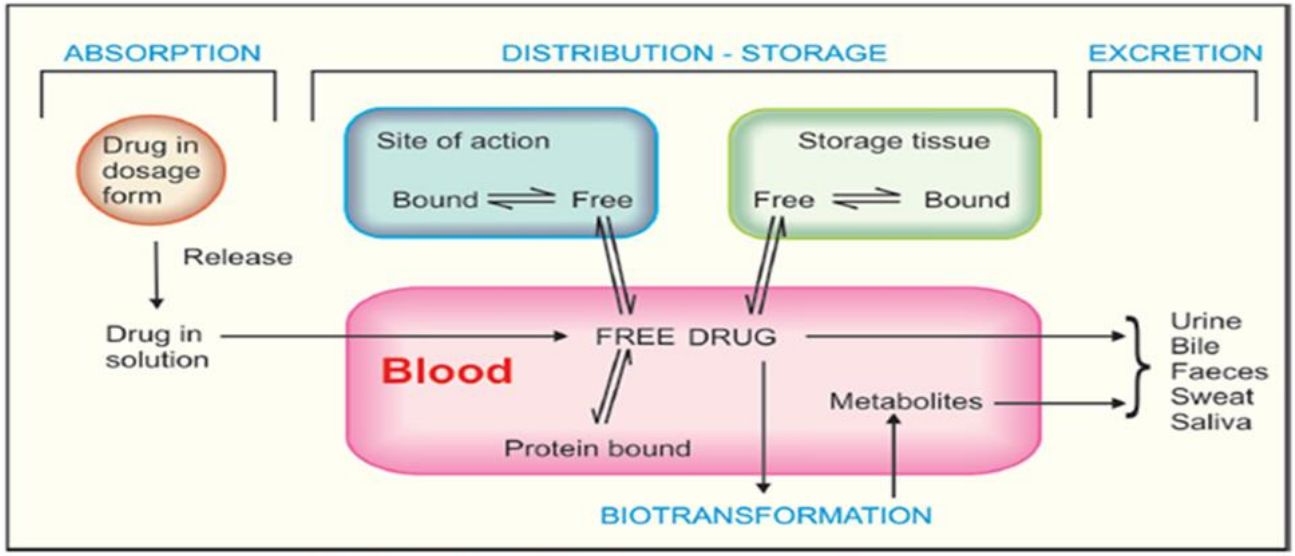
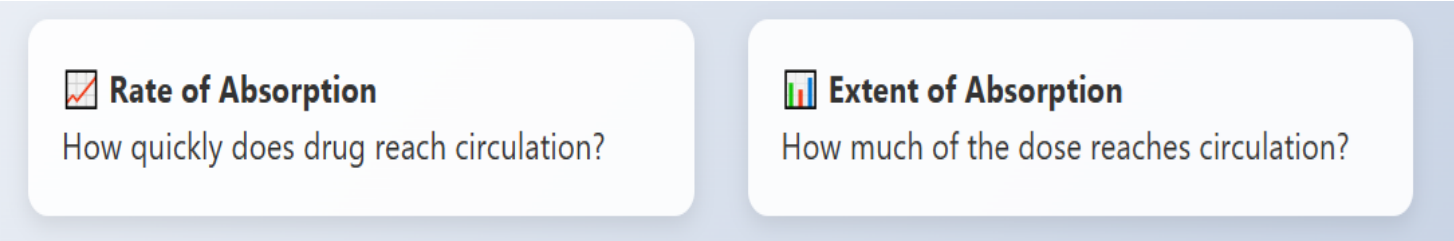


Fig. 2.1: Schematic depiction of pharmacokinetic processes

ABSORPTION

Transfer of drug from administration site to bloodstream except drugs applied for local effect

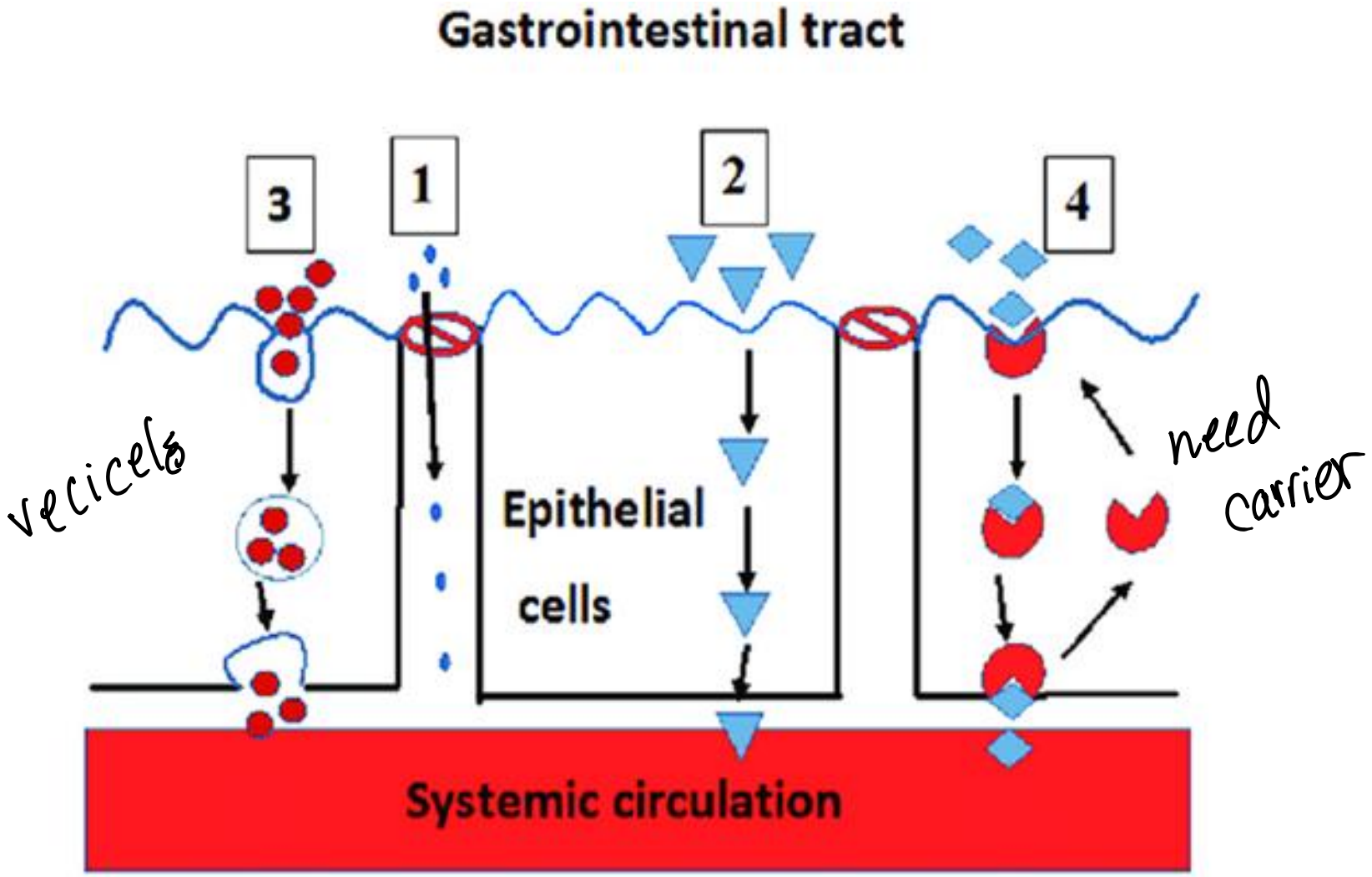


Routes of administration other than intravenous may result in partial absorption and lower bioavailability

Headache Pain

Real-world Example: Taking Tylenol (acetaminophen) by mouth - the tablet must dissolve in your stomach and the drug must cross into your bloodstream to work!

How Drugs Cross Membranes?



Passive Diffusion

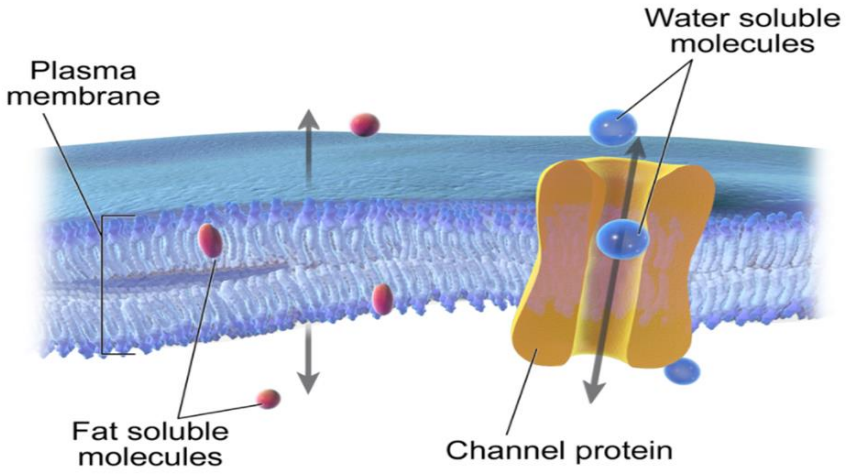
- Most common
- Down concentration gradient
- No carrier/energy required
- Not saturable (no carrier and low structural specificity)

High → Low

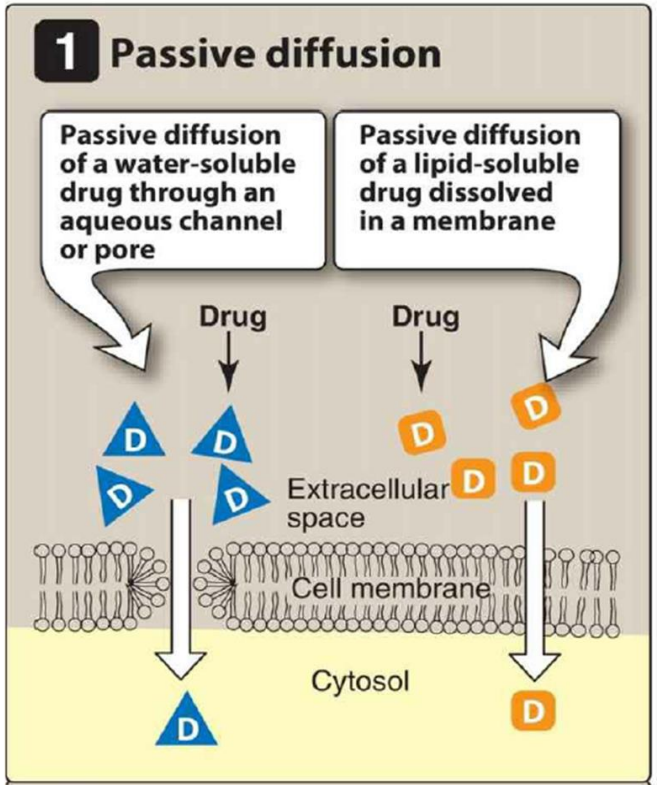
Passive Diffusion

Most common mechanism

- High → Low concentration
- No energy required
- Lipophilic drugs



Diffusion Across the Plasma Membrane

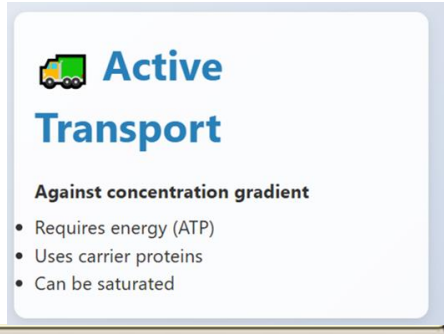


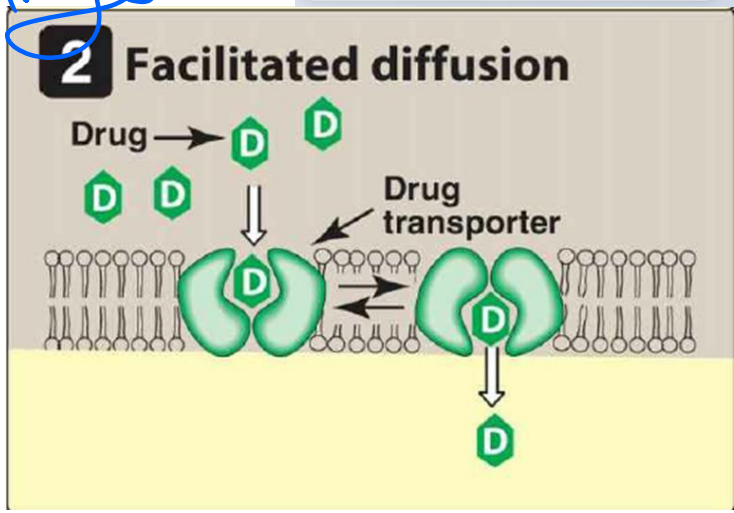


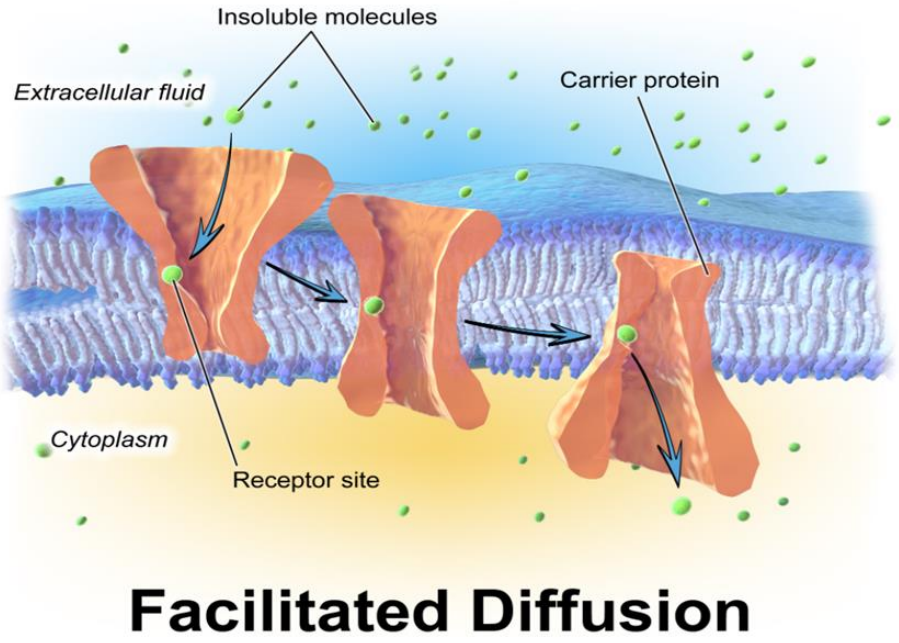
Facilitated Diffusion

- Uses carrier proteins
- No energy is required
- Down concentration gradient
- Can be saturated
- Can be inhibited

specificity ainsi drugs ...







Facilitated Diffusion

- Carrier proteins undergo conformational changes, allowing the passage of molecules into the cells.
- May be inhibited by compounds that compete for the carrier.

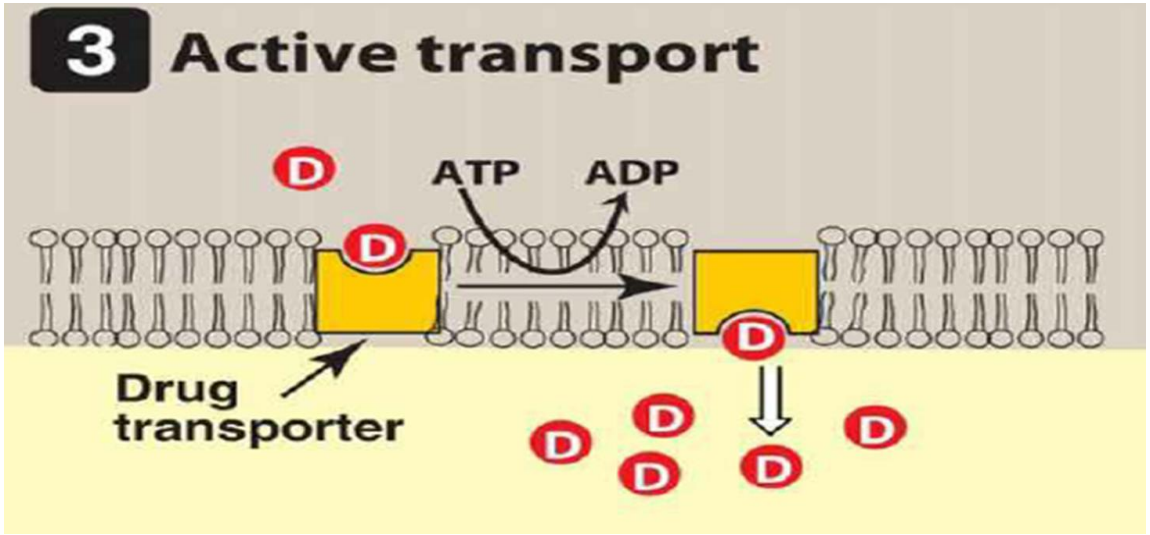
Active Transport

Facilitated Diffusion

Carrier-mediated

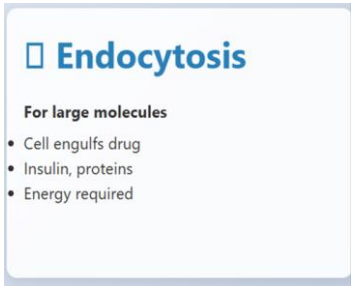
- With concentration gradient
- No energy required
- Uses transporters

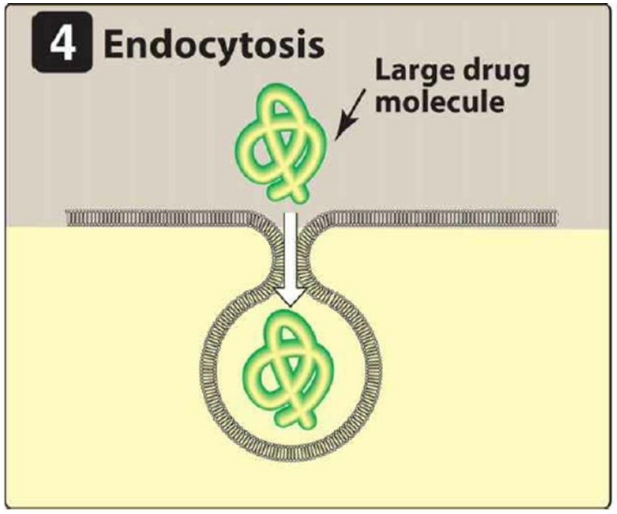
- Against concentration gradient
- Requires energy (ATP)
- Specific carrier proteins that span the membrane.
- Saturable process
- Highly Selective
- competitively inhibited by other cotransported substances.



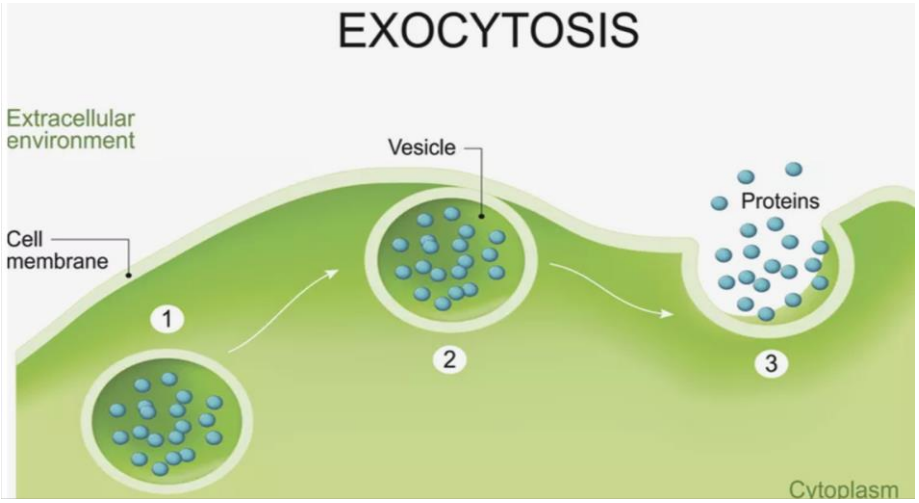
Endocytosis/Exocytosis

- For very large molecules
- Cell membrane engulfment
- Example: Vitamin B12





- Exocytosis is the reverse of endocytosis.
- Many cells use exocytosis to secrete substances out of the cell
- Certain neurotransmitters (norepinephrine) are released by exocytosis.



Factors Affecting Absorption

- **pH Effect:** Acidic drugs better absorbed in stomach, basic drugs in intestine

- **Blood Flow:** More blood flow = faster absorption

- **Surface Area:** Small intestine > stomach (due to villi)

- **Contact Time:** Longer contact = more absorption

- **P-glycoprotein:** Pumps drugs out of cells (drug efflux)

⚠ **Clinical Pearl:** Food can increase or decrease drug absorption depending on the drug. Always check if medication should be taken with or without food!

Physicochemical Factors = Drug Properties

dosage form الها علاقة في ال

- **pH:** Affects ionization state
- **Lipophilicity:** Membrane permeability — كل ما كان Lipophilic راح يعبي ال membrane
- **Molecular size:** Larger = slower
- **Formulation:** Tablet vs solution

solid ال لازم أول اشي يذوب بعدين يصير له Absorption → distribution

بسوله راح يصير له Absorption

Physiological Factors = Environment

- **Blood flow:** ↑ flow = ↑ absorption
- **Surface area:** Small intestine > stomach — كل ما زاد ال surface area راح يزيد ال absorption
- **Contact time:** GI motility affects this
- **Membrane thickness:** Barrier to diffusion

ولازم الدواء يروح من ال stomach لل small intestine

Gastric impeting هاد الخطوة اسمها

Clinical Pearl: Food can increase, decrease, or have no effect on drug absorption - always check specific drug interactions with meals.

pH and Drug Ionization

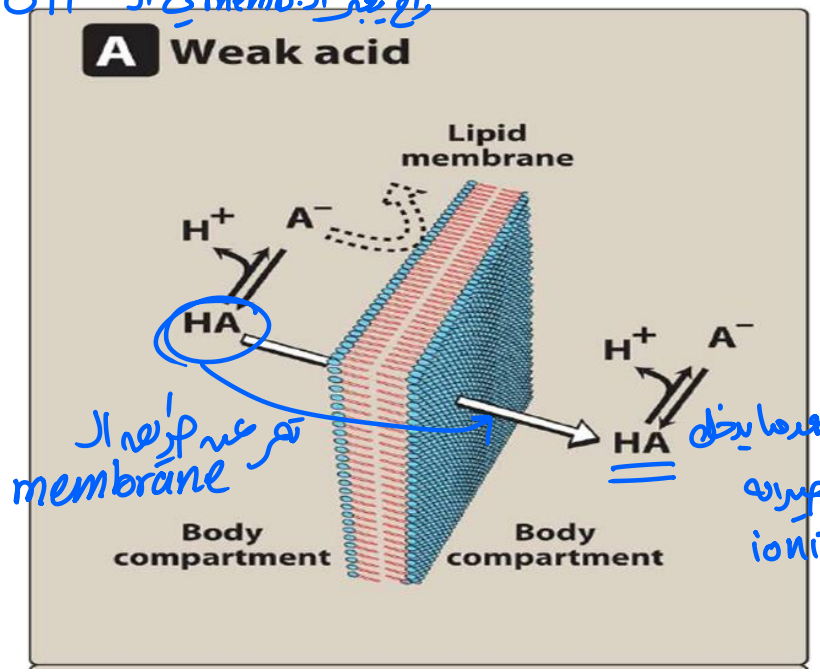
Henderson – Hasselbalch Principle : Uncharged drugs cross membranes more readily

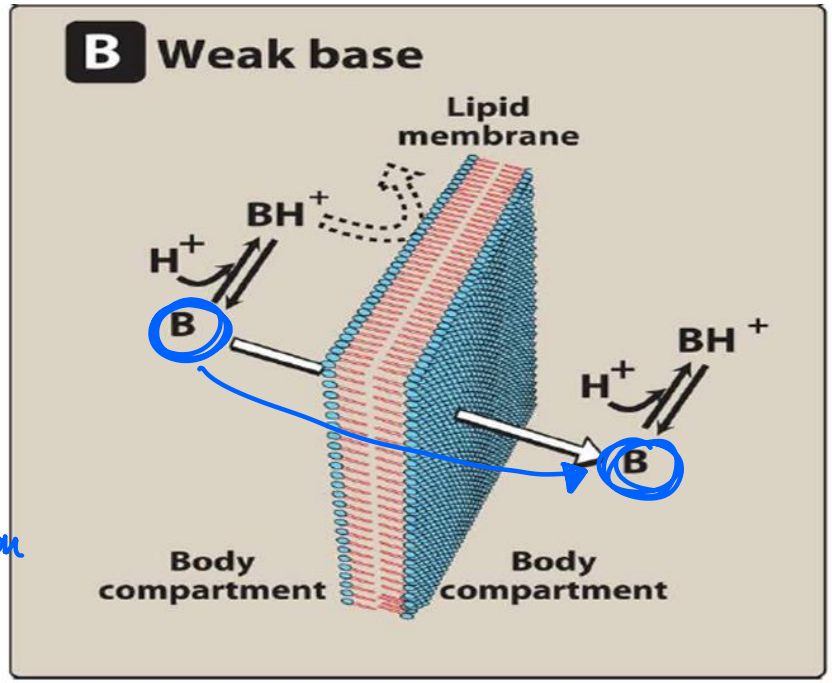
- **Weak acids (Aspirin):** Better absorbed in acidic environment (stomach)
- **Weak bases (Morphine):** Better absorbed in basic(alkaline)environment (intestine)

AH = acid B = base

$AH \rightleftharpoons A^- + H^+$ (ionized)

$B + H^+ \rightleftharpoons BH^+$ (ionized)





PH of the environment

Pka of the drug

Henderson-Hasselbalch Equation

$$pH = pK_a + \log([A^-]/[HA])$$

Key Point: Drug ionization depends on environmental pH and drug pKa

Drug Type	Best Absorbed In	Example Location
Weak Acids (AH)	Acidic environment	Stomach (pH 2.5)
Weak Bases (B)	Basic environment	Intestine (pH 8.0)

pH : at the site of absorption (measurement for the media/ environment)

Pka : ionization constant represents the strength of the weak acid or base,

The pKa is a measure of the strength of the interaction of a compound with a proton.

The lower the pKa of a drug, the more acidic it is.

The higher the pKa , the more basic is the drug.

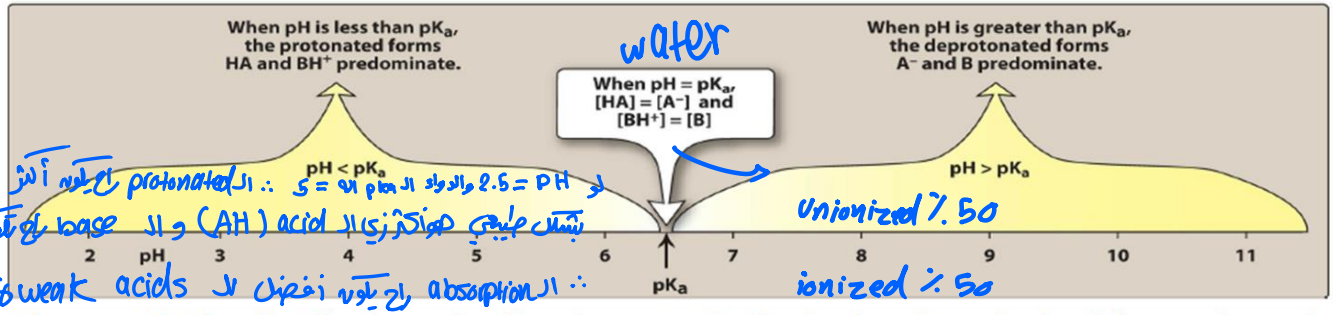


Figure 1.8 The distribution of a drug between its ionized and nonionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

Blood Flow

- Intestines > stomach (better absorption)
- Shock reduces cutaneous blood flow (SC absorption)

Surface Area

- Intestine has 1000× more surface area than stomach
- Brush border with microvilli increases absorption

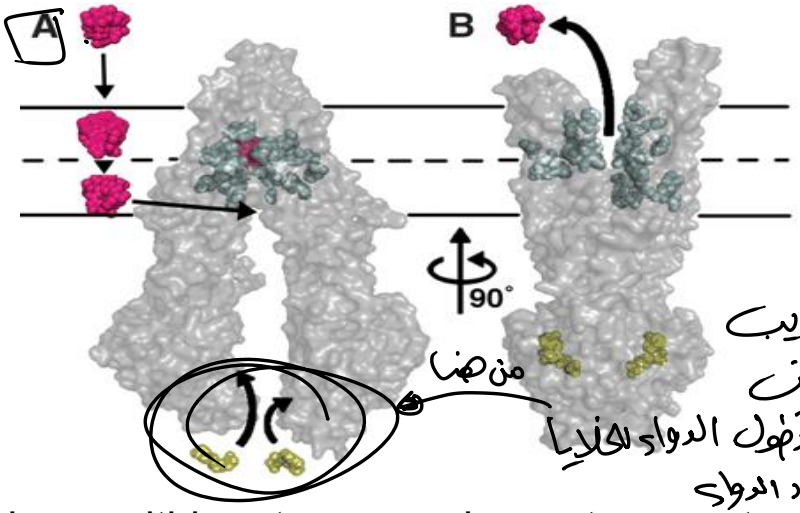
Contact Time

- Diarrhea decreases absorption time
- Food delays gastric emptying (delaying transport to the intestine delays absorption)

Membrane Thickness

Clinical relevance: Shock states reduce peripheral absorption (IM, SC routes less reliable).

P-glycoprotein



The P-glycoprotein is a multidrug transmembrane transporter protein that transports medications across cell membranes. Functions of this protein include

(A) Pumping drugs into the urine for excretion

(B) Transport of drugs into liver hepatocytes

(C) Transport of drugs into fetal circulation for fetal treatment

(D) Transport of drugs from the intestinal lumen to the circulation

(E) Transport of drugs from the bloodstream into brain cells

The answer is A: Pumping drugs into the urine for excretion.
The P-glycoprotein is a multidrug transmembrane transport protein that transports medication across cell membranes. In the kidney, responsibilities include pumping drugs into the urine for excretion.
(B) This protein excretes drugs into bile for excretion in feces.
(C) This protein transports drugs out of fetal circulation via the placenta into the maternal circulation.
(D) This protein transports drugs from the circulation into the intestinal lumen.
(E) This protein transports blood out of the brain cells to protect them from drug toxicities.

Bioavailability (F %)

The rate and extent to which the active ingredient or active moiety is absorbed and becomes available at the site of action.

The fraction of administered drug that reaches systemic circulation unchanged

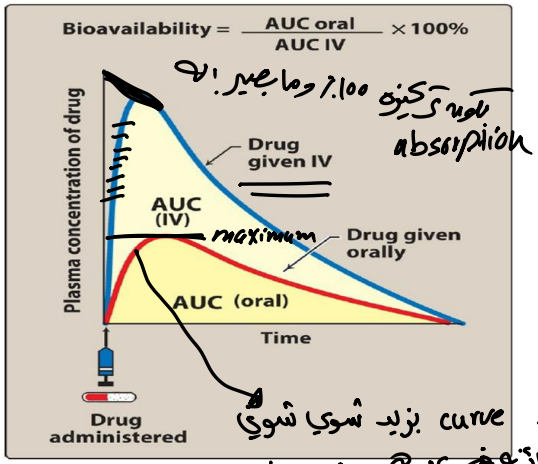
$$\text{Bioavailability (F)} = (\text{Amount absorbed} / \text{Amount administered}) \times 100\%$$

Clinical Example

If 100 mg given orally → 70mg absorbed unchanged

Bioavailability (F) = 70/100 = 0.7 or 70%

Route	Bioavailability	Why?
IV	100%	Goes directly into blood
Oral	Variable	Must be absorbed + first-pass effect
Sublingual	High	Bypasses first-pass metabolism



Absolute Bioavailability = (AUC oral / AUC IV) × 100%

Relative Bioavailability = (AUC $_{\text{test formulation}}$ / AUC $_{\text{reference}}$) × 100%

Bioavailability & First Pass Effect

Bioavailability (F) = (AUC oral / AUC IV) × 100%

Bioavailability Factors

- Extent of absorption
- First-pass metabolism
- Drug formulation
- GI physiology
- Drug interactions
- Solubility of the drug
- Chemical instability

Factors Reducing Bioavailability:

- **First-pass metabolism:** Liver metabolizes drug before reaching circulation
- **Drug solubility:** Too hydrophilic or lipophilic
- **Chemical instability:** Degradation in GI tract
- **Drug Formulation factors:** Particle size, coating, excipients

First-Pass Metabolism

- Hepatic metabolism before systemic circulation
- Can significantly reduce bioavailability
- Bypassed by IV, IM, SC, sublingual routes
- Individual variation in liver enzymes

Anything affects Absorption well affect Bioavailability

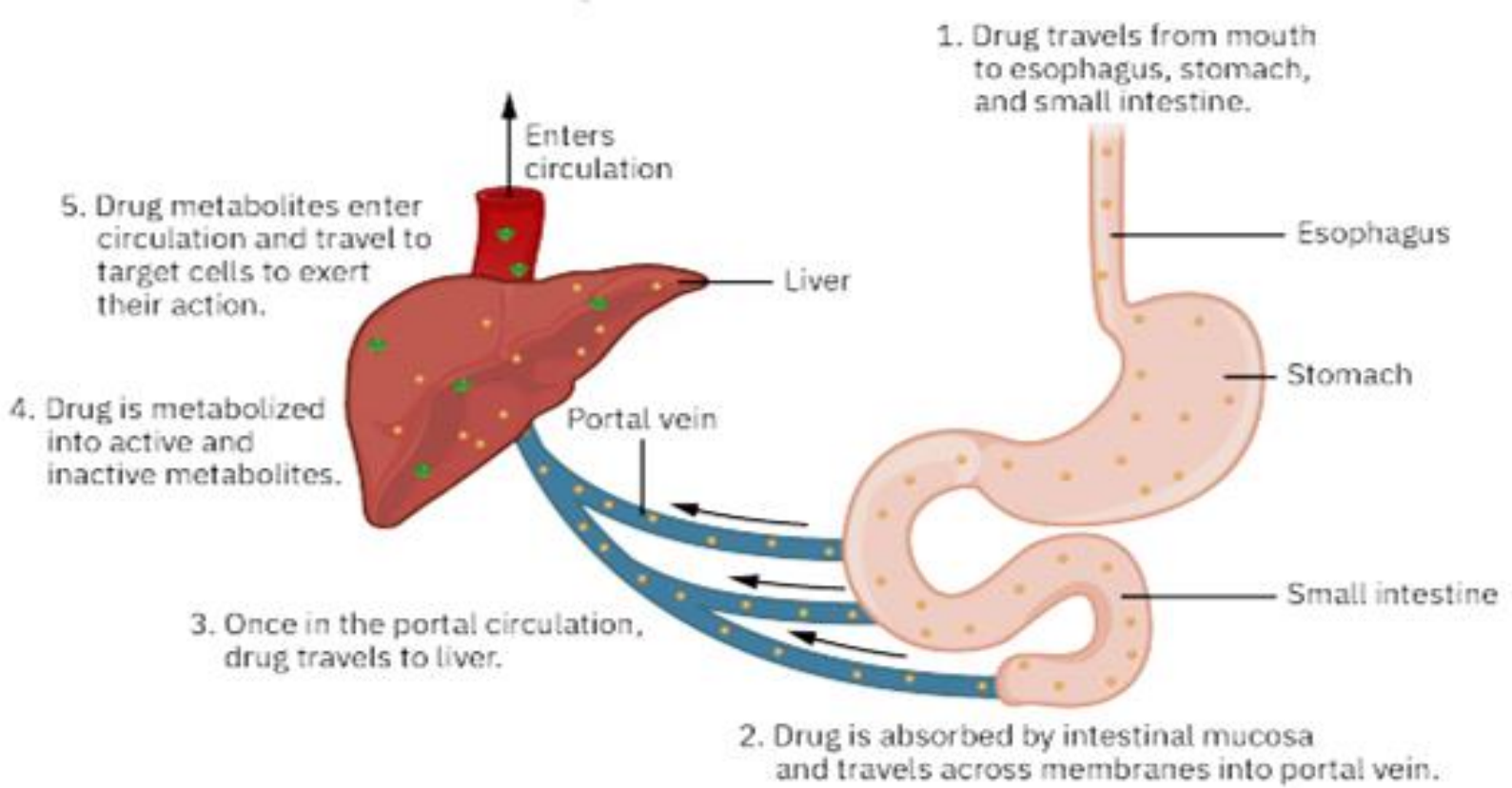


FIGURE 2.3 This figure illustrates how a drug is processed by the body in the first-pass effect. This process prepares a portion of the ingested medication for therapeutic use by the body. (attribution: Copyright Rice University, OpenStax, under CC BY 4.0 license)

First pass effect: Large proportion of a drug is chemically changed into inactive metabolites by the liver.

- Much smaller amount will be bioavailable.

Clinical Significance: Drugs with high first-pass metabolism need higher oral doses or alternative routes

High First-Pass Metabolism Examples:

- **Nitroglycerin:** >90% eliminated (use sublingual/transdermal)
- **Propranolol:** Significant first-pass effect
- **Morphine:** Extensive hepatic metabolism

🎯 High First-Pass Drugs (Low Oral Bioavailability)

- **Propranolol:** ~25% bioavailability
- **Morphine:** ~25% bioavailability
- **Nitroglycerin:** <5% bioavailability (hence sublingual route)
- **Lidocaine:** Extensive first-pass (IV only for systemic effects)

Bioavailability کم به دلیل first-pass زیاد

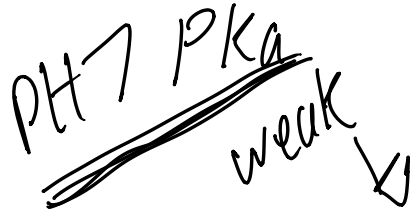
💡 **Clinical Pearl:** Drugs with high first-pass metabolism require higher oral doses or alternative routes to achieve therapeutic levels.

Approximate Volumes of Distribution of Commonly Used Drugs

Drug	Volume of Distribution (L/kg)
Amlodipine	16.0 ± 4
Ganciclovir	1.1 ± 0.2
Ketorolac	0.21 ± 0.04
Lansoprazole	0.35 ± 0.05
Montelukast	0.15 ± 0.02
Sildenafil	1.2 ± 0.3
Valsartan	0.23 ± 0.09

Source: Brunton LL, Lazo JS, Parker KL (editors). *The Pharmacologic Basis of Therapeutics*, 11th edition. New York: McGraw-Hill; 2006. pp. 1798, 1829, 1839, 1840, 1851, 1872, 1883.

Question #1



A weakly basic drug (pKa 7.8) - where is it best absorbed?

A. Stomach (pH 2.5) X

B. Duodenum (pH 6.1) X

C. Jejunum (pH 8.0)

ANSWER: C – Rationale: Basic drugs are better absorbed in basic environments

Bioequivalence and other types of equivalence

Two dosage forms that do not differ significantly in their rate and extent of absorption are termed bioequivalent.

Pharmaceutical equivalents : (products contain the same active ingredient - identical amounts of the identical active drug ingredient (i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms).

Pharmaceutical Equivalent
Same Active Ingredient
Same Dosage Form
Same ROA
Same Dose
Complies with the Same Compendial (e.g. U.S.P.) Requirements
Maybe be different shape, scoring, excipient







Advil®	Pfizer Inc
Midol®	Bayer Inc
Motrin®	Canada, North Macedonia, USA

Pharmaceutical alternatives :(contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester).

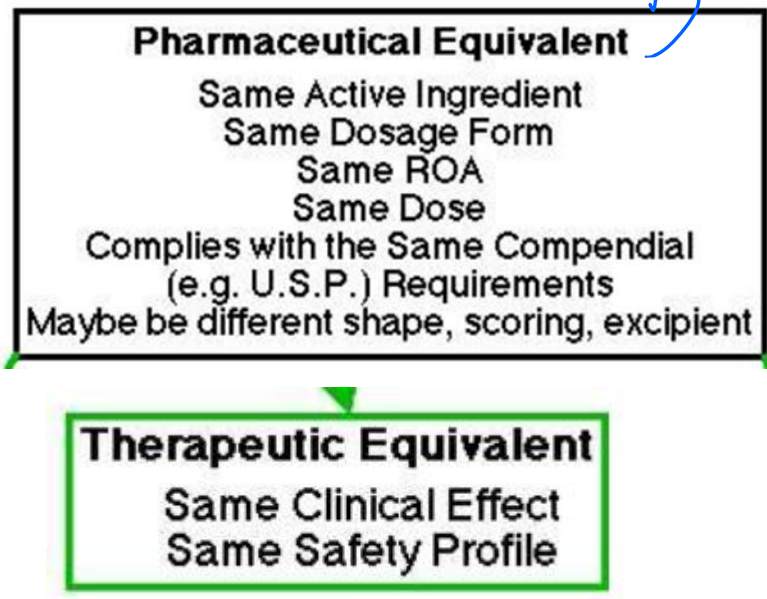


Tetracycline hydrochloride, 250mg capsules vs. Tetracycline phosphate complex, 250mg capsules

Quinidine sulfate, 200mg tablets vs. Quinidine sulfate, 200mg capsules

Therapeutic Equivalent "Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.”

Pharmaceutical equivalents that have been shown to be bioequivalent are therapeutic equivalents.



Question #2

The nurse is giving a medication that has a high first-pass effect. The health care provider has changed the route from PO to IV. What can the nurse expect with the IV dose?

A. The IV dose will be higher because of the first-pass effect.
B. The IV dose will be lower because of the first-pass effect.
C. The IV dose will be the same as the PO dose.
D. The rate of IV infusion must be faster due to first-pass effect.

ANS: B

The first-pass effect is the metabolism of a drug before it becomes systemically available, and it reduces the bioavailability of the drug. This primarily occurs with oral medications. Therefore, IV doses need to be lower than PO doses because of the first-pass effect.

The ADME Journey

Memory Trick: "All Drugs Must Exit"

ADME: The Four Pillars of Pharmacokinetics



ABSORPTION

Drug enters bloodstream from administration site



DISTRIBUTION

Drug travels to target tissues throughout body



METABOLISM

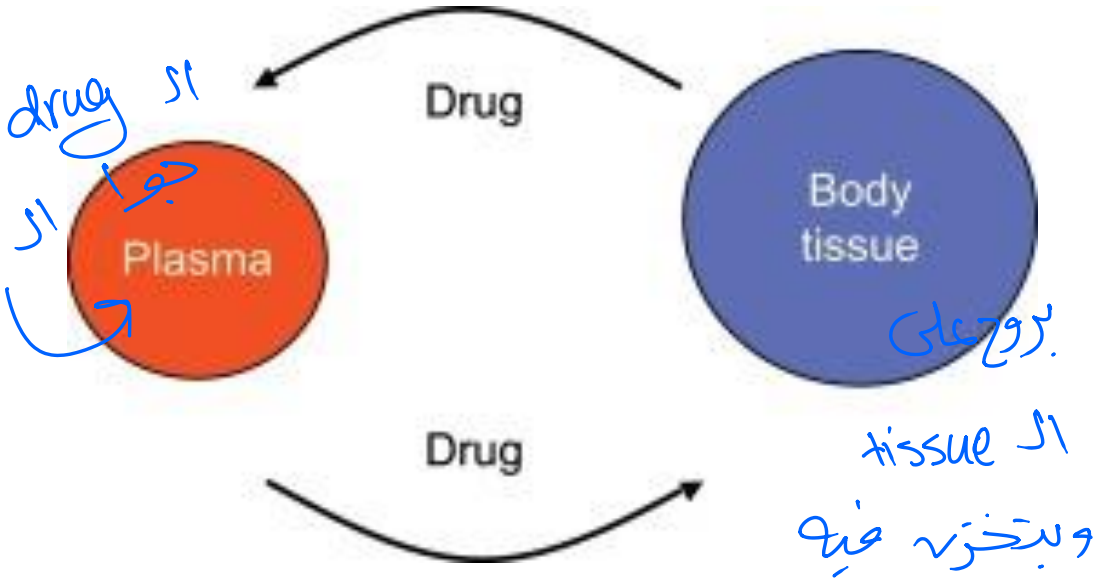
Drug is chemically changed (mainly in liver)

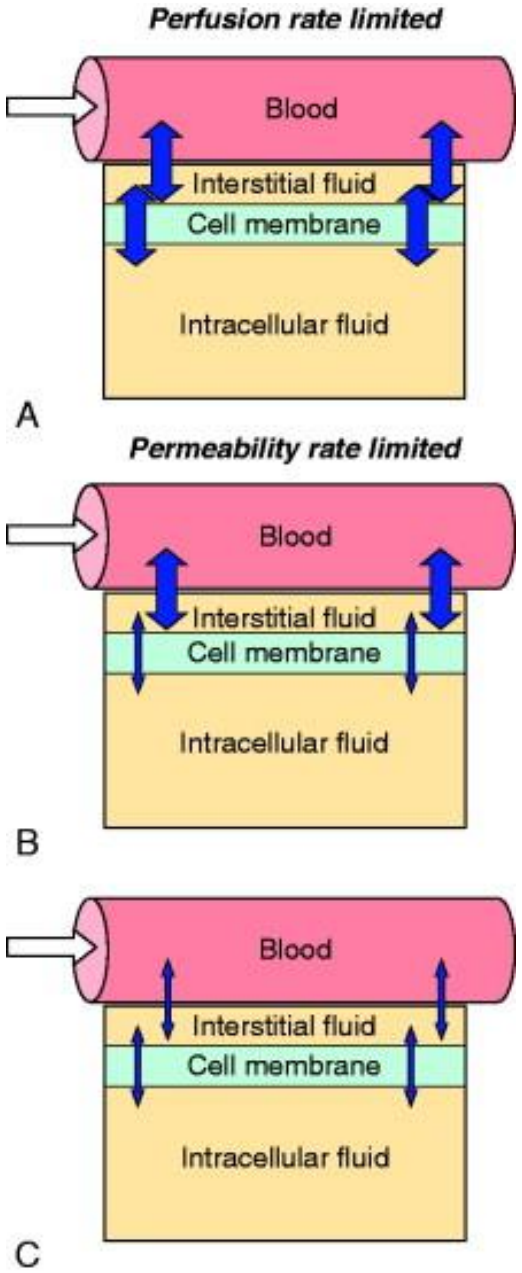


EXCRETION

Drug and metabolites leave the body

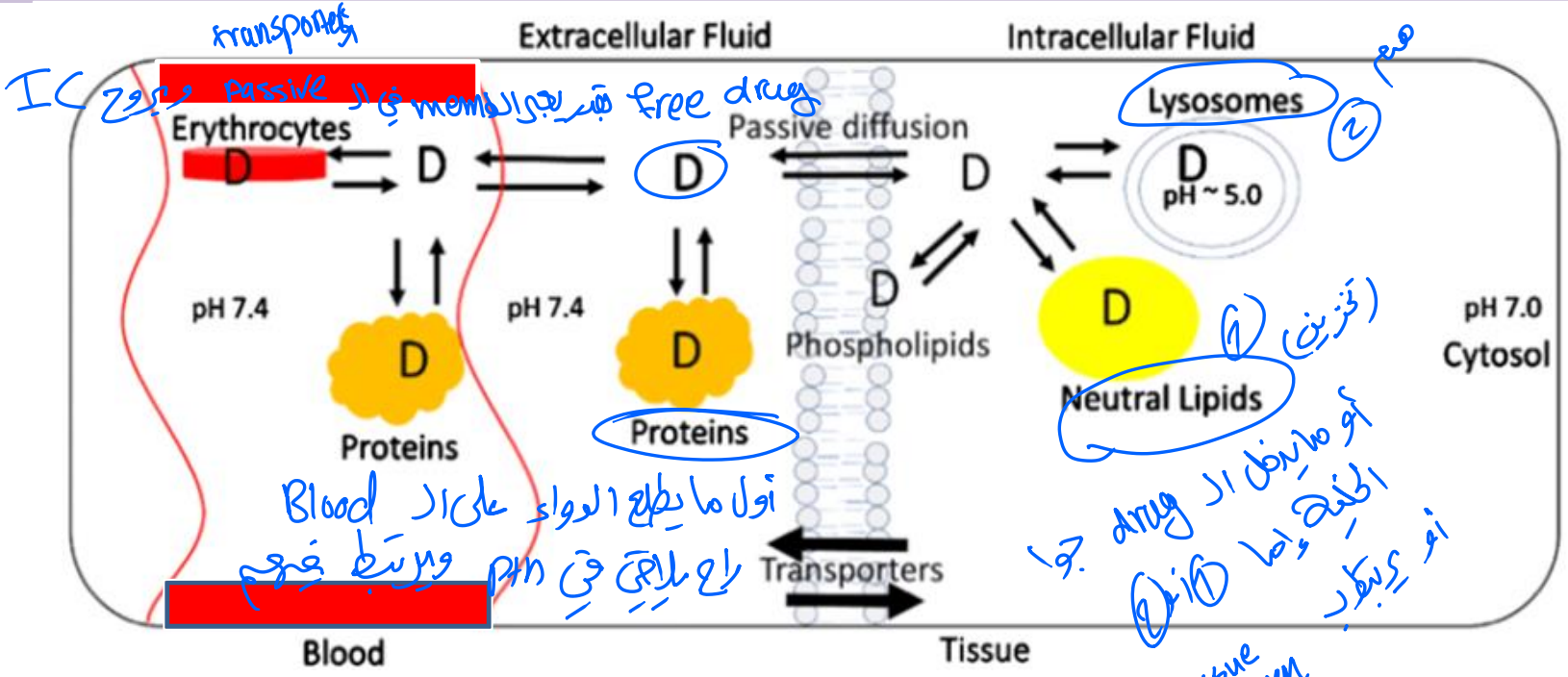
Drug Distribution

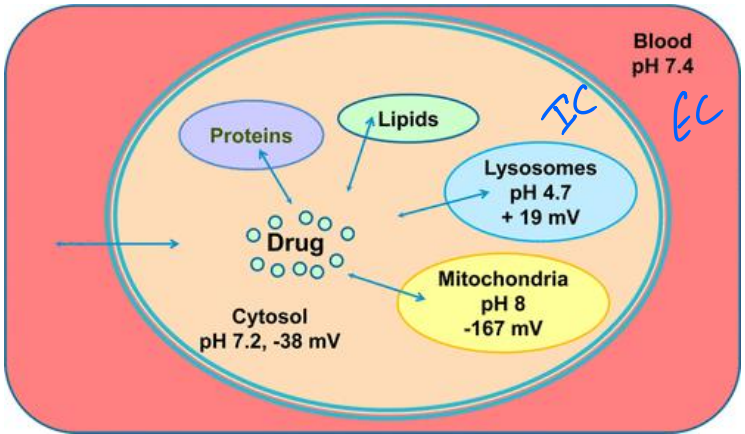




DISTRIBUTION

Reversible movement (transport) of a drug from bloodstream to tissues (site of action)





🌐 DISTRIBUTION

Key Factors

العضو اللي بوصله دم أكتر بيوصلله دوا أكتر زي ال kidney

❤️ **Cardiac Output:** Heart pumps drug around body(Determines overall circulation)

🩸 **Blood Flow :** Vessel-rich organs get priority(The more vascular the area, the higher the concentration of a drug).

🧬 **Protein Binding:** Bound drug= cannot distribute = inactive, unbound = active

💧 **Lipophilicity:** Fat-loving drugs cross membranes easily(Determines membrane crossing)

🧠 **Special Barriers:** Blood-brain barrier protects brain

🏠 **Tissue Binding:** Some drugs accumulate in specific organs

Think of it like this: Your bloodstream is like a highway system delivering packages (drugs) to different neighborhoods (organs) in your body

Factors Affecting Distribution

Rate of distribution

لما القلب يضخ الدم راح يوصلهم أعلى نسبة من الدواء

- **Blood flow:** Vessel-rich organs (brain, liver, kidney) get drugs first
- **Capillary permeability:** Varies by tissue

Extent of distribution

- **Protein binding:** Bound drugs

can't cross membranes

- **pH-Pka** uncharged → absorption
- **Lipophilicity:** Lipophilic drugs dissolve in the lipid membranes and cross membranes easily.

Hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

The major factor influencing the distribution of lipophilic drugs is blood flow to the area.

Blood flow

Rapid onset of action
Short duration of action

How Blood Flow Varies Across Different Tissues ?

VESSEL-RICH ORGANS — HIGH FLOW

Brain | Heart | Liver | Kidneys

Characteristics: Rapid drug distribution, quick onset of effects

SKELETAL MUSCLE — MEDIUM FLOW

Muscles

Characteristics: Moderate drug uptake, acts as drug reservoir

VESSEL-POOR ORGANS — LOW FLOW

Adipose | Skin | Viscera

Characteristics: Slow drug uptake, long-term drug storage

very poor: teeth, bone

KEY CONCEPT: REDISTRIBUTION

A drug's duration of action isn't just about elimination - it's also about **redistribution** between tissues with different blood flow rates. High-flow organs get the drug first, but low-flow tissues can act as "sinks" that pull the drug away from the target site.

CLINICAL EXAMPLE: PROPOFOL ANESTHESIA

Blood flow variation explains why the lipophilic drug propofol has a short duration of action

1 Rapid Onset
High blood flow + lipophilicity = Quick CNS distribution = **Immediate anesthesia**

Brain

2 Redistribution
Drug moves to muscle & adipose tissue, **lowering plasma concentration**

Brain → muscle

3 Recovery
Drug diffuses OUT of CNS (down concentration gradient) = **Consciousness returns**

Capillary permeability

LIVER & SPLEEN

Discontinuous capillaries

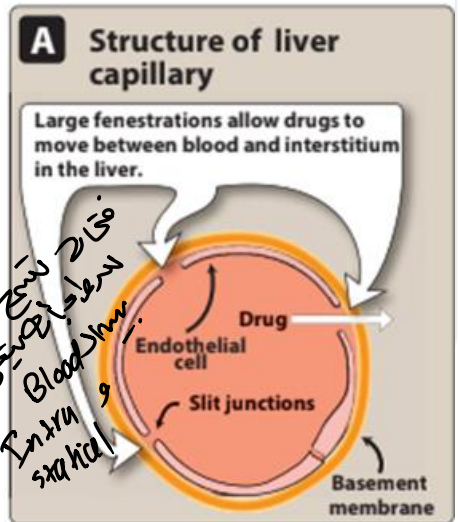
Large slit junctions expose basement membrane

Even large plasma proteins can pass through

HIGH PERMEABILITY

Large proteins ✓

Most drugs ✓



BRAIN (CNS)

Continuous capillaries

NO slit junctions - tight junctions only (BBB)

Drugs must pass THROUGH endothelial cells

LOW PERMEABILITY

BLOOD-BRAIN BARRIER

Tight junctions protect the brain

Lipid-soluble ✓ passive diffusion

Levodopa ✓ (transporter)

Ionized/Polar ✗

Blood-Brain Barrier

Tight junctions between endothelial cells

Lipid-soluble drugs cross easily

Polar/ionized drugs blocked

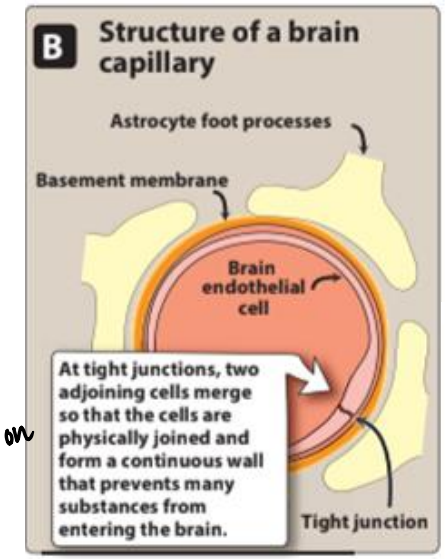
Specific transporters for some drugs

P-glycoprotein efflux pump

Examples:

✅ Cross: Diazepam, morphine

❌ Blocked: Dopamine, quaternary ammonium compounds



MOST OTHER TISSUES

Continuous capillaries

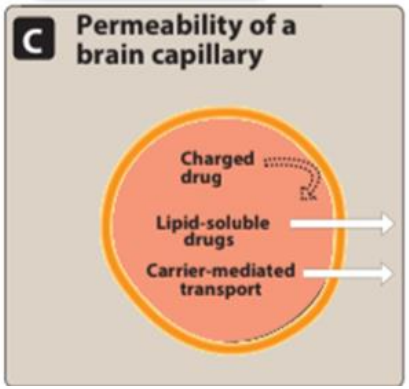
Some slit junctions present

Moderate selectivity

MEDIUM PERMEABILITY

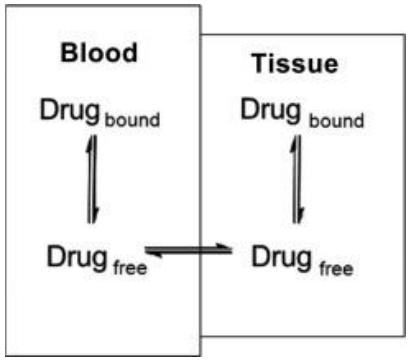
Small molecules ✓

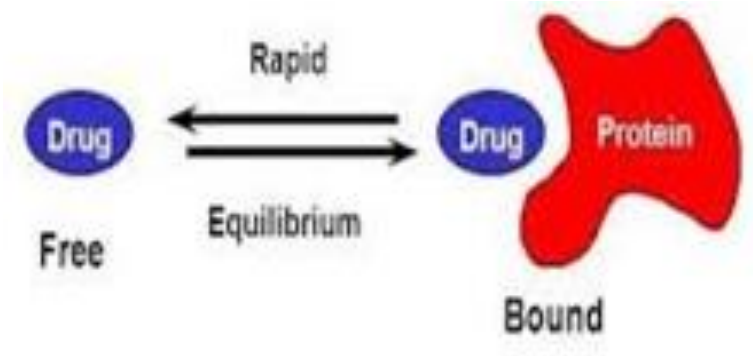
Some proteins ✓

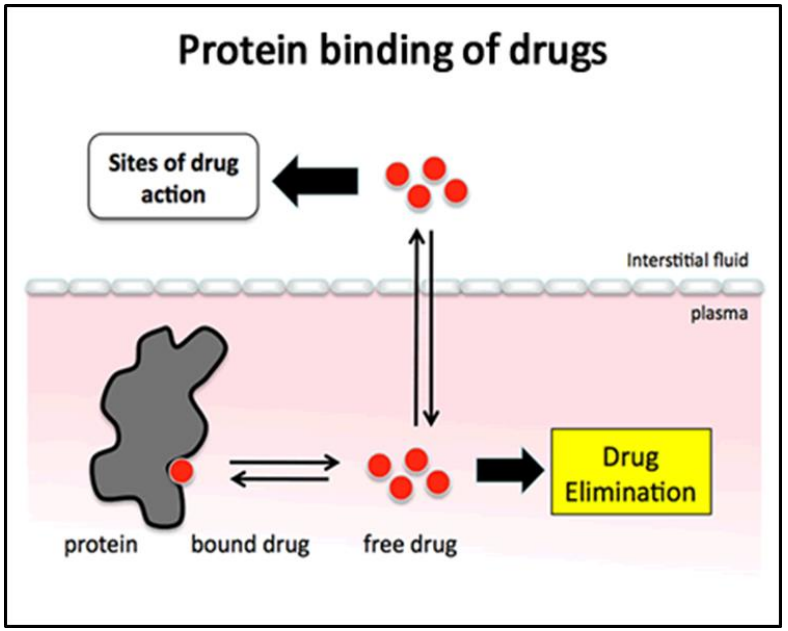


Protein binding

- Drugs bind to proteins in the blood or tissues
- Only a free drug can act at its target site of action
- Albumin is the most common blood protein and carries the majority of protein-bound drug molecules.
- If there is a decrease in the plasma protein binding, this increases the amount of free drug available and will intensify the effects of the drug and may even lead to toxicity







Clinical Pearl: Hypoalbuminemia (liver disease, malnutrition) increases free drug concentration and risk of toxicity for highly protein-bound drugs.

Protein Binding

- **Albumin:** Binds acidic drugs
- **α1-acid glycoprotein:** Binds basic drugs
- Only **free drug** is active
- **Displacement interactions** possible
- Altered in disease states

Highly bound drugs:

- Warfarin (99%)
- Phenytoin (90%)
- Propranolol (90%)

Disease	Influence on plasma protein	Influence on protein drug binding
Renal failure (uremia)	↓ albumin content	Decrease binding of acidic drug , neutral or basic drug are unaffected
Hepatic failure	↓ albumin synthesis	Decrease binding of acidic drug ,binding of basic drug is normal or reduced depending on AAG level.
Inflammatory state (trauma , burn, infection)	↑ AAG levels	Increase binding of basic drug , neutral and acidic drug unaffected

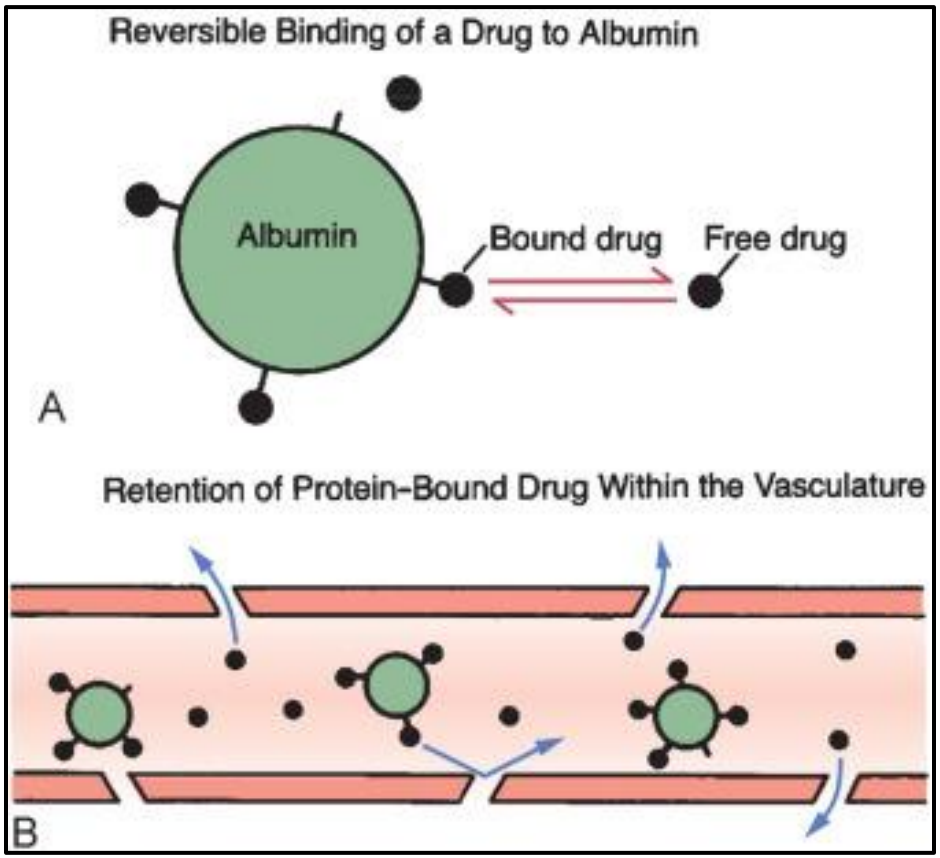
40

	Plasma protein-drug binding	*Tissue-drug binding*
1.	Binding involves weak bonds and thus reversible.	Binding generally involves strong covalent bonds and thus irreversible.
2.	Drugs that bind to plasma proteins have small apparent volume of distribution.	Drugs that bind to extravascular tissues have large apparent volume of distribution.
3.	Half-life of plasma protein bound drug is relatively short.	Half-life of extravascular tissue bound drug is relatively long.
4.	Does not result in toxicity.	Tissue toxicity is common.
5.	Displacement from binding sites is possible by other drugs.	Displacement by other drugs generally does not occur.
6.	Competition between drugs for binding to plasma proteins can occur.	Tissue-drug binding is generally non-competitive.

Drugs compete for protein-binding sites within the Bloodstream.

Drug Interactions – Competition for Binding sites

- Binding site I is shared by phenylbutazone, sulfonamides, phenytoin, and valproic acid.
- Binding site II is shared by the semisynthetic penicillins, probenecid, medium-chain fatty acids, and the benzodiazepines. Some drugs bind to both sites.
- Displacement occurs when a second drug is taken that competes for the same binding site in the protein as the initial drug.



- Outcome of competition of 2 drugs for plasma protein binding ????????

- Drug interaction



KEY DETERMINANTS OF PERMEABILITY



Capillary Structure
Slit junctions vs. tight junctions



Drug Chemistry
Lipophilicity, size, charge



Active Transport
Specific transporters (e.g., L-DOPA)



Molecular Size
Smaller = easier passage

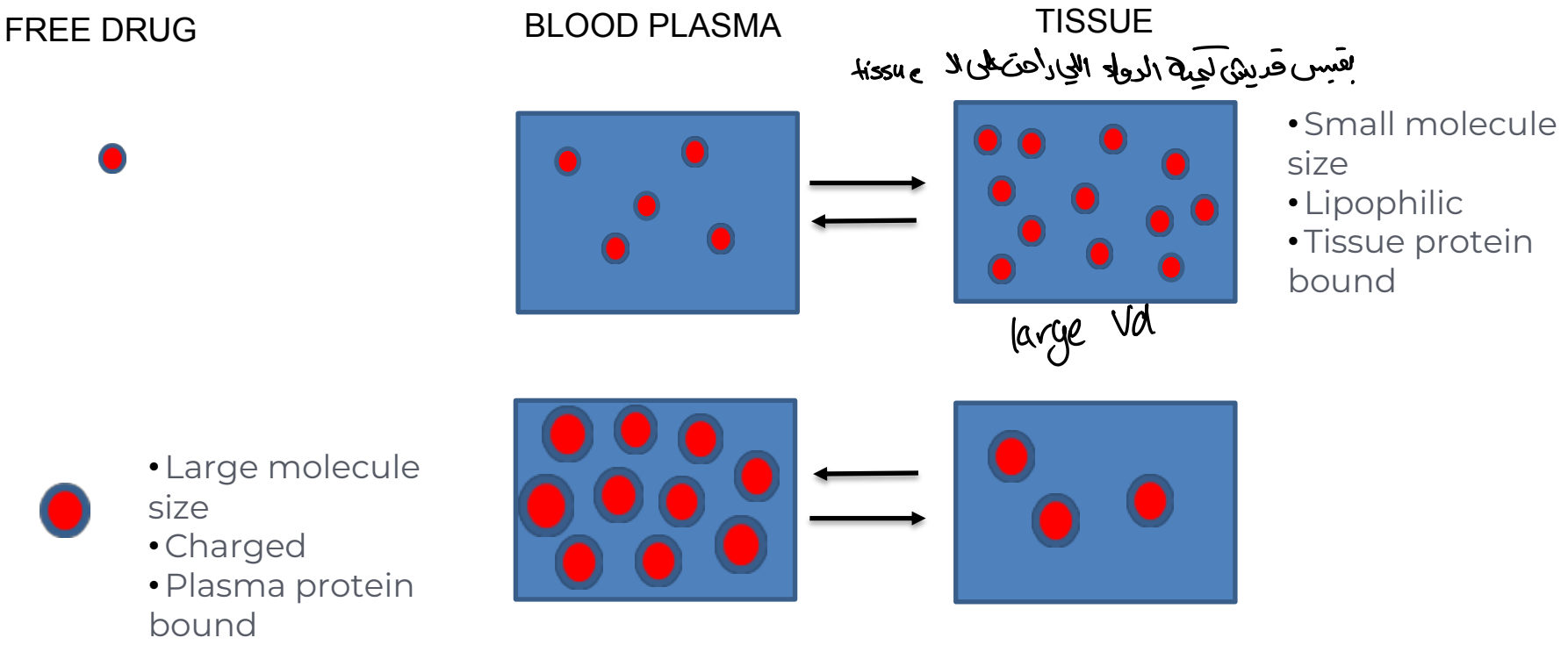
Examples:

- Propofol: High lipophilicity → rapid CNS entry → anesthesia
- Aminoglycosides: Hydrophilic → poor CNS penetration

Volume of Distribution (Vd)

Hypothetical volume of fluid into which a drug appears to be distributed

```
Vd = Total amount of drug in body / Plasma concentration at time0
```



Large Vd = drug likes to hide in tissues!

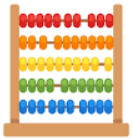
DETERMINATION OF Vd

C = Amount/ Volume

C_p = Dose / Volume

Volume = Dose/Cp

V_d = Dose / C_0



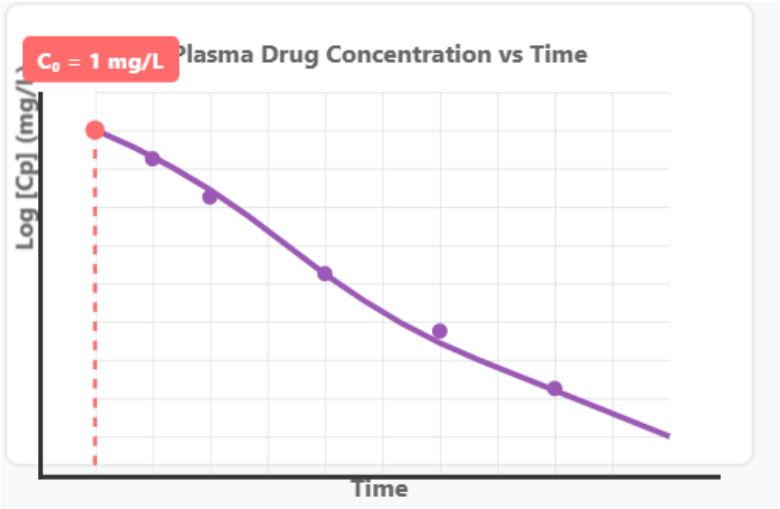
EXAMPLE CALCULATION

Given: 10 mg IV bolus

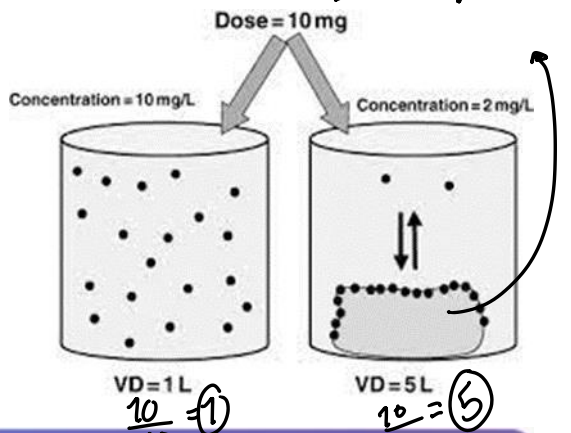
C_0 = 1 mg/L (from graph)

Vd = Dose / C_0

Vd = 10 mg ÷ 1 mg/L = 10 L



كلما زاد تركيز الدواء في الـ tissue زاد الـ Vd



تركيز الدواء أو مادخل على الـ Blood قبل ما يطير له metabolism و distribution

$\frac{10}{10} = 1$ $\quad \frac{10}{2} = 5$

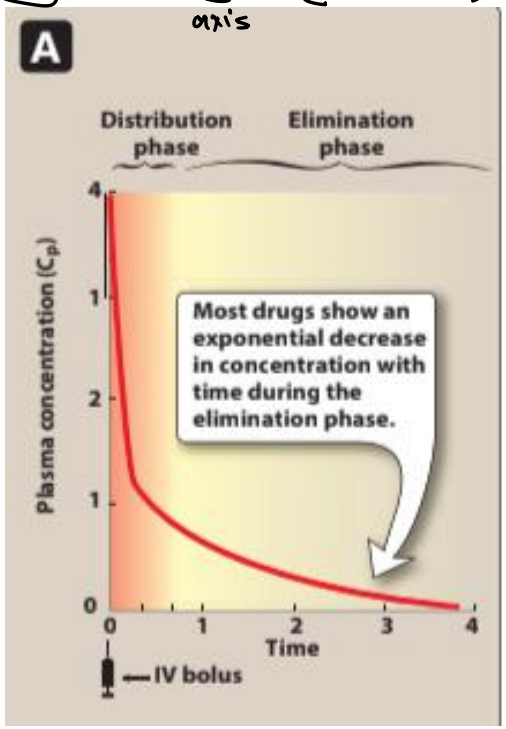
Vd = Dose / C_0

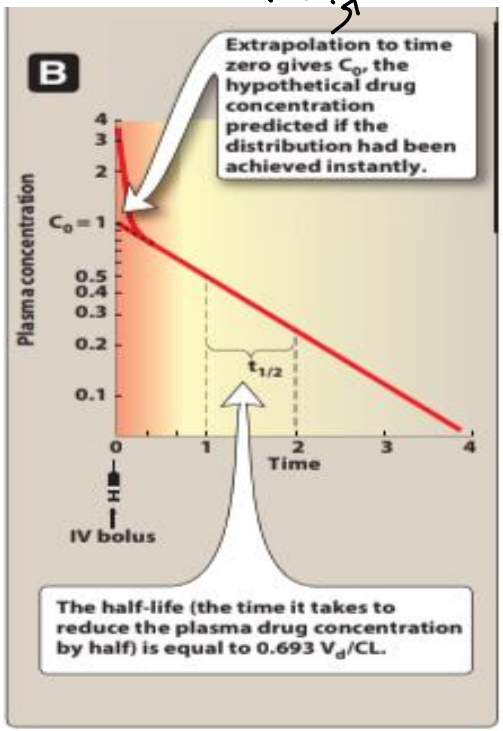
Where C_0 = plasma concentration at time zero (extrapolated from log-linear plot)

كيف أجيبها

C_0 لـ هاد الـ axis

بعد الفش بخليه بدون ما تشيل الـ line ومع الـ extrapolation تلاقي





Apparent Volume of Distribution

The Volume that would accommodate , all the drug in the body if concentration through out the body was the same as in the plasma

مثلاً لو سحبت عينة من الـ Blood = 50 mg/L ولو سحبت من الـ tissue بيوتكون بـ 5 mg/L
فما بيكونوا الاثنين نفس التركيز بلكون اسمه Apparent Vol أعلى Vol

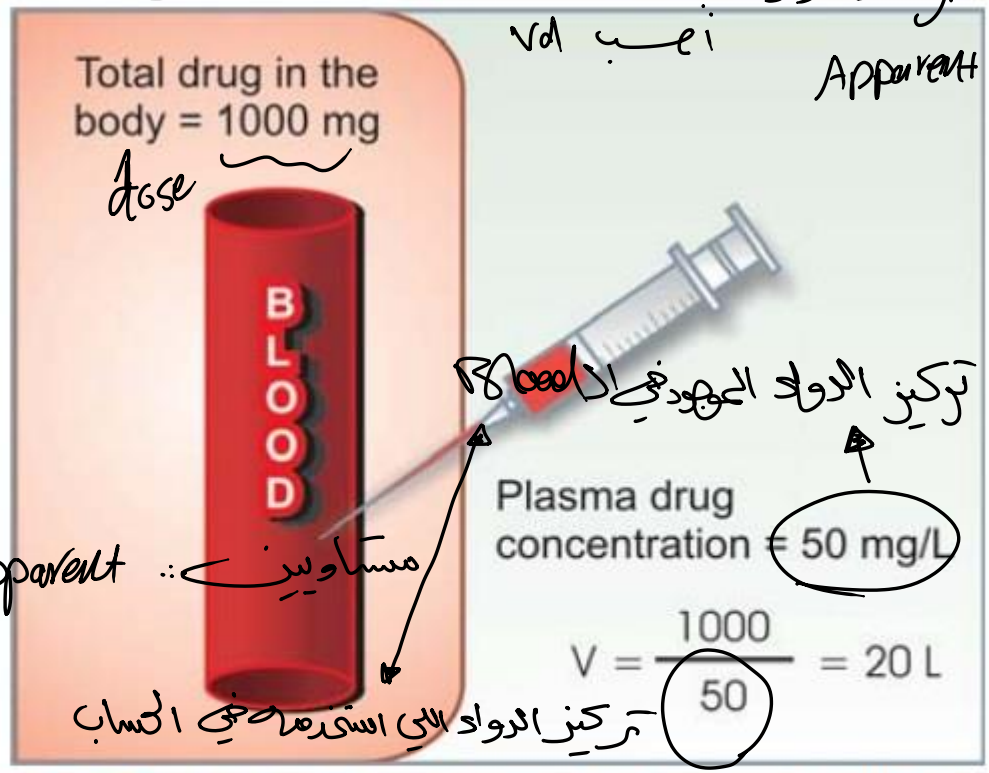


Fig. 2.7: Illustration of the concept of apparent volume of distribution (V).
In this example, 1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L, apparent volume of distribution is 20 L

$$Vd = \frac{\text{Dose of the drug given (Q)}}{\text{Concentration of drug in plasma (Cp)}}$$

So, if Dose given: 100mg &
C_p: 1mg/L {C_p is the plasma concentration}

Then,
$Vd = Dose / C_p$
$Vd = 100/1 = 100\ L$

لو أعطاني الـ Vd هيك مثلاً 0,5 L/kg

هاد ليس الـ Vd الحقيقي
بالتالي لازم أضرب بوزنه المريض مثلاً لو وزنه 70kg

$0,5\ \frac{L}{kg} * 70\ kg = 35\ L$

Compartment	Volume (70kg person)	Drug Characteristics	Example	Clinical Significance
Plasma only	(3-5) ~4L= 5%	Large MW, protein bound	Heparin- warfarin- large proteins	Rapid onset, short duration
Extracellular fluid	(10-15) ~14L= 20%	Small MW, hydrophilic	Aminoglycosides Neuromuscular blockers	Moderate distribution
Total body water	~ 42L=60%	Small MW, lipophilic	Ethanol-phenytoin	Wide distribution
Beyond body water	> 100 L	small molecule and larger molecules	Chloroquine - Digoxin	Tissue binding (Concentrates in tissues) – long t1/2

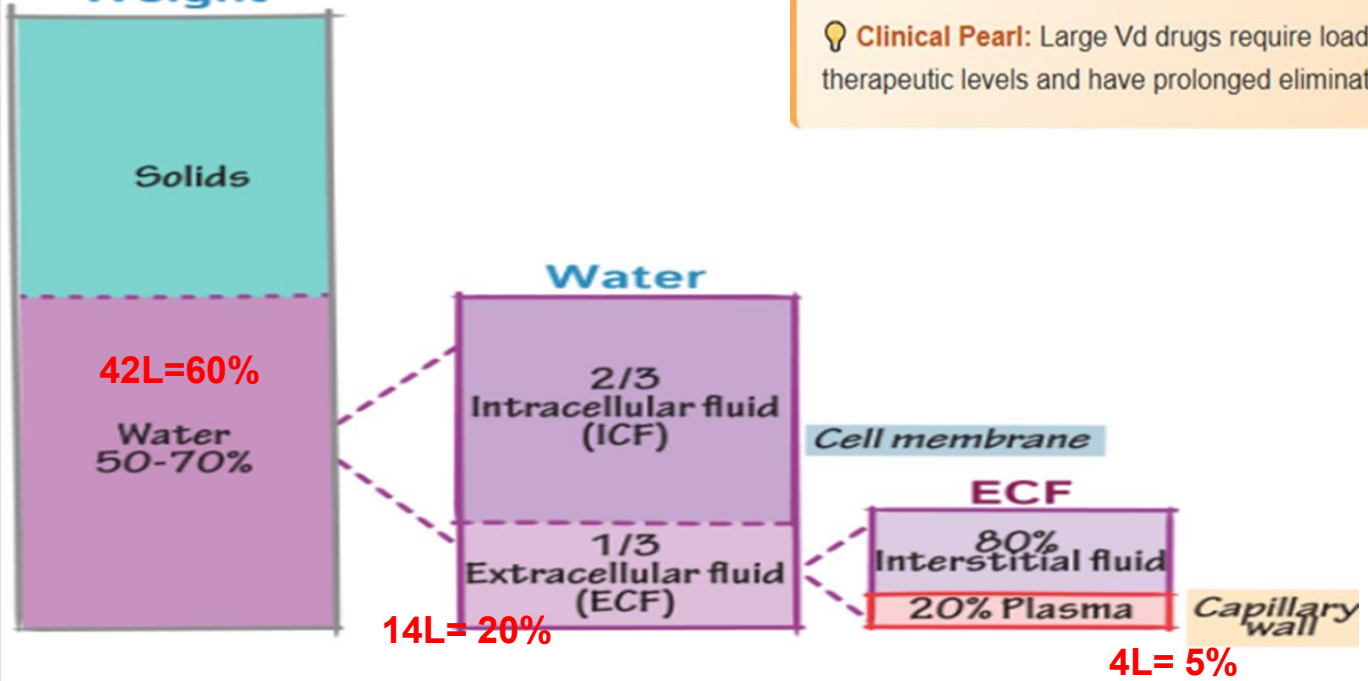
activity

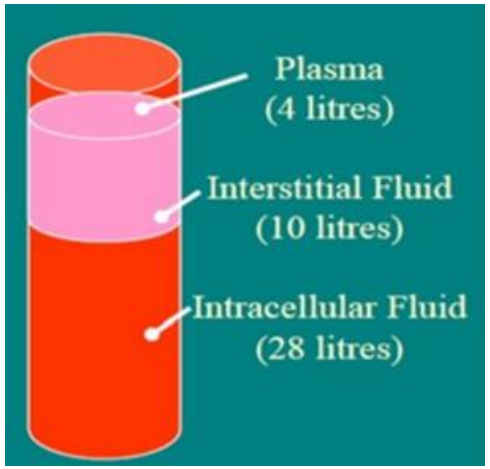
راح يضلوا في الplasma وهذا اشي كويس خطر بيشتغلوا على الـ Blood فاذا فضل بيضلهم حبة عشان يحلوا الـ

أكثر من كمية الماء في الجسم

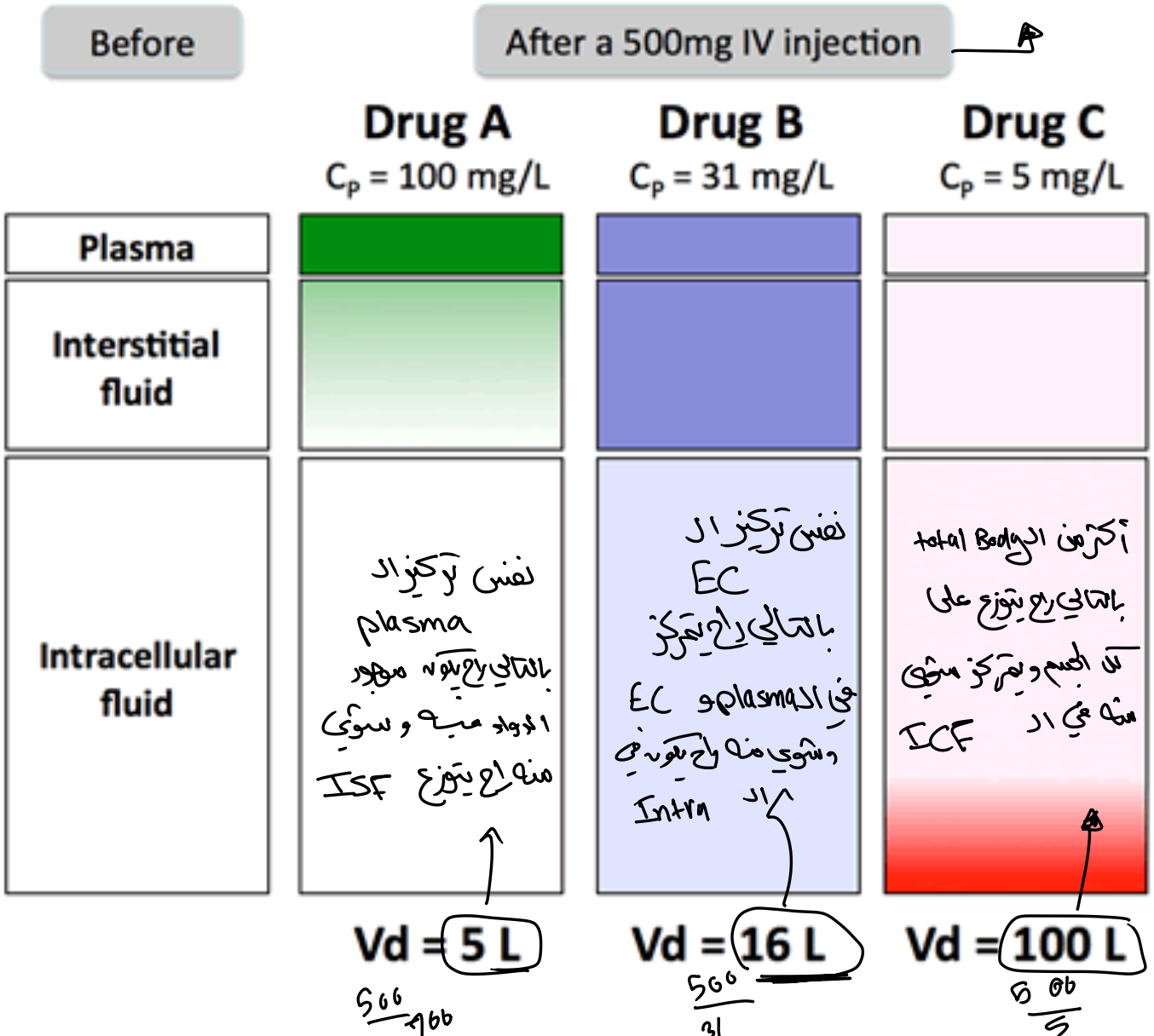
Clinical Significance: Large Vd means drug is sequestered in tissues, longer half-life, need higher loading dose

Clinical Pearl: Large Vd drugs require loading doses to quickly achieve therapeutic levels and have prolonged elimination times.





Volume of distribution





FACTORS AFFECTING Vd

Plasma Protein Binding

↑ Binding = ↓ Vd (drug stays in plasma)

Tissue Binding

↑ Tissue binding = ↑ Vd (drug leaves plasma)

Lipophilicity

↑ Lipophilic = ↑ Vd (tissue penetration)

Molecular Size

↑ Size = ↓ Vd (limited distribution)

SMALL Vd

< 0.2 L/kg

- ✓ Drug stays in plasma
- ✓ Shorter half-life
- ✓ Rapid elimination
- ✓ Easy to dialyze

LARGE Vd

> 1 L/kg

- ⚠ Drug in tissues
- ⚠ Longer half-life
- ⚠ Slower elimination
- ⚠ Drug sequestration



CLINICAL PEARL: (Vd & HALF-LIFE) RELATIONSHIP

Large Vd = Longer Half-life:

When most drug is in extraplasmic space, less is available to elimination organs (liver/kidney). This extends the drug's duration of action.

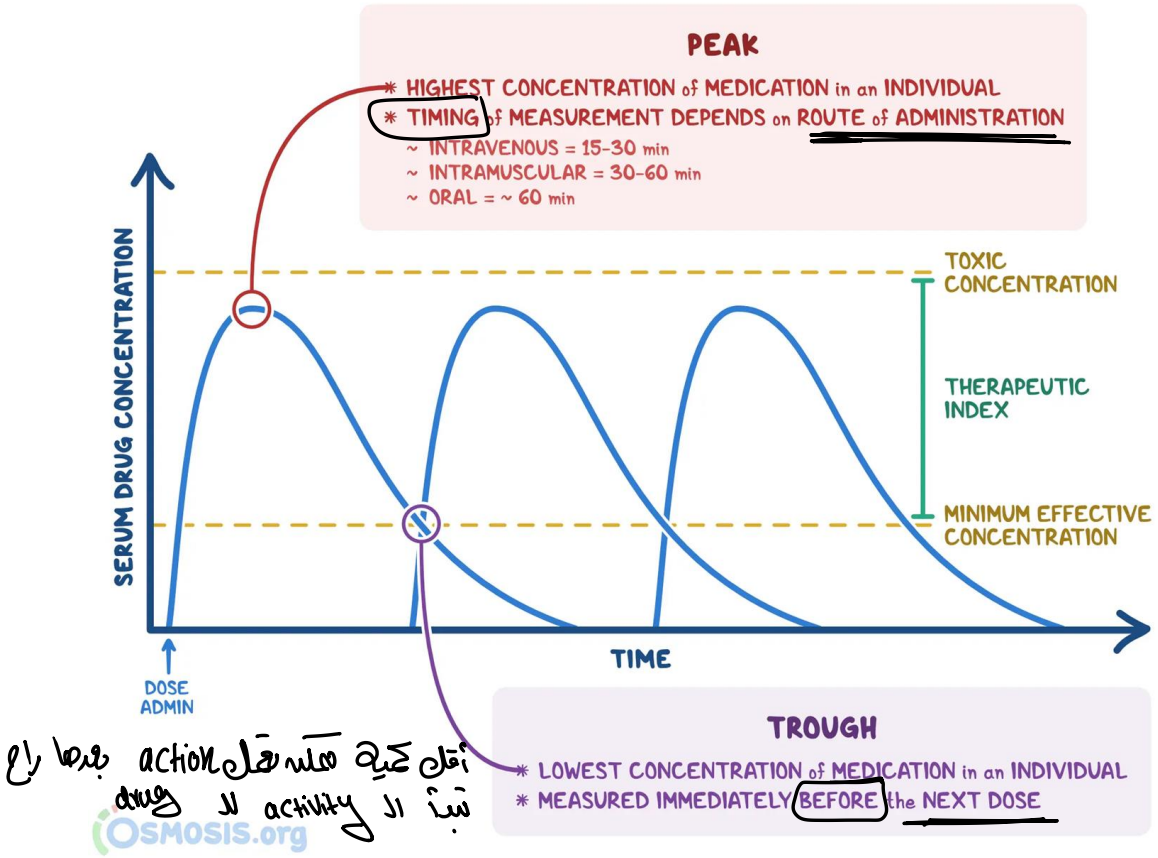
An exceptionally large Vd suggests significant tissue sequestration - think chloroquine accumulating in tissues!

Drug Effects

The length of time until the onset and peak of action and the duration of action play an important part in determining the ***peak level*** and ***trough level*** of a drug.

Peak level: highest blood level of a drug

Trough level: lowest blood level of a drug



trough

lowest C. و أعلى من الـ (Cmax) أو maximal الـ بيبدأ فيه الدواء حيث يكون Peak بالتالي لازم نعطي الدواء

Toxicity: occurs if the peak blood level of the drug is too high

PLASMA DRUG CONCENTRATION VERSUS TIME CURVES (IV)

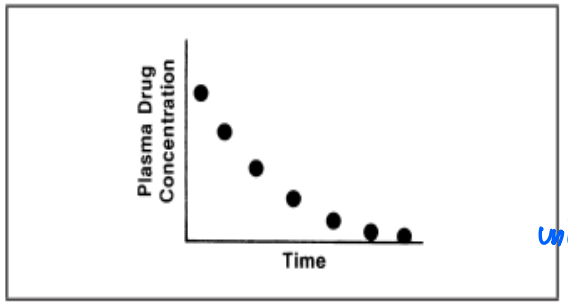


FIGURE 1-24.
Plasma drug concentrations determined at specific time points.

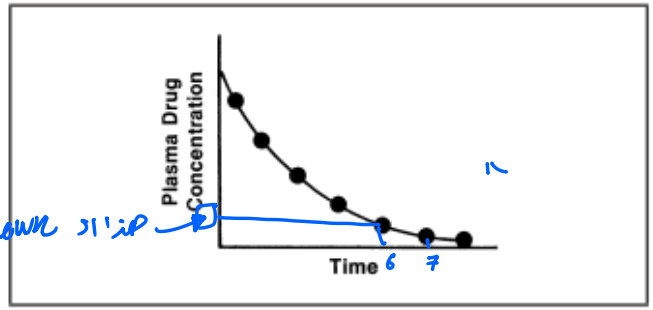


FIGURE 1-25.
Plasma drug concentrations can be predicted for times when they were not determined. Concentrations on the line drawn through the measured concentrations are predicted concentrations.

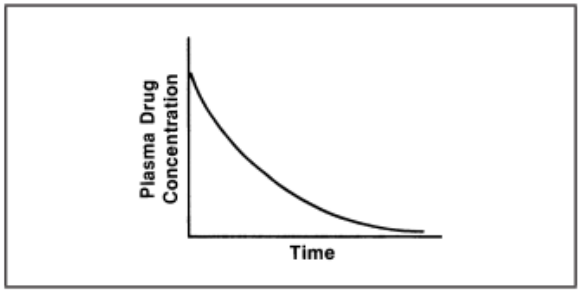


FIGURE 1-23.
Typical plasma drug concentration versus time curve for a one-compartment model.

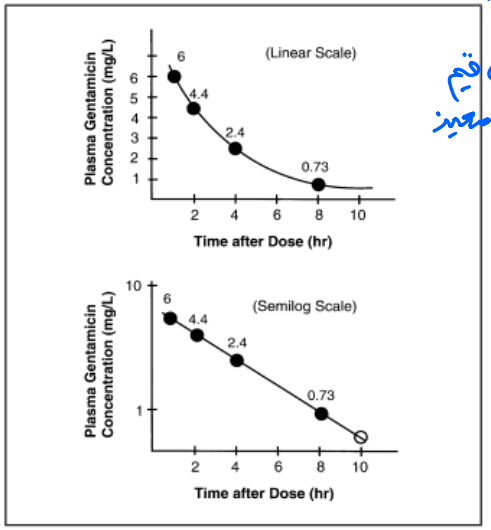


FIGURE 1-29.
Predicting plasma drug concentrations with semilog scale.

Why the plasma concentration of a drug decreases exponentially?

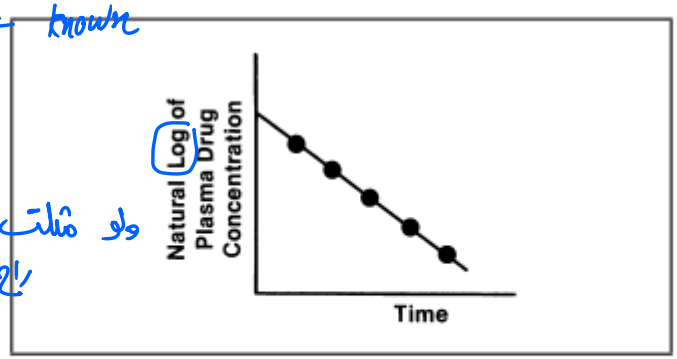
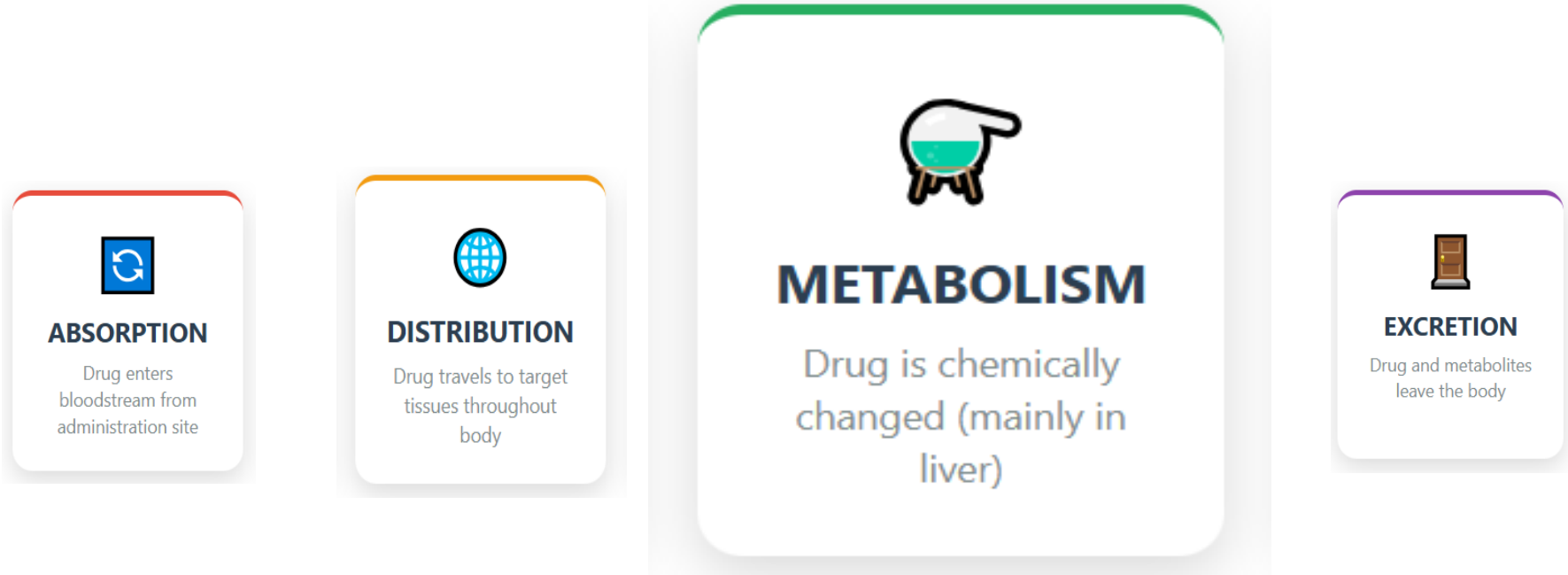


FIGURE 1-26.
With a simple one-compartment, intravenous bolus model, a plot of the natural log of plasma concentration versus time results in a straight line.

The ADME Journey

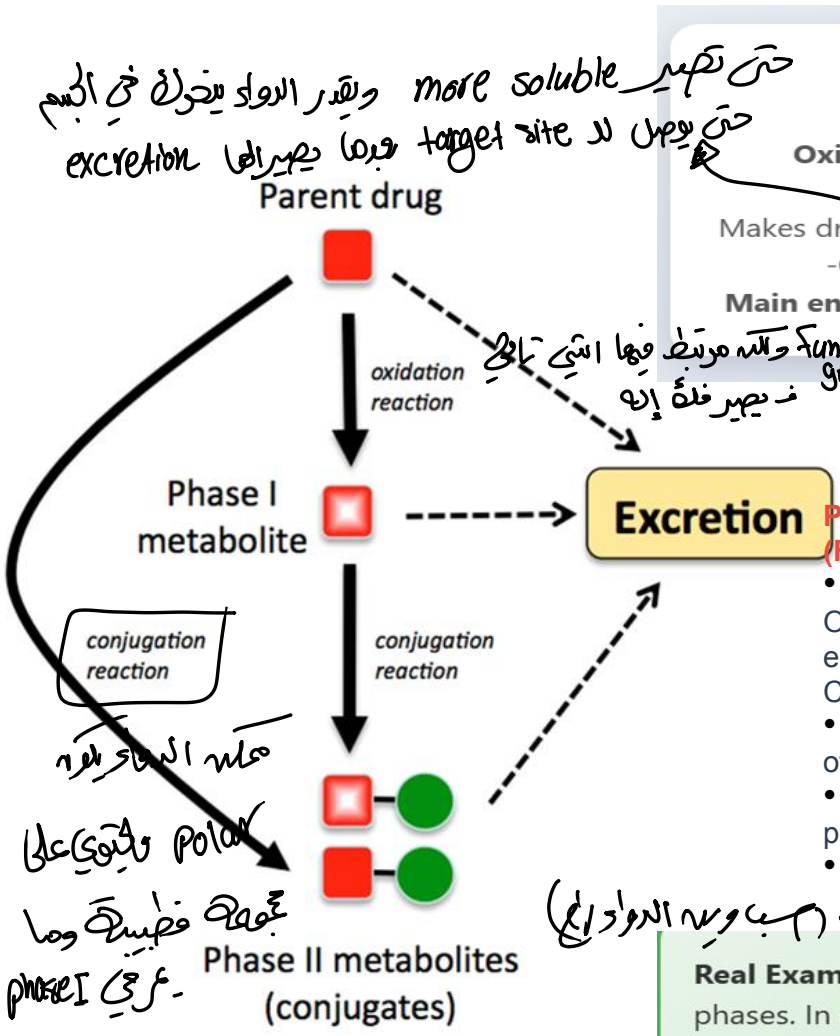
Memory Trick: "All Drugs Must Exit"

ADME: The Four Pillars of Pharmacokinetics



METABOLISM= *biotransformation*

The enzymatic conversion of one chemical compound into another(metabolite).



Phase I

Oxidation, Reduction, Hydrolysis

Makes drug more polar by adding -OH, -NH2 groups

Main enzyme: Cytochrome P450

Goal: Make drugs more polar by adding exposing functional groups

Phase I Reactions (Functionalization)

- **Oxidation:** Most common, adds O or H and O by CYP450 enzymes– in Liver-kidney and CNS
- **Reduction:** Less common, gain of e or H
- **Hydrolysis:** Esterases, proteases
- **Dealkylation**

Phase II

Conjugation

Attaches large polar groups (glucuronide, sulfate)

Result: Very water-soluble compounds

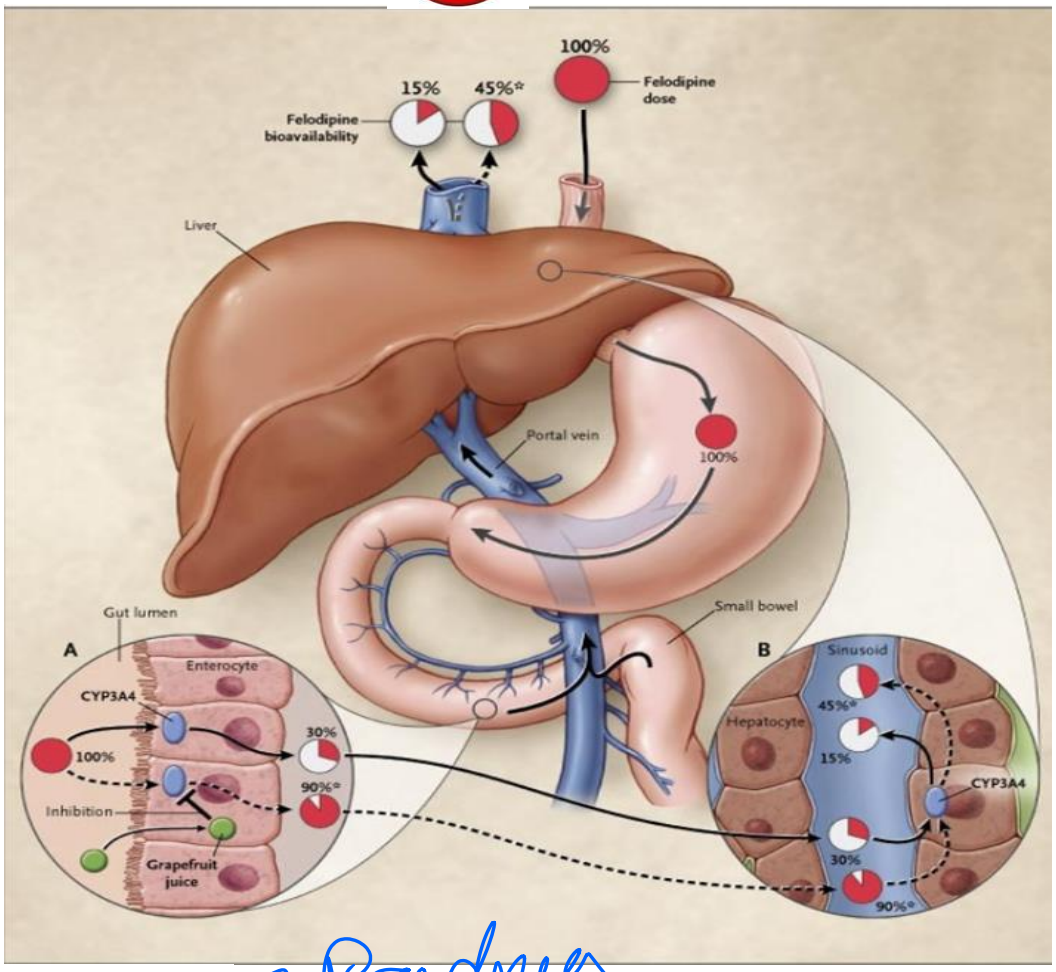
Goal: Make drugs inactive and water soluble , ready for elimination

Phase II Reactions (Conjugation) : conjugation with an endogenous substrate

- **Glucuronidation with (glucuronic acid):** Most common
- **Sulfation with (sulfuric acid)** for small molecules
- **Acetylation with (acetic acid)** or Amino groups
- **Methylation:** Various functional groups

Real Example: Acetaminophen (Tylenol) goes through both phases. In overdose, Phase I can produce toxic metabolites!

METABOLISM



Goals of Metabolism:

- Convert lipophilic → polar compounds
- Facilitate elimination
- Occurs in the liver, some processes occur in the gut wall, lungs and blood plasma

Results in :

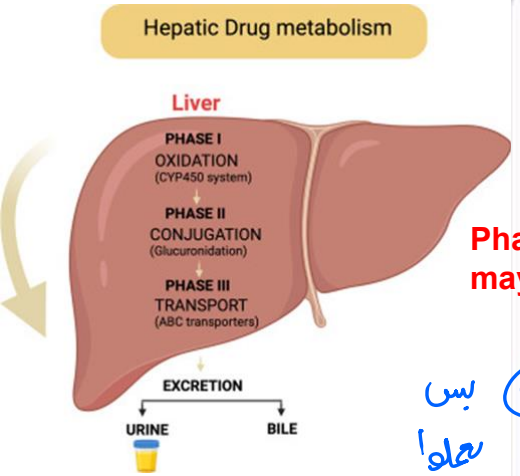
1. **inactive** metabolite
2. more soluble compound and **more potent active** metabolite (as in the conversion of an inactive *prodrug* to its active form),
3. or a **less active** metabolite.
4. No change in activity :

diazepam ------> nordiazepam

6. Produce toxic metabolites : **paracetamol**

Clinical Examples

- **Codeine → Morphine:** Activation
- **Enalapril → Enalaprilat:** Prodrug activation
- **Paracetamol → NAPQI:** Toxic metabolite



بس بعلوا oxidation ؛)

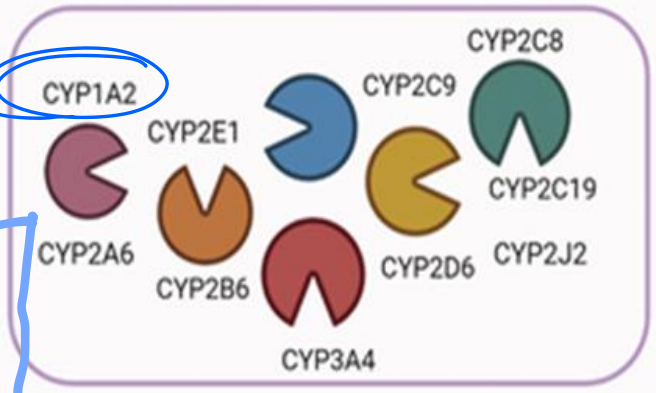
Morphine -6- glucuronide is MORE potent than morphine itself - rare exception to the rule that phas II products are inactive

Drug Metabolism

Phase I

Polar functional groups undergo **oxidation, reduction and hydrolysis**

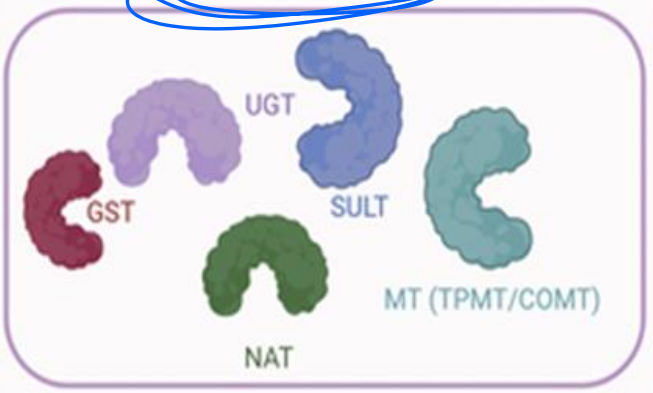
Pharmacologic activity after phase I metabolism may: Increase – Decrease – Unchanged

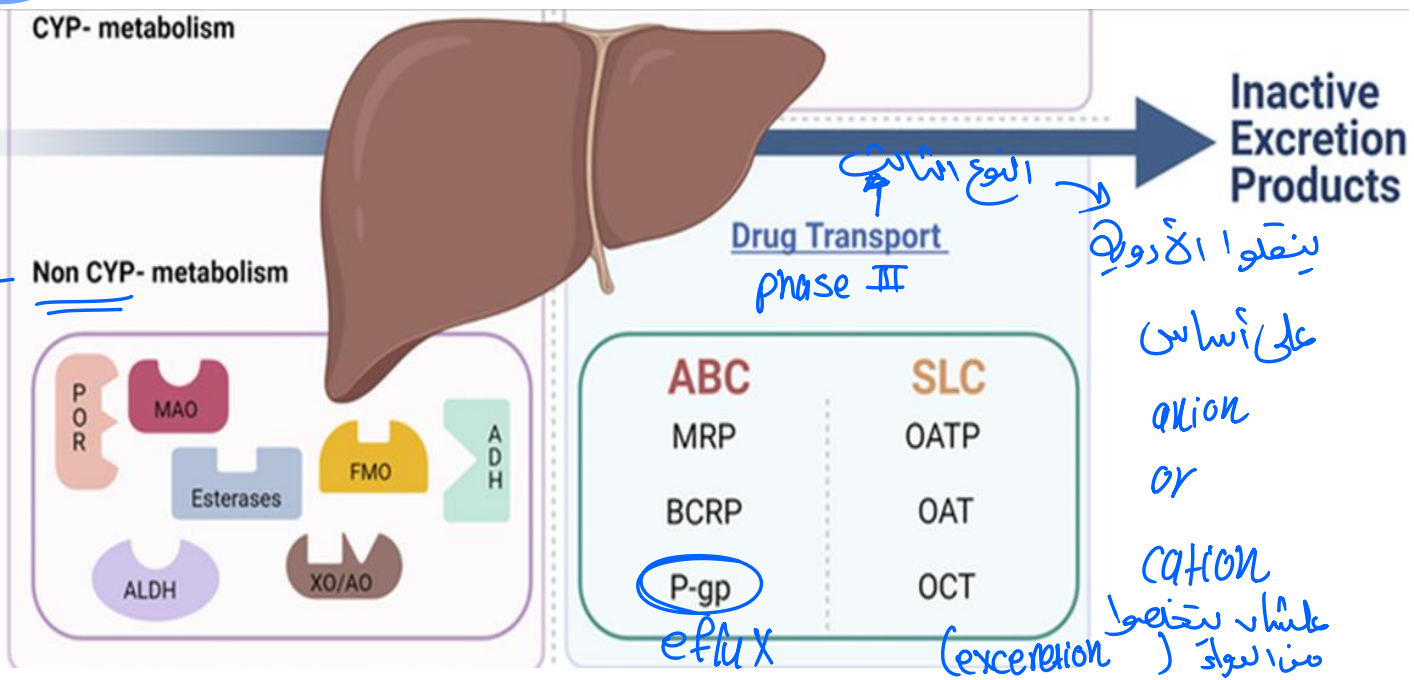


Drug Metabolism

Phase II

Metabolites/parental compounds undergo **glucuronidation, sulfonation, methylation, acetylation, gluthatione and amino acids conjugation**





alkalisation
oxidation
hydrolysis

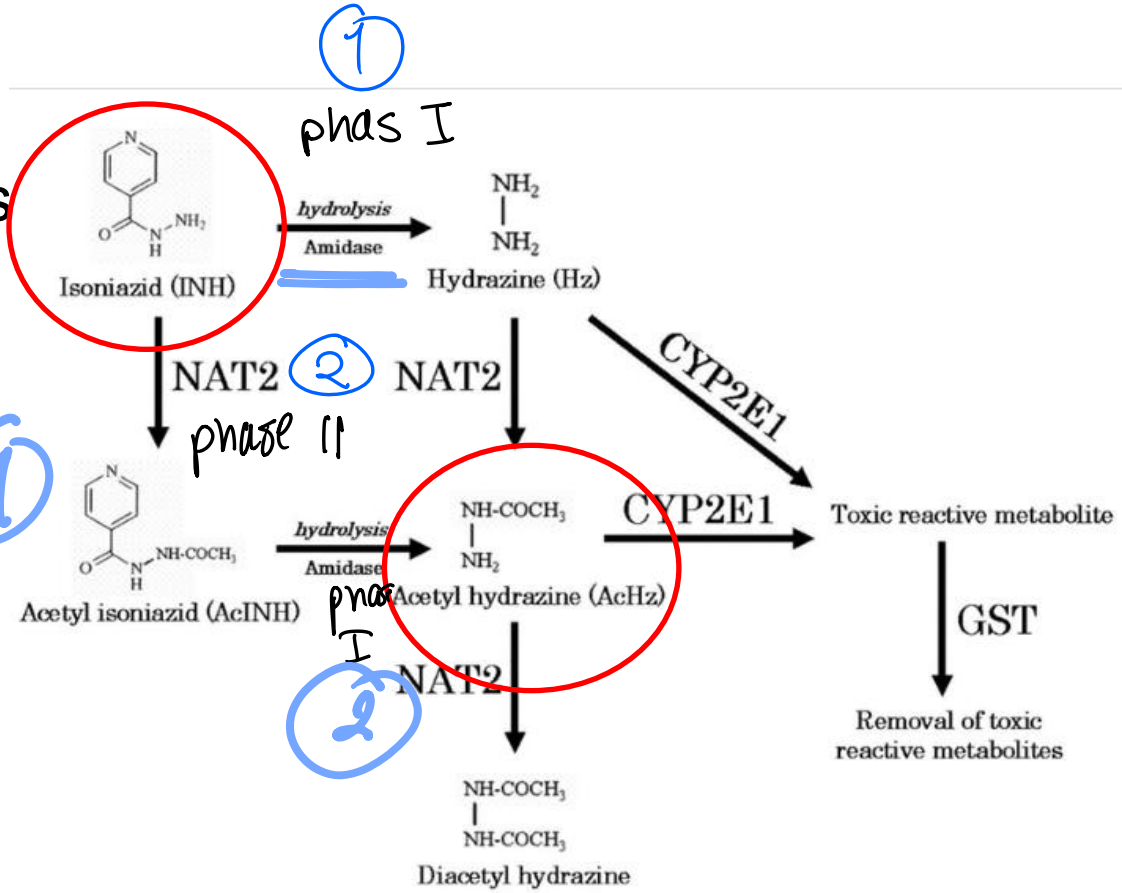
النوع الثاني

بنقلوا الأدوية على أساس anion or cation عشان يتخلصوا منها (excretion) efflux

Reversal of order of the phases

Not all drugs undergo Phase I and II reactions in that order.

Examples : isoniazid can first acetylated (a Phase II reaction by NAT) and then hydrolyzed to isonicotinic acid (a Phase I reaction by amidase).



(phas II) Acetylation يصير قبل (phase I) hydrolysis عشان يصير قبل او ممكن يصير العكس

CYP450 Enzyme System=*microsomal* enzymes

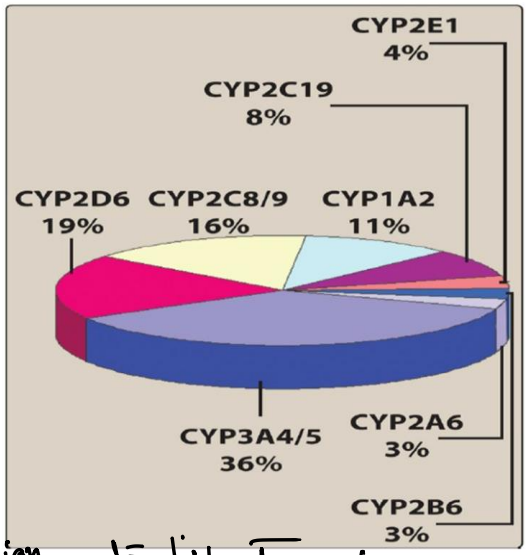
Primary enzyme system responsible for drug metabolism

Location: Mainly liver, also GI tract , lung , Blood

Major isoforms: CYP3A4/5 (36%), CYP2D6 (19%), CYP2C8/9 (16%)

Genetic variability: Affects drug efficacy and toxicity

- Many different P450 isoforms.
- They can modify a large number of substrates.
- One drug may be a substrate for more than one isozyme.



Clinical Significance

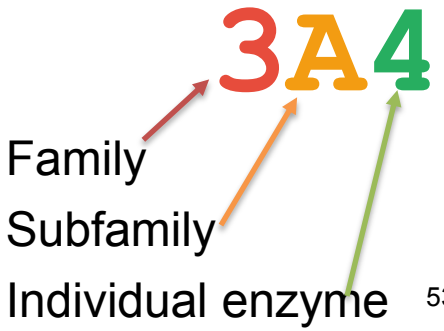
- Genetic polymorphisms
- Drug interactions
- Individual variation
- Poor vs. extensive metabolizers



ال inactivation or activation هاد الانزيمات عملته انها تعمل
و نفس هذه الانزيمات عملته انه يجي دواء اخر يعمل



Naming System



Clinical Pearl: Always check for CYP interactions when starting new medications, especially with narrow therapeutic window drugs like warfarin.

Cytochrome P450 (CYP)

Key Enzymes

CYP3A4/5 - Most important (50% of drugs)

CYP2D6 - Codeine activation → morphine

CYP2C9/19 - Warfarin -Clopidogrel activation (prodrug)

CYP1A2 - Caffeine, theophylline

Key CYP450 Enzymes (Metabolize 90% of drugs)

- **CYP3A4:** 50% of all drug metabolism
- **CYP2D6:** 25% of drug metabolism
- **CYP2C9:** Important for warfarin
- **CYP2C19:** Clopidogrel activation

Clinical Pearl: Morphine-6-glucuronide is MORE potent than morphine itself - rare exception to the rule that Phase II products are inactive!



Clinical Importance: Genetic variations can make some people "poor metabolizers" or "ultra-rapid metabolizers" - affecting drug efficacy and toxicity!

Genetic Polymorphisms in Drug Metabolism

Genetic polymorphisms in metabolizing enzymes can cause : poor – Intermediate – Extensive or Ultra –Rapid metabolized

Clinical Significance

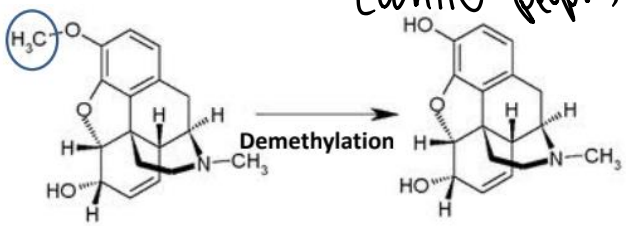
Poor metabolizers → Drug toxicity

Ultra-rapid metabolizers → Treatment failure

Important Examples:

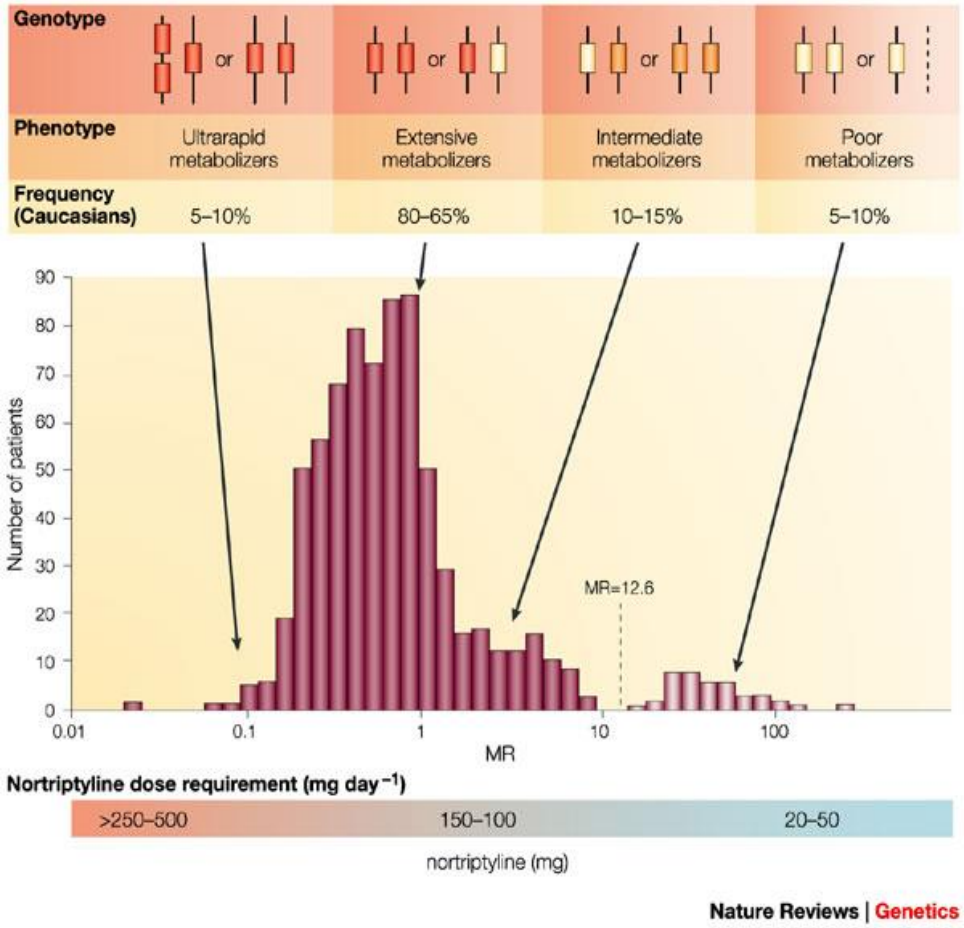
CYP2D6 Polymorphisms

- **Codeine:** Poor metabolizers get no benefit of analgesic effect
- **Ultra-rapid metabolizers:** Risk of morphine toxicity
- Affects 5-10% of Caucasians



CYP2C19 Polymorphisms

- **Clopidogrel:** Poor metabolizers have higher CV events
- FDA warning for genetic testing
- Higher frequency in Asian populations



Pharm Logic Plus

Clinical Pearl: Always consider genetic factors when patients don't respond as expected to standard doses!

Aspect	↑ ENZYME INDUCTION	↓ ENZYME INHIBITION
Mechanism	Increase enzyme activity Result: ↓ Drug levels, ↓ Effect	Decrease enzyme activity Result: ↑ Drug levels, ↑ Toxicity
Common Examples	• Smoking (tobacco) CYP 1A2 • Rifampin • Phenytoin • Carbamazepine	• Grapefruit juice • Ketoconazole • Erythromycin • Cimetidine
Major Drugs	**Rifampin :** Potent CYP3A4 inducer **Phenobarbital :** Multiple enzymes **Carbamazepine :** Auto-inducer **St. John's Wort :** CYP3A4	**Ketoconazole :** Potent CYP3A4 inhibitor **Erythromycin :** Multiple enzymes **Omeprazole :** CYP2C19 **Grapefruit juice :** CYP3A4
Clinical Impact	**herapeutic failure** • Reduced drug efficacy • Need for dose increase • Monitor for treatment failure	**Drug toxicity** • Increased adverse effects • Need for dose reduction • Monitor for toxicity signs

Pharm Logic Plus

Critical Clinical Pearls





Grapefruit Alert:
Inhibits CYP3A4 in intestines, dramatically increasing absorption of statins and calcium channel blockers





HIV Treatment:
Rifampin + **HIV protease inhibitors**
→ Treatment failure due to massive enzyme induction



Bleeding Risk:
Omeprazole + **Warfarin**
→ Increased bleeding risk due to CYP2C19 inhibition

Key Clinical Point

Omeprazole + Warfarin: Increased bleeding risk due to CYP inhibition - Omeprazole inhibits both CYP2C19 and CYP2C9, affecting warfarin metabolism.

Pharm Logic Plus

CYP 450 System Clinical Relevance

Induction Effects:

- ↓ Drug concentrations
- ↓ Therapeutic effect
- May need ↑ doses

Inhibition Effects:

- ↑ Drug concentrations
- ↑ Risk of toxicity
- May need ↓ doses

Enzyme	Key Substrates	Important Inducers	Important Inhibitors
CYP3A4 *(~50% of drugs)*	Cyclosporine, Nifedipine, Simvastatin, Erythromycin, Verapamil	Rifampin, Carbamazepine, Phenobarbital, St. John's Wort	Ketoconazole, Grapefruit juice, Ritonavir
CYP2D6 *(Genetic polymorphism)*	Codeine, Propranolol, Haloperidol, Desipramine	*None significant / None (not inducible)*	Fluoxetine, Paroxetine, Quinidine
CYP2C19 *(Clopidogrel activation)*	Clopidogrel, Omeprazole, Diazepam	Rifampin	Omeprazole, Fluoxetine
CYP2C9	Warfarin, Phenytoin, Ibuprofen, Tolbutamide	Rifampin, Phenobarbital	Fluconazole, Omeprazole

Pharm Logic Plus

Drug Interactions: Inducers, Inhibitors, and Substrates

A Haines BSP, T Smart BSP, A Crawley BSP © www.RxFiles.ca May 2023

Our RxFiles charts contain abbreviated drug interactions; this table provides a bit more detail. **Substrates** are metabolized by the given enzyme. Enzymes that are **induced** metabolize their substrates faster. Enzymes that are **inhibited** metabolize their substrates slower. Example: fluvoxamine is a CYP2C19 inhibitor. When given with amitriptyline it will cause ↑levels (↓metabolism) of amitriptyline.

	1A2	2C9	2C19	3A4	2D6
CYP Inducers					
STRONG	**carbamazepine, primidone, phenobarbital, rifampin**	**CBZ, rifampin, phenobarb, phenytoin, primidone**	**carbamazepine, phenytoin, rifampin**	**apalutamide, carbamazepine, lumacaftor, phenobarbital, phenytoin, primidone, rifabutin, rifampin**	Not inducible.
MODERATE	ritonavir, smoking	dexamethasone, ritonavir, St. John's Wort	St. John's Wort	bosentan, efavirenz, etravirine, modafinil, St. John's Wort	
CYP Inhibitors					
STRONG	**ciprofloxacin, fluvoxamine**	delavirdine, **gemfibrozil**	delavirdine, **fluconazole, fluvoxamine, gemfibrozil**, ticlopidine	atazanavir, boceprevir, **clarithromycin**, cobicistat, indinavir, **itraconazole**, ketoconazole, mifepristone, nefazodone, nelfinavir, paritaprevir, **posaconazole, ritonavir** (part of PAXLOVID), saquinavir, telaprevir, **voriconazole**	**bupropion**, cinacalcet, delavirdine, **fluoxetine, paroxetine, quinidine, ritonavir, terbinafine**, tipranavir
WEAK TO MODERATE	acyclovir, amiodarone, cimetidine, fluconazole, gemfibrozil, norfloxacin, ofloxacin, verapamil	amiodarone, cotrimoxazole, efavirenz, etravirine, fluconazole, fluoxetine, fluvastatin, fluvoxamine, isoniazid, ketoconazole, metronidazole, omeprazole, paroxetine, ticagrelor, quinine, valproate, voriconazole	cannabidiol, cimetidine, cinacalcet, efavirenz, eslicarbazepine, esomeprazole, etravirine, fluoxetine, isoniazid, ketoconazole, moclobemide, modafinil, omeprazole*, oxcarbazepine, voriconazole	amiodarone, aprepitant, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit, imatinib, verapamil	amiodarone, chloroquine, cimetidine, clomipramine, cobicistat, diphenhydramine, dronedarone, duloxetine, fluvoxamine, haloperidol, isoniazid, ketoconazole, methadone, mirabegron, quinine, ticlopidine
CYP Substrates **Levels** ↑ by inhibitors & levels ↓ by inducers.	acetaminophen, amitriptyline, caffeine, clomipramine, **clopidogrel, clozapine**, cyclobenzaprine, desipramine, diazepam, diphenhydramine, duloxetine, erlotinib, estradiol, flutamide, fluvoxamine, haloperidol, imipramine, **methadone**, olanzapine, ondansetron, pomalidomide, propranolol, tizanidine, **theophylline**, verapamil, **warfarin**	abrocitinib , amitriptyline, carvedilol, celecoxib, clomipramine, diazepam, diclofenac, diphenhydramine, doxepin, erdafitinib, fluoxetine, glimepiride, glyburide, ibuprofen, imipramine, indomethacin, irbesartan, lesinurad, losartan, **methadone**, montelukast, naproxen, omeprazole, **phenobarbital**, phenytoin, rosiglitazone, sildenafil, sulfamethoxazole, tamoxifen, valsartan, vardenafil, **warfarin**	abrocitinib, amitriptyline, citalopram, clobazam, clomipramine, clopidogrel, desipramine, diazepam, diphenhydramine, doxepin, escitalopram, indomethacin, mavacamten, **methadone**, **phenobarbital**, **phenytoin**, PPIs, progesterone, propranolol, sertraline, **warfarin**	abemaciclib, alfuzosin, alpelisib, alprazolam, amitriptyline, amiodarone, amlodipine, apalutamide, **apixaban**, aripiprazole, **atorvastatin**, avapritinib, brigatinib, budesonide, buprenorphine, cabozantinib , carbamazepine, chloroquine, citalopram, clarithro-/erythro-mycin, clonazepam, **colchicine**, copanlisib, cyclosporine, darolutamide, deflazacort, dexamethasone, diltiazem, domperidone, donepezil, drospirenone, efavirenz, elagolix, eletriptan elexacaftor, entrectinib, erdafitinib, ergot derivatives, estradiol, fedratinib, felodipine, fentanyl, finerenone, fluticasone, galantamine, gilteritinib, glasdegib, haloperidol, hydrocodone, istradefylline, ivabradine, ivacaftor, larotrectinib, lemborexant, lomitapide, lorlatinib, lumateperone, **lovastatin**, mavacamten, methadone, midazolam, nintedanib, neratinib, nevirapine, nifedipine, olaparib, oral contraceptives, oxycodone, paroxetine, pimavanserin, PKIs (cxcr, PPIs, quetiapine, ribociclib, rifabutin, risperidone, ritonavir, **rivaroxaban**, saxagliptin, sertraline, sildenafil, simvastatin, sunitinib, **tacrolimus**, tadalafil, tamoxifen, tamsulosin, tezacaftor, ticagrelor, tolterodine, tolvaptan, trazodone, triazolam, upadacitinib, ubrogepant, velpatasvir, venetoclax, verapamil, vilazodone, **warfarin**, zopiclone. (Many **oncology** ____: including many -**nibs**)	amitriptyline, amphetamine, aripiprazole, atomoxetine, bisoprolol, carvedilol, chloroquine, clomipramine, clozapine, codeine, cyclobenzaprine, cyclophosphamide, desipramine, dextromethorphan, diphenhydramine, donepezil, doxepin, duloxetine, eliglustat, fesoterodine, flecainide, fluoxetine, fluvoxamine, galantamine, gefitinib, haloperidol, hydrocodone, imipramine, methamphetamine, metoprolol, mirtazapine, nortriptyline, olanzapine, ondansetron, oxycodone, paroxetine, perphenazine, propranolol, risperidone, **ritonavir**, tamoxifen, timolol, tramadol, trazodone, venlafaxine, zuclopenthixol

*Omeprazole & Clopidogrel: omeprazole (and esomeprazole) may ↓ clopidogrel's conversion to active drug. Some evidence suggests not clinically significant. May consider changing PPI to pantoprazole, lansoprazole, or rabeprazole.

P-glycoprotein (p-gp) is an efflux pump; it removes drug from a cell. The results of inhibiting or inducing p-gp depend on its location in the body. However, in the majority of cases inhibiting p-glycoprotein increases drug levels, as the pump is highly prevalent along the intestinal tract (& inhibition here prevents drug from being put back into the gut). For example, dabigatran (p-gp substrate) will have increased levels when given with verapamil (p-gp inhibitor).

P-Gp Inducers	carbamazepine, dexamethasone, phenobarbital, phenytoin, primidone, rifampin, St. John's Wort
P-Gp Inhibitors	amiodarone, **carvedilol**, clarithromycin, cobicistat, **cyclosporine**, **daclatasvir**, diltiazem, dronedarone, duloxetine, erythromycin, grapefruit, indinavir, itraconazole, ketoconazole, ledipasvir, **mefloquine**, mifepristone, nelfinavir, paritaprevir, posaconazole, **propafenone**, quinidine, ritonavir, saquinavir, **simeprevir**, tacrolimus, **tamoxifen**, telaprevir, ticagrelor, velpatasvir, verapamil
P-Gp Substrates	amiodarone, **apixaban**, boceprevir, citalopram, cyclosporine, **dabigatran**, dexamethasone, **digoxin**, diltiazem, **edoxaban**, erythromycin, gilteritinib, indinavir, loperamide, lovastatin, nelfinavir, posaconazole, prednisone, ranitidine, rifampin, ritonavir, **rivaroxaban**, saquinavir, sertraline, sofosbuvir, talazoparib, telaprevir, velpatasvir, verapamil. (**Oncology** meds: including many -nibs)

Organic anion-transporting polypeptides (OATPs) are influx pumps; they pumps drug into a cell. The results of inhibiting OATP depend on its location: if at the kidney, ↑levels; if at the liver, ↑levels; if in the GI tract, ↓levels. For example, simvastatin (OATP substrate in the liver) will have increased levels when given with cyclosporine (OATP inhibitor).

OATP Inhibitors	clarithromycin, cobicistat, cyclosporine, erythromycin, gemfibrozil, grapefruit, ketoconazole, rifampin, ritonavir, saquinavir, telaprevir, velpatasvir & voxilaprevir
OATP Substrates	ARBs, ciprofloxacin, erythromycin, montelukast, revefenacin , statins

The ADME Journey

Memory Trick: "All Drugs Must Exit"

ADME: The Four Pillars of Pharmacokinetics



ABSORPTION

Drug enters bloodstream from administration site



DISTRIBUTION

Drug travels to target tissues throughout body



METABOLISM

Drug is chemically changed (mainly in liver)



EXCRETION

Drug and metabolites leave the body

Excretion

Understanding how drugs leave the body and why people respond differently

Clinical Pearl: Remember: What goes in must come out! But the "how" and "when" varies greatly between patients.

By the end of this presentation, you will understand:

- Four major routes of drug excretion
- How kidneys eliminate drugs (the main pathway!)
- Why the same drug affects patients differently
- Clinical factors that influence drug response
- How to apply this knowledge in practice



Excretion



Removal of unchanged drug from the body

- Renal excretion (primary organ responsible for excretion)
- Biliary excretion
- Bowel excretion
- Lung excretion (Exhaled)
- Breast milk
- Other : sweat-saliva- hair-skin

🔑 **Key Point:** Excretion is the final step in pharmacokinetics, but individual variation affects ALL steps!

Renal Drug Excretion: The Main Event



Blood Filtration → Selective Reabsorption → Waste Excretion

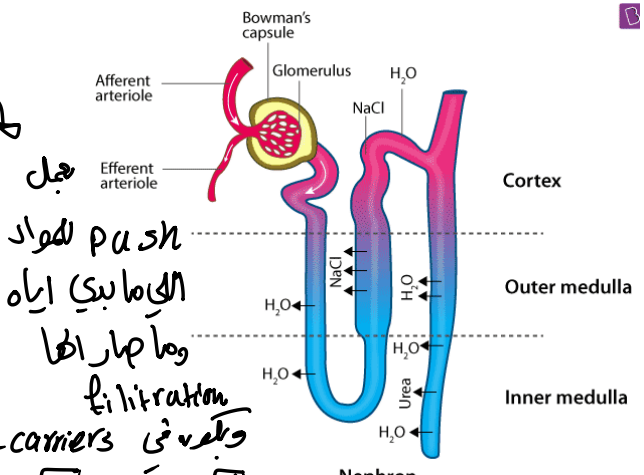
زي الكلوز بدي اياه في الجسم حتى ترجعه لا Blood

1. Glomerular Filtration

- Only free (unbound) drug is filtered
- GFR normally ~125 mL/min
- Reduced in kidney disease

2. Active Tubular Secretion

- Occurs through active transport:
- Two transport systems: anions and cations
- Can cause drug-drug interactions
- Occurs mainly in proximal tubule
- Example: Penicillin and probenecid



هجل push للمواد الكيميائية اياه وطرحها filitration وبتعبر في 2 carriers 1 cation + 1 anion

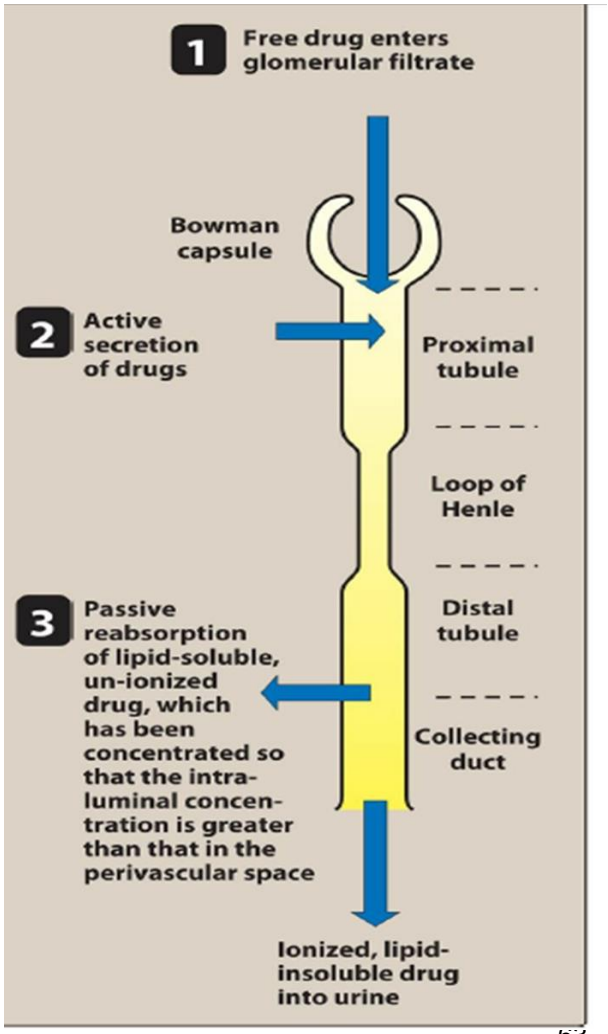
3. Passive Tubular Reabsorption

- Passive reabsorption of lipid soluble and uncharged drugs
- pH affects ionization → unionized to be absorbed
- Ion trapping can enhance elimination → make the drug ionized to prevent reabsorption



What Gets Excreted?

- **Water-soluble drugs** and **metabolites**
- **Ionized forms** (can't cross back into blood)
- **Waste products** that body doesn't need



Ion Trapping for Enhanced Elimination

Principle: Manipulate urine pH to keep drug ionized → prevent reabsorption → enhance elimination

نستخدم هذه الطريقة لعلاج الـ over dose حيث ما أسمح للدواء بأنه يرجع يمتص فنخليه متأين

Weak Acids

Alkalize urine (bicarbonate)

- Phenobarbital overdose
- Salicylate poisoning
- Methanol poisoning

$$HA + HCO_3^- \rightarrow A^- + H_2CO_3$$

(ionized = trapped)

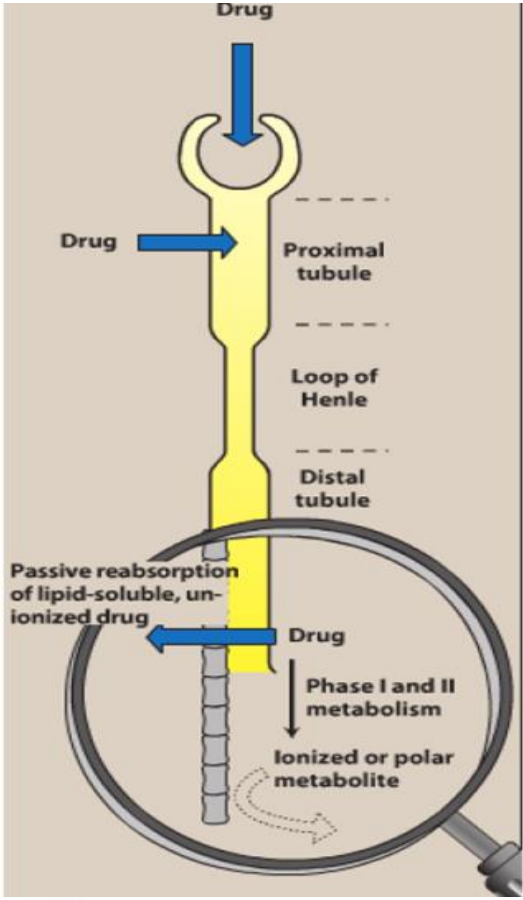
Weak Bases

Acidify urine (ammonium chloride)

- Amphetamine overdose
- PCP intoxication

$$B + H^+ \rightarrow BH^+$$

(ionized = trapped)



Clinical Pearl: Ion trapping is most effective when pKa is within 1-2 pH units of target urine pH

Clinical Application: Overdose Treatment



Real-World Example: Barbiturate/Aspirin Overdose

Problem: Patient overdosed on aspirin (acidic drug)

Solution: Give sodium bicarbonate to alkalinize urine

Result: More aspirin becomes ionized → Can't reabsorb → Faster elimination!

> **Clinical Pearl:** Acid drugs ionize in alkaline urine, basic drugs ionize in acid urine. This is key for overdose treatment!

Drug Type	Urine pH for Excretion	Treatment
Acidic drugs (Aspirin, Barbiturates)	Alkaline (pH > 7)	Sodium bicarbonate
Basic drugs (Amphetamines)	Acidic (pH < 7)	Ammonium chloride

> **Key Point:** **Manipulating urine pH can save lives in overdose situations!**



GI Excretion – Two Pathways

1. Simple Fecal Excretion

Unabsorbed drug passes straight through and exits in feces

2. Enterohepatic Circulation - The Recycling System

first-pass

Liver processes drug

↓

Drug enters bile

↓

Released into intestines

↓

Reabsorbed back to blood

↓

Back to liver - CYCLE REPEATS!

CLINICAL PEARL :**Fat-soluble drugs** love this recycling system - that's why they have longer durations of action!

Respiratory Excretion



When Lungs Do the Work:

1. Volatile anesthetics (like isoflurane)
2. Alcohol (that's why breathalyzers work!)
3. Acetone (in diabetic ketoacidosis)

Other Routes (Miscellaneous)

Route	Clinical Significance
Sweat	Drug testing, skin reactions
Saliva	Drug monitoring, forensics
Breast milk	Infant drug exposure during nursing

Critical for nursing mothers: Many drugs appear in breast milk and can affect the baby!

Clinical Significance

The relative contribution of excretion vs metabolism determines dosing strategies and drug interactions

High Excretion Rate

Example: Aminoglycosides

•Adjust dose in renal impairment

• Monitor kidney function

• Minimal drug interaction

High Metabolism Rate

Example: Warfarin

Consider enzyme inducers/inhibitors

• Genetic testing for metabolism

• Adjust for liver function

يتم التخلص منه عن طريق الـ kidney فلو فيها مشكلة الدواء رح يضل في الجسم بالتالي لازم أقلل الجرعة

Key Clinical Point

Understanding which process dominates helps predict:
• Drug-drug interactions • Dosing in organ impairment • Individual variability

Excretion vs Elimination in Pharmacokinetics

Relationship

Total Elimination = Excretion + Metabolism

Excretion



Physical removal of **unchanged drug** from the body through various routes

Routes of Excretion:

Renal: Kidneys filter drug into urine

Biliary: Liver secretes drug into bile

Pulmonary: Lungs exhale volatile drugs. **Other:** Sweat, saliva, breast milk

Elimination



(metabolism + excretion)

All processes that remove drug from systemic circulation

Includes: Excretion: Removal of unchanged drug

Metabolism: Biotransformation to metabolites

Other clearance: Additional mechanisms

Key Difference

Excretion = Removal of unchanged drug

Elimination = Excretion + Metabolism + Other clearance

Rate of Excretion *vs* Rate of Metabolism

Rate of Excretion

Speed at which **unchanged drug** is physically removed from the body through various routes

$$\textbf{Rate} = CL_r \times C_p$$

CL_r = Renal clearance

C_p = Plasma concentration

Factors Affecting Rate:

Kidney function (GFR, tubular function)

- **Urine pH** (affects ionization) → reabsorption في
- **Plasma protein binding** → مايكون drug قادر
- **Active transport** (renal pumps)
- **Drug concentration** in plasma يروح على kidney

Rate of Metabolism

Speed at which drug is biotransformed (chemically transformed) into metabolites by enzymatic processes usually in the liver

$$\textbf{Rate} = CL_m \times C_p$$

CL_m = Metabolic clearance

C_p = Plasma concentration

Factors Affecting Rate:

Enzyme activity (CYP450 system)

- **Genetic polymorphisms**
- **Age and liver function**
- **Drug interactions (induction/inhibition)**
- **First-pass effect**

Overall Elimination Rate : Rate of Elimination = Rate of Excretion + Rate of Metabolism

$$(CL_r + CL_m) \times C_p = CL_total \times C_p$$

Drug Elimination Kinetics

Understanding First-Order and Zero-Order Elimination Processes

Once a drug enters the body, elimination begins immediately through three major routes. The plasma concentration decreases exponentially, with a constant fraction eliminated per unit time.



Zero–Order vs First–Order Kinetics



Zero-Order Kinetics (Nonlinear)

Characteristic: Constant amount eliminated per unit time
Examples: Aspirin (high doses), Ethanol, Phenytoin
Half-life: Variable (enzymes saturated)
Half-life increases with dose

First-Order Kinetics (Linear)

Characteristic: Constant fraction eliminated per unit time
Examples: Most drugs at therapeutic doses
Half-life: Constant (50% reduction each $t_{1/2}$)
Most drugs follow this pattern

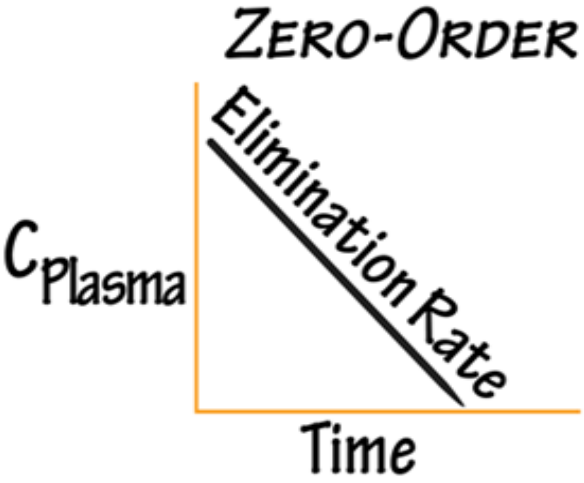
Zero-Order Kinetics Examples (PEAS):

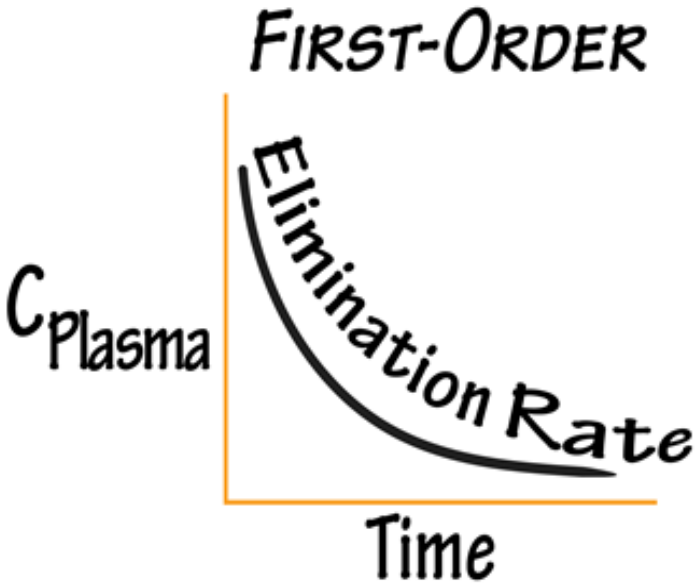
Ethanol: Fixed amount metabolized per hour

Phenytoin: At therapeutic doses

Aspirin: At high doses

Salicylates : Overdose





0 Zero-Order Kinetics

Saturation kinetics

- Constant **amount** eliminated per time
- Linear on regular plot
- Half-life increases with dose
- Elimination enzymes saturated

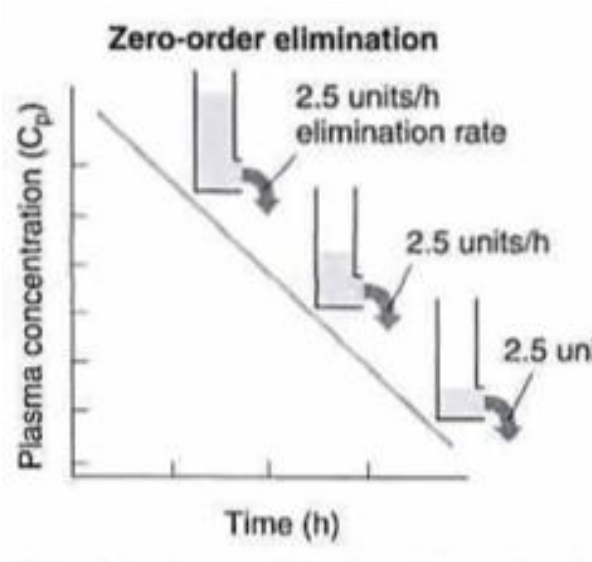
$$C(t) = C_0 - kt$$
(Half-life not constant)

يعني مثلاً كل 2.5 ساعة في 2.5 unit راح يصير اها elimination

وكل ما زادت ال dose راح تزيد ال half-life

وبعتمد على انزيمات حيث لو زادت ال dose راح يصير اها saturation

وهون ال elimination يصير ثابت



First-Order Kinetics

Most common (95% of drugs)

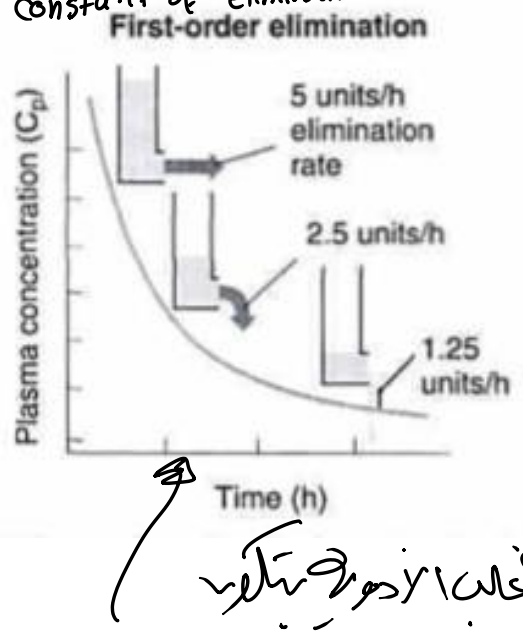
- Constant **fraction** eliminated per time
- Linear on semi-log plot
- Half-life remains constant
- Elimination proportional to concentration

نسبة معينة من الدواء راح يصير اها elimination في وقت معين

$$C(t) = C_0 \times e^{(-kt)}$$
$$t_{1/2} = 0.693/k$$

وهنا ال $t_{1/2}$ بتبقى ثابت

لل drug constant of elimination



أعلى ازدحام بتكون

Half-Life and Clearance

Clinical Pearl

Half-life considerations: Drug half-life is often used as a measure of clearance because, for many drugs, the volume of distribution (V_d) remains relatively constant. However, factors like tissue sequestration, protein binding changes, or altered metabolism can affect these relationships.

Half-Life ($t_{1/2}$)

- Time to reduce plasma concentration of a given drug by 50% from the body
- 5 half-lives = 97% elimination (steady state)= effectively removed from the body.
- Independent of dose (first-order kinetics)

$$t_{1/2} = 0.693 / K_{elimination}$$

لا تعتمد على dose ال

كمية الدواء اللي بصير ال absorption = كمية الدواء اللي بصير ال elimination

يعني مجموعة من الثبات لتركيز الدواء في الجسم وهذا يعني انه الدواء وصل لـ therapeutic activity

Drug Clearance

The amount of drug cleared from the body per unit of time

Total Body Clearance: Volume of plasma cleared of drug

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

Clinical Situations Affecting Clearance → تعرف كيف بصير الدواء elemination فلو الشخص عنده مشكلة بكلها

Clearance (CL) Types: Hepatic, Renal, Total body clearance
intestine, bile, milk

↓ Clearance (↑ t½):
- Heart failure
- Liver cirrhosis
- Kidney disease
- Drug interactions (inhibition)
- Elderly patients

↓ blood flow → ↓ blood in kidney (Blood 25%) → ↓ CL

↓ enzymetic activity + ↓ function of the liver & kidney → ↓ CL

Requires dose reduction or ↑ dosing interval

↑ Clearance (↓ t½): metabolism زيادة في
- Enzyme induction
- Pregnancy (↑ GFR)
- Hyperthyroidism → زيادة افراز الغدة الدرقية
- ↓ Protein binding → drug ما راح يلتصق في تم تزنيخ في البروتينات وراح يلتصق في free زيادة في كمية

May require ↑ dose or ↓ dosing interval

Drug Clearance Formula

$$CL = (0.693 \times V_d) / t_{1/2}$$

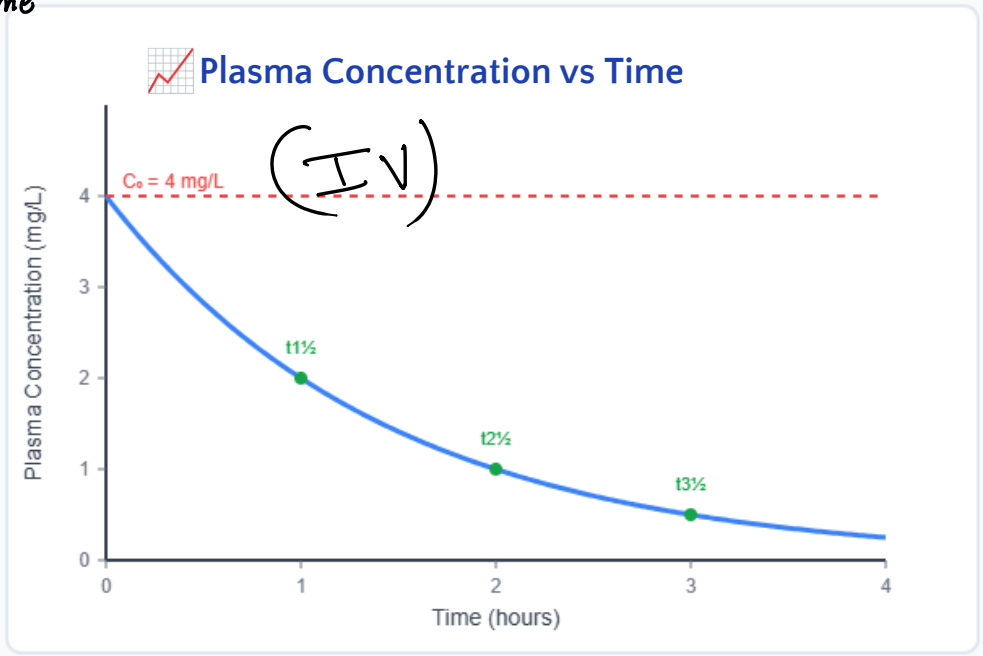
Where:
CL = Total clearance (amount of drug cleared per unit time) (hepatic + renal)
V_d = Apparent volume of distribution = amount (dose) / volume
$t_{1/2}$ = Elimination half-life
0.693 = Natural logarithm constant (ln 2)

بستفيد من Vd و CL بأنه أوصل الدواء لل steady state حيث أحافظ على الدواء بتركيز ثابت في الجسم وبوصل إلها بعد ١، ٢، ٤ +1/2 (maintenance dose) منها أجا مفروض

له أعطي الدواء كل عدد معين من الساعات أكثر من مرة

Clinical Applications

- **Loading dose:** Depends on Vd
- **Maintenance dose:** Depends on clearance
- **Dosing interval:** Usually 1-2 half-lives



Key Insight: Extrapolation to time zero gives C_0, the hypothetical drug concentration if distribution had occurred instantly.

Question # 3

A drug has $t_{1/2}$ = 4 hours and V_d = 50 L
Calculate: Total clearance (CL) ?

Solution: CL= 0.693 x Vd / t1/2

CL = (0.693 × 50 L) / 4 h = 8.66 L/h
Interpretation: 8.66 liters of plasma are completely cleared of drug every hour

Question # 4

A drug has a half-life of 12 hours. How long to reach steady state?

Answer: 4-5 × 12 hours = 48-60 hours

Question #5

- A drug has a half-life of 12 hours. How long to reach steady state?

- **Answer:** 4–5 × 12 hours = 48–60 hours

Question # 6

A weakly basic drug (pKa 7.8) - where is it best absorbed?

- A. Stomach (pH 2.5)
- B. Duodenum (pH 6.1)
- C. Jejunum (pH 8.0)

Answer: Basic drugs are better absorbed in basic environments

Dosing Regimens

Dosage regimen is defined as the manner in which a drug is administered.

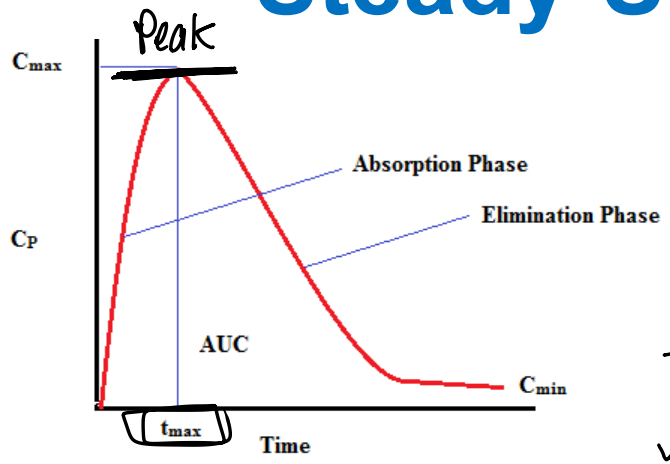
Dosage regimen is composed of:

1. The magnitude of each dose (dose size)
2. The frequency with which the dose is repeated (dosing interval)

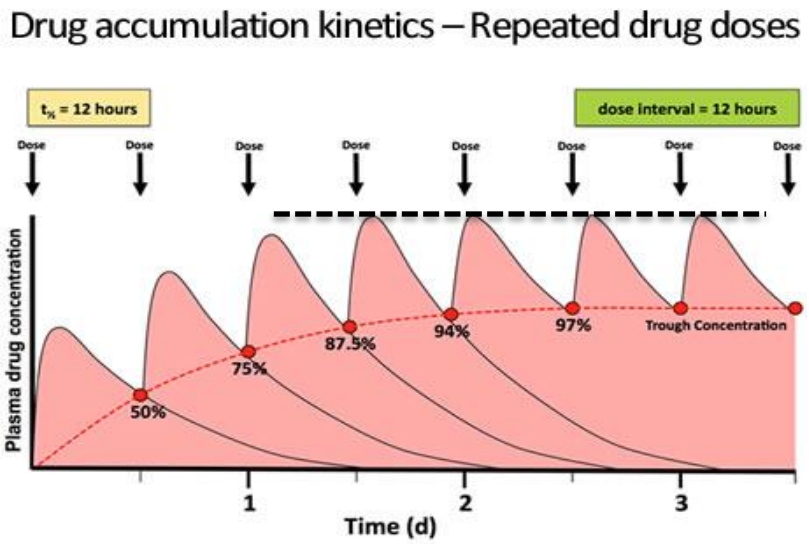
- ❖ Some drugs like antiemetics and anthelmintics, need only a single dose that provide effective treatment. No drug accumulation and no need for a constant therapeutic plasma concentration
- ❖ Many drugs like antimicrobials, antihypertensives and antiarrhythmics require continuation of drug : IV infusion or (multiple doses) at appropriate intervals over a period of time

An optimal dosage regimen is to: identify a dose that preserves **clinical benefit** (maximum benefit) with **optimal tolerability** (least adverse effects)

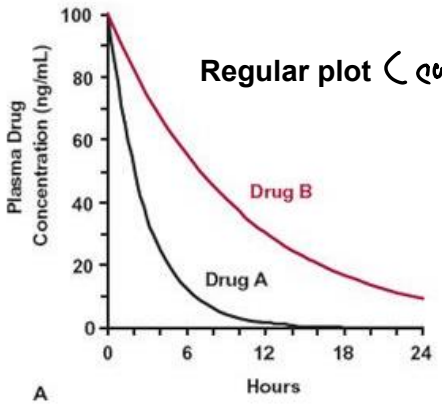
Steady-State Pharmacokinetics

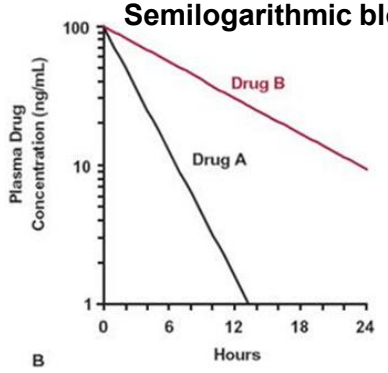


بعد جرعة واحدة
فقط بتأثر RoA
بصير فيه absorption

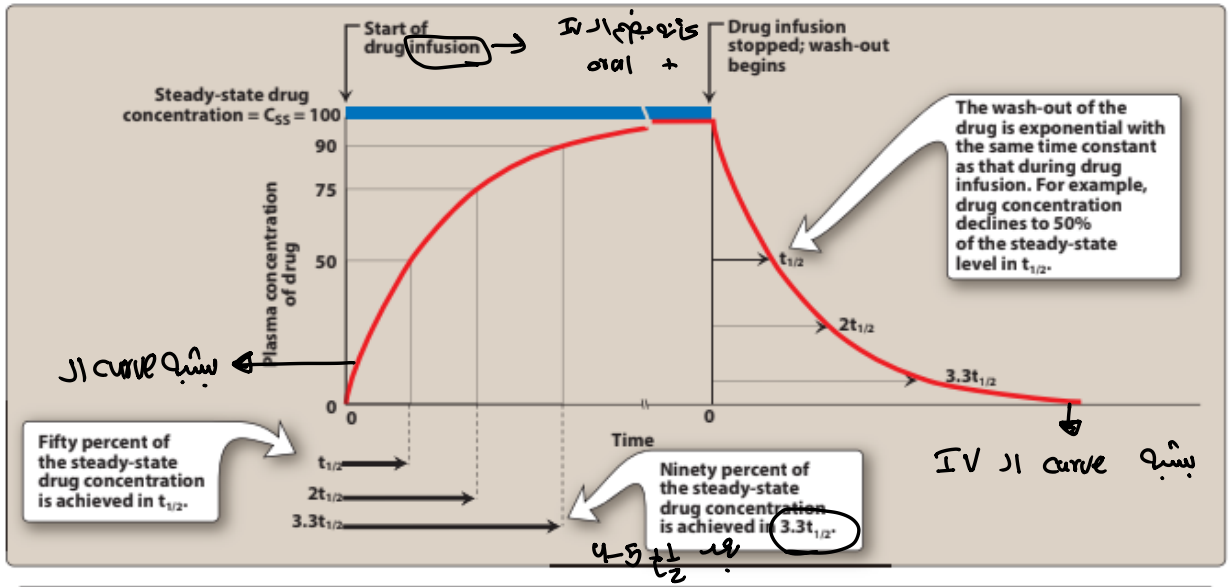


بعض الجرعة الثانية
بتعطى قبل ما يصير
عند الـ elimination
بشكل كامل عشان
أحافظ على الـ steady state
للعلاج في جسم المريض





oral



بشبه الـ curve

بشبه الـ IV curve

Figure 1.22
Rate of attainment of steady-state concentration of a drug in the plasma after intravenous infusion.

Steady-State Pharmacokinetics

In continues dosage regimens, the drug accumulates until a steady state occurs

Steady State Definition:

Rate of drug input = Rate of drug elimination

Time to Steady State

- **Achieved in 4-5 half-lives**
- 50% of steady state at 1 half-life
- 75% of steady state at 2 half-lives
- 87.5% of steady state at 3 half-lives
- 90% of steady state at 3.3 half-lives

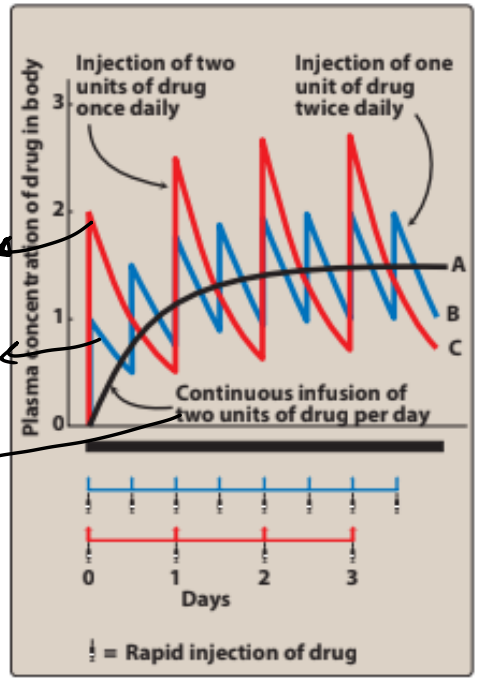


Figure 1.23
Predicted plasma concentrations of a drug given by infusion **(A)**, twice-daily injection **(B)**, or once-daily injection **(C)**. Model assumes rapid mixing in a single body compartment and a half-life of 12 hours.

Bioavailability

Steady-State Concentration (Css) = (Dosing Rate × F) / Clearance

Factors Affecting Steady State

↑ Steady-State Levels:

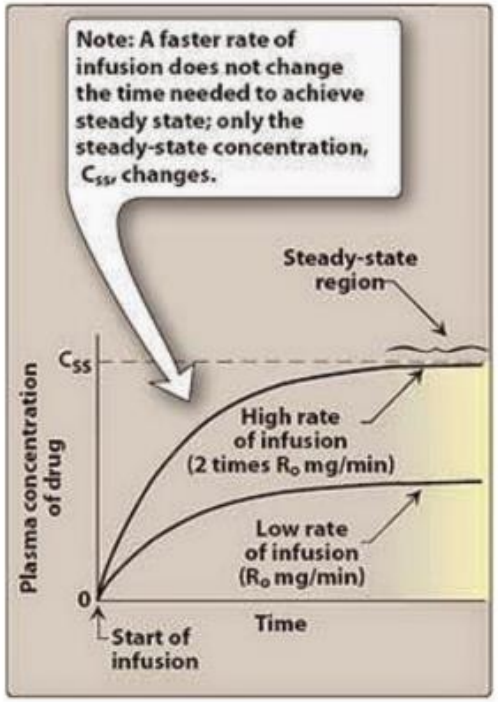
- ↑ Dosing rate →
- ↓ Clearance (kidney/liver disease)
- ↓ Metabolism (enzyme inhibition)

↓ Steady-State Levels:

- ↓ Dosing rate
- ↑ Clearance
- ↑ Metabolism (enzyme induction)

Influence of the rate of drug infusion on the steady state

The steady state plasma concentration (Css) is directly proportional to the infusion rate



Effect of infusion rate on the steady-state concentration of drug in the plasma. (Ro = rate of infusion of a drug.)

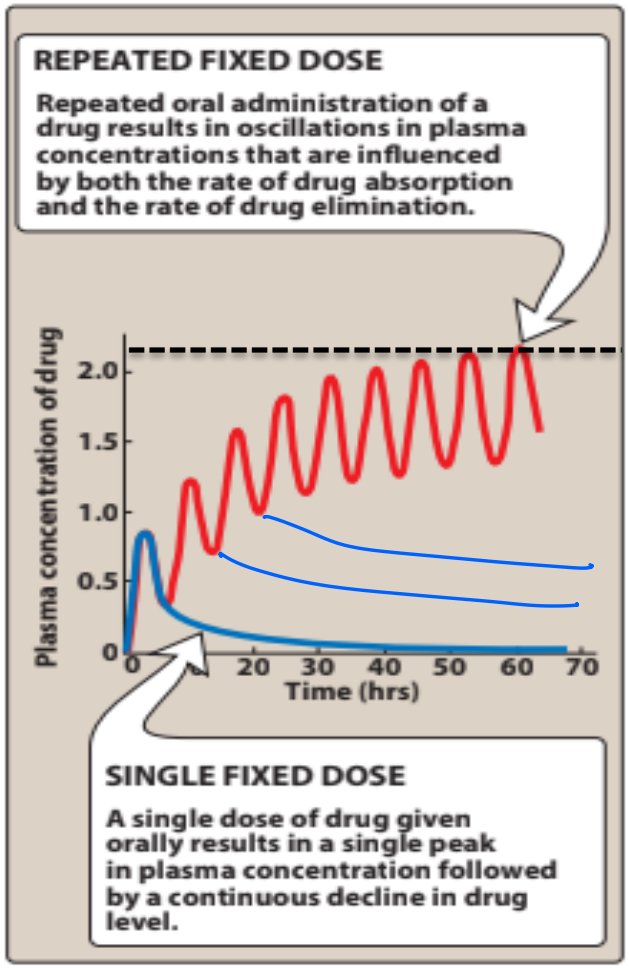
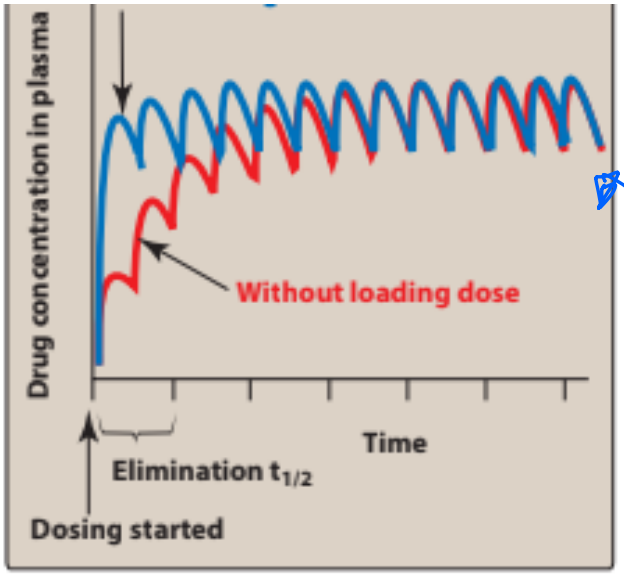


Figure 1.24
Predicted plasma concentrations of a drug given by repeated oral administrations.

هنا بعض الدواء رح أخرى قبل ما يتصير راح elimination steady state عشان أحافظ على ال



طريقة توصل لل steady state بسرعة مرة بعد ما تعطي أعطي dose أكبر من مرة

HOW CAN WE REACH STEADY STATE FROM THE BEGINNING ?

Loading Dose

```
Loading Dose = Vd × Target Concentration / F
```

Use when: Need rapid therapeutic levels

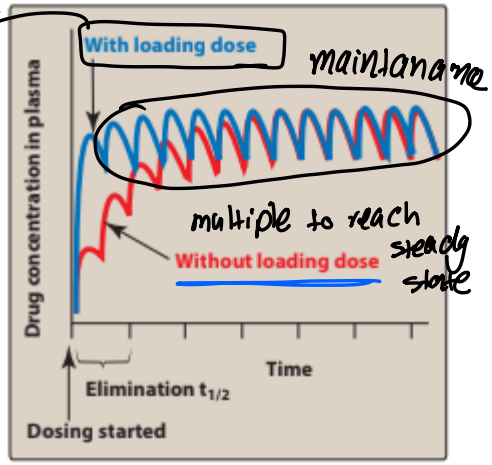


Figure 1.25
Accumulation of drug administered orally without a loading dose and with a single oral loading dose administered at t = 0.

Maintenance Dose

```
Maintenance Rate = CL × Target Concentration / F
```

Used for: Maintaining steady state

Clinical Scenarios

- **Status Epilepticus:** IV loading dose needed
- **Heart Failure:** Digoxin maintenance dosing
- **Renal Disease:** Dose adjustment required



Loading Dose Calculations

When to Use Loading Dose:

- Need rapid therapeutic effect
- Drug has long half-life
- Serious conditions (arrhythmias, infections)

Loading Dose = (Vd × Target Plasma Concentration) / F

For IV: Loading Dose = Vd × Target Plasma Concentration
(F = 1 for IV)

Loading doses ↑ risk of toxicity - monitor closely!

Clinical Examples:

Drug	Indication	Loading Dose Strategy
Digoxin	Heart failure	10-15 µg/kg IV over 24 hours
Phenytoin	Status epilepticus	15-20 mg/kg IV
Vancomycin	Serious infections	25-30 mg/kg IV

Dose Adjustment Calculations

When to Adjust Doses:

- Organ dysfunction (kidney, liver)
- Drug interactions
- Therapeutic drug monitoring results

Volume of Distribution Applications:

لو بدي أزود الجرعة — التركيز اللي بدي أوصله — التركيز الحالي

$$\text{Additional Dose} = Vd \times (C_2 - C_1)$$

Clinical Pearl: Example: Digoxin level is 1.0 ng/mL, target is 1.5 ng/mL

Vd = 7 L/kg × 70 kg = 490 L

Additional dose = 490 L × (1.5 - 1.0) ng/mL = 245 µg

Maintenance Dose Adjustment:

C_2 C_1

$$\text{New Dose} = \text{Old Dose} \times (\text{Target Level} / \text{Current Level})$$

dose adju. لا تعمل غير بعد half-lifes 3-4 لازم استنى

Wait for steady state (4-5 half-lives) before making dose adjustments!

Clinical Applications

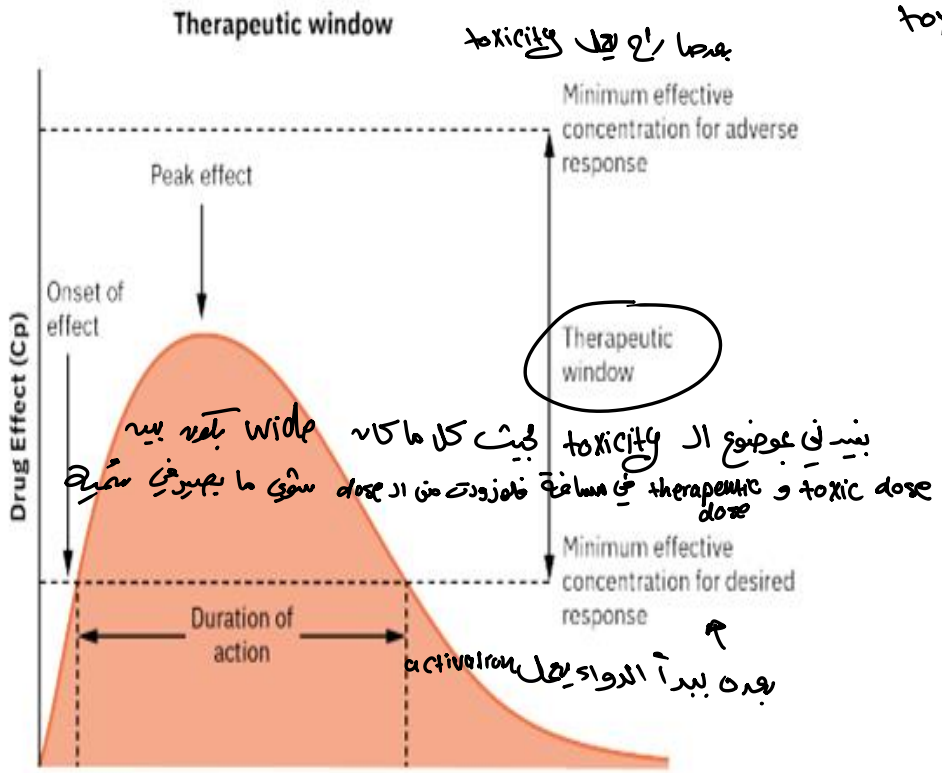


FIGURE 2.4 The therapeutic window of a medication includes the onset, peak, and duration of the medication. (attribution: Copyright Rice University, OpenStax, under CC BY 4.0 license)

Therapeutic Drug Monitoring

- **When to monitor:** Narrow therapeutic window
- Non-linear kinetics
- High inter-patient variability

Commonly Monitored Drugs:

- **Digoxin:** Narrow therapeutic range
- **Phenytoin:** Zero-order kinetics
- **Lithium:** Renal elimination
- **Aminoglycosides:** Nephrotoxicity/ototoxicity

Special Populations

- **Elderly:** Reduced clearance, altered Vd
- **Pediatric:** Immature metabolism
- **Renal disease:** Reduced clearance
- **Hepatic disease:** Reduced metabolism

Therapeutic Drug Monitoring (TDM)

> **Clinical Pearl:** Always wait for steady state before interpreting drug levels (unless toxicity suspected)

When to Monitor Drug Levels:

- Narrow therapeutic window
- Serious toxicity potential
- Large inter-patient variability
- Correlation between levels and effect



Drug	Therapeutic Range	Sample Timing	Toxicity Signs
Digoxin	1.0-2.0 ng/mL	Trough (before dose)	Arrhythmias, GI symptoms
Phenytoin	10-20 µg/mL	Trough	Ataxia, nystagmus
Vancomycin	15-20 µg/mL (trough)	Pre-dose	Nephrotoxicity, ototoxicity
Lithium	0.6-1.2 mEq/L	12h post-dose	Tremor, confusion

90% protein Binding

Clinical Application Scenarios

Scenario 1: Patient on warfarin starts omeprazole

Concern: CYP2C9 inhibition → ↑ warfarin levels → bleeding risk

Action: Monitor INR closely, consider dose reduction

Scenario 2: Phenobarbital

> **Clinical Pearl: Scenario 1:** Patient on warfarin starts omeprazole
>
> **Concern:** CYP2C9 inhibition → ↑ warfarin levels → bleeding risk
>
> **Action:** Monitor INR closely, consider dose reduction

> **Clinical Pearl: Scenario 2:** Phenobarbital

Why Patients Respond Differently?



The Big Question in Medicine

"Why doesn't the same drug work the same way in every patient?"



لـ التزام المريض بأخذ الدواء بمواعيده

Key point : Individual variation is why "one size fits all" doesn't work in medicine!

Age & Weight Factors

Age Considerations

1. **Infants & Children**: More sensitive to drugs
2. **Elderly**: Slower metabolism, more side effects
3. **Young Adults**: "Standard" drug responses

Weight & Dosing

Standard adult dose calculated for: **150 lbs = 70 Kg** , ages 16-65

Protein Binding يقل والعكس tissue كمية الدواء

Patient Weight	Dose Adjustment	Reason
100 lbs (small)= 45 Kg	Reduce dose	Less tissue to distribute to
200-300 lbs (large) = (90- 136) kg	May increase dose	More tissue volume

But weight isn't everything! Body composition (fat vs. muscle) matters just as much.

Pharmacokinetics in Special Populations



Pediatrics

- ↑ Vd/kg (more water)
- Immature enzyme systems
- ↓ Protein binding
- Immature kidney function



Geriatrics

- ↓ Vd for water-soluble drugs
- ↓ Albumin levels
- ↓ Hepatic metabolism
- ↓ Renal clearance

Pregnancy

- ↑ Plasma volume (↑ Vd)
- ↑ Renal clearance
- Hormonal effects on enzymes
- ↓ Albumin concentration

Critical Illness

- Altered protein binding
- ↓ Hepatic blood flow
- Fluid shifts affecting Vd
- Multi-organ dysfunction

Beers List of Medications

A list of medications that are generally considered potentially inappropriate for older adults

غير مناسبة للاستخدام عند ٦٥

A set of recommendations developed by the American Geriatrics Society (AGS) to improve medication safety in older populations

The recommendations are specifically tailored for individuals aged 65 and older

The most recent update to the AGS Beers Criteria was in 2023. The next update is expected in 2026 (as the updates are typically every three years)

- **Certain antihistamines** (like diphenhydramine)
- **Certain NSAIDs**:

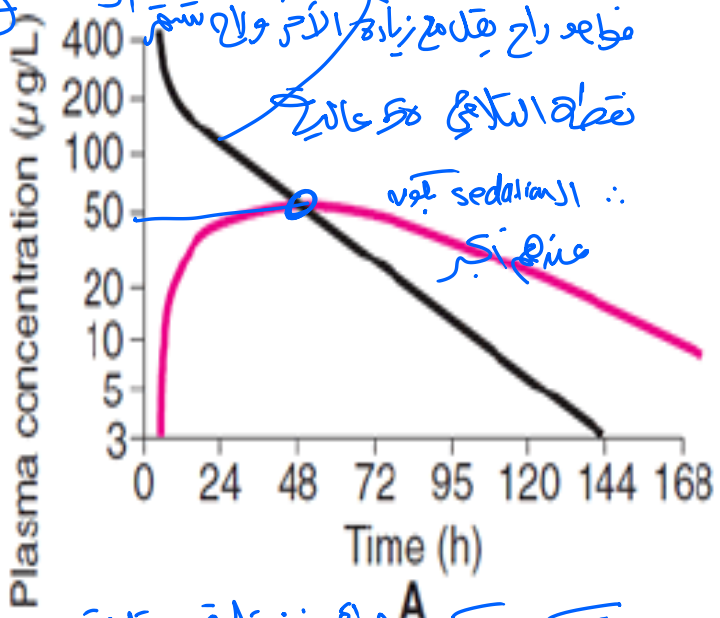
Some nonsteroidal anti-inflammatory drugs (like indomethacin) due to risks of gastrointestinal bleeding and kidney problems.

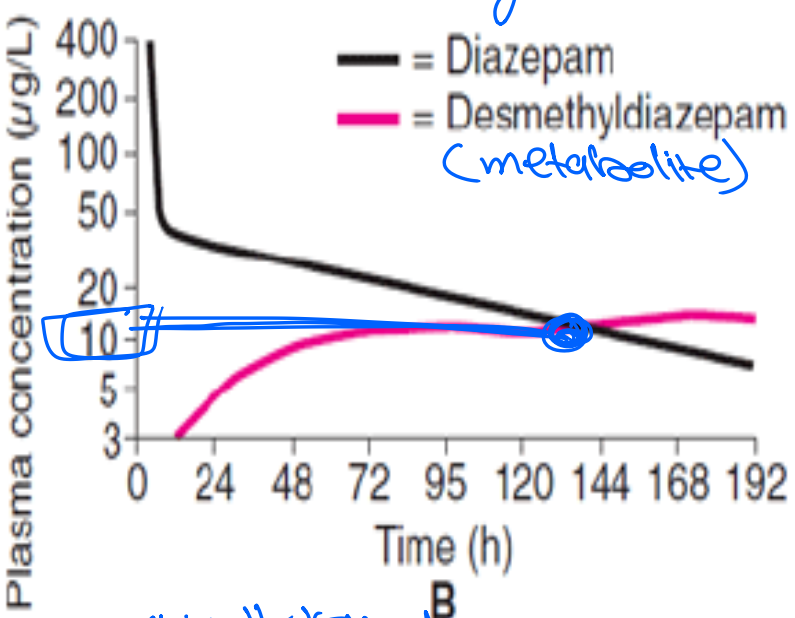
- **Certain sedative-hypnotics**:
- Some sleep medications (like zolpidem) due to risks of falls, confusion, and other side effects.
- **Certain antipsychotics**:
- Some antipsychotics due to risks of stroke, cognitive decline, and other side effects.
- **Certain muscle relaxants**:
- Some muscle relaxants due to risks of sedation, falls, and other side effects.

Pharm Logic Plus

Comparison of Pharmacokinetic Outcomes for Diazepam in a Younger Man (A) and an Older Man (B)

Diazepam is metabolized in the liver to desmethyldiazepam through P-450 enzymes. Desmethyldiazepam is an active sedative, which is excreted by the kidneys. 0 = time of dosing. (Adapted from Greenblatt DJ, Allen MD, Harmatz JS, Shader RI: Diazepam disposition determinants. *Clin Pharmacol Ther* 27:301–312, 1980. doi: 10.1038/clpt.1980.40)





https://www.msdmanuals.com/professional/multimedia/image/comparison-of-pharmacokinetic-outcomes-for-diazepam-in-a-younger-man-a-and-an-older-man-b

MSD
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Sex Differences & Body Fat



Characteristic of Females & Males Clinical Impact
Body Fat : Higher % affects lipid-soluble drug distribution
Body Water : Lower % affects Water-soluble drugs ……..more concentrated in females

What This Means Clinically?

- Females may experience **stronger effects** from water-soluble drugs
- Lipid-soluble drugs **last longer** in patients with more body fat

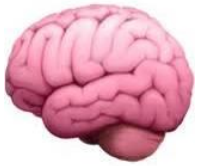
Same dose ≠ same effect between sexes

This is why many drugs now have sex-specific dosing recommendations!
Examples: dose adjustments for : Zolpidem, methylphenidate, and dabigatran.

Genetics & Psychological Factors

Genetic Variation

1. Inherited enzyme patterns from parents
2. Some people missing key enzymes → slow drug metabolism
3. Result: Same drug, very different effects!



Emotional State Impact

Example: Anxious patient may need higher dose of sedative than calm patient

- Stress hormones affect drug metabolism → cortizole
- Anxiety can counteract sedating effects
- Mental state influences physical response

> **Clinical Pearl:** Always consider the patient's mental state when prescribing - it's not just about the diagnosis!

The Placebo Effect - Mind Over Medicine

What is the Placebo Effect?

Patient improvement due to belief in treatment, not the treatment itself

إنا المريض مقتنع بأنه هذا الدواء لو أخذه راح يخبب وفعلاً يخبب وكله بسبب قناعته
بس عيادة عندنا achve دواء ما فيه مقتنع إنه راح يخبب بسبب راح يخبب بعض الدكتور يعطي المريض

Patient Attitude= Expected Outcome

Actual Response Positive, hopeful "This will help me" ⟶ Often reports improvement

Actual Response Negative, skeptical "Nothing will work" ⟶ Often reports no improvement

> **Clinical Pearl:** Up to 30% of patients improve with placebo treatment alone! Use this to enhance patient care through positive communication.

Key point : The placebo effect is real medicine - harness it ethically to improve patient outcomes!

Pharm Logic Plus

Clinical Bottom Line

Personalized medicine starts with understanding these principles!

Every patient is unique - adjust your approach accordingly.

Pharmacokinetics Summary

Remember ADME:

Absorption → Distribution → Metabolism → Elimination

Key Clinical Concepts



- Thorough understanding of pharmacologic principles is essential for safe, quality nursing practice.
- Application of principles enables the nurse to provide safe and effective drug therapy.

Pharm Logic Plus

Clinical Decision Making:

- **Loading dose** based on Vd
- **Maintenance dose** based on clearance
- **Dosing frequency** based on half-life
- **Route selection** based on bioavailability and patient factors

Clinical Pearl: Understanding pharmacokinetics helps optimize drug therapy for individual patients!



Key Takeaways

🎯 Absorption

- pH and pKa relationship
- Bioavailability factors
- First-pass metabolism

🌐 Distribution

- Volume of distribution
- Protein binding effects
- Blood flow importance

Metabolism

- CYP450 system
- Drug interactions
- Genetic variations

Excretion

- Renal clearance
- Ion trapping
- Dose adjustments

Pharm Logic Plus





Thank you




"Tell me and I forget; teach me and I may remember; but involve me and I learn."
Benjamin Franklin
UMKC
School of Pharmacy

General Pharmacology

Esmaa Motawe

PhD in Pharmacology and Toxicology/ Pharmaceutical Sciences

2025

June 24, 2025

PharmacoDYNAMICS

"What Drugs Do to the Body"



Journey of Discovery:

From drug molecules to healing effects

Understanding Drug-Body Interactions & Mechanisms of Action





Learning Objectives



By the end of this lecture, you will be able to:

- **Define** pharmacodynamics and its clinical importance
- **Classify** different types of drug targets and receptors
- **Explain** drug-receptor interactions and binding mechanisms
- **Interpret** dose-response curves and their clinical significance
- **Differentiate** between agonists, antagonists, and partial agonists
- **Calculate** therapeutic index and understand drug safety
- **Recognize** unusual drug responses and their mechanisms

Question #1

A patient is complaining of severe pain and has orders for morphine sulfate. The nurse knows that the route that would give the slowest pain relief would be which route?

A. IV
B. IM
C. Subcutaneous
D. PO

ANS: D

Parenteral routes result in the fastest absorption and therefore also the fastest effects.



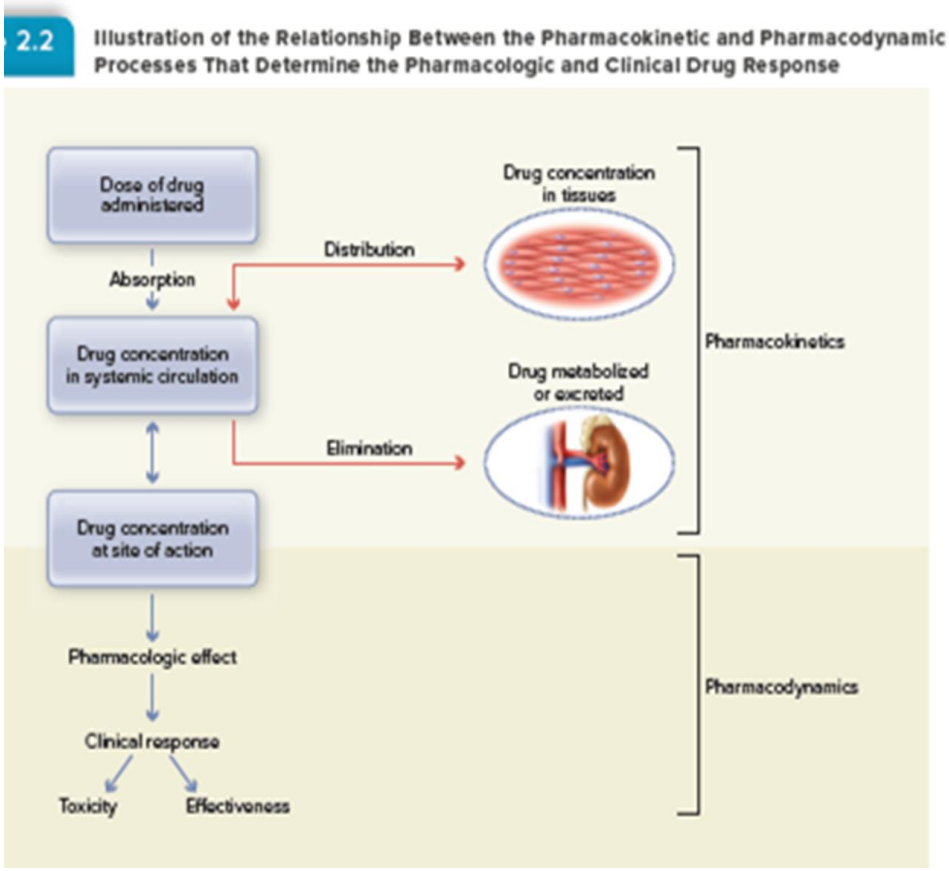
What is Pharmacodynamics?

The study of what the drug does to the body

The study of biochemical and physiological effects of drugs and their mechanisms of action

Key Components:

- **Mechanism of Action:** How drugs work at molecular level
- **Drug-Target Interactions:** Binding to specific biomolecules
- **Dose-Response Relationships:** Effect magnitude vs. drug amount
- **Time Course:** Onset, duration, and offset of effects



Clinical Pearl: Understanding pharmacodynamics helps predict drug efficacy, select appropriate doses, and anticipate adverse effects in patients.

Pharmacodynamics

The study of what the drug does to the body

- The mechanism of drug actions in living tissues
- Therapeutic effect
- Mechanism of action
- Drug–receptor relationships
- Enzymes
- Nonselective Interactions



Mechanism of Drug Action

Drugs exert effects through specific biological interactions, primarily at receptor sites. These interactions can initiate signal transduction pathways, resulting in diverse cellular responses depending on the drug's nature and concentration.



Drug Targets in the Body

Where Drugs Act?



Types of Drug Targets:

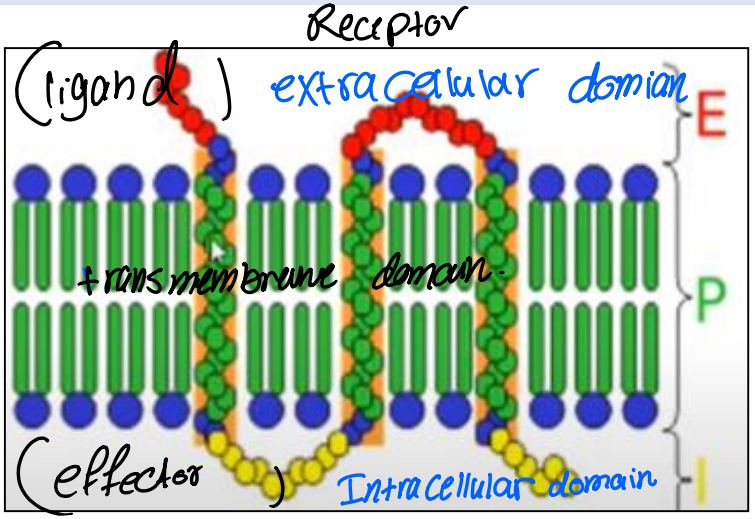
- **Receptors:** Most common target (~50% of drugs)
- **Enzymes:** Inhibition or activation
- **Ion Channels:** Control cellular excitability
- **Transport Systems:** Neurotransmitter reuptake could inhibit the reuptake
- **Nucleic Acids:** DNA/RNA interactions

Drug Receptors

Macromolecular components (usually proteins) that interact with drugs to produce biological responses

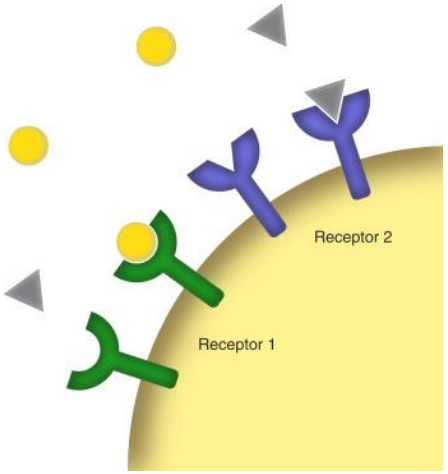
The receptor molecule has :

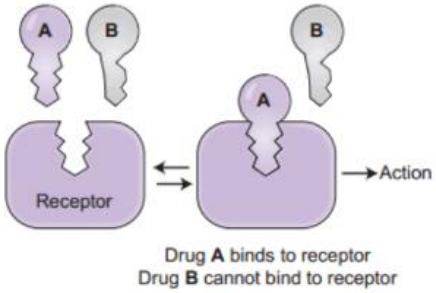
1. **Ligand binding domain**
2. **Effector domain** : undergoes a functional conformational change



Receptor Characteristics:

- **Specificity:** Selective binding to particular ligands
- **Affinity:** Strength of drug-receptor binding
- **Intrinsic Activity:** Ability to produce response after binding
- **Location:** Cell surface (membrane), cytoplasm, or nucleus



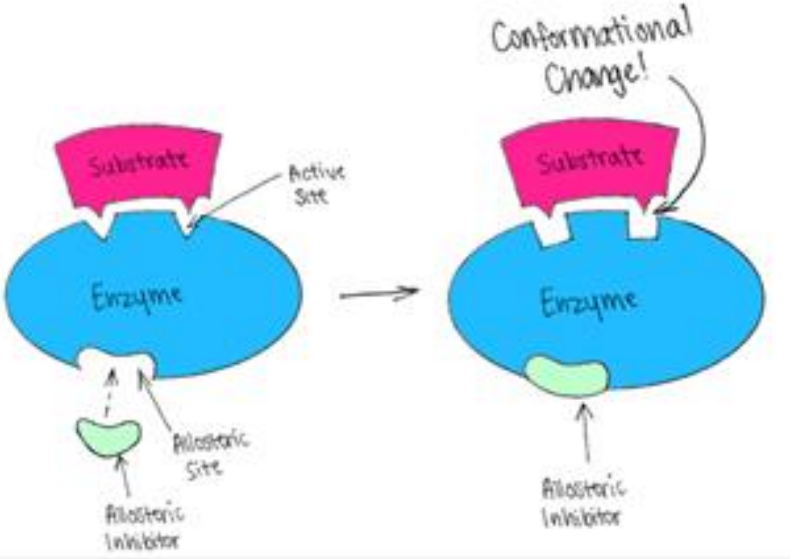


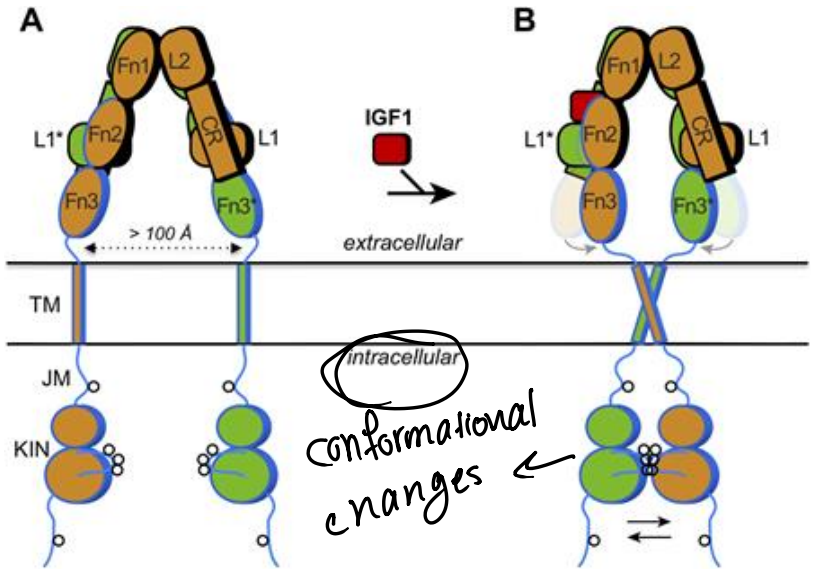
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Receptor-Mediated Action

Pharmacodynamics involves receptor-mediated responses which activate intracellular processes. When a drug binds to its specific receptor, it induces a conformational change, triggering a series of biochemical reactions that result in physiological effects.





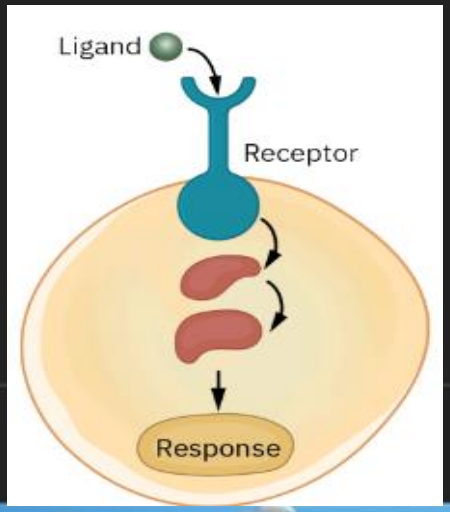


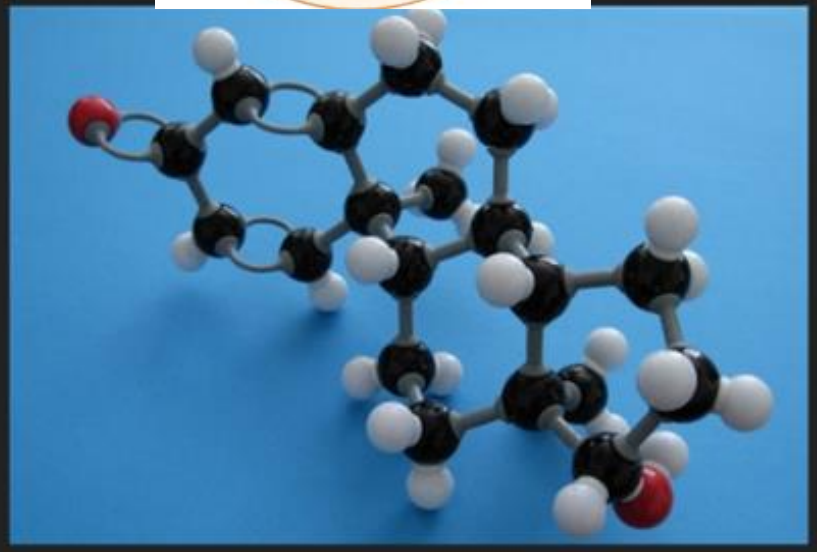
Key Concept: Drug selectivity depends on receptor specificity. Higher selectivity = fewer side effects!

Drug-Receptor Interactions

The response I will have → يتناسب طرديًا مع عدد الـ drug اللي اترتبط في الـ receptors وتوفا الـ drug-receptor complex

The binding of drugs to receptors forms a drug-receptor complex, pivotal for initiating physiological responses. The specificity of this interaction influences the therapeutic and side effects of drugs, highlighting the importance of target receptor selection.





الـ receptors موجودين بشكل طبيعي في الجسم من قبل ما يصرف دواء يرتبط فيه، فهو طبيعي لما يرتبط

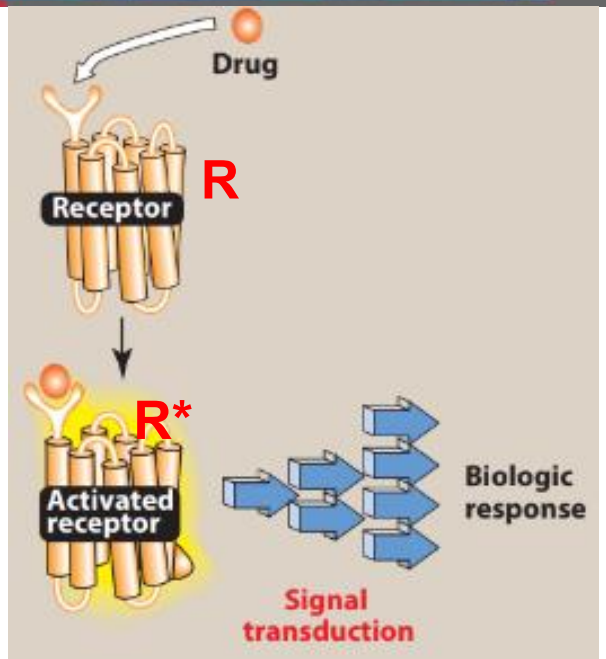
- These receptors do not exist specifically to bind with drugs
- They naturally bind with endogenous substances such as neurotransmitters or hormones.
- Due to the nature of drugs as chemical agents, they also can interact at receptor sites.
- The interaction between a drug and a receptor is what comprises the drug's mechanism of action or the drug's effect.

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Types of Receptors

Receptors can be classified into four main categories: ligand-gated ion channels, G-protein coupled receptors, enzyme-linked receptors, and intracellular receptors. Each receptor type plays a distinct role in mediating drug effects and signal transduction mechanisms.



في Balance بين حالة الreceptor بأنه يكون receptor إما inactive أو active وبين الـ inactive يكون بأنه يفضل

R ⇌ R*

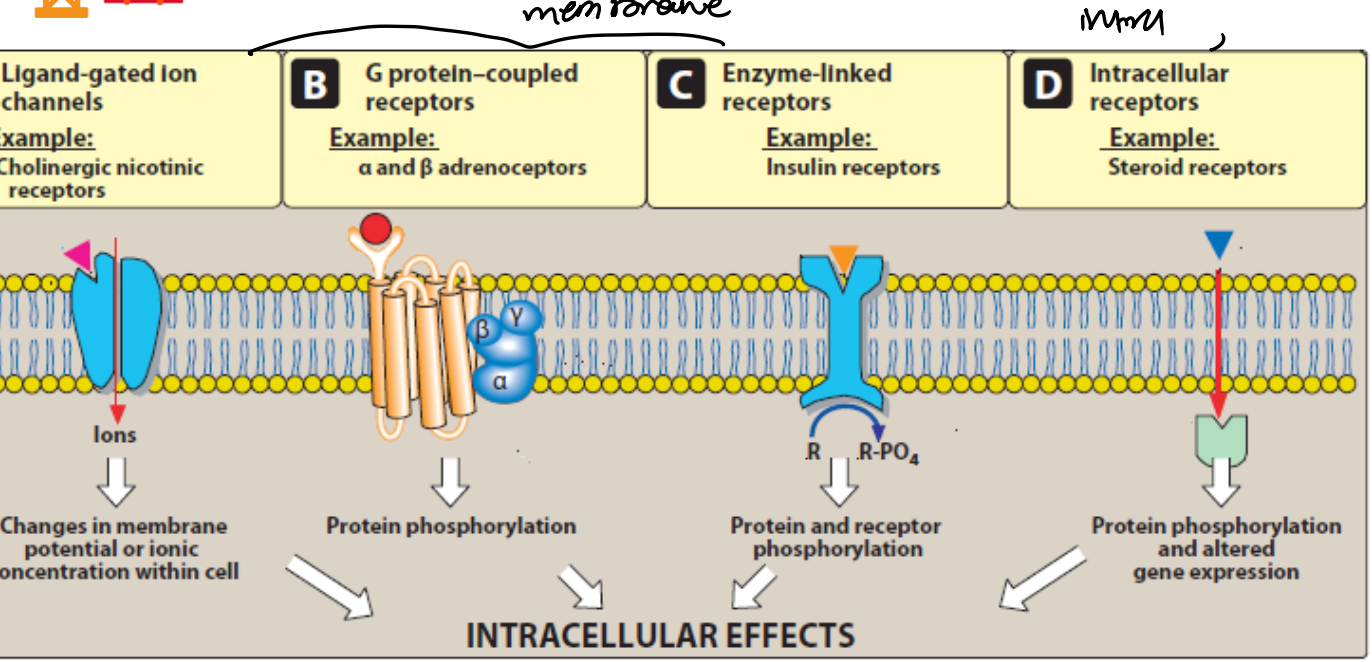
زيادة (ينفعل)

Receptor

3 أنواع

- membrane surface receptor
- نوع Intracellular receptors

Major Types of Receptors



1 Ion Channels

Speed: Milliseconds

Function: Rapid neurotransmission

Example: Nicotinic receptors

2 G-Protein Coupled

Speed: Seconds-Minutes

Function: Signal amplification

Example: β-adrenergic receptors

3 Enzyme-Linked

Speed: Minutes-Hours

Function: Growth, metabolism

Example: Insulin receptors

4 Intracellular

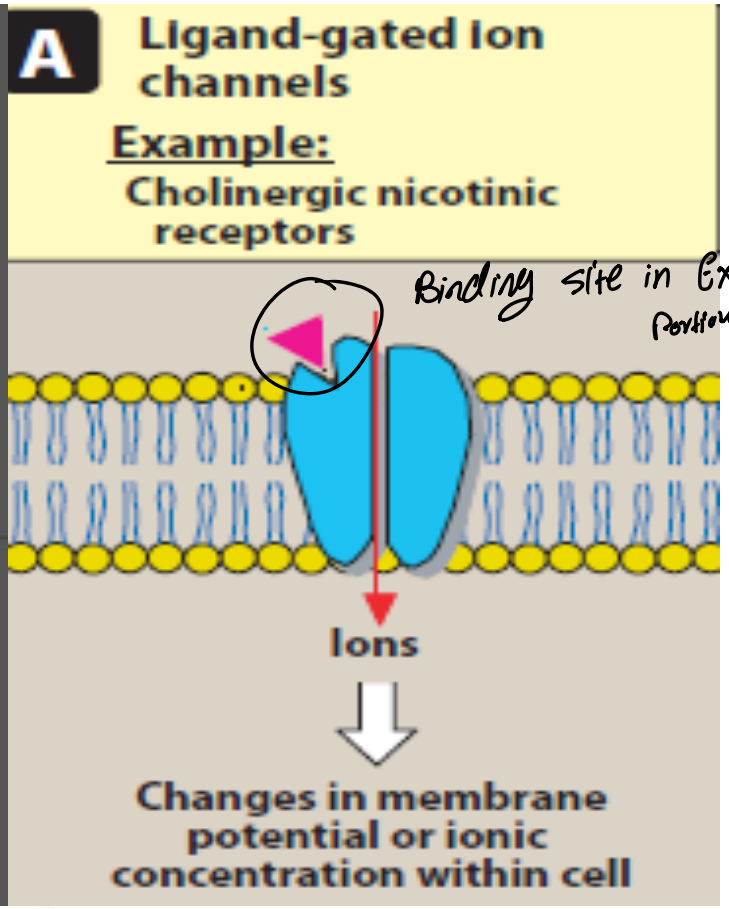
Speed: Hours-Days

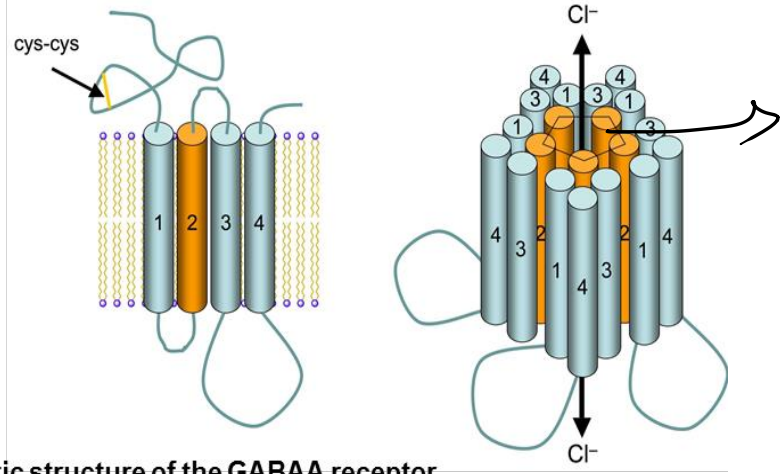
Function: Gene expression

Example: Steroid receptors

Ligand-Gated Ion Channels

These receptors are integral membrane proteins that open in response to ligand binding, allowing ions to flow across the membrane rapidly. They play critical roles in synaptic transmission and muscle contraction, with examples including nicotinic acetylcholine receptors that mediate fast synaptic signaling.





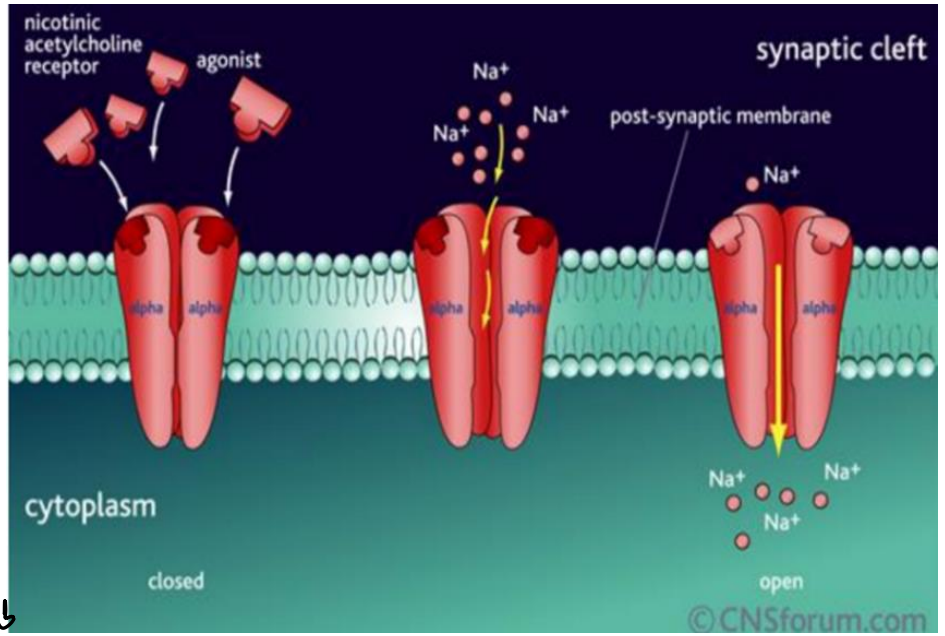
The schematic structure of the GABAA receptor

pentameric
5 ومكونة من

Transmembrane ligand-gated ion channels

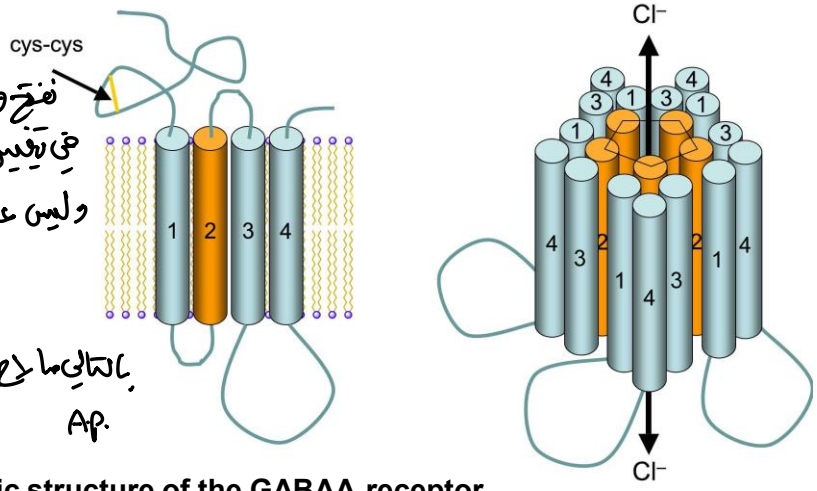
Nicotinic receptors : stimulation by acetylcholine results in sodium influx and potassium out flux, generating an action potential in a neuron or contraction in skeletal muscle.

GABA receptors : stimulation of the γ-aminobutyric acid (GABA) receptor increases chloride influx and hyperpolarization of neurons.



Voltage-gated ion channels may also possess ligand-binding sites that can regulate channel function.

Examples : local anesthetics bind to the voltage-gated sodium channel, inhibiting sodium influx and decreasing neuronal conduction.

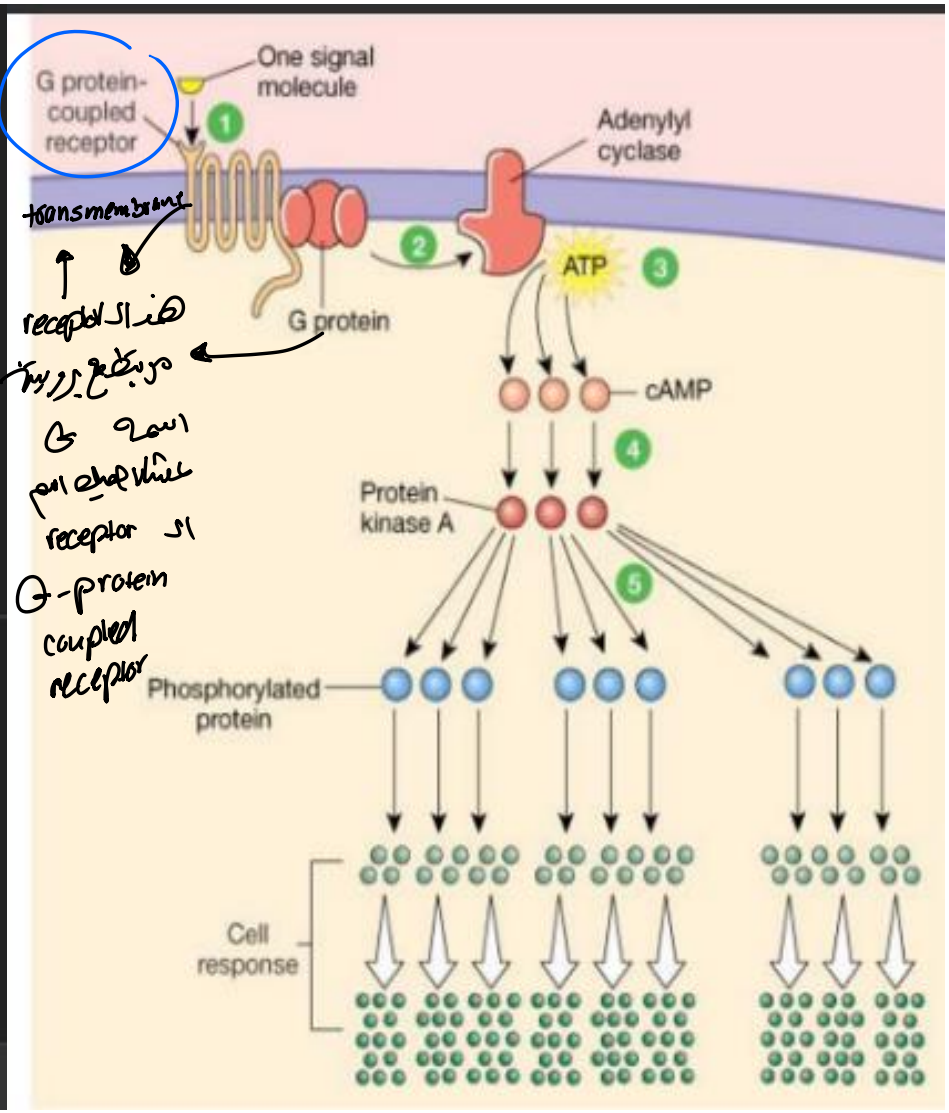


The schematic structure of the GABAA receptor

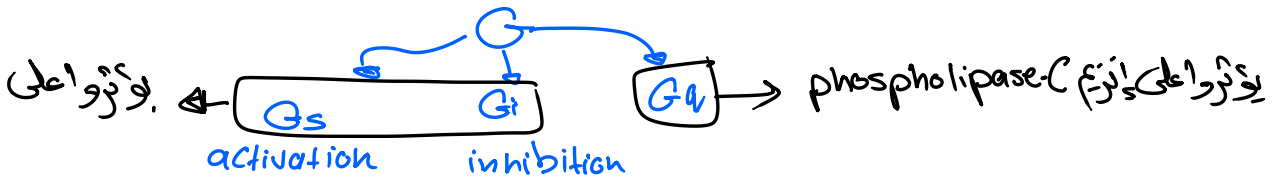
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G-Protein Coupled Receptors

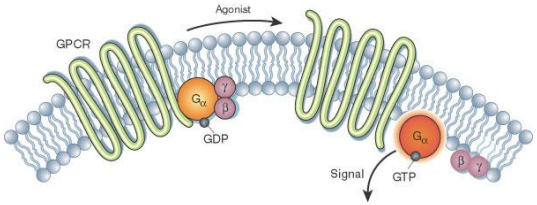
These are versatile receptors that activate intracellular G-proteins upon ligand binding, initiating downstream signaling pathways that can regulate cellular activities. They are involved in numerous physiological processes, including vision and olfaction, and represent a major target for pharmacological intervention.

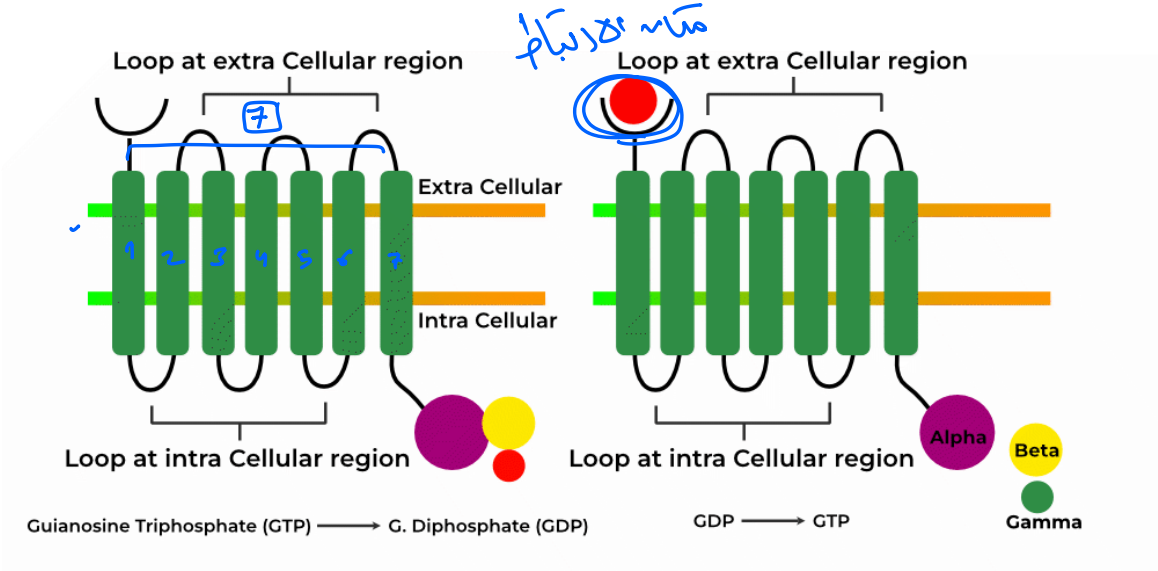


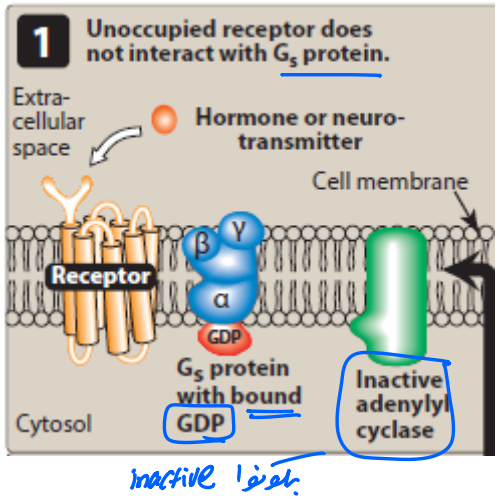
Adenylyl cyclase

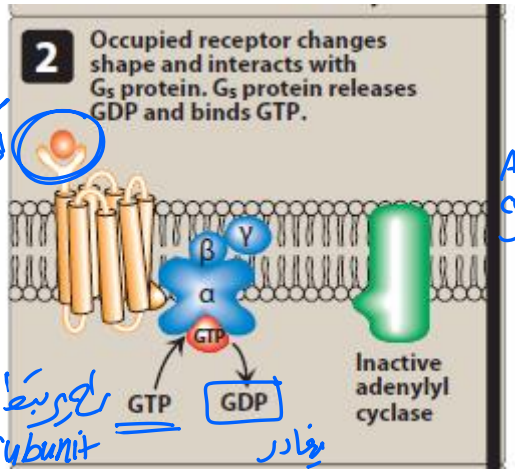


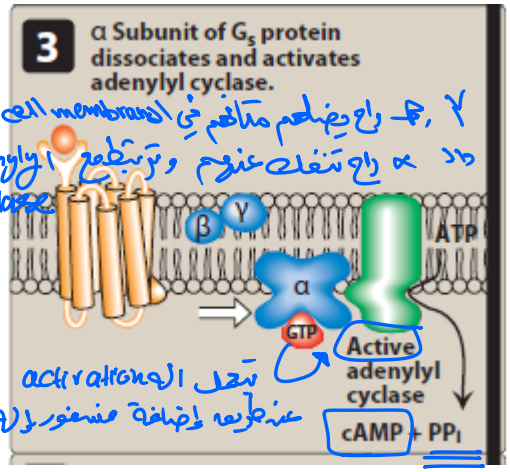
Transmembrane G protein–coupled receptors(GPCR)

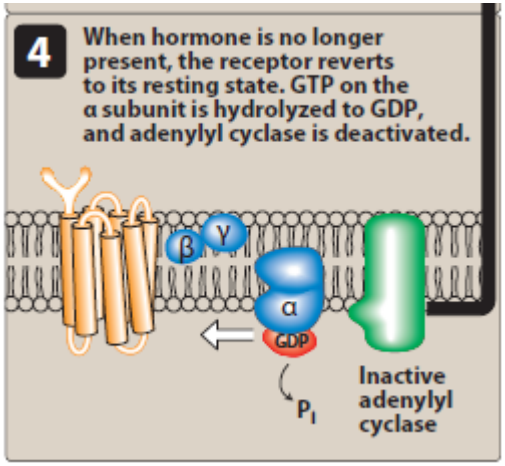




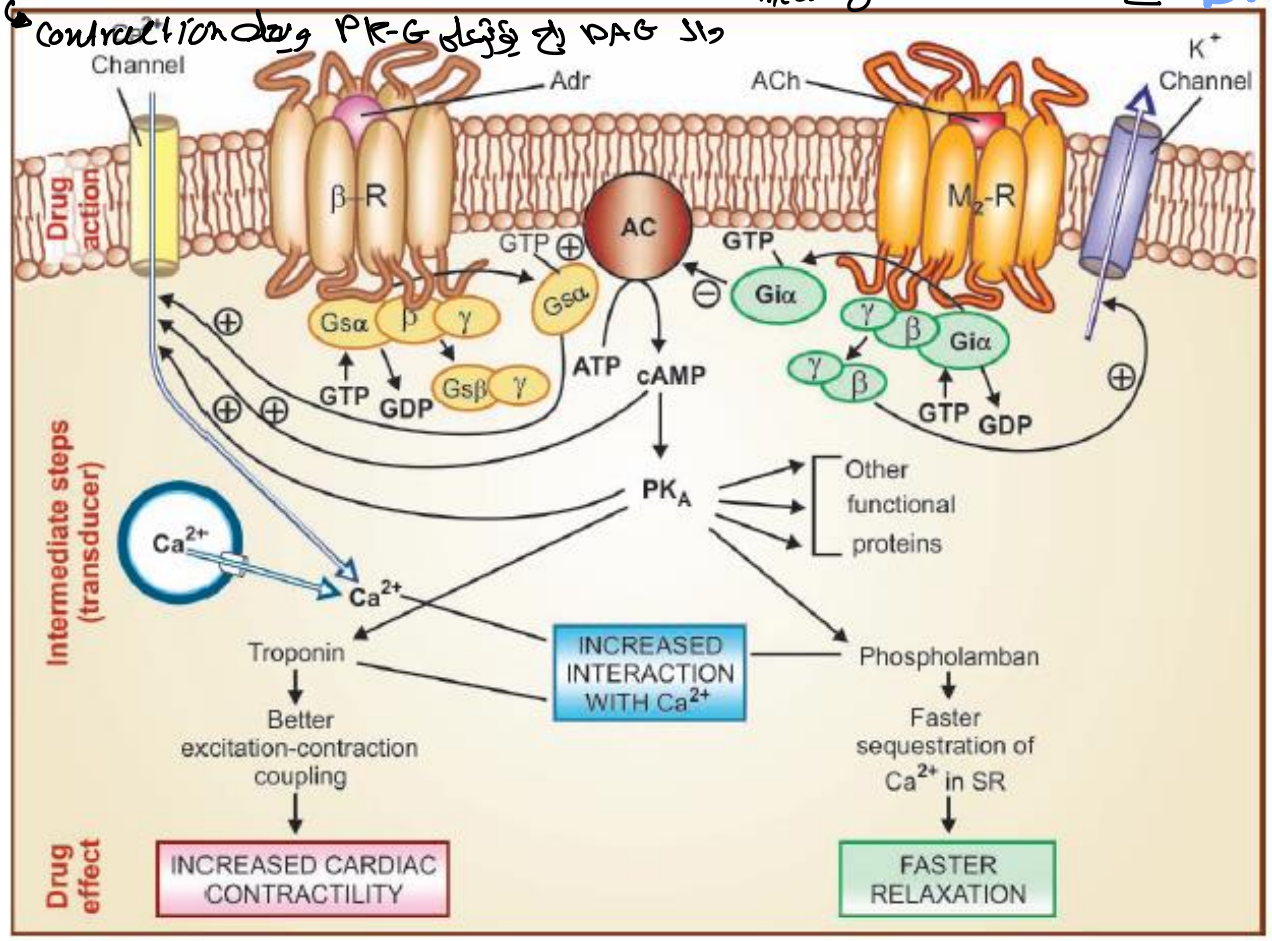


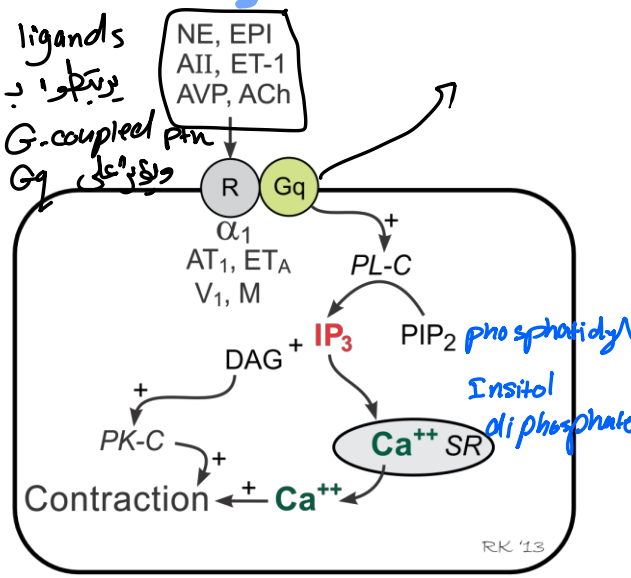






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R, receptor; Gq, phospholipase C-coupled Gq-protein; PL-C, phopholipase C; PIP_2, phosphatidylinositol biphosphate; IP_3, inositol triphosphate; DAG, diacylglycerol; PK-C, protein kinase C; SR, sarcoplasmic reticulum; NE, norepinephrine; AII, angiotensin II; ET-1, endothelin-1; AVP, arginine vasopressin; ACh, acetylcholine; α_1, alpha$_1$-adrenoceptor; AT_1, type 1 angiotensin receptor; ET_A, type A endothelin receptor; V_1, vasopressin type 1 receptor; M, muscarinic receptor.

Gq activates phospholipase C, generating two other second messengers: inositol 1,4,5-trisphosphate **(IP3)** and diacylglycerol **(DAG)**. DAG and cAMP activate different protein kinases within the cell, leading to a myriad of physiological effects. IP3 regulates intracellular free calcium concentrations, as well as some protein kinases.

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Enzyme-Linked Receptors

These receptors exhibit intrinsic enzyme activity or are closely associated with enzymes that become activated upon ligand binding. A classic example is the insulin receptor, which phosphorylates target proteins, thus influencing metabolic responses and cellular growth.

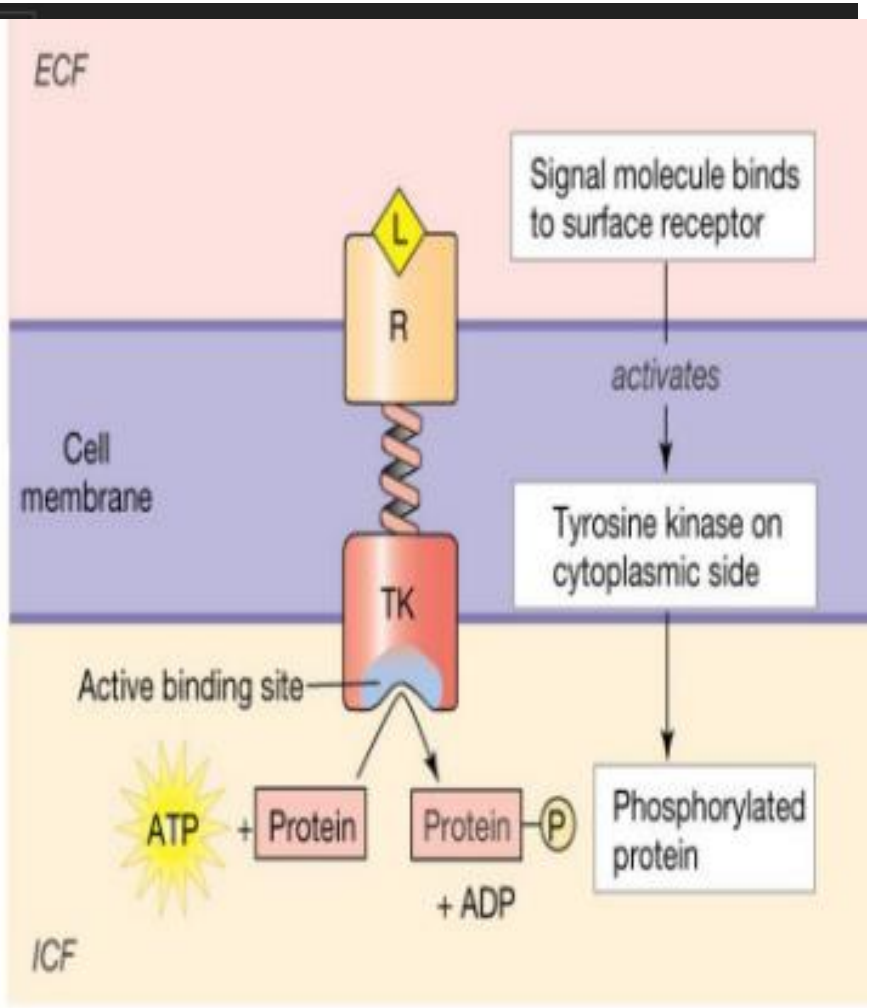
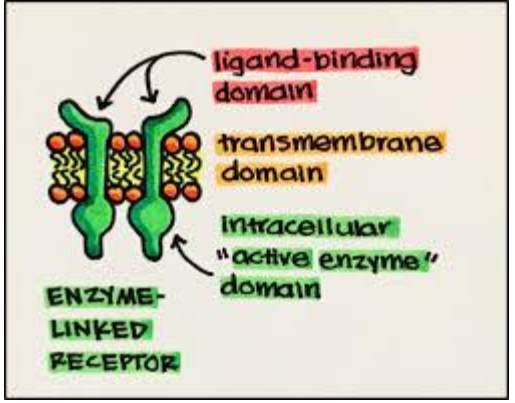


Figure 6-10: Tyrosine kinase, an example of a receptor-enzyme

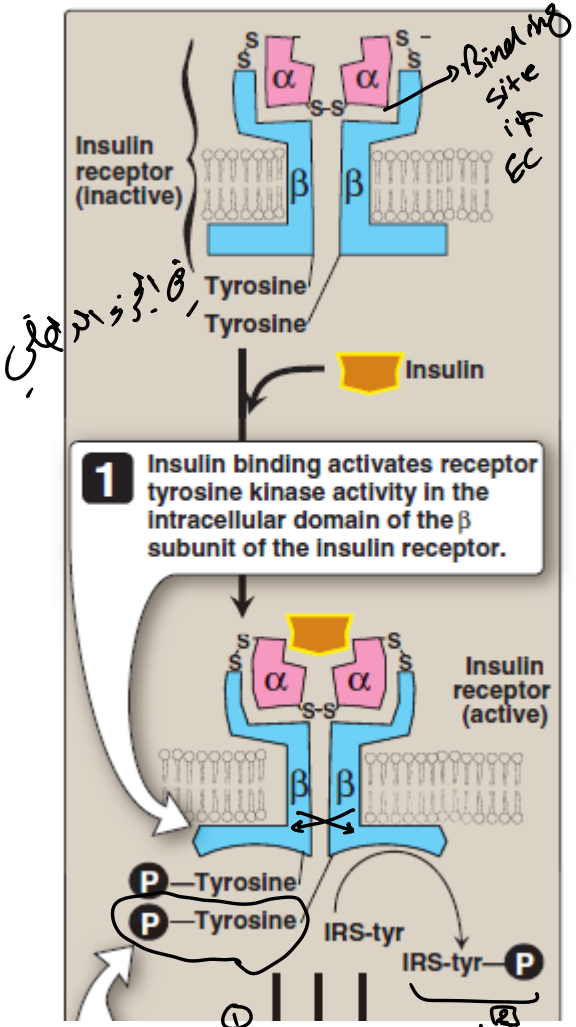
Enzyme-linked receptors

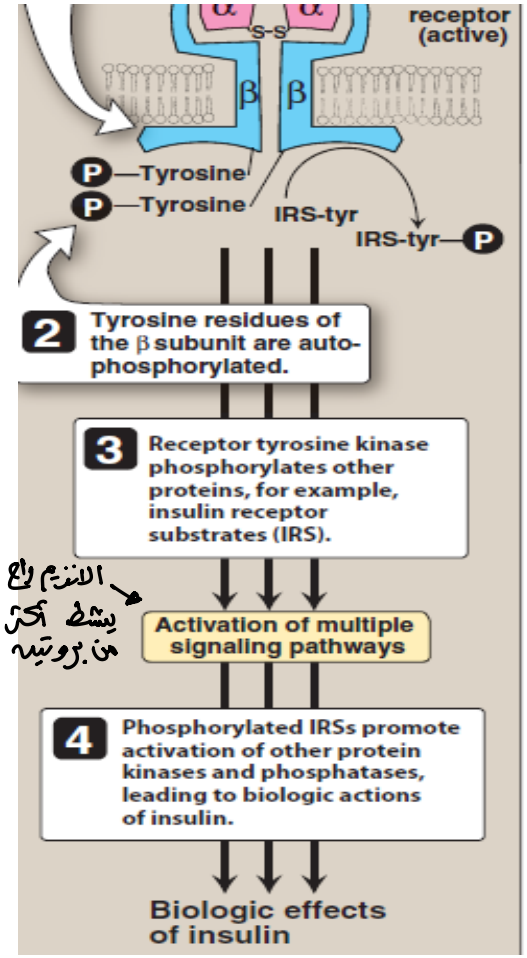


This family of receptors consists of a protein that may form dimers or multi subunit complexes.
When activated, these receptors undergo conformational changes resulting in increased cytosolic enzyme activity, depending on their structure and function

This response lasts on the order of minutes to hours

Examples : Insulin-
Growth factor-
Atrial Natriuretic Peptide
platlet derived

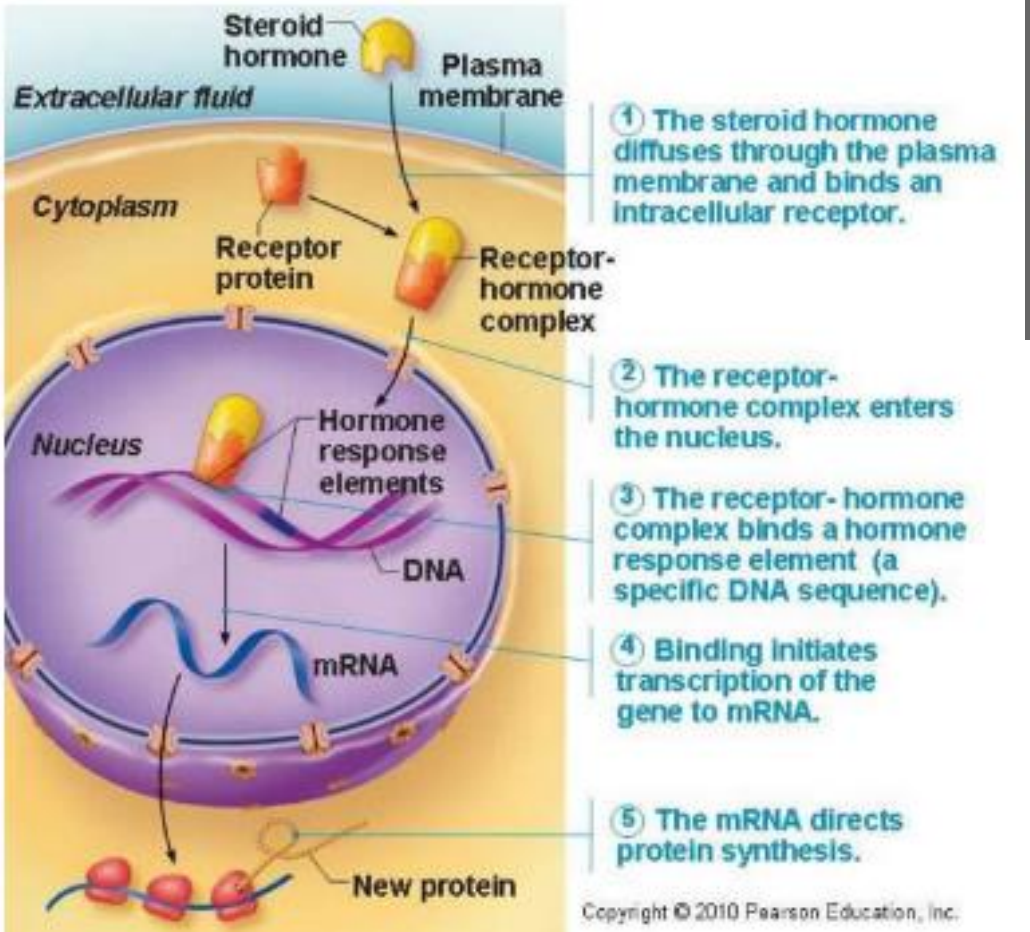




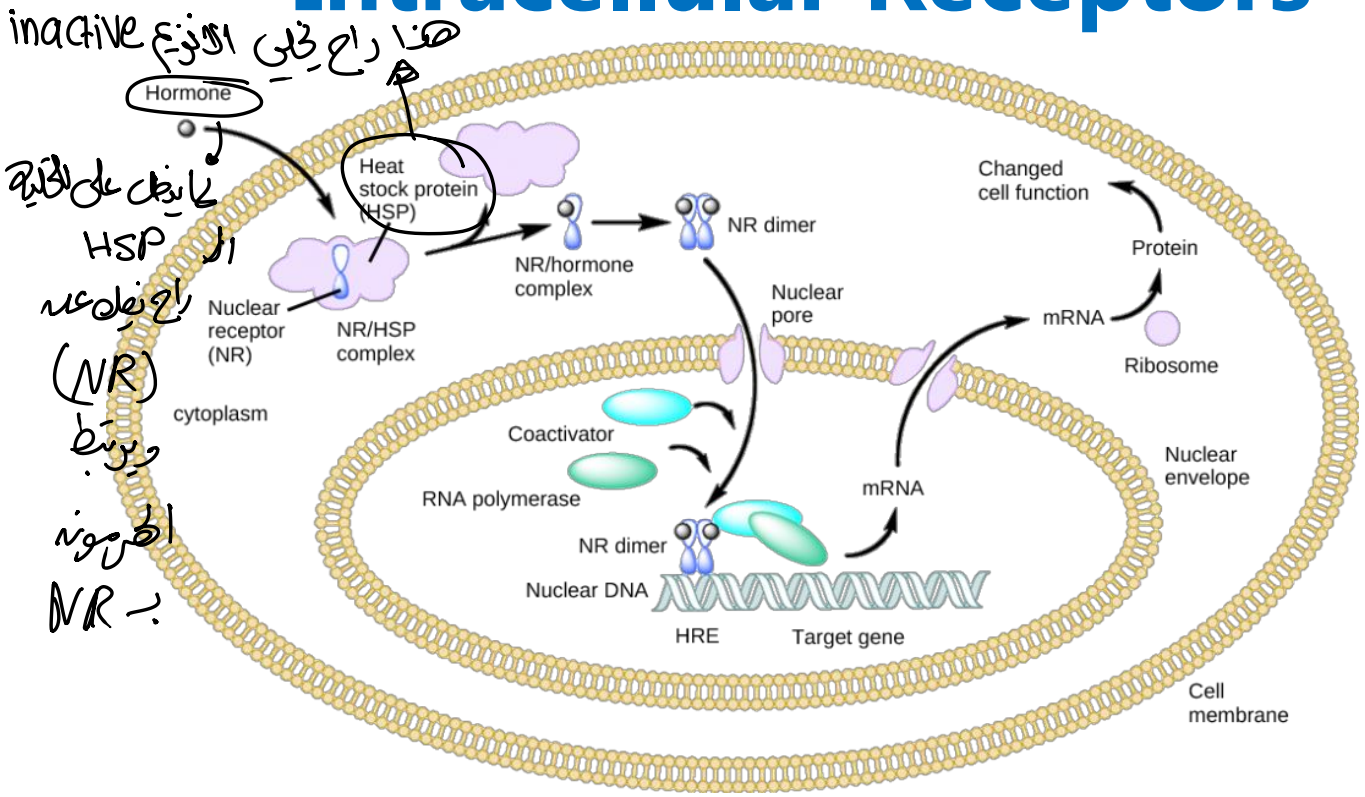


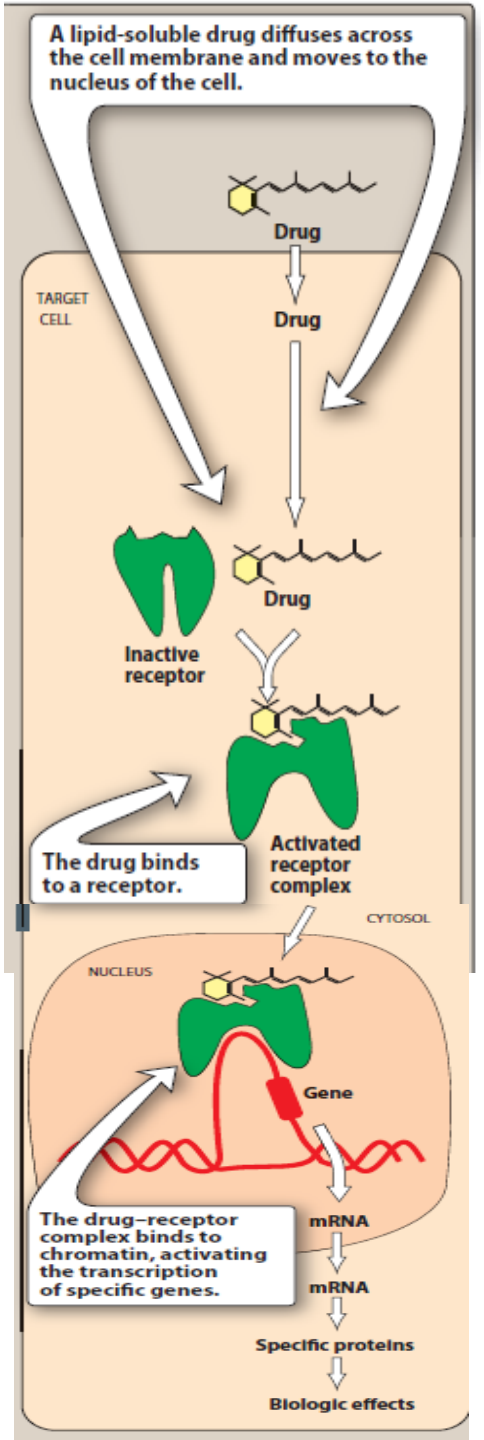
Intracellular Receptors

These receptors reside inside the cell and bind to lipid-soluble ligands that can cross cell membranes. Upon ligand binding, they often regulate gene transcription, impacting long-term physiological changes, exemplified by steroid hormone receptors that alter gene expression in target tissues.



Intracellular Receptors





- Lipid-derived (soluble) hormones such as **steroid hormones** diffuse across the membranes of the endocrine cell.
- Once outside the cell, they bind to transport proteins that keep them soluble in the bloodstream.
- At the target cell, the hormones are released from the carrier protein and diffuse across the lipid bilayer of the plasma membrane of cells.

Question #2

Which of the following does NOT result from hormones binding to intracellular hormone receptors?

A. The receptor complex affects the synthesis of mRNA in the cell.

B. The receptor complex affects the synthesis of DNA in the cell.

C. A cell signaling pathway is induced.

D. The receptor complex affects protein production in the cell.

DNA synthesis is not affected by hormone receptors inside of the cell. No additional DNA can be made inside of the cell but protein synthesis from the DNA can be affected.

Other lipid-soluble hormones that are not steroid hormones, such as **vitamin D** and **thyroxine**, have receptors located in the nucleus.
The hormones diffuse across both the plasma membrane and the nuclear envelope, then bind to receptors in the nucleus.
The hormone-receptor complex stimulates transcription of specific genes.

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Characteristics of Signal Transduction

Key Features of Signal Transduction

Signal transduction systems have evolved sophisticated mechanisms to:

- **Amplify weak signals** - Transform small stimuli into robust cellular responses
- **Protect cells from overstimulation** - Prevent cellular damage from excessive signaling

Why These Features Matter

These characteristics ensure cells can detect subtle environmental changes while maintaining homeostasis and preventing signal-induced damage.

The Power of Molecular Multiplication

Core Principle

G protein-linked and enzyme-linked receptors can amplify both the **intensity** and **duration** of signals far beyond the original stimulus.



Amplification Mechanisms:

- **Intensity Amplification:** Single agonist-receptor complex activates multiple G proteins
- **Duration Amplification:** Activated G proteins persist longer than the original stimulus
- **Cascade Effects:** Each step in the pathway can further multiply the signal

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Albuterol Example



The Result

A brief drug-receptor interaction creates a prolonged and amplified cellular response, ensuring therapeutic effectiveness even with short-lived drug binding.

Spare Receptors

Maximum Response, Minimal Occupancy

Systems where only a fraction of total receptors need to be occupied to elicit a maximal response are said to have "spare receptors."

(Antagonist)

Clinical Examples:

Insulin Receptors

99% of receptors are "spare"

Provides immense functional reserve

Ensures adequate glucose uptake even with receptor loss

Critical for maintaining glucose homeostasis

Cardiac β-Adrenoceptors

Only 5-10% are spare receptors

Limited functional reserve

Most receptors must be occupied for maximum contractility

Clinical implication: Little reserve in failing hearts

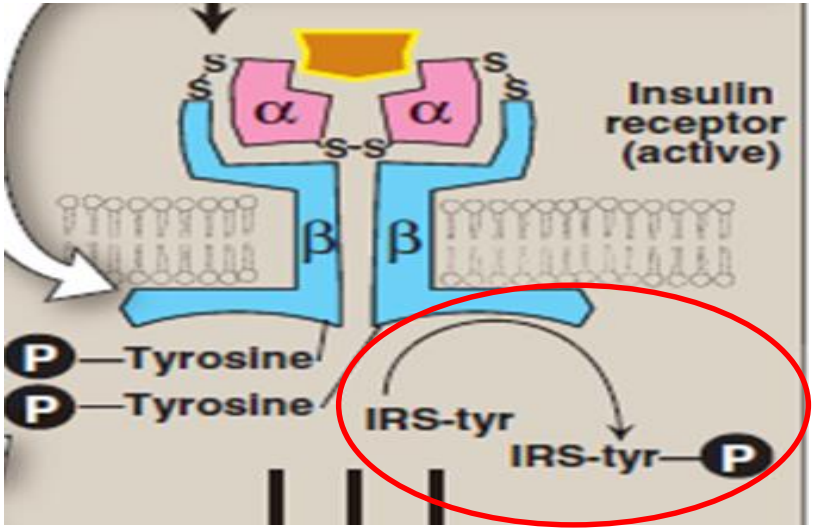
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Insulin Receptor: A Case Study

Receptor Tyrosine Kinase Signaling

Signal Amplification in Action

Each activated insulin receptor can phosphorylate **multiple IRS proteins**, which then activate numerous downstream kinases and phosphatases, creating a cascade of biological effects.



Insulin Signaling Pathway

1. Insulin binding activates receptor tyrosine kinase activity in the β subunit
2. Tyrosine residues of the β subunit undergo autophosphorylation
3. Activated receptor phosphorylates insulin receptor substrates (IRS)
4. Phosphorylated IRS proteins activate multiple signaling pathways

Cellular Protection Mechanisms

Guarding Against Overstimulation

Why Protection is Necessary ?

Without regulatory mechanisms, continuous or excessive stimulation could lead to:

Cellular exhaustion
Metabolic disruption
Cell death
Loss of signal specificity

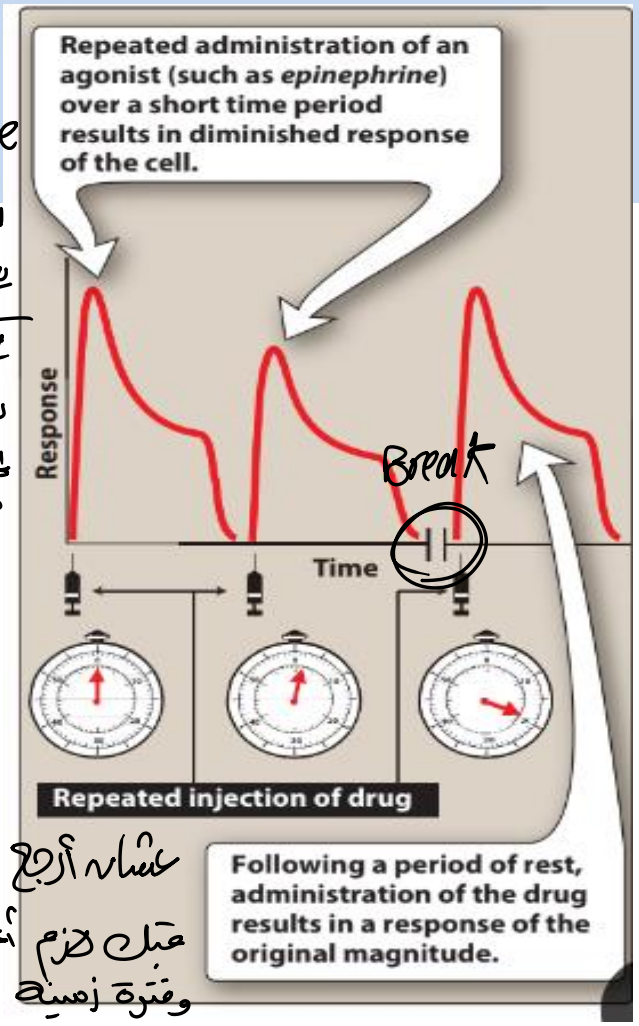
Key Protective Mechanisms:

Desensitization

- Temporary reduction in receptor responsiveness following repeated or prolonged stimulation

⬇ Down-regulation

- Actual reduction in the number of receptors available at the cell surface



Clinical Relevance

Understanding these mechanisms is crucial for:
Drug dosing strategies
Avoiding tolerance development
Optimizing therapeutic outcomes

Summary

Signal Transduction Characteristics

Signal Amplification

- Multiplies signal intensity
- Extends signal duration
- Enables spare receptor systems
- Ensures robust cellular responses

Cellular Protection

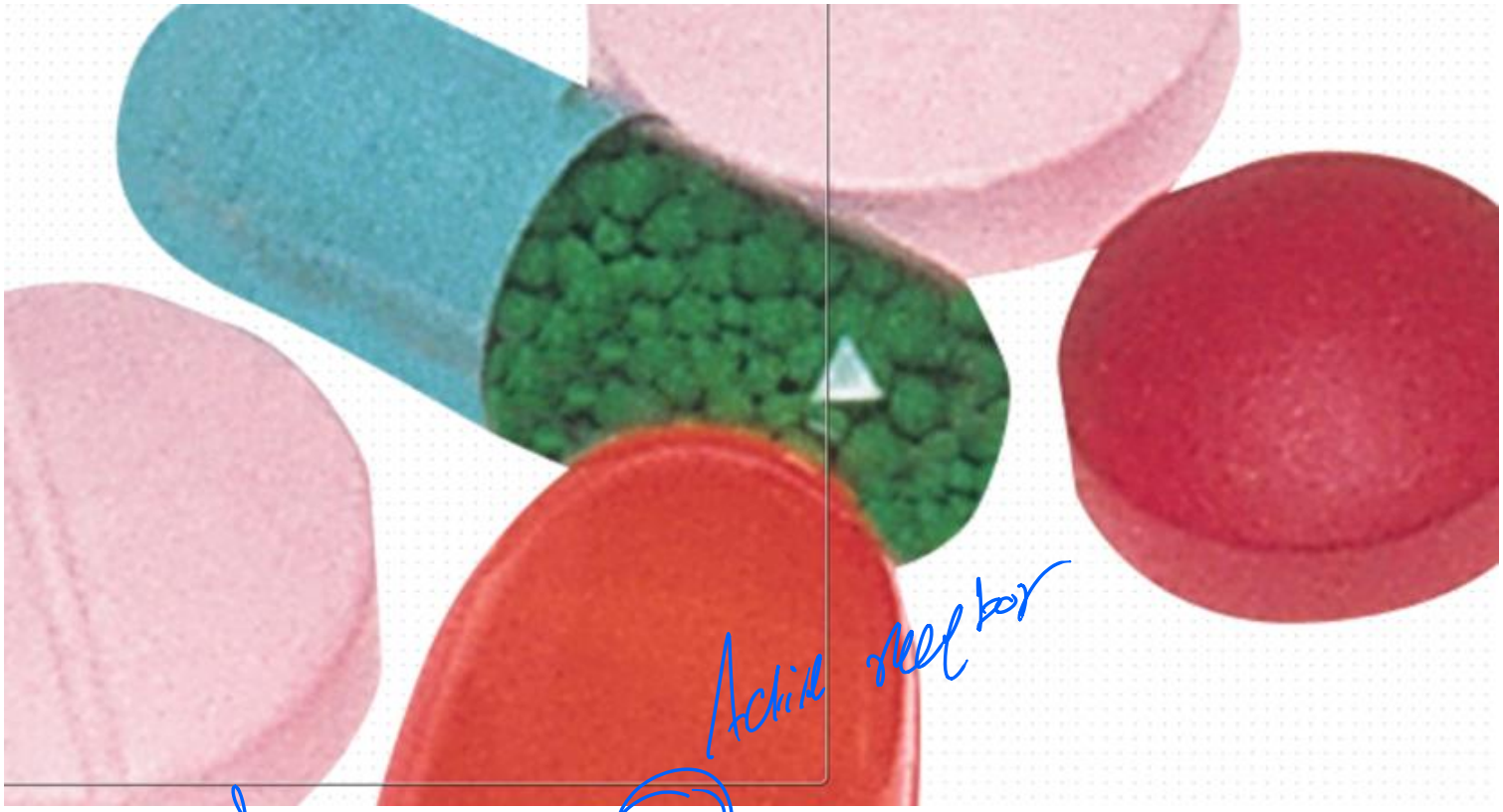
- Prevents overstimulation
- Maintains cellular homeostasis
- Includes desensitization
- Includes down-regulation

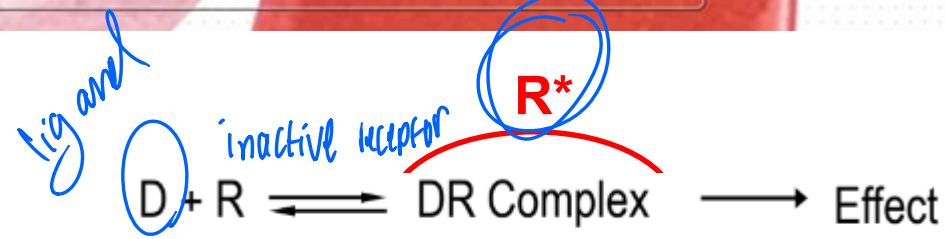
Clinical Significance : These characteristics explain why:

- Small amounts of hormones can have large effects
- Drugs can lose effectiveness over time (tolerance)
- Some tissues have greater functional reserves than others
- Receptor systems are robust yet regulated

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Drug – Receptor Binding & Effects





Affinity : Measure of how strongly a drug binds to its receptor

- High affinity = tight binding, low concentrations needed
- Low affinity = weak binding, high concentrations needed

Efficacy (Intrinsic Activity) : Ability of bound drug to produce a biological response= the magnitude of response a drug causes when it interacts with a receptor

- Full efficacy = maximum possible response
- Partial efficacy = submaximal response
- Zero efficacy = no response (antagonist)

Efficacy is dependent on the number of drug–receptor complexes formed and the intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response).

Maximal efficacy of a drug (Emax) assumes that all receptors are occupied by the drug, and no increase in response is observed if a higher concentration of drug is obtained.

Potency : Amount of drug needed to produce a given effect

- High potency = small dose required
- Low potency = large dose required

minimal amount of the drug to reach the therapeutic effect

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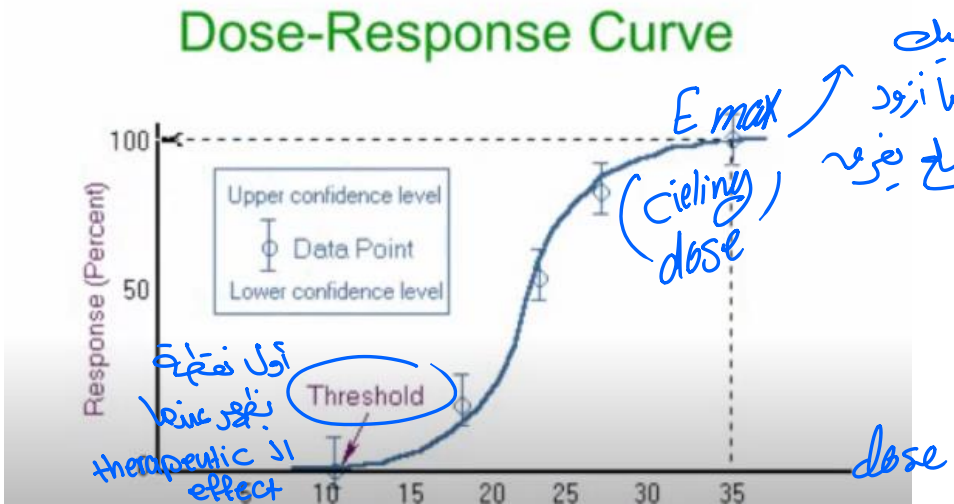
Establishes :

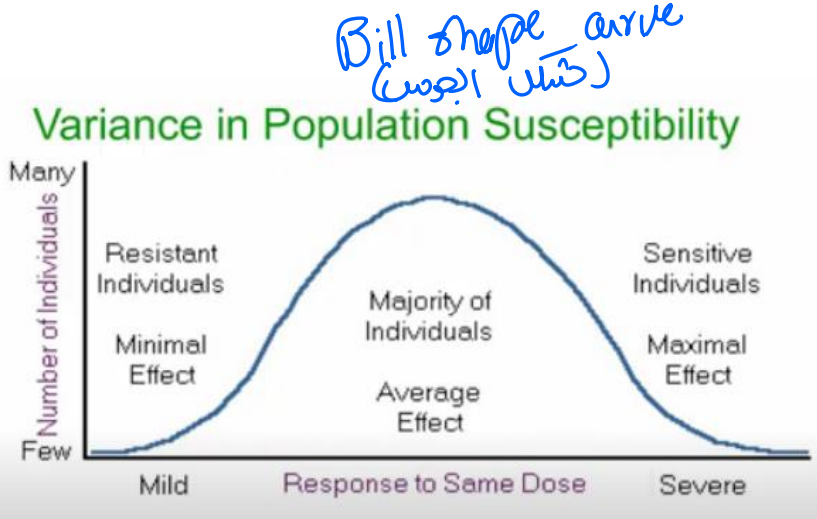
1. Causality
2. Lowest dose for effect
3. Rate of injury (Toxicology)

Dose-Response Curves

Dose-response curves illustrate the relationship between drug concentration and the magnitude of response, enabling the characterization of drug potency and efficacy. The graphical representation aids in understanding pharmacological effects and potential side effects as the dose escalates.







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Graded Dose-Response Relations

Graded dose-response relations depict how increasing drug doses incrementally induce more significant biological responses up to a maximum effect. This relationship informs the understanding of drug potency and aids in selecting appropriate therapeutic dosages.

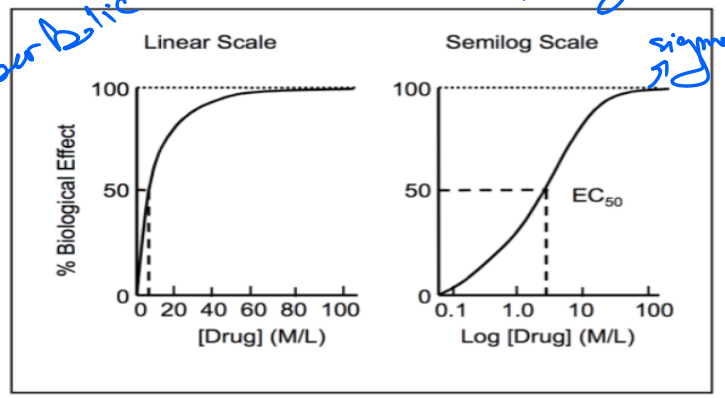


maximal effect ك ما نوصل ك Biological response كل ما نزود ال dose بـ يزيد ال

Graded dose-response curve:(A response to a drug) such that as the dose of drug increases the
intensity of the response increases. A graded dose- response relationship can be measured on a continuous scale

Graded Dose-Response Curve

Shows: How response intensity changes with dose?



Log Scale Transforms hyperbolic curve to a sigmoid (almost a straight line)

- The relation between doses and responses will be linear
- Better understanding and interpretation can be drawn from
- By this way we can choose optimized dose of substance (i.e. EC50, EC80) for mechanistic studies
- Easier to analyze mathematically

Key Parameters:

- **EC_{50}:** Concentration producing 50% maximal response
- **Threshold:** Minimum dose for detectable effect (just-noticeable)
- **Ceiling:** Dose beyond which no additional effect (produces maximum effect)

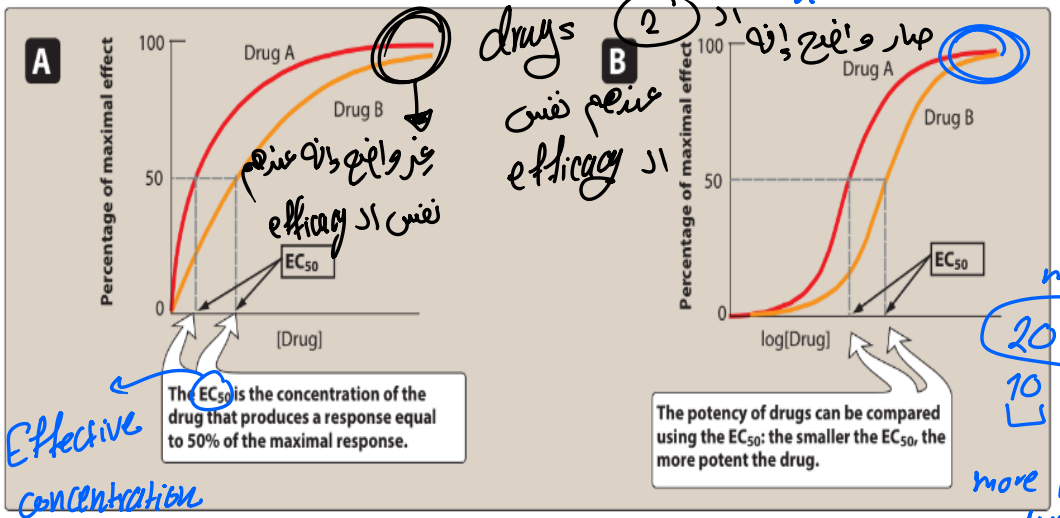
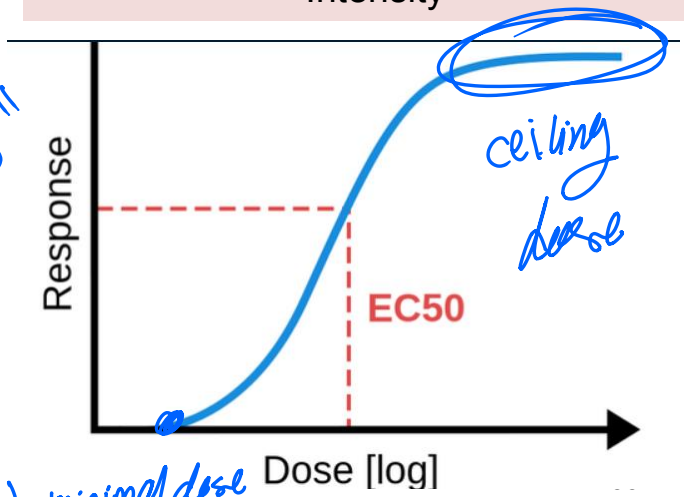
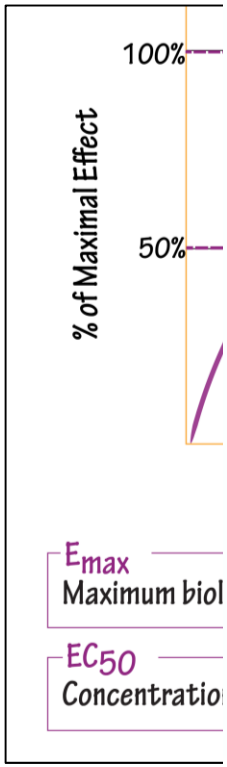


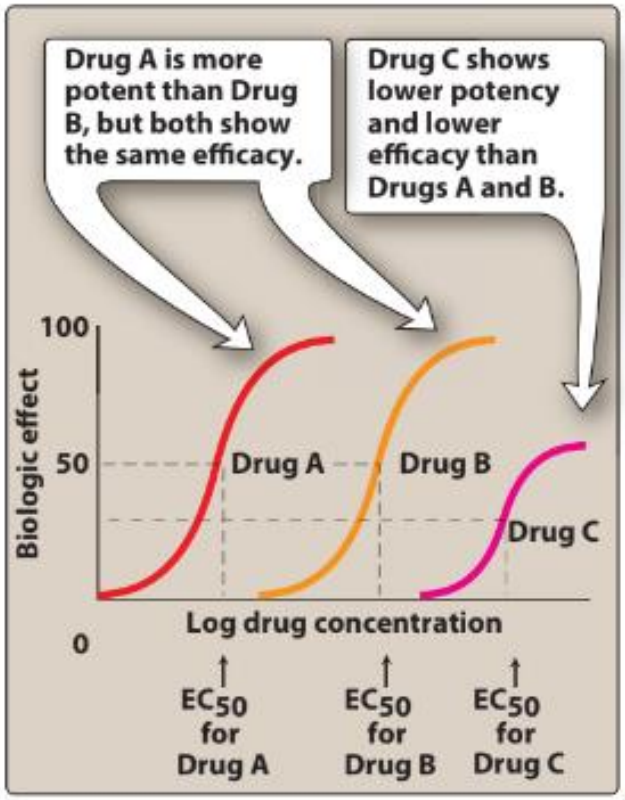
Figure 2.7
The effect of dose on the magnitude of pharmacologic response. **Panel A** is a linear graph. **Panel B** is a semilogarithmic plot of the same data. EC_{50} = drug dose causing 50% of maximal response.

Sigmoid Curve: Dose → Response Intensity



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A/C almost the same efficacy but B lower efficacy

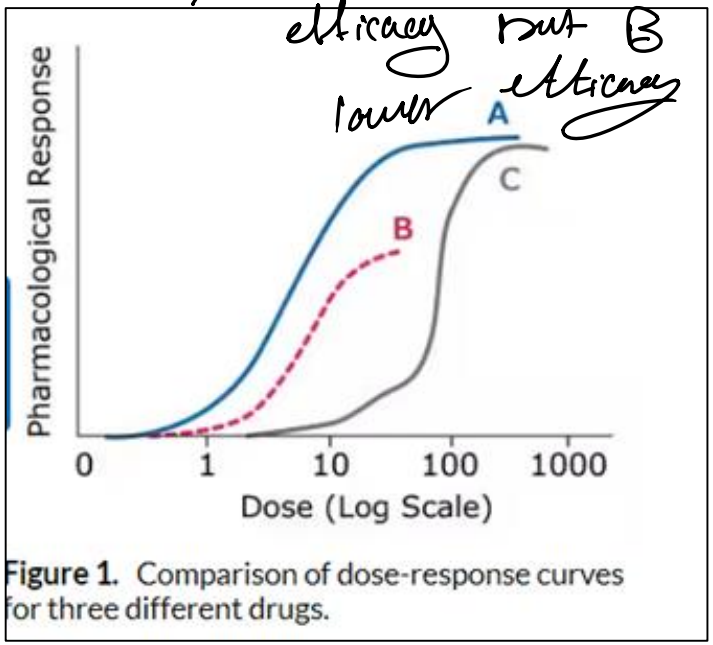
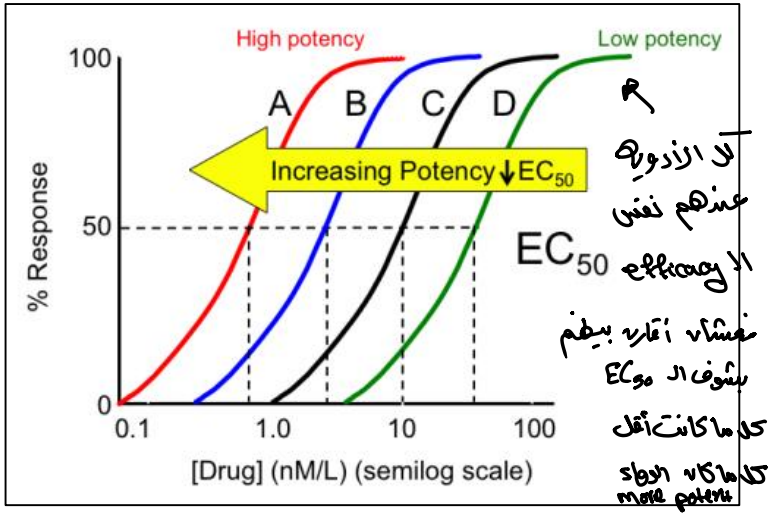
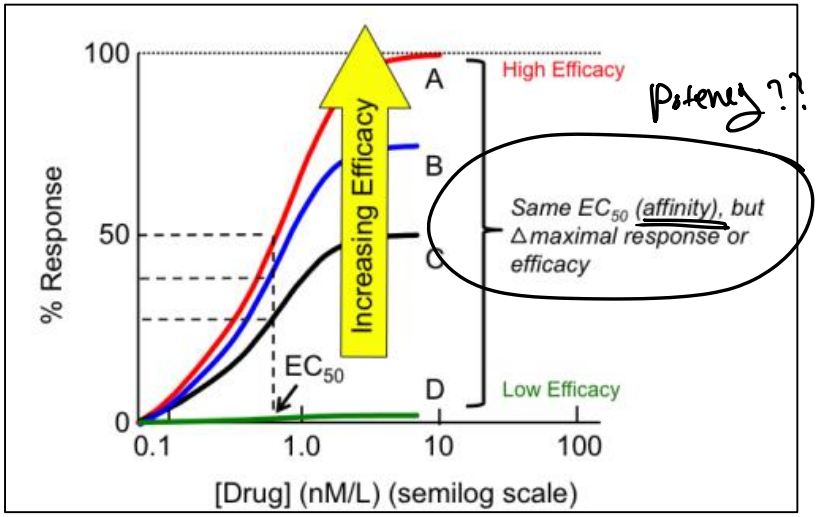


Figure 1. Comparison of dose-response curves for three different drugs.



آل الأدوية عندهم نفس الـ efficacy بس اختلفت أقارب بيظهر بشوف الـ EC50 كل ما كانت أقل كل ما كان الدواء more potent



Potency ??

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QUANTAL DOSE–RESPONSE RELATIONSHIPS

Relationship between the dose of the drug and the proportion of a population that responds to it.

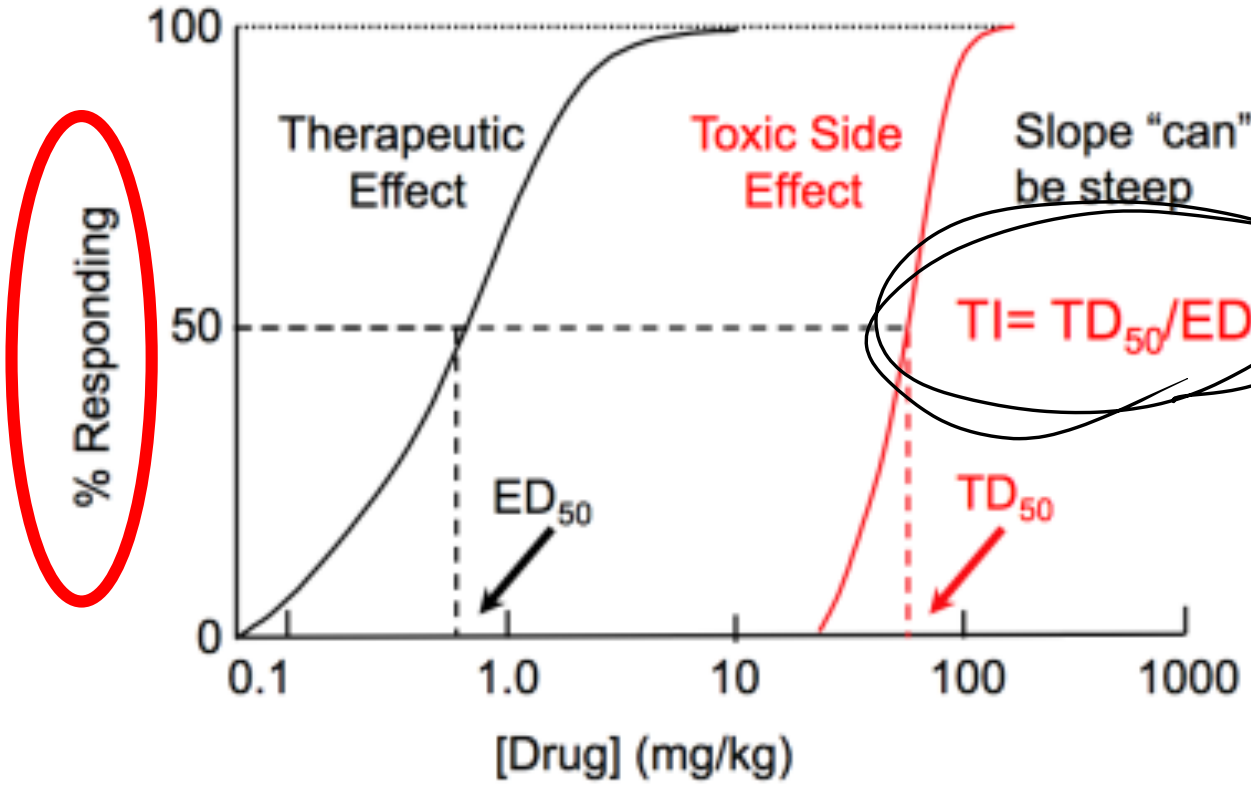
بستفيد منها بإنه أعرف الجرعة اللي تناسب أغلب الناس

Quantal dose–response curves are useful for determining doses to which most of the population responds.

They have similar shapes as log dose–response curves

ED50 is the drug dose that causes a therapeutic response in half of the population

Drug Safety - Therapeutic Index



ED50 : Median **Effective Dose 50** ; the dose at which 50% of the population or sample manifests a given effect.

TD50 : Median **Toxic Dose 50** - dose at which 50% of the population manifests a given toxic effect

LD50 : Median **Lethal Dose 50** - dose which kills 50% of the subjects

Threshold, ED50, EC50, Ceiling

The threshold dose is the minimum amount needed to elicit a response. ED50 represents the effective dose for 50% of the population, while EC50 indicates the concentration at which 50% of the maximal effect is achieved. Ceiling effects refer to the point where increases in dose result in no additional response, guiding clinicians in safe prescribing practices.



Clinical Significance: Log-dose scales make curves linear, easier to analyze, and help determine optimal dosing strategies.

What do we want : more potency or more efficacy ?

A drug with greater efficacy is more therapeutically beneficial than is one that is more potent

Effect of drug concentration on receptor binding

R*

$$\text{Drug} + \text{Receptor} \rightleftarrows \text{Drug–receptor complex} \rightarrow \text{Biologic effect}$$

$$D + R \underset{\text{Affinity}}{\rightleftharpoons} DR \text{ Complex} \longrightarrow \text{Effect}$$

$$\frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]}$$

$$K_d = \frac{[\text{Receptor}] \times [\text{Ligand}]}{[\text{R-L complex}]}$$

constant dissociation

K_d is a measure of chemical binding and may or may not exactly correlate with the EC_{50} value, depending on receptor signaling mechanics.
it gives a strong measure of the receptor's affinity to bind a drug molecule

The higher the Kd value, the weaker the interaction and the lower the affinity, and low K_d indicating high binding affinity and usually indicating a correspondingly low EC_{50} value.

.

The curve has the shape of a rectangular hyperbola (Figure A).
As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity.

The binding of the drug to its receptor initiates events that ultimately lead to a measurable biologic response.

أول ما يرتبط العوا في الـ receptor بيبدأ الـ

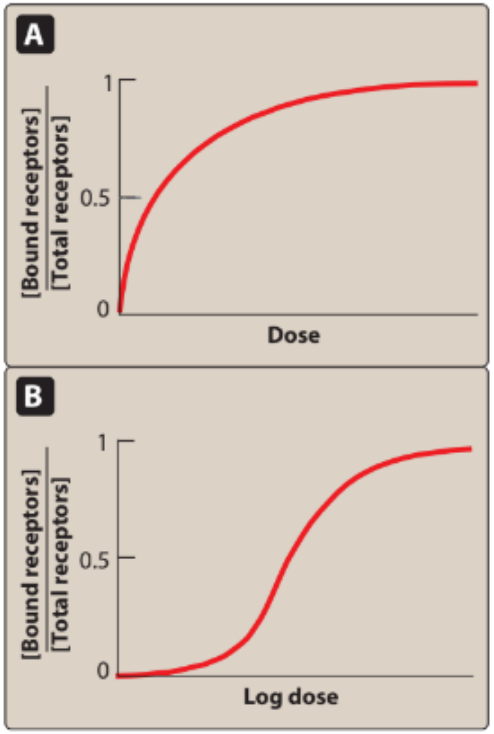


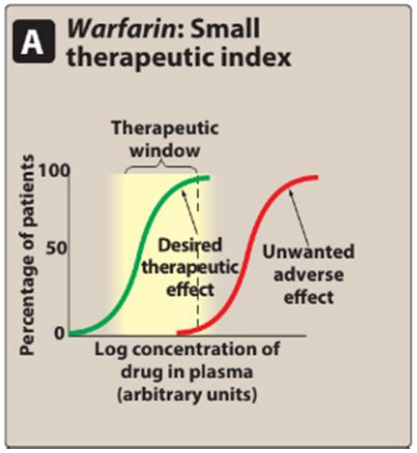
Figure 2.9
The effect of dose on the magnitude of drug binding.

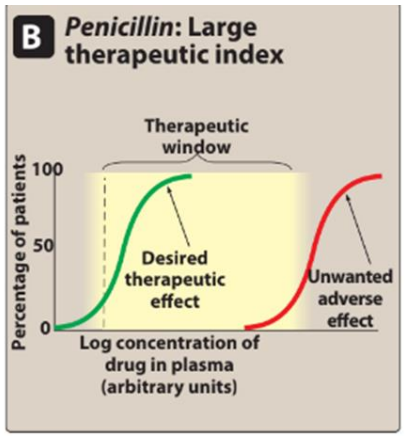
Therapeutic Index & Drug Safety

Therapeutic Index (TI) = TD_{50} / ED_{50}
or
TI = LD_{50} / ED_{50}

Safety Definitions:
ED_{50}: Median Effective Dose (50% show therapeutic effect)
TD_{50}: Median Toxic Dose (50% show toxicity)
LD_{50}: Median Lethal Dose (50% mortality)

Therapeutic Index	Safety Profile	Clinical Examples
High TI (>10)	Safe, wide therapeutic window	Penicillin, Ibuprofen
Low TI (<2)	Dangerous, narrow therapeutic window	Warfarin, Digoxin, Lithium





INTRINSIC ACTIVITY: Agonist and Antagonist Drugs based on drug-receptor interactions



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Agonist Drugs

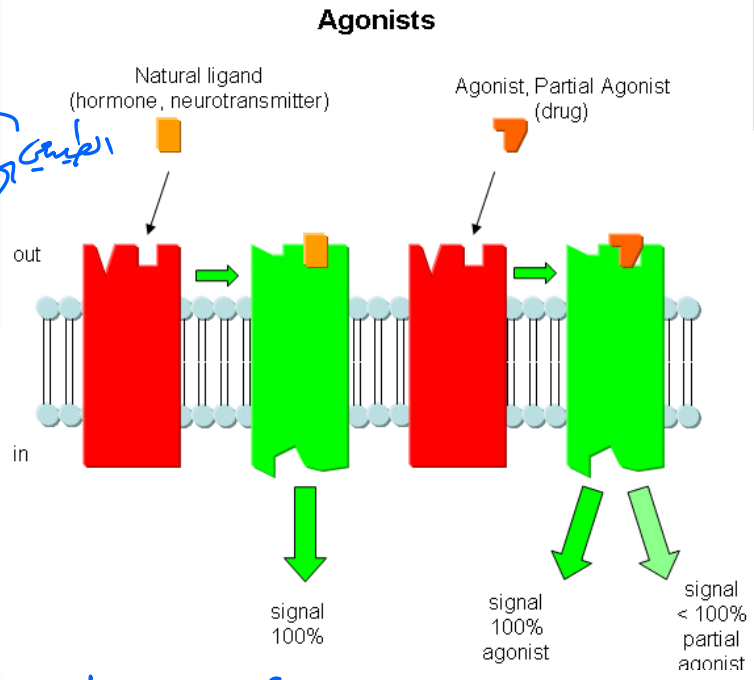
Drugs that bind to receptors and produce a biological response

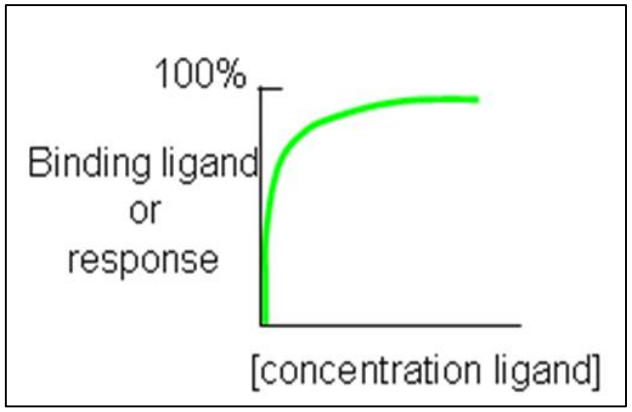
Full Agonist

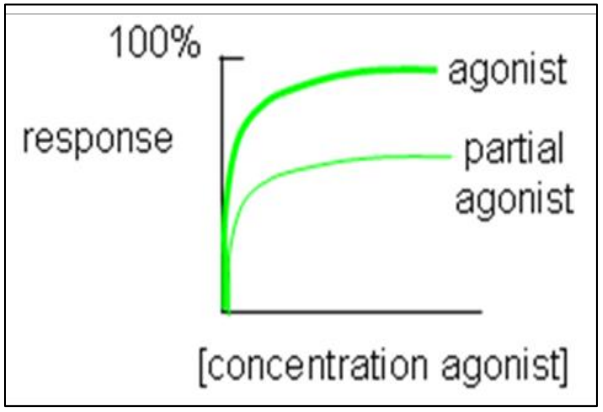
- Produces maximal response
- High intrinsic activity (= 1)
- Mimics endogenous ligand
- **Example:** Morphine at μ-opioid receptors

Partial Agonist

- Produces submaximal response
- Moderate intrinsic activity (0 < IA < 1)
- Can act as functional antagonist
- **Example:** Buprenorphine







Clinical Pearl: Partial agonists have a "ceiling effect" - safer in overdose situations!

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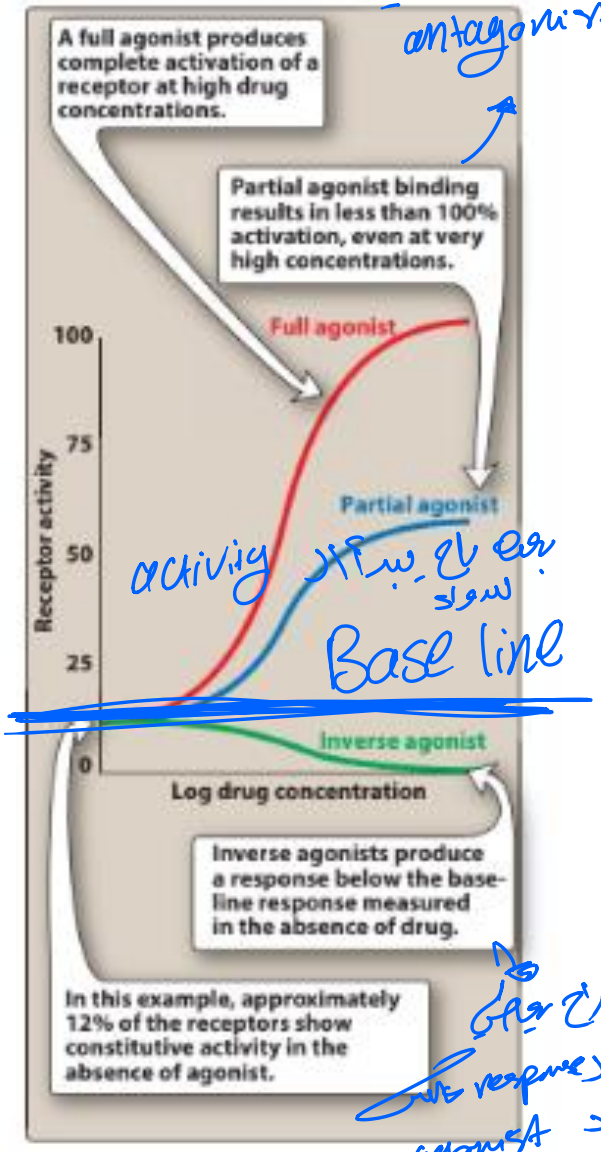
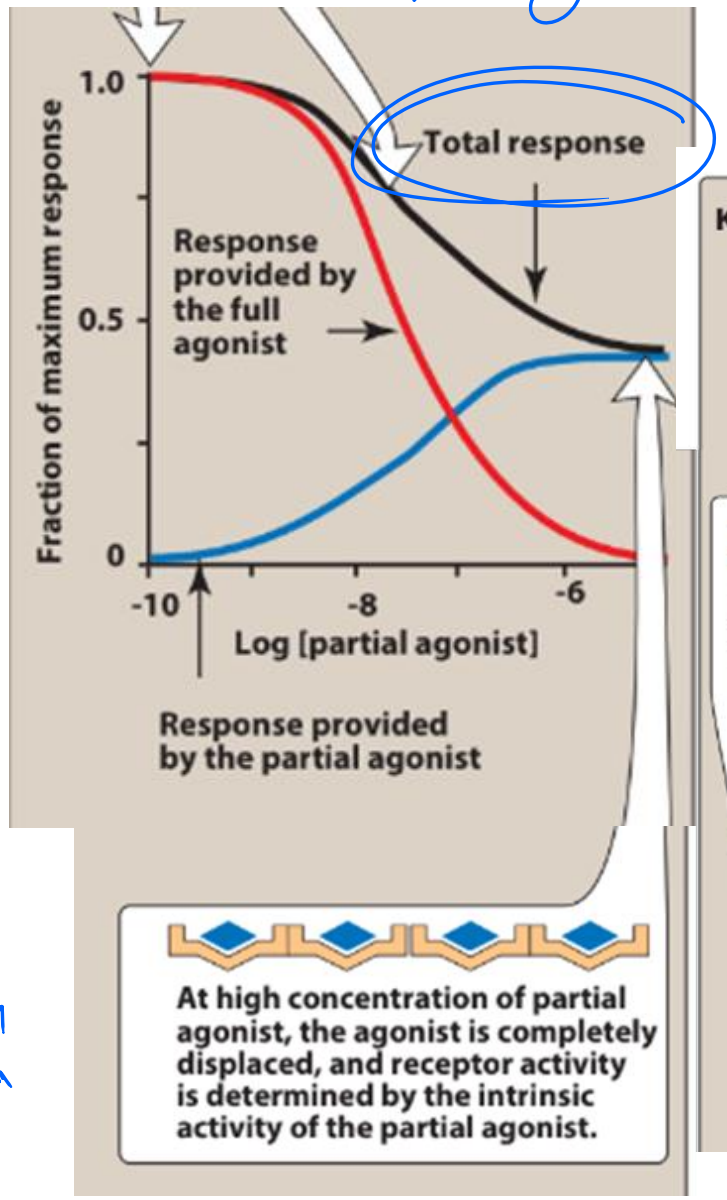
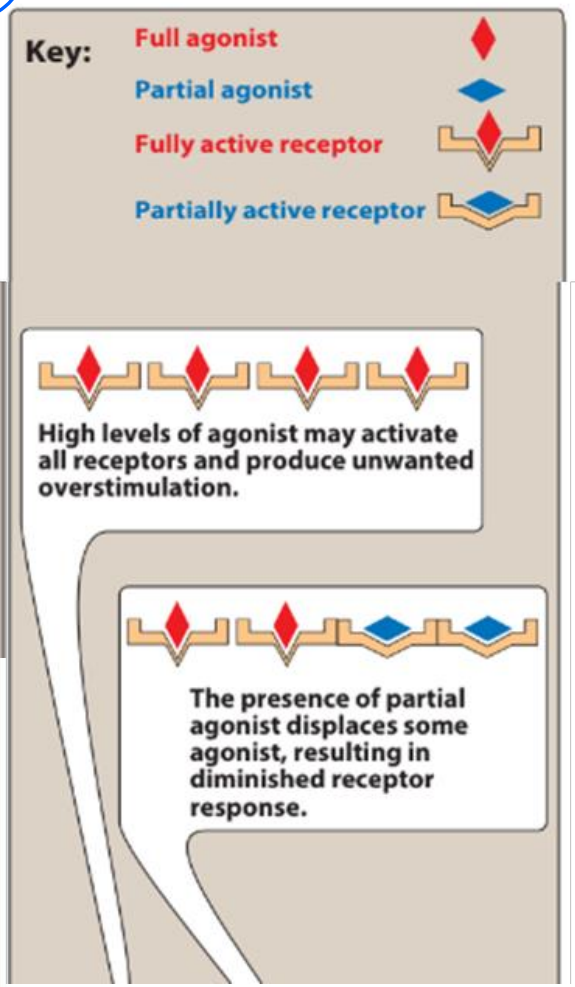


Figure 2.11
Effects of full agonists, partial agonists, and inverse agonists on receptor activity.

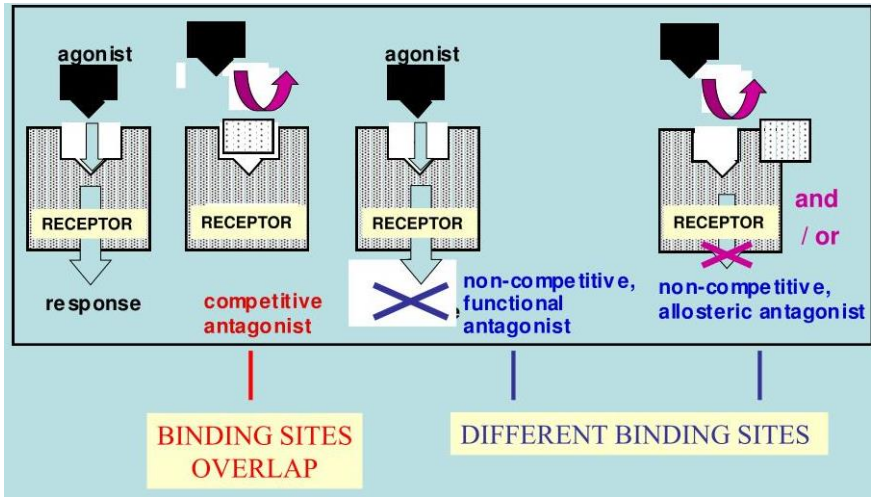




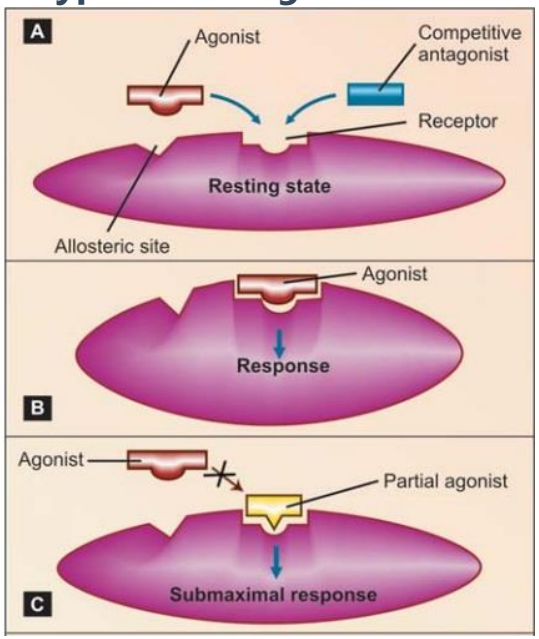
Antagonist Drugs

prevent the ligand to Bind with the receptors

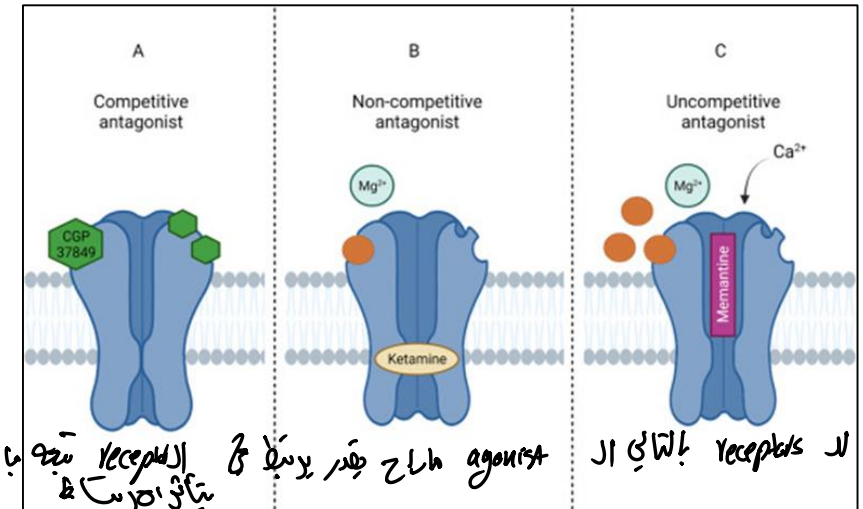
- **Drugs that bind to receptors but produce no response (possess zero intrinsic activity) and block agonist effects.**
- Has no effect in the absence of an agonist but can decrease the effect of an agonist when present

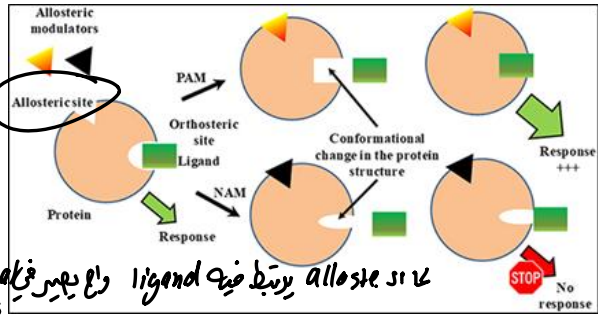


Types of Antagonists:



agonist ال و antagonist ال كلاهما يتنافسوا على نفس receptor ال



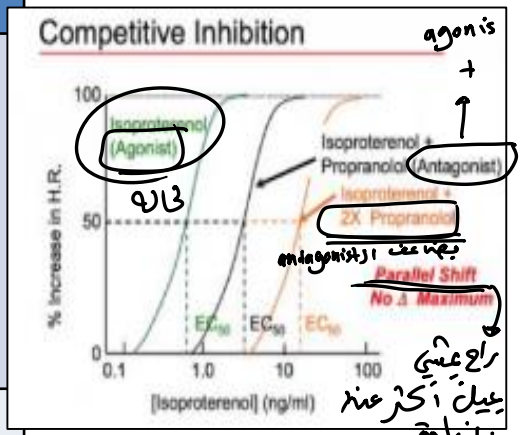


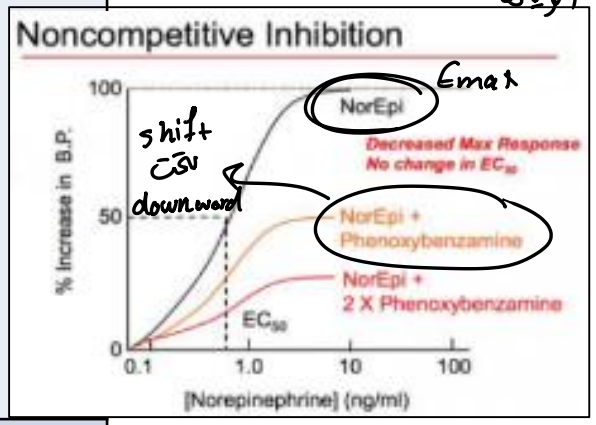
موقع مغاير

conformational changes ويتغير في ligand يرتبط فيه allosteric ال

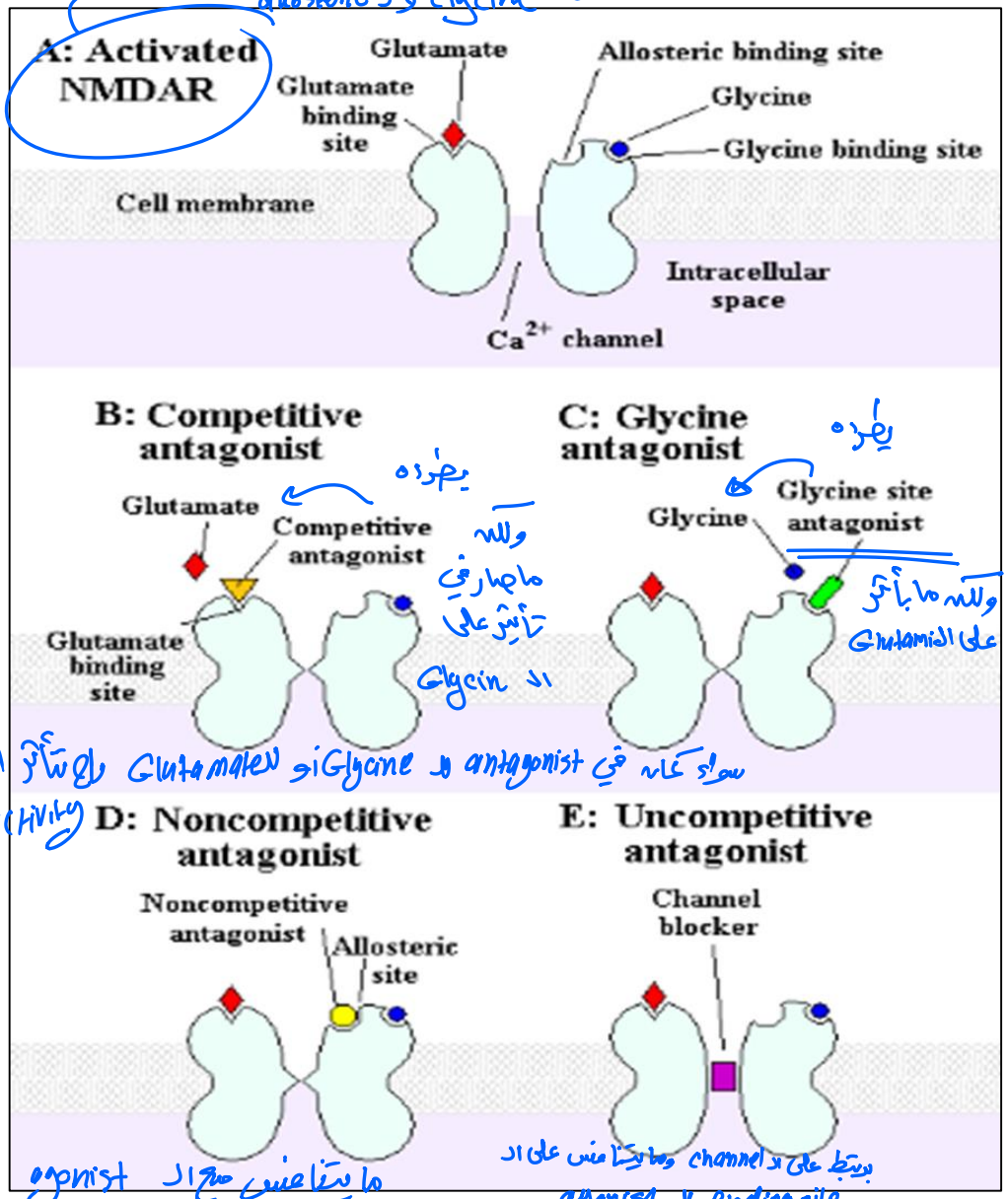
Type	Mechanism	Reversibility	Example
Competitive	• Binds to same site as agonist • shift the agonist dose–response curve to the right (increased EC50) without affecting Emax	Reversible-(Surmountable)	• **Naloxone** (opioid antagonist) • The antihypertensive drug **terazosin** competes with the endogenous ligand norepinephrine at α1-adrenoceptors
Non-competitive	• Binds irreversibly at different site (bind covalently to the active site of the receptor, reducing the number of receptors available to the agonist. • Downward shift of the Emax, with no shift of EC50 values	Irreversible (The effect cannot be overcome by adding more agonist)	**Phenoxybenzamine**

Allosteric	• Binds to different site.
	• changes receptor and prevents the receptor from being activated by the agonist
	  • Downward shift of the Emax
	  • No change in the EC50 value of an agonist
		Variable	• **Benzodiazapines** at GABA receptors
			• **Picrotoxin**, which binds to the inside of the GABA-controlled chloride channel. Then No chloride can pass through the channel, even when the receptor is fully activated by GABA.





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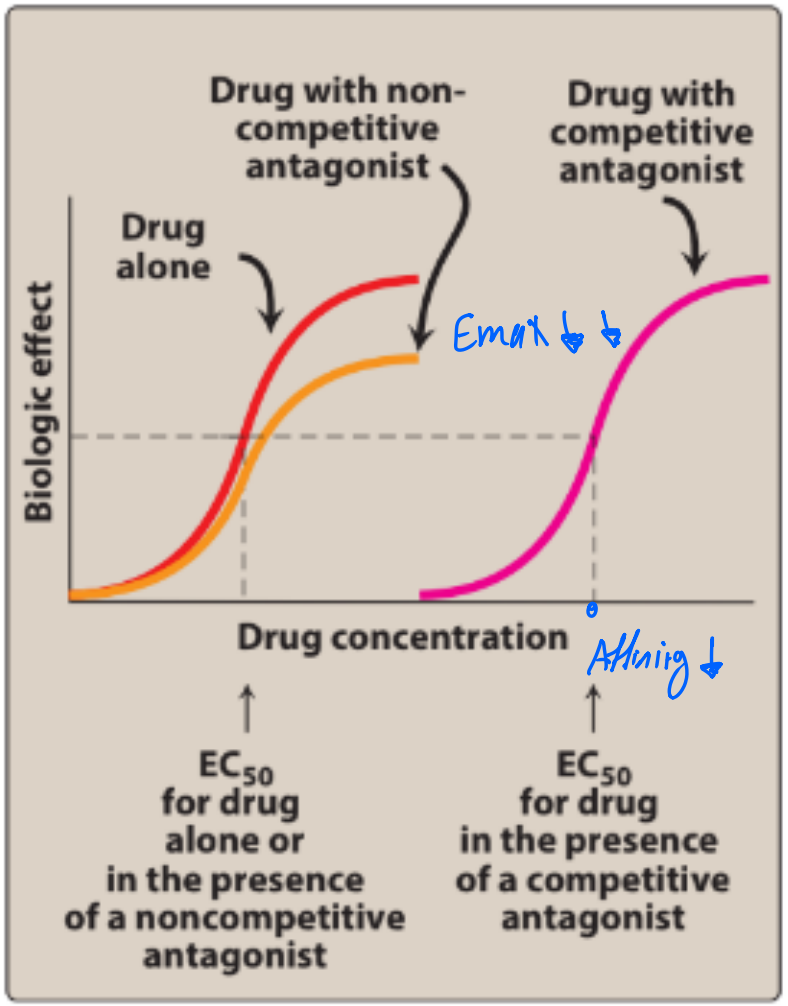


Figure 2.13
Effects of drug antagonists. EC_{50} = drug dose that shows 50% of maximal response.

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Special Drug Interactions

Inverse Agonist

Produces opposite effect to agonist

Stabilizes inactive receptor state

Example: Some benzodiazepine inverse agonists

Functional Antagonist

Opposes agonist through different receptor

Physiological antagonism

Example: Insulin vs. Glucagon

Chemical Antagonist

Neutralizes drug by chemical reaction

No receptor involvement

Example: Antacids neutralizing acid

- Some receptors show a spontaneous conversion from R to R* in the absence of an agonist.
- Inverse agonists stabilize the inactive R form and cause R* to convert to R.
- Inverse agonists have an intrinsic activity less than zero
- They exert the opposite pharmacological effect of agonists.



Remember: Understanding these interactions helps predict drug combinations and potential therapeutic strategies.

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Unusual Drug Responses

Response Type	Definition	Clinical Significance
Idiosyncratic	Unusual, unpredictable response	Often genetic basis, requires dose adjustment
Hyporeactive	Less than normal response	May need higher doses
Hyperreactive	Greater than normal response	Use lower doses, monitor closely
Hypersensitivity	Allergic/immunological reaction	Avoid drug, have emergency treatment ready
Tolerance	Decreased response over time	May need dose escalation
Tachyphylaxis	Rapid tolerance development	Consider drug holidays or alternatives

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Clinical Applications
How Pharmacodynamics Guides Clinical Practice?

Drug Selection
- Choose drugs with appropriate efficacy for condition severity
- Consider selectivity to minimize side effects
- Evaluate therapeutic index for safety margin

Dosing Strategies
- Use ED_{50} data to determine starting doses
- Consider individual patient factors (age, genetics, disease)
- Monitor for unusual responses and adjust accordingly

Drug Combinations
- Synergistic effects: Combined efficacy > individual effects
- Antagonistic effects: One drug reduces another's efficacy
- Additive effects: Combined efficacy = sum of individual effects

Key Takeaways

Drug-Receptor Binding

Affinity + Efficacy = Clinical Response

Dose-Response

Guides optimal dosing strategies

Therapeutic Index

Determines drug safety margin

Drug Types

Agonists activate, Antagonists block

Clinical Bottom Line: Understanding pharmacodynamics enables rational drug therapy, optimal dosing, prediction of drug interactions, and improved patient safety. Always consider the patient's individual factors when applying these principles!

Summary

- Thorough understanding of pharmacologic principles is essential for safe, quality practice.
- Application of principles enables us to provide safe and effective drug therapy.

Pharmacotherapeutics

The clinical use of drugs to prevent and treat diseases

- Defines principles of drug actions—the cellular processes that change in response to the presence of drug molecules
- Drugs are organized into pharmacologic classes.
- Contraindications
- Acute therapy
- Maintenance therapy
- Supplemental (or replacement) therapy
- Palliative therapy
- Supportive therapy
- Prophylactic therapy
- Empiric therapy
- Monitoring
- Therapeutic response
- Adverse effects
- Toxic effects
- Therapeutic index
- Drug concentration
- Patient condition

Tolerance: decreasing response to repeated drug doses

Dependence: physiologic or psychological need for a drug

Physical dependence: physiologic need for a drug to avoid physical withdrawal symptoms

Psychological dependence: known as addiction and is the obsessive desire for the euphoric effects of a drug

Drug interactions

1. Additive effects
2. Synergistic effects
3. Antagonistic effects
4. Incompatibility

Adverse drug event (ADE)

Adverse drug withdrawal event

Adverse drug reactions

- Pharmacologic reaction
- Hypersensitivity (allergic) reaction
- Idiosyncratic reaction
- Drug interaction

WHAT IS NEXT ?

DRUG INTERACTIONS


"Tell me and I forget; teach me and I may remember; but involve me and I learn."
Benjamin Franklin
UMKC
School of Pharmacy

General Pharmacology

Esmaa Motawe

PhD in Pharmacology and Toxicology/ Pharmaceutical Sciences

2025

PharmacoDYNAMICS



"What Drugs Do to the Body"

Understanding Drug-Body Interactions & Mechanisms of Action



DRUG INTERACTIONS

Understanding Mechanisms, Clinical Significance, and Management

Understanding drug interactions is essential for safe, individualized therapy

Learning Objectives



By the end of this lecture, you will be able to:

- Define drug interactions and their clinical significance
- Understand pharmacokinetic vs pharmacodynamic interactions
- Identify major CYP450 enzyme interactions
- Recognize high-risk drug combinations
- Learn the mechanisms behind drug interactions
- Identify high-risk drug combinations commonly seen in elderly patients
- Explain why drug interactions are more common in older adults
- Recognize Beers Criteria recommendations
- Define key terminology related to drug metabolism and transport
- Apply clinical strategies to prevent and manage drug interactions



What is Drug Interactions?

The quality, state, or action of two or more drugs acting on each other, potentially altering their therapeutic effects or safety profile.

Drug Interactions: A Major Healthcare Challenge

10-20% of adverse drug reactions causing hospitalizations are due to drug interactions

Clinical Reality: **Alert** fatigue from computer warnings can contribute to missed interactions - **clinical judgment is key**!

Clinical Pearl: Most clinically significant drug interactions involve pharmacokinetic mechanisms, particularly metabolism via CYP450 enzymes.

When to Consider Drug Interaction

🚨 Starting a Drug

لازم أسأل عن الأدوية اللي بياخدها المريض

Always check before prescribing new medications

📊 Adjusting Doses

Dose changes can alter interaction risk

🛑 Discontinuing Drugs

Stopping interacting drugs affects remaining medications

لأن ممكن بعض الأدوية أكثر من دواء مع بعض تقوي الـ activity

مع بعض وإما أكثر أو أقل



High-Risk Populations

Older Adults: ↓ liver function, ↓ kidney function, ↓ lean muscle mass,
↑ body fat, ↑ polypharmacy

Key Resources

Drug Interaction Databases:

- Lexicomp Drug Interactions
- Micromedex Drug Interactions
- Drugs.com Interaction Checker
- CredibleMeds.org (QT prolongation)
- Pharmacists consultation
- www.drugs.com
- www.hiv-druginteractions.org

Guidelines & References:

- American Geriatrics Society Beers Criteria
- RxFiles Drug Interaction Charts
- Stockley's Drug Interactions
- Clinical pharmacy consultations

Remember:

Always consult multiple sources and consider the clinical context. When in doubt, consult a pharmacist or clinical specialist.

Pharmacokinetics PK Interactions

Absorption: pH changes, binding, motility
Distribution: Protein binding, transporters
Metabolism: Enzyme induction/inhibition CYP
Excretion: Renal/biliary mechanisms

Absorption Interactions

Chelation (Binding)

Mg^{2+}, Ca^{2+}, Fe^{3+} bind to drugs

Examples: Fluoroquinolones, Tetracyclines, Levothyroxine

antibiotics

+ Choestyramine or Charcol use with multiple drugs

pH Dependent

Changes in gastric pH affect absorption

Examples: PPIs with Itraconazole, Iron

Proton pump inhibitors

P-Glycoprotein

Efflux pump affecting intestinal absorption

Examples: Digoxin, Quinidine

Grapefruit Effect

Inhibits intestinal CYP3A4

Examples: Simvastatin, Calcium channel blockers

Clinical Management

Separate interacting medications by at least 2 hours when dealing with chelation or binding interactions.

Distribution Interactions

Protein Binding Displacement

When two highly protein-bound drugs compete for binding sites, the free (active) fraction increases.

low TI — بالتالي بيزيد الـ side effects — free هنا بيزود الـ

Classic Examples

- Valproic acid + Phenytoin (90% ptn Binding)
- Warfarin + Aspirin (low TI)
- Highly protein-bound drugs (>90%)

P-Glycoprotein Effects

Reduces drug uptake into CNS

- Cancer chemotherapy
- Protease inhibitors
- Verapamil

Clinical Pearl: Distribution interactions are typically only clinically significant for drugs with narrow therapeutic windows

Metabolism Interactions:
Metabolism: The Major Player

Why Metabolism Matters Most ?

Metabolism is the **most common reason** for clinically significant drug interactions.

Major CYP450 Enzymes (The "Big 5")

- **CYP3A4** - Metabolizes ~50% of drugs
- **CYP2D6** - Not inducible, high genetic variability
- **CYP2C9** - Warfarin metabolism
- **CYP2C19** - Clopidogrel activation
- **CYP1A2** - Caffeine, theophylline

Prodrug : Requires metabolism to become active
Example: Clopidogrel → metabolized by CYP2C19 → active metabolite prevents cardiovascular events

OATP Transporter: Organic Anion-Transporting Polypeptide moves drugs into cells for excretion
Effect: OATP inhibition increases drug levels

excretion عشان ال Blood لل cell من ال drug يرجعوا ال

P-glycoprotein (P-GP): Drug efflux pump in gut, liver, kidney, blood-brain barrier. Pumps medications out for excretion
Effect: P-GP inhibition increases drug levels

drugs levels ↑ ← Blood لل intestine من ال Absorption يؤثر على ال inhibition induction العلاجات ال intestine موجود على

Enzyme Inducers vs Inhibitors

CYP Substrate : Medication metabolized by a CYP enzyme
Example: Atorvastatin is a CYP3A4 substrate

CYP Inducer: Medication that increases CYP enzyme production → faster metabolism of substrates
Example: Carbamazepine (CYP3A4 inducer)

CYP Inhibitor: Medication that decreases CYP enzyme activity → slower metabolism of substrates
Example: Clarithromycin (CYP3A4 inhibitor)

Common Inducers

↑ Metabolism = ↓ Drug Levels EXCEPT ?

- **Carbamazepine**
- **Dexamethasone**
- **Efavirenz**
- **Phenobarbital**
- **Phenytoin**
- **Rifampin**
- **St. John's Wort**
- **Effect: Gradual (>1 week for full**

Common Inhibitors

↓ Metabolism = ↑ Drug Levels
Except ???

- **Azole antifungals**
- **Clarithromycin/Erythromycin**
- **Ritonavir** (in Paxlovid)
- **Grapefruit**
- **Ciprofloxacin**
- **Cotrimoxazole**

Effect: Rapid (1-2 days)

⚠ Pay Special Attention When Paired With:

- HCV meds,
- HIV meds,
- anticonvulsants,
- immunosuppressants,
  - amiodarone,
  - dronedarone,
  - methadone,
  - Digoxin
  - , theophylline,
  - warfarin

These interactions can easily cause patient harm!

the opposite occurs with prodrugs ...they have an active metabolite

Pharm Logic Plus

CYP3A4: The Most Important

Why CYP3A4 Matters

Metabolizes approximately **50% of all drugs** and is highly susceptible to induction and inhibition.

Inducers	Inhibitors	Important Substrates
• Rifampin • Carbamazepine • Phenytoin • St. John's Wort	• Ketoconazole • Clarithromycin • Grapefruit juice • Ritonavir	•Simvastatin/Atorvastatin • Cyclosporine • **Oral contraceptives** • Fentanyl

High-Risk Combinations

- **Rifampin + Oral contraceptives** → Contraceptive failure
- **Grapefruit + Simvastatin** → Rhabdomyolysis risk
- **Ketoconazole + Fentanyl** → Respiratory depression

CYP2D6: The Genetic Variable

Ultra rapid metabolisers
Rapid metabolisers
poor metabolizers

Unique Characteristics

- **Not inducible** - Only inhibition matters
- **High genetic polymorphism** - 7% of Caucasians are poor metabolizers
- **Affects many psychiatric drugs**

الانزيم بيشتغل لحظم أدوية الاكتئاب فلو كان الشخص poor أو ultra Rapid ما راح يستفيد من الدواء

Important Substrates
- Codeine (activation)
- Tramadol
- Metoprolol
- Tamoxifen

Major Inhibitors
- Fluoxetine
- Paroxetine
- Bupropion
- Quinidine

أدوية الاكتئاب substrates + inhibitors

inactive (pro-drug)

Codeine won't work in CYP2D6 poor metabolizers because it can't be converted to morphine!

active form

	1A2	2C9	2C19
CYP Inducers			
STRONG	**carbamazepine, primidone, phenobarbital, rifampin**	**CBZ, rifampin, phenobarb, phenytoin, primidone**	**carbamazepine, phenytoin, rifampin**
MODERATE	ritonavir, smoking	dexamethasone, ritonavir, St. John's Wort	St. John's Wort
CYP Inhibitors			
STRONG	**ciprofloxacin, fluvoxamine**	delavirdine, **gemfibrozil**	delavirdine, **fluconazole, fluvoxamine, gemfibrozil,** ticlopidine
WEAK TO MODERATE	acyclovir, amiodarone, cimetidine, fluconazole, gemfibrozil, norfloxacin, ofloxacin, verapamil	amiodarone, cotrimoxazole, efavirenz, etravirine, fluconazole, fluoxetine, fluvastatin, fluvoxamine, isoniazid, ketoconazole, metronidazole, omeprazole, paroxetine, ticagrelor, quinine, valproate, voriconazole	cannabidiol, cimetidine, cinacalcet, efavirenz, eslicarbazepine, esomeprazole, etravirine, fluoxetine, isoniazid, ketoconazole, moclobemide, modafinil, omeprazole*, oxcarbazepine, voriconazole
CYP Substrates **Levels** ↑ by inhibitors & levels ↓ by inducers.	acetaminophen, amitriptyline, caffeine, clomipramine, **clopidogrel**, **clozapine**, cyclobenzaprine, desipramine, diazepam, diphenhydramine, duloxetine, erlotinib, estradiol, flutamide, fluvoxamine, haloperidol, imipramine, **methadone**, olanzapine, ondansetron, pomalidomide, propranolol, tizanidine, **theophylline**, verapamil, **warfarin**	abrocitinib , amitriptyline, carvedilol, celecoxib, clomipramine, diazepam, diclofenac, diphenhydramine, doxepin, erdafitinib, fluoxetine, glimepiride, glyburide, ibuprofen, imipramine, indomethacin, irbesartan, lesinurad, losartan, **methadone**, montelukast, naproxen, omeprazole, **phenobarbital**, phenytoin, rosiglitazone, sildenafil, sulfamethoxazole, tamoxifen, valsartan, vardenafil, **warfarin**	abrocitinib, amitriptyline, citalopram, clobazam, clomipramine, clopidogrel, desipramine, diazepam, diphenhydramine, doxepin, escitalopram, indomethacin, mavacamten, **methadone**, **phenobarbital**, **phenytoin**, PPIs, progesterone, propranolol, sertraline, **warfarin**

بعمل خطرة side effect
بقلل المناعة وبجيب الريتن
cancer تأثيره
لذلك لازم عشان أعرف أعمل
ال Blood test بيت أكون متأكدة
وإنه ما بعمل وبتأثر الجرعة والتفسير

Pharm Logic Plus

	3A4	2D6
CYP Inducers		
STRONG	**apalutamide, carbamazepine, lumacaftor, phenobarbital, phenytoin, primidone, rifabutin, rifampin**	Not inducible.
MODERATE	bosentan, efavirenz, etravirine, modafinil, St. John's Wort	
CYP Inhibitors		
STRONG	atazanavir, boceprevir, **clarithromycin**, cobicistat, indinavir, **itraconazole**, ketoconazole, mifepristone, nefazodone, nelfinavir, paritaprevir, **posaconazole**, **ritonavir** (part of PAXLOVID), saquinavir, telaprevir, **voriconazole**	**bupropion**, cinacalcet, delavirdine, **fluoxetine**, **paroxetine**, **quinidine**, **ritonavir**, **terbinafine**, tipranavir
WEAK TO MODERATE	amiodarone, aprepitant, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit, imatinib, verapamil	amiodarone, chloroquine, cimetidine, clomipramine, cobicistat, diphenhydramine, dronedarone, duloxetine, fluvoxamine, haloperidol, isoniazid, ketoconazole, methadone, mirabegron, quinine, ticlopidine
CYP Substrates **Levels** ↑ by inhibitors & levels ↓ by inducers.	abemaciclib, alfuzosin, alpelisib, alprazolam, amitriptyline, amiodarone, amlodipine, apalutamide, **apixaban**, aripiprazole, **atorvastatin**, avapritinib, brigatinib, budesonide, buprenorphine, cabozantinib , carbamazepine, chloroquine, citalopram, clarithro-/erythro-mycin, clonazepam, **colchicine**, copanlisib, cyclosporine, darolutamide, deflazacort, dexamethasone, diltiazem, domperidone, donepezil, drospirenone, efavirenz, elagolix, eletriptan elexacaftor, entrectinib, erdafitinib, ergot derivatives, estradiol, fedratinib, felodipine, fentanyl, finerenone, fluticasone, galantamine, gilteritinib, glasdegib, haloperidol, hydrocodone, istradefylline, ivabradine, ivacaftor, larotrectinib, lemborexant, lomitapide, lorlatinib, lumateperone, **lovastatin**, mavacamten, methadone, midazolam, nintedanib, neratinib, nevirapine, nifedipine, olaparib, oral contraceptives, oxycodone, paroxetine, pimavanserin, PKIs (cancer), PPIs, quetiapine, ribociclib, rifabutin, risperidone, ritonavir, **rivaroxaban**, saxagliptin, sertraline, sildenafil, simvastatin, sunitinib, **tacrolimus**, tadalafil, tamoxifen, tamsulosin, tezacaftor, ticagrelor, tolterodine, tolvaptan, trazodone, triazolam, upadacitinib, ubrogepant, velpatasvir, venetoclax, verapamil, vilazodone, **warfarin**, zopiclone. (Many **oncology** (meds): including many **-nibs**)	amitriptyline, amphetamine, aripiprazole, atomoxetine, bisoprolol, carvedilol, chloroquine, clomipramine, clozapine, codeine, cyclobenzaprine, cyclophosphamide, desipramine, dextromethorphan, diphenhydramine, donepezil, doxepin, duloxetine, eliglustat, fesoterodine, flecainide, fluoxetine, fluvoxamine, galantamine, gefitinib, haloperidol, hydrocodone, imipramine, methamphetamine, metoprolol, mirtazapine, nortriptyline, olanzapine, ondansetron, oxycodone, paroxetine, perphenazine, propranolol, risperidone, **ritonavir**, tamoxifen, timolol, tramadol, trazodone, venlafaxine, zuclopenthixol

Excretion Interteractions

Occurs when one drug affects how another drug is eliminated from the body, primarily through the kidneys or liver.
ion
Excretion affect the rate at which a drug is excreted, leading to changes in its concentration in the body. → side effects

Clinical Significance:
Increased risk of toxicity : for drugs with a narrow therapeutic index
Reduced efficacy: if a drug's excretion is increased, its concentration decreases, potentially reducing its therapeutic effect
Increased susceptibility in vulnerable populations: when renal or hepatic function is impaired

INCREASE / Decrease in pH: Changes in urinary pH can affect the reabsorption of weak acids and bases, altering their excretion rates.

Inhibit OAT : Drugs can compete for transport proteins in the renal tubules, affecting the secretion of other drugs.

For example, NSAIDs can inhibit the renal excretion of methotrexate.

Examples of Excretion Drug Interactions

Aminoglycoside antibiotics : reduce glomerular filtration rate and increase the concentration of other renally excreted drugs like digoxin.

NSAIDs: competes with methotrexate for renal tubular secretion, increasing the risk of methotrexate toxicity.

Lithium: Renal excretion of lithium can be affected by other drugs that alter sodium balance or renal blood flow.

Organic anion-transporting polypeptides (OATPs) are influx pumps; they pumps drug into a cell.

The results of inhibiting OATP depend on its location:

if at the kidney, ↑levels; if at the liver, ↑levels; if in the GI tract, ↓levels.

Example: simvastatin (OATP substrate in the liver) will have increased levels when given with cyclosporine (OATP inhibitor).

OATP Inhibitors: clarithromycin, cobicistat, cyclosporine, erythromycin, gemfibrozil, grapefruit, ketoconazole, rifampin, ritonavir, saquinavir, telaprevir, velpatasvir & voxilaprevir

OATP Substrates : ARBs, ciprofloxacin, erythromycin, montelukast, revefenacin , statins

Pharmacodynamic Interactions

- **Additive/Synergistic:** Same effects combine
- **Antagonistic:** Opposing effects compete

Example: Aspirin + Warfarin = ↑ bleeding risk

Avoid Opposing Mechanisms

Cholinergic vs Anticholinergic Conflict

AChEIs (donepezil) + Anticholinergics (amitriptyline)

Result: Medications cancel each other out - reduced therapeutic effect

Dopamine Pathway Conflict

Dopamine Agonists (levodopa) + Dopamine Antagonists (metoclopramide)

Result: Competing actions → ↓ therapeutic effect

Clinical Logic: When medications have opposing mechanisms of action, they essentially work against each other, reducing therapeutic effectiveness and potentially causing adverse effects.

Always consider the pharmacological mechanisms when combining medications - avoid therapeutic conflicts!

High-Risk Toxicity Interactions

QT Prolongation — Life-Threatening Combinations

Risk: Torsades de pointes (potentially fatal arrhythmia)
Management: Baseline ECG, avoid if QTc >500ms

Serotonin Syndrome

Combination: MAOIs + SSRIs
Symptoms: Agitation, hyperthermia, muscle rigidity
Management: Discontinue drugs immediately

Nitrates + PDE5 Inhibitors: Synergistic increase in cGMPts (potentiate hypotensive effects)

Hyperkalemia

Combination: ACE inhibitors + Spironolactone + NSAIDs
Risk: Cardiac arrhythmias, paralysis
Management: Regular K+ monitoring

Bleeding Risk

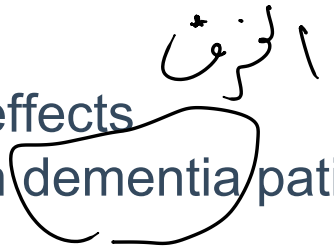
Combination: Warfarin + Aspirin + NSAIDs
Management: Consider PPI for GI protection

When Drugs Don't Work: Interactions Causing Loss of Efficacy

Aspirin + NSAIDs
Problem: NSAIDs block aspirin's antiplatelet effect
Solution: Take aspirin 2 hours before NSAID, or use acetaminophen

Levodopa + Antipsychotics
Problem: Dopamine agonist vs antagonist
Solution: Use quetiapine if antipsychotic needed

Donepezil + Anticholinergics
Problem: Competing cholinergic effects
Solution: Avoid anticholinergics in dementia patients



Clinical Pearl: Always consider if a patient's "treatment failure" might be due to a drug interaction!

Must-Know Interactions

Lithium + Diuretics →
↑ Lithium levels by 25-50%
Monitor levels closely

Azathioprine + Allopurinol
Use only 25% of azathioprine dose
Risk: Severe myelosuppression

Digoxin + Quinidine
Halve digoxin dose
P-glycoprotein inhibition

Methotrexate + NSAIDs
Competitive renal excretion
Can cause MTX toxicity

Clinical Pearl: These interactions are frequently tested because they require specific dose adjustments and have clear mechanisms.

High-Risk Medication Classes

Anticonvulsants

Carbamazepine, phenobarbital, phenytoin

Antifungals

Fluconazole (azole antifungals)

HIV/HCV Medications

Lopinavir, efavirenz, ombitasvir, sofosbuvir

Immunosuppressants

Tacrolimus, cyclosporine

Cardiac Medications

Amiodarone, dronedarone, digoxin

Others

Methadone, lithium, theophylline, warfarin

Antibiotic Interactions - Short Term, Big Impact

Four Antibiotics to Watch:

Cotrimoxazole, Ciprofloxacin, Clarithromycin, Erythromycin

تؤثر على بعض العلاجات

Hospital Admission Cases:

Cotrimoxazole + ACEIs/ARBs/NSAIDs/Spironolactone → Hyperkalemia

Cotrimoxazole + Glyburide → Hypoglycemia

Cotrimoxazole + Warfarin → ↑ Bleeding Risk

Clarithromycin + Digoxin → Digoxin Toxicity

Despite short-term use, antibiotics can cause clinically significant drug interactions leading to hospitalization in older adults.

Essential Clinical Pearls

Grapefruit Effect (CYP3A4 Inhibitor)

↑ levels of atorva-, lova-, simvastatin ALS

Safe if: Low statin dose (atorvastatin 10-20mg), infrequent grapefruit, or using rosuvastatin/pravastatin

Nitrates + PDE5 Inhibitors - MUST Space!

Wait **24 hours** after sildenafil or vardenafil

Wait **48 hours** after tadalafil duration of action ↑ d/t

Warfarin Management Strategy

✗ Don't adjust dose proactively when starting/stopping interacting med

✓ Check INR in 4-6 days and adjust reactively

Calcium Supplement Spacing

Space from levothyroxine by **≥2 hours**

Consider holding during oral fluoroquinolones or tetracyclines

Herbal Products

Garlic, ginkgo, ginseng → ↑ bleeding with warfarin

Always inquire about herbal use!

Clinical Management Strategies

Systematic Approach to Drug Interactions

1. Prevention

- Choose drugs with fewer interactions when possible
- Consider alternative drugs (e.g., rosuvastatin instead of simvastatin)
- Use comprehensive drug interaction checkers

2. Monitoring

- Therapeutic drug monitoring (TDM) for narrow therapeutic index drugs
- Clinical monitoring for signs of toxicity or efficacy loss
- Laboratory monitoring (INR, electrolytes, etc.)

3. Dose Adjustment

- Reduce dose when adding inhibitors
- Increase dose when adding inducers
- Gradual adjustments with close monitoring

4. Timing Separation

- Separate administration times (especially for absorption interactions)
- Usually 2-4 hours apart

Drug Interactions in Older Adults



Why Focus on Older Adults?

Higher prevalence: More common than in general population

Polypharmacy: Up to 25% of Canadians >65 take >10 medications regularly

Physiological changes: Age-related changes affect drug handling

Multiple comorbidities: Complex treatment regimens increase interaction risk

Key Point: Medications can easily accumulate in the aging body, significantly increasing the risk of drug interactions.

Why Are Drug Interactions More Common in Older Adults?

1. Polypharmacy & Multiple Comorbidities

- More medications = higher interaction probability
- Complex treatment regimens for multiple diseases
- Example: COPD patient needing antibiotics + steroids while having diabetes/osteoporosis

2. Pharmacokinetic Changes

- ↓ **Liver function:** Decreased metabolism → drug accumulation
- ↓ **Kidney function:** Decreased excretion → drug accumulation
- ↓ **Gastric acid:** Reduced absorption of acid-dependent drugs
- **Volume of distribution changes:** ↓ muscle mass, ↑ body fat
- ↓ **Protein binding:** ↑ free (active) drug levels
- ↓ **GI motility:** Altered absorption patterns

3. Pharmacodynamics Changes in Aging

Pharmacodynamic Changes in Aging

Altered Drug Sensitivity

Older adults experience changes in how they respond to medications, independent of drug concentrations

Examples of Increased Sensitivity:

- **Antiepileptics:** More likely to cause sedation
- **Tamsulosin:** Higher risk of hypotension
- **QT-prolonging drugs:** Increased age = higher risk of dangerous arrhythmias

Examples of Decreased Sensitivity:

- **Influenza vaccine:** Requires "high-dose" formulation for adequate protection
- **Some receptor responses:** Less responsive receptors

Clinical Impact: Standard doses may cause more side effects OR be less effective in older adults

Pharm Logic Plus

Important High-Risk Combinations in Older Adults

Critical Interactions to Remember:

- **Opioids + Benzodiazepines:** Avoid - increased overdose risk
- **Trimethoprim-Sulfamethoxazole + Sulfonylureas:** Hypoglycemia risk
- **Trimethoprim-Sulfamethoxazole + ACEIs/ARBs:** Hyperkalemia risk
- **Risperidone + Furosemide:** Increased mortality in dementia
- **Multiple anticholinergics:** Additive cognitive effects
- **≥3 CNS-active drugs:** Increased fall/fracture risk

Hyperkalemia Risk Combinations:
ACEIs + ARBs + Cotrimoxazole + Spironolactone + NSAIDs + K+ supplements

Pharm Logic Plus

Choosing Medications with Fewer Interactions

Drug Class	Fewer Interactions	More Interactions
Statins	Rosuvastatin, Pravastatin	Atorvastatin, Lovastatin, Simvastatin
Antidepressants	Citalopram, Escitalopram, Venlafaxine	Fluoxetine, Paroxetine, Duloxetine
Anticonvulsants	Gabapentin, Levetiracetam, Pregabalin	Carbamazepine, Phenytoin
Macrolides	Azithromycin	Clarithromycin, Erythromycin
PPIs	Lansoprazole, Pantoprazole	Omeprazole, Esomeprazole

Clinical Management Strategies in Old Adults

1. Optimize Drug Therapy

Fewer medications = fewer interactions. Always question necessity of each drug.

2. Check for Interactions at Critical Times

- Starting a medication
- Adjusting doses
- Discontinuing medications

3. Use Multiple Information Sources

- Pharmacists
- Drug interaction databases (Lexicomp, Micromedex)
- Specialized websites (drugs.com, crediblemeds.org)
- Product monographs

4. Understand Interaction Mechanisms

Knowledge of how interactions occur helps predict effects and guide management

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Case Study: Multiple Interactions

Patient: 78-year-old male

Conditions: Atrial fibrillation, heart failure, diabetes, depression, chronic pain

Current medications: Warfarin, digoxin, metformin, glyburide, sertraline, oxycodone

New prescription: Clarithromycin for pneumonia

Potential Interactions:

Clarithromycin + Warfarin: CYP inhibition → ↑ bleeding risk

Clarithromycin + Digoxin: P-GP inhibition → ↑ digoxin levels

Oxycodone (CNS depressant): Monitor for increased sedation

Management:

Consider azithromycin instead of clarithromycin

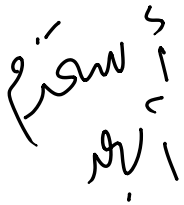
If clarithromycin necessary: monitor INR closely, watch for digoxin toxicity signs

Patient education on bleeding/toxicity symptoms

✓ Choosing Safer Alternatives

Lipid-Lowering

Fewer interactions: Rosuvastatin, Pravastatin
More interactions: Atorva-, lova-, simva-statin



Anticoagulants

Fewer interactions: DOACs (apixaban, rivaroxaban)
More interactions: Warfarin

Antidepressants

Fewer interactions: Sertraline, citalopram, venlafaxine
More interactions: Fluoxetine, paroxetine, fluvoxamine

Macrolides

Fewer interactions: Azithromycin
More interactions: Clarithromycin, erythromycin

Anticonvulsants

Fewer interactions: Gabapentin, lamotrigine, levetiracetam
More interactions: Carbamazepine, phenytoin

Acid-Reducing

Fewer interactions: Lansoprazole, pantoprazole
More interactions: Omeprazole, esomeprazole

Remember: Drug interactions are ONE consideration - efficacy, safety profile, patient factors, and evidence base also matter!

Disclaimer: Perfect drugs are hard to come by!
For example, citalopram has fewer CYP interactions but may prolong QT at high doses. Always weigh all factors when selecting medications.

Key Takeaways

Remember the "3 R's" of Drug Interactions:

- **Recognize:** High-risk patients and drug combinations
- **Research:** Check interactions before prescribing
- **Respond:** Choose safer alternatives or monitor closely

Priority Actions:

Always consider patient age and comorbidities
Choose drugs with fewer interaction potential when possible
Involve pharmacists in complex cases
Educate patients about interaction risks
Monitor closely when interactions are unavoidable

Most Important: Drug interactions are preventable causes of adverse events. Your vigilance can save lives!

Key Takeaways

Essential Points for Clinical Practice

Always check for drug interactions when prescribing, especially with narrow therapeutic index drugs or in elderly patients taking multiple medications.

Most Important
CYP3A4 interactions
Affects 50% of drugs

Most Dangerous
QT prolongation
Serotonin syndrome

Remember: ALWAYS

- Use interaction checkers in clinical practice
- Consider patient-specific factors (age, kidney/liver function)
- Monitor for both toxicity AND loss of efficacy
- Document interaction management in patient records

Most Common
Metabolism interactions
CYP450 enzymes

Most Preventable
Absorption interactions
Separate by 2 hours







Thank you



Always weigh all factors when selecting medications

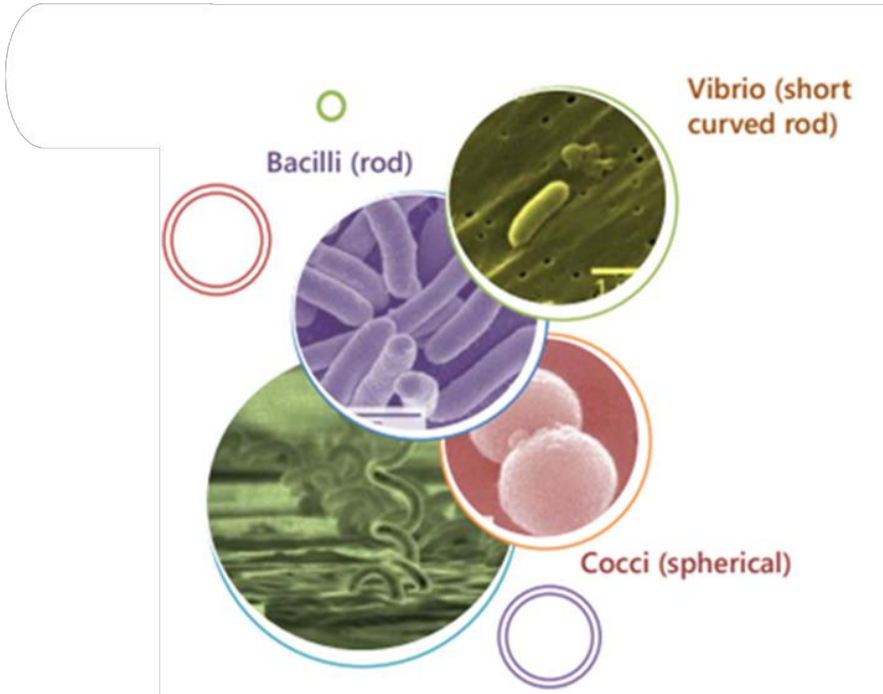
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"Tell me and I forget; teach me and I may remember; but involve me and I learn."
#بعد الميد فارما
Benjamin Franklin
UMKC
School of Pharmacy

General Pharmacology

26.7.2025

GENERAL PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY



Esmaa Motawe

2025

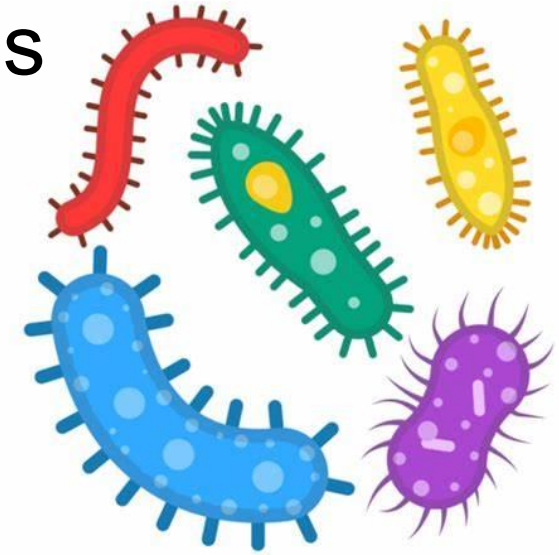
GENERAL PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY



The Science of Fighting Infections in 2025

What We'll Explore

- Selective toxicity principles
- Resistance mechanisms
- PK/PD optimization
- Clinical decision-making
- Future challenges



By the Numbers

15M
Deaths annually from infections

25%
Of global deaths are infection-related

Think About This: If bacteria can double every 20-30 minutes, how many bacteria could theoretically exist after just 24 hours starting from a single cell?

Antibiotics And Antimicrobials

سشبيه لمركب آخر من مادة طبيعية مثلاً الـ Penicillin أصله natural ثم تصنيع مركبات أخرى شبيهة المادة الطبيعية اللي فيها فروقات بسيطة

An **antibiotic** is a product of metabolism or a synthetic analogue of a natural substance that antagonizes the growth and/or survival of one or more species of microorganism when taken in small doses and which does not significantly harm the host.

يقضي على نمو البكتيريا وتكاثرها في جرعة صغيرة ولا يؤثر على الانسان بسبب اد

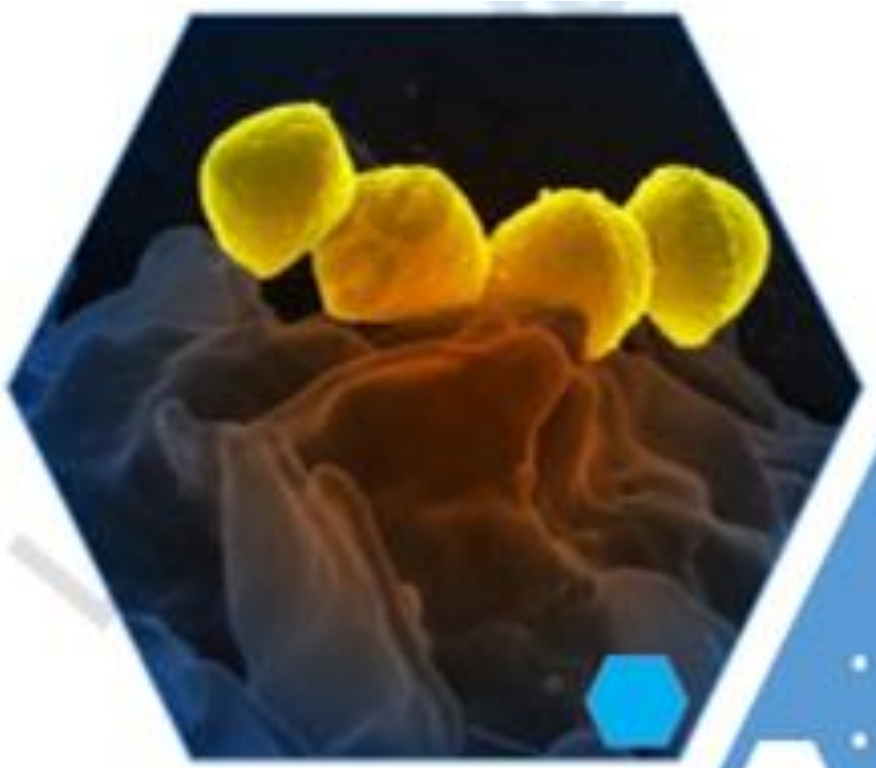
The key is **selective toxicity**. Bacteria are considered plants and we are animals. Thus there are significant biochemical differences between bacteria and us.

يعني الدواء راح يلاقي هدفه القضاء على البكتيريا اللي تعتبر من خلية النبات ولا يقضي ولا يضر الانسان الذي يعتبر من خلية الحيوان

An **antimicrobial agent** is a **wholly synthetic agent** that kills or inhibits microbes.

تم تصنيعه بشكل كامل في المختبر ولا يوجد فيه اي مواد تم تصنيعها بشكل طبيعي لحالها

What causes Infection?



- Bacteria
- Viruses
- Parasites
- Fungi
- Other

Historical Impact

30 years
Increased life expectancy

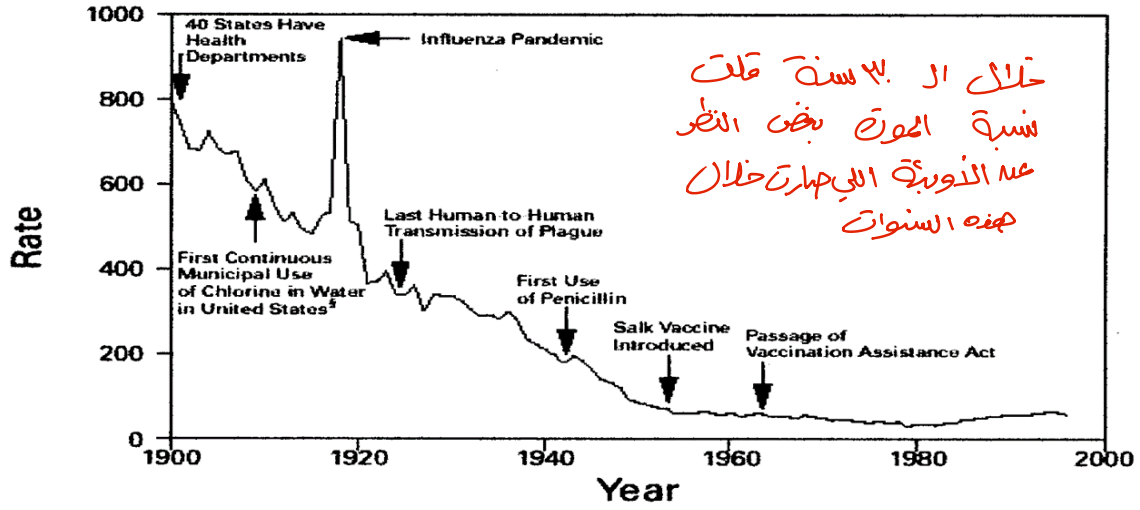
- 1900: 30% of deaths in children <5 years
- 1997: Reduced to 1.4%
- Leading causes: TB, pneumonia, diarrhea
- Improvement from: living standards, public health, vaccines, antibiotics

Current Global Burden

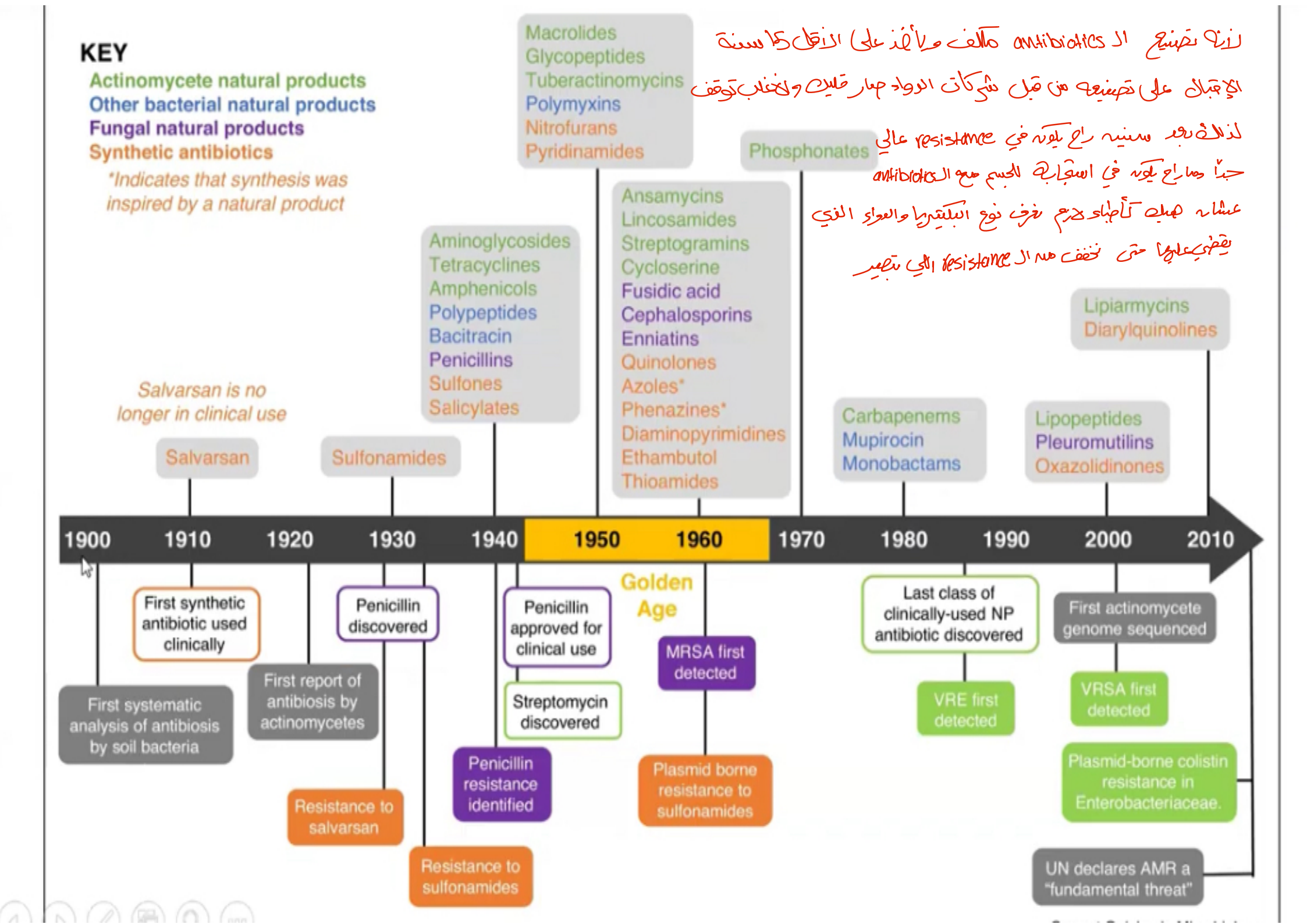
15M
Deaths annually from infections

25%
Of global deaths are infection-related

MRSA alone is 6th leading cause of death in US (170,000 deaths annually)



- Historical Perspective: How did the introduction of antimicrobials represent "an ecological disaster for bacteria"? What does this tell us about the inevitability of resistance?



لذلك تصنيع الـ antibiotics مكلف وبأخذ على الأقل كل سنة
الإقبال على تصنيعه من قبل شركات الدواء صار قليل ولأغلب توقف
لذلك بعد سنين راح يكون في resistance عالي
جدًا صار يكون في استجابة الجسم مع الـ antibiotics
عشان هيك تأطباء يدرسوا نوع البكتيريا والعواء الذي
يقضي عليها حتى نخفف هذه الـ resistance اللي بتصير

The "Perfect" Antibiotic

An Impossible Dream? NO

✓ Ideal Characteristics

- High potency, broad spectrum
- Low host toxicity
- Bactericidal action ((dead bacteria do not mutate)
- No resistance development
- Good tissue penetration
- Specific in its action (no side effects, no effect on normal flora)
- Multiple administration routes
- Non-allergenic (No interference with natural body defenses against infection
- Compatible with other anti-infective agents
- Cost-effective

Reality Check

There are NO ideal antibiotics!

Every antimicrobial represents a compromise between efficacy, safety, and resistance potential.

Critical Thinking: Why might a bactericidal drug be preferred over a bacteriostatic one? Consider the phrase "dead bacteria do not mutate."

Treatment Strategies

From Empirical to Precision Medicine

Empirical	Definitive	Prophylactic
Best guess based on likely pathogens	Targeted therapy based on culture results	Preventive treatment for high-risk situations

The pathogen has not yet been identified
Broad-spectrum therapy may be needed for serious infections when the identity of the organism is unknown or the site possibly have a polymicrobial infection

The pathogen and its drug sensitivity has been determined so the best antibiotic can be applied.

Ideally the drug chosen should be narrow in spectrum. Because of the spread of resistance to antibiotics, it is increasingly difficult to practice in this way, especially in a community setting

A potential pathogen is identified and antimicrobial chemotherapy is applied in a preventive sense to healthy individuals.

The 48-Hour Window

Empirical therapy typically lasts ~48 hours while waiting for:

- Culture results
- Sensitivity testing
- Species identification
- Clinical response assessment

Koch's Modern Postulates

1. Diagnose disease carefully
2. Isolate & identify microorganism
3. Determine antibiotic susceptibility
4. Select targeted therapy

Clinical Scenario: A 75-year-old patient presents with pneumonia. Blood cultures are pending. What factors would influence your empirical antibiotic choice?

Empirical Antibacterial Therapy

Empiric antimicrobial therapy should be **broad** enough and **intensive** enough to cover all of the likely pathogens although they have yet to be definitively identified and their drug sensitivity ascertained.

The **period of uncertainty** is usually about **48 hours after admission**.

Empiric therapy is instituted as soon as practical but not before a sample of infected material is obtained for analysis.

Characteristically it is broad spectrum in nature.

Empiric therapy is based upon:

- Patient history
- Site and characteristics of infection
- Recent experience

Definitive Antibiotic Chemotherapy

Definitive therapy is instituted as soon as possible (ASAP)
This represents the ideal.
It requires the isolation and identification of the infectious microorganism and determination of its antimicrobial sensitivity.
Ideally the drug chosen should be narrow in spectrum.
Because of the spread of resistance to antibiotics, it is increasingly difficult to practice in this way, especially in a community setting.

Koch's Postulates

صحابي اكتشف كل بكتيريا شو الأمراض اللي تسببها

Robert Koch, a German scientist-physician, was a pioneer in establishing the relationship between specific bacterial pathogens and specific infectious diseases. He was active in the latter part of the 1800s. Today Koch's findings are adapted to provide the scientific framework for specific antimicrobial chemotherapy.

1. Diagnose the disease carefully.
2. Isolate a microorganism from infected material that is not present or not present in large numbers in healthy individuals and identify it as to genus, species (and antibiotic susceptibility).

بياخد الـmicroorganism وبعزلها في شخص هي سليم ، بعدهيك بيراقب اذا ظهرت عليه نفس أعراض المرض للشخص اللي أخذ منه عينة الـmicroorganism وهك

3. (Infect a healthy volunteer with the suspected microorganism)
4. (The disease now occurs in the volunteer with all of its characteristics)

الأمور هيك صارت لازم ناخذ عينة من المريض ونفحصها مثلا أي microorganism بجل المرض ونعطي الدواء على هذا الأساس

5. (The identical microorganism is recovered from the newly diseased individual)

The parenthetical steps (items 3-5) are only now used in the laboratory to identify the causes of new infectious diseases. Steps 1 and 2 have become routine in deciding on therapy.

Chemotherapy should have an experimental basis whenever possible. Activity *in vitro* does not guarantee activity *in vivo*

The Gram Stain

The **Gram stain** (Gram is a man's name*) distinguishes between classes of bacteria by a color that develops based upon significant differences in the composition of their cell walls and membranes (differential staining)

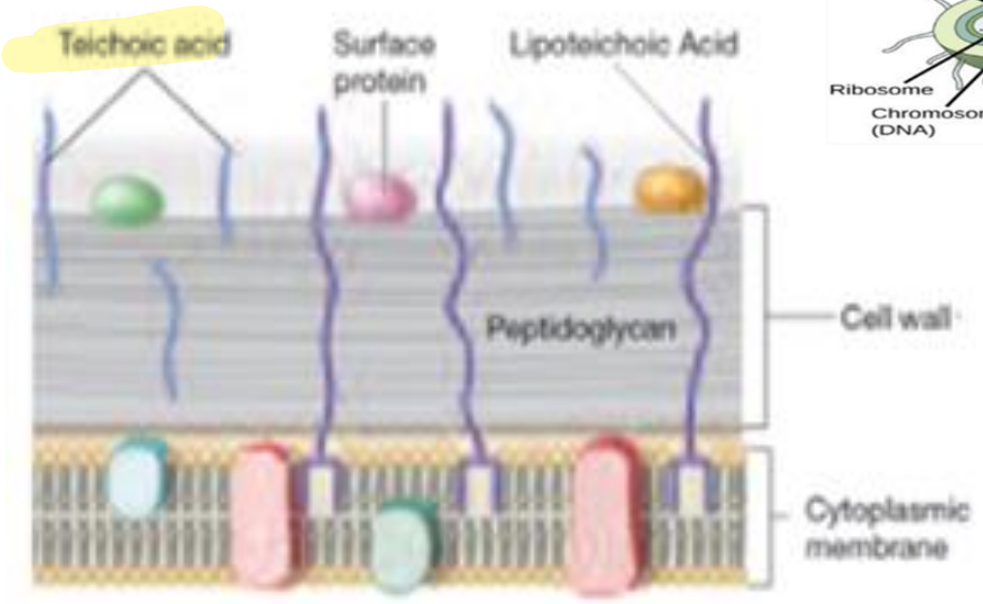
In the early days of medical microbiology when a microscope was the common diagnostic tool, specific dyes for particular cells made it much easier to see otherwise transparent cells in a background of host cells.

Today the Gram stain is especially useful

*Hans Christian Joachim Gram (1853-1938) was a Danish microbiologist.

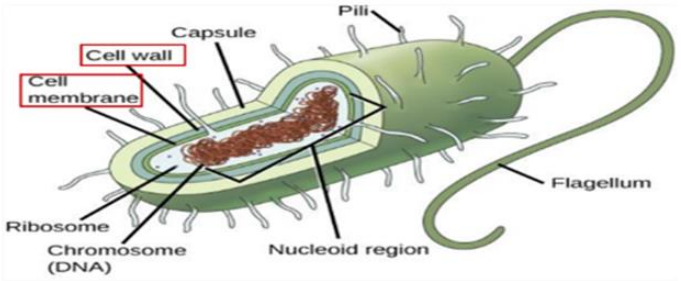
Bacteria

Gram positive

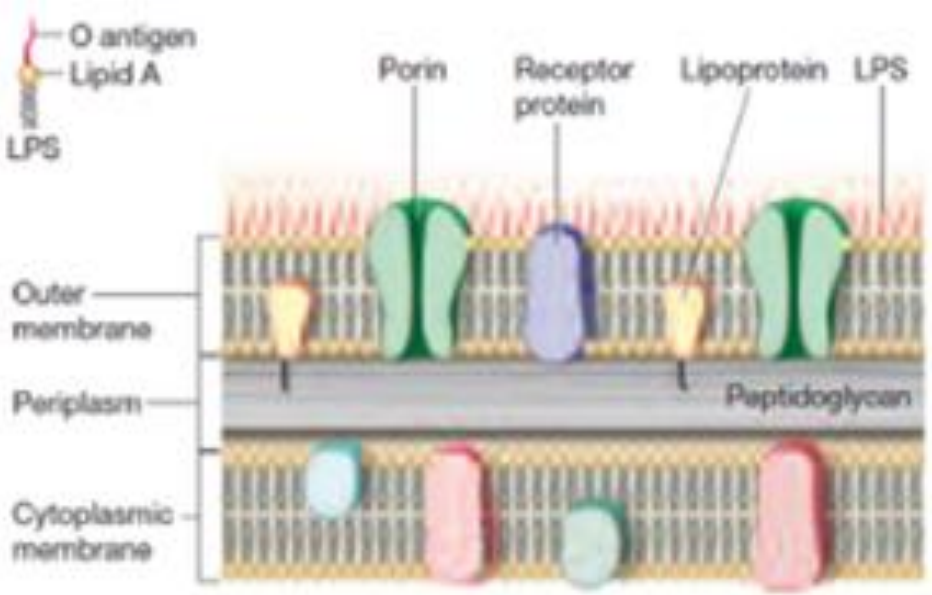


Cell Wall of Gram Positive Organism

Gram positive = blue/purple stained. **Many** comparatively safe antimicrobial choices are possible but resistance is common.



Gram negative



Cell Wall of Gram Negative Organism

لا تستغربي مع ال stain و بيطلع لوان زي ماهو بنشوف cell wall في جرثومة عالـ membrane وهنا بالأغلب pink

Gram negative = pink stained.

Few comparatively safe antimicrobial choices are possible. Resistance is common. The Gram negative bacteria have a much more complex cell wall and are more resistant to uptake of antibiotics than are Gram positives.

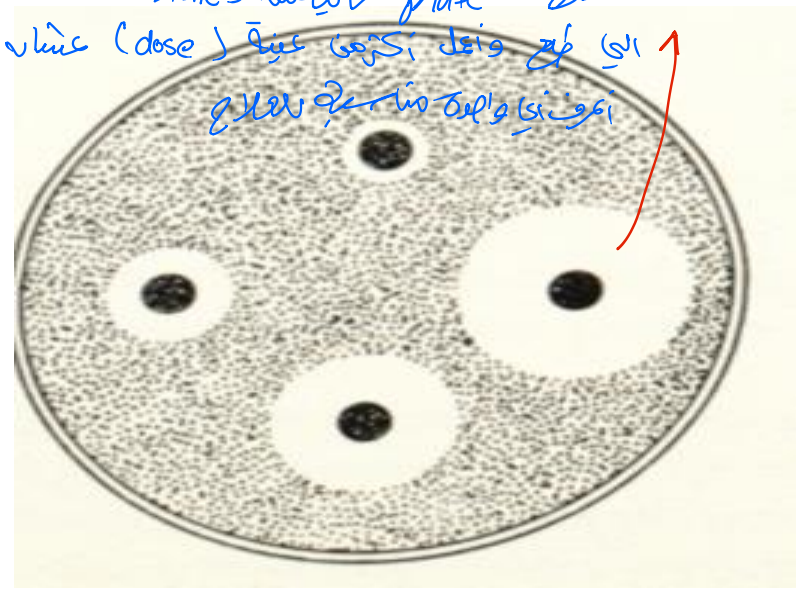
Kirby-Bauer Susceptibility Discs

This methodology is used in the diagnostic laboratory and is increasingly important due to drug resistance.

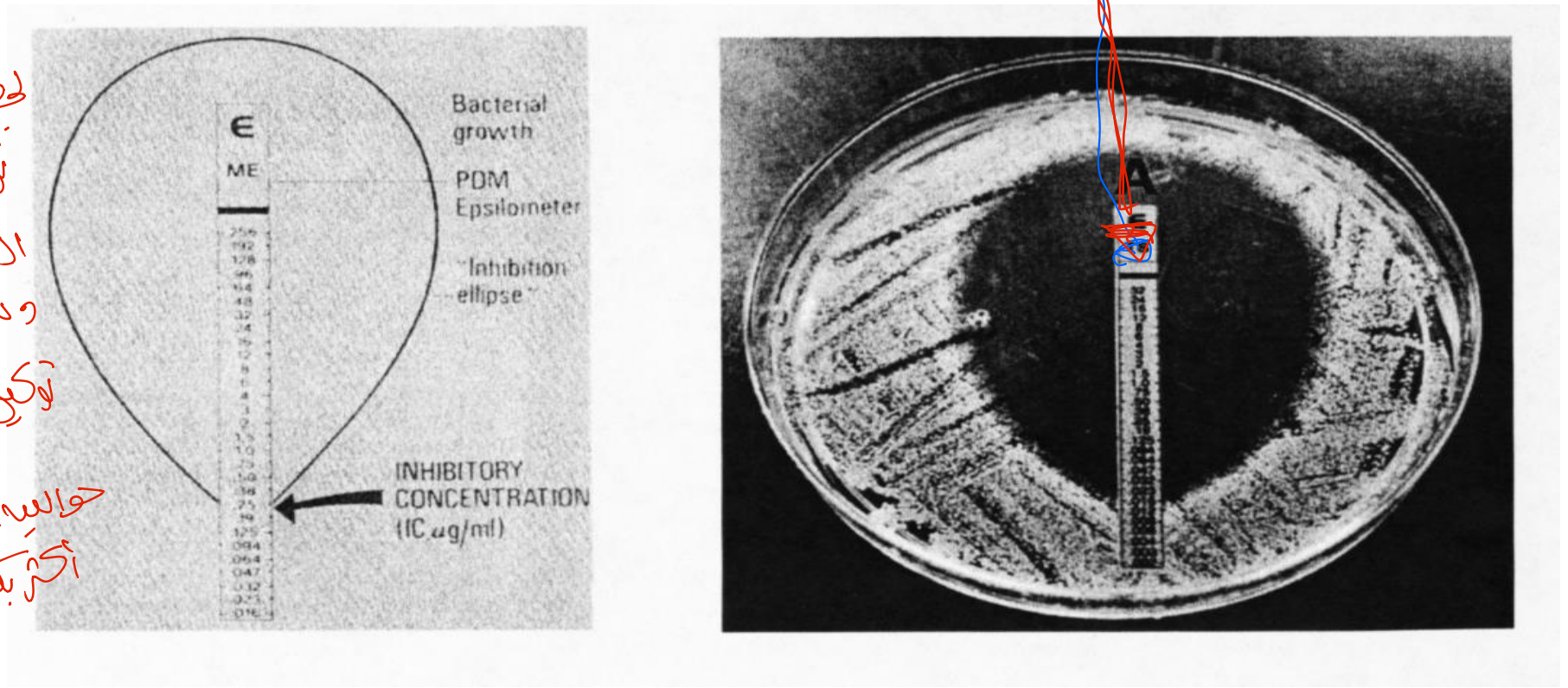
Infected material from a patient (before treatment is started!) is used to inoculate a plate.

Sterile filter paper discs impregnated with standard doses of representative antibiotics are placed on the inoculated plate.

Following incubation there will be a clear zone of inhibition surrounding discs that inhibit or kill the microorganism. The zone diameter is related logarithmically to antibiotic potency. The growth usually takes overnight incubation.

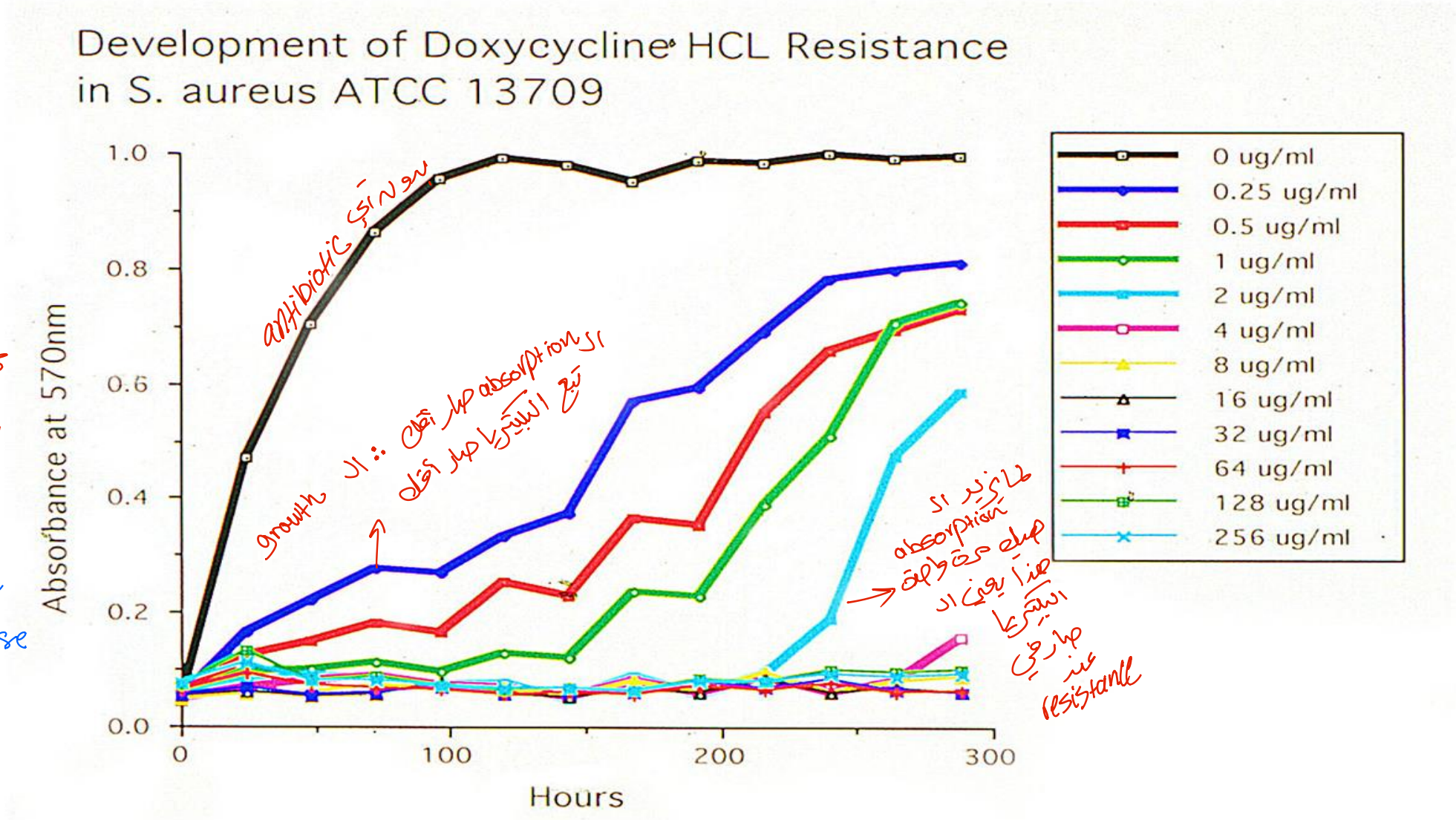


Gradient Strip Test



Another format for testing sensitivity is the gradient strip. A filter paper disc impregnated with increasing concentrations of an antibiotic is placed on a Petri dish containing suitable microbiological media and seeded with a pathogen. This is incubated. From the resulting inhibition area one can determine the mic and the general concentration dependency of the activity.

Bacterial Resistance As A Function of Antibiotic Dose



one notes the no-effect dose. If the dose is high, then no growth is observed in nearly 10 days even though this antibiotic is static. At intermediate doses, the bug recovers!

MIC, MBC & Resistance

Understanding Drug Effectiveness

Key Concepts



MIC: Minimum Inhibitory Concentration

MBC: Minimum Bactericidal Concentration

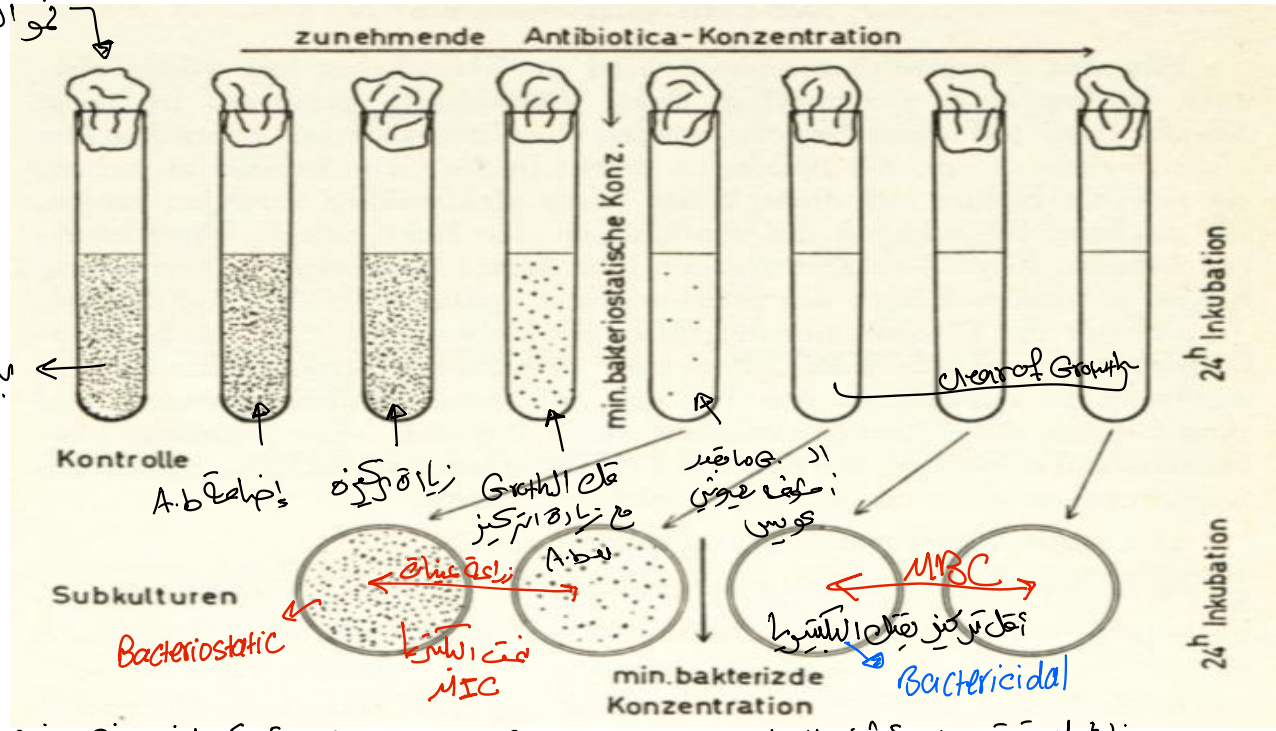
MIC-50: Inhibits 50% of strains tested

Broth نمو البكتيريا في وسط سائل

أقل تركيز يحل inhibition

أقل تركيز يسبب قتل للبكتيريا

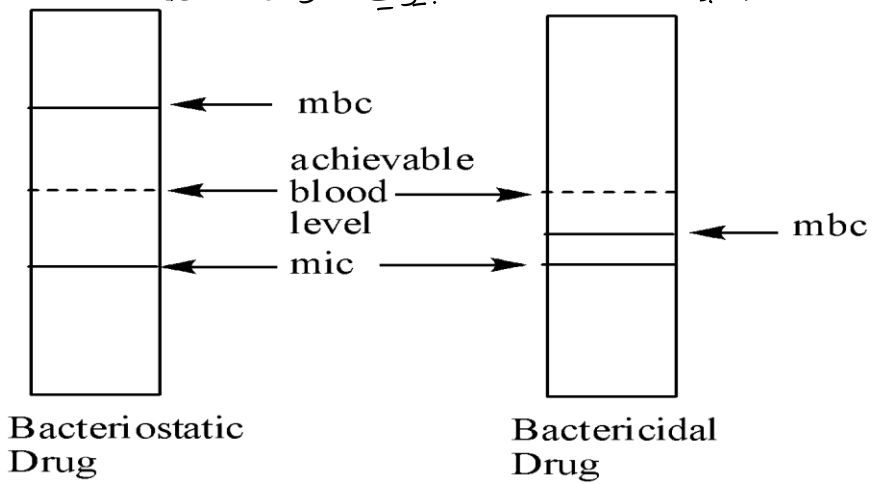
antibiotic بدون أي



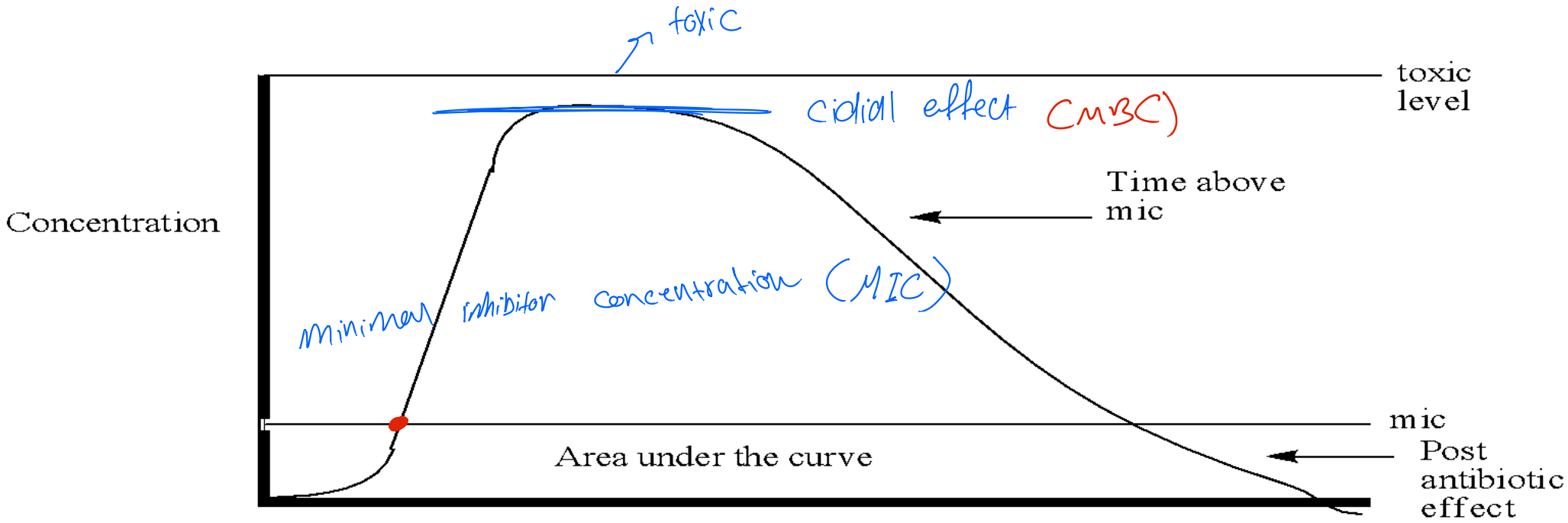
Growth in broth is determined by turbidity following incubation of test tubes containing increasing amounts of antibiotic.

The ***mic* value** is the last tube showing no visible growth. More information is needed to determine whether it is bacteriostatic or bactericidal.

The ***mbc* value** is determined by removing an aliquot of the medium from a tube that showed no growth in the above test and diluting it in fresh medium without antibiotic. Incubation then shows either growth (stasis) or not (bactericidal).



Predictors Of Clinical Success



Time dependent killing occurs during the time when the concentration exceeds the mic.
Concentration dependent killing occurs as a function of the ratio of the area under the curve divided by the mic.

Time above mic is a good predictor for β-lactam drugs whereas auc/mic is more predictive for macrolide antibiotics.

Minimum inhibitory concentration (MIC) (for bacteriostatic agents):

The lowest concentration of antibiotic that inhibits bacterial growth.

Minimum bactericidal concentration (MBC) (for bactericidal agents):

Determines the minimum concentration of antibiotic that kills the bacteria under investigation.

Spectrum of antibiotic

Narrow spectrum: a chemotherapeutic agents acting only on a limited group of microorganisms.

Broad spectrum: a chemotherapeutic agents acting on a wide variety of microbial species.

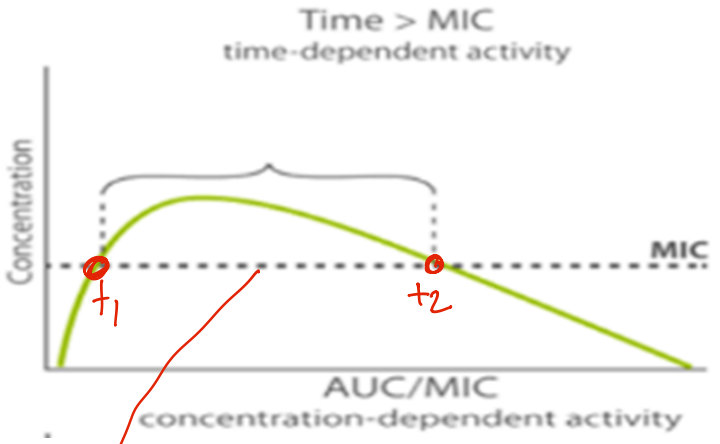
Pharmacokinetics & Pharmacodynamics

Optimizing Drug Exposure

Time-Dependent Killing

β-lactams, Clindamycin, Tetracyclines

- Duration above MIC matters most
- No post-antibiotic effect
- Frequent dosing needed
- Target: >40-70% time above MIC



Common Examples:

- **Beta Lactams**
- **Macrolides** except Azi
- **Vancomycin**

Clindamycin

Tetracyclines

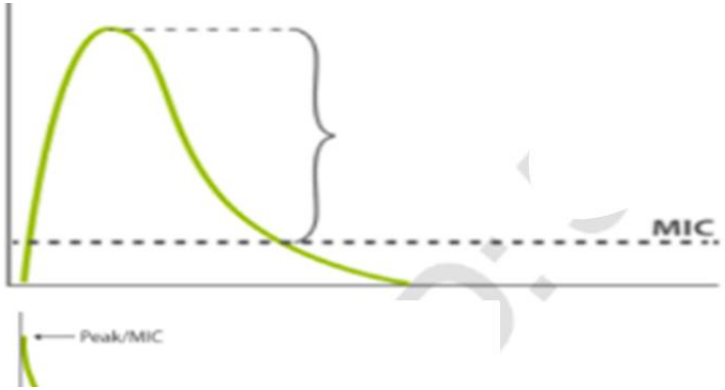
above the optimal concentration

t1, t2

Concentration-Dependent Killing

Fluoroquinolones, Aminoglycosides, Metronidazole

- Peak levels/AUC:MIC ratio crucial
- Post-antibiotic effect present
- Once-daily dosing possible
- Higher peaks = better outcomes



- **Quinolones**
- **Aminoglycosides**

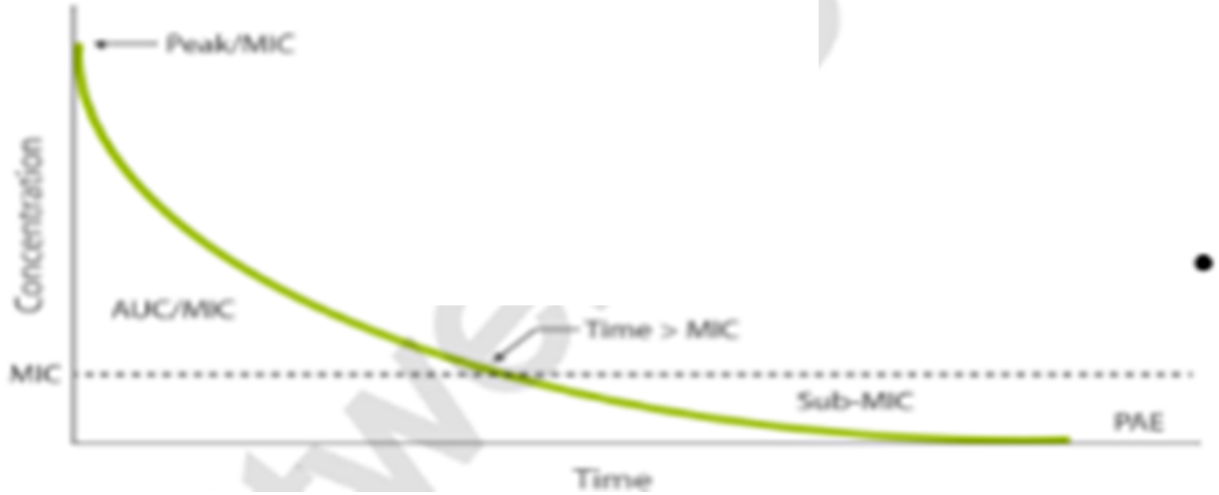
F: FQ except cipro
A : AMG
Me: Metronidazole
Az : Azithromycin
D: Daptomycin

□ Post-Antibiotic Effect (PAE)

Continued bacterial suppression even when drug levels fall below MIC. This phenomenon allows for:

- Extended dosing intervals
- Potential for single-dose therapy
- Improved patient compliance

حتى بعد ال MIC راح يكون لسا في activity للدواء



- **Aminoglycosides**

Post-Antibiotic Effect (PAE)

Some antibiotics, the inhibitory effect persists for a while after the drug concentration falls to low levels.
The microbe does not resume growth for a while even though the amount of drug present is below the MIC value.
The microbe is clearly not yet recovered during this time.

Explanation: higher drug concentrations may remain inside the cells than is measured in body fluids.

The practical consequence: possibly achieve a cure without continual administration of the antibiotic.

This is likely to result in bacterial resistance unless therapy is very closely monitored.

With some drugs (notably **fluoroquinolones and aminoglycosides**) the ratio of the area under the curve to the T1/2 is more useful in effecting a cure than is the more traditional continuous time above the MIC(PAE).

Clinical Application: You're treating a patient with gentamicin. Should you give 80mg every 8 hours or 240mg once daily?
Explain your reasoning.

Aminoglycosides مثل gentamycin لأن
dose dependent يعني
كلما زاد التركيز

The Effect of Pharmacokinetic Factors

يقدر يوصل للمكان المناسب و بالتركيز المناسب

- An antibiotic must **reach the site of the infection** promptly and in adequate concentrations.
- It must also persist at the site **long enough** to inhibit or kill the microorganism.

Obviously influential in achieving this is

1. The route of administration,
2. Ability to reach the tissue in which the infection is present,
3. Satisfactory freedom from interference by serum protein binding,
4. An acceptable clearance rate from the body, لو ارتبط مع أعتبره كأنه غير موجود لأنه مارح يوصل لل target
5. The ability to penetrate into encysted infections.

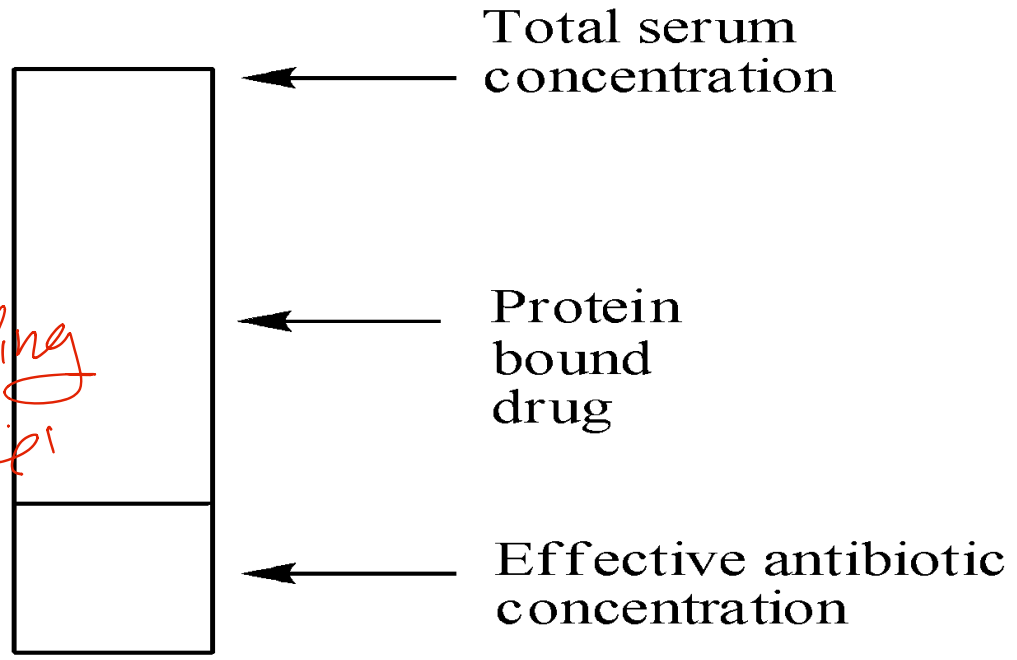
Effect Of Serum Protein Binding

The portion of an antibiotic dose that is bound to serum proteins is believed to be antibiotically ineffective unless the binding is freely reversible.

Tight and excessive protein binding is regarded to represent a site of loss. This effect can be estimated by measuring the *mic* with and without serum proteins added to the *in vitro* test. Any difference in potency seen by comparing this data is regarded as the effect of tight serum protein binding.

Highly and tightly protein bound drugs are ineffective for septicemias and most tissue infections.

If binding is tight, a prolonged excretion half-life can be expected since under normal circumstances, urine is a protein-free filtrate.



Some Dosage Considerations

The first dose of an antibiotic is given as soon as possible. Subsequent doses should not be missed.

Oral medication is preferred for outpatient or home-patient therapy

In severe infections, parenteral therapy is preferred. This should be done with care. Too many I.V.s are hard on a patient. Push followed by drip is common.

Ideally both oral and parenteral forms of an antibiotic should be available so that experimentation with a new antibiotic is not needed following release from hospital.

Development Of Fever During Chemotherapy

لازم أفتح وأظهر كيس صديد الدواء يوصل للجرثومة

- If this occurs, have all abscesses drained to make sure that the drug is reaching the bacteria at the infection site.
- The fever may be due to drug allergy (penicillins).
- The wrong antibiotic may have been prescribed.
- If an infection develops during prophylactic use of an antibiotic, then one usually has to change to a different antibiotic.

الدواء اللي بعطيه قبل ظهور نتيجة ال culture ممكن يكون خطأ
ويعطيه حرارة وأعراض جانبية بالتالي بوقف أغير الدواء بسرعة

Bacterial Growth Is Rapid

Many bacteria divide every 20-30 minutes so, if all the progeny survive, all participate and adequate food is available, 24 hours sees a remarkable number of colony forming units. Assume 30 minutes:

One hour	**4 cells**	**14 hrs.**	**268,435,456**
Two hours	**16**	**16 hrs.**	**1,073,741,824**
Four hours	**256**	**18 hrs.**	**68,719,476,736**
Six hours	**4096**	**20 hrs.**	**1,099,511,627,776**
Eight hours	**65,536**	**22 hrs.**	**17,592,186,044,416**
Ten hours	**1,048,576**	**24 hrs.**	**281,474,976,710,656!**
Twelve hrs.	**16,777,216**		

This is why one institutes therapy as soon as possible. It also shows why only a few cells need to become resistant before massive resistance is seen.

By contrast, under ideal circumstances, two humans and their progeny can produce a maximum of up to 282 offspring in 100 years!

Resistance: The Evolutionary Arms Race

Understanding the Enemy

Resistance Mechanisms

- **Transformation:** Uptake of resistance genes
- **Transduction:** Viral gene transfer
- **Conjugation:** Plasmid transfer
- **Mutation:** Spontaneous changes

Bacterial Multiplication

281 Trillion

Bacteria from 1 cell in 24 hours

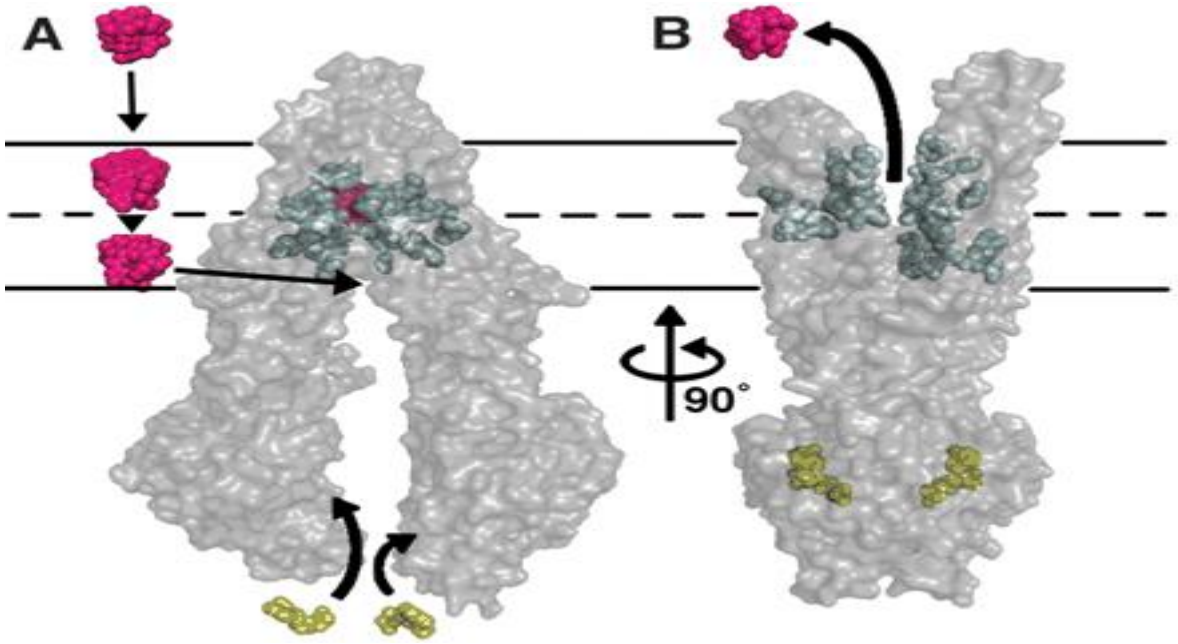
Compare to humans: Maximum 282 offspring in 100 years!

Evolutionary Puzzle: Why is antibiotic resistance described as "co-evolution in action"? What does this mean for our long-term strategy against infections?

P-Glycoprotein: The Bacterial Bouncer: Drug (Antibiotic) Exporting p-Glycoprotein

This efflux pump actively removes antibiotics from bacterial cells, acting like a molecular bouncer that kicks drugs out before they can work.

البروتين يلي بيطرد الدواء برميه عربي وبيطرده بالتالي المريض ما بستفيد من الدواء وبصير في resistance للبكتريا



An X-ray picture of the p-glycoprotein has been published leading to the model on the left. In A, the drug enters the membrane from the exterior and enters the exporter through an opening. It binds in this large cavity. In B, ATP enters the interior portion of the cavity and causes a large conformational movement closing this opening and cause an opening of the top of the protein allowing the bound drug (drugs) to escape back outside of the cell.

Resistance And Persistence

استمرار نمو الmicroorganism حتى بوجود تركيز معين من ادوية التي عملوا عليها دراسة وايه مستهاد التركيز الحقيقي يوقفالنمو

Resistance is continued cell growth in the presence of a concentration of an antibiotic that stops cell growth in a sensitive strain of microbe.

Resistance can either be acquired or intrinsic and is inevitable.

Clinical resistance is increasingly common and is threatening a return to the old days (up until about the mid 1930's) when we were essentially defenseless against bacterial infections. Many common infections are now hard to treat.

البكتيريا راح تفرز انزيمات تدمر الantibiotic

Clinical resistance is most often due to antibiotic-destroying enzymes encoded by R-factor genes, efflux pumps, and other proteins interfering with treatment. Often resistance includes several antibiotic types. It is rapidly spread between bacteria.

Laboratory resistance is most often due to alterations in the biochemical target of the antibiotic in bacterial cells rather than to alterations in the structure of the drug. Often such resistance is restricted to a single antibiotic family. Synchronous with cell division.

تغير الtarget لل antibiotic بسبب تغير تركيب الدواء

About Resistance

- Convenience and laziness are the main causes of antibiotic resistance attributable to humans.
- Patients demanding antimicrobials for non-responsive conditions (viral infections) or who use them inappropriately (early cessation of therapy) and those who feel them to livestock are often causes but often are not the direct sufferers of the consequences
- Presently resistant bacteria threaten mostly children, the aged, cancer patients, chronically ill and AIDS sufferers
- Negative financial incentives and bad luck contribute to a pessimistic future outlook
- No action today will lead to no cure tomorrow
- The gains from antibiotic overuse are private but the consequences are public
- A massive investment in genomics, proteomics, and combinatorial chemistry has not lead to corresponding therapeutic advances in antimicrobial chemotherapy.
- A return to massive empiric screening methods faces a seemingly implacable law of diminishing returns
- The public price is particularly cruel in the low and moderate income communities where cheaper generic agents of low power and high resistance instances are often the only realistically available choices and are often available over the counter!

Modern Clinical Challenges

Beyond Simple Infections

Healthcare-Associated Infections

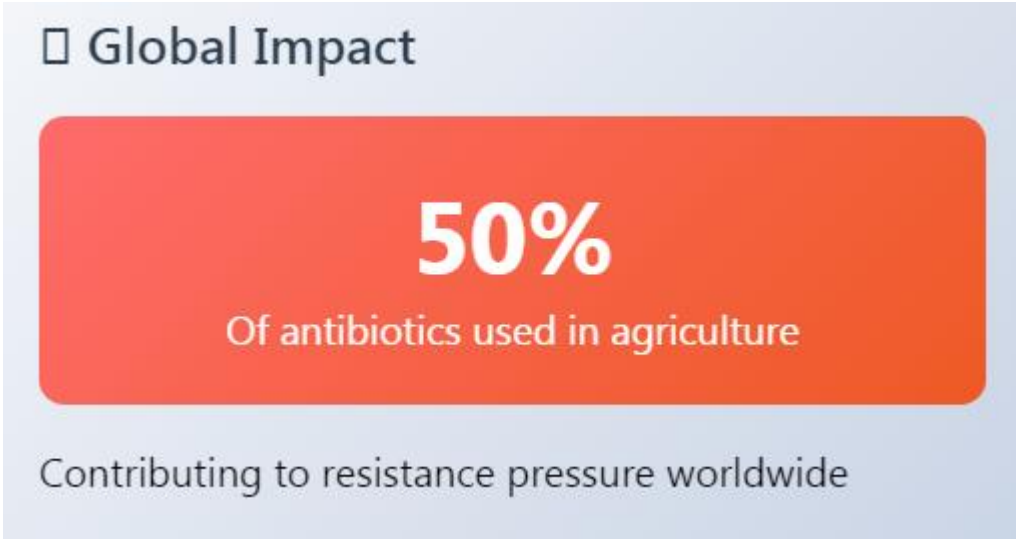
- Occur >48 hours after admission
- Often multidrug-resistant
- MRSA is #6 cause of death in US
- More virulent organisms

Biofilms: The Hidden Enemy

- Bacteria in protective "cities"
- 1000x more resistant to antibiotics
- Common on medical devices
- Difficult to penetrate

Antibiotic Harms

- 27% vs 15% adverse events (antibiotic vs placebo)
- 8x higher risk of yeast infections
- C. difficile-associated diarrhea
- Allergic reactions (5-10% report penicillin allergy)



⚖ **Ethical Dilemma:** A patient demands antibiotics for viral bronchitis. How do you balance individual patient autonomy with public health concerns about resistance?

educate the patient about the concern of resistance

Infections

Community-associated infections (CA)

An infection that is acquired by a person who has not been hospitalized or had a medical procedure (e.g., dialysis, surgery, catheterization) within the past year

Health care–associated infections(HA)

بسبب دخول المستشفى

- Contracted in a hospital or institutional setting
- were not present or incubating in the patient on admission to the facility
- Occurs more than 48 hours after admission
- More difficult to treat because causative microorganisms are often drug resistant and the most virulent
- Methicillin-resistant *Staphylococcus aureus* (MRSA) is most common.
- Previously known as *nosocomial*

Virulence Factors

The severity of bacterial diseases is often increased due to the secretion of proteinaceous virulence factors.

For example, *Staphylococcus aureus* secretes **phenol-soluble modulin proteins (PSMs)** that help the organism to evade immune defenses. These proteins destroy immune cells enhancing the deleterious effects of the infection. These proteins are particularly prevalent in MRSA infections.

Killing the organism through antibiotics does not promptly resolve many infections as the toxins are still present.

R. Wang et al., Nature Medicine (2007)10:1038.

Resistance Timeline

Drug	FDA Approval Date	Date of First Reported Resistance
Penicillin	1943	1940
Streptomycin	1947	1947
Tetracycline	1952	1956
Methicillin	1960	1961
Nalidixic Acid	1964	1966
Gentamicin	1967	1969
Vancomycin	1972	1987
Cefotaxime	1981	1981
Linezolid	2000	1999

ASM News (2004) 70:283.

Resistance develops rapidly!

- Penicillin: 1943 → 1940 (before approval!)
- Methicillin: 1960 → 1961
- Lincomycin: 2000 → 1999

⚖ **Dosing Dilemma:** If higher doses can overcome resistance, why don't we always use maximum doses? Consider the resistance emergence curve.

Origin And Sharing Of Resistance Genes

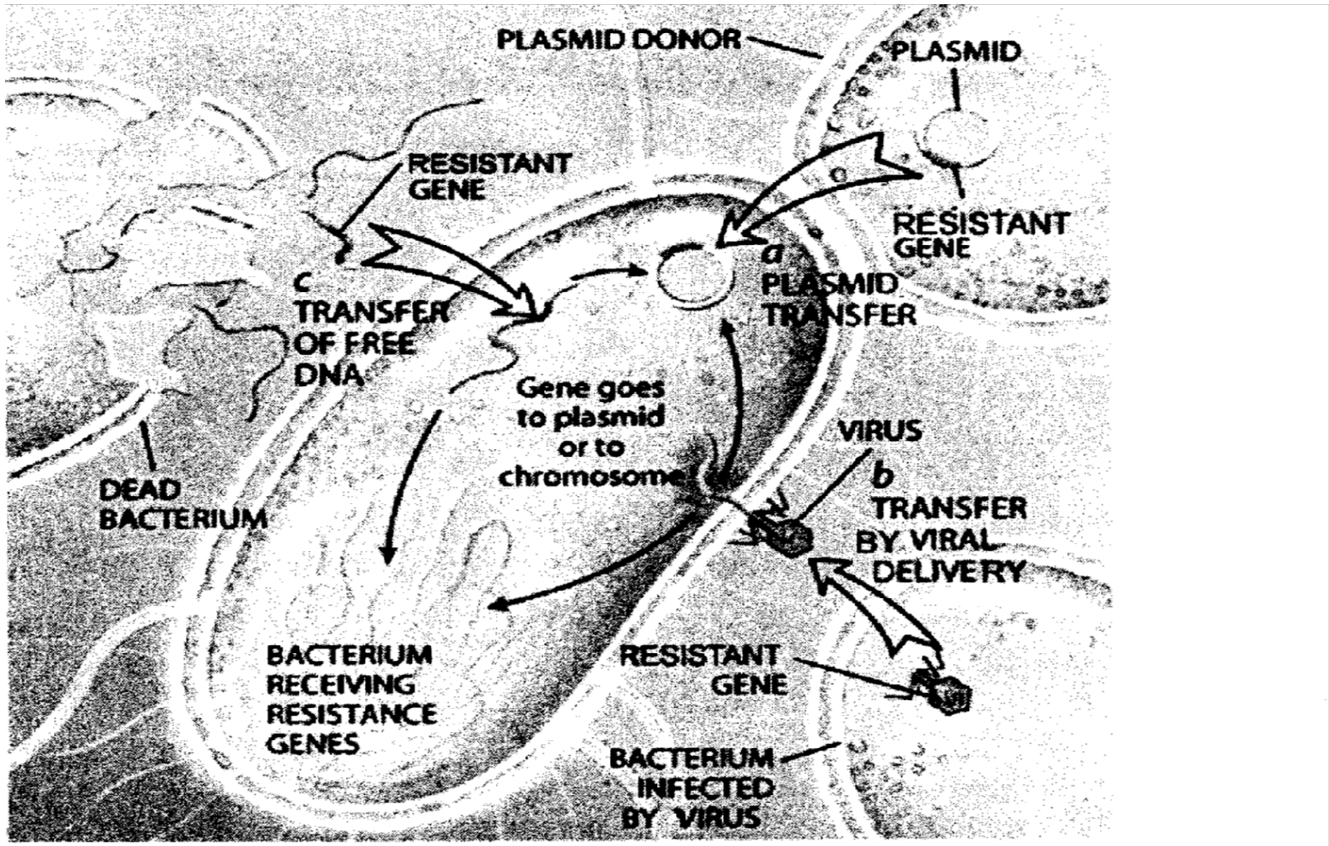
- Inaccurate repair of normal genes followed by selection/mutation.

- Transformation (uptake of resistance genes from extracellular sources).

- Transduction (a virus picks up a resistance gene from a cell and injects it into another bacterium).

- Plasmid transfer from a donor to a recipient cell (conjugation).

- Stable incorporation into a cell's chromosome or plasmid.

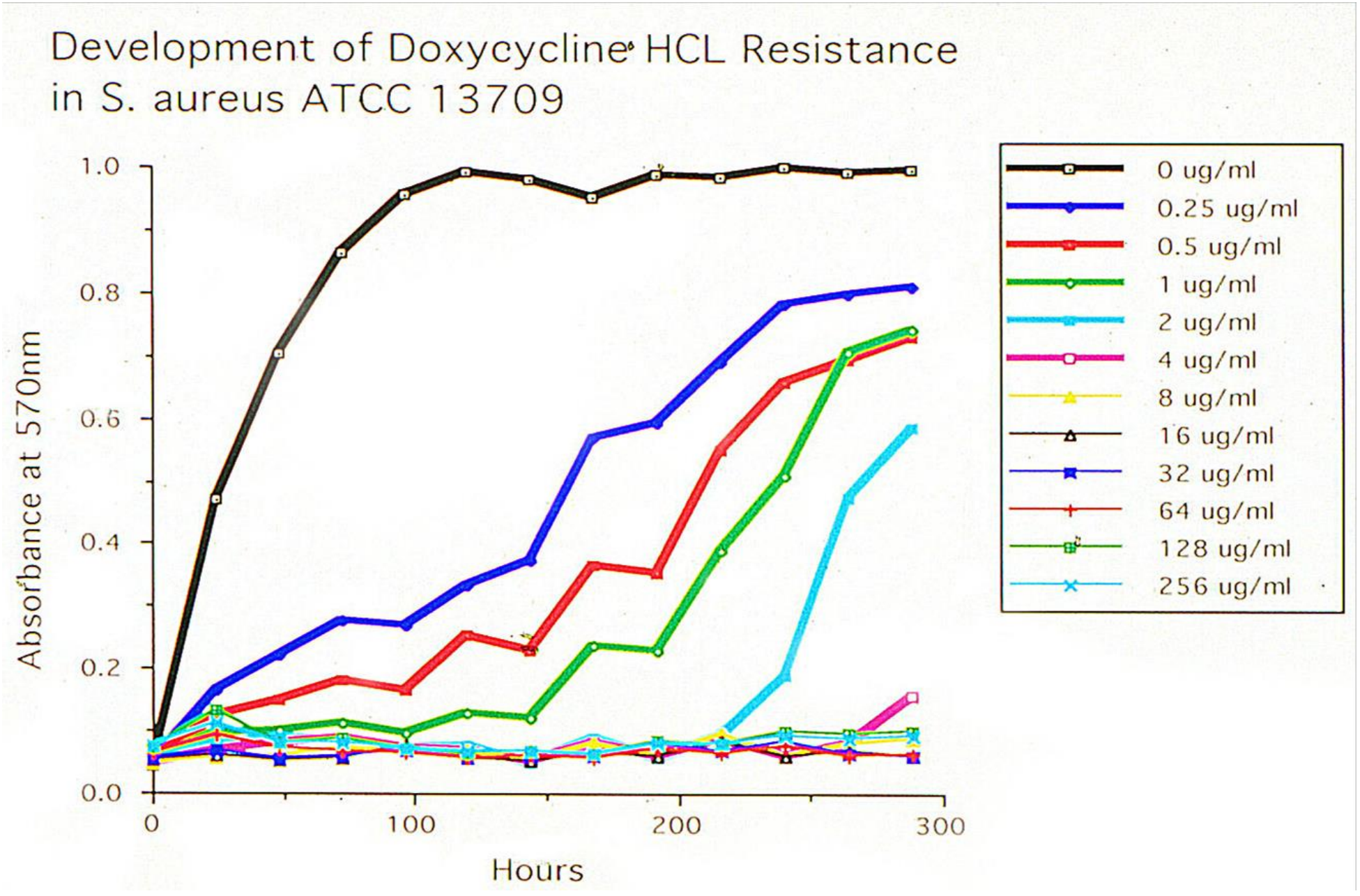


S. Levy (1998) *Sci. Amer.* **278**:46

Human Factors Contributing To The Resistance Problem

*Misdiagnosis
*incorrect empiric therapy
*poor patient compliance
*increasing elderly and immunocompromised population
*decreased use of public health measures
*increased use of high risk behaviors
*widespread use of antibiotics in animal feed stocks
*collecting severely ill patients in hospitals and care centers
*persistent poverty
*increased international travel
*decreased research emphasis
*decreased use of immunization
*decreased emphasis on personal cleanliness

RESISTANCE EMERGENCE AS A FUNCTION OF DOSE



Commentary On Resistance

Resistance طول ماغي بكتيريا مع الحيوي

Antibiotic resistance is a fundamental feature of natural existence and co-evolution

*Its effects can be ameliorated but not avoided

*The introduction of antimicrobials was an ecological disaster for bacteria and resistance is their response

*Fecundity and genetic versatility is their weaponry

*Incorrect antibiotic usage contributes positive selecting pressure that makes the matter worse

*Commensal (“bystander”) bacteria can be efficient sources of antimicrobial resistance genes.

An irony: use of antibiotics creates resistance; resistance creates need for antibiotics. Where will it end? “Use them and loose them!” (not or).

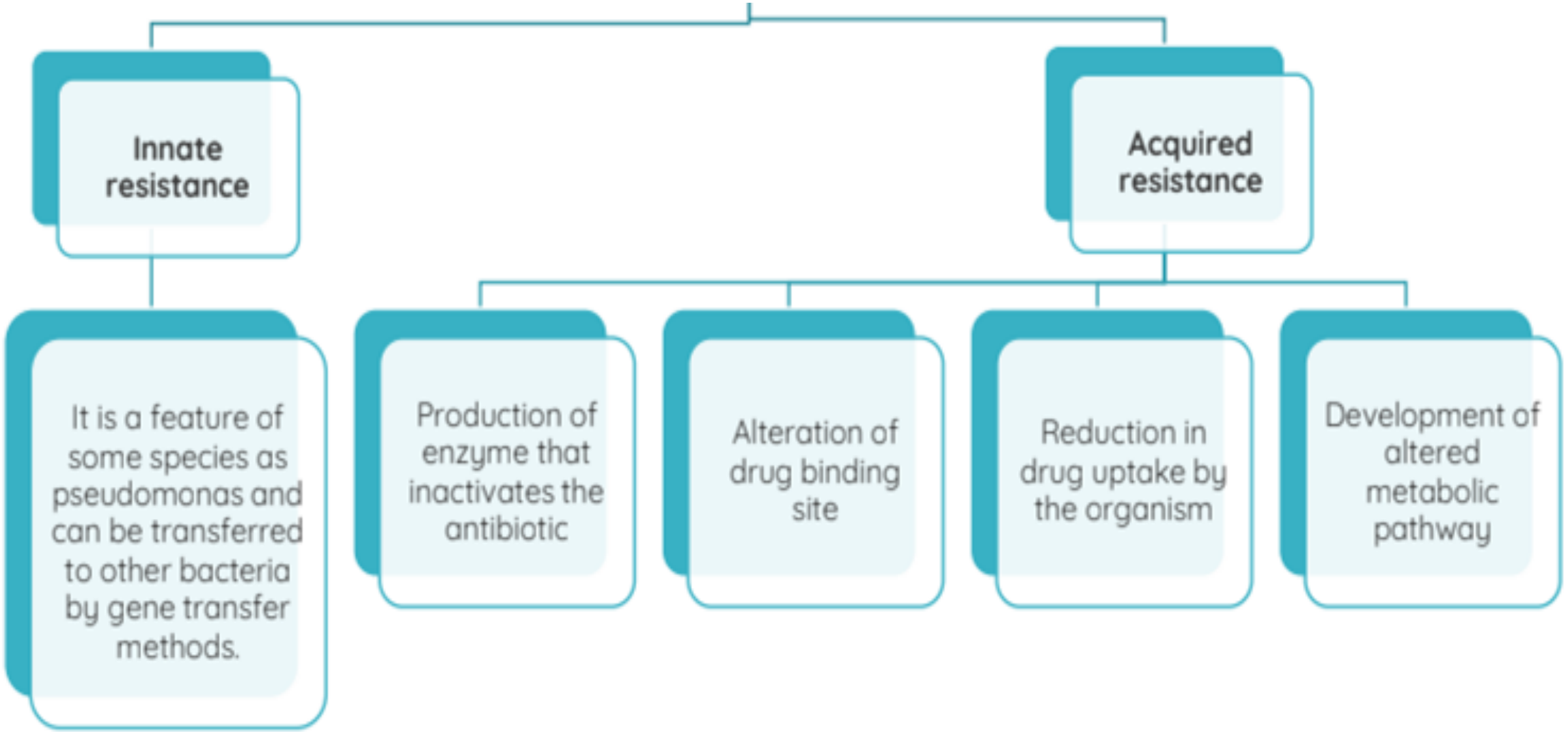
كارثة استخدام مضرة

Resistance Emergence During Therapy. Persistence.

Persistence is often puzzling but is usually attributed to failure of the drug to reach the site of infection in sufficient quantities. Cysts and growth inside cells are often involved.

Development of **resistance during therapy** is most often associated with poor patient compliance, failure to complete the course of therapy, skipping doses, sharing medication, or to the wrong choice of drug.

Resistance


Innate resistance
It is a feature of some species as pseudomonas and can be transferred to other bacteria by gene transfer methods.
Acquired resistance
Production of enzyme that inactivates the antibiotic
Alteration of drug binding site
Reduction in drug uptake by the organism
Development of altered metabolic pathway

Biofilms

Normally bacteria are **planktonic** (floating as single cells or in loose aggregations of cells), under some circumstances they aggregate amongst various cellular materials and adhere as a **skin-like colony.**

Antibiotics often penetrate into biofilms with considerable difficulty and bacteria in them are relatively immune to drug treatment as compared to planktonic bacteria.

Biofilms can create significant difficulties to patients suffering from dental caries and to those who have implanted devices such as catheters and replaced mechanical joints.

Bacteria such as **pseudomonads**, **staphylococcus** and **Escherichia coli** are commonly associated with biofilms.

What about antimicrobial resistance?

Resistance to an antibacterial can develop quickly.Strains of Streptococcus pneumoniae resistant to levofloxacin were documented in the same year levofloxacin was introduced to the market.

Rare, but worrisome, reports of bacteria resistant to every available antimicrobial can be found in the literature.

The good news is that when prescribing patterns change, resistance rates decline.

NNH as low as 1??? Every course of antibiotic is likely to result in some emerging resistance which could affect the next choice of antibiotic regimen for that individual, especially if within 3 months of the previous antibiotic. Of course, the NNH for catastrophic resistance would be much higher.

Final Thoughts:

- There are many more harms than can be covered here! For example: serum sickness like reactions, pulmonary fibrosis with nitrofurantoin, tooth discoloration with Tetracyclines.
- A quote : Harms speak louder when there is little or no benefit to offset them!

Antibiotic Combinations

Combinations of drugs are often employed to enhance the likelihood of treatment success or to decrease the chances of resistance development.

preferable to use single agents in the past.

يفضل بكونها من فترة زمنية

Combinations are defensible when synergy is demonstrable and desirable.

('Static + 'static) and ('cidal + 'cidal) are more often successful combinations.

Drawbacks to combinations are السلبيات

1. The dangers of supra-infections,
2. The increased risk of side effects and
3. The higher costs.

May be used more frequently soon in order to combat resistance.

Synergy, Additivity, Indifference And Antagonism

Synergy is found when a combination of two antimicrobials produces a greater effect than when either agent is used alone in the appropriate concentration.

Additivity is found when a combination of two antimicrobials produces the same effect regardless of the relative concentrations of the two agents.

Indifference is found when the effect is determined virtually entirely by the concentration of the more potent of the two agents.

Antagonism is found when the effect of combining two antimicrobial agents produces a smaller inhibition or kill than when either agent is used alone in the appropriate concentration.

The Fractional Inhibitory Concentration Index is obtained in order to make these judgements. One graphs the results produced from various ratios varying from 1.0 – O and 0 – 1.0 of the two agents.

Bacteriostatic agents frequently are antagonistic when added to bactericidal agents.

Prophylactic Use Of Antibiotics

Prophylactic use of antibiotics is not uncommon, especially by surgeons before bowel surgery or the implantation of devices.

This use is not favored because of fears of resistance emergence.

Success with prophylactic use of antibiotics is most likely when a specific pathogen is likely to be encountered and when a given procedure is highly likely to lead to a nosocomial infection.

Agricultural Use Of Antimicrobials

About half of all antibiotics used in the US are used for agricultural purposes.

Such use facilitates weight gain in economically important large animals and reduces the cost of meat.

Fear of resistance emergence in humans or in improperly prepared foods is leading to enhanced regulation. In Europe such use is often banned.

Post Infection Diseases

- Post infection antigenic mimicry can lead to autoimmune diseases not responsive to antimicrobial chemotherapy. Then the consequences of disease are treated rather than their causes.
- Examples include **peptic ulcers** after *Helicobacter pylori* infections, **cancer** after herpesvirus 8, **Lyme arthritis** after *Borrelia burgdorferii*, and **rheumatic fever** after scarlet fever or streptococcal sore throat.
- A number of investigators believe that atherosclerosis is likely to be a consequence of chronic inflammation brought about by a persistent infection.

Bacterium → Antibody Surveillance → MHC Presentation → Antibody Production → Antibody Production → Cure of Infection and possibly Antibody Mimicry → Inflammatory Disease → Tissue Damage → Disease.

Antibiotic Harms: Harms speak louder when there is little or no benefit to offset them!

Antibiotics are a valuable resource and judicious use is important.
For many serious infections (e.g. pneumonia, bacterial meningitis, sexually transmitted infections) the benefits of antibiotics clearly outweigh potential harms. However, for conditions that are primarily viral (e.g. pharyngitis, acute sinusitis, acute bronchitis), the benefits are minimal and likely outweighed by harms.

In a meta-analysis (10 trials, 2450 patients) comparing antibiotics to placebo for acute rhinosinusitis : The antibiotics used in this meta-analysis included **penicillins**, **macrolides**, and **tetracyclines**.
common adverse events (such as nausea, vomiting, diarrhea, or abdominal pain) occurred in **27% of patients on** antibiotics versus **15%** on placebo (NNH = 8-12). Trials examining other populations have found similar numbers of adverse events.

A recent meta-analysis comparing amoxicillin or amox/clav to placebo found risk of yeast infection (candidiasis) to be about **8x higher** in those on antibiotics (NNH = 23).

Allergic reactions can occur with any antibiotic; penicillin is particularly well studied.
About 5-10% of patients will self-report a penicillin allergy
The vast majority of these reactions are delayed reactions, occurring days to weeks after initiating therapy, and do not typically indicate a true allergy.

Anaphylaxis occurs in about 0.01% of patients taking penicillin; about **10% of these reactions are fatal** (i.e. 0.001% of all patients prescribed penicillin).

Selection of Antimicrobial Agents

1. **The organisms susceptibility to a particular agent**

2. **The site of the infection (the blood–brain barrier):** The penetration and concentration of an antibacterial agent in the CSF are influenced by the following :

1. Lipid solubility 2. Molecular weight 3. Protein binding 4. Susceptibility to transporters or efflux pumps

3. **Patient factors**

- Immune system
- Renal and hepatic dysfunction
- Poor perfusion
- Age
- Pregnancy and lactation
- Patient status & Route of administration: Oral route is chosen for mild infections, and is favorable for outpatients

Lactating , Pregnant

Renal failer → Elimination ✗

Parenteral route is used for more serious infections, or when anti-microbial agent of choice has poor GI absorption

4. **The safety and efficacy of the drug**

5. **The cost of therapy**.

Most patients require empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing).

Actions of Antibiotics : **Bacteriostatic Vs Bactericidal**

أي antibiotic ممكن يكون واحد منهم حسب التركيز اللي واخدة منه

A **bacteriostatic** agent will prevent the growth and/or multiplication of a bacterium without killing it. **Bacteriostatic agents kill bacteria by inhibiting further growth of the bacteria. Success with this form of agent is dependent upon the presence of a functioning immune system.**

Incubation of the inhibited organism in fresh medium lacking antibiotic will result in growth. Inhibition requires less drug than is required for killing bacteria.

A **bactericidal** agent will kill the bacterium. **Bactericidal agents actively destroy existing bacteria. Classifications are not absolute.** Incubation of the killed organism in fresh medium lacking antibiotic will not result in growth.

In the **laboratory** we can almost always employ enough antibiotic that we can observe a bactericidal effect. In some cases the 'cidal versus 'static dose differs substantially: With tetracycline, the difference is approximately **40-fold** for many bacteria; with penicillin the difference is only about **2-4 fold**.

Bacteriostatic يعني استخدام dose المفروض تبقى toxic ممكن تكون Bacteriocidal لأن

يعني هنا: استخدام Bacteriocidal dose لأنه مريض على بطن

In the **clinic**, one can easily achieve a bactericidal dose in patients with penicillin so it is called a bactericidal agent. In the clinic, pharmacokinetic factors prevent us from achieving a bactericidal dose with tetracyclines so for practical purposes it is called a bacteriostatic agent. (In other words **agents may be bacteriostatic in most situations but bactericidal at high concentrations, or bacteriostatic against some organisms and bactericidal against others.**

In this course, when we use these terms, we will use the clinical meaning rather than the microbiological meaning.

Future of Antimicrobial Therapy

Innovation & Stewardship

Optimization Strategies

- Use susceptible organisms only
- Optimize PK/PD parameters
- Monitor patient response closely
- Minimize exposure duration
- Prevent inappropriate use
- Enhance vaccination programs

Emerging Approaches

- Combination therapies
- Novel drug targets
- Personalized medicine
- Rapid diagnostics
- Phage therapy
- Antimicrobial peptides

Minimum inhibitory concentration (MIC) (for bacteriostatic agents):

The lowest concentration of antibiotic that inhibits bacterial growth.

Minimum bactericidal concentration (MBC) (for bactericidal agents):

Determines the minimum concentration of antibiotic that kills the bacteria under investigation.

Spectrum of antibiotic

Narrow spectrum: a chemotherapeutic agents acting only on a limited group of microorganisms.

Broad spectrum: a chemotherapeutic agents acting on a wide variety of microbial species.

OPTIMIZING OUTCOMES & PREVENTING RESISTANCE

Optimizing outcomes of infection

1. Use a drug to which the organism is susceptible
2. Optimize drug for infection (right drug, dose, route and duration) to maximize effect → cure infection or prevent infection
3. Monitor patient response to infection frequently
4. Optimize PK/PD to reduce risk of toxicity and increase efficacy
5. Minimize antibiotic exposure (ie. duration of therapy) to reduce resistance and adverse effects eg. C. difficile-associated diarrhea

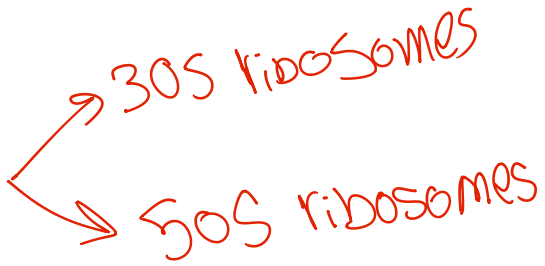
Reducing Risk of Antimicrobial Resistance

1. Avoid inappropriate use of antibiotics
2. Avoid sub-therapeutic doses
3. Avoid prolonged duration of therapy
4. Optimize dosing based on PK & PD properties (appropriate dose for patient)
5. Vaccinate
6. Use the most appropriate empiric drug for the pathogen suspected based on local antibiogram; streamline/de-escalate when possible

Empiric treatment

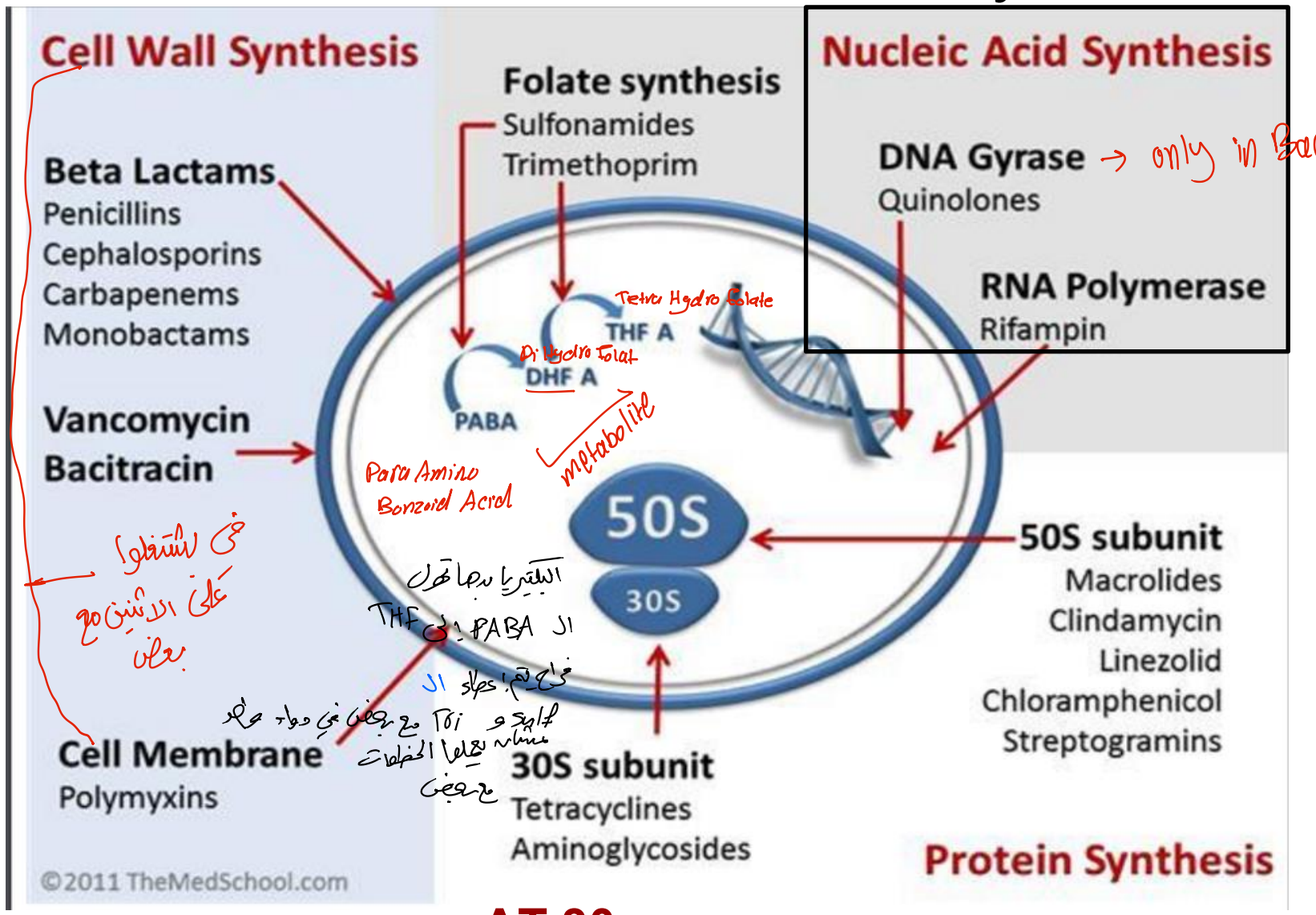
Antibiotic Therapy: Mechanism of Action

- **Interference with cell wall synthesis**
- **Interference with protein synthesis**
- **Interference with DNA replication**
- **Acting as a metabolite to disrupt critical metabolic reactions inside the bacterial cell**



- Penicillins
- Cephalosporins
- Macrolides
- Quinolones
- Aminoglycosides
- Tetracyclines
- Sulfonamides

Basic Sites of Antibiotic Activity



AT 30

DNA synthesis inhibitors :
FMN
F: FQ
M: Metronidazole
N: Nitrofurantoin

Cell wall synthesis
DNA replication
RNA replication
Antimetabolites : Folate synthesis
Protein synthesis (30S ribosomes)
Protein synthesis (50S ribosomes

WHAT IS NEXT ?

CELL WALL SYNTHESIS INHIBITORS





Thank you




"Tell me and I forget; teach me and I may remember; but involve me and I learn."
Benjamin Franklin
UMKC
School of Pharmacy

General Pharmacology

GENERAL PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY

2025

Esmaa Motawe

interdisciplinary PhD in Pharmacology &Toxicology/ Pharmaceutical Sciences

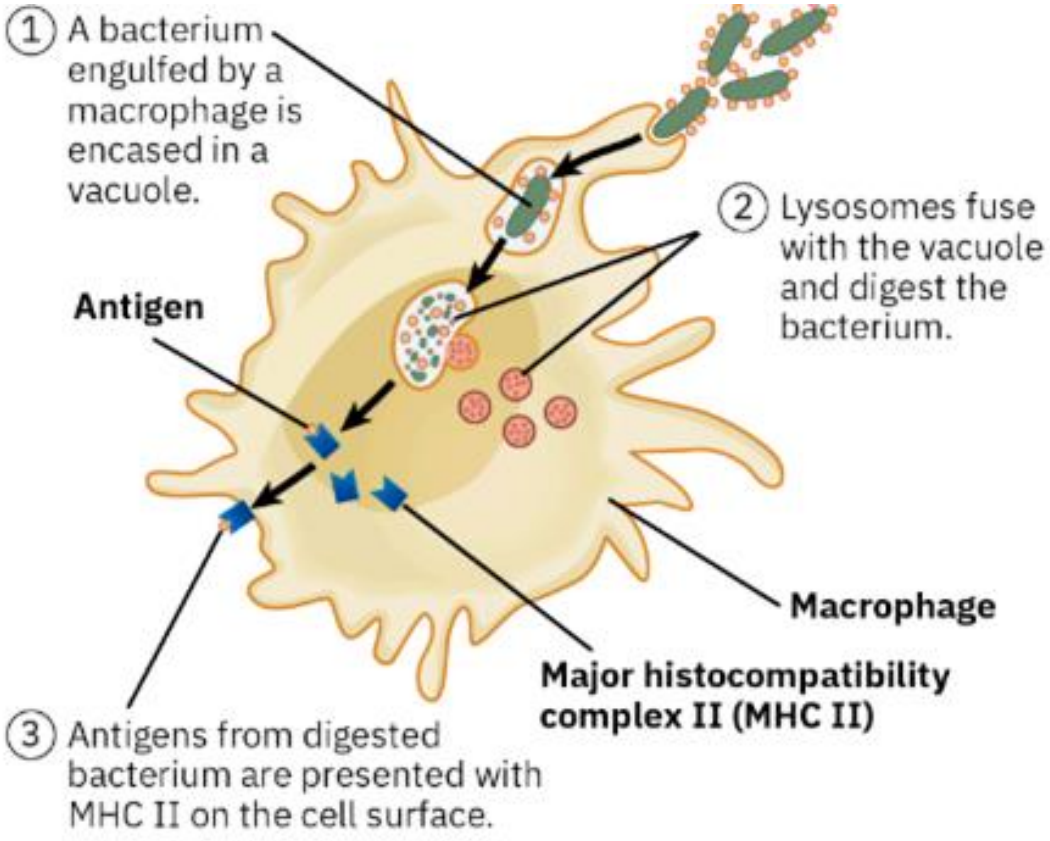
يتولد الإنسان فيها

Bacteriostatic drugs الـimmunity هي الدفاع الـمساعد لـ

- **Innate immunity** is the body's first line of defense against many types of organisms. It includes physical barriers
- The immune system is a complex network of cells, tissues, and organs that work together to protect the body from harmful substances, such as pathogens, such as the skin, the acidic pH of the stomach, phagocytic cells (e.g., macrophages), and the inflammatory cascade
- This type of immunity does not require prior exposure to an organism to provide protection and is not specific to any type of microorganism. Innate forms of immunity work quickly, within minutes to hours.
- **Adaptive immunity**, also known as acquired immunity, is highly specific to individual microorganisms. Adaptive immunity works through various immune cells with the ability to recognize specific targets (antigens) as belonging to the self or as foreign. When the body detects foreign antigens, the adaptive immune system can mount a response against the pathogen to eliminate it

تتكون بعد التعرض للـPathogen

- . Adaptive immunity is initially slow upon the first exposure to an antigen, but it has a "memory" that allows it to mount fast responses upon repeated exposure to that same pathogen. This immune memory is durable and able to last the individual's whole life in some cases. This same process is how some vaccines work to induce immunity to organisms.



CELL WALL SYNTHESIS INHIBITORS

Penicillins

- *Amoxicillin** AMOXIL
- *Ampicillin*** GENERIC ONLY
- *Dicloxacillin** GENERIC ONLY
- *Nafcillin* GENERIC ONLY
- *Oxacillin* GENERIC ONLY
- *Penicillin G* PFIZERPEN
- *Penicillin G benzathine* BICILLIN L-A
- *Penicillin G benzathine and penicillin G procaine* BICILLIN C-R
- *Penicillin V** GENERIC ONLY

CARBAPENEMS

- *Doripenem* DORIBAX
- *Ertapenem* INVANZ
- *Imipenem/cilastatin* PRIMAXIN
- *Meropenem* MERREM

MONOBACTAMS

- *Aztreonam* AZACTAM

cephalosporins

- *Cefaclor** GENERIC ONLY
- *Cefadroxil** GENERIC ONLY
- *Cefazolin* ANCEF, KEFZOL
- *Cefdinir** OMNICEF
- *Cefepime* MAXIPIME
- *Cefixime** SUPRAX
- *Cefotetan* CEFOTAN
- *Cefoxitin* MEFOXIN
- *Cefprozil** CEFZIL
- *Ceftaroline* TEFLARO
- *Ceftazidime* FORTAZ
- *Ceftriaxone* GENERIC ONLY
- *Cefuroxime*** CEFTIN, ZINACEF
- *Cephalexin** KEFLEX

β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS

- *Avibactam + ceftazidime* AVYCAZ
- *Clavulanic acid + amoxicillin* AUGMENTIN
- *Sulbactam + ampicillin* UNASYN
- *Tazobactam + ceftolozane* ZERBAXA
- *Tazobactam + piperacillin* ZOSYN
- *Vaborbactam + meropenem* VABOMERE

LIPOGLYCOPEPTIDES

- *Dalbavancin* DALVANCE
- *Oritavancin* ORBACTIV
- *Telavancin* VIBATIV

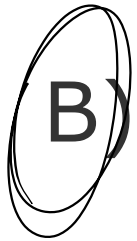
OTHER ANTIBIOTICS

- *Colistin* COLY-MYCIN M
- *Daptomycin* CUBICIN
- *Fosfomycin* MONUROL
- *Polymyxin B* GENERIC ONLY
- *Vancomycin* VANCOCIN

Quick Question

What makes bacterial cell walls unique targets for antibiotics?

A) Human cells also have cell walls



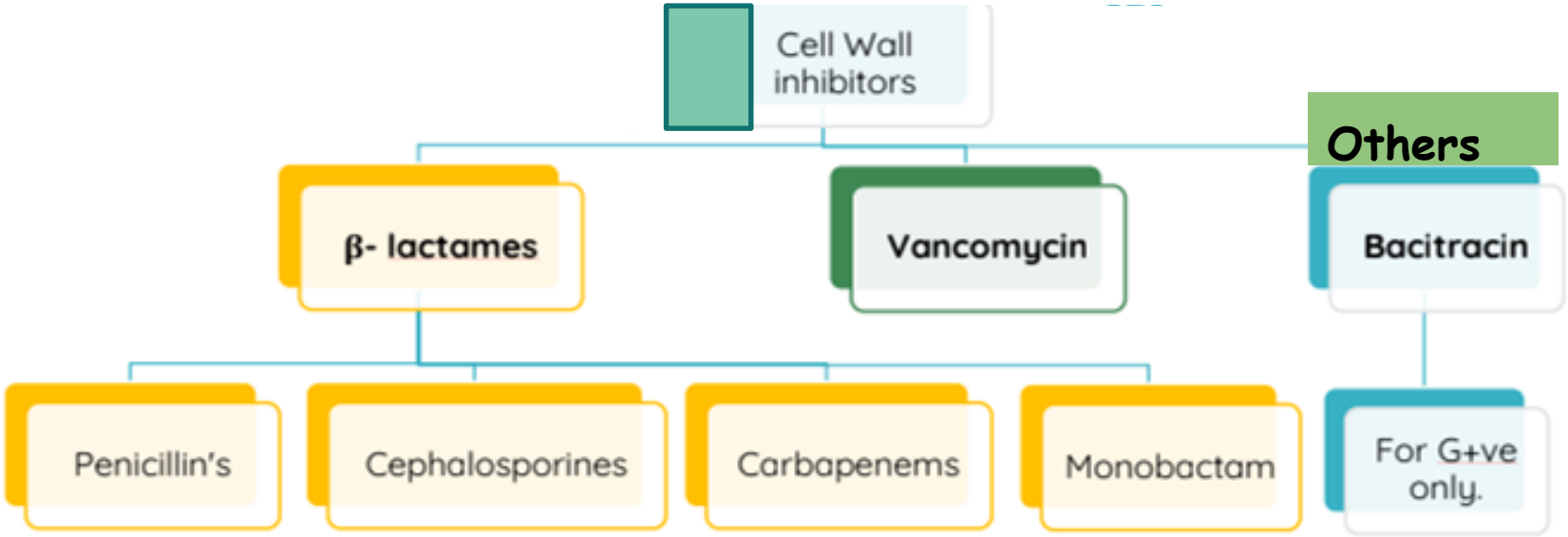
B) Bacterial cell walls contain peptidoglycan, which humans don't have

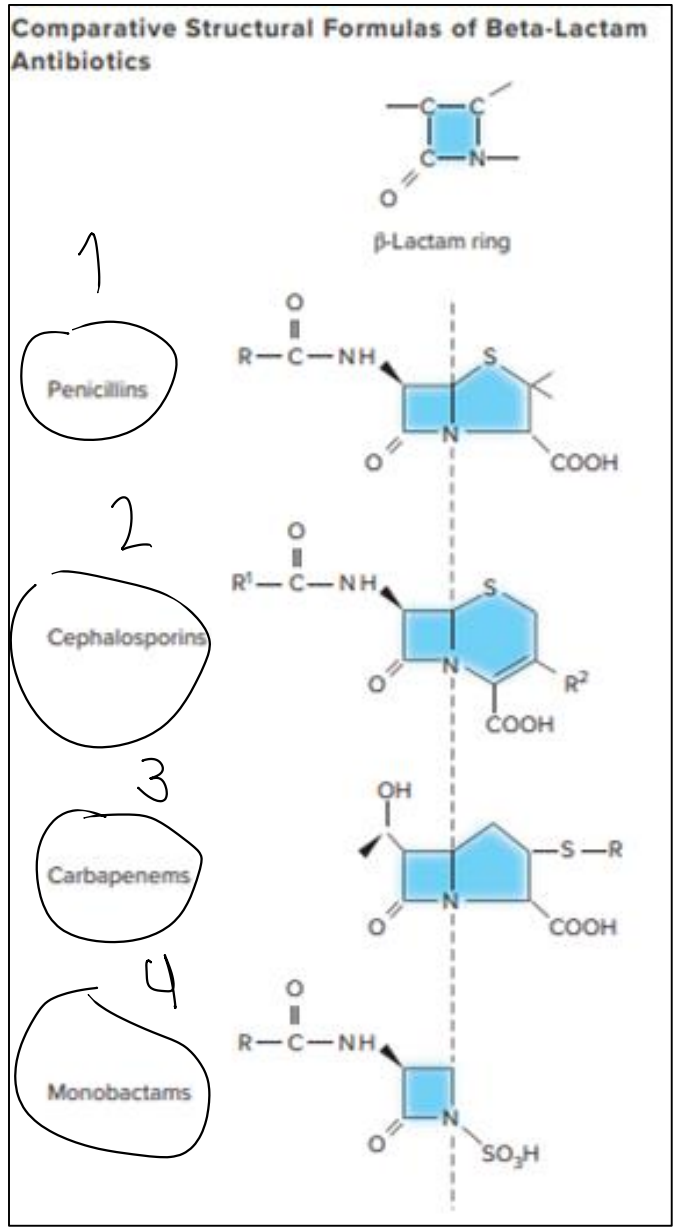
C) Cell walls are always the strongest part of bacteria

Correct Answer: B
Bacterial cell walls contain peptidoglycan, a unique structure not found in human cells, making it an excellent selective target for antimicrobial therapy!

Inhibitors Of Cell Wall Synthesis

- **B-LACTAMS (PENICILLINS- CEPHALOSPORINS- CARBAPENEMS-MONOBACTAMS)**
- **VANCOMYCIN**
- **OTHERS(Bacitracin- Telavancin-Fosfomycin- Polymyxin Colistin)**





Three Stages of Cell Wall Synthesis

Stage 1
Inside Cell

Precursor formation

Inhibitor: Cycloserine

Stage 2
Cell Membrane

Transport & Peptidoglycan formation

Inhibitors: Bacitracin, Vancomycin

Stage 3
Outside Cell

Cross-linking peptidoglycan chains

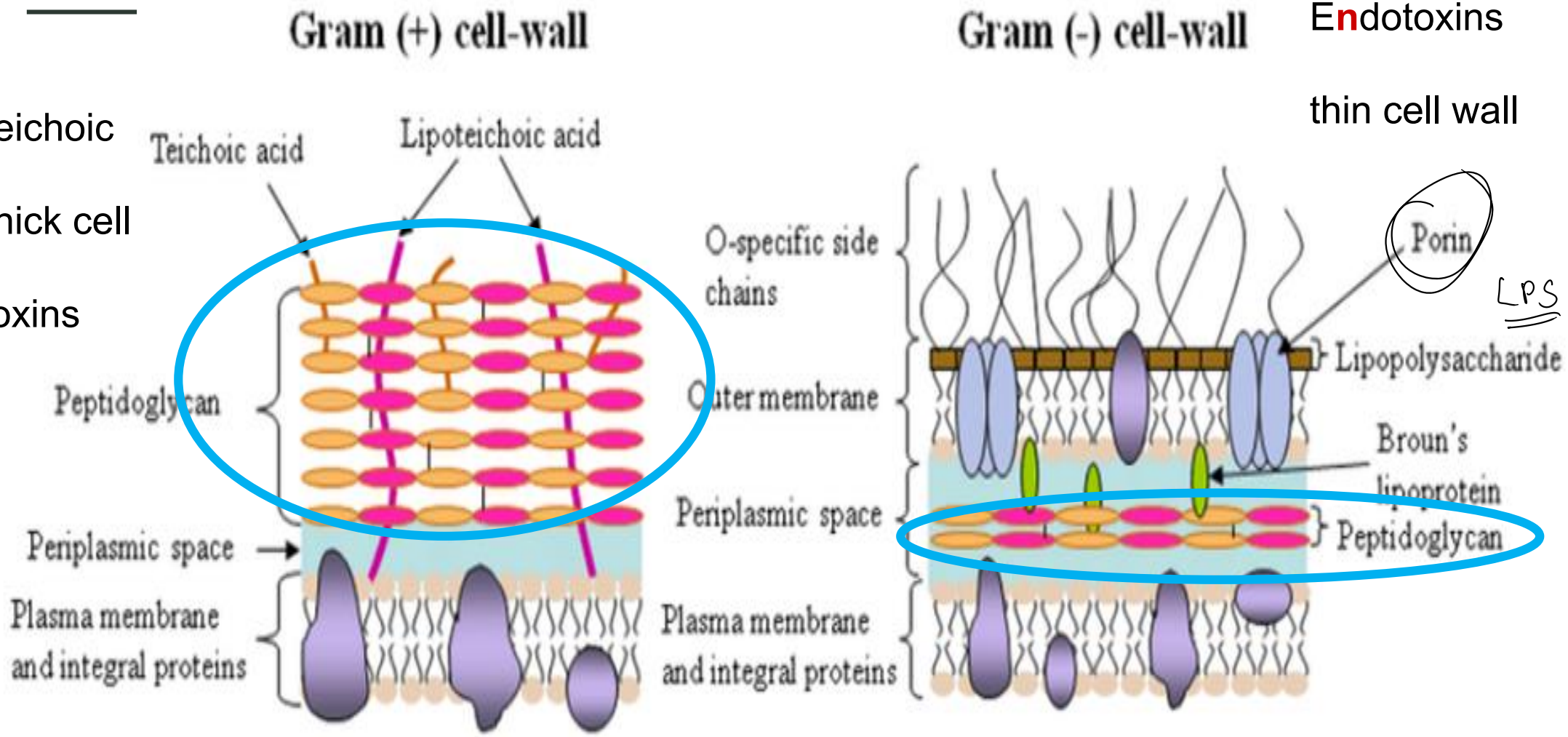
Inhibitors: Penicillins, Cephalosporins

Tei

T= Teichoic acid
T= Thick cell wall
Exotoxins

Negative
Endotoxins

thin cell wall



Outer membrane : consists of lipopolysaccharides (LPS) including lipid A (endotoxin)

Bacterial Morphology and Some Common Bacterial Arrangements

Bacterial form	Bacterial arrangement	Classification
Cocci		
Pairs		Diplococci
Chains		Streptococci
Clusters		Staphylococci
Bacilli		
Straight		Bacilli
Short curved		Vibrio
Spirillum		
Twisted		Spirilla
Twisted		Borrelia
Twisted		Treponema

lyme disease

syphalis

BACTERIA OVERVIEW

GRAM POSITIVE	GRAM NEGATIVE
Staphyloccocus aureus (*S. aureus*)	*Proteus spp*, *E. coli*, *Klebsiella spp* (PEcK)
Coagulase negative staphylococcus	*H. influenzae*, *Moraxella catarrhalis*, *Neiserria gonorrhoeae*, *N. meningitidis*
Streptococci (*S. pneumoniae*, *S. viridans*, Group A = *S. pyogenes*, Group B streptococci)	*Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter*, *Enterobacter* (SPACE)
Enterococcus (*faecalis* & *faecium*), *Listeria monocytogenes*	Providencia spp, Indole-positive Proteus spp (SPICE)

ATYPICAL	ANAEROBES
Legionella	Oral anaerobes: *Peptostreptococcus*, *Fusobacterium*, *Prevotella*
Mycoplasma	Gut anaerobes: *Bacteroides fragilis*, *Clostridium* species
Chlamydia	

ATYPICAL BACTERIUM

Rickettsia
- Obligate intracellular bacterium
- Transmitted by bites from ticks, mites, lice, etc.

Chlamydia
- Obligate intracellular bacterium
- NO ATP metabolism
- Tetracycline-type or macrolide-type antibiotics

Mycoplasma
- NO cell walls
- Tetracycline-type or macrolide-type antibiotics

Licensed to

Staphylococcus aureus. An Example of the Impact of Resistance on Infectious Diseases

Staphylococcus aureus is the bacterium most commonly isolated worldwide from infections of the **bloodstream**, **lower respiratory tract**, and **skin** and **soft tissues**.

The natural habitat of this bacterium is the skin and soft tissues and body surfaces. It causes a wide variety of diseases ranging from fairly trivial skin lesions to life-threatening septicemias. It is associated with a variety of wounds that spread to systemic problems. It is commonly found in humans with about 30% of healthy individuals being colonized in the anterior nares from whence it can serve to feed infections.

The organism is **one of the most successful in developing resistance mechanisms** towards antibiotic chemotherapy.

In the United Kingdom it causes 20,000 cases annually of which HALF are resistant and about 4% result in death.

In hospitals, methicillin-resistant *S. aureus (MRSA)* infections have been increasing by 10-15% annually in the US and Western Europe.

Recently resistance to vancomycin, the drug of last resort, has been reported suggesting that we will soon be defenseless against this organism in too many cases.

MRSA (methicillin-resistant *Staphylococcus aureus*)

Staph aureus was originally susceptible to all penicillins. However, today Staph aureus is reliably resistant to penicillin, amoxicillin, and ampicillin through beta-lactamase production. In response, beta-lactamase-resistant antibiotics were invented, like methicillin, cloxacillin, and oxacillin. Further, beta-lactamase inhibitors like clavulanic acid were invented.
Cloxacillin and amox-clav are able to kill methicillin-sensitive Staph aureus (MSSA). Unfortunately, Staph aureus resistant to methicillin (i.e., MRSA) soon emerged via a different mechanism (First identified in hospitals in 1980, it is increasing rapidly in incidence).
, specifically expression of an alternate penicillin binding protein that has lower affinity for beta-lactams. Therefore, MRSA is resistant to most beta-lactams.
Community-Associated MRSA (CA-MRSA) is defined as MRSA in patients who have not been hospitalized in the previous 12 months. often treatable by oral antibiotics (notably TMP/SMA, TCs, Clin, Line, Van) CA-MRSA is less likely to be multi-drug resistant.

When hospital acquired it is hard to treat (usually by extended spectrum β-lactams).
Increasingly ca-MRSA is equilibrating with ha-MRSA.
The infections are usually skin and soft tissue (SSTI) targeted.
Hand washing is an effective means of prevention.

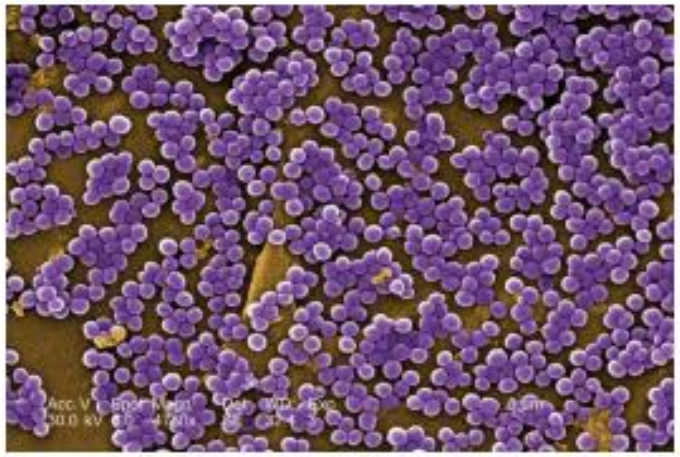


A ruptured MRSA abscess
Draining abscesses is important.

Threat of MRSA becoming resistant to all antibiotics currently available

- No longer seen just in hospitals; it has spread to the community setting, and approximately 50% of staphylococcal infections contracted in the community involve MRSA

كان مش بس بيشوفوها في المستشفى وصاروا بيشوفوها برا كمان في البيئة يعني زاد انتشارها



A Scanning Electron Micrograph of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteria

This organism was also resistant to vancomycin.

Source: Janice Carr/CDC

VRE: usually seen in urinary tract infections (UTIs)

Newer antibiotics have been developed to successfully treat VRE and MRSA.

VRE و MRSA لي بطوروها عشان تعالج اد

Multidrug-Resistant Organisms

ESBL

- Organisms that produce ESBL are resistant to all beta-lactam antibiotics and aztreonam.
- Can be treated only with carbapenems or sometimes quinolones
- Use of carbapenems: resistance occurred; production of carbapenemase, which renders all carbapenems ineffective
- Tigecycline and colistimethate → يتم علاجها عن طريق

Multidrug-Resistant Organisms

Organisms that are resistant to one or more classes of antimicrobial drugs

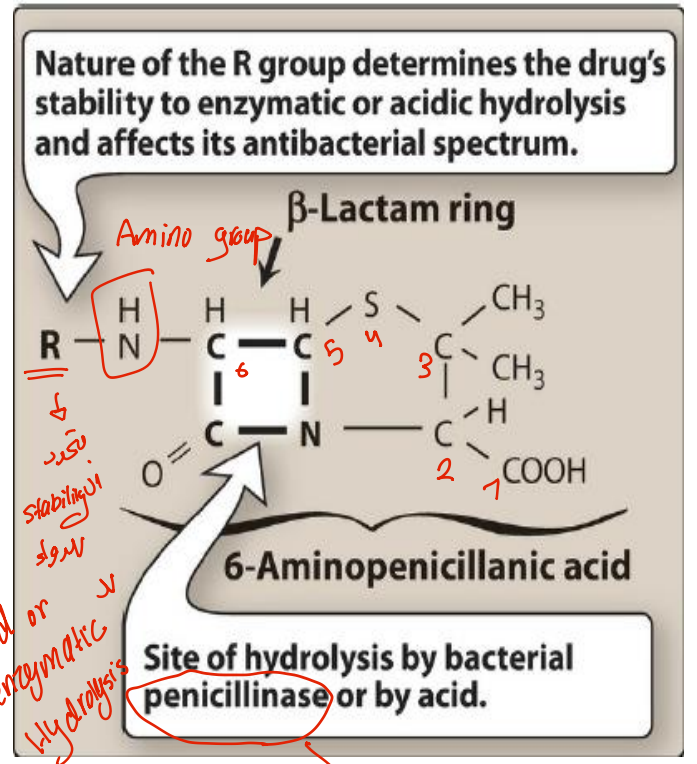
- Methicillin-resistant *Staphylococcus aureus* **(MRSA)**
- Vancomycin-resistant *Enterococcus* **(VRE)**
- Organisms producing extended-spectrum beta-lactamases **(ESBLs)**
- Carbapenem-resistant Enterobacteriaceae **(CRE)**

Beta-Lactam Antibiotics : Penicillins

B- lactam Ring

:

- Inhibits transpeptidase
- Active against rapidly growing organisms synthesis a peptidoglycan cell wall
- Bactericidal/ time dependent effect.
- Substrate for b-lactamases → degredation
- An unstable structure: Acid labile- Immunogenic breakdown products



R side chain affects:

- Antimicrobial spectrum
- Stability to stomach acid
- Cross-hypersensitivity
- Susceptibility to bacterial degradative enzymes (β-lactamases).
- Allergy to Pencillins

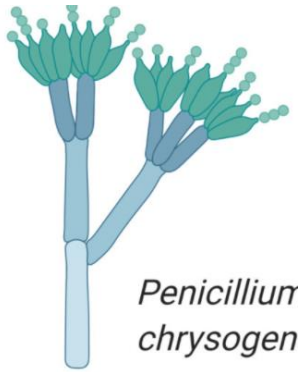
Drug (*Trade Name*)	Route	Remarks
First generation		**Main indication: Gram-positive infections**
Penicillin G (*Pfizerpen*)	IM, IV	Produces high plasma levels, short duration of action
Penicillin G benzathine (*Bicillin*)	IM	Penicillin G is slowly released from injection site over 28 days, provides low plasma levels
Penicillin G procaine (*Wycillin*)	IM	Penicillin G is slowly released from injection site over 12–24 hrs
Penicillin V (*V-Cillin, Pen-Vee K*)	PO	Resists acid destruction in stomach; used to treat minor throat and ear infections
Penicillinase resistant		**Main indication: Resistant staphylococcal infections**
Cloxacillin (*Tegopen*)	PO	Resistance to the destructive actions of penicillinase; used to treat resistant staphylococcal infections
Dicloxacillin (*Dynapen*)	PO	
Nafcillin (*Unipen*)	IM, IV	
Oxacillin (*Prostaphlin*)	PO, IM, IV	
Second generation		**Main indication: Gram-positive/common gram-negative**
Amoxicillin (*Amoxil*)	PO	**Infections** (e.g., *Escherichia coli, Haemophilus influenzae*)
Amoxicillin/clavulanic acid (*Augmentin*)	PO	Broader spectrum than first generation; amoxicillin
Ampicillin (*Omnipen*)	PO, IM, IV	provides higher plasma levels; *Augmentin* and *Unasyn*
Ampicillin/sulbactam (*Unasyn*)	IM, IV	indicated when penicillinase-producing bacteria present
Third generation		**Main indication: Serious gram-negative infections**
		(e.g., *Proteus vulgaris, Pseudomonas aeruginosa*)
Carbenicillin indanyl (*Geocillin*)	PO	Only for the treatment of urinary tract infections
Ticarcillin disodium (*Ticar*)	IM, IV	Broad spectrum, generally reserved for pseudomonal
Ticarcillin/clavulanic acid (*Timentin*)	IM, IV	and other serious gram-negative infections; *Timentin* for resistant infections
Fourth generation		**Main indication: Serious gram-negative infections**
Mezlocillin sodium (*Mezlin*)	IM, IV	(e.g., *Klebsella pneumoniae, P. aeruginosa*)
Piperacillin (*Pipracil*)	IM, IV	Increased effectiveness compared to third-generation
Piperacillin/tazobactam (*Zosyn*)	IV	drugs; also effective against gram-positive and anaerobic infections; *Zosyn* indicated for resistant infections

Extend mechanism

Penicillins

- Natural penicillins
- Penicillinase-resistant penicillins
- Aminopenicillins
- Extended-spectrum penicillins

Penicillin G and *penicillin V* are obtained from fermentations of the fungus Penicillium chrysogenum



Penicillium chrysogenum



- **Natural penicillins**
  - Penicillin G (The prototype)
  - Penicillin V (Acid resistant)

  Good for Gram-positive
- **Penicillinase-resistant drugs:**
  - Nafcillin
  - Cloxacillin
  - Oxacillin
  - Dicloxacillin

  Anti-staphylococcal
- **Aminopenicillins (Broad Spectrum)**
  - Amoxicillin
  - Ampicillin

  Cover more organisms
- **Extended-spectrum drugs(Antipseudomonal)**
  - Carbenicillin
  - Piperacillin
  - Ticarcillin
  - Piperacillin/tazobactam

  Antipseudomonas

Penicillin G IM , IV (oral X)

- Most streptococci are very sensitive to *penicillin G*, but *penicillin*-resistant streptococci viridans and Streptococcus pneumoniae isolates are emerging.
- Penicillin G is more active against Neisseria sp. and anaerobes

- Majority of Staphylococcus aureus (greater than 90%) are now penicillinase producing and therefore **resistant to *penicillin G***.

- *T*he drug of choice for the treatment of gas gangrene (Clostridium perfringens) and syphilis (Treponema pallidum

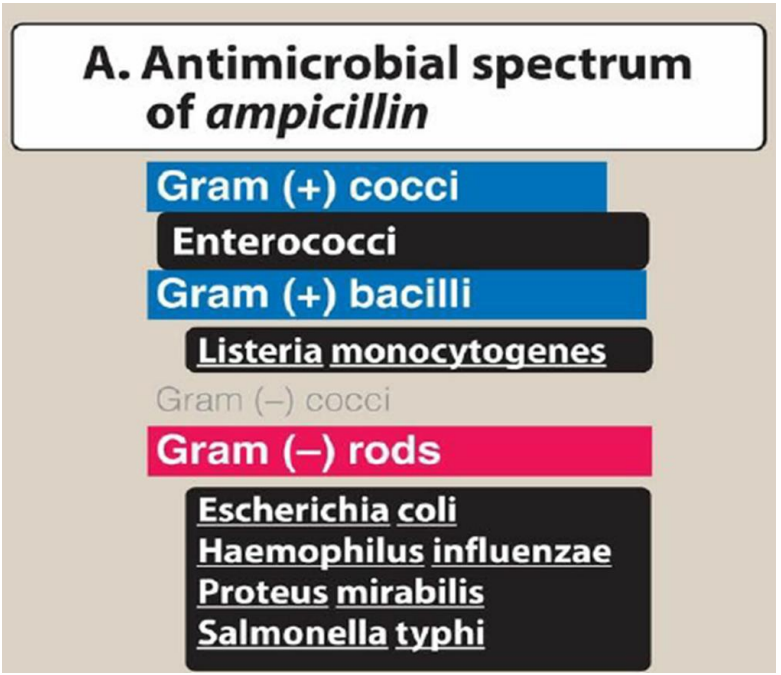
Penicillin V

- Only available in oral formulation: *Penicillin V* is more acid stable than is *penicillin G* and is the oral agent employed in the treatment of less severe infections

- Spectrum similar to that of *penicillin G*
- It is not used for treatment of severe infections because of its limited oral absorption.

Semisynthetic penicillins: Extended-spectrum penicillins: Aminopenicillins – ampicillin and amoxicillin

- Broad spectrum
- Do not work against beta-lactamase producers (i.e. Pseudomonas, Proteus, Klebsiella, etc)
- Extends the gram-negative antimicrobial activity of aminopenicillins to include Haemophilus influenzae, Escherichia coli, and Proteus mirabilis
- *Ampicillin* (with or without the addition of *gentamicin*) is the drug of choice for the gram-positive bacillus Listeria monocytogenes and susceptible enterococcal species.
- Widely used in the treatment of respiratory infections
- Both are acid resistant but more amoxicillin is absorbed by the intestinal tract than ampicillin after an oral dosage
- Food interferes with absorption of ampicillin but not amoxicillin



Excretion

- Renal excretion (inhibited by probenecid)
- In breast milk

Therapeutic uses

Upper respiratory tract infections - Otitis media

Uncomplicated urinary tract infections

Acute bacterial meningitis in children

Typhoid fever

Prophylactically by dentists in patients of high risk to bacterial endocarditis

These drugs are coformulated with β-lactamase inhibitors, such as *clavulanic acid* or *sulbactam*, to combat infections caused by β-lactamase–producing organisms.

β-lactamase Inhibitors: The Superhero Partners



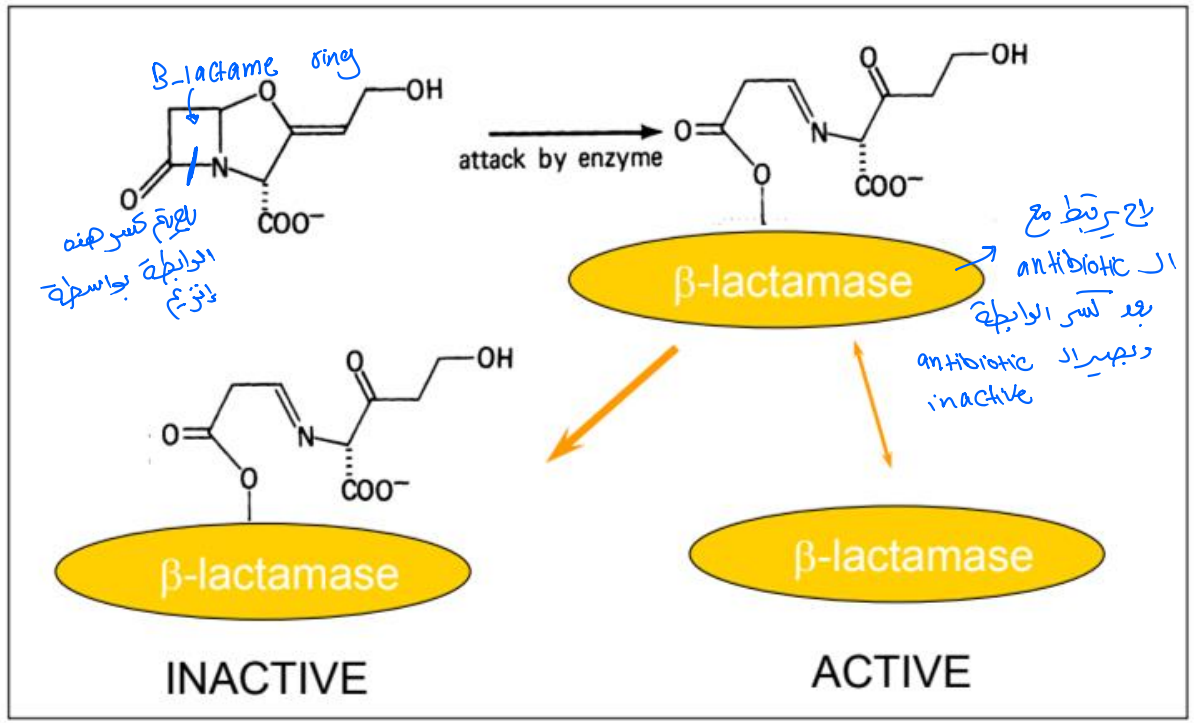
How They Work:

β-lactamase inhibitors bind to and inactivate β-lactamase enzymes, protecting the antibiotic from destruction

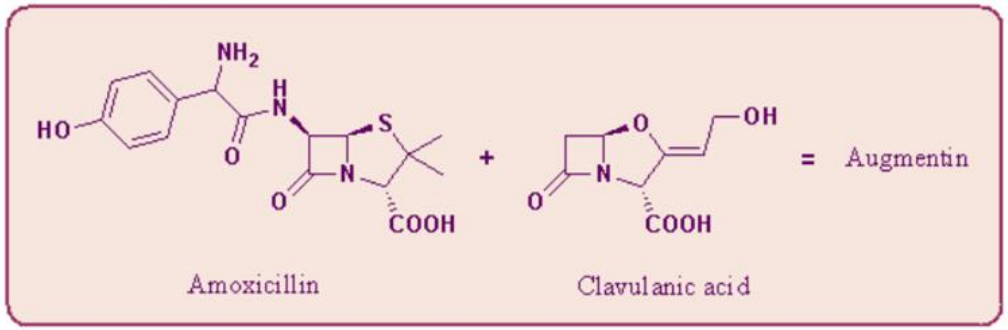
- Clavulanic acid (clavulanate)
- Tazobactam
- Sulbactam
- Avibactam

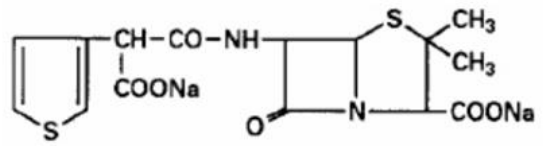
Examples of Combination Agents

- Ampicillin/sulbactam (Unasyn)
- Amoxicillin/clavulanic acid (Augmentin)
- Ticarcillin/clavulanic acid (Timentin)
- Piperacillin/tazobactam (Zosyn)
- Ceftazidime/avibactam (Avycaz)



Augmentin® or Augmentin BID®



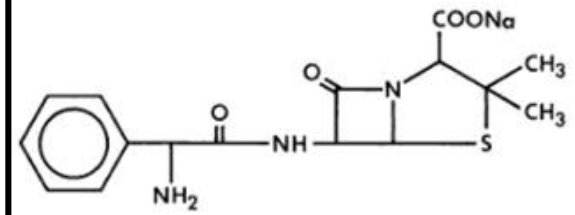


Ticarcillin

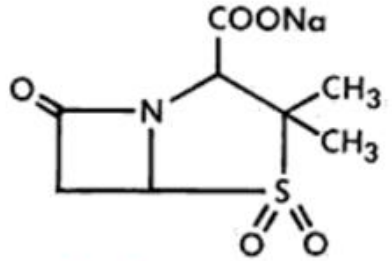
- Timentin® injection: Ticarcillin + Clavulanic Acid

Unasyn® (injection)

- Ampicillin Sodium + Sulbactam Sodium



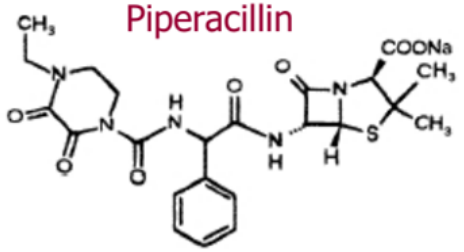
Ampicillin



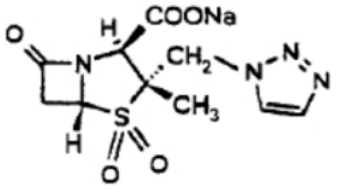
Sulbactam

Tazocin®
Piperacillin + Tazobactam

Piperacillin



Tazobactam

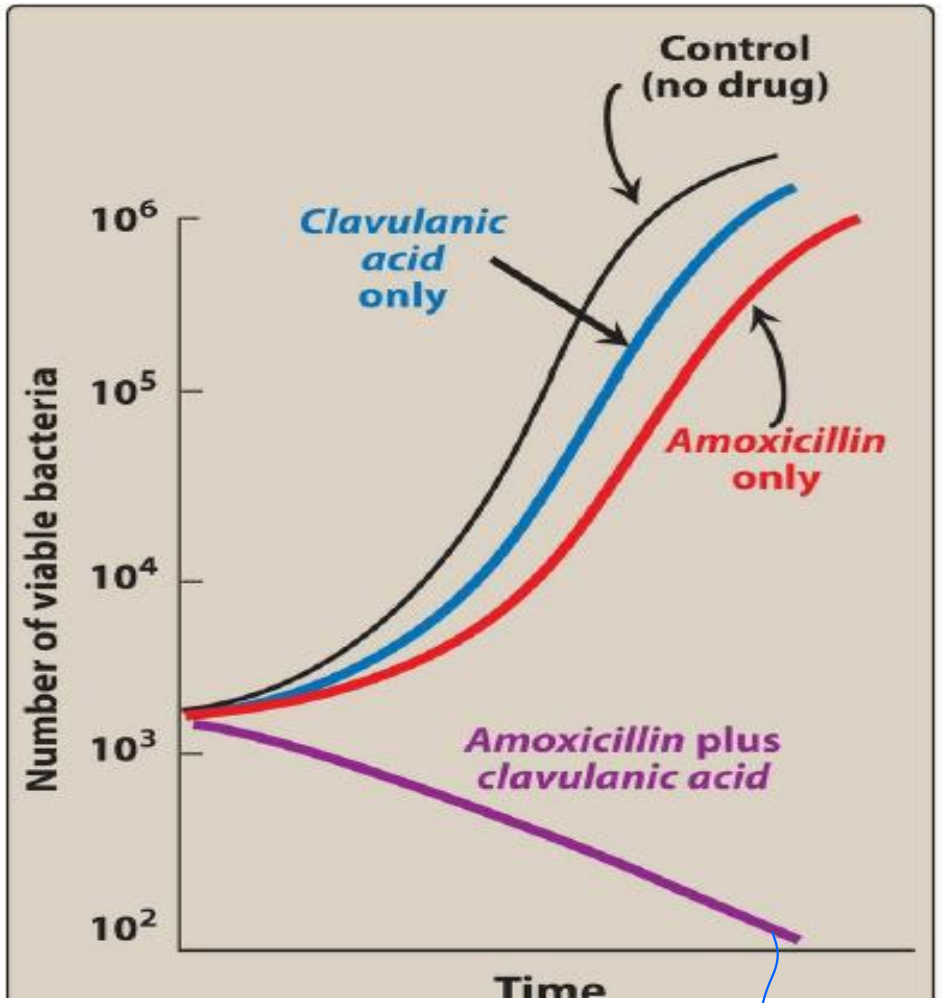


- Piperacillin: Antipseudomonal penicillin
- Tazobactam: inhibits the action of bacterial β-lactamases

الحركي بيشبه تركيب ال Penicillin
والمتبسط منه ع بالتالي أسهل على B-lactamase
SATC وانه يرتبط مع ال Penicillin بالتالي تروح ال free وبتعمل شغلها بجهل

- Amoxicillin + Clavanulic acid
- Decreased resistance Staphylococcus aureus (MSSA)

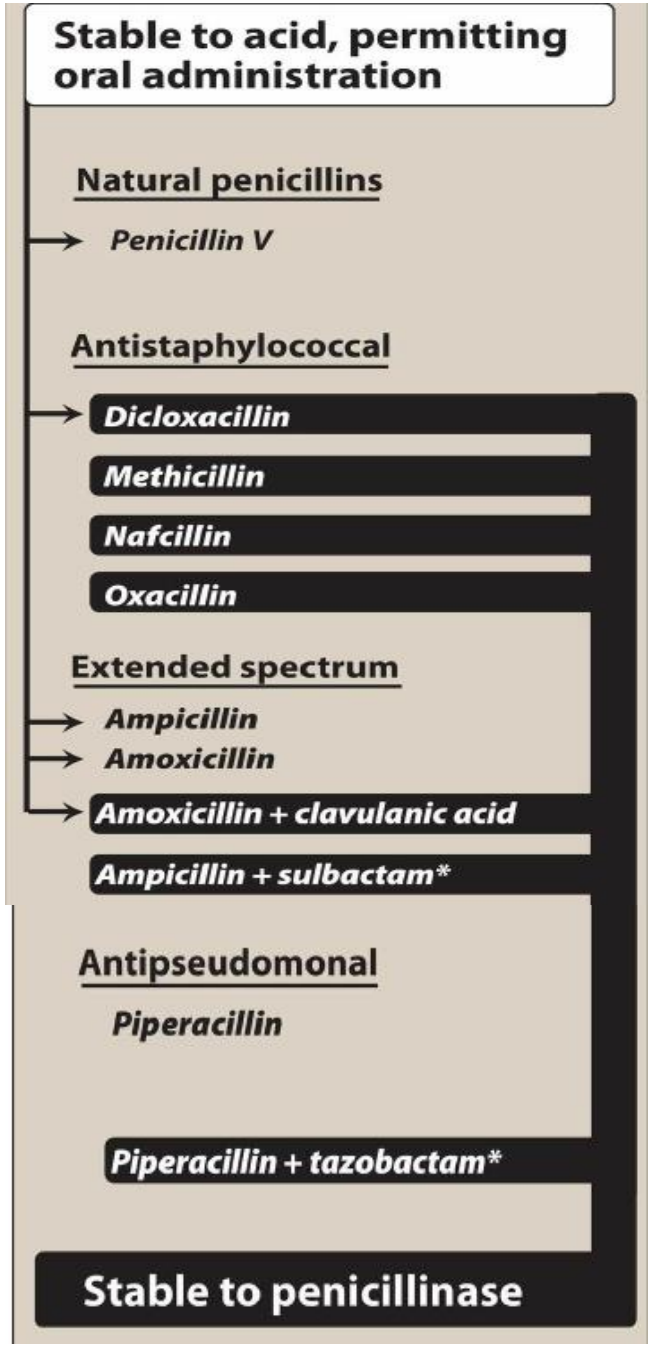
MRSA is resistant to most available beta lactams



1+1=3 لما أعطيتهم مع بعض تم القضاء على البكتيريا بصورة أكبر

Antistaphylococcal penicillins

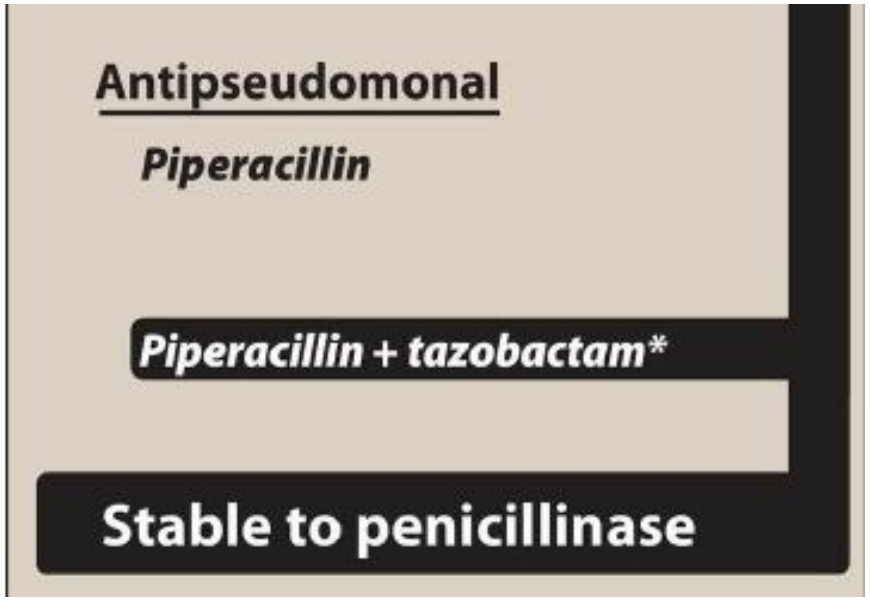
- *Methicillin* , *nafcillin* , *oxacillin* , and *dicloxacillin*
- β-lactamase (penicillinase)-resistant penicillins
- **penicillinase-producing staphylococci, including MSSA**
- *methicillin* is not used clinically>>>> interstitial nephritis
- No activity against gram-negative infections



Antipseudomonal penicillin

Piperacillin

↳ +ve + -ve
↳ widly spectrum
↳ more potent
↳ يؤثر على



- Activity against **Pseudomonas aeruginosa**

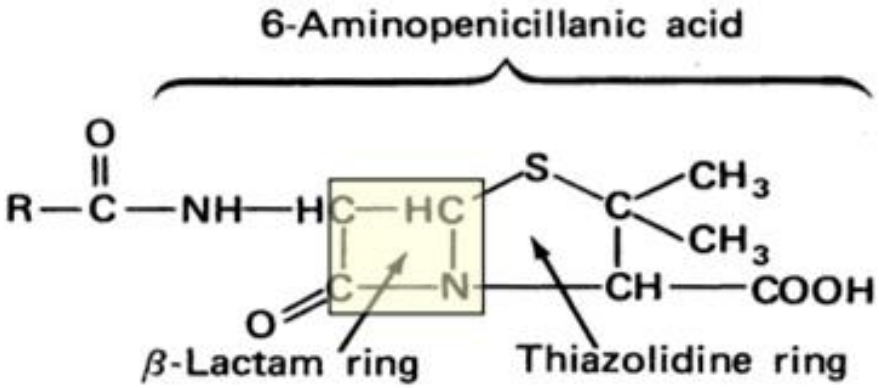
↳ لما أجمع مع بعض راح تزيد ال spectrum بنقطة

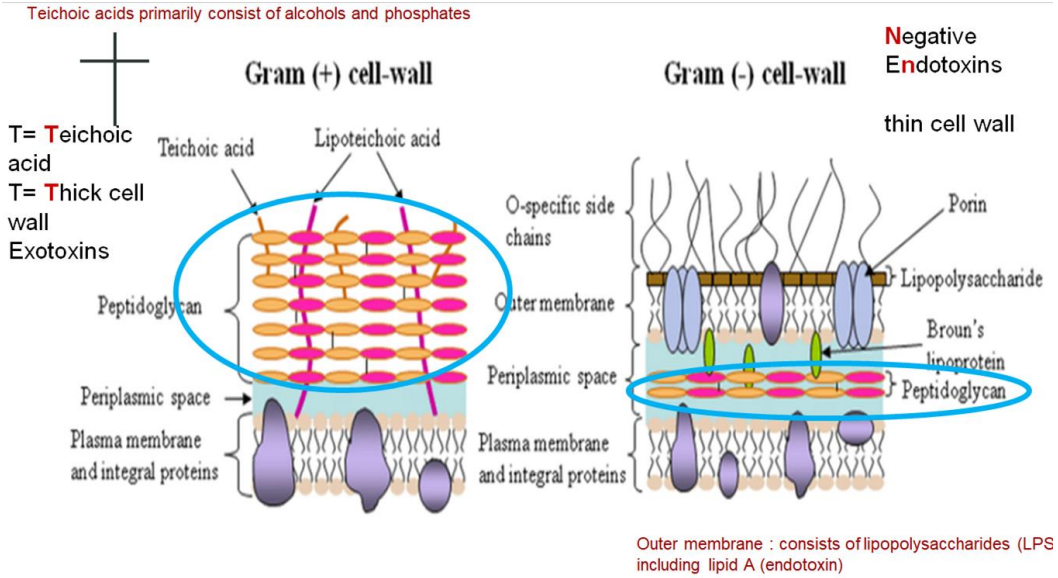
- Formulation of *piperacillin* with *tazobactam* extends the antimicrobial spectrum to include penicillinase-producing organisms (for example, most **Enterobacteriaceae** and **Bacteroides species**)

B-Lactam Antibiotics

- Bactericidal/ time dependent effect.
- Substrate/ target for (B-lactam**ases)**
- **Inhibits transpeptidase**
- **Active against rapidly growing organisms that has is**

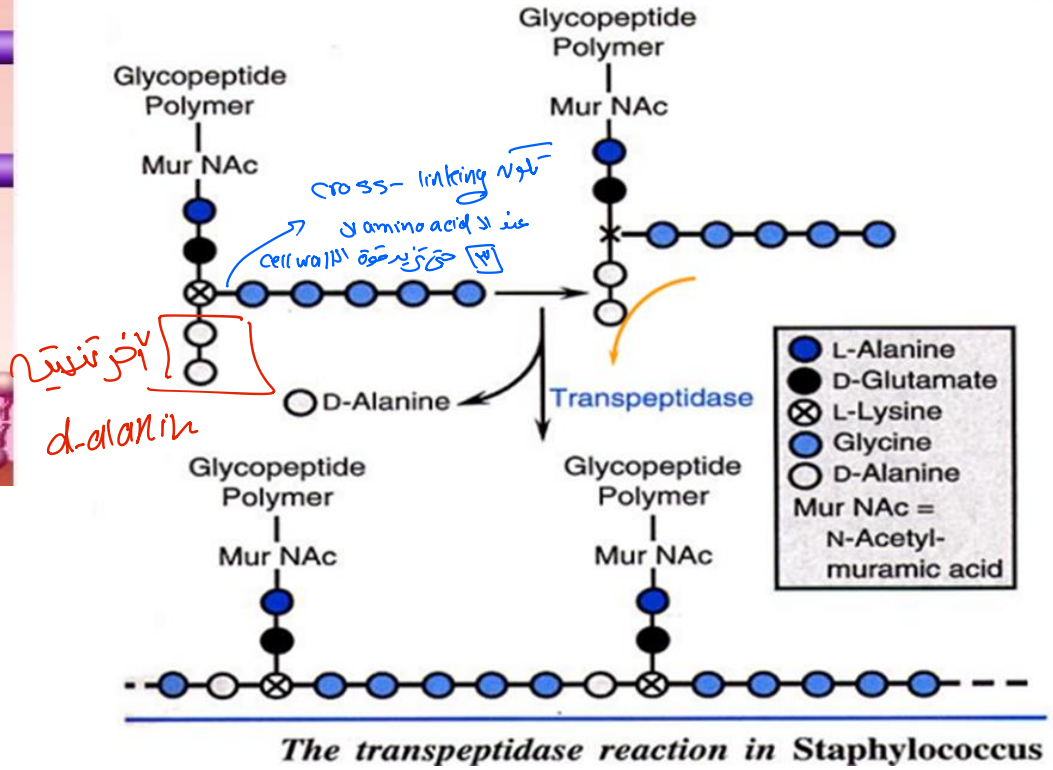
a <u>peptidoglycan cell wall (</u>which organisms have a peptidoglycan wall?)







Transpeptidase Reaction



The transpeptidase reaction in **Staphylococcus**

Last step of bacterial cell wall synthesis is the cross-linking of adjacent peptidoglycan strands by a process known as transpeptidation

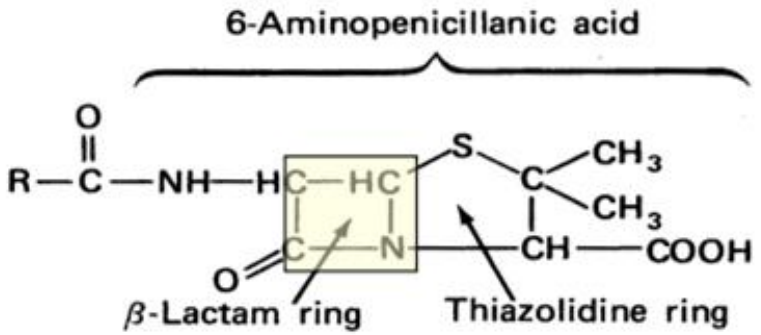
Peptidoglycan provides structural integrity and shape to bacterial cells

Penicillins: Mechanism of Action

1. Penicillin-binding proteins (PBP):

Bacterial enzymes involved in the synthesis of the cell wall.

Alterations in some of these **target molecules** provide the organism with resistance to the penicillin's.

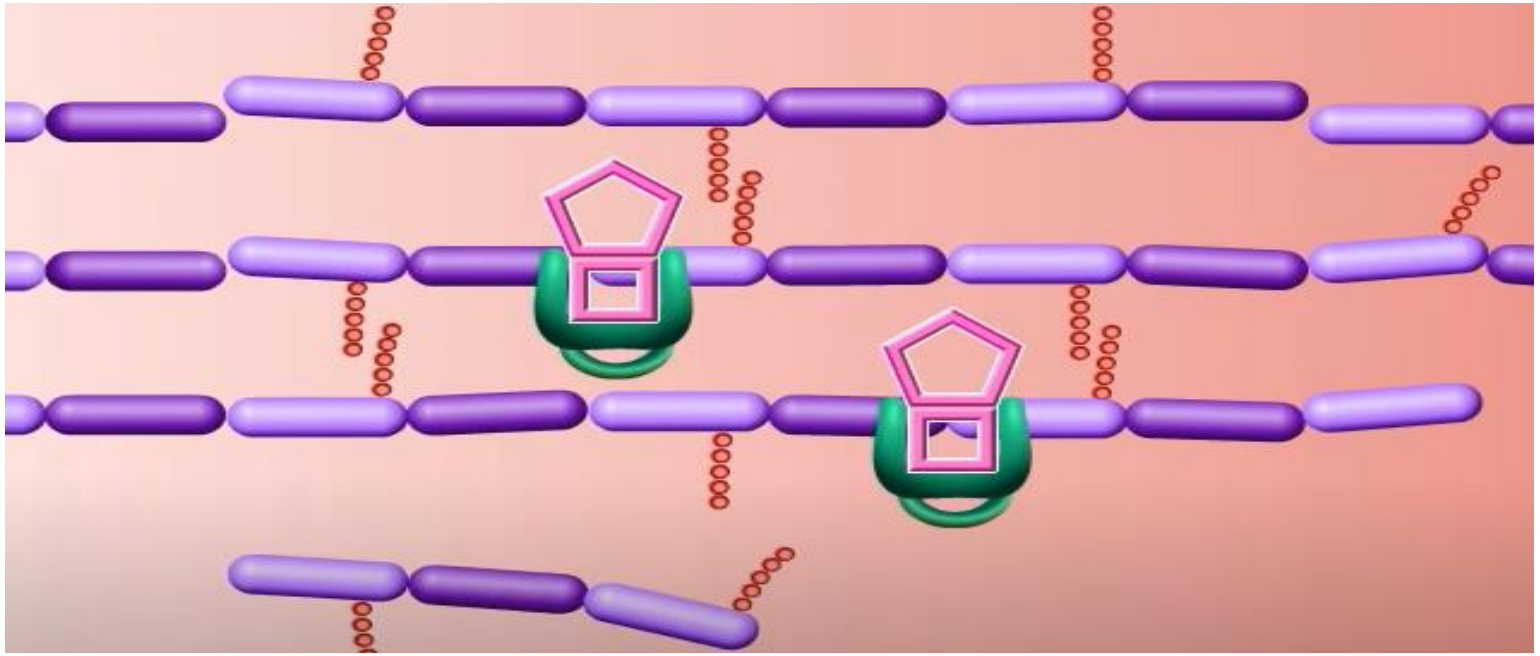


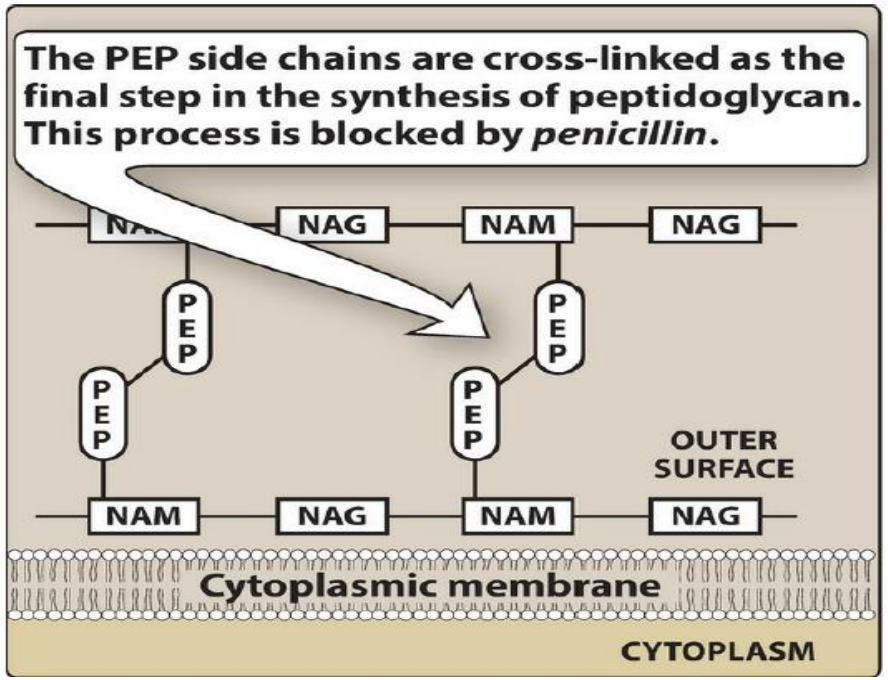
- Penicillins enter the bacteria via the cell wall.
- Inside the cell, they bind to **penicillin-binding protein**.
- Once bound, normal cell wall synthesis is disrupted.
- Result: Bacteria cells die from cell lysis.
- Penicillins do not kill other cells in the body

ماذا تكون روابط الـ (cross-linking) بالـ cell wall المتكونة

2. Inhibition of transpeptidase: Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains.

Penicillin's inhibit this transpeptidase-catalyzed reaction





Penicillins structurally resemble the terminal portion of the peptidoglycan strand, they compete for and bind to enzymes called penicillin-binding proteins (PBPs), which catalyze transpeptidase and facilitate cross-linking of the cell wall → weakened cell wall and ultimately cell death

آخر متتين (d-Alanin و d-Alanin) peptidoglycan الجزء الأخير من ربط ببعض يشبه Penicillin لذلك transpeptidase يحل محل Penicillin الـ competition حتى يتفوق عليه بالتالي يصير خلل

فإذا ارتبط بالـ transpeptidation يمنع الـ well cell wall ← death

3. Production of autolysins:

Degradative enzymes

Participate in the normal remodeling of the bacterial cell wall.

The β-lactam Ring

What is the primary target of the β-lactam ring in penicillins?

A) DNA polymerase

B) Ribosomal proteins

C) Transpeptidase enzyme

D) Cell membrane lipids

Correct Answer: C - Transpeptidase enzyme
The β-lactam ring inhibits transpeptidase, preventing cross-linking of peptidoglycan chains!

Resistance Mechanisms

Which is NOT a mechanism of penicillin resistance?

A) β-lactamase production

B) Altered penicillin-binding proteins (PBPs)

C) Efflux pumps

D) Increased drug uptake

Resistance

antibiotic ← inhibition هعمل

1- β-Lactamase production (Enzyme inactivation): A major cause of resistance to the penicillin and are an increasing problem

- Gram-positive organisms secrete β-lactamases extracellularly, whereas gram -negative bacteria inactivate β-lactam drugs in the periplasmic space.

2- Decreased permeability to the drug (intrinsic resistance) :

- Reduced penetration of drug into the cell is a greater concern in gram-negative organisms, which have a complex cell wall that includes aqueous channels called porins.
- An excellent example of a pathogen lacking high permeability porins is **Pseudomonas aeruginosa**

الدواء اعضوظ يدخل عن طريقها Porin فلما تقل البنفازيق بتبقها مايدخل الدواء كتير

3- Active transport of the drug out of cells: P-Glycoproteins → وانا بطرد الدواء لـ

Efflux pump, which actively removes antibiotics from the site of action, can also reduce the amount of intracellular drug (for example, **Klebsiella pneumoniae**).

4- Altered PBPs:

تغيرشكل البروتين حتى لا Penicillins مايقدر يرتبط فيهم

- Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth.
- This explains **MRSA** resistance to most commercially available β-lactams.

Penicillins: Indications

- Prevention and treatment of infections caused by susceptible bacteria, such as:
  - **Gram-positive bacteria**, including *Streptococcus* spp., *Enterococcus* spp., *Staphylococcus* spp.

- Streptococcus - pneumoniae, meningitis, pharyngitis, endocarditis, rheumatic fever
- Staphylococcal skin and wound infections
- Meningococcus
- Syphilis
- Clostridia - tetanus, gangrene
- H. influenzae - pneumonia
- Acute UTI - E. Coli, Pseudomonas, enterococci

Pharmacokinetics

- **Routes of administration:**

Penicillin V, *amoxicillin* with *clavulanic acid, amoxicillin*, and *dicloxacillin* are available only as oral preparations. Others are effective by the oral, IV, or IM routes

- **Depot forms**

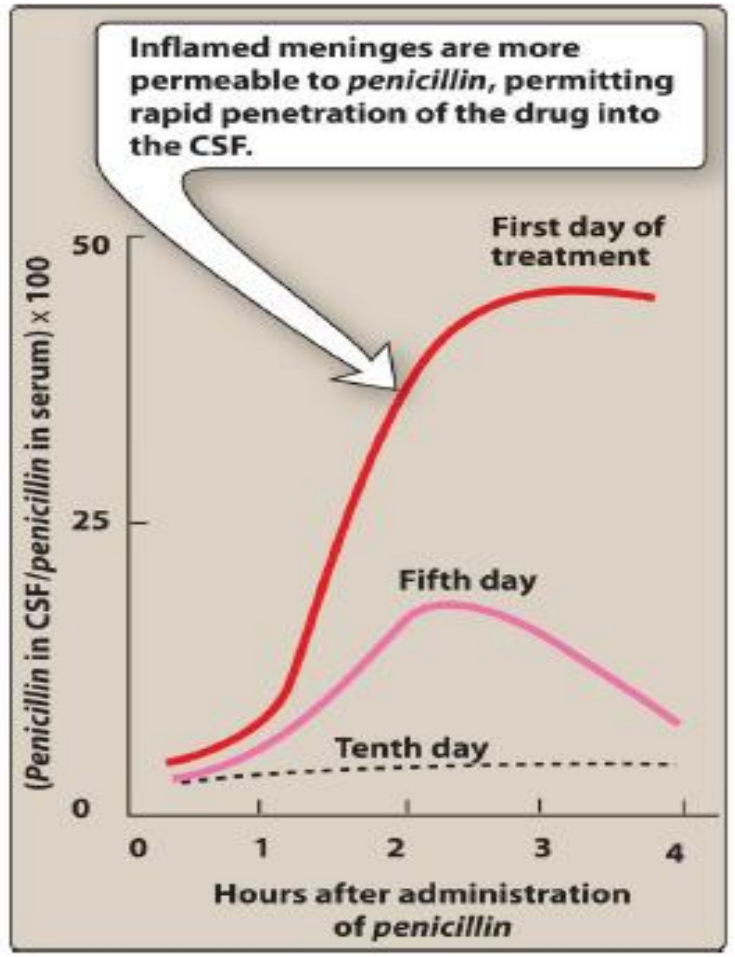
Procaine penicillin G and *benzathine penicillin G* are administered IM and serve as depot forms.

They are slowly absorbed into the circulation and persist at low levels over a long time period

- **Distribution:**

The β-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none nhave been shown to have teratogenic effects.

penetration into bone or cerebrospinal fluid (CSF) is insufficient for therapy unless these sites are inflamed



Metabolism	Excretion
Metabolism of the β-lactam antibiotics is usually insignificant	The primary route of excretion is through the organic acid (tubular) **secretory system of the kidney** as well as by glomerular filtration
	Patients with impaired renal function must have dosage regimens adjusted
Nafcillin and oxacillin are primarily metabolized in the liver	Nafcillin and oxacillin are primarily metabolized in **the liver,** they do not require dose adjustment for renal insufficiency
	Penicillins are also excreted in **breast milk**

Penicillins: Contraindications

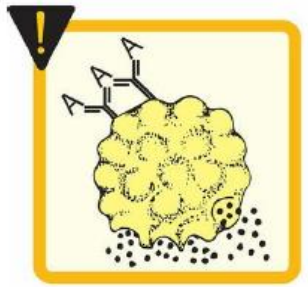
- Usually safe and well-tolerated medications
- Contraindicated: **known drug allergy**
- Type of reaction that occurs in patients who state they are allergic to penicillins
- Not all end in "**cillin**" (e.g., Zosyn, Augmentin)
- Many medication errors have occurred when a penicillin drug called by its trade name is given to a patient with a penicillin allergy.

Penicillins: Adverse Effects

- **Allergic reactions** to the penicillins occur in 0.7% to 4% of treatment courses.
  - Urticaria, pruritus, angioedema → تورّم الجلد
- Patients allergic to penicillins have an increased risk of allergy to other beta-lactam antibiotics.
- Only patients with a history of throat swelling or hives from penicillin should not receive cephalosporins.

Type-1

مشتركة بنوع R-group وأعراضها تشوفها وحدة


Hypersensitivity


Diarrhea


Nephritis


Neurotoxicity

Common adverse effects

- Nausea, vomiting, diarrhea, abdominal pain
- Other adverse effects are less common.

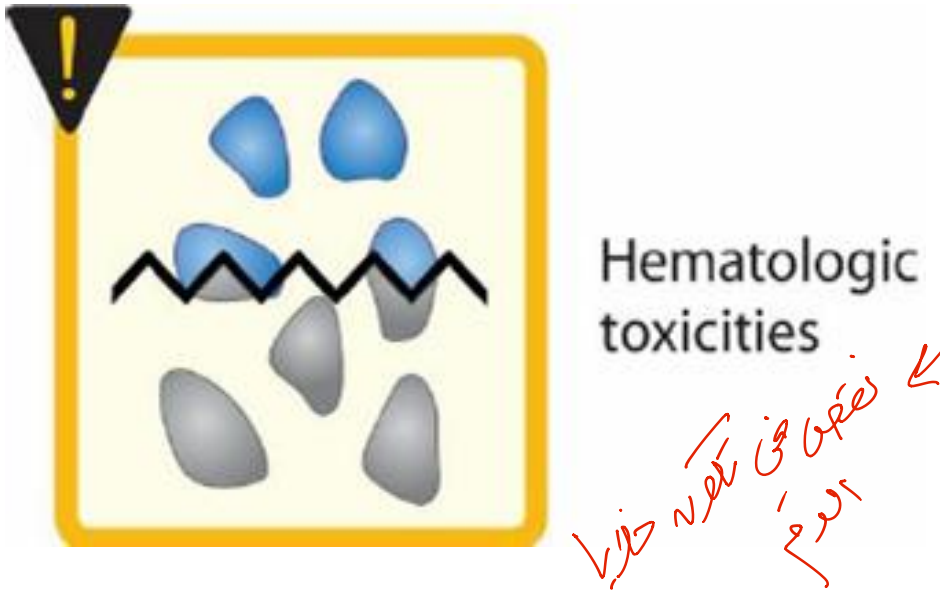
BETA-LACTAM ALLERGIES

DEFINITION

***IMMUNOLOGIC HYPERSENSITIVITY REACTION** to an antibiotic in the beta-lactam class*

Classification	Symptoms	Time Frame
Type I – Anaphylactic Rxn	Hives, angioedema, bronchospasm, hypotension, laryngeal edema, abdominal issues	Symptoms start *within 1 hour* of ingestion of *initial dose*
Type II Cytotoxic	Thrombocytopenia, interstitial nephritis, hemolytic anemia	
Type III Immune complex formation	Serum sickness syndrome	
Type IV Cell Mediated Hypersensitivity	Contact dermatitis, maculopapular eruptions, SJS	Symptoms start after days of treatment

Licensed



Hematologic toxicities

Decreased coagulation may be observed with high doses of *piperacillin* and *nafcillin* (and, to some extent, with *penicillin G*). Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts 7zshould be monitored weekly for such patients

- Large doses (>20 million IU/day) given to patients with renal failure can cause lethargy, confusion, twitching, and seizures
- Dizziness, tinnitus, headache, hallucinations
- Pseudomembranous colitis due to Clostridium difficile overgrowth

Serious adverse events are associated with all antibiotics

Large, long-term randomized controlled trials are uncommon, and so it is difficult to put a precise estimate on how prevalent these events are.

However, some adverse events include:

Clostridium difficile infection: associated most often with clindamycin (RR≈4), cephalosporins, and fluoroquinolones; risk varies depending on patient factors.

Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, & other severe skin reactions: these events occur a few times per 100,000 antibiotic prescriptions. **Cotrimoxazole** in particular has a higher association than most other antibiotics.

QT prolongation: associated most often with **macrolides** (esp. clarithromycin and erythromycin) and **fluoroquinolones** (esp. levofloxacin and moxifloxacin). Risk of QT prolongation is also dependent on other factors (e.g. cardiac, metabolic, other drugs, etc.).

Tendon rupture with fluoroquinolones: one large cohort study found a risk of 3.5% for tendon rupture in **adults over the age of 65**

Hyperkalemia with cotrimoxazole: in older adults taking medications which can raise potassium (such as ACEIs, ARBs, spironolactone, or NSAIDs), **cotrimoxazole** was associated with sudden death (NNH ≈ 300).

Contraceptive failure/drug interaction? Birth control failure is a well-documented event with **rifampin**. It is thought to be unlikely with other antibiotics, although a backup birth control method is still recommended.

Penicillins: Interactions

- **MANY** interactions!
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Oral contraceptives (Failure)
  - Warfarin (Increase INR)
  - Others (probenecid)- advantageous

يزيد سيولة الدم

سائل كريتين

يمنع الـ excretion تبع الـ Penicillins وعندهشين يصير الجسم على شكل carriers

بالتالي الـ Penicillins راح يبقى داخل الـ blood وقت أطول

Probenecid BENURYL 500mg tab ✗ ⊗ Compounded only by some pharmacies PL	• Prolongs penicillin levels by competitively inhibiting their excretion. Give 30-45min prior to IV β-Lactam dose. • Occasionally useful when IV therapy is needed in an outpatient setting to ↑ convenience / ↓ home care visits (e.g. in cellulitis to ↓ IV cefazolin dosing to q24h).[23] • AE: flushing, rash, GI upset, dizziness, headache.	**Peds:** 40mg/kg/day po divided q6h **Adult:** 500mg po QID 30-45 min prior to IV abx Alternate: 1-2g daily 30 min pre-cefazolin **Max:** 2000-3000mg/day	$19 $19 $19-23

tablets

Question #1

A patient is receiving Augmentin (**amoxicillin and clavulanic acid**) liquid solution through a percutaneous endoscopic gastrostomy tube. What is the purpose of the clavulanic acid?

A. It works synergistically with the antibiotic to improve potency.

B. It inhibits the action of the enzymes produced by beta-lactamase–producing bacteria.

C. It protects the antibiotic from the harmful gastric acid secretions in the stomach.

D. It enhances the absorption of the antibiotic in the small intestine.

ANS: B

The clavulanic acid works to inhibit the action of the enzymes produced by the bacteria, which would normally inactivate the antibiotic.

Nursing Implications

Penicillins

- Take **oral doses with water** (not juices) because acidic fluids may nullify the drug's antibacterial action.
- Monitor patients taking penicillin for an allergic reaction for at least 30 minutes after administration.

Penicillins

Generic/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	Dosing (Adult, Pediatric, Usual Max)	$/10d
Penicillins: Binds to penicillin binding proteins on bacterial cell walls, inhibiting cell wall biosynthesis. Bactericidal. Demonstrates time-dependent killing. • **AE**: rash, nausea, vomiting, diarrhea, melanoglossia. **Rare**: allergic reactions, cytopenias, acute interstitial nephritis. Aminopenicillins (amoxicillin, ampicillin) ↑ risk of SJS (but rare → 2-3 per 100,000 patients).[6] • **DI**: can ↑INR with warfarin; ?may cause oral contraceptive failure. **M**: signs of anaphylaxis. True penicillin anaphylactic allergy: 0.01% of population. **PK**: Amoxicillin and amox/clav have excellent bioavailability.			
Amoxicillin AMOXIL, g 125, 250mg chew tab cherry 25, 50mg/mL susp strawberry, banana, sugar free, berry ☺ ❄ 250, 500mg cap 1st trimester: ?cleft lip/palate. Amoxicillin risk 2-4/1000 vs baseline risk of 1-2/1000	• **Coverage**: *Streptococci*; *Enterococcus faecalis*; *Listeria*; *N. meningitidis*. • **Useful in**: upper respiratory tract infections; sinusitis; acute otitis media; dental procedure prophylaxis; low-risk AECOPD. *Strep pneumo* resistance only 3% in Canada for community-treated infections.[4] • High pediatric doses (e.g. 90mg/kg/day) can overcome moderate *Strep pneumo* resistance in acute otitis media & community acquired pneumonia. Risk factors for PRSP: recent antibiotic use, daycare, not given PREVNAR. • Consider watchful waiting in acute otitis media for suitable children (see page 78). • Excellent bioavailability. Achieves high concentrations in the middle ear.	**Peds**: 40-50mg/kg/day divided q8-12h 75-90mg/kg/day divided q8-12h if risk of *Strep pneumo* resistance max 3g/day **Adult**: **500**-1000mg po q8h **Max**: 1000-4000mg/day	$17 $22-32 $40
Amox/Clavulanate CLAVULIN, g • Strength listed is **amoxicillin** component. Clavulanate component is 125mg. • **Coverage** as per amoxicillin, plus: MSSA, many Enterobacteriaceae; *Haemophilus influenzae*; *Moraxella*; many anaerobes. • **Max dose**: 2000-4000mg/day • **Useful in**: bite wounds; respiratory tract infections; high-risk AECOPD • ↑ diarrhea vs amoxicillin NNH=10.[2,3] Less diarrhea with q12h dosing vs q8h.	**Amox:clav ratio →**		
	2:1 (tab) q8h $23 • **Adults**: 250mg tab q8h • Often for less serious infections, or renal dysfunction (q12-24h). • Note: two 250mg tabs are not equal to one 500mg tab	**4:1 (tab, susp) q8h $23-27** • **Adults**: 500mg tab q8h • **Peds**: 25, 50mg/mL susp ❄ rasp-orange dosed at 20-40mg/kg/day divided q8h	**7:1 (tab, susp) q12h $23** • **Adults**: 875mg tab q12h • **Adults**: may give 875mg of suspension q12h if difficulty swallowing • **Peds**: 40, 80mg/mL susp rasp-orange ❄ dosed at 45mg/kg/day divided q12h **Decreased diarrhea** with ratios e.g. **7:1** that allow for **q12h** (3.4% vs q8h 5.9%).[2]	**14:1 (combo) q12h $69** **Peds**: Use when targeting 90mg/kg/day in PRSP: -45mg/kg/d plain amoxicillin PLUS -45mg/kg/d amox-clav 7:1 susp
Ampicillin, g 250, 500mg cap 1st trimester: see amoxicillin	• **Coverage**: *Streptococci*; *Enterococcus faecalis*; *Listeria*; *N. meningitidis*. [Same spectrum as amoxicillin.] • **Useful in**: some UTIs with sensitive enterococcus; meningitis (IV formulation, as part of combo therapy). • **Disadvantages vs amoxicillin**: ↓ absorption, ↓ convenience (q6h), & ↑ AE (diarrhea, due to incomplete absorption). Good CSF penetration. Useful in severe listeria infections due to availability of an IV formulation.	**Peds**: 50-100mg/kg/day divided q6h **Adult**: 500mg po q6h **on empty stomach** **Max**: 2000mg/day	$26 $45 $45
Cloxacillin, g 25mg/mL susp cherry ❄ 250, 500mg cap	• **Coverage**: MSSA by definition; some *Streptococci* (penicillin covers more *Streptococci* species). • **Useful in**: Skin and soft tissue infections (where primarily MSSA). Narrow-spectrum agent; often used as step-down therapy when MSSA is known pathogen. • Methicillin, oxacillin, & dicloxacillin options in countries outside of Canada and have equivalent spectrum.	**Peds**: 50-100mg/kg/day divided q6h **Adult**: 500mg po q6h **on empty stomach** **Max**: 4000mg/day	$111 $72 $134
Penicillin V Potassium PEN-VK, g 25mg/mL sol'n fruity ❄ 60mg/mL sol'n fruity ✗▼❄ 300mg (480,000 unit) tab	• **Coverage**: *Streptococci*; oral anaerobes (e.g. *Actinomyces*, *Clostridium perfringens*, *Peptostreptococci*, *Propionibacterium*). Still no resistance with Group A *Streptococcus* (aka *Streptococcus pyogenes*). • **Useful in**: bacterial pharyngitis; rheumatic fever prophylaxis (prophylactic dose is 250mg po q12h) • q12h dosing in pharyngitis appears effective.	**Peds**: 25-50mg/kg/day divided q6-12h **Adult**: 300-600mg po q6h **on empty stomach** 600mg po q12h option in pharyngitis **Max**: 3000mg/day	$31 $19 $22

Antibiotics During Pregnancy/Lactation		Safe / Likely Safe / Caution / Contraindicated			
		1st Trimester	2nd Trimester	3rd Trimester	Lactation
PEN	Amoxicillin ± clav / Ampicillin	?cleft lip/palate ≤0.4%			(with clavulanate)
	Cloxacillin / Penicillin V				
CEPHALOSPORINS					

ABX against MRSA

CLean ur VaLiD Dox e Carolina Cotton Toy

CL = Clindamycin

Va = Vancomycin Li = Linezolid D = Daptpmycin

Dox = Doxycycline

Carolina = Ceftaroline

Cotton = Cotrimaxazole

T = Tigacycline

صاحبي ولا Penicillin حبتي
بيشتغل ضدال MRSA

نفس الـ B-lactam drug في الـ Penicillins

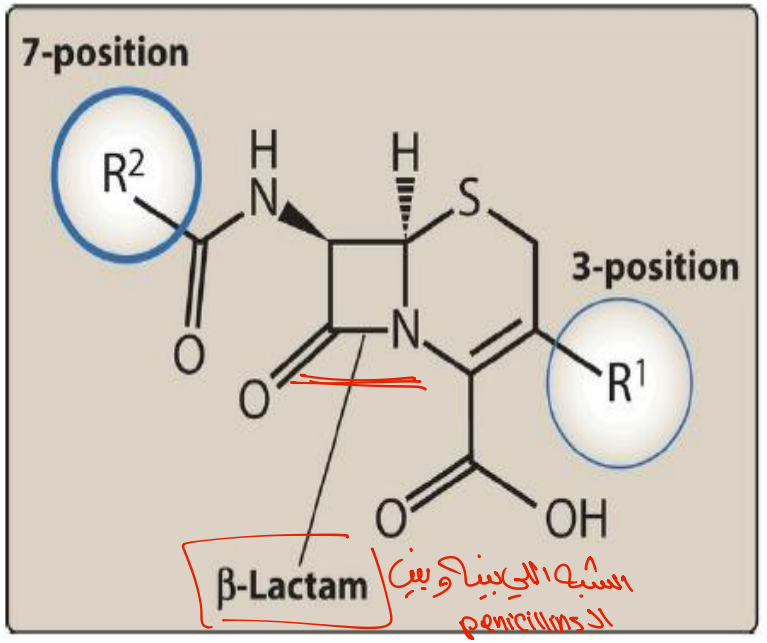
Cephalosporins

مختلف عن الـ Penicillins في نوع البكتيريا اللي بتؤثر عليها

ونوع الـ infection

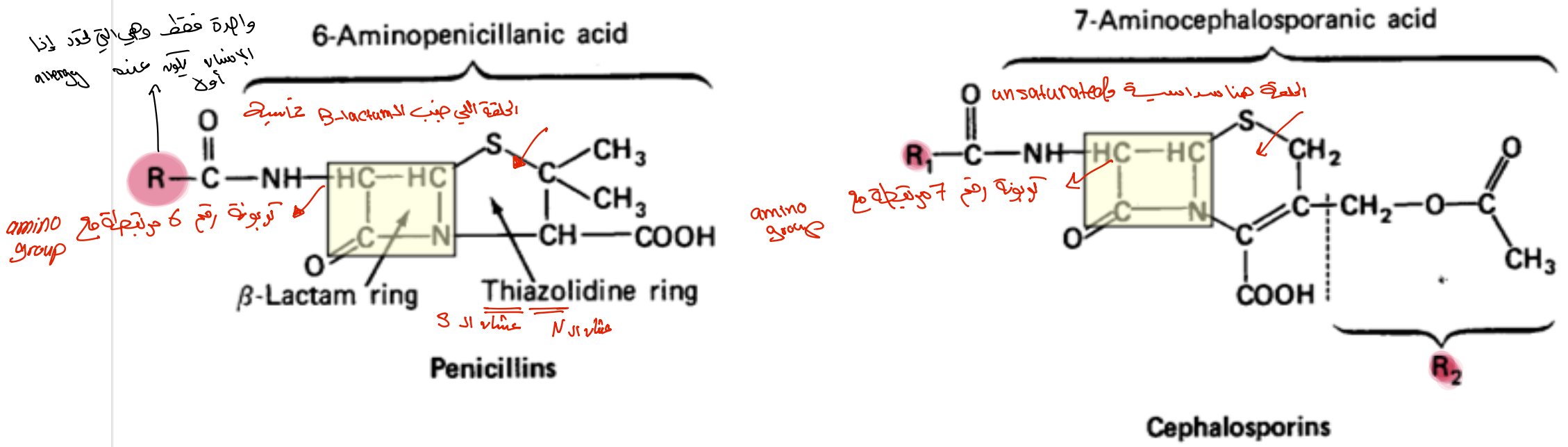
Cephalosporins

- Semisynthetic antibiotics
- Structurally and pharmacologically related to penicillins
- Bactericidal action
- Broad spectrum
- Divided into groups according to their antimicrobial activity



- First generation- Second -Third -Fourth and Fifth generation based largely on their bacterial susceptibility patterns and resistance to β-lactamases

Cephalosporins Are Structurally Similar to Penicillin's



Cephalosporins: The Generations

مع الـ generation الـ expand spectrum تزيد

Cephalosporin Generations (available in Canada)

1st	2nd	3rd	4th
cephalexin (po)	cefprozil (po)	cefixime (po)	cefepime (IV/IM)
cefadroxil (po)	cefoxitin (IV/IM)	ceftriaxone (IV/IM)	cefiderocol (IV) FDA
cefazolin (IV/IM)	cefuroxime (po/IV/IM)	ceftazidime (IV/IM)	**Advanced/combo**
	cefaclor D/C (po)	cefotaxime (IV/IM)	ceftobiprole (IV)
			ceftolozane* (IV)
			ceftaroline (IV) via SAP

هذا التوقيع السومه

هاد الـ 1st فيه مقطع

*ceftolozane available in combo with tazobactam ZERBAXA

Each generation has expanded spectrum and improved resistance to β-lactamases

Cephalosporins: First Generation

- **Good** gram-positive coverage
- **Poor** gram-negative coverage
- Parenteral and oral (PO) forms
- Examples
  - Cefadroxil (Duricef, Ultracef)
  - Cephradine (Velosef)
  - Cefazolin (Ancef) : (Ancef and Kefzol): intravenous (IV) or intramuscular (IM)
  - Cephalexin (Keflex): PO
- Used for surgical prophylaxis and for **susceptible staphylococcal infections (MSSA)**
- Modest activity against Proteus mirabilis, E. coli, and K. pneumoniae
- Most oral cavity anaerobes like Peptostreptococcus are sensitive

Cephalosporins: Second Generation

- **Good** gram-positive coverage but weaker than first
- **Better** gram-negative coverage than first generation against gram-negative organisms, such as H.influenzae, Klebsiella species, Proteus species, Escherichia coli, and Moraxella catarrhalis.
- Examples
  - Cefaclor (Ceclor)
  - Cefprozil (Cefzil)
  - Cefoxitin (Mefoxin)
  - Cefuroxime (Zinacef)
  - Cefotetan (Cefotan)

Penicillins ↓ resistance ... Penicillinase ... 2nd G ... otitis media / Pneumonia / UTI + E.Coli ... anaerobes ... Klebsia

- **Cefoxitin and cefotetan** covers anaerobes such as Bacteroides fragilis >>>>> neither drug is first line because of the increasing prevalence of resistance among B. fragilis

maningitist ال لعلاج

Third generation

ime
one

- **Ceftriaxone, cefotaxime, ceftazidime, cefixime, cefdinir**
- They have an important role in the treatment of infectious diseases.

(pneumonia , maningitis) لي بصيروا يستخدموا في المستشفيات

- They are less potent than first-generation cephalosporins against MSSA.

- They have enhanced activity against gram-negative bacilli, including β-lactamase producing strains of H. influenzae and Neisseria gonorrhoeae
- *Ceftazidime* has activity against P. aeruginosa; however, resistance is increasing
- They are associated with significant "collateral damage," including the induction of antimicrobial resistance and development of Clostridium difficile infection

Clostridium وبناء GIT في normal flora ال وبالتالي بقتل resistance بسبب بصير في وبالتالي المشكلة هيني رح عالجوا

Fourth generation

Cefepime → هذا الموجود في السوق حالياً → لازم ناخذه Parentral

- *Cefepime* has a wide antibacterial spectrum, with activity against streptococci and staphylococci (but only those that are *methicillin* susceptible)

- *Cefepime* is also effective against aerobic gram-negative organisms, such as Enterobacter species, E. coli, K. pneumoniae, P. mirabilis, and **P. aeruginosa**

Gram -ve ← البكتيريا السالبة للغرام

لا بدي أختار antibiotic الها راح نحاول اختبار local antibiogram

يعني كل منطقة راح تكون في الها بكتيريا معينة فتوقفها وبتقل الـ infection وبالمستشفى هاد المنطقة بيجمع نتائج الحزعة للمرضى

وبحدد الـ antibiotic على هذا الأساس وهيك منلم حتى نقلل الـ Resistance

Advanced generation (Fifth Generation)

- **Ceftaroline** is a broad-spectrum, advanced-generation cephalosporin.
- It is the only β-lactam in the United States with activity against MRSA, and it is indicated for the treatment of complicated skin and skin structure infections and community-acquired pneumonia
- In addition to its broad gram-positive activity, it also has similar gram-negative activity to the third-generation cephalosporin *ceftriaxone*
- Doesn't cover P. aeruginosa, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, and Acinetobacter baumannii.

هذا الجدول حتى نعرف مين PO ومين Parenteral

Drug (*Trade Name*)	Route	Remarks
First generation		
Cefadroxil (*Duricef*)	PO	Used to treat common gram-positive and gram-negative infections, including *Klebsiella pneumoniae*; cefazolin is preferred for chemoprophylaxis
Cefazolin (*Kefzol*)	IM, IV	
Cephalexin (*Keflex*)	PO	
Cephradine (*Velosef*)	PO, IV	
Second generation		
Cefaclor (*Ceclor*)	PO	Indicated primarily for gram-negative infections; are more resistant to the actions of beta-lactamases; increased activity against *N. gonorrhoeae, H. influenzae,* and *K. pneumoniae*
Cefonicid (*Monocid*)	IM, IV	
Cefotetan (*Cefotan*)	IM, IV	
Cefoxitin (*Mefoxin*)	IM, IV	
Cefprozil (*Cefzil*)	PO	
Cefuroxime (*Ceftin*)	PO, IV	
Loracarbef (*Lorabid*)	PO	
Third generation		
Cefdinir (*Omnicef*)	PO	Indicated for serious gram-negative infections that are resistant to other cephalosporins; increased activity against *K. pneumoniae, P. aeruginosa*; ceftriaxone is lipid soluble and penetrates the blood–brain barrier for use in meningitis; ceftriaxone also has the longest half-life and is the drug of choice for resistant gonorrhea
Cefixime (*Suprax*)	PO	
Cefoperazone (*Cefobid*)	IM, IV	
Cefotaxime (*Claforan*)	IM, IV	
Ceftazidime (*Fortaz*)	IM, IV	
Ceftriaxone (*Rocephin*)	IM, IV	
Ceftazidime/avibactam (*Avycaz*)	IV	Combination with a beta-lactamase inhibitor to treat pneumonia, complicated urinary tract infections, and complicated intra-abdominal infections
Fourth generation		
Cefepime (*Maxipime*)	IM, IV	Similar to third generation; broad-spectrum activity; demonstrates greater resistance to beta-lactamase inactivating enzymes; indicated when there is resistance to third-generation cephalosporins
Ceftolozone/tazobactam (*Zerbaxa*)	IV	
Fifth generation		
Ceftaroline (*Teflaro*)	IV	Used to treat pneumonia and skin and soft-tissue infections

Pharmacokinetics

Distribution:

All cephalosporins distribute very well into body fluids.

- Adequate therapeutic levels in the CSF, regardless of inflammation, are achieved with only a few cephalosporins.
- For example, ***ceftriaxone* and *cefotaxime***

Elimination:

- Cephalosporins are eliminated through tubular secretion and/or glomerular filtration .
- Therefore, doses must be adjusted in renal dysfunction to guard against accumulation and toxicity.
- One exception is ***ceftriaxone***, which is excreted through the bile into the feces.

CEPHALOSPORIN COMPARISONS

1st Generation	• Cefazolin, Cephalexin
2nd Generation	• Cefaclor, Cefotetan, Cefoxitin, Cefuroxime
3rd Generation	• Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone
4th Generation	• Cefepime

Gram (+) Coverage

Gram (-) Coverage

Ceftaroline: "5th generation" or "advanced generation"
Similar to 3rd generation, but added MRSA coverage

First-generation cephalosporins

Gram (+) cocci
- Staphylococcus aureus*
- Staphylococcus epidermidis
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) rods
- Escherichia coli
- Klebsiella pneumoniae
- Proteus mirabilis

Second-generation cephalosporins

Gram (+) cocci
- Staphylococcus aureus*
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) cocci
- Neisseria gonorrhoeae

Gram (–) rods
- Enterobacter aerogenes
- Escherichia coli
- Haemophilus influenzae
- Klebsiella pneumoniae
- Proteus mirabilis

Anaerobic organisms**

Third-generation cephalosporins

Gram (+) cocci
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Anaerobic streptococci

Gram (–) cocci
- Neisseria gonorrhoeae

Gram (–) rods
- Enterobacter aerogenes
- Escherichia coli
- Haemophilus influenzae
- Klebsiella pneumoniae
- Proteus mirabilis
- Pseudomonas aeruginosa†
- Serratia marcescens

Fourth-generation cephalosporins

Antibacterial coverage comparable to that of the third-generation class; however, demonstrate greater stability against β-lactamases

Cephalosporins are divided into 1st , 2nd , 3rd , 4th and 5th generations according to their spectrum.

As the 1st, 2nd and 3rd generations progress they an increase in the sensitivity of gram-negative microorganisms and a decrease in the sensitivity of gram-positive microorganisms .

The 4th and 5th generations show activity towards both.

Clinical Scenario

A patient with bacterial meningitis needs empirical treatment. Which cephalosporin would be most appropriate?

A) Cephalexin (1st gen)

B) Cefuroxime (2nd gen)

C) Ceftriaxone (3rd gen)

D) Cefaclor (2nd gen)

عشان يقدر يدخل الـ CSF

Nursing Implications

Cephalosporins

- Assess for penicillin allergy; may have cross-allergy.
- Give orally administered forms **with food** to decrease GI upset even though this will delay absorption.
- Some of these drugs may cause a disulfiram (Antabuse)-like reaction when taken with alcohol.

Resistance

Penicillins نفس ال

- Resistance to the cephalosporins is either due to the hydrolysis of the beta-lactam ring by β-lactamases or reduced affinity for PBPs.

Cephalosporin and β-lactamase inhibitor combinations

3rd

Ceftazidime + *avibactam*

2g

β-lactamase inhibitor

500mg

Broad gram-negative activity including Enterobacteriaceae and P. aeruginosa



Resist hydrolysis against broad spectrum β-lactamases (AmpC, ESBL, carbapenemases) with the exception of metallo-β-lactamases

Used to treat infections due to multidrug-resistant pathogens

Adverse effects

- Like the penicillins, the cephalosporins are generally well tolerated. However, allergic reactions are a concern

- Hypersensitivity reactions

- Cross-reactivity between penicillin and cephalosporins is around 3% to 5% and is determined by the **similarity in the side chain**, not the β-lactam structure

- The highest rate of allergic cross-sensitivity is between *penicillin* and first-generation cephalosporins.

Cephalosporins: Binds to penicillin binding proteins on bacterial cell walls, inhibiting cell wall biosynthesis. Bactericidal. Demonstrates time-dependent killing. Gram-negative coverage increases as generation increases. All cephalosporins lack coverage of *Listeria*, atypicals, MRSA, & *Enterococci* (**LAME**). Gonorrhea resistance to cefixime ~ 2% in Canada (combine cefixime with a macrolide due to resistance + to add chlamydia coverage).[4,5]

- **AE**: rash, nausea, diarrhea. **Rare**: allergic reactions, cytopenias.
- **DI**: can ↑INR with warfarin; ?may cause oral contraceptive failure. **M**: signs of anaphylaxis. Risk of allergy cross-sensitivity between cephalosporins and penicillins is low - see Antibiotic Overview page.

Cephalexin KEFLEX, g 25, 50mg/mL orange-banana ☺ ❄ 250, 500mg tab PIL	• 1st-generation cephalosporins. • **Coverage**: *Streptococci*; MSSA; ?*Proteus*; *E. coli*; *Klebsiella*. (PEK) • **Useful in**: skin and soft tissue infections; step down option from IV cefazolin. • Take with food to reduce GI upset.	**Peds**: 25-100mg/kg/day po divided q6h **Adult**: 500mg po q6h (max 4000mg/day)	$29 $30-50
Cefadroxil DURICEF, g 500mg cap ✗ ▼ PIL		**Peds**: 30mg/kg/day po divided q6h **Adult**: 500mg po q12h (max 1000mg/day)	$30 $30
Cefprozil CEFZIL, g 25, 50mg/mL susp bubblegum ☺ ❄ 250, 500mg tab PIL	• 2nd-generation cephalosporins. • **Coverage**: *Streptococci*; MSSA; *Moraxella*; *Haemophilus influenzae*; *Proteus*; *E. coli*; *Klebsiella*. (H PEK) • **Useful in**: low-risk AECOPD; community-acquired pneumonia. • Cefuroxime has poor bioavailability (37% fasting; 52% with food). Cefprozil has excellent bioavailability.	**Peds**: 15-30mg/kg/day po divided q12h **Adult**: 500mg po q12h (max 1000mg/day)	$18 $29
Cefuroxime axetil CEFTIN, g 25mg/mL susp, 250mg sachet tutti-fruiti ❄ 250, 500mg tab PIL		**Peds**: 20-30mg/kg/day po divided q12h **Adult**: 500mg po q12h **with food** (max 1g/d)	$29 $42
Cefixime SUPRAX, g 20mg/mL susp strawberry ☺ 400mg tab PIL	• 3rd-generation cephalosporin. **Coverage**: *Streptococci*; *Moraxella*; *Haemophilus influenzae*; ?*Enterobacter*; *Neisseria*; *Proteus*; *E. coli*; *Klebsiella*; *Serratia*. (HEN PECKS) • **Useful in**: gonorrhea (800mg po x1 dose + azithro); pyelonephritis or complicated UTIs; low-risk AECOPD.	**Peds**: 8mg/kg po q24h **Adult**: 400mg po q24h **Max**: 400mg/day	$29 $44 $44
Ceftriaxone Injection ROCEPHIN, g 1, 2, 10g vials for injection (IM/IV) ✗ ⊗ PIL Don't need dose adj	• 3rd-generation cephalosporin with excellent gram-negative coverage (e.g. *Citrobacter*, *E. coli*, *Klebsiella*, *Morganella*, *Proteus*, *Serratia*). • Used in hospitalized pts for empiric coverage of gram-negative infections; also useful in an out-patient setting (e.g. one-time IM dose for gonorrhea; initial treatment of suspected pyelonephritis while waiting for cultures).	**Peds**: 50mg/kg IM/IV q24h **Adult**: 1000-2000mg IM/IV q24h **Max**: 2000mg/day	$23-46 (1 dose)

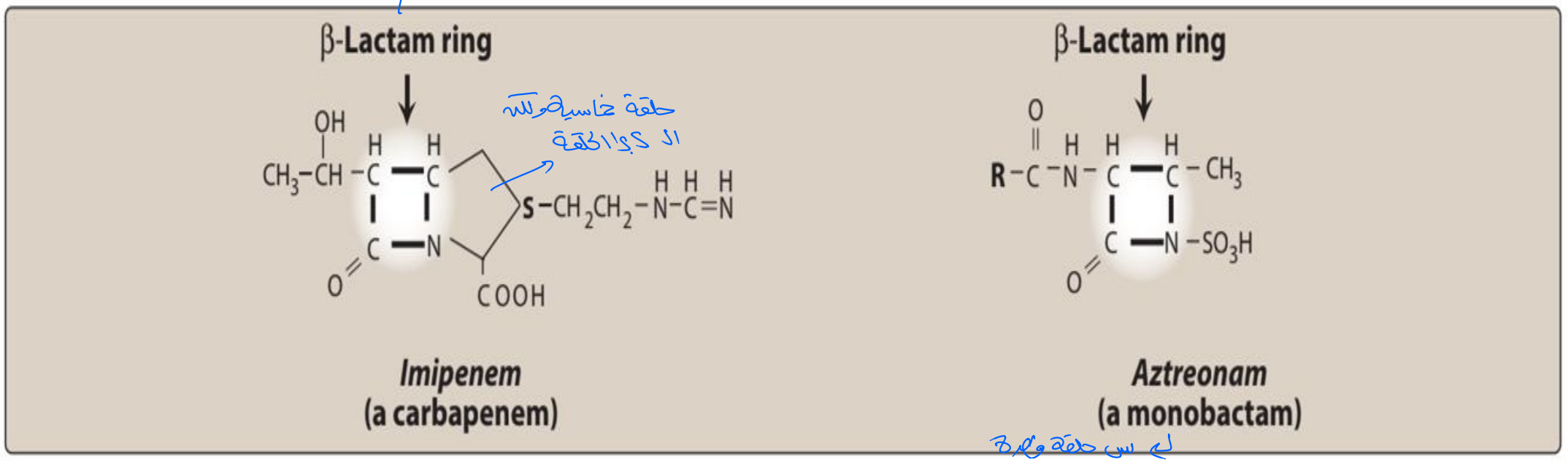
dose adjustment + kidney low

لو طلع المريض من المستشفى المريض بستخدم جرعات الدوا

Discontinued Products: Penicillin V Benzathine **PEN-VEE** suspension; cefaclor **CECLOR** tablet

CARBAPENEMS and MONOBACTAMS

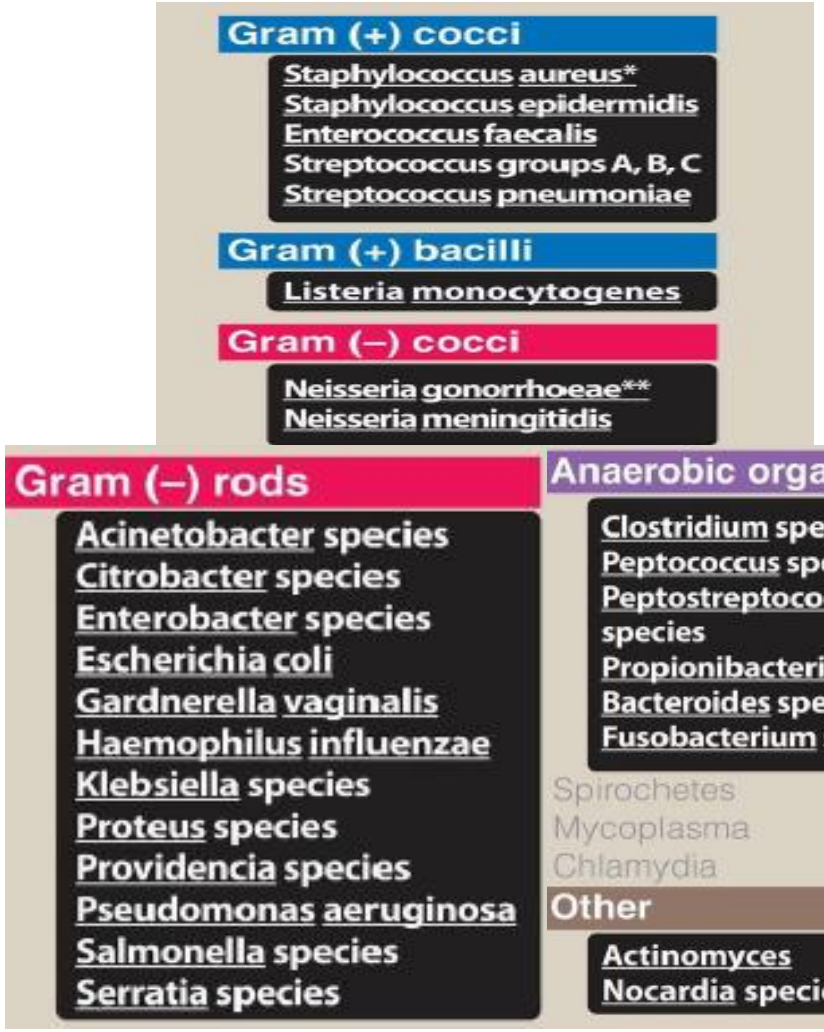
cell wall inhibition



Carbapenems: The Heavy Artillery

BROAD SPECTRUM

- Broadest antibacterial action of any antibiotics to date
- Reserved for **complicated body cavity** and **connective tissue infections** in acutely ill hospitalized patients
- Must be **infused over 60 minutes**
- May cause drug-induced seizure activity
  - This risk can be reduced with proper dosage.



Carbapenems (Cont.)

- Imipenem/cilastatin (Primaxin)
  - Used for treatment of bone, joint, skin, and soft tissue infections; many other uses
  - Cilastatin inhibits an enzyme that breaks down imipenem.
- Meropenem (Merrem)
- Doripenem (Doribax)

Newer Agents

- **Meropenem:** No cilastatin needed
- **Doripenem:** Prolonged infusions



- Ertapenem (Invanz) : Unlike other carbapenems, *ertapenem* **lacks** coverage against P. aeruginosa, Enterococcus species, and Acinetobacter species

Carbapenem/β-lactamase inhibitor combination

- Meropenem-vaborbactam is a combination of a carbapenem and a β-lactamase inhibitor.

Imipenem-Cilastatin (Primaxin®)

- Imipenem: carbapenem antibiotic
- Cilastatin: prevents renal degradation
- Must be given together

- Imipenem-cliastatin-relebactam

It is approved for the treatment of complicated urinary tract infections including pyelonephritis.

- This combination agent has activity against Enterobacteriaceae producing a broad spectrum of β-lactamases, except metallo-β-lactamases.

Clinical Uses:

- Hospital-acquired infections
- Multi-drug resistant organisms
- Serious polymicrobial infections
- Reserved for resistant cases

Warning: Risk of seizures with high doses!

Pharmacokinetics

Administered IV and penetrate well into body tissues and fluids,including the CSF when the meninges are inflamed.

Meropenem is known to reach therapeutic levels in bacterial meningitis even without inflammation

These agents are excreted by glomerular filtration.

Adverse effects

- High levels of *imipenem* may provoke seizures; however, the other carbapenems are less likely to do so.

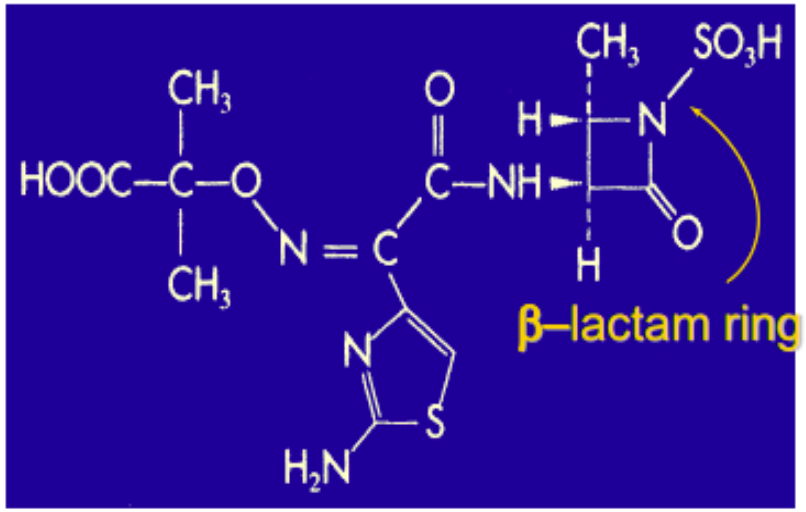
- While those with true *penicillin* allergy should use carbapenems cautiously, the cross-reactivity rate seen in studies is very low (less than 1%).

Monobactams

- Aztreonam (Azactam)
  - Synthetic beta-lactam antibiotic
  - Primarily active against aerobic gram-negative bacteria (*E. coli*, *Klebsiella* spp., *Pseudomonas*spp.)
  - Lacks activity against gram-positive organisms and anaerobes
  - Bactericidal
  - Parenteral use only
  - Low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other β-lactams.
  - Safe alternative for treating patients who are allergic to other penicillins, cephalosporins, or carbapenems
  - Used for moderately severe systemic infections and UTIs

X oral

AZTREONAM



يعني ده أغلب مرضى الـ β-lactam عندهم allergy والعكس صح

so save يعني ← monobactams لـ sensitive

استخدمه بدل لـ Penicillin

ANTIBIOGRAM

Know your antibiogra before prescribing antimicrobials

Source: St. Anne's Hospital

Blood Isolates – % Susceptible

≥80% Susceptible
70-79% Susceptible
≤69% Susceptible

	#	%	Ampicillin	Amoxicillin-Clavulanic acid	Penicillin	Piperacillin-Tazobactam	Meropenem	Ertapenem	Cloxacillin	Cefazolin	Ceftriaxone	Ceftazidime	Clindamycin	Erythromycin	Doxycycline	Ciprofloxacin	Moxifloxacin	Trimethoprim-Sulfamethoxazole	Gentamicin	Tobramycin	Amikacin	Vancomycin	Linezolid
L BACTERIA	104	–	8	15		26	37	31		11	22							30					
L GRAM-NEGATIVE BACTERIA	38	100	5	26		43	91	71		16	40	50				66		63	89	91	94		
bsiella pneumoniae	10	26	0	50		50	90	90		30	60	60				70		60	70	70	100		
cherichia coli	9	24	22	56		67	100	100		33	89	89				44		78	100	100	100		
udomonas aeruginosa	5	13				80	80					100				100			100	100	100		
Enterobacter cloacae	3	8	0	0		0	100	100		0	0	0				100		100	100	100	100		
Stenotrophomonas maltophilia	3	8															100	100					
ALL GRAM-POSITIVE BACTERIA	66	100	9	9		17	8	8	8	8	12		4	2				10				94	
Coagulase-negative staphylococci	40	61				0	0	0	0	0			0	0	100			0				100	100
Enterococcus faecium, all isolates	11	17	0	0		0																64	
- vancomycin-susceptible	7	11	0	0		0																100	
- vancomycin-resistant (VRE)	4	6	0	0		0																0	75
- vancomycin-susceptible (vanA+)	0	0																					
Staphyloccocus aureus, all isolates	6	9				83	83	83	83	83			38	21	100			100				100	100
- methicillin-susceptible	5	8				100	100	100	100	100			25	25	100			100				100	100
- methicillin-resistant (MRSA)	1	2				0	0	0	0	0			100	0	100			100				100	100
Enterococcus faecalis, all isolates	6	9	100	100		100																100	
- vancomycin-susceptible	6	9	100	100		100																100	
- vancomycin-resistant (VRE)	0	0																					
Viridans group streptococci*											100											100	

resistance يعني ما بصير عنده مشان

مش دايمًا بستخدمه

Vancomycin (RESERVE ANTIBIOTICS)

The MRSA Fighter

فانكو كلمة الي بجاربها

Vancomycin(RESERVE ANTIBIOTICS)

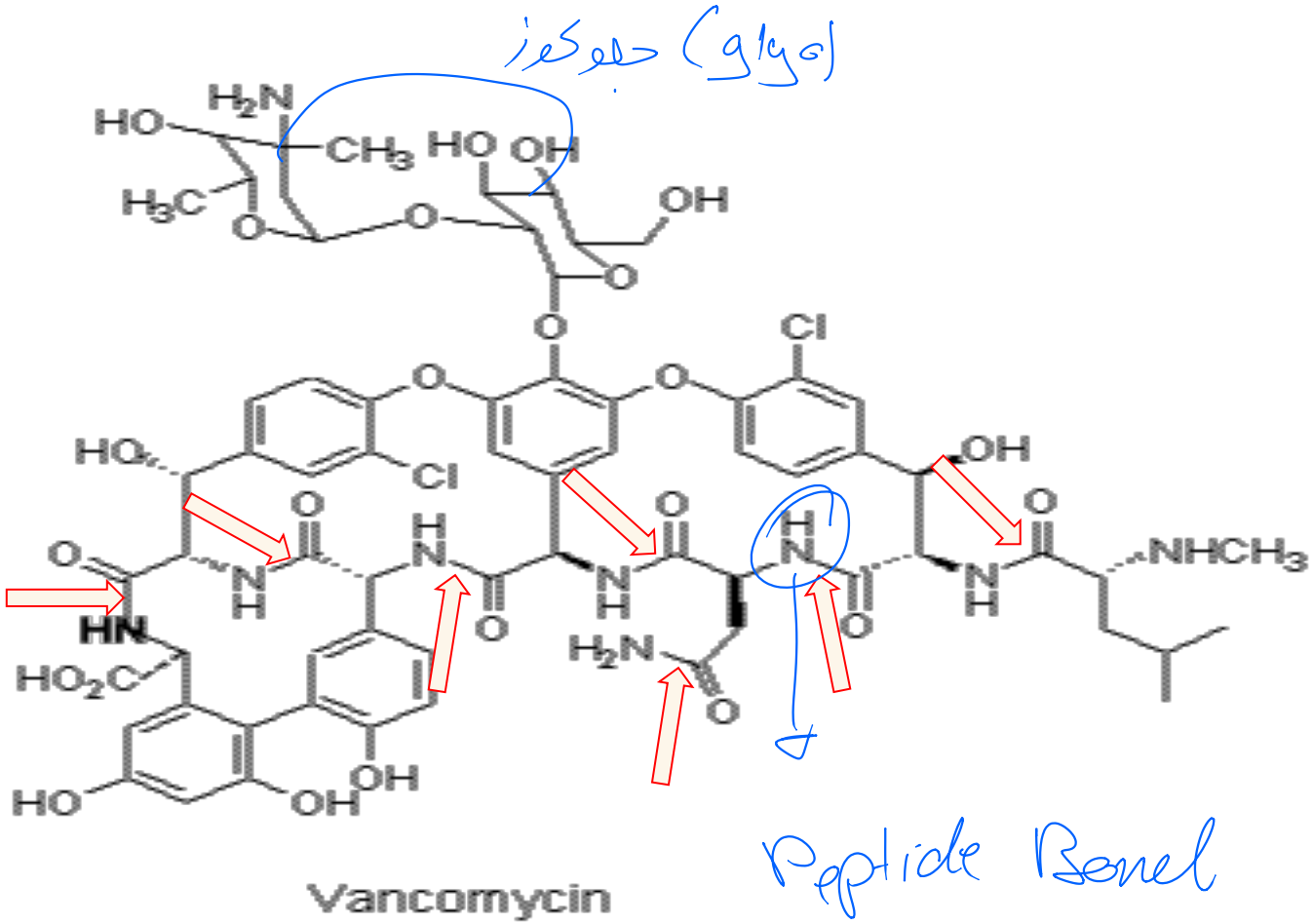
Vancomycin is a complex glyco**peptide** antibiotic produced by fermentation of *Nocardia orientalis*.

GIT تكسير منال لاحيصرفيه orally يوخذ أخذه

orally ماينفع أعطيه :.

The drug is available as a **water-soluble** hydrochloride that is not soluble in ethanol.

لأنه السكر بذوب في الماء



Mechanism: Prevents polymerization of peptidoglycan at Stage 2 (cell membrane)

Spectrum:

- Gram-positive only
- MRSA and MRSE
- Enterococcus
- C. difficile (oral route) → normal flore ~> لوزاد عددها رح تعمل مشاكل الاسهال بالتالي vancomycin رح يشتغل عليها وبشكل وبشكل local عشان هيك بنفع أعطيه oral فقط هاد الحالة

Major Side Effect:

● **Red Man Syndrome**

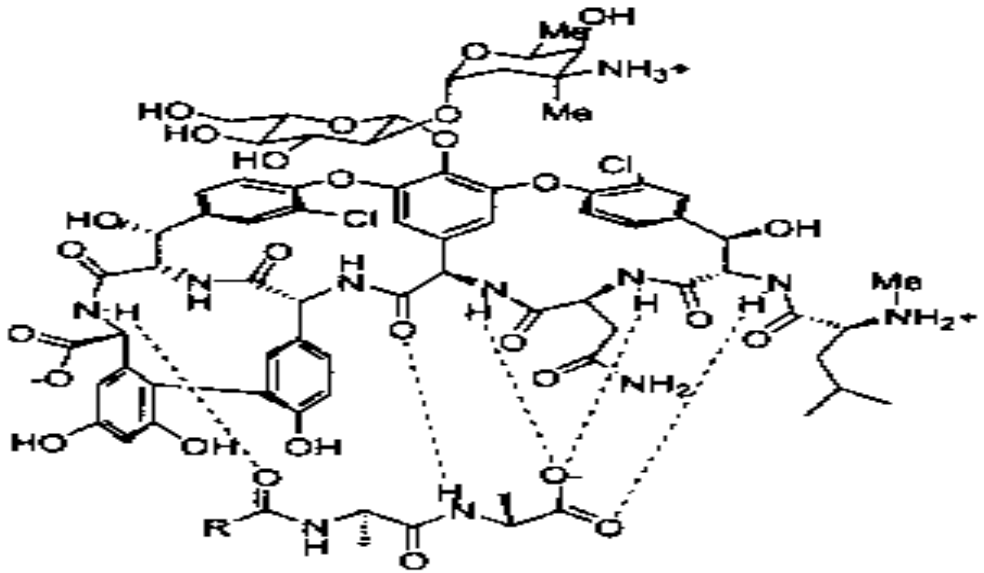
Histamine release from rapid IV infusion

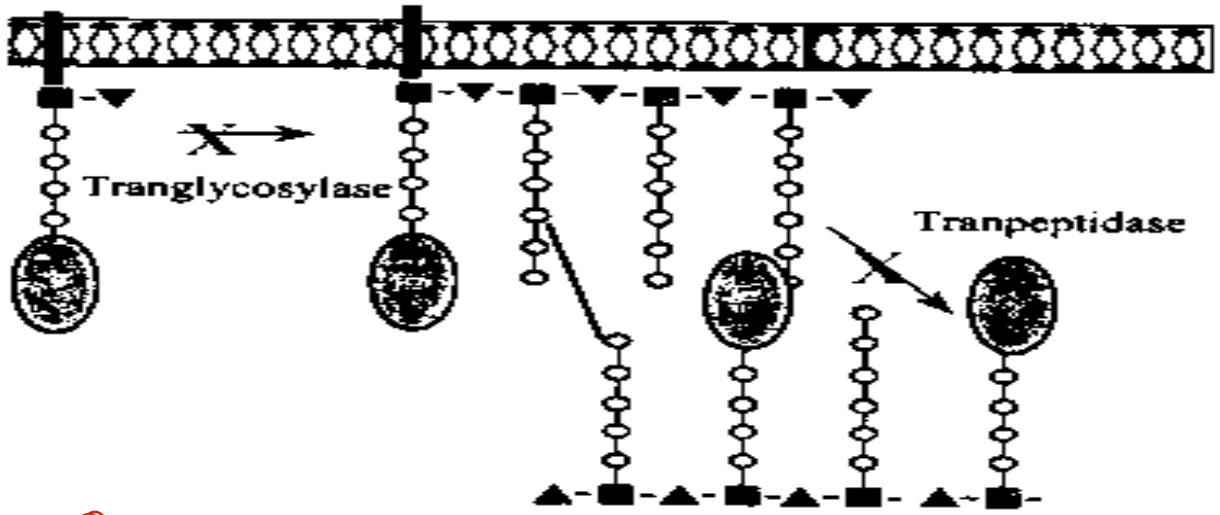
Prevention: Slow infusion over 1-2 hours

Other Toxicities:

- Nephrotoxicity (monitor levels)
- Ototoxicity (rare)

Glycopeptides: Mechanism of Action





- Binds to N-Acyl-D-Ala-D-Ala through 5 hydrogen bonds
- note non-covalent interaction
- Inhibition of transglycosylase and transpeptidase activities

The drug binds to the substrate of the enzyme that penicillins and cephalosporins inhibit. It inhibits both the transglycosylase and transpeptidase actions. Some authorities believe that the drugs act as dimers.

يمنع تكون ال cell wall

Molecular Mode Of Action

Vancomycin is bactericidal following binding to acyl-D-ala-D-ala peptides and so inhibits bacterial cell wall biosynthesis at the same step as the *beta*-lactam antibiotics do **but** by a very different mechanism.

They are water soluble organic bases.

They are not significantly serum protein bound.

Bactericidal mainly against **Gram positives** and **anaerobes**

Vancomycin

- Active against aerobic and anaerobic gram-positive bacteria, including MRSA, *methicillin*-resistant Staphylococcus epidermidis (MRSE), Enterococcus spp., and
- Clostridium difficile

Hospital

Nosocomial pneumonia

Meningitis

Skin and soft tissue infections

The drug is especially useful against (MRSA), MDR strains of *Streptococci,* enterococci, and orally against *Clostridium difficile*.

Clinical Uses And Resistance Emergence

It does not enter the bacterial cells but rather inhibits peptidoglycan biosynthesis at the surface.

Until very recently, no resistance against vancomycin was known but recently some enterobacter (*Enterococcus faecalis*, for example) and a few instances of vancomycin resistant MRSA have been encountered in the clinic.

reserve الدواء على قائمة ال وضع تم لهذا vancomycin مقاومة يكتسب لم عشان بالتالي D-ala تغيير تقوم البكتيريا

These strains are found to be resistant following alteration of one of the D-ala groups in their cell wall precursors to a lactate residue. Recently a plasmid has been found in *Staph. aureus* (MRSA) that passes this gene to previously sensitive strains. It apparently originated in *E. faecalis.*

Because of this emerging problem vancomycin has been placed on the reserve list.

High level resistance requires alteration in five genes.

Vancomycin (Vancocin)

- Treatment of choice for **MRSA** and other **gram-positive** infections
- Oral vancomycin is indicated for the treatment of antibiotic-induced colitis (*C. difficile*) and for the treatment of staphylococcal enterocolitis.
- Must monitor blood levels to ensure therapeutic levels and prevent toxicity
- May cause ototoxicity and nephrotoxicity

Toxicity And Other Properties

- Vancomycin toxicity includes hearing loss and nephrotoxicity. Vertigo and tinnitus are less commonly reported.
- Avoparcin. Law of unintended consequences. Agricultural use responsible for considerable clinical drug resistance to vancomycin.

Vancomycin is not appreciably absorbed from the GI tract, except in colitis, and so mainly is given parenterally following which it is widely distributed in the body.

The kidneys excrete the drug.

IV administration is painful and can cause severe phlebitis unless the drug is given by slow drip.

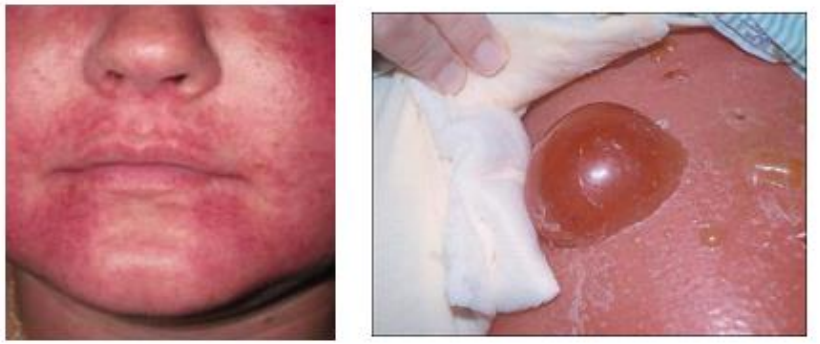
Vancomycin (Vancocin)

هذا السبب الأساسي ← تؤدي إلى

rapid diffusion ... بسبب release of Histamine ... يؤدي بسبب

infusion for one hour or more

- **Red man syndrome** may occur
  - Flushing or itching of head, neck, face,
    - upper trunk
  - Antihistamine may be ordered to
    - reduce these effects.



Red Man Syndrome
(Erythrodermatitis)

interaction

- Additive **neuromuscular blocking effects** in patients receiving neuromuscular blockers
- Should be infused over 60 minutes
- Rapid infusions may cause hypotension.

Red man syndrome

⚠ Safety First!

A patient develops flushing and urticaria during vancomycin infusion. What should you do?

A) Stop immediately and switch antibiotics

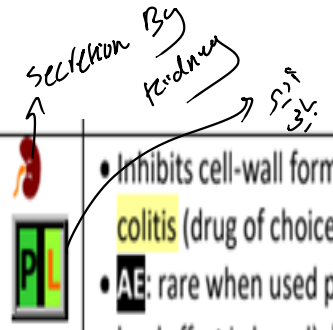
B) Continue but give antihistamines

C) Slow the infusion rate and give antihistamines

D) Increase the dose

Nursing Implications

- Before beginning therapy, assess drug allergies; hepatic, renal, and cardiac function; and other laboratory study results.
- Be sure to obtain a thorough patient health history, including immune status.
- Assess for conditions that may be contraindications to antibiotic use or that may indicate cautious use.
- Assess for potential drug interactions.
- It is *essential* to obtain cultures from appropriate sites *before* beginning antibiotic therapy.
- Instruct patients to take antibiotics exactly as prescribed and for the length of time prescribed; they should not stop taking the medication early even if they feel better.Assess for signs and symptoms of superinfection: fever, perineal itching, cough, lethargy, or any unusual discharge
- For safety reasons, check the name of the medication carefully because there are many drugs that sound alike or have similar spellings.
- Each class of antibiotics has specific adverse effects and drug interactions that must be carefully assessed and monitored.



Vancomycin VANCOCIN, g 125, 250mg cap ☎ ▼; 500 & 1000mg IV vials See *C. diff* guidelines [IDSA'21, AMMI'18] & RxFiles pg 95.	• Inhibits cell-wall formation. **Coverage**: The only oral use is for treatment of *Clostridioides* [previously *Clostridium*] *difficile* colitis (drug of choice in *most C. diff* infections; if second recurrence of *C. diff* infection, taper over ~7-13wks). • **AE**: rare when used po. **DI**: Usually no significant drug interactions. **M**: Essentially no oral absorption (used po for local effect in bowel); however, dialysis patients may require a random vancomycin level if toxicity suspected. If ↑↑ *C. diff* relapses after tx, consider Taper Regimen: Week 1&2: 125mg qid; Wk 3: 125mg TID; Wk 4: 125mg BID; Wk 5: 125mg daily; Then, 125mg q2-3days x 2-8 weeks (Total: 7-13 Wks).	**Peds**: 40mg/kg/day po divided q6h **Adult**: 125mg po q6h **Max**: 500mg po q6h if ↓BP, shock, ileus, megacolon {If severe complicated C. diff consider adding metronidazole 500mg IV q8h}	$234 $234 $856

Methenamine mandelate MANDELAMINE 500mg po q6h $34 ⊗ P L creates acidic urine; indicated for UTI prophylaxis, but not first line (limited evidence);[22] likely inefficacious in catheterized patients; **AE**: rash, GI upset, bladder irritation, ↑LFTs; **DI**: α-agonists, β-agonists, amphetamines, sulfonamides, acetazolamide, antacids; **M**: Urinalysis, periodic LFTs. **CI**: severe hepatic dysfunction, gout.

Dalbavancin XYDALBA 500mg/vial ✓≥18y ABSSSTI; coverage MSSA, MRSA, GAS, GBS, enterococcus faecalis; no gram negative. 1500mg x 1 or 1000mg day 1 then 500mg day 8, admin over 30mins. Caution: Child-Pugh Class B&C,CrCl <30.

USA: **Oritavancin** ORBACTIV 400mg/vial ✓≥18y ABSSSTI; coverage gram positive including MRSA. 1200mg x 1 IV over 3 hours; new formulation KIMYRSA decreases infusion time to 1 hour.

USA: **Lefamulin** XENLETA a pleuromutilin ABX given 600mg po ac q12h or 150mg IV q12h for CAP, also has in vitro MRSA activity but limited clinical data; **AE**: N/V/D, ↑LFTs, ↑QTc; **CI**: pregnancy; **DI**: 3A4, pgp.

Probiotics: probably effective for prevention of ABX associated diarrhea NNT~12 [Pattani'13,JAMA'12 (low quality of evidence)]; possibly for *C.difficile* associated diarrhea prevention [Cochrane'17] but [IDSA'17 → insufficient data] **CI**: immunosuppressed/critically ill. See pg 93-94.[20,21]

Question #3

A 58-year-old man is receiving vancomycin as part of the treatment for a severe bone infection. After the infusion, he begins to experience some itching and flushing of the neck, face, and upper body. He reports no chills or difficulty breathing. What should the nurse suspect?

A. An allergic reaction has occurred.
B. An anaphylactic reaction is about to occur.
C. The medication will not be effective for the bone infection.
D. The IV dose may have infused too quickly.

ANS: D

These symptoms are known as *red man syndrome* and may occur during or after an infusion of vancomycin. This syndrome is characterized by flushing or itching of the head, face, neck, and upper trunk area. Symptoms can usually be alleviated by slowing the rate of infusion to at least 1 hour. Red man syndrome is bothersome but usually not harmful. Rapid infusions may also cause hypotension.

Clinical Applications Quick Reference

- ☐ **Pneumonia:** Penicillin G, Cefotaxime, 3rd gen cephalosporins
- ☐ **Meningitis:** Ceftriaxone, Cefotaxime, Ampicillin (in children)
- ☐ **Sepsis:** 3rd/4th gen cephalosporins, Carbapenems
- ● **UTI:** Amoxicillin, Ampicillin, 1st gen cephalosporins
- ☐ **MRSA :** Vancomycin, newer agents (Daptomycin, Linezolid)
- ☐ **C. difficile :** Vancomycin (oral), Metronidazole

Lipoglycopeptides

- ***Telavancin* , *oritavancin*, and *dalbavancin***

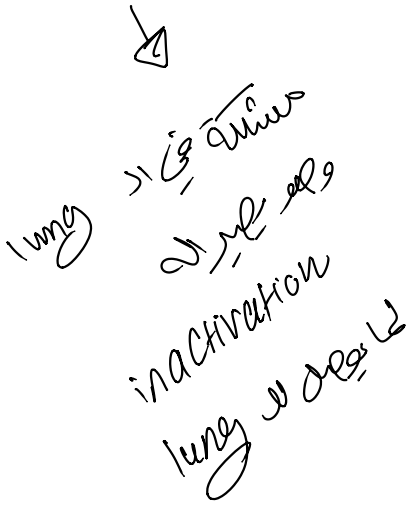
- gram-positive bacteria

- They are more potent than *vancomycin* and may have activity against *vancomycin*-resistant isolates.

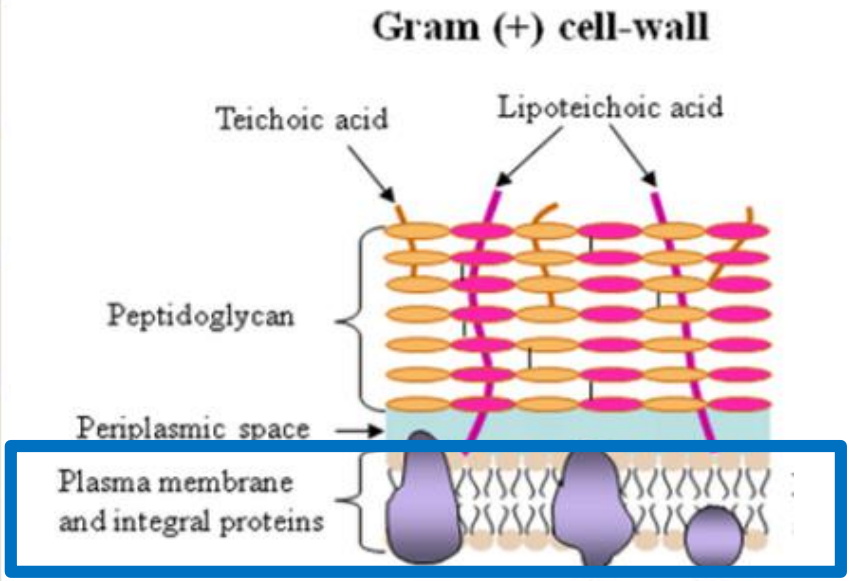
- *Telavancin* in clinical practice may be limited by its adverse effect profile, which includes nephrotoxicity, risk of fetal harm, and interactions with medications known to prolong the QTc interval

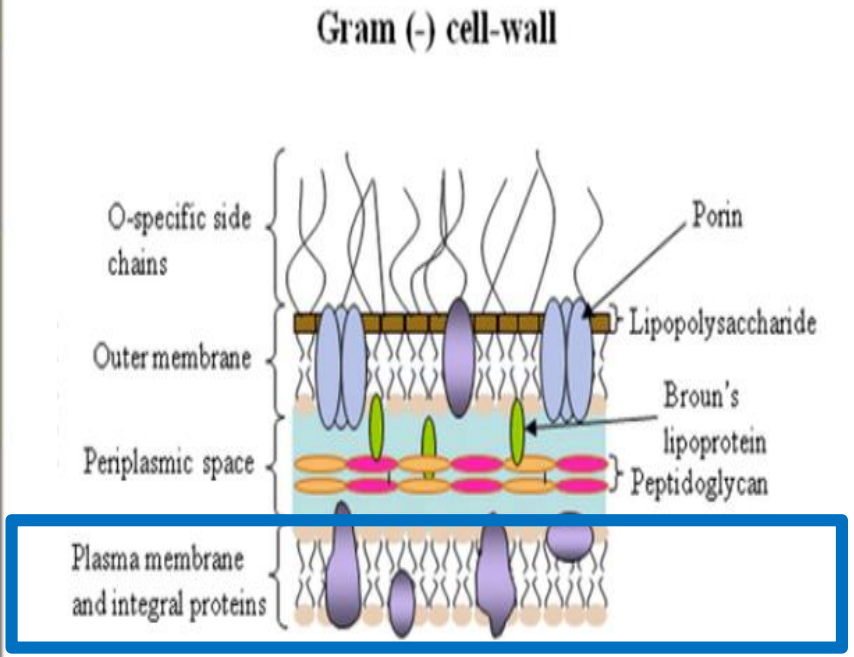
Daptomycin

- Resistant gram-positive organisms, including MRSA and *vancomycin*-resistant enterococci (VRE)
- *Daptomycin* is inactivated by pulmonary surfactants; thus, it should *never* be used in the treatment of pneumonia.
- *Daptomycin* is dosed **IV** once daily.



	VANCOMYCIN	DAPTOMYCIN	TELAVANCIN
Mechanism of Action	Inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization	Causes rapid depolarization of the cell membrane, inhibits intracellular synthesis of DNA, RNA, and protein	Inhibits bacterial cell wall synthesis; disrupts cell membrane
Pharmacodynamics	Time dependent Bactericidal	Concentration dependent Bactericidal	Concentration dependent Bactericidal
Common Antibacterial Spectrum	Activity limited to gram-positive organisms: Staphylococcus aureus (including MRSA), Streptococcus pyogenes, S. agalactiae, penicillin-resistant S. pneumoniae, Corynebacterium jeikeium, *vancomycin*-susceptible Enterococcus faecalis, and E. faecium		
Unique Antibacterial Spectrum	Clostridium difficile (oral only)	*Vancomycin*-resistant E. faecalis and E. faecium (VRE)	Some isolates of *vancomycin*-resistant enterococci (VRE)
Route	IV/PO	IV	IV
Typical Administration Time	60- to 90-minute IV infusion	2-minute IV push 30-minute IV infusion	60-minute IV infusion
Pharmacokinetics	Renal elimination Normal half-life: 6–10 hours Dose is adjusted based on renal function and serum trough levels	Renal elimination Normal half-life: 7–8 hours Dose is adjusted based on renal function	Renal elimination Normal half-life: 7–9 hours Dose is adjusted based on renal function
Unique Adverse Effects	Infusion related reactions due to histamine release: Fever, chills, phlebitis, flushing (red man syndrome); dose-related ototoxicity and nephrotoxicity	Myalgias, elevated hepatic transaminases and creatine phosphokinases (check weekly), and rhabdomyolysis (consider holding HMG-CoA reductase inhibitors [statins] while on therapy)	Taste disturbances, foamy urine, QTc prolongation, interferes with coagulation labs (PT/INR, aPTT, ACT), not recommended in pregnancy (box warning recommends pregnancy test prior to initiation)
Key Learning Points	Drug of choice for severe MRSA infections; oral form only used for C. difficile infection; resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of *vancomycin* to receptor molecules; monitor serum trough concentrations for safety and efficacy	*Daptomycin* is inactivated by pulmonary surfactants and should never be used in the treatment of pneumonia	Use with caution in patients with baseline renal dysfunction (CrCl < 50 mL/min) due to higher rates of treatment failure and mortality in clinical studies; any necessary coagulation labs should be drawn just prior to the *telavancin* dose to avoid interaction





Fosfomycin, Bacitracin & Polymyxins

Three Unique Antibiotic Classes

Fosfomycin

Phosphonic acid derivative
Broad-spectrum bactericidal

Bacitracin

Polypeptide antibiotic
Topical gram-positive coverage

Polymyxins

Cationic polypeptides
Last-resort MDR therapy

Learning Objectives

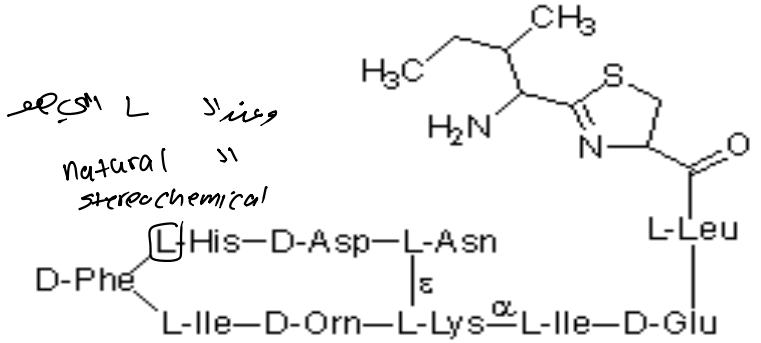
- Understand unique mechanisms of action for each antibiotic class
- Identify appropriate clinical applications and limitations
- Recognize important toxicity profiles and monitoring requirements
- Apply knowledge of resistance patterns in clinical decision-making

These antibiotics represent distinct mechanisms of action and clinical applications in modern antimicrobial therapy.

Bacitracin (RESERVE ANTIBIOTICS)

Bacitracin is a cyclic **lipopeptide** produced by fermentation of *Bacillus subtilis*.

Some of its amino acids belong to the **D**-stereochemical family; The presence of **Zn ion** enhances its activity.



Bacitracin A

Commercial bacitracin is a mixture of **three related substances**, A, B and C. Component A is the major one.

Used topically or parenterally mainly;
water and alcohol soluble.

Sterile solid preparations are reasonably stable but its solutions deteriorate rapidly by oxidation at room temperature so should **be refrigerated** and its solutions should not be kept for more than a week.

Solutions of bacitracin are neutral to slightly acidic.

Bacitracin precipitates when mixed with many heavy metal salt solutions and benzoates, tannins, salicylates, and some detergents inactivate it so **admixtures must be made with care**.

Bacitracin - Properties

- **Bacitracin** is bactericidal or bacteriostatic depending on the organism exposed to it and the effective concentration to which bacteria are exposed;
- Very little bacterial resistance is seen when bacitracin is used against susceptible microorganisms.
- **Bacitracin** is occasionally used for refractory infections caused by Gram-positive microorganisms but beta-lactams or vancomycin are preferred when possible.
- Oral bacitracin is occasionally used for treatment of pseudomembranous colitis.
- **Bacitracin** interferes with bacterial cell wall formation at a late step in the sequence - probably at the dephosphorylation step of the phospholipid carrier.
- Bacitracin also damages bacterial plasma membranes.

Bacitracin is not absorbed from the GI tract but is rapidly and well absorbed following IM injection wherefore it is widely distributed in the body except for the CNS.

The drug is excreted in the urine following injection and in the feces following oral use.

Systemic use of bacitracin is associated with

1. severe renal tubule and glomerular necrosis, and nausea, vomiting, diarrhea and skin rashes also are seen.
2. Occasionally neurotoxicity involving neuromuscular blockade involving respiratory depression is also seen.

Question #5

The nurse identifies Zosyn as being a member of which group?

A. Cephalosporins
B. Macrolides
C. Penicillins
D. Sulfonamides

ANS: C

Zosyn is a penicillin. The nurse should be aware of the fact that many times, these drugs are referred to by their trade names and do not always end in “cillin,” such as with Zosyn and Augmentin.

Fosfomycin

Fosfomycin MONUROL, g 3g oral powder sachet New: 2, 4 & 8g IV vials ✗ ⊗ • No renal dosing required x 1 dose • Usually no significant DI	PL	• Inhibits cell-wall formation. Bactericidal. **Coverage**: *Enterobacterales; Enterococci; ?Staphylococci.* Often coverage even if multi-drug resistance (ESBL-producing organisms, *Pseudomonas*, VRE). • **Useful in**: Uncomplicated cystitis, but reserve for allergy or resistance to nitrofurantoin or TMP/SMX. Avoid if suspected pyelonephritis or complicated UTI. Safe in pregnancy but usually better options. Prostatits. • AE: GI upset, diarrhea, headache, hypokalemia. Significant adverse effects rare with short-course use.	**Peds**: 2000mg x 1 dose po Sanfords **Adult**: 3g x 1 dose po **on empty stomach** **Max**: 3g x 1 dose Administration: dissolve sachet in ½ cup water	$26 $26 $26

Inhibits the enzyme enolpyruvyl transferase, a key step in peptidoglycan synthesis

It is indicated for urinary tract infections caused by E. coli or E. faecalis and is considered first-line therapy for acute cystitis

The drug is excreted in its active form in the urine and maintains high concentrations over several days, allowing for a one-time

ميزته إنه لمرة واحدة فقط

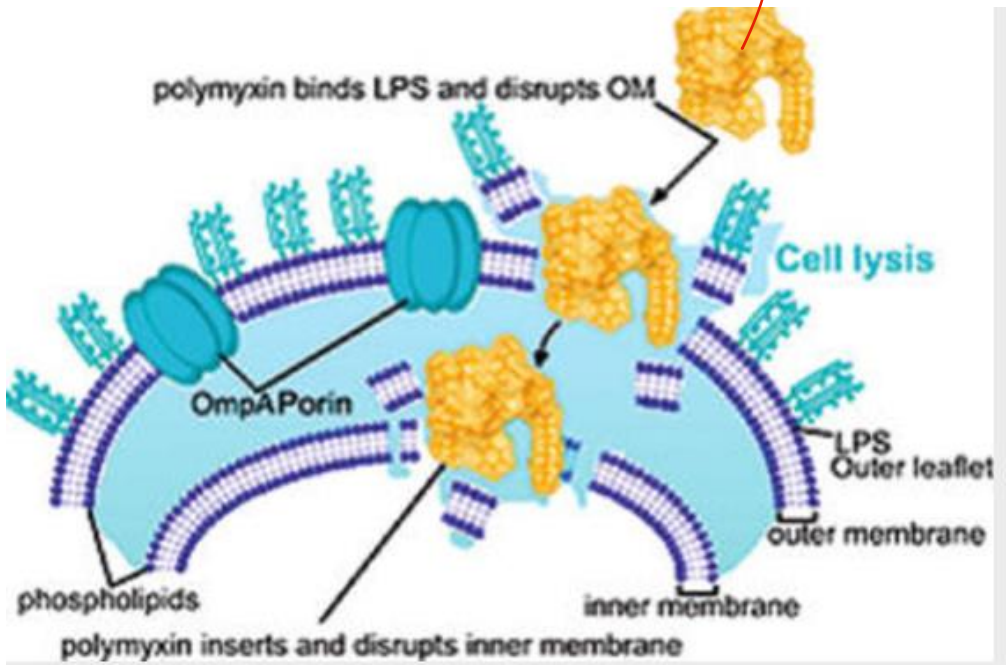
ونقطة لحاظ على تركيزه في الجسم لأكثر من يوم

Polymyxins

Cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria

***polymyxin B* and *colistin* (*polymyxin E*)**

- Gram-negative bacteria, including P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter spp., and Enterobacter spp
- *Colistin* is only available as a prodrug, *colistimethate sodium*, which is administered IV or inhaled via a nebulizer
- The use of these drugs has been limited due to the increased risk of nephrotoxicity and neurotoxicity (for example, slurred speech, muscle weakness)
- Salvage therapy for MDR



Antibiotics During Pregnancy/Lactation		Safe / Likely Safe / Caution / Contraindicated			
		1st Trimester	2nd Trimester	3rd Trimester	Lactation
PEN	Amoxicillin ± clav / Ampicillin	?cleft lip/palate ≤0.4%			(with clavulanate)
	Cloxacillin / Penicillin V				
CEPHALOSPORINS					

ABX against MRSA

CLean ur VaLiD Dox e Carolina Cotton Toy

CL = Clindamycin

Va = Vancomycin Li = Linezolid D = Daptpmycin

Dox = Doxycycline

Carolina = Ceftaroline

Cotton = Cotrimaxazole

T = Tigacycline

🎓 Final Challenge!

Which statement about cell wall inhibitors is MOST accurate?

A) They are all bacteriostatic

B) They are generally bactericidal and time-dependent

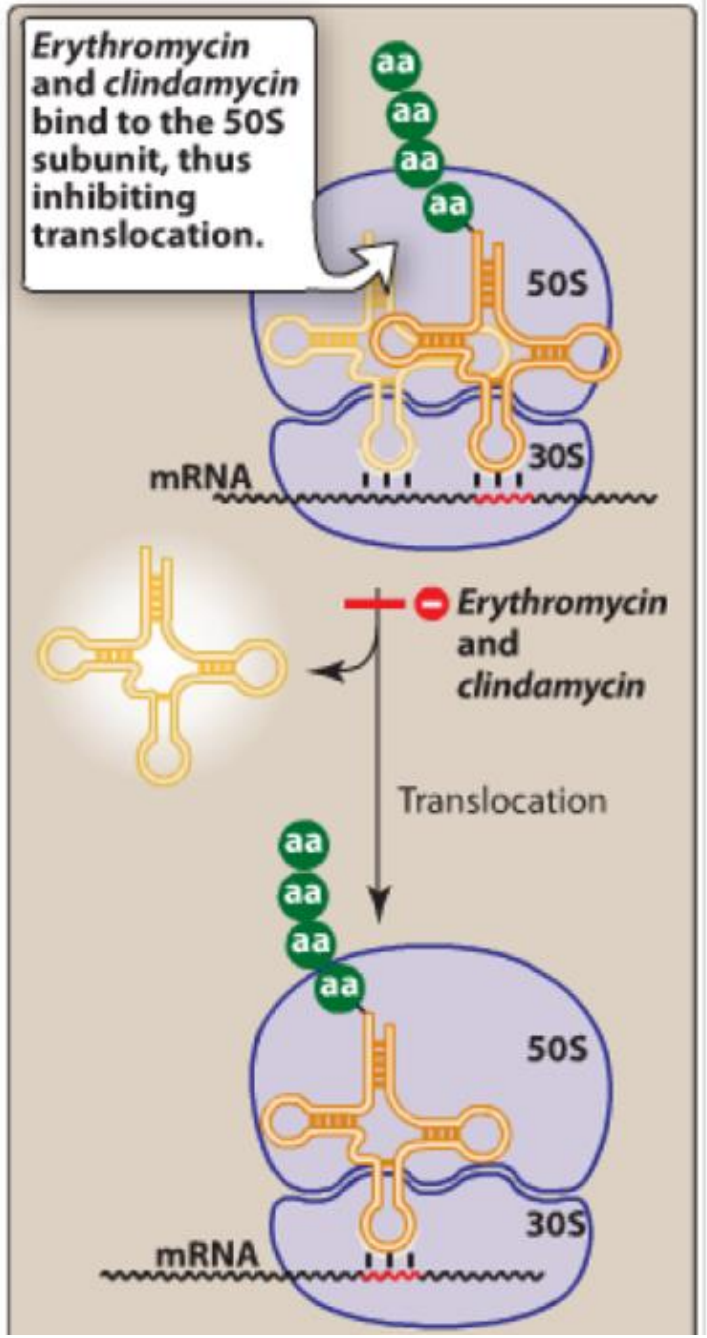
C) They work best against non-growing bacteria

D) They have no cross-resistance patterns

Correct Answer: B - They are generally bactericidal and time-dependent
Cell wall inhibitors kill bacteria (bactericidal) and their effectiveness depends on time above MIC, not peak concentration!

What is NEXT?

PROTEIN SYNTHESIS INHIBITORS







Thank you



"Tell me and I forget; teach me and I may remember; but involve me and I learn."

Benjamin Franklin



General Pharmacology

GENERAL PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY

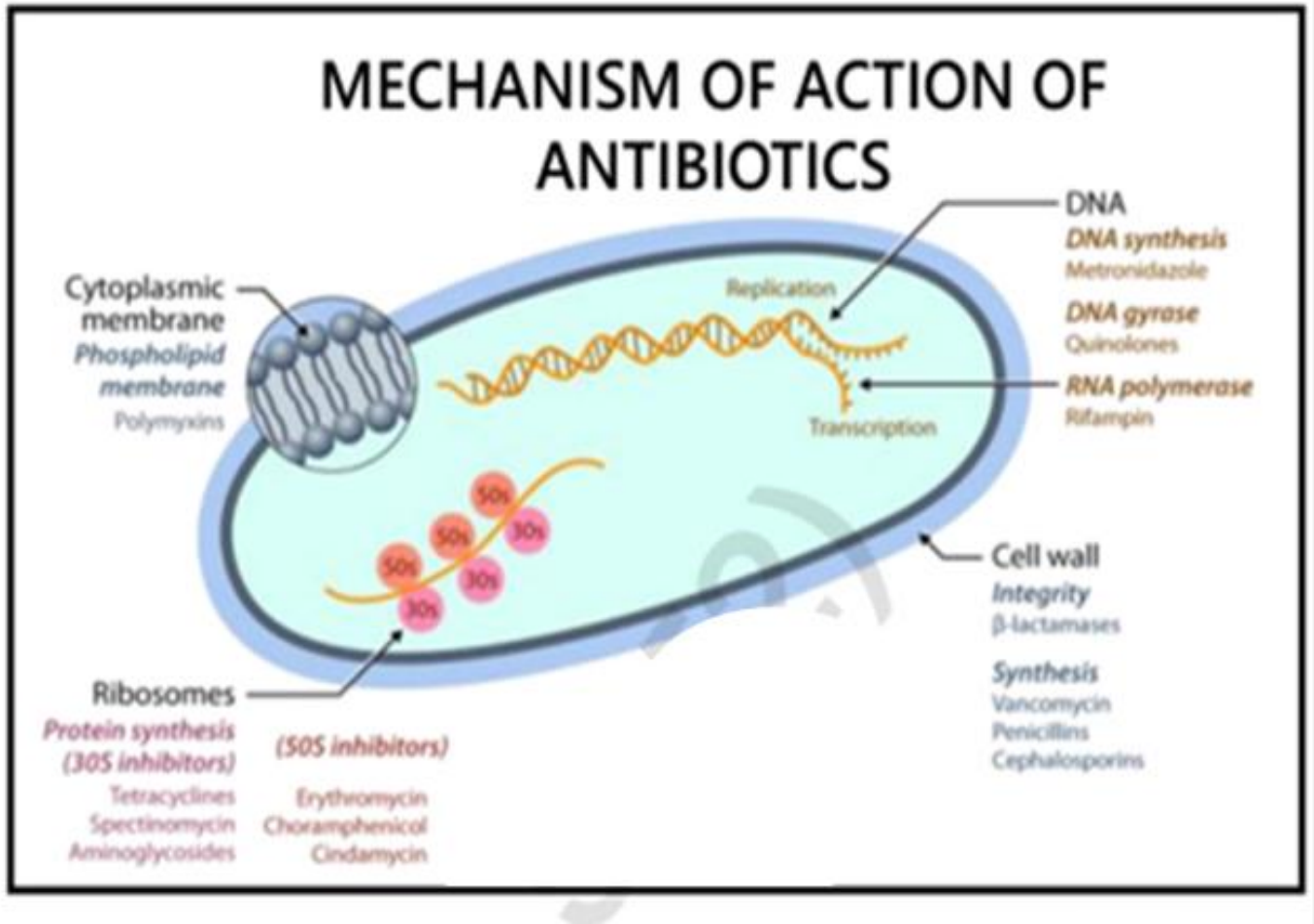
2025

Esmaa Motawe

interdisciplinary PhD in Pharmacology &Toxicology/ Pharmaceutical Sciences

Antibiotic Therapy: Mechanism of Action

- Interference with cell wall synthesis
- **Interference with protein synthesis**
- Interference with DNA replication
- Acting as a metabolite to disrupt critical metabolic reactions inside the bacterial cell



Cell Wall Inhibitors

Penicillins
Cephalosporins
Carbapenems,
Glycopeptides
Beta Lactam-Beta Lactamase Inhibitors
Daptomycin
Fosfomycin

Protein Synthesis Inhibitors

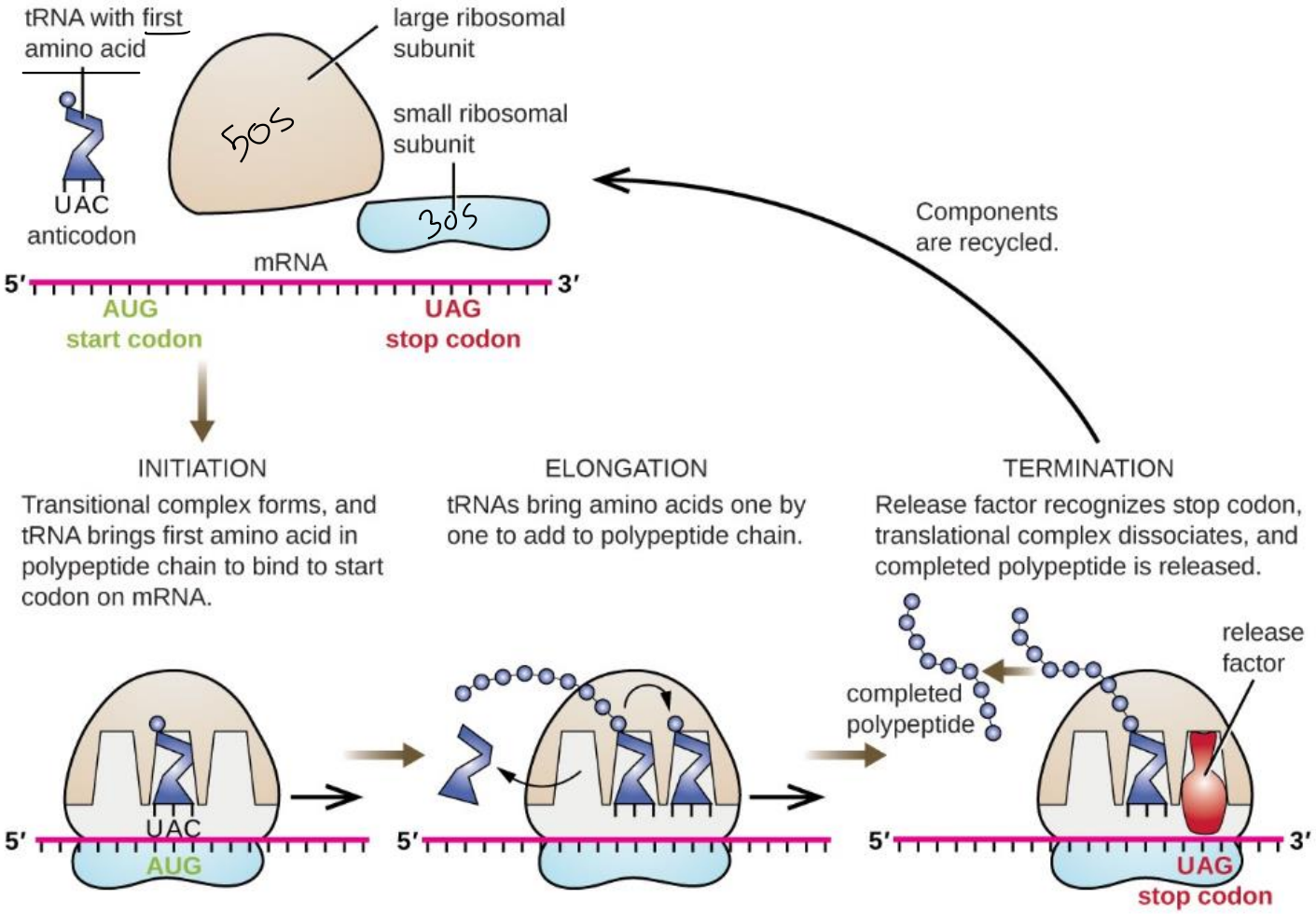
Macrolides
Aminoglycosides
Tetracyclines/Glycylcyclines
Clindamycin
Linezolid

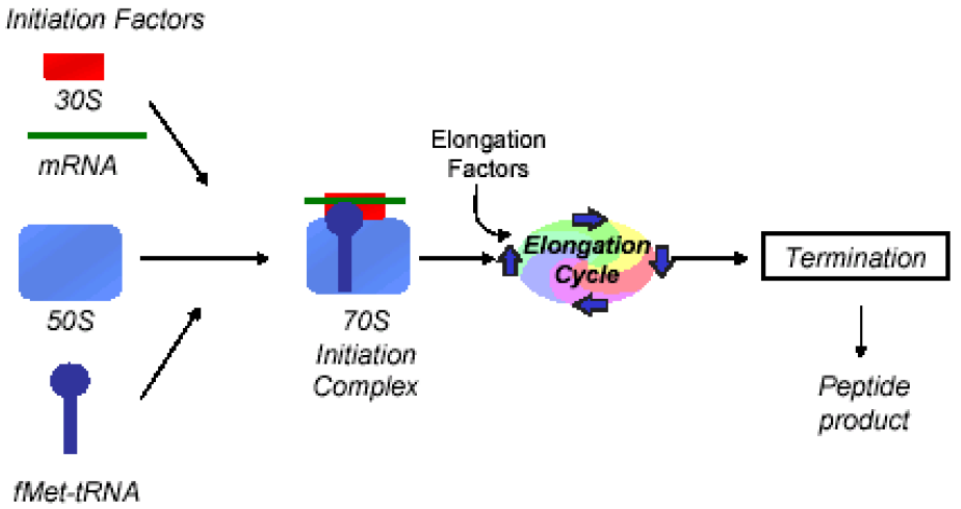
PROTEIN SYNTHESIS INHIBITORS

Learning Objectives:

Understand mechanisms, spectrum, pharmacokinetics, and clinical applications of major protein synthesis inhibitors







Protein synthesis (30S ribosomes)
Inhibitors

AT 30 (AMG and Tetracyclines)

Protein synthesis (50S ribosomes)
Inhibitors

Mastering the Art of Stopping Bacterial Translation

50S Subunit + 30S Subunit = 🎯 TARGET

Demeclocycline DECLOMYCIN
Doxycycline DORYX, VIBRAMYCIN
Minocycline MINOCIN
Tetracycline GENERIC ONLY

GLYCYLCYCLINES

Tigecycline TYGACIL

AMINOGLYCOSIDES

Amikacin GENERIC ONLY
Gentamicin GENERIC ONLY
Neomycin GENERIC ONLY
Streptomycin GENERIC ONLY
Tobramycin TOBI, TOBREX

MACROLIDES/KETOLIDES

Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin E.E.S., ERY-TAB
Telithromycin GENERIC ONLY

MACROCYCLIC

Fidaxomicin DIFICID

LINCOSAMIDES

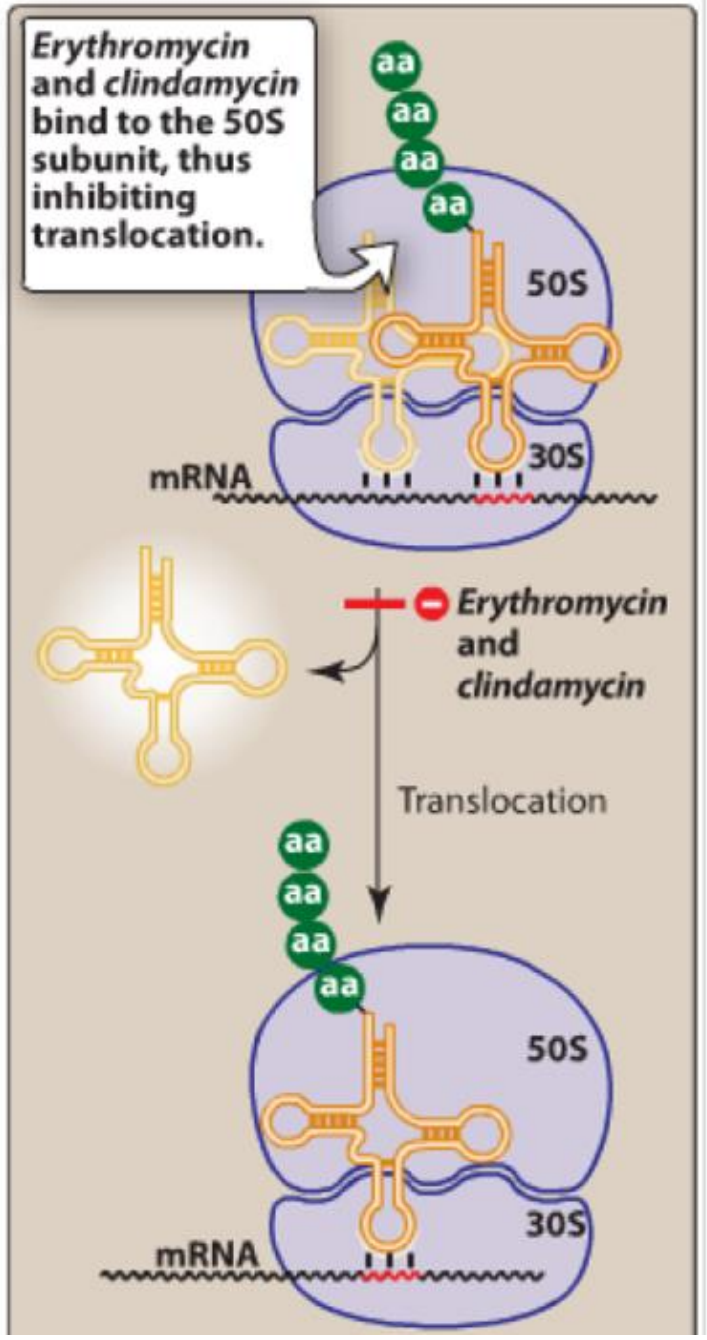
Clindamycin CLEOCIN

OXAZOLIDINONES

Linezolid ZYVOX
Tedizolid SIVEXTRO

OTHERS

Chloramphenicol GENERIC ONLY
Quinupristin/Dalfopristin SYNERCID



📚 Major Categories

Five Key Classes of Protein Synthesis Inhibitors

Macrolides
50S Ribosome
Erythromycin, Azithromycin, Clarithromycin

Aminoglycosides
30S Ribosome
Gentamicin, Tobramycin, Amikacin

Others
Various Targets
Chloramphenicol, Linezolid

Lincosamides
50S Ribosome
Clindamycin

Tetracyclines
30S Ribosome
Doxycycline, Minocycline

🤔 **Think About It:**

Why do you think most protein synthesis inhibitors are bacteriostatic rather than bactericidal?

لأن الـ Bacteriostatic طالما بوقفوا نمو البكتيريا ومابيخلي تنمو وبوقف نشاط البكتيريا ولما نوصل لهون بروح نوصل لفوق cell wall
والـ Bacteriostatic بحتاجوا على الـ dose ∴ الـ Bacteriostatic للاعطاء بنفس الـ dose Bactericidal
بالتعريف بالبنية أخف على الإنسان
وهذا أفضل
أغلب وليس الكل

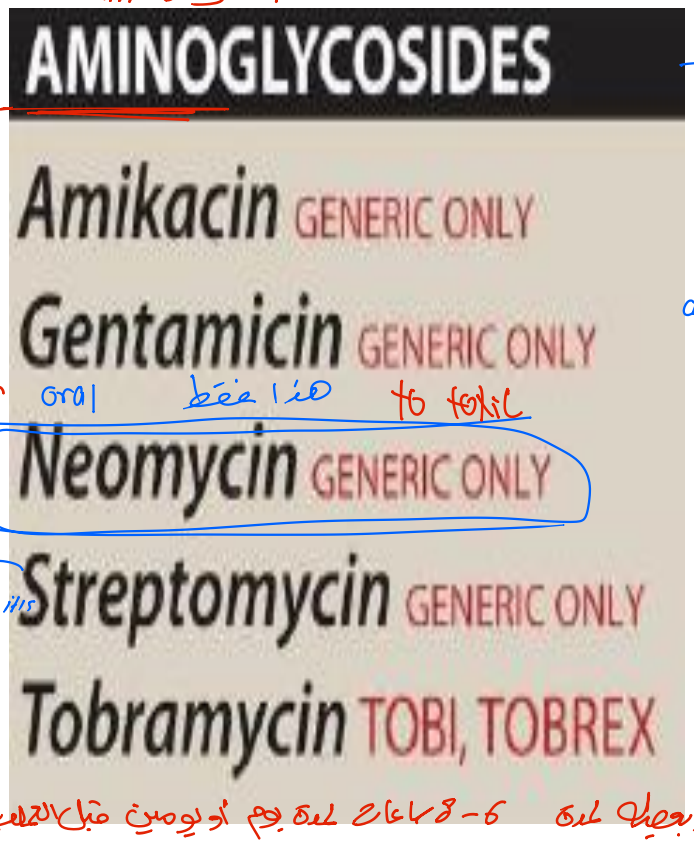
AMINOGLYCOSIDES(AMG): X-mycin OR X-micin *Concentration-Dependent Killers*

cellular function

production, Growth, maintinance مع في الحفاظ على الـ Protein وال Protein synthesis inhibitors تعني لـ

∴ لما أمنع تكون البروتينات راح يؤثر على حياة البكتيريا

amino group



يحتوي على سكر water soluble drug ∴

absorption وصاح يعبر الـ membranes مثل الـ

local or oral هذا فقط to toxic

Oral يعني ما في منوع

T.B maningitis
X pregnancy

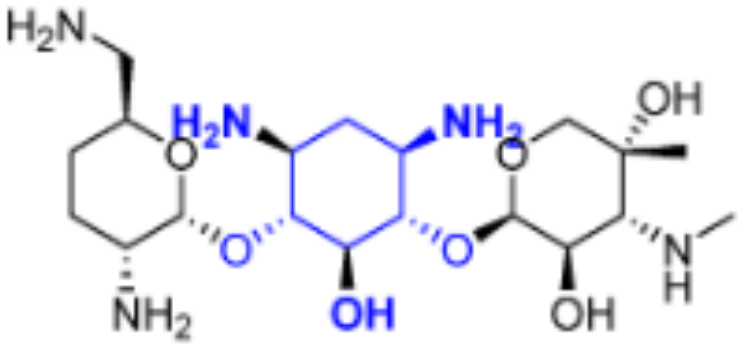
neomycin orally إذا كان يعطى الـ absorption عليه ضعيفة اكثر شي مثلا عشان يعبر orally normal flora بس عشان يثبط وبعطيه لمدة 6-8 أسابيع لمدة يوم أو يومين قبل العملية

Aminoglycosides include: TANGS:

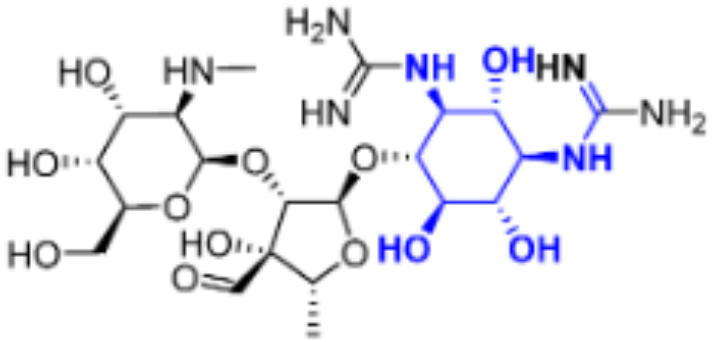
Tobramycin
Amikacin
Neomycin
Gentamicin
Streptomycin

أغلب الـ Bacteriostatic يربط البكتيريا مع reversibaly

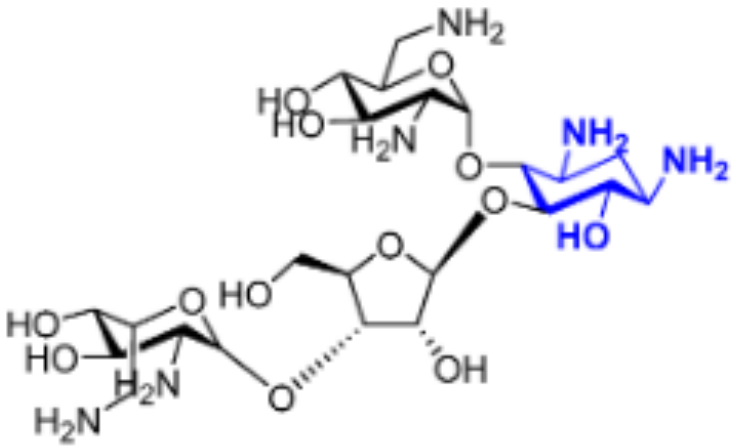
+kanamycin



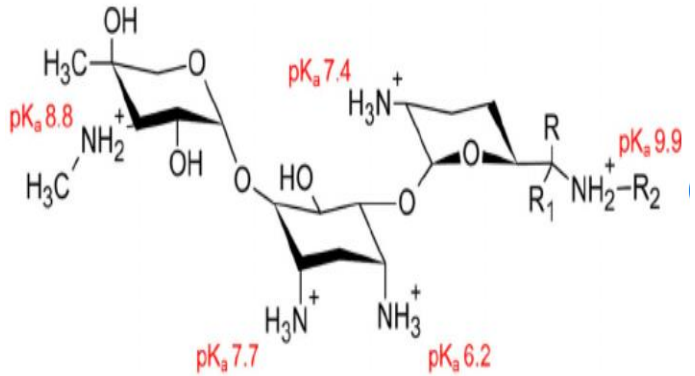
Gentamicin

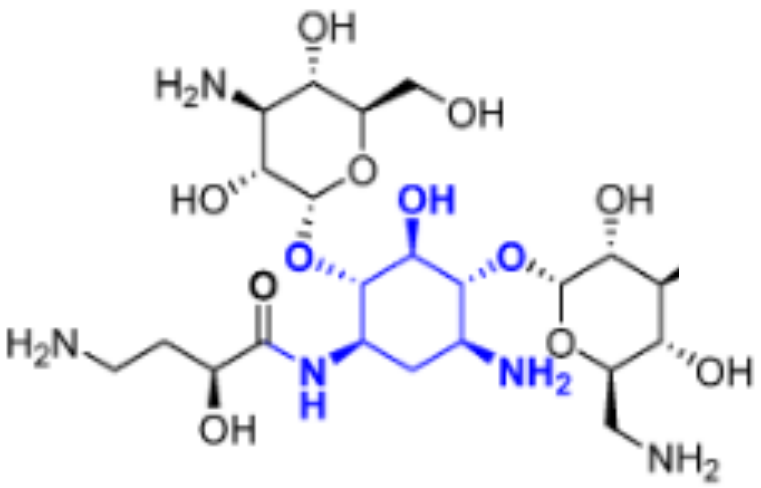


Streptomycin

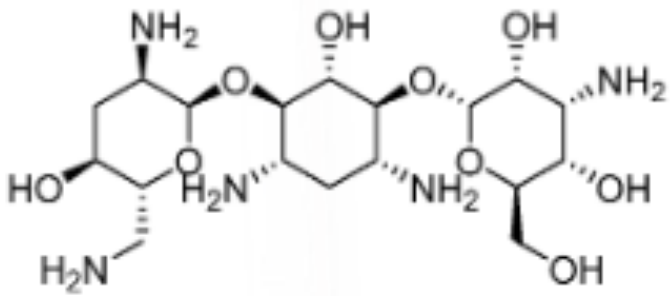


Neomycin B





Amikacin



Tobramycin

AMINOGLYCOSIDES(AMG):

🎯 Unique Features

interfering with protein synthesis inhibitors

- **Target:** 30S ribosome + misreading of mRNA
- **Activity:** BACTERICIDAL (concentration-dependent)
- **PAE:** Post-antibiotic effect present
- **Synergy:** With β-lactams against Gram-positives

AMINO:
Against **A**erobic gram negatives
Mainly bactericidal
Inhibit protein synthesis at 30s subunit
Nephrotoxic
Ototoxic

Gentamicin Most common Gram-negative coverage	**Tobramycin** Anti-Pseudomonas Inhaled for CF	**Amikacin** Broadest spectrum Resistant to most enzymes	**Streptomycin** Anti-TB Historical importance

sugar (water soluble)

💎 **Clinical Pearl:** Remember: Aminoglycosides are polar cations - they DON'T cross cell membranes well, requiring IV/IM administration!

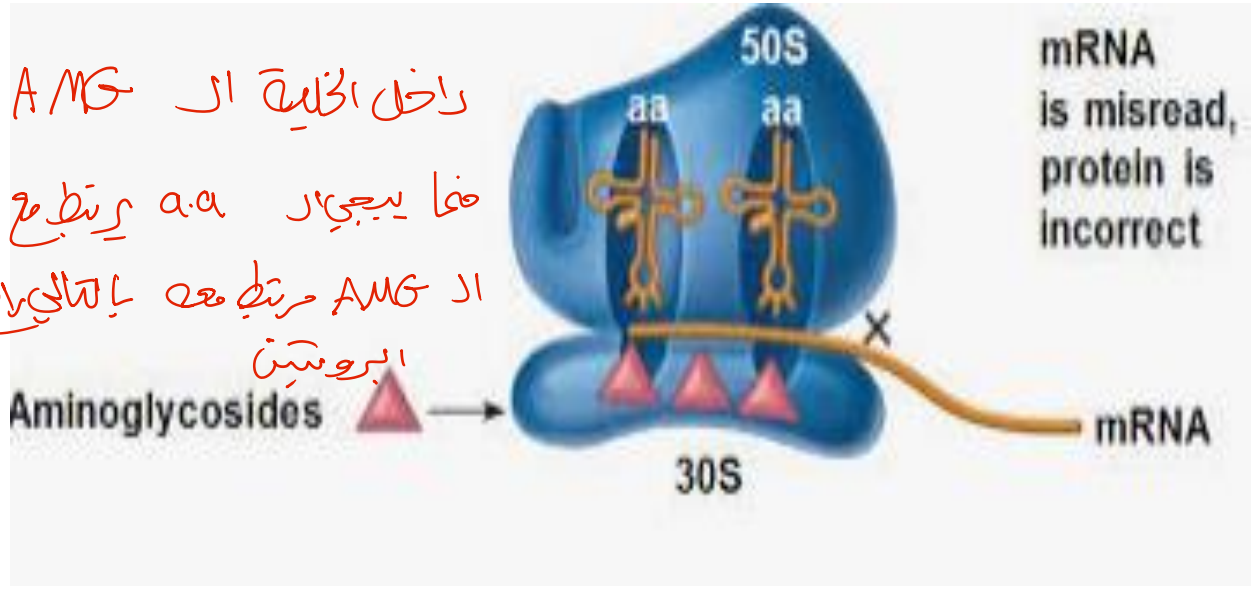
NOT ORAL

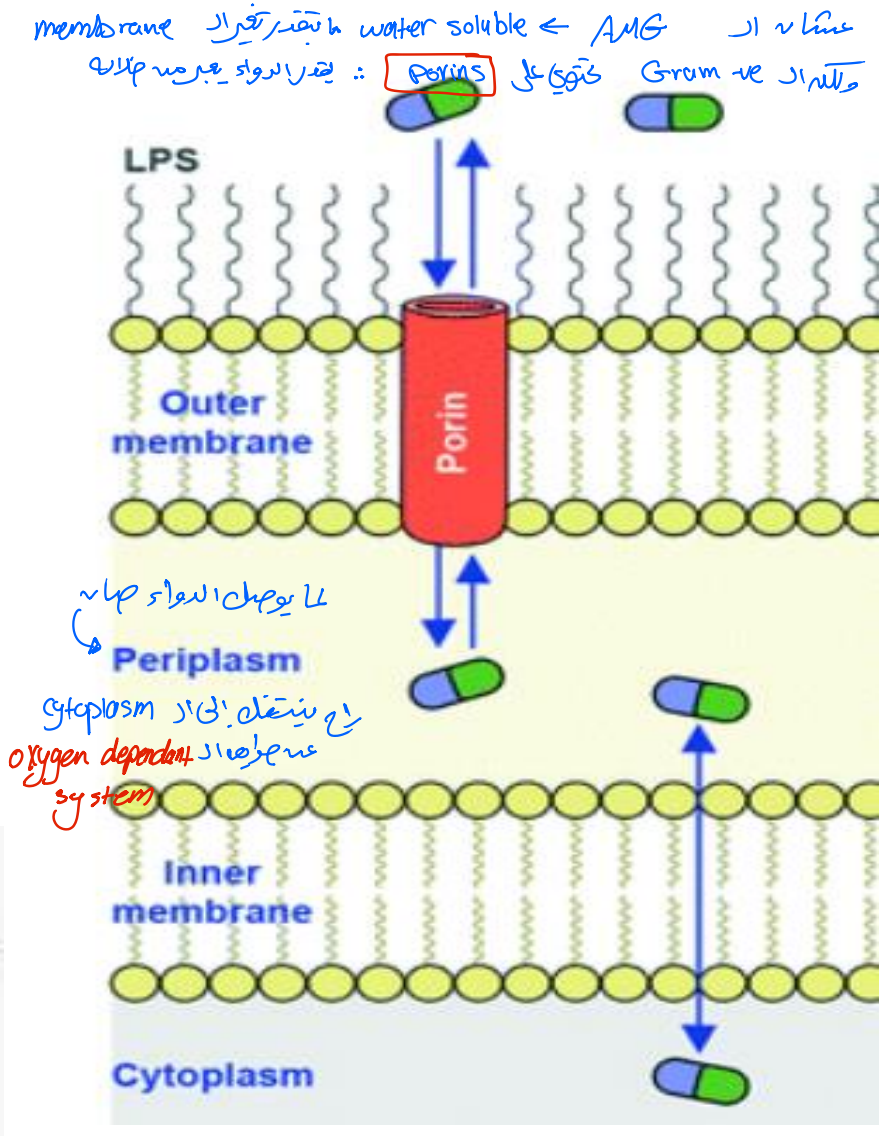
Mechanism of action

AMG diffuse through porin channels in the outer membrane of susceptible organisms.

Have an oxygen-dependent system that transports the drug across the cytoplasmic membrane.

Inside the cell, they bind the 30S ribosomal subunit, where they interfere with assembly of the functional ribosomal apparatus and/or cause the 30S subunit of the completed ribosome to misread the genetic code

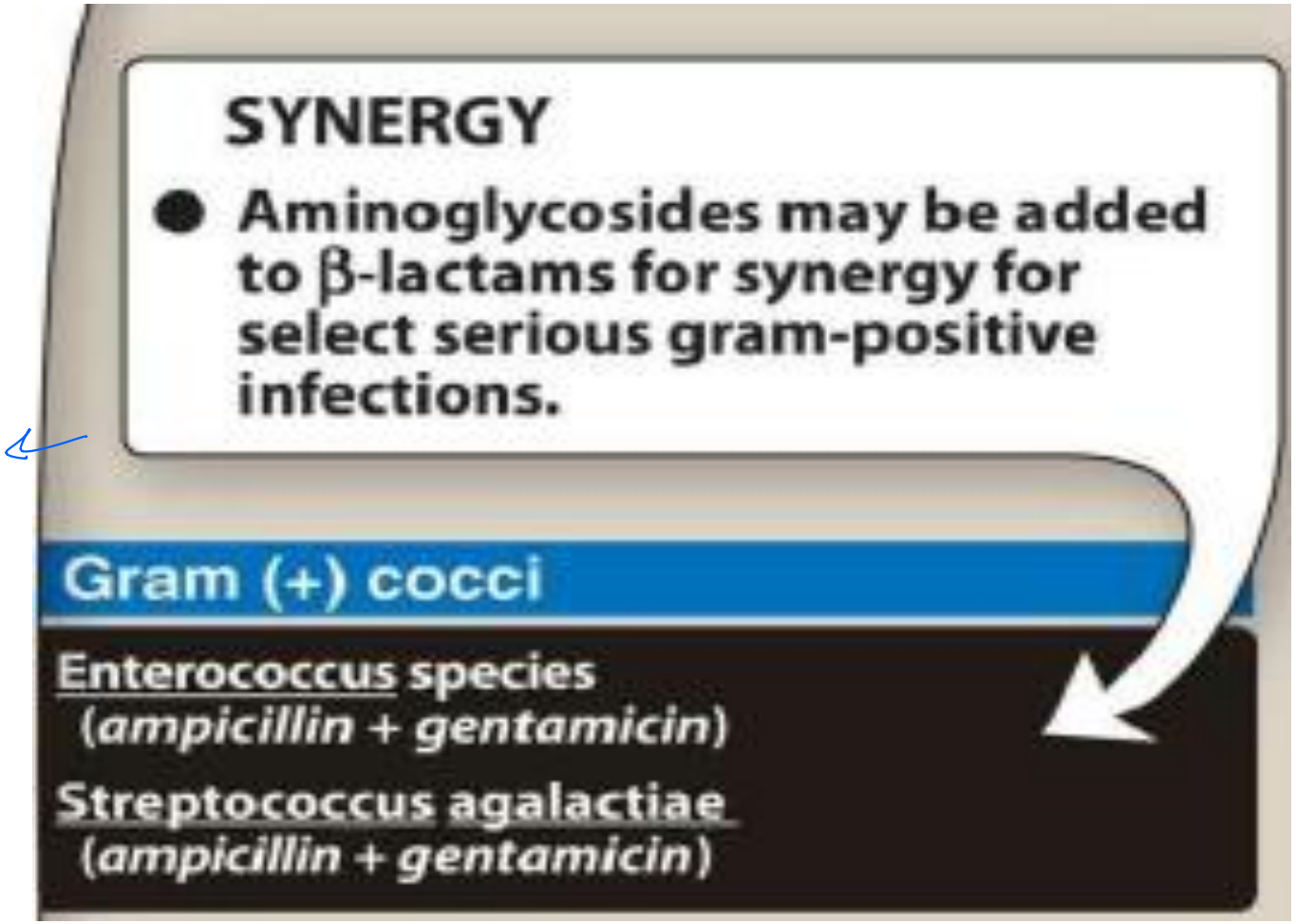




Antibacterial spectrum

Multi Drug Resistance

- **Aerobic gram-negative bacilli, including those that may be MDR**
- Pseudomonas aeruginosa
- Klebsiella pneumoniae
- Enterobacter sp.



تشتغل على الـ G+ve فقط إذا أخذناه مع الـ β-lactam

كيف؟ راح يصير synergy حيث إنه الـ β-lactam راح ترتبط في الـ cell-wall وتكسره بالتالي الـ AMG تنفذ وتقتل الخلية

Serious Gram +ve Activity وصارت

mechanism of action هاد بتختلف عن timing concentration dependent

عبارة عن Adverse effect لو قلنا انه (هدرش إني أنا معطية الدواي)

١- تعتمد على المدة

٢- تعتمد على التركيز

Adverse effects

Side effects of Aminoglycosides include:

remember of NANO:

Neurotoxicity

Allergic reactions

Nephrotoxicity

Ototoxicity

AMG Toxicity

High Risk, High Reward

Balance يؤثر على ال
Streptomycin, Gentamycin
most toxic يؤثر على السمع
kanamycin, neomycin, Amikacin

irreversible ← يكون غالبًا

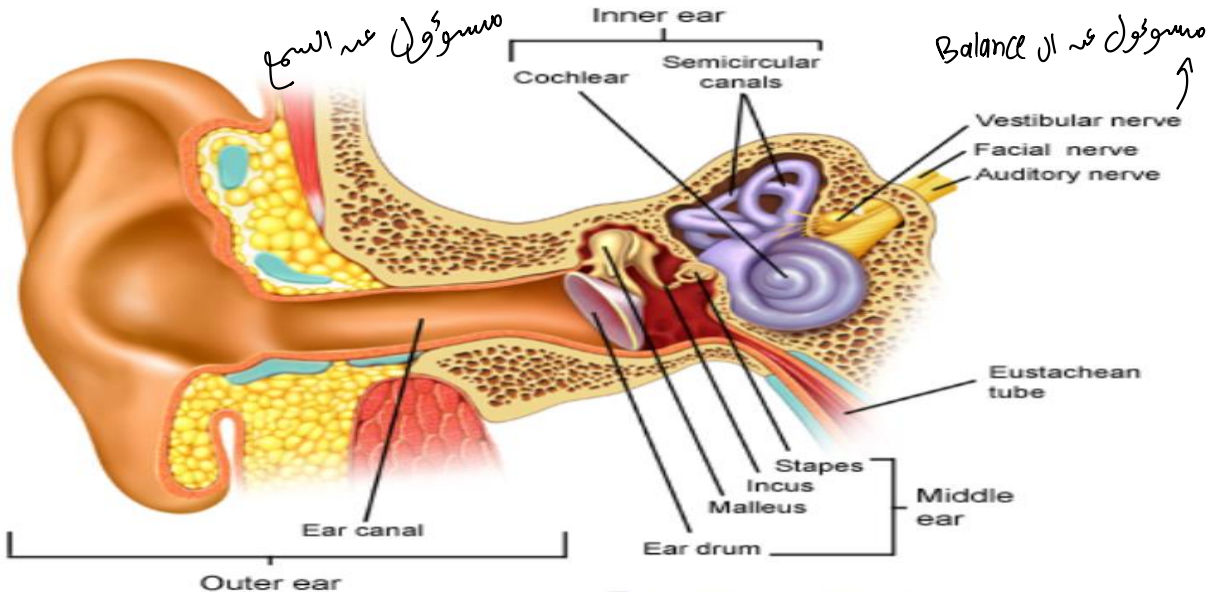
Ototoxicity

- Destruction of hair cells in cochlea
- Can affect hearing AND balance
- May be irreversible
- Risk factors: high dose, prolonged therapy

* أكثر من 5 أيام *

concomyen واعطيه جرعة كبيرة, اذا المريض عنده renal dysfunction أعطه أدوية ثانية زيادة ototoxic أدوية أخرى تقتل

Ototoxicity (vestibular and auditory)



- AMG accumulate in the endolymph and perilymph of the inner ear. (mechanism of action)
- Deafness may be irreversible and has been known to affect developing fetuses.
- Patients simultaneously receiving concomitant ototoxic drugs, such as *cisplatin* or loop diuretics

cancer ال ototoxicity أدوية تقتل ال

وممكن يعطيك (طنين الأذن) tennitis راح يقل ال سمعي فقدان السمع



Nephrotoxicity

- Acute tubular necrosis (ATN)
- Usually reversible if caught early
- Monitor creatinine closely → trough + peak بأخذينة عشان
  - trough: قبل الجرعة الثانية بساعتين تقريبًا
  - peak: بعد ما أعطي الجرعة بشوي
- Dose adjustment needed

عشان نعرف عالأغلب المريض راح AKI يزعل

creatinine وشوف نسبة kidney function أعمل فحص دم

CATC)

- Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes. راح يتجمع في الـ proximal tubule
- This results in kidney damage ranging from mild, reversible renal impairment to severe, potentially irreversible acute tubular necrosis

Nephrotoxicity

وكمان لو أخذت مع أدوية أخرى بتعمل nephrotoxicity



Penicillin, cephalosporin, vancomycin, NASID + Maghnesium

Table 53.1: Comparative toxicity of aminoglycoside antibiotics (tentative)

Systemically used aminoglycoside	Ototoxicity		Nephrotoxicity
	vestibular	cochlear	
1. Streptomycin	++	±	+
2. Gentamicin	++	+	++
3. Kanamycin	+	++	++
4. Tobramycin	+±	+	+
5. Amikacin	+	++	++
6. Sisomicin	++	+	++
7. Netilmicin	+	+	++

Neomycin → most nephrotoxicity

Neuromuscular paralysis

- Associated with a rapid increase in concentration (high doses infused over a short period) or concurrent administration with neuromuscular blockers.
- Patients with myasthenia gravis are particularly at risk.

لو اديتي neostagmin بتروح الأعراض

Paralysis



Allergic reactions

- Contact dermatitis is a common reaction to topically applied *neomycin.*

حكة

Skin rash



AMG (PK/PD)

(Dose dependent)

AMINOGLYCOSIDES DOSING CONSIDERATIONS

- Administer every 8-24hours for synergy (G+ve) and as treatment (G-ve).
- Must monitor pre (“trough”) & post (“peak”) levels when multiple daily dosing used
- Trough levels only are required for extended once daily dosing
- Achieve high peak serum levels to ensure efficacy for serious gram negative bacterial infection
- Aminoglycosides are most commonly known for PAE against gram negative organisms

ONCE DAILY DOSING

interval ... dose adjusment ...

- PAE makes it possible for less frequent dosing
- Avoid once daily dosing in pregnant patients, severe renal impairment, cirrhosis, burns
- Advantage of once daily dosing: no need for peak levels, less risk of nephrotoxicity, similar efficacy for most infection (see above exceptions) ↑ compliant
- Disadvantage: Associated with higher risk for ototoxicity compared to multiple daily dosing (if used long term)

Clinical Scenario

- **You're treating a 70-year-old diabetic with gentamicin for a serious Gram-negative infection. On day 4, creatinine rises from 1.2 to 1.8 mg/dL. What's your next move?**

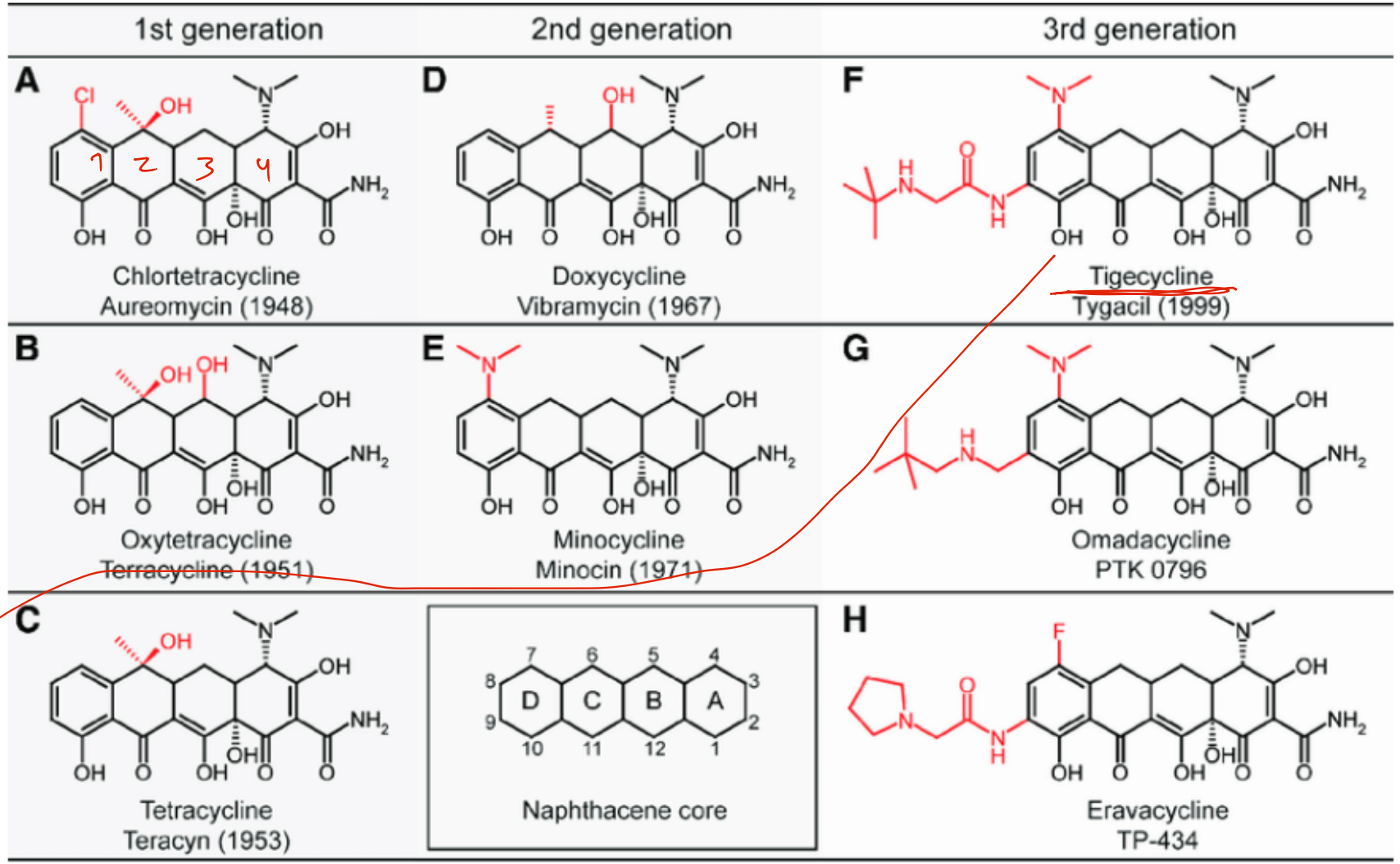
1. A) Continue same dose, recheck tomorrow
2. B) Reduce dose based on new creatinine clearance
3. C) Stop gentamicin immediately
4. D) Add furosemide to increase urine output

Monitoring: Peak and trough levels, daily creatinine, baseline audiometry for prolonged therapy

TETRACYCLINES: *Broad-Spectrum Workhorses*

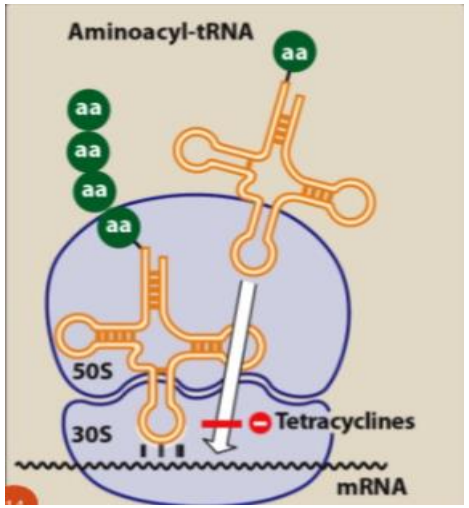
Demeclocycline DECLOMYCIN
Doxycycline DORYX, VIBRAMYCIN
Minocycline MINOCIN
Tetracycline GENERIC ONLY

- The first tetracycline was discovered was discovered in 1948
- Doxycycline and minocycline are the most frequently prescribed
- ~~Tetracycline~~>>> glycylcyclines



Mechanism of Action

- **Target:** 30S ribosomal subunit: Concentrate intracellularly in susceptible organisms. The drugs bind reversibly to the 30S subunit of the bacterial ribosome.
- This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis

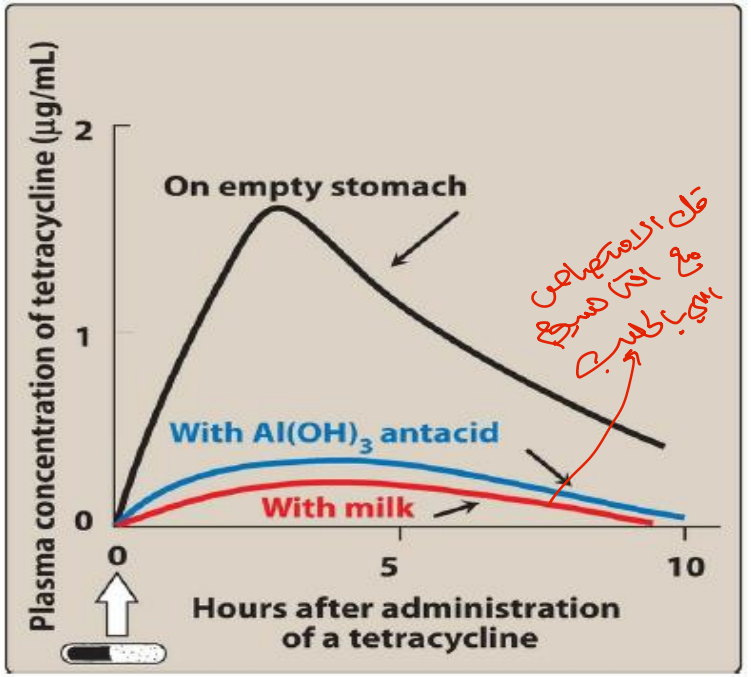


- **Effect:** Inhibits tRNA binding to mRNA
- **Activity:** Bacteriostatic, broad spectrum, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species (rickettsia). Chlamydia infections

Pharmacokinetics

Absorption: Administration with dairy products or other substances contain divalent and trivalent cations (magnesium, calcium and aluminum antacids, or iron supplements) decreases absorption.

- Tetracycline-metal complexes (chelates)



Exception: Doxycycline bioavailability (95%) with or without food

+ Minocycline

Drug	Half-life	CNS Penetration	Elimination
Tetracycline	6-12 hrs	Poor	Renal
Doxycycline	12-16 hrs	Good	Hepatic
Minocycline	11-16 hrs	Excellent	Hepatic

Distribution

- Penetration into most body fluids is adequate.
- **Minocycline> doxycycline> tetracycline**
- Only *minocycline* and *doxycycline* achieve therapeutic levels in the cerebrospinal fluid
- All *tetracyclines* cross the placental barrier and concentrate in fetal bones and dentition.

Elimination

By the Kidney

Tetracycline is primarily eliminated unchanged in the urine (glomerular filtration)

Doxycycline (80-90% in feces) is preferred in patients with renal dysfunction, as it is primarily eliminated via the bile into the feces.

Tigecycline is eliminated through feces as unchanged

Drug	Half-life	CNS Penetration	Elimination
Tetracycline	6-12 hrs	Poor	Renal
Doxycycline	12-16 hrs	Good	Hepatic
Minocycline	11-16 hrs	Excellent	Hepatic

Tetracyclines in Practice

Clinical Applications & Special Considerations

Primary Indications

Rickettsial Infections
Rocky Mountain Spotted Fever

Atypical Pneumonia
Mycoplasma, Chlamydia

Dermatology
Acne vulgaris

STIs
Chlamydia, some Gonorrhea

Effects on calcified tissues

- Deposition in the bone and primary dentition occurs during the calcification process in growing children.
- This may cause discoloration and hypoplasia of teeth and a temporary stunting of growth.
- The use of tetracyclines is limited in pediatrics.





Avoid in pregnancy



Deposition of drug in bones and teeth

⚠ **Key Contraindication:** Pregnancy and children <8 years (tooth staining!)

Phototoxicity

- Severe sunburn may occur in patients receiving a tetracycline who are exposed to sun or ultraviolet rays.
- Patients should be advised to wear adequate sun protection.



Phototoxicity



GI disturbance

⚠ **Side Effects**

GI Distress
Nausea, vomiting, diarrhea

Photosensitivity
Increased sunburn risk

Tooth Staining
Permanent in children

Vestibular dysfunction (with minocycline)

- Dizziness, vertigo, and tinnitus may occur particularly with *minocycline*, which concentrates in the endolymph of the ear and affects function.



Pseudotumor cerebri

- Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults.
- Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.



Resistance

- **Efflux pump** expels drug out of the cell, thus preventing intracellular accumulation.
- **Enzymatic inactivation** of the drug and production of bacterial proteins that prevent Tetracyclines from binding to the ribosome
- Resistance to one tetracycline does not confer universal resistance to all Tetracyclines

يعني ممكن شخص يكون الناس بكونه في
عنده نفس الأعراض فلازم أعتمد على الـ lab result

بوقف استعمالها
قبل 3 أيام
typhoid
vaccine

قبل 14 يوم
with digoxin → ↓ effect of
cholera
vaccine

Contraindications: pregnant, lactating, Children < 8y

drug interactions
↑ INR of warfarin (زي زيبروسولة اوي)

Glycylcyclines

Tigecycline, a derivative of *minocycline*, is the first member of the glycylcycline antimicrobial class.

MOA:bacteriostatic action , reversibly bind to the 30S ribosomal subunit

Spectrum: Tigecycline exhibits broad-spectrum activity includes **MRSA**, MDR streptococci, VRE, extended-spectrum β-lactamase–producing Gram negative bacteria, **Acinetobacter baumannii**, and many anaerobic organisms

Tigecycline is not active against Pseudomonas species

Indicated for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia

Pharmacokinetics

Distribution : large volume of distribution (7-9 L/kg). It penetrates tissues well but achieves low plasma concentrations. It is a poor option for bloodstream infections.

PO عن طريق الفم

Hepatic

Elimination : The primary route of elimination is biliary/fecal. No dosage adjustments are necessary for patients with renal impairment

Adverse effects

- Tigecycline is associated with significant nausea and vomiting. Acute pancreatitis, including fatality, has been reported.

عشان هيك الدكاترة ما بوصفوا الدواء يسبب وفيات كتير

- **Black box warning (increase mortality)**
- Other adverse effects are similar to those of the tetracyclines and include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered in pregnancy.

Tetracyclines: Inhibits bacterial protein synthesis. Bacteriostatic. *Streptococcus pneumoniae* resistance ≈ 15% in Regina (2022).

- **AE**: **Common**: GI upset (DOX = MIN < TET), photosensitivity (DOX > TET > MIN; esp. UVA, & dose-dependent i.e. less of a problem at DOX 100mg/day). Use Sunscreen SPF 15-30, especially if long-term use. Sit up after taking for at least 30 mins, and take with a full glass of water, to reduce risk of esophageal irritation & ulceration. MIN: hyperpigmentation of skin (rare, bluish or brown) & mucous membrane with long-term use, lightheadedness, dizziness, vertigo, ataxia, drowsiness & fatigue. **Rare**: rare azotemia with renal insufficiency, pseudotumor cerebri (benign intracranial hypertension). MIN: rare lupus-like reaction, vestibular toxicity, autoimmune hepatitis & hypersensitivity syndrome (case reports; implicated far more often in hypersensitivity reactions than other tetracyclines).
- **CI**: pregnancy, children <8 years (bone lesions, staining & deformity of teeth), severe renal or hepatic dysfunction; DOX: myasthenia gravis (possible association with muscle weakness).
- **DI**: ↓ GI absorption: Fe^{++}, bismuth, Al^{+++}, Ca^{++}, Mg^{++} (separate dose by 2 hr); ↑ INR and bleeding risk with warfarin; may ↓ oral contraceptive effectiveness; isotretinoin (intracranial hypertension/hemorrhage).
- **M**: if using MIN **long-term**, consider LFTs & antinuclear factor baseline & q3-4 months and monitoring for skin hyperpigmentation.

Doxycycline = DOX DOXYCIN, g 100mg cap, tab	• **Coverage**: Broad spectrum agent → *Staphylococci* (& often MRSA); *Strep pneumoniae*; *Moraxella*; *Haemophilus influenzae*; many atypicals; many anaerobes including spirochetes. • **Useful in**: pneumonia; low-risk AECOPD, purulent SSTIs; rickettsia; acne; Lyme disease prophylaxis (x1dose) & treatment; malaria prophylaxis. Dosing at 100mg once daily OK in acne & malaria prophylaxis. • **Better absorption on empty stomach** (↑ 20%), **but may take with food to improve tolerability** if necessary.	**≥8 yrs**: 2-5mg/kg/day po divided q12h **Adult**: 200mg stat, then 100mg q12h or 200mg stat, then 100mg daily **Max**: 200mg/day	$23 $23 $17 $23
Minocycline = MIN MINOCIN, g 50, 100mg cap	• **Coverage**: Broad spectrum agent → *Staphylococci*; *Strep peumoniae*; *Moraxella*; *Haemophilus influenzae*; many atypicals; many anaerobes including spirochetes. • **Useful in**: ~~acne~~, *Stenotrophomonas maltophilia* infection 200mg q12h (alternative to TMP/SMX) • **AE**: blue-black/grey or muddy brown hyperpigmentation of skin/mucosa (↑ long-term use). • Due to association with serious rare AE, some suggest avoiding minocycline (doxycycline safer and effective).	**≥8 yrs**: 4mg/kg po; then 4mg/kg/d po ÷ q12h **Adult**: 200mg x 1; then 100mg po q12h **Max**: 200mg/day	$24 $14 $14
Tetracycline = TET TETRACYN, g 250mg cap	• **Coverage**: Broad spectrum agents → *Staphylococci*; *Strep pneumoniae*; *Moraxella*; *Haemophilus influenzae*; many anaerobes including spirochetes. • **Useful in**: acne; actinomycosis; periodontitis. • **Take TET on empty stomach** - absorption is ↓ by food & dairy.	**≥8 yrs**: 25mg/kg/day po divided q6h **Adult**: 250mg po q6h **on empty stomach** **Max**: 2000mg/day	$14 $14 $18

Discontinued: Erythromycin/Sulfisoxazole PEDIAZOLE suspension; Erythromycin Ethylsuccinate ERYPED suspension; Telithromycin KETEK tablet. **USA Products**: Omadacycline NUZYRA CAP, SSTI

MACROLIDES : *The Penicillin Alternative*

بعطى Penicillin لل no allergy لو كان المريض عنده

أزيثرو ACET

reversible بعيد عن الـ 30

🎯 Mechanism of Action

- **Target:** 50S ribosomal subunit (irreversible binding)
- **Effect:** Inhibits translocation of peptidyl tRNA
- **Activity:** Bacteriostatic (bactericidal at high concentrations)

MACROLIDES/KETOLIDES
Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin E.E.S., ERY-TAB
Telithromycin GENERIC ONLY

💎 **Clinical Pearl:** Macrolides concentrate in macrophages and neutrophils, making them excellent for intracellular pathogens!

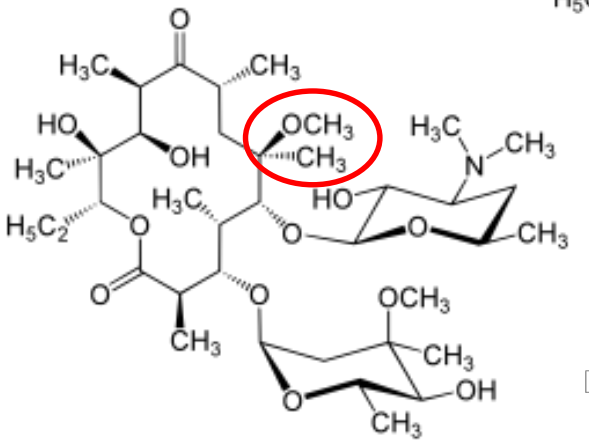
Macrolides & Ketolides (ACER &T)

- Azithromycin (Zithromax)
- Clarithromycin (Biaxin)
- Erythromycin (E-mycin, E.E.S, others)
- Roxithromycin

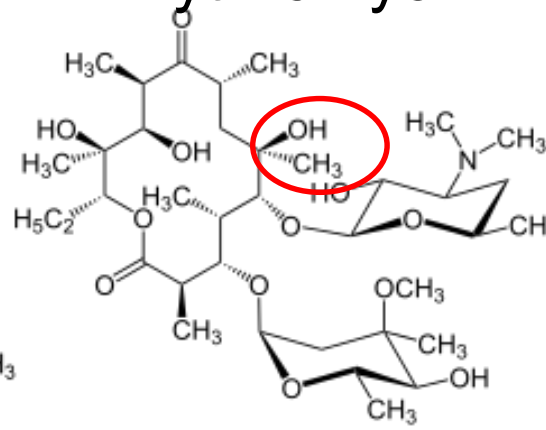
- Telithromycin (Ketolides)

- Fidaxomicin (Dificid, Dificlir) Derevative

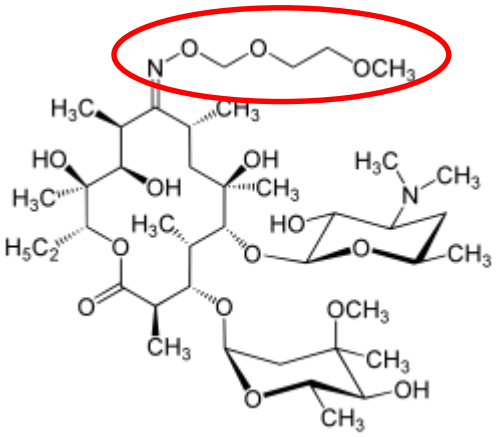
Clarithromycin



Erythromycin



Roxithromycin



Macrolides: Mechanism of Action

- Prevent protein synthesis within bacterial cells : They bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting translocation steps of protein synthesis.
- Bacteriostatic- Bacteria will eventually die
- In high enough concentrations, may also be bactericidal

MAcrolides: Indications

- Strep infections

  Streptococcus pyogenes (group A beta-hemolytic streptococci)

- Mild to moderate upper and lower respiratory tract infections

  Haemophilus influenza

- Spirochetal infections

  Syphilis and Lyme disease

- Gonorrhea, Chlamydia, Mycoplasma

منسبب

sexual transmited diseases

Atypical bacteria: Chlamydia, Legionella and the Mycoplasma

traveller diarrhyca

Erythromycin

Effective against many of the same organisms as penicillin G

Alternative in patients with penicillin allergy

Clarithromycin

Activity similar to erythromycin:

Haemophilus influenzae

Chlamydia, Legionella, Moraxella,

Helicobacter pylori

Azithromycin

Less active than Erythromycin against streptococci and staphylococci

More active against respiratory pathogens such as H. influenzae and Moraxella catarrhalis

Telithromycin

Antimicrobial spectrum similar to *azithromycin*. The structural modification within ketolides neutralizes the most common resistance mechanisms that render *macrolides* ineffective.

Increase Spectrum

food gentle tablets

A — capsules, empty stomach

Increase cyclosporine conc (drug-drug interactions)

suspension, food, tablets

CE — tablet, capsule — empty stomach

CYP

Inhibit 3A4 and P glycoprotein

R

ACER

drug-drug interactions

absorped By small intestine

Pharmacokinetics

Absorption

- Erythromycin base is destroyed by gastric acid; thus, either enteric-coated tablets or esterified forms of the antibiotic are administered and all have adequate oral absorption .
- Clarithromycin, azithromycin, and telithromycin are stable in stomach acid and are readily absorbed.
- Food interferes with the absorption of *erythromycin* and *azithromycin* but can increase that of *clarithromycin*. *Telithromycin* is administered orally without regard to meals.
- ACER : NO dose adjustment
- ***Erythromycin* and *azithromycin* are available in IV formulations**.

available IV formation

	Erythro-mycin	Clarithro-mycin	Azithro-mycin	Telithro-mycin
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	68	10
Conversion to an active metabolite	No	Yes	No	Yes
Percent excretion in urine	< 15	30–50	< 10	13

dose adjustment

In general not from urine

Erythromycin
$t_{1/2}$ = 1.6 hrs
⚠ CYP3A4 inhibitor

Clarithromycin
$t_{1/2}$ = 4 hrs
Acid stable

Azithromycin
$t_{1/2}$ = 35-40 hrs
Best tolerated

? Clinical Challenge

Test Your Macrolide Knowledge

A 25-year-old patient with penicillin allergy presents with community-acquired pneumonia. You want to prescribe a macrolide but notice they're taking warfarin for a prosthetic heart valve. Which macrolide would be the SAFEST choice?

CYP 1A

1. A) Erythromycin - shortest half-life
2. B) Clarithromycin - better GI tolerance

} CYP 3A4 inhibitors

3. C) Azithromycin - least drug interactions
4. D) Any macrolide is equally safe

CYP inhibitor ↓ CYP

Key Learning Point: Always consider drug interactions, especially with CYP3A4 substrates like warfarin!

Critical Thinking:

rapidly absorped with good tissue penetration, Post antibiotic effect

Why might azithromycin be preferred for outpatient treatment despite its long half-life?

• gives with or without food, minimal drug-drug interactions, $t_{1/2}$ = 3 days (once daily dose) → more convenient

Macrolides: Adverse Effects

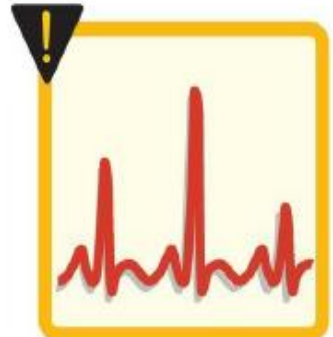
- GI effects, primarily with erythromycin
  - Nausea, vomiting, diarrhea, hepatotoxicity, flatulence, jaundice, anorexia

- Azithromycin and clarithromycin: fewer GI adverse effects, longer duration of action, better efficacy, better tissue penetration


GI disturbance


Jaundice


Ototoxicity

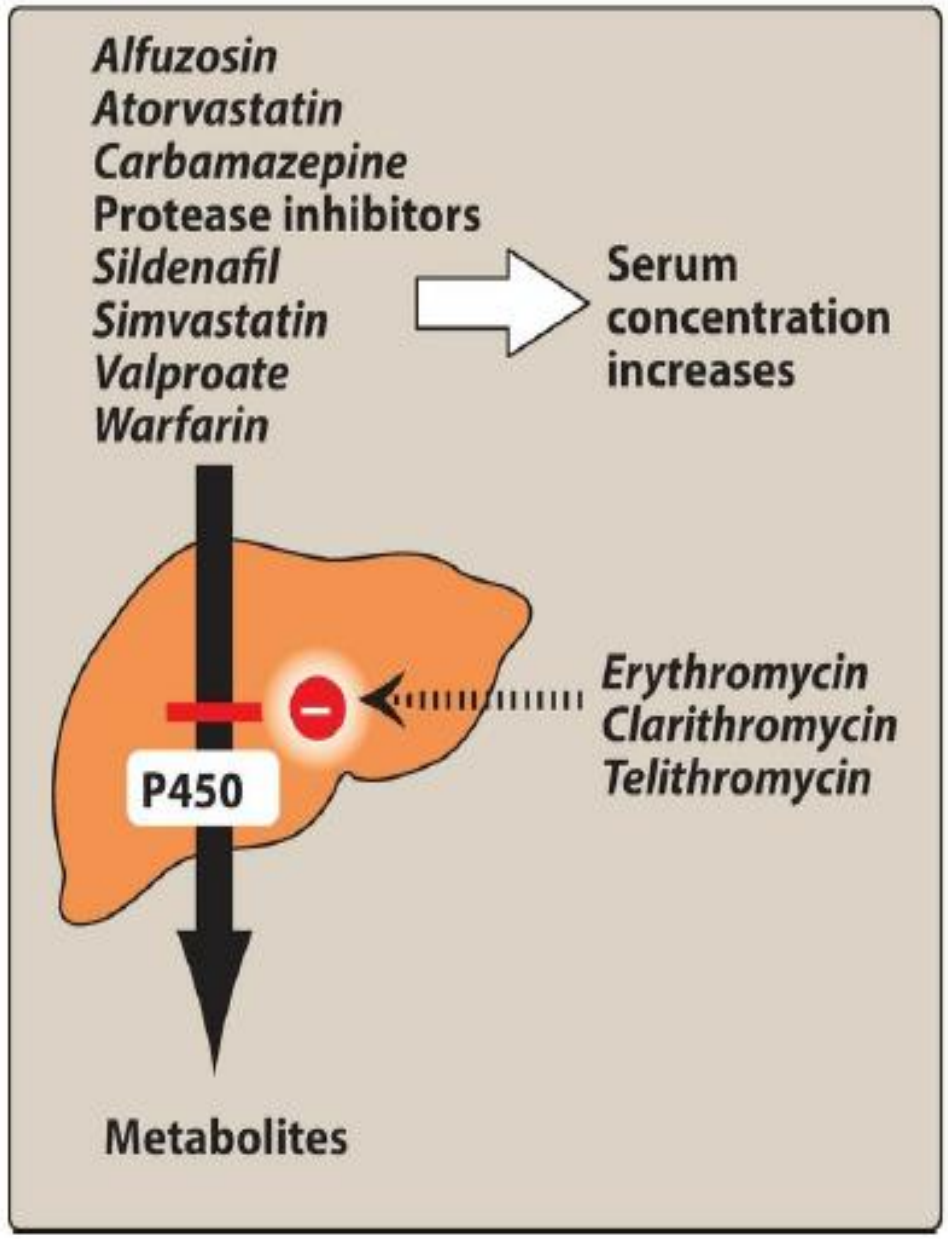

QTc prolongation

Contraindications

- Hepatic dysfunction .Severe hepatotoxicity with *telithromycin* has limited its use.

Drug Interactions

- Erythromycin, Telithromycin, and Clarithromycin inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulation of these compounds.



Macrolide Resistance

Understanding the Enemy's Defense

Resistance Mechanisms

Target Site Alteration

- Methylation of 23S rRNA
- MLS_B resistance pattern
- High-level resistance (MIC >64 µg/ml)
- Affects ALL macrolides

Enzymatic Inactivation

- Esterases
- Phosphotransferases
- Usually drug-specific
- Lower level resistance

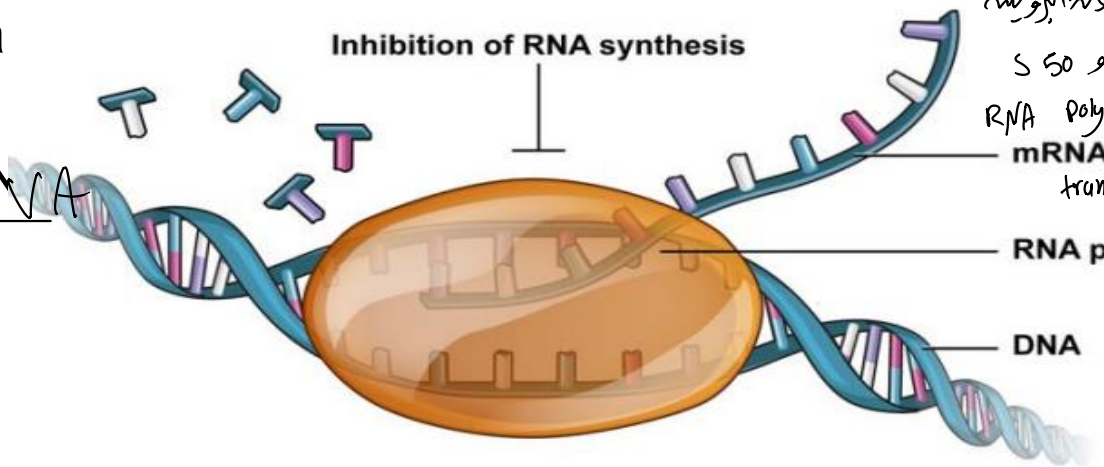
Clinical Correlation:

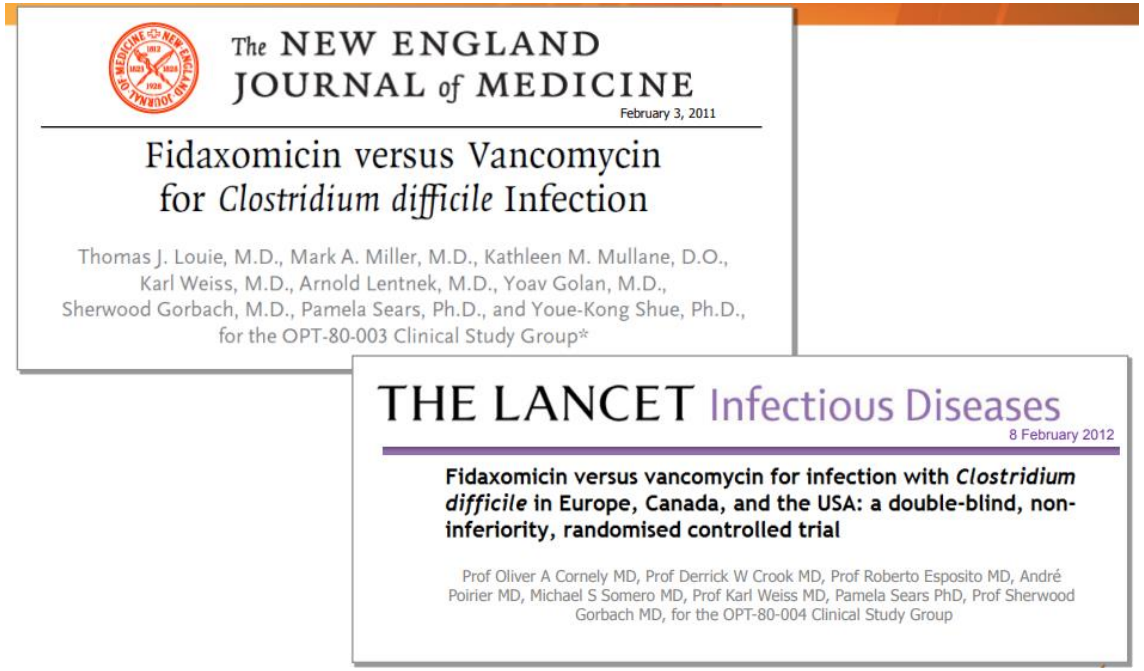
If a Streptococcus pneumoniae isolate shows high-level resistance to erythromycin, what can you predict about its susceptibility to clindamycin and streptogramins?

Generic/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	Dosing (Pediatric, Adult, Usual Max)	$/10d
Macrolides: Inhibits bacterial protein synthesis. Bacteriostatic. Demonstrates concentration-dependent with time-dependence. Reserve when possible; useful for Streptococcal URTI in context of beta-lactam allergy. • AE: GI upset (erythromycin highest incidence); ↑ LFTs; headache; insomnia; QTc prolongation (clarithromycin = erythromycin > azithromycin). **Rare**: ototoxicity (usually rev & dose-related), infantile hypertrophic pyloric stenosis. • Caution in myasthenia gravis (possible association with muscle weakness). **Pregnancy**: new data suggests ↑ risk malformations e.g. CV, vs penicillin esp 1st trimester; Azithromycin 1g x 1 dose tx of STIs eg. Chlamydia likely okay.[251] • DI: Clarithromycin and erythromycin CYP3A4 & p-glycoprotein inhibitors (clarithromycin > erythromycin) → increased levels of alfuzosin, alprazolam, amitriptyline, amiodarone, apixaban, calcium channel blockers, colchicine, digoxin, domperidone, haloperidol, lomitapide, midazolam, paroxetine, quetiapine, risperidone, rivaroxaban, sertraline, statins (atorva-, simva-, lova-statin), tamsulosin, tolterodine, warfarin, & others. See RxFiles Drug Interactions pg 217-220. • M: LFTs, CBC (with prolonged therapy). No coverage of MRSA. Minimal CNS penetration. *Streptococcus pneumoniae* resistance in SK (2021/2022) = 20-30%. Increased macrolide doses do not overcome *Streptococcus pneumoniae* resistance whereas higher beta lactam doses may overcome intermediate resistance e.g. amoxicillin dosing for AOM.			
Azithromycin ZITHROMAX, g 20, 40mg/mL susp cherry ☺ ❄ 250mg tab 600mg tab ☎▼; 500mg IV vials After reconstitution, suspension may be kept at room temperature. Excellent bioavailability	• **Coverage**: *Streptococcus; N. gonorrhoeae; Moraxella; Haemophilus influenzae; Legionella*; many atypicals. • **Useful in**: pneumonia; upper respiratory tract infections; low-risk AECOPD; sexually transmitted infections including chlamydia and gonorrhea; MAC prophylaxis in HIV pts; pertussis (aka whooping cough); travelers' diarrhea (in kids, or travel to Asian countries), but shigella resistance is increasing. • Long half-life → 5 day treatment ≈ 10 days therapeutic levels. Appears more likely to lead to resistance than clarithromycin, as its long-half life results in prolonged sub-inhibitory levels at the end of therapy. • Caution: safety <6mos is unknown. • ?↑ CV risk → some retrospective cohort studies have found ↑ risk of cardiovascular mortality compared to amoxicillin (estimated 47 additional deaths per 1 million courses), although other studies have found no risk.[16-19] • Has additional anti-inflammatory activity (occasionally used chronically in COPD, cystic fibrosis, etc. to ↓ pulmonary inflammation – but efficacy is limited).	**Peds**: 10mg/kg day 1; 5mg/kg days 2-5 or 20mg/kg po daily x 3 days **Adult**: 500mg day 1; 250mg days 2-5 500mg daily x 3 days in bacterial sinusitis & others 500mg IV daily x 3 days **Max**: 500mg/day Gonococcal STI therapy: azithromycin 1000mg stat + cefixime 800mg stat (or ceftriaxone IM x1 if anogenital, pharyngeal infection, or in men who have sex with men)	$21 $16 $69 $26
Clarithromycin BIAXIN, g 25, 50mg/mL susp fruity 250, 500mg tab 500mg XL tab (take with food)	• **Coverage**: *Streptococcus; Moraxella; Haemophilus influenzae; Legionella*; many atypicals. • **Useful in**: pneumonia; upper respiratory tract infections; low-risk AECOPD. • ?↑ CV risk.[378] • Keep reconstituted suspension at room temperature. • XL tab = with food & once daily. Regular tab = ± food. • CI: domperidone (QTc prolongation and cardiac arrhythmias). • Caution: safety <6mos is unknown.	**Peds**: 15mg/kg/day po divided q12h **Adult**: 500mg po q12h (or 1000mg XL daily cc) **Max**: 1000mg/day	$24 $23-38
Erythromycin, g **D/C'23** ERYC 250, 333mg cap Erythromycin base 250mg tab Erythromycin Stearate 250mg tab (500mg ✗▼) Erythromycin Estolate 50mg/mL susp ☺❄ Non-estolate: Estolate:	• Erythromycin ethyl succinate 5mg/mL susp via compounding pharmacy, ~$100/100mL. **Other products D/C.** • **Coverage**: *Streptococcus; Moraxella; Legionella*; many atypicals. (Unlike other macrolides, lacks *H. influenzae* coverage - therefore not recommended as empiric therapy for pneumonia in adults or in AECOPD. Reasonable option for pneumonia in kids < 12 years as *H. influenzae* uncommon in this group.) • **Usually reserved. May be useful in**: upper respiratory tract infections; acne; pneumonia if culture + sensitivity. • Has been used to increase GI motility e.g. in gastroparesis, but resistance concerns & development of tachyphylaxis with long-term use limit this indication.[11] • Estolate formulation: CI in **pregnancy** (↑ maternal hepatotoxicity), but best in kids as most acid stable. • Empty stomach ideal for increased absorption, but if not tolerated, taking with food decreases GI upset. • ERYC may be sprinkled on food. Erythromycin unsafe in porphyria.	**Peds** (Estolate D/C): 30-40mg/kg/day po div q6h ERYC: 333mg po q8h Base: 250mg po q6h Stearate: 250mg po q6h Max: 2000mg/day	$21 $35 $20 $20 $28-61

Fidaxomicin: (Dificid): newest macrolide

- Macrocyclic antibiotic with a structure simila to the macrolides- Minimal absorption
- *Fidaxomicin* acts on the sigma subunit of RNA polymerase, thereby disrupting bacterial transcription, terminating protein synthesis
- Very narrow spectrum of activity limited to Gram-positive aerobes and anaerobes
- It is used primarily for its bactericidal activity against Clostridium difficile. Indicated only for the treatment of *C. difficile*–associated diarrhea
- *Fidaxomicin* has minimal systemic absorption and primarily remains within the gastrointestinal tract (92% of dose recovered in stool)
- The most common adverse effects are nausea, vomiting, and GI bleed.
  - Pregnancy category B




The NEW ENGLAND JOURNAL of MEDICINE
February 3, 2011

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

THE LANCET Infectious Diseases
8 February 2012

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Prof Oliver A Cornely MD, Prof Derrick W Crook MD, Prof Roberto Esposito MD, André Poirier MD, Michael S Somero MD, Prof Karl Weiss MD, Pamela Sears PhD, Prof Sherwood Gorbach MD, for the OPT-80-004 Clinical Study Group

LINCOSAMIDES

Clindamycin



The Anaerobe and Bone Infection Specialist

متخصص في عدوى العظم

🎯 Key Features

- **Target:** 50S ribosome (same site as macrolides)
- **Spectrum:** Anaerobes + Gram-positives
- **Distribution:** Excellent bone penetration
- **Route:** PO, IV, IM, topical

Aerobic → staph + strep

activity ما له أي

Gram -ve مع تنبيه

Bacteriostatic

✅ Indications

oral → Clostridium

Gut → Bacteroids

Anaerobic Infections
(except brain abscesses)

Osteomyelitis
+ Ciprofloxacin

Skin/Soft Tissue
Staph infections

❌ Major Side Effect

C. difficile Colitis
Pseudomembranous colitis
Bloody diarrhea, fever, cramps
Treatment: Stop clindamycin, start metronidazole or vancomycin

⚠ Clinical Alert:

Why should you avoid anti-peristaltic agents when treating C. difficile colitis?

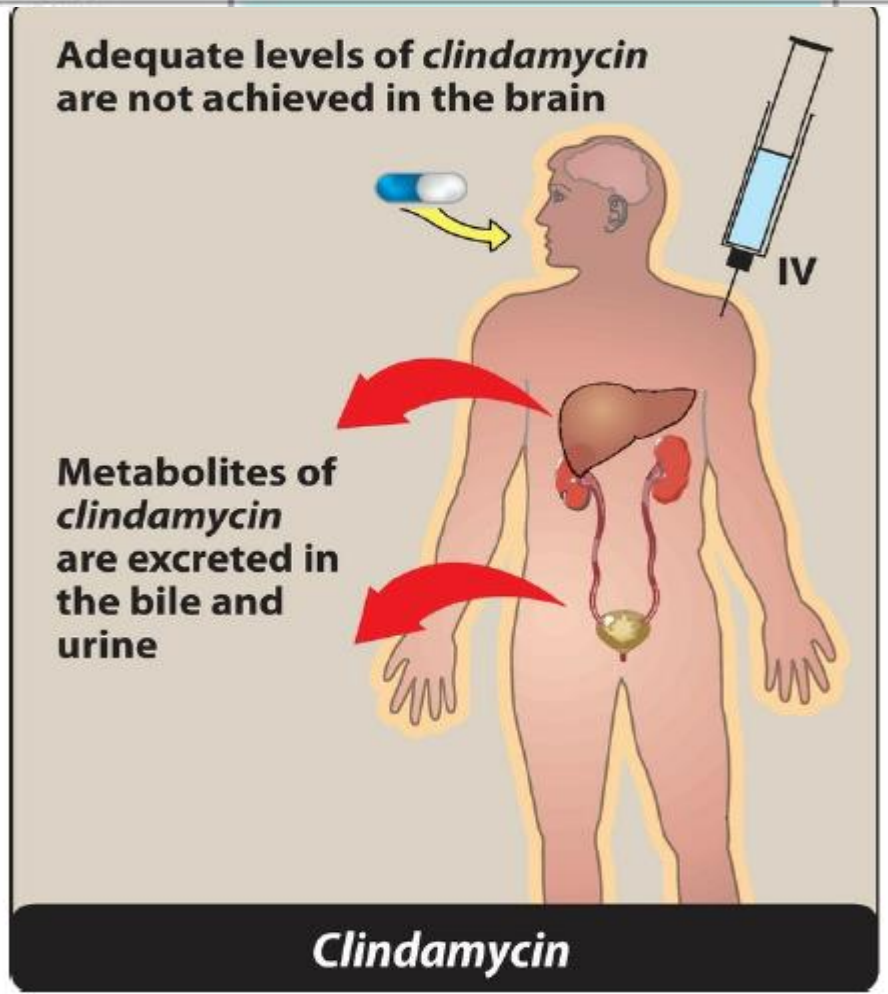
لأنو هاد بوقف الاسهال وأنا صار بدي أوقف الاسهال عشان البكتيريا تنزل برع أطلع أنو بدي تقضي وتخلص من البكتيريا

Oral & IV Antibiotics (continued): Miscellaneous Agents

Treat with adequate dose & appropriate duration for specific infection — A Crawley BSP, L Regier BSP M LeBras BSP, PharmD www.RxFiles.ca July 2023

Generic/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	Dosing (Pediatric, Adult, Usual Max)	$/10d
Clindamycin DALACIN C, g 150, 300mg cap 15mg/mL soln cherry DO NOT REFRIGERATE; 150mg/mL IV (300, 600, 900mg vials) Excellent bioavailability	• Inhibits bacterial protein synthesis. Bacteriostatic; concentration-dependent with time-dependence killing. **Coverage**: *Staphylococci*; oral anaerobes; MRSA check local antibiogram. Inducible *Staph* & *Strep* resistance. • **Useful in**: skin and soft tissue infections; dental infections (although usually safer options). ↓ toxin production of *Strepto-* & *Staphylo -cocci* (useful to ↓ toxic shock syndrome in necrotizing fasciitis - give in combo with penicillin). ?appendicitis + ceftriaxone.[C054] AE profile plus increasing resistance limits role. • AE: nausea, diarrhea, rash (rare: SJS), ↑ LFTs, esophageal irritation. Rare: leukopenia, thrombocytopenia. Higher risk of *C. difficile* than other agents. • Caution: severe liver disease (monitor LFTs). • DI: May decrease effect of erythromycin (competitive binding to same bacteria protein site). • M: Signs of *C. difficile* infection (watery diarrhea ≥3 times/day); CBC, LFTs & SCr if prolonged therapy.	**Peds**: 10-30mg/kg/day po divided q6h **Adult**: 300-450mg po q6-8h 300-600mg IV Q8h x 5 days **Max**: 1800mg/day Administration: take capsules with a full glass of water to lessen esophageal irritation risk.	$34 $25-30 $104-112 $39

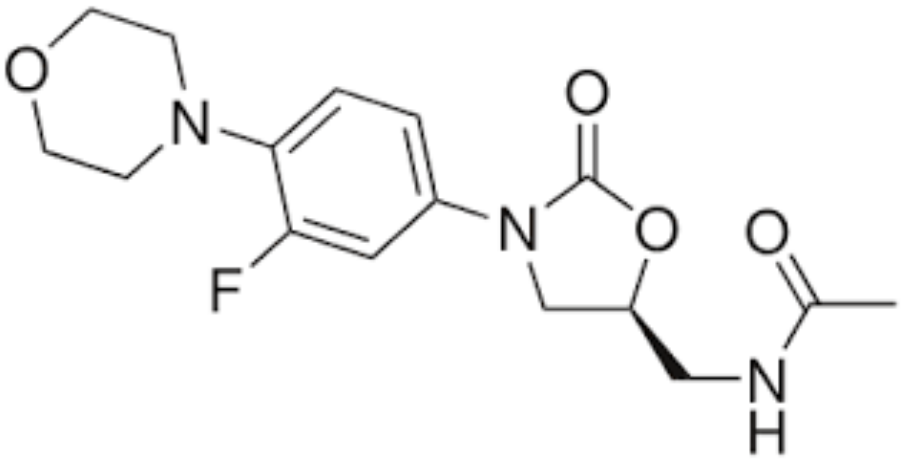
- Available in both IV and oral formulations
- Complete absorption
- Oral *clindamycin* is limited by gastrointestinal intolerance.
- It distributes **well** into all body fluids (bone, joint, soft tissue) but exhibits poor entry into the CSF.
- *Clindamycin* undergoes extensive oxidative metabolism to active and inactive products and is excreted into bile and urine.
- **Low urinary excretion of active drug limits its clinical utility for urinary tract infections**



Oxazolidinones: *The MRSA/VRE Game Changer*

Linezolid and tedizolid

Gram positive organisms, including resistant isolates such as *methicillin*-resistant Staphylococcus aureus, VRE, *penicillin*-resistant streptococci.





NEW Linezolid (Oxazolidinones)

Revolutionary Mechanism

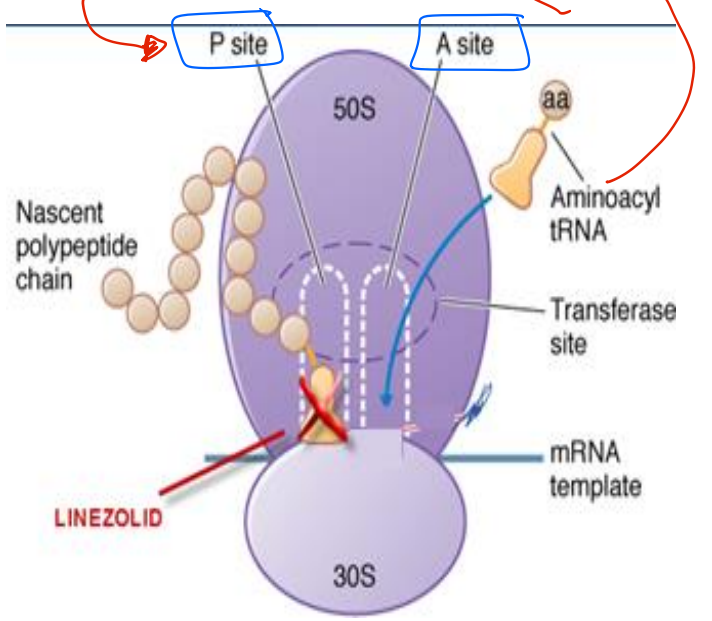
- **Target:** 50S ribosome at peptidyl transferase (P) site
- **Unique:** Prevents formation of initiation complex

- **Activity:** Bacteriostatic against most organisms, *linezolid* has bactericidal activity against streptococci.

- Against gram-positive organisms such as staphylococci, streptococci, and enterococci, Corynebacterium species and Listeria monocytogenes.

- There is no cross resistance with other antibacterials. Because of its unique mechanism of action, linezolid is active against strains that are resistant to multiple other agents.

- **Bioavailability:** 100% oral bioavailability



✅ Advantages

Broad Gram-Positive Coverage
MRSA, VRE, VRSA

Well Tolerated
Generally safe profile

Excellent Oral Option
Only good oral option for VRE/MRSA

No need for dose adjusment

Adverse effects: Gastrointestinal upset, nausea, diarrhea, headache, and rash.

Thrombocytopenia, usually in patients taking the drug for longer than 10 days.

Irreversible peripheral neuropathies and optic neuritis causing blindness have been associated with greater than 28 days of use

⚠ Limitations

↓platletes → anemia

Thrombocytopenia
With prolonged therapy (>2 weeks)

Weak MAOI Activity
Avoid tyramine-rich foods
أجبنة العتيقة والسمك المخمر

Cost
Expensive medication

Clinical Case:

A patient with MRSA pneumonia needs to be discharged but requires 2 more weeks of IV antibiotics. What makes linezolid an attractive option?

Linezolid ZYVOXAM, g; USA: ZYVOX 600mg tab ☎▼; 2mg/mL IV ✗ (600mg bags) 100mg/5mL susp ☎▼ NIHB prior approval = treatment of: VRE; MRSA with vancomycin intolerance Excellent bioavailability	• Inhibits bacterial protein synthesis. Usually bacteriostatic, but bactericidal against *Streptococci*. **Coverage**: *Streptococci*; *Enterococci* (including VRE); *Staphylococci* (including MRSA). • PK: penetrates into bone/joint. • **Useful in**: multi-drug resistant infections (including pneumonia, skin and soft tissue, etc.). **Alternative to vancomycin** (e.g. MRSA with vancomycin intolerance; vancomycin-resistant *Enterococci*). • **AE**: HA, N/V/D, rash, ↑ LFTs. Rare ↑ QTc; (but more common if >10-14d therapy): reversible myelosuppression (↓ platelets, anemia, leukopenia); peripheral/optic neuropathy; lactic acidosis[/hepatic failure]; ↓sz threshold, ↓Na+. • **DI**: ↑ serotonin syndrome risk with SSRIs (? if clinically meaningful), MAOIs, etc. Rifampin decreases levels. • **M**: CBC weekly; ophthalmic tests if >3 months therapy.	**Peds**: 30mg/kg/day po divided q8h **Adult**: 600mg po q12h 600mg IV q12h x 5 days **Max**: 1200mg/day po	$250 $400 $2375 $400



Chloramphenicol

Powerful but Dangerous

🎯 Mechanism

- **Target:** 50S ribosome (peptidyl transferase)
- **Activity:** Bacteriostatic, broad spectrum
- **Binding:** Reversible

💀 Gray Baby Syndrome

- Fatal toxicity in neonates
- Onset: 2-9 days after treatment
- Symptoms: vomiting, respiratory distress, abdominal distention, cyanosis
- Ashen-gray color, hypothermia

🩸 Bone Marrow Toxicity

- **Dose-related:** Anemia, leukopenia, thrombocytopenia
- **Idiosyncratic:** Aplastic anemia (potentially fatal)
- Monitor: CBC with differential

Current use is restricted to life-threatening infections when other antibiotics fail - primarily typhoid fever and topical eye infections

Ethical Dilemma:

Given its toxicity profile, under what circumstances would you still consider using chloramphenicol in 2025?

Resistance Mechanisms Summary

Know Your Enemy's Tactics

Drug Class	Primary Resistance	Clinical Impact	Overcoming Strategy
Macrolides	23S rRNA methylation (MLS_B)	Cross-resistance with lincosamides	Ketolides (limited use)
Tetracyclines	Efflux pumps	Variable cross-resistance	Glycylcyclines (tigecycline)
Aminoglycosides	Modifying enzymes	Drug-specific patterns	Amikacin (broadest stability)
Clindamycin	Same as macrolides	MLS_B resistance	D-test to detect inducible resistance
Linezolid	23S rRNA mutations	Rare but concerning	Newer oxazolidinones in development

Molecular Medicine

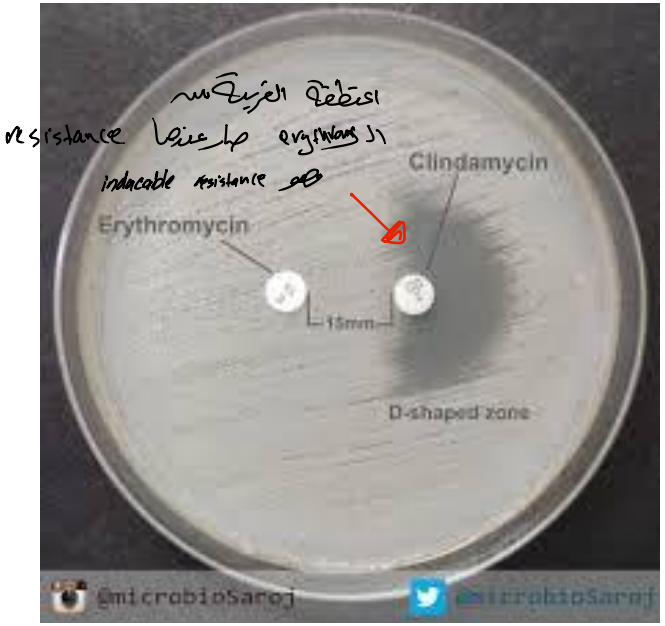
A lab reports S. aureus as "erythromycin-resistant, clindamycin-sensitive" but the D-test is positive. What does this mean for therapy?

A) Clindamycin is safe to use

B) Avoid clindamycin due to inducible resistance

C) Use higher doses of clindamycin

D) The D-test result is irrelevant



Zone of inhibition around the clindamycin disc will be flattened or blunted on the side facing the erythromycin disc, creating a "D" shape.

🎯 Clinical Decision Framework

Choosing the Right Protein Synthesis Inhibitor

💼 Patient Factors

- **Age:** Avoid tetracyclines in children <8 years
- **Pregnancy:** Avoid tetracyclines, chloramphenicol
- **Renal function:** Dose-adjust aminoglycosides
- **Hepatic function:** Caution with erythromycin
- **Drug interactions:** Consider CYP3A4 inhibition

Pathogen Factors

- **Intracellular:** Macrolides, tetracyclines
- **Anaerobes:** Clindamycin, chloramphenicol
- **MRSA/VRE:** Linezolid, clindamycin
- **Gram-negative:** Aminoglycosides
- **Atypicals:** Macrolides, tetracyclines

صارلي عندو جرح وما التأم وصار تآكل
و بآكتيريا

Complex Case Challenge:

A 45-year-old diabetic presents with necrotizing fasciitis. Blood cultures grow MRSA and Bacteroides fragilis. The patient has a penicillin allergy and mild renal impairment (CrCl 45 mL/min). Design your antibiotic regimen:

Consider: Polymicrobial infection, MRSA coverage, anaerobic coverage, renal function, allergy history → Penicillin X

MRSA → Clindamycin / او بيجي دوائين عشان نغطي الاشياء اللي عنده

💎 **Clinical Pearl:** Remember: Combination therapy is often needed for polymicrobial infections - think about coverage gaps and synergistic effects!

🎓 Final Challenge

Master-Level Clinical Reasoning

Ultimate Clinical Scenario:

A 28-year-old pregnant woman (32 weeks) presents with severe community-acquired pneumonia. Sputum Gram stain shows Gram-positive cocci in chains. She's allergic to penicillin (anaphylaxis) and has been taking warfarin for a pulmonary embolism earlier in pregnancy. Her creatinine is normal. What's your antibiotic choice and why?

🤔 Consider:

- Pregnancy safety
- Severe penicillin allergy
- Warfarin interaction
- Likely pathogen (S. pneumoniae)
- Severity of illness

Penicillins ✗ → macrolides
Azithromycin

💡 Key Learning Points:

- Always consider pregnancy category
- Drug interactions matter
- Severity may override usual cautions
- Alternative agents exist
- Multidisciplinary consultation

🎯 Take-Home Messages:

- **Mechanism matters:** Understanding how drugs work helps predict efficacy and resistance
- **Patient-specific factors:** Age, pregnancy, organ function, allergies guide choice
- **Resistance is real:** Know patterns and how to overcome them
- **Toxicity surveillance:** Monitor for predictable adverse effects
- **Combination therapy:** Sometimes necessary for complex infections

💎 **Clinical Pearl:** Excellence in antimicrobial therapy requires integrating pharmacology, microbiology, and clinical medicine. Keep learning, keep questioning, and always put patient safety first! 🌟





Thank you




"Tell me and I forget; teach me and I may remember; but involve me and I learn."
Benjamin Franklin
UMKC
School of Pharmacy

General Pharmacology

Esmaa Motawe

PhD in Pharmacology and Toxicology/ Pharmaceutical Sciences

2025

Antifungal Drugs

injection or oral → systemic

DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOSES

Amphotericin B VARIOUS
Anidulafungin ERAXIS
Caspofungin CANCIDAS
Fluconazole DIFLUCAN
Flucytosine ANCOBON
Itraconazole SPORANOX
Ketoconazole NIZORAL
Micafungin MYCAMINE
Posaconazole NOXAFIL
Voriconazole VFEND

it's toxicity is high can't give systemic

for the skin (local)

DRUGS FOR CUTANEOUS MYCOSES

Butenafine LOTRIMIN ULTRA
Butoconazole GYNAZOLE
Clotrimazole LOTRIMIN AF
Ciclopirox PENLAC
Econazole ECOZA
Griseofulvin GRIFULVIN V, GRIS-PEG
Miconazole FUNGOID, MICATIN, MONISTAT
Naftifine NAFTIN
Nystatin MYCOSTATIN
Oxiconazole OXISTAT
Sertaconazole ERTACZO
Sulconazole EXELDERM
Terbinafine LAMISIL
Terconazole TERAZOL
Tioconazole VAGISTAT-1
Tolnaftate TINACTIN

Figure 42.1
Summary of antifungal drugs.

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MYCOLOGY

- Mycology is scientific study of fungi, eukaryotes with membrane-bound nuclei and many membrane-bound organelles
- Thick, rigid wall containing complex polysaccharides (chitin and glucans) Plasma membrane stabilized by ergosterol
- Replication is asexual or sexual or both, depending on species
- Most fungi produce spores in both sexual and asexual reproduction. Asexual reproduction by fragmentation, budding, or producing spores
- Transmission to hosts by direct contact, ingestion, or respiratory route

Fungi

- Very large and diverse group of microorganisms, including yeasts and molds
- Fungal infections also known as *mycoses*
- Some fungi are part of the normal flora of the skin, mouth, intestines, and vagina.
- Systemic, cutaneous, subcutaneous, and superficial



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Fungi (Cont.)

- Cutaneous, subcutaneous, and superficial: infections of various layers of the *integumentary* system (skin, hair, or nails)
- Fungi that cause integumentary infections are known as dermatophytes.

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DERMATOPHYTES

- Only affect epidermis, hair and nails
- •Infections are called dermatomycoses or cutaneous mycoses
- Trichophyton infects hair, skin or nails
- Microsporum infects hair or skin
- Epidermophyton infects skin and nails

	Location
Tinea capitis	Scalp
Tinea pedis	Feet
Tinea unguium	Nails
Tinea cruris	Groins

Tinea corporis

Tinea Barbea

Body

mustach

Yeasts

Single-cell fungi

Reproduce by budding

Can be used for:

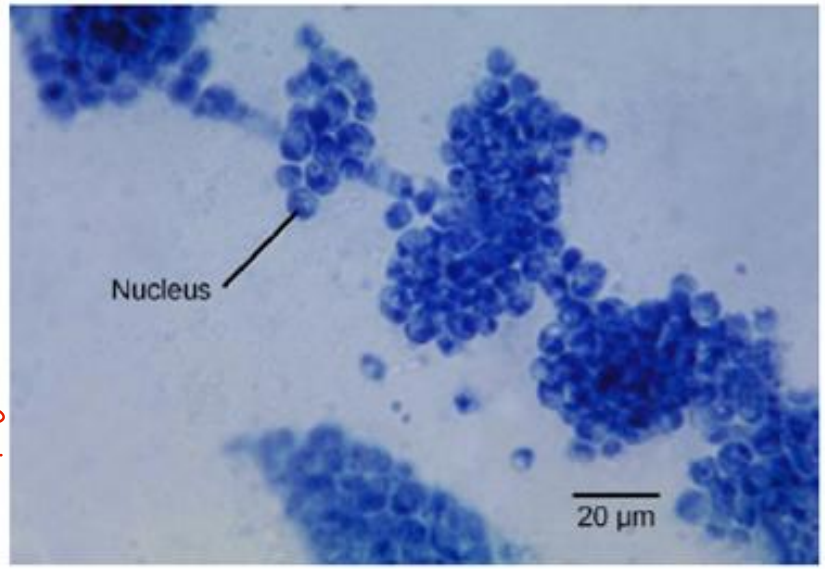
- **Baking**
- **Alcoholic beverages**

Molds

Multicellular

Characterized by long, branching filaments called hyphae

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normal flora وعبارة عن Yeast هي
ولكن إذا قلت المناعة راح تتحول لـ
(الجرثوم) جبيلك infection

Figure 24.3 Candida albicans. *Candida albicans* is a yeast cell and the agent of *candidiasis* and *thrush*. This organism has a similar morphology to coccus bacteria; however, yeast is a eukaryotic organism (note the nucleus). (credit: modification of work by Dr. Godon Roberstad, CDC; scale-bar data from Matt Russell)

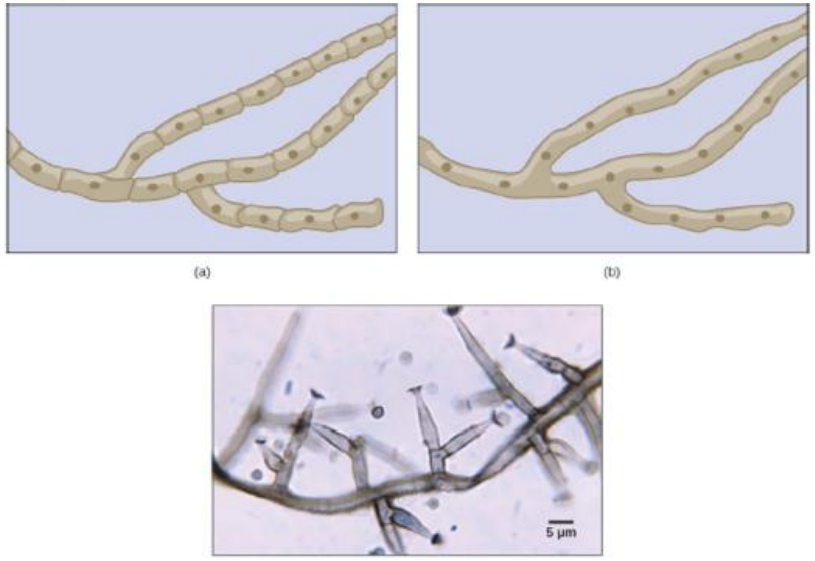


Figure 24.5 Fungal hyphae. Fungal hyphae may be (a) septated or (b) coenocytic (coeno- = "common"; -cytic = "cell") with many nuclei present in a single hypha. A bright field light micrograph of (c) *Phialophora richardsiae* shows septa that divide the hyphae. (credit c: modification of work by Dr. Lucille Georg, CDC; scale-bar data from Matt Russell)

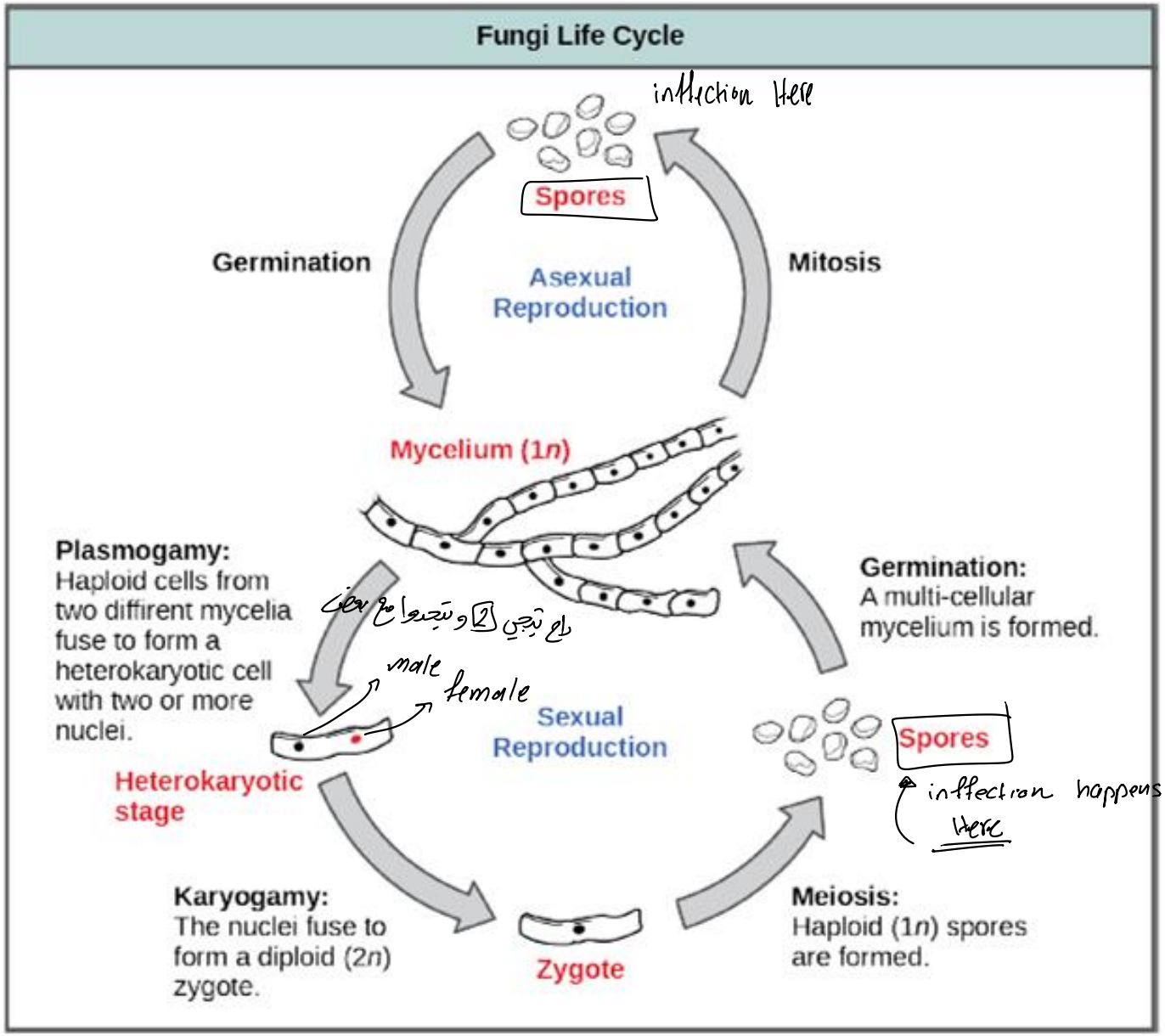
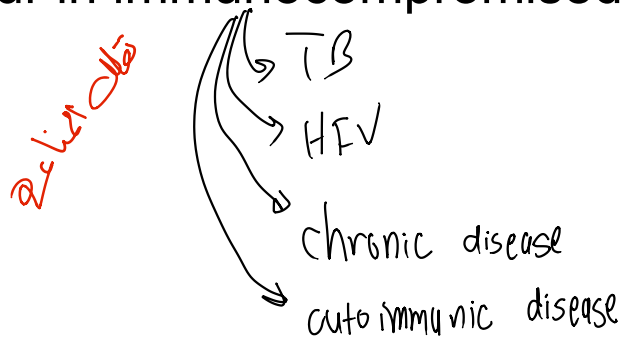


Figure 24.8 Generalized fungal life cycle. Fungi may have both asexual and sexual stages of reproduction.

Mycotic Infections

- Four general types:
  - Cutaneous
  - Subcutaneous
  - Superficial
  - Systemic
    - Can be life threatening
    - Usually occur in immunocompromised host

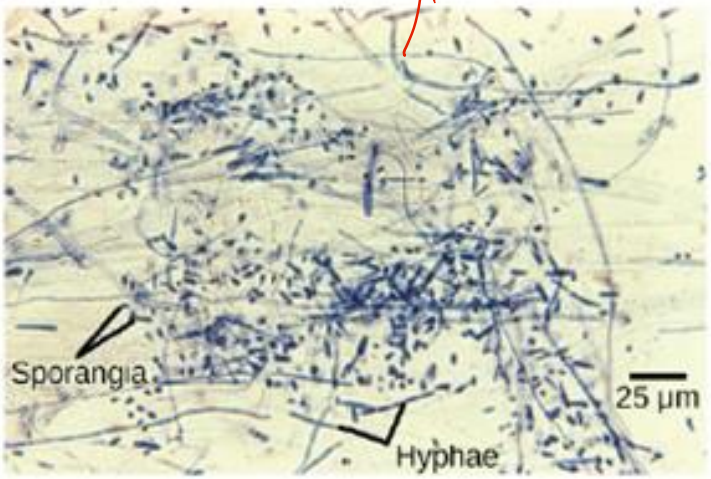


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تسبب عدوى تشبه أعراض الانفلونزا وهي من عدوى فطرية

تصيب scalp ال







(a) (b) (c)

Figure 24.27 Fungal diseases of humans. (a) Ringworm presents as a red ring on skin; (b) *Trichophyton violaceum*, shown in this bright field light micrograph, causes superficial mycoses on the scalp; (c) *Histoplasma capsulatum* is an ascomycete that infects airways and causes symptoms similar to influenza. (credit a: modification of work by Dr. Lucille K. Georg, CDC; credit b: modification of work by Dr. Lucille K. Georg, CDC; credit c: modification of work by M. Renz, CDC; scale-bar data from Matt Russell)

Mycotic Infections : *Candida albicans*

- May follow antibiotic therapy, antineoplastics, or immunosuppressants (corticosteroids)
- May result in overgrowth and systemic infections
- Growth in the mouth is called *thrush* or *oral candidiasis.*
- Common in newborn infants and immunocompromised patients
- Vaginal candidiasis
  - Yeast infection
  - Pregnancy, women with diabetes mellitus, women taking oral contraceptives

- *Candida albicans* is a yeast-like opportunistic pathogen
- Opportunistic pathogens normally HARMLESS and become pathogenic
- Overgrowth of target pathogen = superinfection

Cause?	*Infection?*	*Treatment?*
• ΔpH • Host immune defenses • Normal population altered causing overgrowth	• Vulvovaginal candiasis • Thrush	• Miconazole • Clotrimazole • Caspofungin

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Question #1

fungal infection نوع من

A patient has developed an aspergillosis infection. Which tissue does the aspergillosis affect?

A. Skin
B. Nails
C. Blood
D. Lungs

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Answer to Question #1

ANS: D

The primary tissue affected by aspergillosis is the lungs.

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ASPERGILLUS

Genus of ubiquitous, filamentous fungi acting as opportunistic pathogens

AIRBORNE

- Affects immunocompromised patients e.g. cancer, lung disease
- Transmission: inhalation of *Aspergillus* spores (conidia)

INFECTION

- Eye or lung infection
- Aflatoxin poisoning by mycotoxin produced by fungi causing hepatic cancer and cirrhosis

اسم ← toxin

يعني المرض العضوي خطير ولازم يتم معالجته

TREATMENT

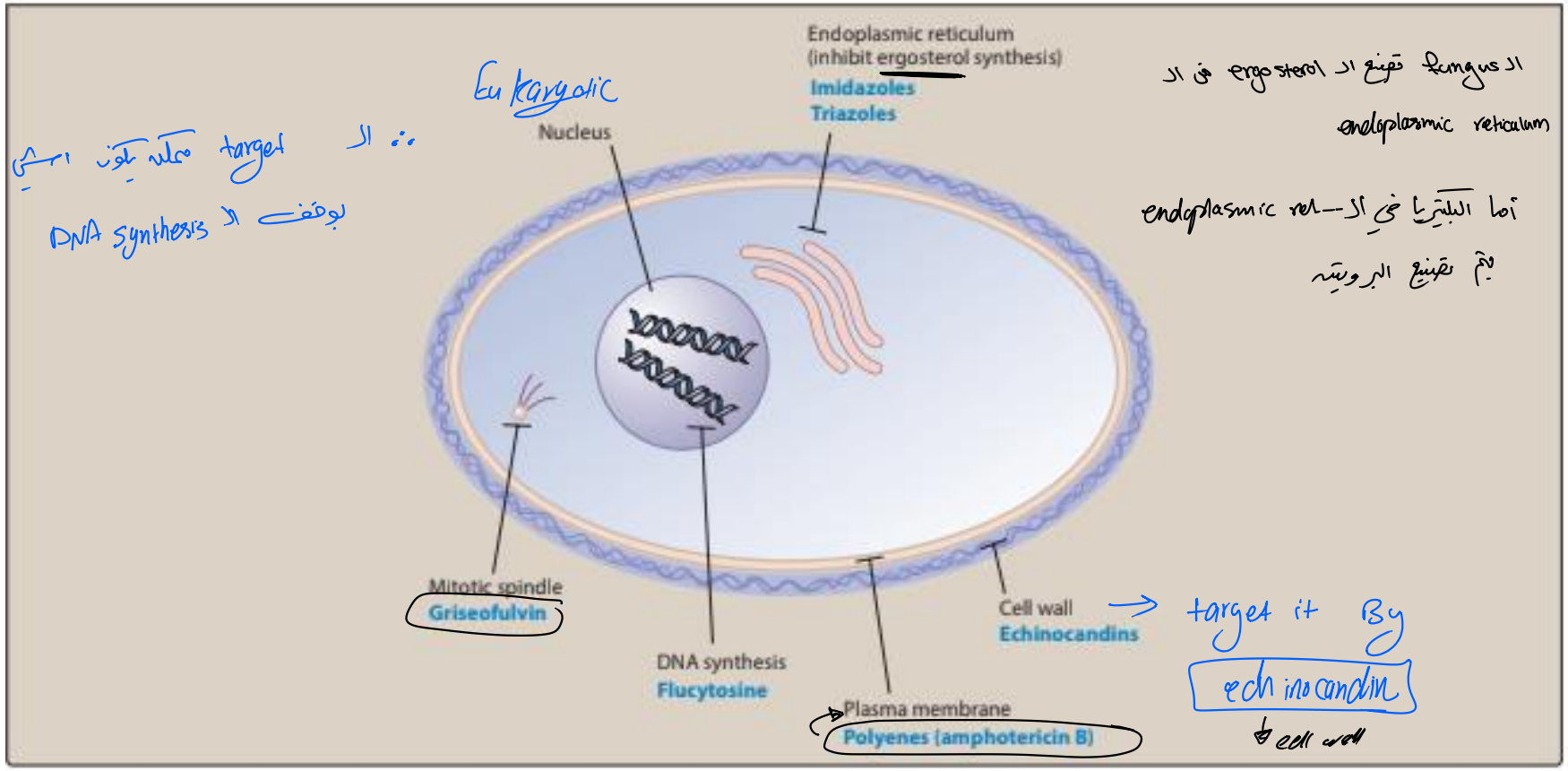
- Caspofungin *(Cancidas)*, member of echinocandin group
- Voriconazole, member of triazole group

Antifungal Drugs

- Drugs used to treat infections caused by fungi
- Systemic
  - Amphotericin B, caspofungin, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, micafungin, nystatin, terbinafine, posaconazole, anidulafungin, and voriconazole
- Topical
- **Ophthalmic: natamycin**

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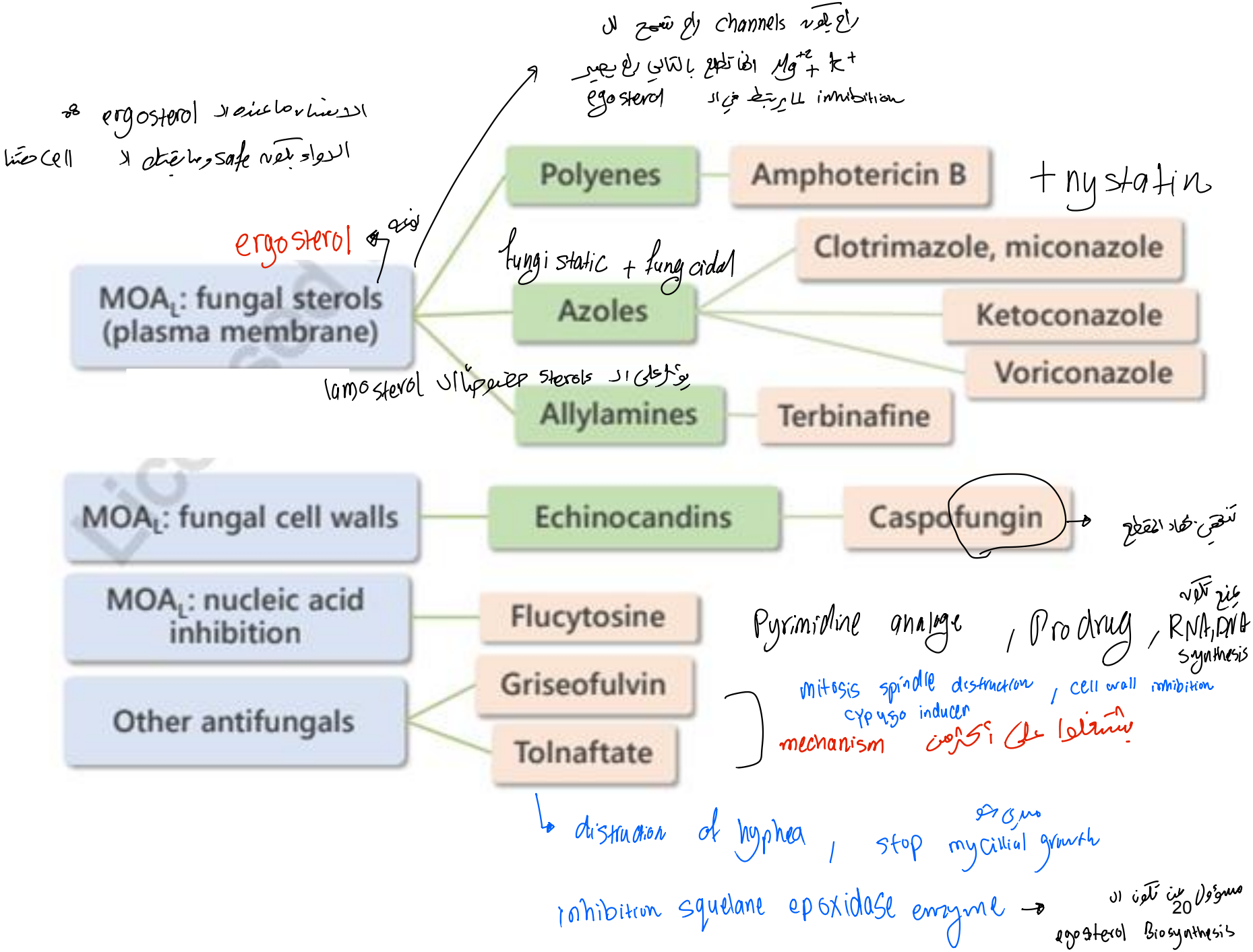
Cellular targets of antifungal drugs.



Antifungal Drugs (Cont.)

- Broken down into major groups based on their chemical structure
  - **Synthetic triazoles**: fluconazole, itraconazole, voriconazole
  - **Echinocandins**: caspofungin (cell wall)
  - **Synthetic allylamine**: terbinafine
  - **Polyenes**: amphotericin B, Amphotec (B), Abelcet (B), AmBisome (B), nystatin

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ergosterol
MOA$_L$: fungal sterols (plasma membrane)
Polyenes
Amphotericin B
+nystatin
Azoles
Clotrimazole, miconazole
Ketoconazole
Voriconazole
Allylamines
Terbinafine
MOA$_L$: fungal cell walls
Echinocandins
Caspofungin
MOA$_L$: nucleic acid inhibition
Flucytosine
Other antifungals
Griseofulvin
Tolnaftate
fungistatic + fungicidal
Pyrimidine analog
Prodrug
RNA, DNA synthesis
mitosis spindle destruction
cell wall inhibition
mechanism
distruction of hyphea
stop mycilial growth
inhibition squelane epoxidase enzyme
20 steps
ergosterol Biosynthesis

Mechanism of Action : Flucytosine

- **Antimetabolites:** Flucytosine is the only antifungal antimetabolite. It works by being converted to 5-fluorouracil (5-FU) in the fungal cell. **Also known as *5-fluorocytosine (5-FC)***
  - Taken up by fungal cells and interferes with DNA synthesis
  - 5-FU inhibits the enzyme thymidylate synthase as well as DNA, RNA, and protein production in fungal cells, leading to arrested growth.
  - Result: fungal cell death
  - Older drug; newer drugs are more commonly used

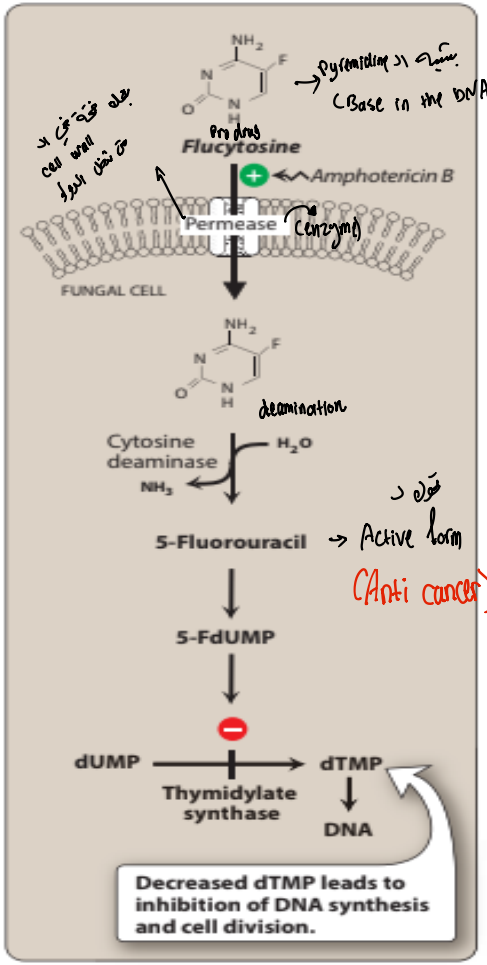


Figure 42.7
Mode of action of *flucytosine*. 5-FdUMP = 5-fluorodeoxyuridine 5′-monophosphate; dTMP = deoxythymidine 5′-monophosphate.

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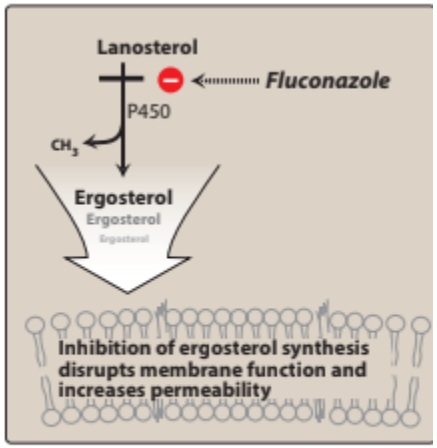


Figure 42.8
Mode of action of azole antifungals.

Mechanism of Action (Cont.)

- Griseofulvin
  - Disrupts cell division
  - Result: inhibited fungal mitosis (cell division)
  - Older drug; newer drugs are more commonly used

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Mechanism of Action (Cont.)

- Polyenes: amphotericin B and nystatin
  - These are broad-spectrum antifungals that bind to ergosterol in the fungal cell membrane, leading to membrane breakdown and fungal cell death.
  - Result: fungal cell death
  - Do not bind to human cell membranes or kill human cells
- Amphotericin B is used intravenously to treat severe systemic fungal infections.
- Nystatin is used orally for infections such as oropharyngeal candidiasis (thrush). Nystatin is not absorbed systemically when taken orally or topically; therefore, itis ineffective for systemic infections.

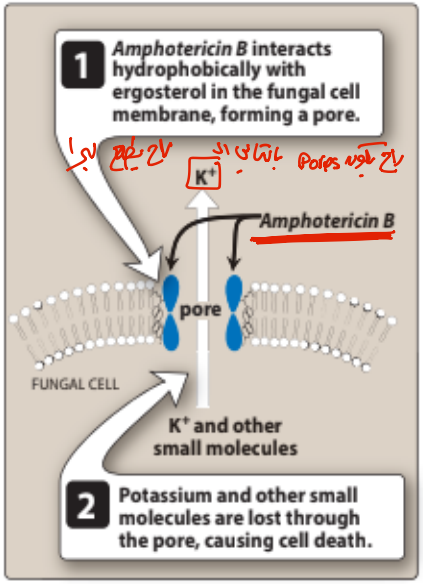


Figure 42.4
Model of a pore formed by *amphotericin B* in the lipid bilayer membrane.

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- **Imidazoles and triazoles**: ketoconazole, fluconazole, itraconazole, voriconazole
  - The azole antifungals include two broad classes: imidazoles and triazoles.
  - Examples of imidazoles include clotrimazole, miconazole, and ketoconazole.
  - Examples of triazoles include fluconazole, voriconazole, and posaconazole.
  - Inhibit fungal cell cytochrome P-450 enzymes, resulting in cell membrane leaking. These drugs work by inhibiting the enzyme 14-alpha-sterol demethylase. This enzyme is necessary for the fungal cell to produce ergosterol, which is then transferred to the cell membrane. Inhibition of this enzyme leads to arrest of fungal cell growth.
  - Result: altered cellular metabolism and fungal cell death

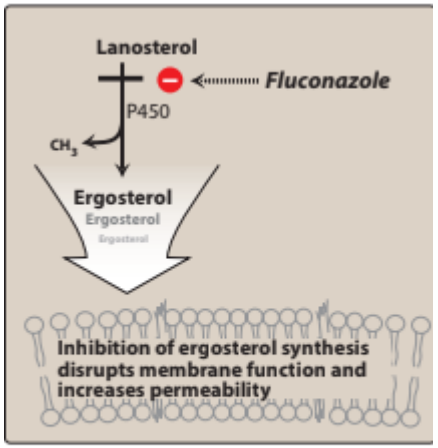


Figure 42.8
Mode of action of azole antifungals.

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Mechanism of Action (Cont.)

- Echinocandins: caspofungin, micafungin, and anidulafungin
  - These work by inhibiting the enzyme 1,3-beta-glucan synthase, which is responsible for providing structural integrity to the fungal cell wall.Inhibiting this enzyme decreases glucan synthesis(essential components of fungal cell walls) and disrupts the cell wall.
  - Result: fungal cell death

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Table 7.7 lists antifungal drugs and typical routes and dosing for adult and pediatric clients.

Drug	Routes and Dosage Ranges
Amphotericin B (Fungizone)	*Progessive, potentially life-threatening fungal infections:* *Adults:* 0.25–0.3 mg/kg IV daily over 2–6 hours. Total daily dose of 1.5 mg/kg should not be exceeded.
Anidulafungin (Eraxis)	*Candida:* *Adults:* 200 mg IV on day 1, then 100 mg IV once daily. *Children:* 3 mg/kg (not to exceed 200 mg) on day 1, followed by a once daily IV maintenance dose of 1.5 mg/kg (not to exceed 100 mg) thereafter for 14 days. *Esophageal candidiasis:* *Adults:* 100 mg IV loading dose on day 1, followed by a 50 mg IV once daily maintenance dose for 14 days.
Fluconazole (Diflucan)	*Oropharyngeal or esophageal candidiasis:* *Adults:* 200 mg orally on the first day, followed by 100 mg orally once daily for 2 weeks to prevent relapse.
Flucytosine (Ancoban)	*Symptomatic cystitis:* *Adults:* 50–150 mg/kg/day administered in divided doses at 6-hour intervals for 10 days.
Nystatin (Nystat)	*Oropharyngeal candidiasis:* *Adults and children:* Swish and swallow 400,000–600,000 units 4 times daily for 7–14 days. Continue for 48 hours after symptoms resolve and a negative culture is obtained. *Infants:* 200,000 units 4 times daily using a dropper.

TABLE 7.7 Drug Emphasis Table: Antifungal Drugs (source: https://dailymed.nlm.nih.gov/dailymed/)

Indications

- Systemic and topical fungal infections
- Drug of choice for the treatment of many severe systemic fungal infections is amphotericin B.
- Choice of drug depends on type and location of infection
- Fluconazole: passes into the cerebrospinal fluid and inhibit the growth of cryptococcal fungi, effective in the treatment of cryptococcal meningitis

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Question #2

infection on nails

A patient is diagnosed with onychomycosis. The nurse anticipates use of which medication for the treatment of this condition?

A. Terbinafine (Lamisil)
B. Voriconazole (Vfend)
C. Fluconazole (Diflucan)
D. Amphotericin B (Amphocin, Fungizone)

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Answer to Question #2

ANS: A

Terbinafine (Lamisil) is indicated for the treatment of onychomycosis (fungal infection of fingernail or toenail). Voriconazole (Vfend) is indicated for the treatment of invasive aspergillosis and other major fungal infections in patients who do not tolerate or respond to other antifungal drugs. Fluconazole (Diflucan) is indicated for the treatment of vaginal candidiasis, oropharyngeal and esophageal candidiasis, systemic candidiasis, and cryptococcal meningitis. Amphotericin B (Amphocin, Fungizone) is indicated for the treatment of systemic infections with broad spectrum of fungi.

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Antifungal Drugs: Contraindications

- Most common: drug allergy, liver failure, kidney failure, and porphyria (for griseofulvin)
- Itraconazole: contraindicated treatment of onychomycoses in patients with severe cardiac problems
- Voriconazole can cause fetal harm in pregnant women.

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Antifungal Drugs: Adverse Effects

Amphotericin B

- Cardiac dysrhythmias
- Neurotoxicity; tinnitus; visual disturbances; hand or feet numbness, tingling, or pain; convulsions
- Renal toxicity, potassium loss, hypomagnesemia
- Pulmonary infiltrates
- Fever, chills, headache, nausea, occasional hypotension, gastrointestinal (GI) upset, anemia

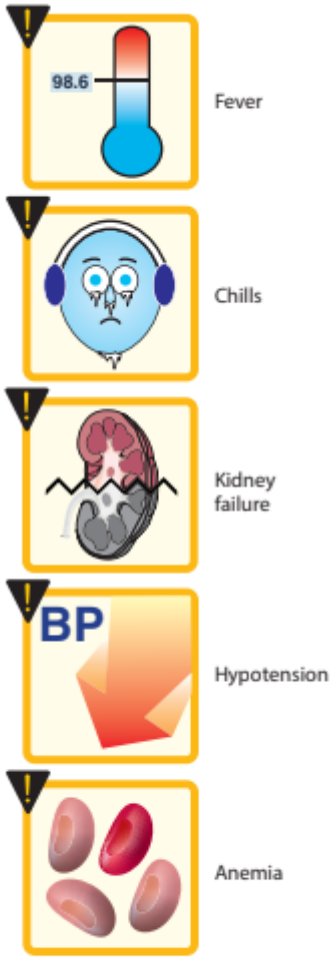


Figure 42.6
Adverse effects of *amphotericin B.*

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Amphotericin B: Adverse Effects: Prevention

- Prescribers commonly order various premedications: antiemetics, antihistamines, antipyretics, and corticosteroids.
- Prevent or minimize infusion-related reactions to amphotericin B
- Likelihood of such reactions can also be reduced by using longer-than-average drug infusion times (i.e., 2 to 6 hours).

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Question #3

A patient is receiving amphotericin B lipid complex. The nurse knows which as an advantage of the lipid formulations of this drug?

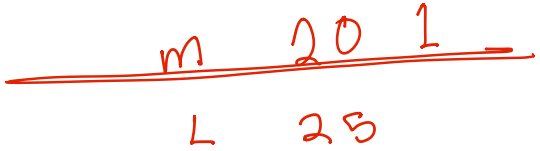
A. They have a lower cost.
B. They can be administered quickly.
C. They take longer to be absorbed.
D. They cause fewer adverse effects.

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Answer Question #3

ANS: D



Lipid formulations of amphotericin B have been developed in an attempt to decrease the incidence of its adverse effects and increase its efficacy. There are currently three lipid preparations of amphotericin B: (1) amphotericin B lipid complex (Abelcet), (2) amphotericin B cholesteryl complex (Amphotec), and (3) liposomal amphotericin B (AmBisome). These lipid dosage forms have a much higher cost than conventional amphotericin B and for this reason are often used only when patients are intolerant of or have an infection refractory to nonlipid amphotericin B.

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Antifungal Drugs: Adverse Effects

- **Fluconazole**
  - Nausea, vomiting, diarrhea, stomach pain
  - Increased liver enzymes
  - Use with caution in patients with renal and liver dysfunction
- **Nystatin** local
  - Nausea, vomiting, anorexia, diarrhea, rash

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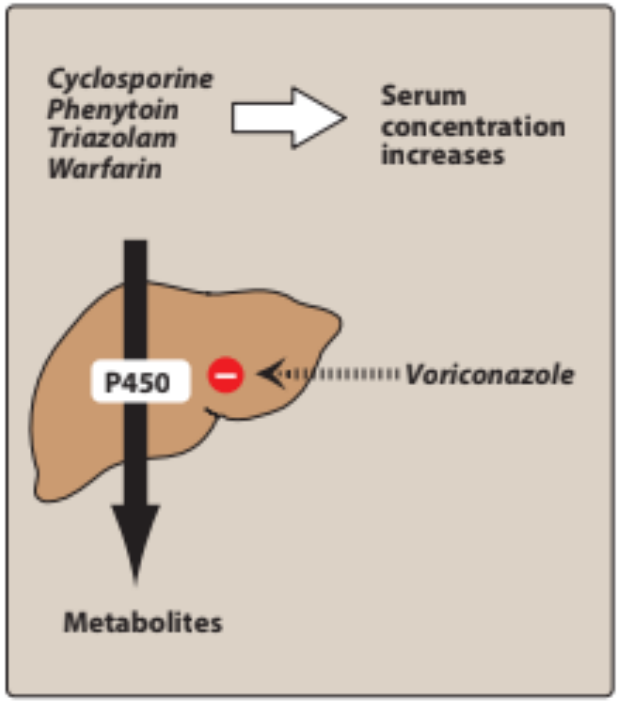
Antifungal Drugs: Contraindications

- Liver failure
- Renal failure
- Porphyria (griseofulvin)
- Drug allergy

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Antifungal Drugs: Interactions

- Many antifungal drugs are metabolized by the cytochrome P-450 enzyme system. (azoles)
- Co-administration of two drugs that are metabolized by this system may result in competition for these enzymes and thus higher levels of one of the drugs.



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Some oral and intravenously administered azole antifungals are strong inhibitors of CYP3A4.

Affected medications will have higher levels in the body and increase the risk for drug toxicity.

Table 7.8 is a drug prototype table for antifungal drugs featuring fluconazole. It lists drug class, mechanism of action, adult dosage, indications, therapeutic effects, drug and food interactions, adverse effects, and contraindications.

Drug Class Azole antifungal **Mechanism of Action** Inhibits fungal cytochrome P450 activity, decreasing ergosterol synthesis and inhibiting cell membrane formation	**Drug Dosage** *Oropharyngeal or esophageal candidiasis:* *Adults:* 200 mg orally on the first day, followed by 100 mg orally once daily for 2 weeks to prevent relapse.
Indications Treatment of fungal infections caused by susceptible fungi **Therapeutic Effects** Treats fungal infections caused by susceptible organisms	**Drug Interactions** CYP3A4 substrates Amiodarone Heart Carvedilol B-Blocker Diazepam **Food Interactions** No significant interactions
Adverse Effects Headache Skin rash Abdominal pain Diarrhea Dizziness QT interval prolongation	**Contraindications** Hypersensitivity Pregnancy Coadministration with QT interval–prolonging drugs Caution: Central nervous system impairment Renal impairment

TABLE 7.8 Drug Prototype Table: Fluconazole (source: https://dailymed.nlm.nih.gov/dailymed/)

Nursing Implications

- Before beginning therapy, assess for hypersensitivity, possible contraindications, and conditions that require cautious use.
- Obtain baseline vital signs, complete blood count, liver and renal function studies, and electrocardiography.
- Assess for other medications used (prescribed and over the counter) to avoid drug interactions.
- Follow the manufacturer's directions carefully for reconstitution and administration.
- Monitor vital signs of patients receiving intravenous (IV) infusions every 15 to 30 minutes.
- During IV infusions, monitor input and output to identify adverse effects.

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Question #4

Fifteen minutes after an infusion of amphotericin B was started, the patient begins to complain of fever, chills, muscle pain, and nausea. His heart rate has increased slightly, but his blood pressure is down to 100/68 mm Hg. What is the nurse's priority?

A. Notify the prescriber immediately.
B. Recognize an impending anaphylactic reaction and stop the infusion.
C. Assess for other symptoms of this expected infusion-related reaction.
D. Slow the infusion to reduce these adverse effects.

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Answer to Question #4

ANS: C

Almost all patients who receive amphotericin B experience fever, chills, hypotension, tachycardia, malaise, muscle and joint pain, anorexia, nausea and vomiting, and headache. For this reason, antihistamines, acetaminophen (an antipyretic), and antiemetics may be given as pretreatment to reduce these expected effects.

عشان هيك عشان أتأكد إذا هاد الأعراض طبيعية وهاد كرد فعل مرافق
وشوف الوضع إذا خطرة

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Nursing Implications

- Amphotericin B
  - To reduce the severity of the infusion-related reactions, pretreatment with an antipyretic (acetaminophen), antihistamines, antiemetics, and corticosteroids may be given.
  - Use IV infusion pumps and the most distal veins possible. for regular infusion of the drug.
  - Some oral forms should be given with meals to decrease GI upset; others require an empty stomach—be sure to check.

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Question #5

A patient is taking nystatin (Mycostatin) in an oral troche form for oral candidiasis. Which instruction is correct?

A. Allow the troche to dissolve slowly in the mouth.
B. Swish the medication in the mouth and then swallow it.
C. Chew the troche thoroughly to activate the medication.
D. Swallow the troche whole without chewing.

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Answer to Question #5

ANS: A

Oral troche or lozenge forms of this medication should be allowed to dissolve slowly in the mouth without chewing.

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Nursing Implications

- Nystatin given as an oral lozenge or troche should be slowly and completely dissolved in the mouth (not chewed or swallowed whole).
- Nystatin suspension should be swished thoroughly in the mouth as long as possible before swallowing.
- Monitor for therapeutic effects.
  - Easing of symptoms of infection
  - Improved energy levels
  - Normal vital signs, including temperature
- Monitor carefully for adverse effects.

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CLIENT TEACHING GUIDELINES

The client taking an antifungal should:

- Alert their health care provider about any signs of allergic reactions, including throat swelling, severe itching, rash, or chest tightness.
- Alert their health care provider about any recent antifungal medication use prior to starting therapy.
- Alert their health care provider that they are taking these medications, including the dose and frequency.
- Take the drug with food if it causes an upset stomach.
- Take a missed dose as soon as they remember; however, they should *not* take double doses.
- Alert their health care provider about starting any new medications that may interact with their antifungal therapy.

FDA BLACK BOX WARNING

يس في systemic وطيره بس الحياة داعوت
بسبب أعراضه الجانبية الخطيرة

Amphotericin B

Amphotericin B should be used primarily for treatment of clients with progressive and potentially life-threatening fungal infections; it should not be used to treat noninvasive forms of fungal disease such as oral thrush, vaginal candidiasis, and esophageal candidiasis in clients with normal neutrophil counts.





Thank you


"Tell me and I forget; teach me and I may remember; but involve me and I learn."
Benjamin Franklin
UMKC
School of Pharmacy

General Pharmacology

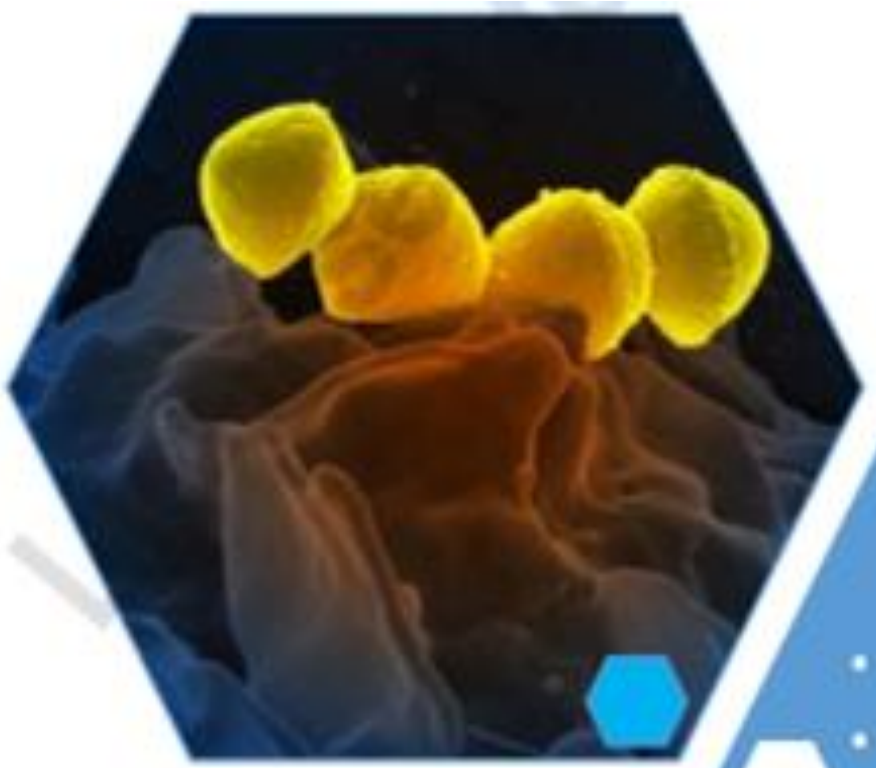
GENERAL PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY

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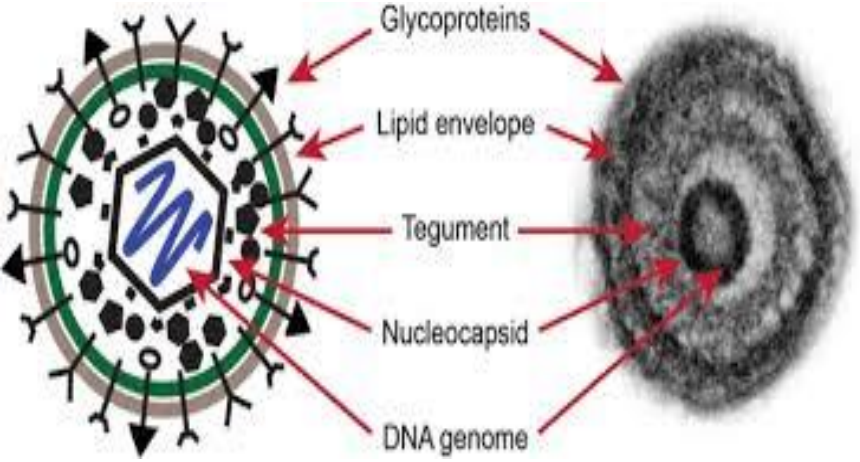
What causes Infection?



- Bacteria
- Viruses
- Parasites
- Fungi
- Other

ANTIVIRALS

A Cartoon Illustrating Generic Virus Components (Virion)



attachment for host

Surface Glycoproteins

Viral Coat

protection

Protein Envelope

Capsid

Viral Enzymes and Proteins

Viral Nucleic Acids (DNA or RNA)(Core)

The virion is the complete package. Crystalline viruses have various shapes when viewed by electron microscopy (spheres, icosahedrons, etc.) and not all viruses have all of the component parts illustrated.

Important Terms

Viruses are submicroscopically small obligate parasites that infect living cells and take over their biochemistry so as to produce more virus particles. Both **DNA and RNA viruses** are known.

The **viral core** consists of single or double stranded RNA or DNA molecules.

The **capsid (viral protein coat)** surrounds the viral core and consists of a membrane and a glycoprotein coat.

The **envelope** is an optional protein coat surrounding the capsid.

The viral coat encloses the virion. Coat glycoproteins are antigenic. Some of these glycoproteins also serve to attach the virus to target-cell surface receptors. They also dictate the shape of the virion, function to cause penetration, uncoating and release of the viral core.

The **virion** is the complete viral package containing most or all of the above component parts.

General Principles of Virology

- out side the host they are non living
- only inside the host they can replicate

Viral replication

- A virus cannot replicate on its own.
- It must attach to and enter a host cell.
- It then uses the host cell's energy to synthesize protein, DNA, and RNA.

Viruses enter the body through at least four routes:

- Inhalation
- Ingestion
- Transplacentally
- Inoculation

Viruses are difficult to kill because they live inside the cells.

- Any drug that kills a virus may also kill cells.

there is no spesificity for virus only

Viruses are packaged DNA or RNA molecules that absolutely require use of the biosynthetic capabilities of specifically (targeted host animal cells)for their reproduction, energy and substrates.

راح تهجم الـHost خلية الفايروس راح تقضي على كل شي حولي عندها

The invaded cells ultimately become non-functional and die.

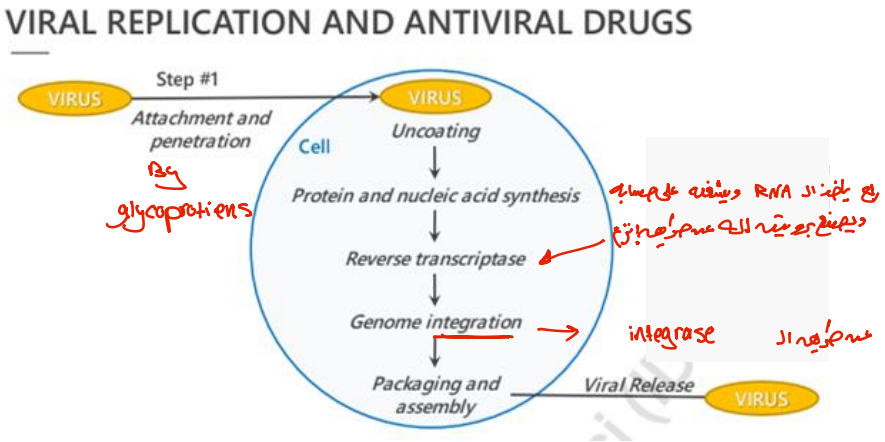
Cell death, loss of function, and cross-reactivity of antibodies are the main causes of pathology.

Treatment consists of preventing viral entry, reproduction and release**.**

Drugs are classified into groups as:

- Antimetabolites
- Inhibitors of viral nucleic acid formation
- Inhibitors of late viral protein biosynthesis and process
- Preventers of attachment or penetration of viruses
- Inhibitors of viral assembly and release
- Antibodies

حتى نمنع دخول virus او تكاثره



These are often used in combinations.

At the end of this section the student is expected to discuss knowingly these and additional features of antiviral chemotherapy.

Strategy of Antiviral Treatment

أفضل علاج

Historically the best treatments for viral infections are preventative or vaccination.

Viruses live in human cells and utilize the host's cellular "machinery" for many of their biochemical processes thus the opportunities for selective chemotherapy are more limited than those presented by bacteria.

Bacteria are monocellular plants with a distinct biochemistry so are comparatively target rich compared with viruses.

Previously most antiviral chemotherapy involved attacking the DNA and RNA of the viruses. This was narrow in spectrum and relatively toxic to host cells as well.

Increasingly antiviral chemotherapy involves the use of combinations of agents with different modes of action in order to minimize resistance development.

إذا بدي أعتني على الـ virus راح أعتني على الـ host cells كمان فالكيماوي بكون كتير ضرر

Infection of Cells by Viruses

Viruses gain entry into susceptible animal cells by first attaching themselves by surface glycoproteins to cell surface protein or carbohydrate receptors. These are very specific proteins so individual viruses have rather specific cell targets.

Penetration takes place by one of several mechanisms.

1. Some inject their viral core through the cell membrane using enzymes.
2. Others enter intact by various methods: **fusion of the viral envelope** with the plasma membrane or by **endocytosis** (engulfment of the virion to produce an endosome/vesicle which fuses with lysosomes that remove the viral coat.

Early genes incorporate the viral nucleic acids into the host cell genome and alter its biochemistry so as to reproduce the virus. Late genes are involved in the synthesis of the viral capsid, envelope, etc. Self assembly takes place to produce multiple copies of the virus for export. Export takes place by fusion with the cell membrane followed by budding or pinching off and release.

Viral Reproduction of Their Nucleic Acids

For infection to succeed, viral nucleic acids must be converted into proteins and new viral nucleic acids in host (infected) cells and these must be assembled for export.

DNA viruses have their DNA incorporated into the genome of target cells (recombination) whereupon host cells reproduce the virus particles. Some DNA viruses have a DNA polymerase of their own that multiplies the viral DNA prior to incorporation.

RNA viruses have various mechanisms for the replication of their RNA.

Type 1 have single stranded RNA that can be transcribed directly as mRNA into proteins by the ribosomes of infected cells.

Type 2 have antisense RNA that must be transcribed into sense RNA before it can be reproduced. These viruses have an RNA-dependent RNA polymerase (not present in the host) that performs this function thus making multiple copies of mRNA molecules that are transcribed for host ribosomes to use.

Type 3 have a reverse transcriptase (RNA-dependent DNA polymerase) (not present in uninfected cells) that translates their double stranded RNA into DNA which becomes incorporated into host cell genomic DNA for replication.

Viral Illnesses

- Smallpox (poxviruses)
- Sore throat
- Conjunctivitis (adenoviruses)
- Warts (papovaviruses)
- Gastroenteritis (rotaviruses, Norwalk-like viruses)
- Hepatitis (hepadnaviruses)

- Most viral illnesses are bothersome but survivable.
- Effective vaccines have prevented some illnesses.
- Effective drug therapy is available for a small number of viral infections.

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Some Typical Virus Diseases

DNA viruses **1. Herpes Family**
Herpes I or II (Herpes (herpesviruses);
Chicken pox (varicella);
Shingles (varicella zoster);
Mononucleosis (HSV and Epstein-Barr);
CNS motor disease (cytomegalovirus=CMV)
2. Adenoviruses
3. Hepatitis B
3. Human papilloma viruses
4. Human parovirus

opportunistic viruses → يعني لو الإنسان مناعته ضعيفة راح تصيبه فيه وأصلاً كانت موجودة لا مسببة

RNA viruses (R viruses : Rhino-Rota-Rabis-Rubella)- Hepatitis Except B- polio virus- yellow fever virus- MMR (Measles, Mumps (myxovirus); .

Influenza(orthomyxoviruses), Rabies (rabdovirus); صرع الكلب Respiratory Syncytial Virus(RSV),

Yellow Fever, Encephalitis (arbovirus); Respiratory infections (coronaviruses, Common Cold (rhinovirus));

Poliomyelitis (enterovirus); AIDS(Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome); Leukemia (retrovirus)

Immune Response To Viruses

The immune response recognizes viruses surface proteins as “foreign” and marks them for clumping and digestion.

1. **Macrophage engulfment**
2. **Digestion of virus and display of fragments on surface (APC)** → راح يتقطع الى اجزاء صغيرة تظهر على سطح الخلية عشان يعرفها الـ APC
3. **APC’s bind to CD-4 cells of thymus origin** (Antigen presenting cells) IL-1, 2, 3, 4, 5
4. **Primed CD-4 cells mature, produce cytokines, and recruit other cells**
5. **Some mature CD-4 cells become memory cells**
6. **Virions are clumped by antibodies and phagocytized** → راح تبقى الها انتجينات حتى تقضي عليها وتبقى خزنت معلومات عنها
7. **Natural killer cells (CD-8) are formed to kill virus particles**
8. **Some mature CD-8 cells also become memory cells**

Virus Therapy

1. **Prevention of exposure**
2. **Use of immunostimulant drugs**
3. **Vaccination**
4. **Chemotherapy : Antiviral chemotherapy historically has proven to be difficult because of the great similarity between virus infected and normal host cells.**

Antiviral drugs kill or suppress the virus by destroying virions or inhibiting the ability of viruses to replicate; controlled by current antiviral therapy.

Immunoglobulins are concentrated antibodies that can attack and destroy viruses.

Today, inhibition of specific virus enzymes and functioning proteins has proven more successful than killing cells or damaging their DNA/RNA.

- **Viruses controlled by current antiviral therapy**
  - Cytomegalovirus (CMV)
  - Hepatitis viruses
  - Herpesviruses
  - HIV
  - Influenza viruses (the “flu”)
  - Respiratory syncytial virus (RSV)
  -
- **Key characteristics of antiviral drugs**
  - Able to enter the cells infected with virus
  - Interfere with viral nucleic acid synthesis, regulation, or both
  - Some drugs interfere with ability of virus to bind to cells.
  - Some drugs stimulate the body’s immune system.

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Antiviral Drugs

- Opportunistic infections
  - Occur in immunocompromised patients
  - Would not normally harm an immunocompetent person
  - Require long-term prophylaxis and antiinfective drug therapy
  - Can be other viruses, fungi, bacteria, or protozoa

لا تؤثر على الأشخاص الذي عندهم مناعة قوية

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Antiviral Drugs

- Antiviral drugs
  - Used to treat infections caused by viruses other than HIV

- Antiretroviral drugs
  - Used to treat infections caused by HIV, the virus that causes AIDS

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Antiviral Drugs

Best responses to antiviral drugs are in patients with competent immune systems.

A healthy immune system works synergistically with the drug to eliminate or suppress viral activity.

- **Adamantane antivirals** :Amantadine, Rimantadine :
- **Neuroaminidase enzyme inhibitors:** Oseltemavir PO and Zanamivir inhalation
- **NUCLEIC ACID ANALOGS**:

1. Guanosine analog: Acyclovir- Ganciclovir- Ribavirin- Entecavir- Valacyclovir and vanganciclovir
2. Cytosine analog: Lamuvidine-Cidofovir
3. Thymidine analog :Telbivudine

NS3/4A serine protease inhibitors :Boceprevir and telaprevir

- **Acyclic guanosine nucleoside derivative** :Penciclovir and famciclovir:
- **Fluorinated pyrimidine nucleoside analog** : Trifluridin
- **A phosphonoformate (a pyrophosphate derivative):** Foscarnet:
- Interferon:

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Question #1

An 82-year-old woman is unable to take the influenza vaccine because of allergies, but she has been exposed to the virus through a family reunion. She does not yet have symptoms of the flu. Which option would be best for her?

A. She should receive the flu vaccine as soon as possible.
B. She should receive zanamivir (Relenza) in the inhalation form.
C. She should begin oral oseltamivir (Tamiflu) therapy when symptoms begin.
D. She should begin oral oseltamivir (Tamiflu) therapy as soon as possible.

NOTE: *No input is required to proceed.*

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Answer to Question #1

ANS: D

Oseltamivir (Tamiflu) is the only one indicated for prophylaxis of influenza infection. Both oseltamivir and zanamivir can be used to treat active influenza illness.

Treatment with oseltamivir and zanamivir ideally should begin within 2 days of symptom onset.

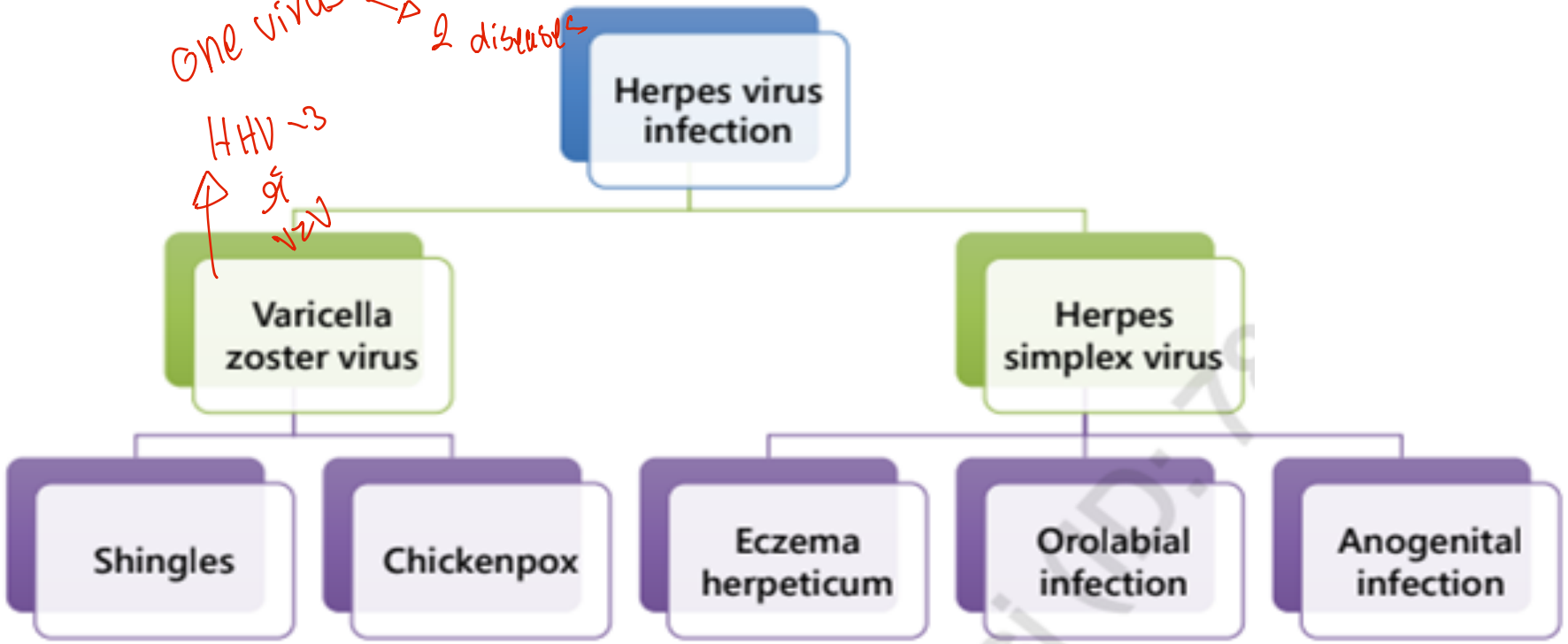
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Herpes Simplex and Varicella-Zoster Virus Infections

- Herpesviridae (DNA viruses)
  - HSV-1 (oral herpes)
  - HSV-2 (genital herpes)
  - Chickenpox and shingles (HHV-3 or VZV)
  - Epstein-Barr (HHV-4)
  - CMV (HHV-5)
  - Human herpesviruses 6 and 7 are not especially clinically significant; immunocompromised patients
  - Kaposi's sarcoma (HHV-8)

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Herpes Simplex and Varicella-Zoster Virus Infections



one virus → 2 diseases

HHV-3 أو VZV

HSV-1

(Blisters)

Shingles (HHV-3 or VZV)

Painful: opioids for pain control

Postherpetic neuralgias

Acyclovir may speed recovery; best results are generally seen when the antiviral drug is started within 72 hours of symptom onset.

Zostavax

Chickenpox → children (HHV-3 or VZV):

varicella virus vaccine

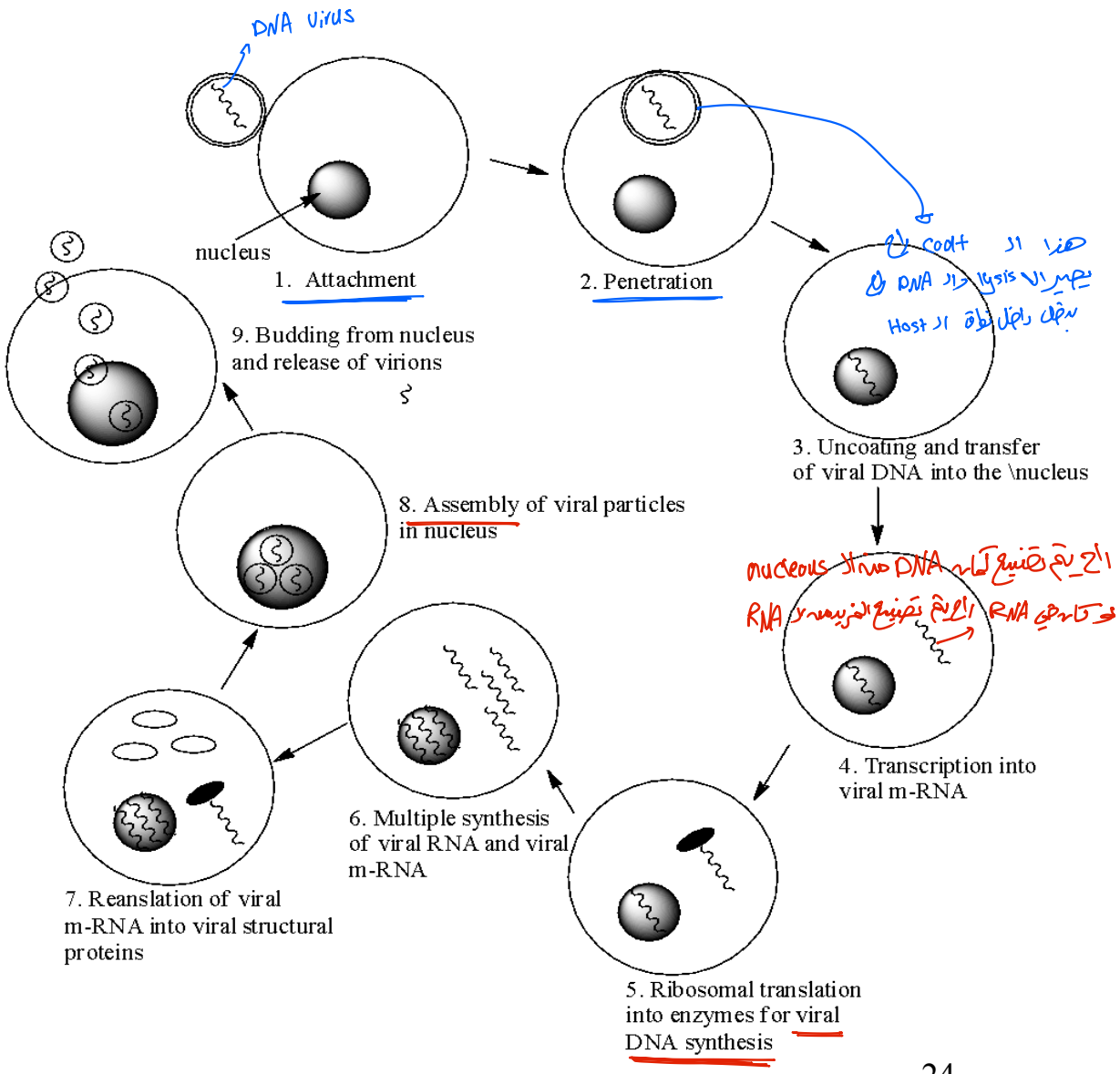
Herpesviridae HSV-2 (genital herpes)

- Highly transmissible
- "Neonatal" herpes

The Herpes Virus Infectious Cycle

1. Attachment to cell surface receptors.
2. Penetration of the cell membrane.
3. Un-coating, viral DNA translocates to nucleus
4. Integration into nuclear DNA by an integrase Transcription (DNA into RNA)
5. Translation into viral enzymes
6. Synthesis of viral DNA
7. Translation into viral pre-protein Viral protease cuts into functional proteins
8. Assembly into virions
9. Budding and release into the exterior

Cycle repeats



Genital Herpes Virus Disease

Genital herpes and cold sores are caused by herpes simplex Type 1 (HSV-1) and Type 2 (HSV-2) viruses (DNA type) and is spread by intimate contact.

Most commonly HSV-1 infections occur above the waist and HSV-2 below.
HSV-1 is generally milder and a person with one of these infections can contract the other as well.

About 1/6th of the US population has genital herpes. Keep the area dry and clean during outbreaks and avoid physical contact from the first appearance of symptoms (tingling, itching, burning) until all of the sores are healed (not just scabbed-over). Wash carefully with soap and water if contact has occurred.
There are accurate blood tests for diagnosis.
No vaccine is yet available but may appear soon. A vaccine will not be useful for those already infected.
THERE IS NO CURE. L-lysine in the diet inhibits HSV formation whereas L-argenine promotes it. This seems to involve the amino acid composition of the capsular proteins. HSV is latent in nerves between episodes. Passage of neonates through a diseased birth canal is dangerous and can readily lead to blindness or even death.

Herpes Zoster (Shingles)

This painful disease is caused by the same virus as that which causes chicken pox.

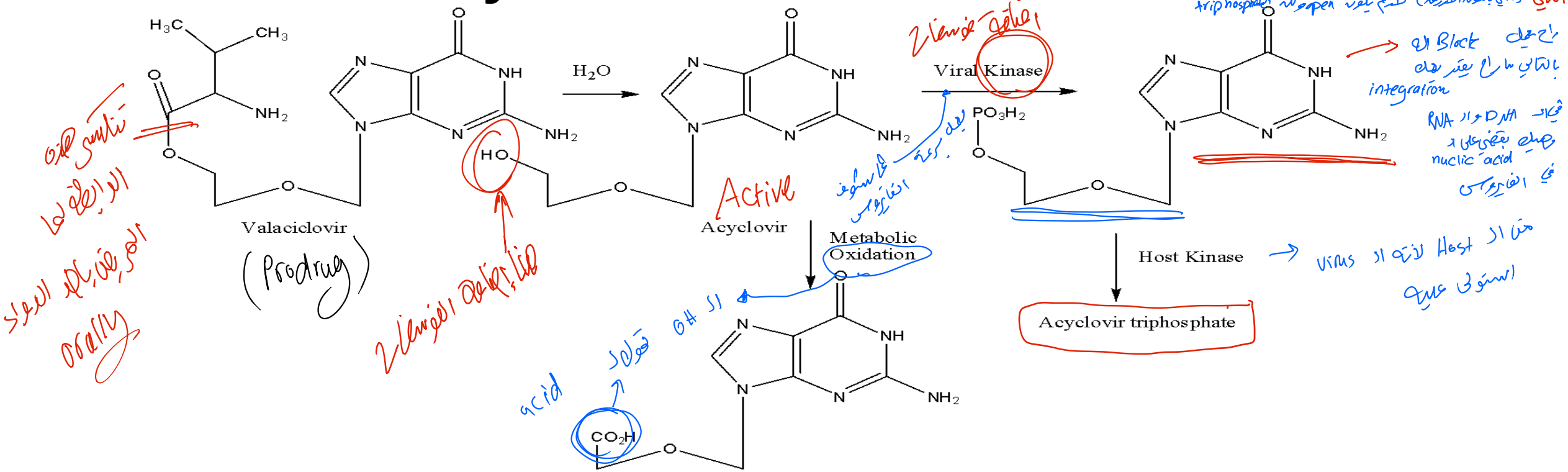
About 1/5 of those who get chicken pox get herpes zoster. Between active episodes it lies dormant in nerve cells (as is the case with HSV).

Immune suppression is associated with herpes zoster outbreaks. Severe pain and blistering of the trunk and buttocks are commonly experienced. Blisters on the eye can lead to blindness.

إذا أنا مسكت الـ blister راح تنفخ وتفقع ولا لمست السائل بتجيبها معاك
العين راح يصير عمى بالفيروس

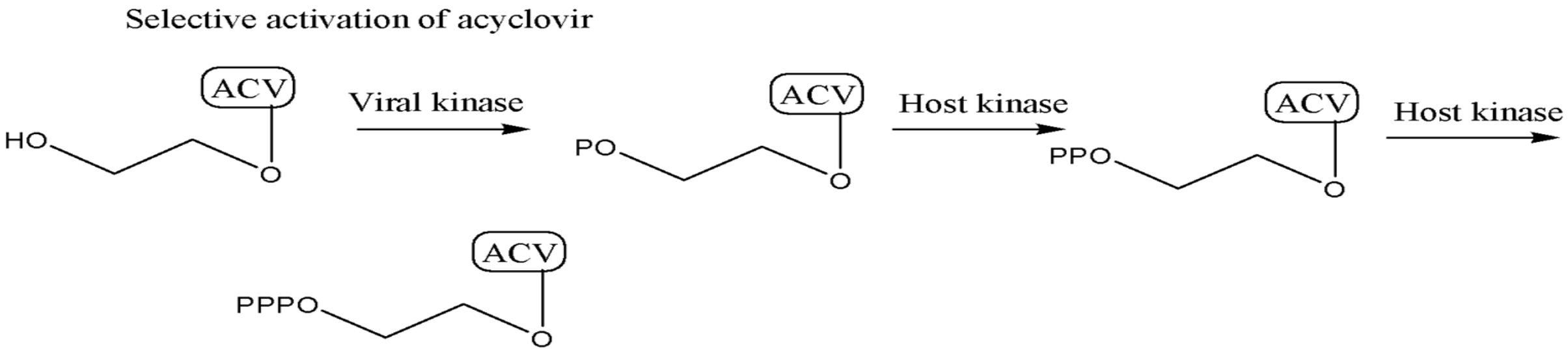
Herpes zoster can be transmitted by contact with weeping blisters. Spontaneous resolution is common and reoccurrence is uncommon.

Acyclovir And Valaciclovir



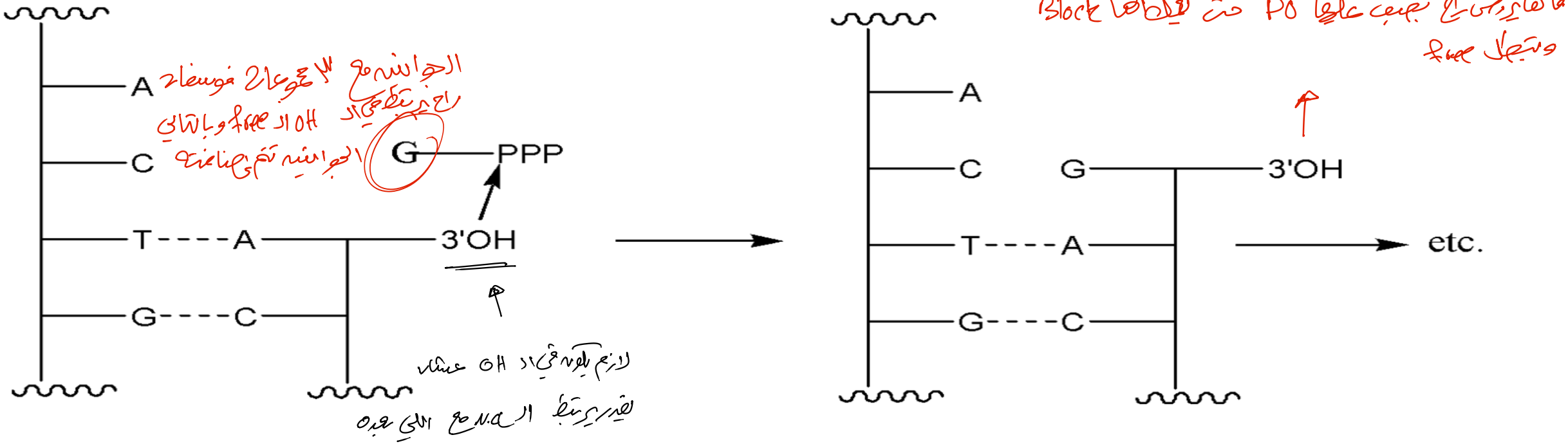
The virus produces a virus specific thymidine kinase. The host cell thymidine kinase almost totally fails to monophosphorylate acyclovir this being done by a viral kinase in a slow (rate determining) step. A host kinase phosphorylates the monophosphate, however, to the triphosphate which product inhibits the DNA polymerase and is a DNA chain growth terminator. This sequence accounts for the selectivity of the agent (lethality is demonstrated almost exclusively to virus infected cells). Resistance takes place by mutation of the viral kinase to greater substrate selectivity or by a decrease in production of the viral enzyme. Patients and their care givers should be instructed to use a barrier when applying the ointment to avoid auto-inoculation. Valacyclovir is a prodrug of acyclovir. Acyclovir is available orally, topically and by injection. Its use decreases the duration and frequency of outbreaks.

Molecular Mode of Action of Acyclovir: Selective Activation



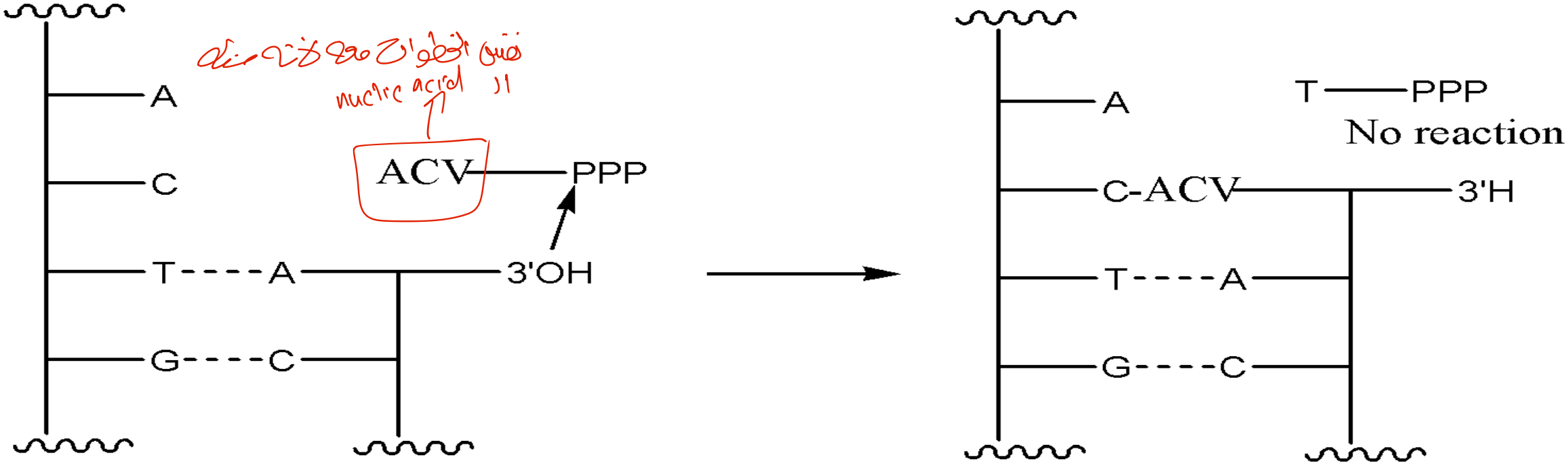
Molecular Mode of Action of Acyclovir: Obligate DNA Chain Termination

1. Normal polymerization of DNA



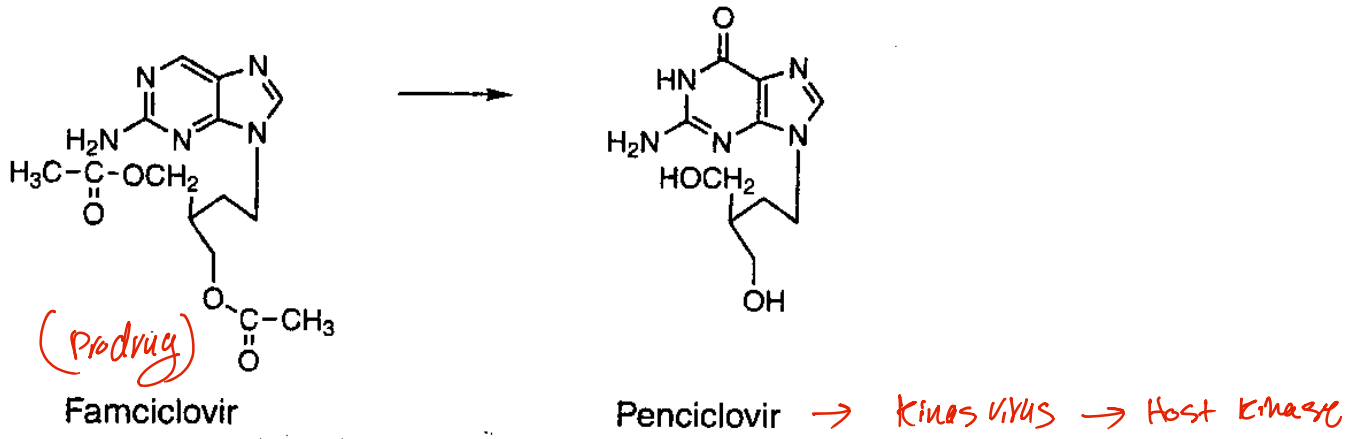
Molecular Mode of Action of Acyclovir: Obligate DNA Chain Termination

2. Chain termination by acyclovir



The lack of a nucleophilic C-3' hydroxyl in acyclovir prevents chain extention of DNA.

Famcyclovir And Penciclovir



FAMCICLOVIR is a prodrug of penciclovir used orally for treatment of herpes zoster, genital herpes and hepatitis B. PENCICLOVIR is its active metabolite requiring both oxidation and hydrolysis for conversion. Penciclovir itself is poorly water soluble and is not significantly absorbed when taken orally.

It is monophosphorylated by the viral kinase in infected cells and this is converted to the triphosphate which inhibits viral DNA polymerase.

These agents are also examples of the molecular dissection mode of drug design.

Penciclovir is about 100-times less active than acyclovir but is present in much higher concentrations and for a longer time in infected cells so is clinically roughly equivalent.

Influenza Is Caused By An RNA Virus

WWW.CDC.GOV/NCIDOD/DISEASES/FLU/FLUINFO

A highly infectious respiratory disease (nose, throat, lungs) spread by inhaling flu virus-containing droplets expelled by a flu sufferer. Hand to mouth spread is also common. Contagious for at least a week early in the infection. It differs from colds in having fever, headaches and extreme exhaustion.

Adults have several infections over the years so build up some tolerance. Children do not have this advantage so suffer more severely.

Us flu season = Nov□Apr. 10-20% of the U.S. population gets it each year; 36,000 die. "Old man's friend"

"STOMACH FLU" (DIARRHEA) IS NOT FLU (influenza).

Three forms of virus: A, B, C. Normal reservoir is birds and pigs and index sources of the virus tend to be farms raising both. The virion contains several different RNA molecules contributing to the ease of mutation. The virus passes poorly between fowl and humans but readily to pigs. The virus passes readily from pigs to humans. Thus a three-species spread is often involved.

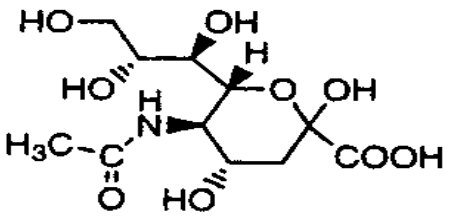
Give annual flu shots. Don't give antibiotics and don't give aspirin to children or teen agers.

1918-1919 pandemic □ 500,000 us deaths/20-50m worldwide.

Influenza - 2

- The flu virus capsid encloses three key proteins: RNA polymerase, neuraminidase (aids the virus in penetrating the target cells by cleaving N-acetylneuraminic acid (N-AMA) from the glycoproteins and glycolipids in the protective mucous layer, and hemagluttinin (which aids the virus in attaching to host cell membranes by binding to the N-AMA.
- Following binding, the virus enters by endocytosis following a conformational shift of the hemagglutinin. The viral RNA is released into the cell.
- The viral RNA copies the RNA which migrates to the nucleus and serves as a mRNA leading to copying of the viral proteins.
- Self assembly, migration to the cell membrane, budding and release follow.
- The extreme virulence of the 1918 influenza strain is believed to be the consequence of two point mutations in the hemagglutinin that allowed the virus to pass from one mammalian species to another far more readily than is normally the case. The specific nature of the hemagglutinin dictates majorly the kinds of cells to which the virus can bind.

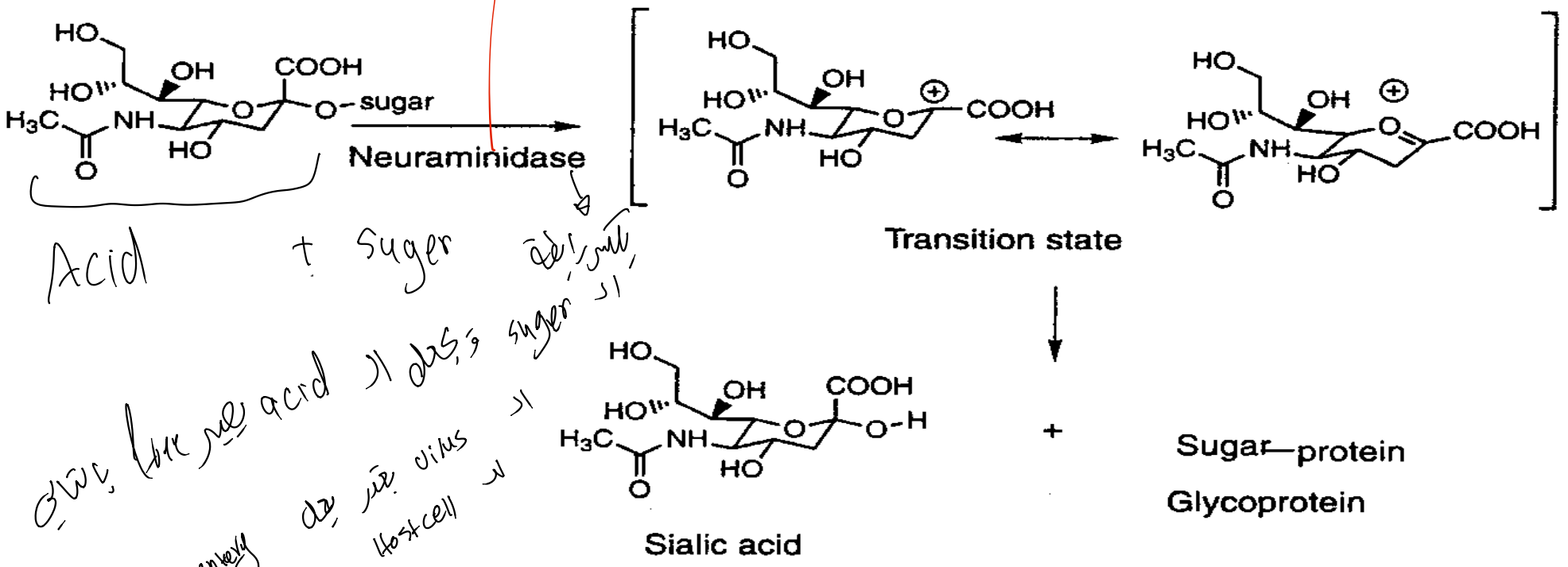
Sialic Acid And Neuraminidase



Sialic acid

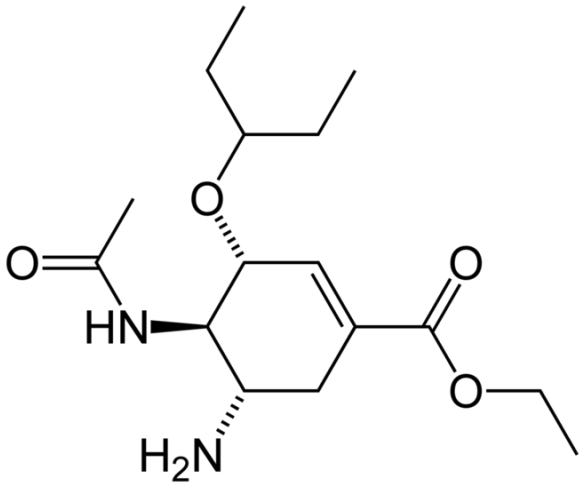
(Act as receptor)

mono schavid important for virus to enter the Host cell

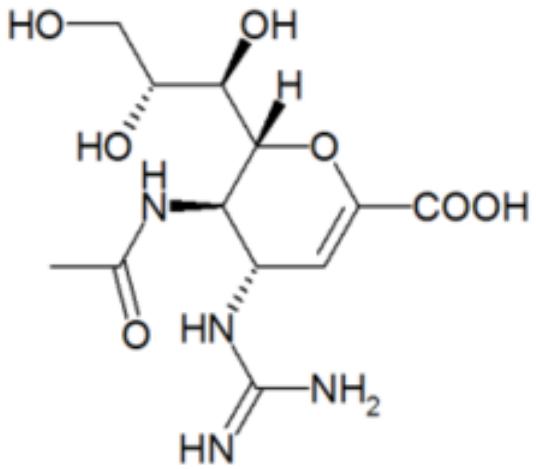


Oseltamivir and Zanamivir

Started within 48 hours of symptoms, oral oseltamivir is rapidly converted to its active form (by ester hydrolysis) and decreases the severity and duration of symptoms caused by influenza A or B.
It is also effective prophylactically.
Zanamivir does not need hydrolysis to be active.
These drugs inhibit neuraminidase. They are transition state inhibitors.



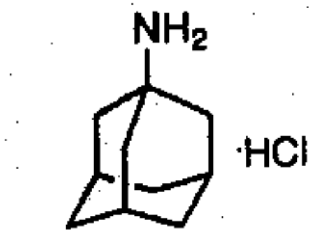
Olseltamivir



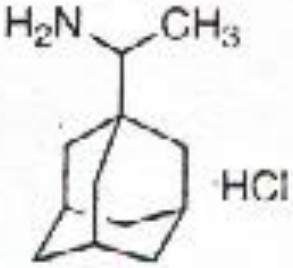
Zanamivir

Amantadine And Rimantadine

prophylaxis of the influenza



Amantadine



Rimantadine

These agents are used for influenza A prophylaxis and treatment. Amantadine is also used for rubella (German Measles) treatment.

They are used for the whole exposure period and have a half life of 15-20 hours.

They are 50-70% effective if given before exposure. Resistance is common so their use is fading.

The mechanism of amantadine's and rimantadine's antiviral activity involves binding in the ion channel of a viral protein, M2, which is required for the viral particle to become "uncoated" by endocytosis once taken inside a cell.

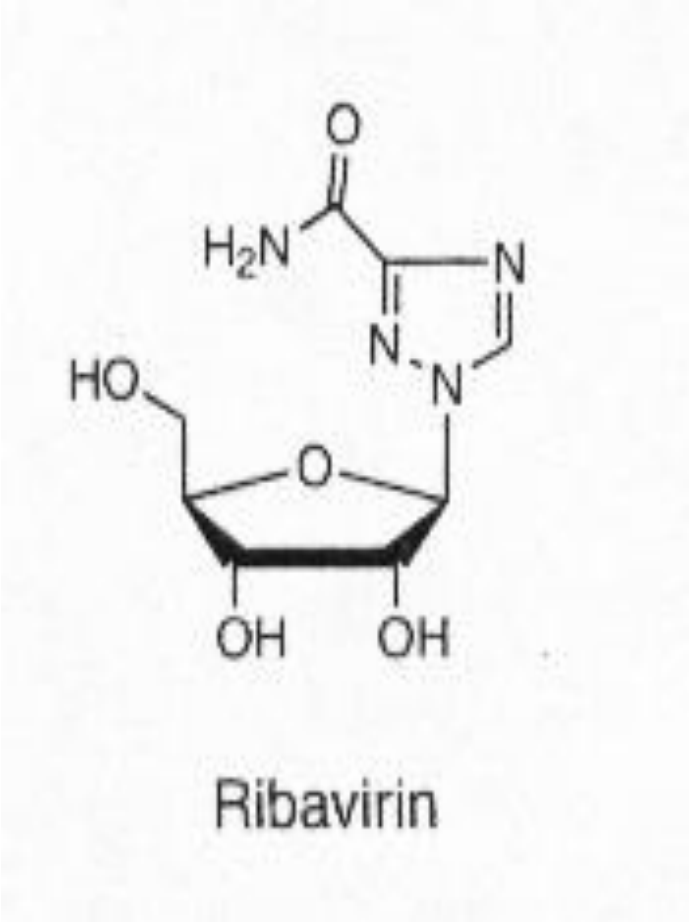
Respiratory Syncytial Virus Disease (RSV)

RSV is the leading cause of lower respiratory tract infections in infants and young children.

***a.* 2/3 of babies get RSV during the first year of life and almost 100% have it by two years of age as it is highly infectious. It is spread by droplets or via hand contact. Visiting family and friends want to hold the baby but must be cautioned to scrub in order to prevent RSV.**
This is particularly important if the child is at home. Mostly this virus causes a mild URT infection resembling a cold but in some children, esp. premature children and those with chronic RT infections, it can progress to a severe, life-threatening LRT infection.
Hand washing and avoiding exposure to other children and smoking is important in prevention.

There is no vaccine. It is treated with either ribavirin or palivizumab.

Ribavirin



Ribavirin

Ribavirin is used for treatment of respiratory syncytial virus infections.
It is a molecularly dissected analog of guanosine.
It is broad spectrum against DNA and RNA viruses.

The triphosphate is made intercellularly and inhibits virus-specific DNA and RNA polymerases by a mechanism that is yet unclear.

Cytomegalovirus Disease

CMV is ubiquitous and infects between 50-85% of US adults by 40 years of age. Fetuses are particularly prone to infection.

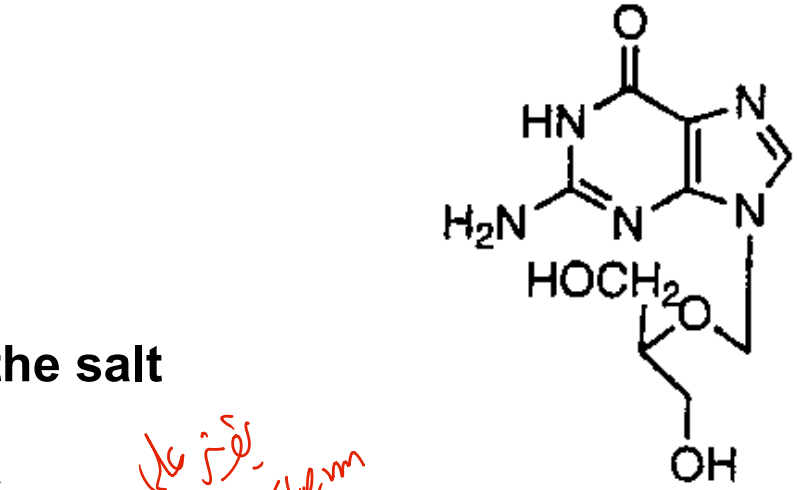
Most adults getting infected after birth suffer only very mild symptoms (resembling mononucleosis) and the virus remains viable but dormant thereafter. Chemotherapy is applied only in severe cases.

Immune suppression can reactivate the infection in which case the infection can be serious. Severe symptoms include liver damage and blindness. The virus is shed in excreta and is spread by intimate contact with various body fluids or by organ transplantation with an infected organ. Hand washing is the simplest effective prophylactic action.

The highest risk situation is for a woman who has her first infection while pregnant. The newborn may suffer hearing loss, visual impairment or diminished mental and motor function or be still born or fail to thrive. CMV belongs to the herpes virus family.

Ganciclovir and Valganciclovir

GANCICLOVIR SODIUM is used parenterally as the salt or orally as the free base for treatment of cytomegalovirus retinitis or as cytomegalovirus prophylaxis in HIV and transplant patients.



Ganciclovir (DHPG)

Oral administration is inefficient in achieving blood levels. Ganciclovir is activated by host cell kinases to the triphosphate thus is a prodrug.

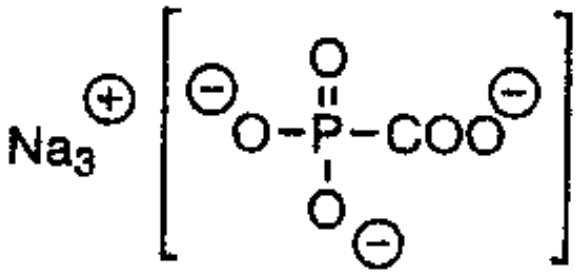
The virus lacks a suitable kinase. Ganciclovir is an inhibitor of DNA polymerase and is a chain terminator.

It is much more active than acyclovir against CMV but is less selective for viral DNA.

Valganciclovir is an oral prodrug of ganciclovir and has largely replaced it since oral use achieves similar blood levels to that achieved by IV administration.

It is a monovaline ester that benefits from active transport across the gut wall into the blood stream where it is activated by hydrolysis.

Foscarnet



Foscarnet sodium

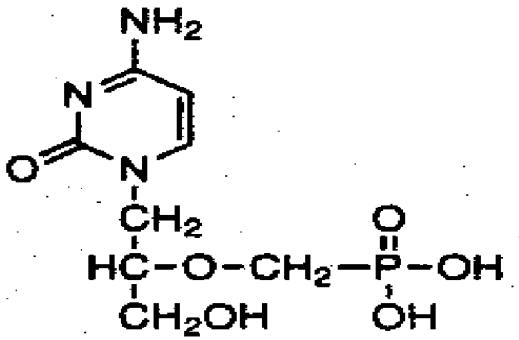
FOSCARNET SODIUM is used parenterally for cytomegalovirus retinitis; mucocutaneous herpes simplex; and cytomegalovirus prophylaxis in AIDS patients.

It is an organic analog of inorganic pyrophosphate. It does not require host cell or viral activation and inhibits herpes virus DNA polymerase directly.

It is more costly and less well tolerated than ganciclovir. Infusion requires large volumes of solution and careful control of infusion rates.

It produces significant side effects including kidney problems.

Cidofovir



Cidofovir
1-[(S)-3-hydroxy-2-(phosphonomethoxy)propyl]cytosine

CIDOFOVIR is an injectable agent used for treatment of cytomegalovirus retinitis especially when treatment with ganciclovir and foscarnet has proven unsuccessful. The drug is broad spectrum against herpes viruses. It inhibits DNA biosynthesis by having a special affinity for viral DNA polymerase in contrast to host cell DNA polymerase to which it does not bind significantly. It is also a DNA chain terminator. It is given once a week for two weeks and then once every two weeks. About ¼ of patients discontinue the drug due to severe side effects.

It inhibits mitochondrial polymerase leading to lactic acid formation causing this toxicity.

The organophosphorous group overcomes resistance due to non-functioning of mutated viral kinases in resistant viruses. Polarity is decreased by the sidechain oxygen making the pKa similar to that of a phosphate analog.

Cidofovir penetrates poorly into cells but once in stays a long time giving substantial antiviral potency. It is much more potent *in vivo* than *in vitro.*

Interferon Therapy

Interferons are certain proteins produced by some cells in response to viral infection.

These prevent subsequent infection by other viruses. The precise mechanism by which they do this is obscure but appears to involve modulation of the immune response.

Interferons are produced by recombinant means and must be injected. Primed T cells also produce interferons.

Interferon Alpha and Peginterferon Alfa are clinically available. Pegylation is the attachment of polyethyleneglycol molecules to a large molecule to enhance its water solubility and to mask it from the body's immune and degradation systems.

Acquired Immunodeficiency Disease Syndrome (AIDS)

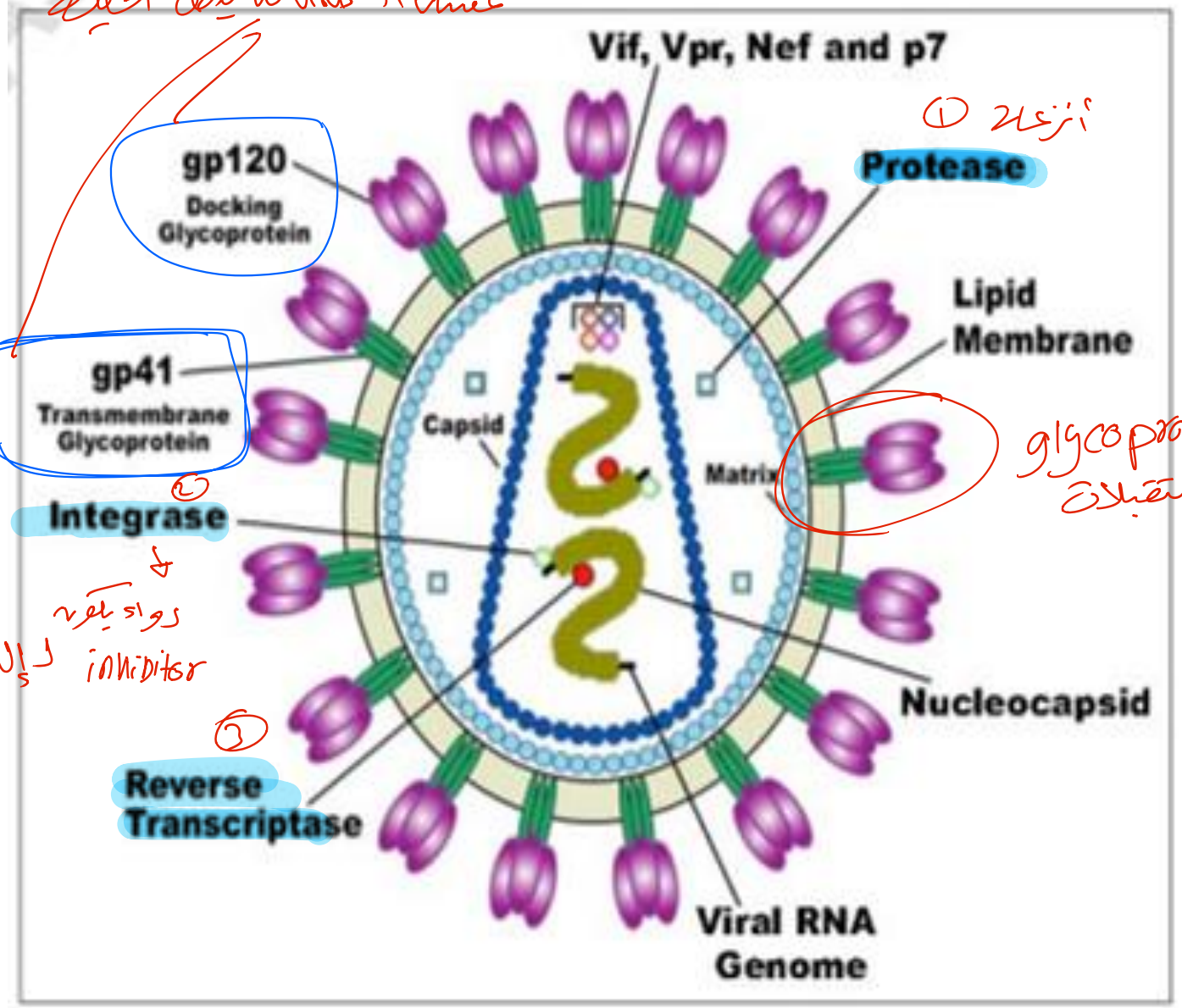
AIDS is a highly lethal virus disease caused by infection with HIV (human immunodeficiency virus) – an RNA virus. The virus targets human T-4 lymphocyte cells, which are the primary cells of the humeral and cellular resistance systems. Death of these cells leads to a profound immunosupression that makes the patient highly susceptible to infections of all kinds, but often by organisms normally of low invasiveness but of high virulence.

AIDS is highly contagious and lethal unless treated aggressively.

The number of infected individuals is increasing logarithmically.

AIDS is believed to be significantly under-reported but official reports indicate over 42 million sufferers world-wide, mostly in resource-limited countries but more than 5 million such in the USA as well.

Approximately 25 million have died already from AIDS.



RNA Retro virus

HIV1: North America and Western Europe

HIV2: West Africa : less virulent and less easily transmitted.

2 single stranded RNA

Acquired Immunodeficiency Disease Syndrome (AIDS)

Once believed to be associated primarily with certain male homosexual practices, it is now well established that it can also be transmitted as a consequence of heterosexual contact with infected individuals.

It can also be transmitted by contact of open wounds with infected body fluids.

In some parts of the world, infection is commonly due to use of medical procedures involving contaminated materials (hypodermic needles, etc.).

This is a retroviral (HIV = human immunodeficiency virus) infection spread by intimate contact between susceptible individuals leading to exchange of body fluids including viral particles.

It can also be spread by use of contaminated materials that penetrate the skin (hypodermic needles, scalpels, etc.).

Acquired Immunodeficiency Disease Syndrome (AIDS)

Treatment has shifted to earlier and more continuous use of drug combinations. Viral load (level of HIV RNA levels and CD-4 cell count are important. Persons with low viral loads have a better prognosis and are less able to pass the infection to partners.

Resistance to AIDS chemotherapy develops easily with the earlier drugs. It is crucial that continuous therapeutic drug levels be maintained to prevent genetic drift to resistance. In contrast to DNA, RNA is not carefully proofread during construction so damage to DNA is readily propagated. To delay this, cocktails (mixtures of antiviral agents) are now commonly used. This is expensive. AIDS mortality can be controlled in this manner. No cure is in sight.

Prospects for an effective vaccine are dim. A curative drug will not put an end to the disease.

A variety of opportunistic pathogens are associated with AIDS infections: *Pneumocystis carinii*; Mycobacterium species including avium and tuberculosis are examples. (The mortality of TB in AIDS patients approaches 80%). *Candida albicans*, Cytomegalovirus, Kaposi's sarcoma, Burkitt's lymphoma, *etc*., are also associated with AIDS.

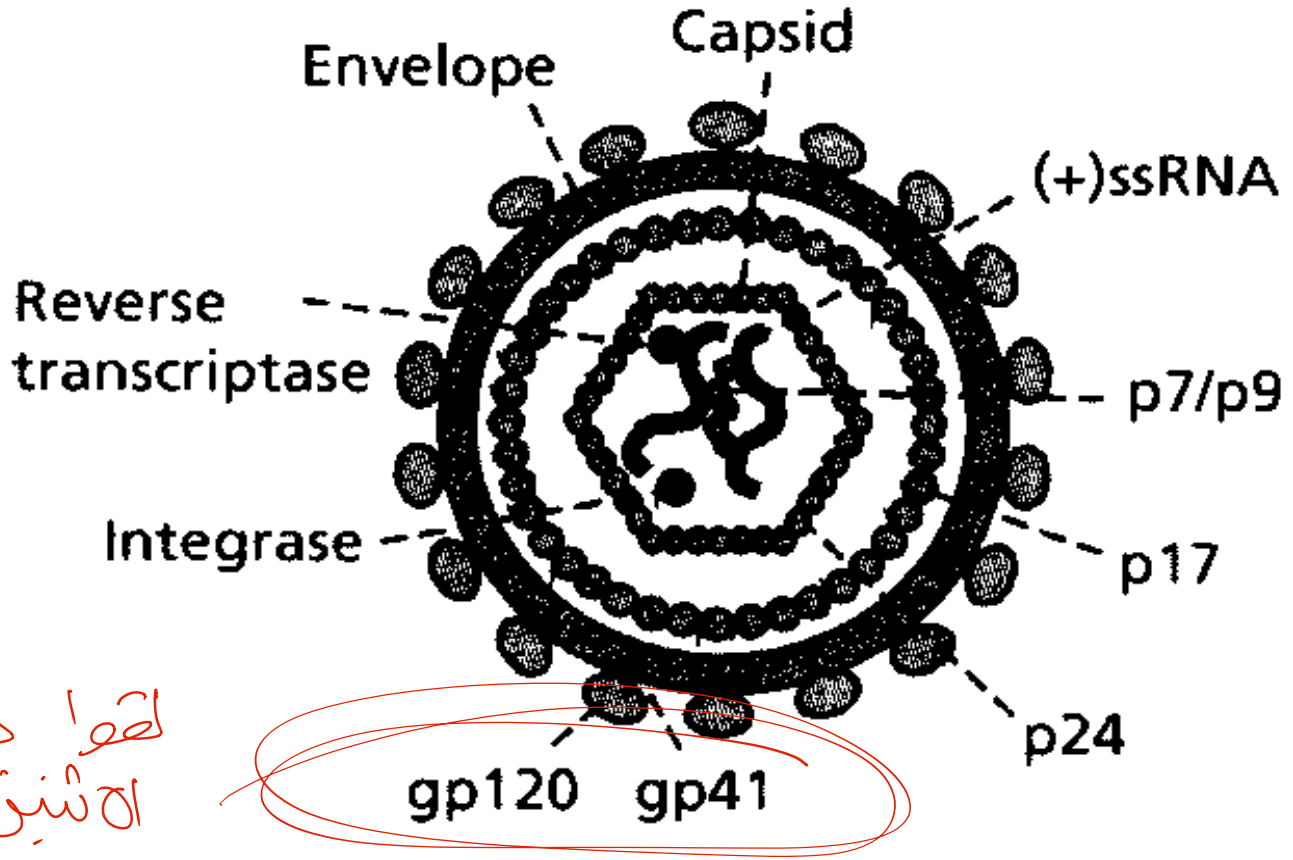
Acquired Immunodeficiency Disease Syndrome (AIDS)

In the 1980s, AIDS sufferers had a life expectancy of less than two years. Following the development and use of anti AIDS cocktails, many individuals now have survived for 10-20 years. This is certainly a good thing.

Unfortunately, however, there are now increasing reports of premature ageing syndrome, especially memory loss, among these drug-maintained individuals.

The unanticipated nature and causes of this problem are under investigation.

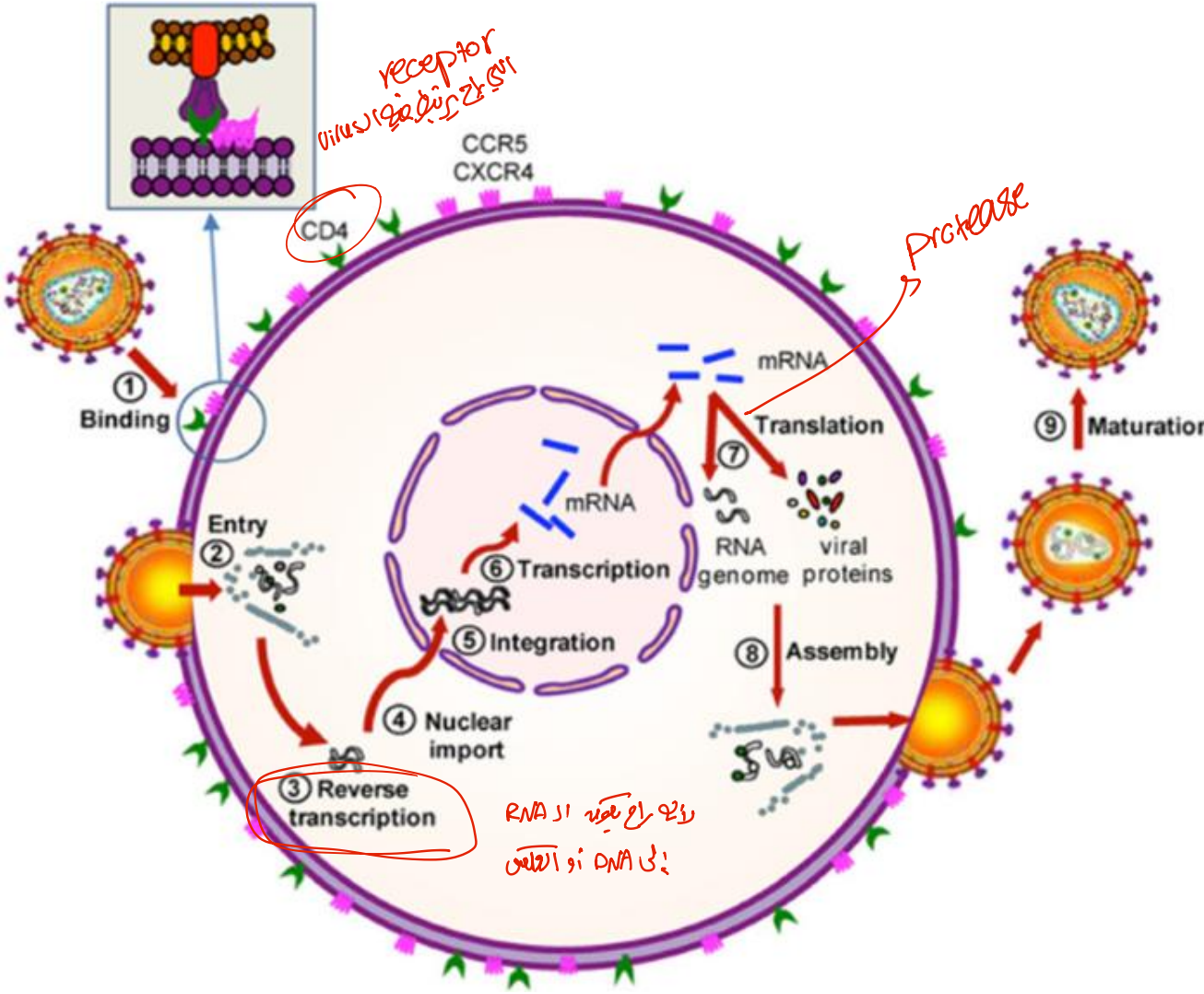
HIV: Retrovirus Taxonomy



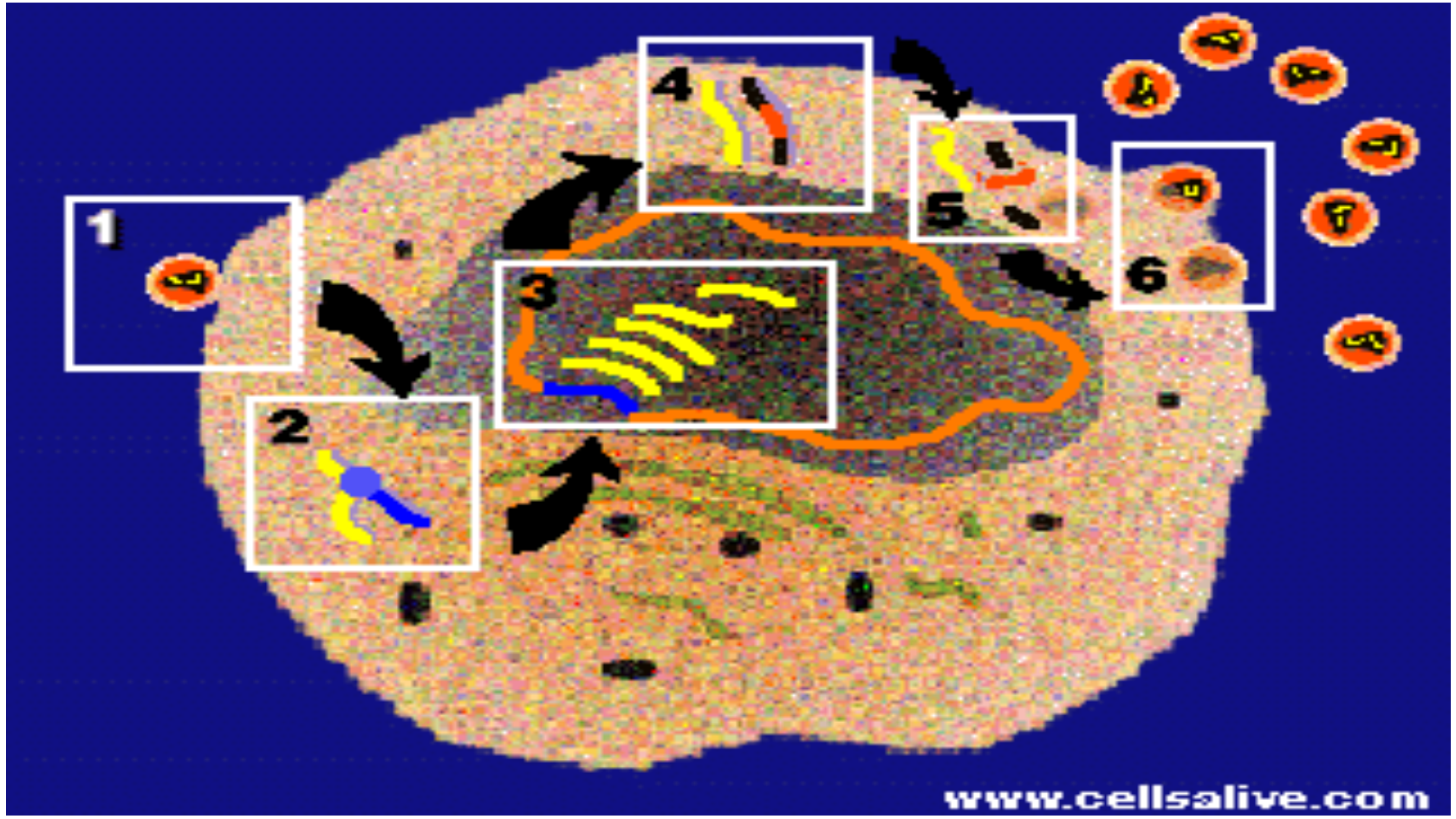
On the surface of the envelope is the targeting glycoproteins. gp120 attaches to the CD4 protein of host T-cells and undergoes conformational shifts so that the gp41 protein can anchor the virus to the T-cell surface. A conformational shift allows virus and T-cells to fuse and the nucleocapsid enters the cell and releases its RNA and enzymes. Reverse transcriptase

The HIV Infection Cycle

1. Attachment of gp120 to cell surface receptors (CD4 of host T-cells).
2. Conformational change of gp120 allowing gp41 to anchor the virus to the T cell surface chemokine proteins (CCR5 and CXCR4).
3. gp120 is removed allowing gp41 to reach the cell surface and anchor the virus to the cell surface. Gp41 changes its conformation leading to fusion of the membranes of the virus and the T-cell.
4. The nucleocapsid enters the cell and the viral capsid is enzymatically dissolved releasing the RNA and enzymes into the cytoplasm.
5. Viral reverse transcriptase (RNA dependent DNA polymerase) synthesizes viral DNA and degrades the RNA strand.
6. This proviral DNA is incorporated into the infected T cell's DNA by viral integrase.
7. The altered segment can become dormant or be activated. When activated, viral DNA and three large, inactive, proenzymes are produced.
8. Cellular proteases cleave one into gp120 and gp41 which are incorporated into the cell membrane.
9. The other two pre-proteins are incorporated into the cell membrane.
10. Residual host cell proteins are destroyed after marking with ubiquitin.
11. The package assembles and is exported by budding and viral protease completes the cutting of the pre-proteins into viral structural proteins and enzymes.
12. Cycle repeats



A Pictorial Summary of the AIDS Virus Infection Cycle



1. Getting in
2. Reverse transcription (RNA to DNA)
3. Integration into genome, making much viral RNA
4. Translation into viral proteins
5. Viral protease cleaves into functional proteins
6. Assembly, budding and release

The AIDS Virus Has At Least Three Unique Target Enzymes And Two Target Proteins Useful As Chemotherapy Targets

اذا استهدفت واحد منهم راح امنع دخول الـ virus الى الداخل

Enzymes:

1.A Reverse Transcriptase (RNA-Dependent **DNA Polymerase**)

2.Integrase Strand Transfer (In contrast to other viruses, this **integrase** **inserts its DNA into human DNA)**

3.HIV Protease

Protein Targets:

1. CCR5

2. Fusion Protein gp41 (A transmembrane glycoprotein subunit of the viral envelope facilitating fusion of the viral and host cell membranes and thus entry of the virus into the cell.

Fusion Inhibitor

Enfuvirtide is an expensive polypeptide and is the only fusion inhibitor currently available.

After HIV binds to the host cell surface, a conformational change occurs in the transmembrane glycoprotein subunit (gp41) of the viral envelope. This facilitates fusion of the viral and host cell membranes and thus entry of the virus into the target cell.

Enfuvirtide prevents this conformational shift.

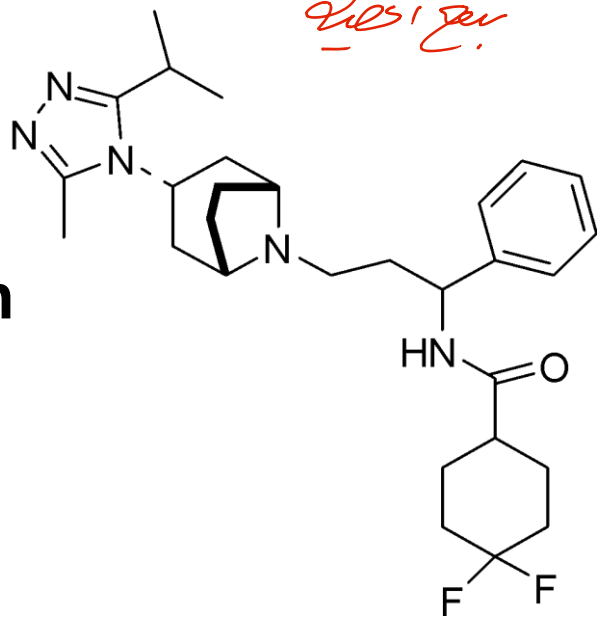
It is given S.C and patients frequently experience pain at the injection site.

Inhibition Of HIV-1 Penetration (Entry) Into CD-4 Cells by Maraviroc.

active in resistance

HIV-1 penetrates into its target cells after fusing its viral membranes with the target cell membranes.
Viral gp-41 in combination with a co-receptor called CCR5 serves to do this.

Enfurvitide is a 36-mer peptide that inhibits fusion by inhibiting a conformational change needed for the penetration reaction to proceed. It is not used as a single agent but rather as a cocktail component. It must be administered subcutaneously.



Maraviroc

Maraviroc binds to AIDS co-receptor proteins and prevents viral entry into target cells.

It is active against cells resistant to other antiretroviral agents but resistance to Maraviroc has occurred.

Inhibition Of HIV Reverse Transcriptase

Being a retrovirus, the viral message must be transcribed into DNA before it can be reproduced.

A viral enzyme called reverse transcriptase (RNA dependent DNA polymerase) has this function.

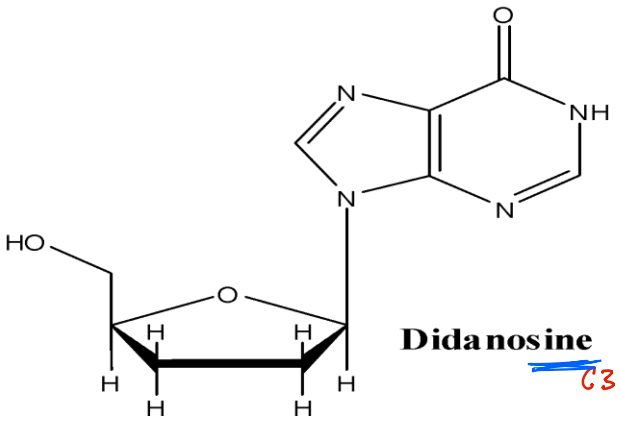
Uninfected human host cells lack this enzyme.

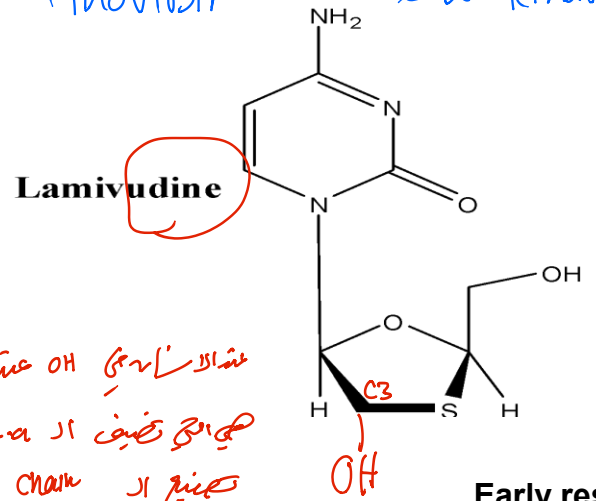
The synthesis of new DNA and RNA requires a source of phosphorylated nucleic acid bases and their enzyme-catalyzed assembly into specific polymers.

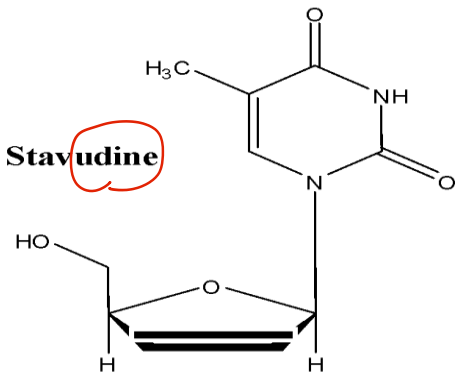
Inhibition of reverse transcriptase or its function prevents the spread of the HIV infection.

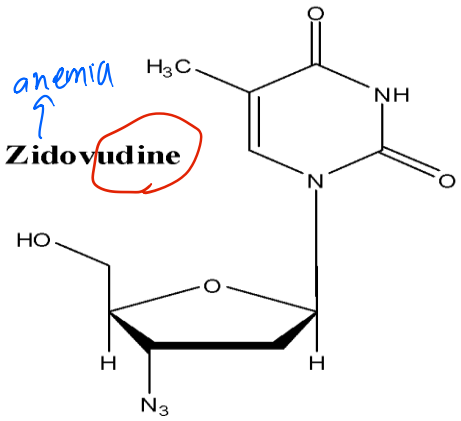
Unfortunately resistance develops readily to this class of antiviral agent.

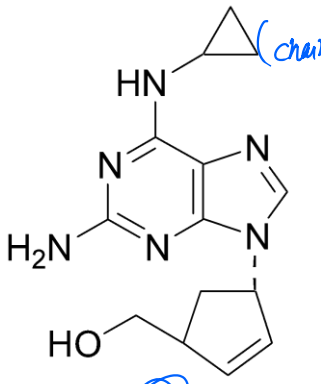
Nucleoside-based Reverse Transcriptase Inhibitors NRTIs) X-vir, X-vudine , Didanosine, Emtricitabine

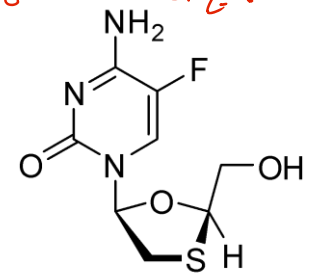












Abacavir

Emtricitabine

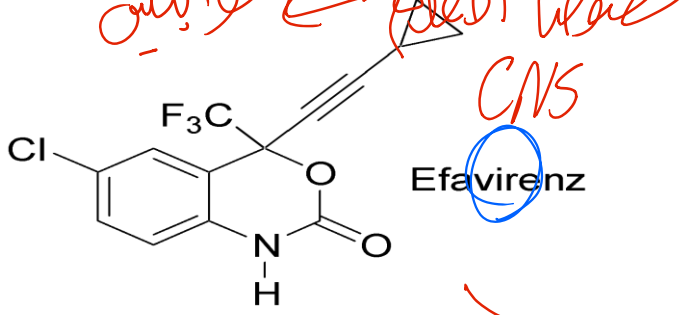
Early resistance development to the above four has eroded their popularity.

These agents lack the C-3' hydroxyl so are chain terminators when activated by triphosphorylation. They compete for the active site of reverse transcriptase.

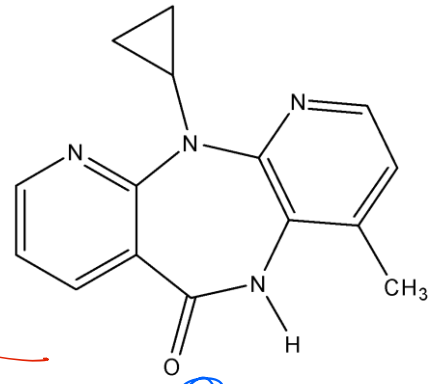
Note that the stereochemistry of emtricitabine and lamivudine are reversed from normal at the anomeric center. This decreases mitochondrial toxicity due to greater selectivity of the kinases.

A class effect is the possibility of potentially fatal lactic acidosis with hepatic steatosis.

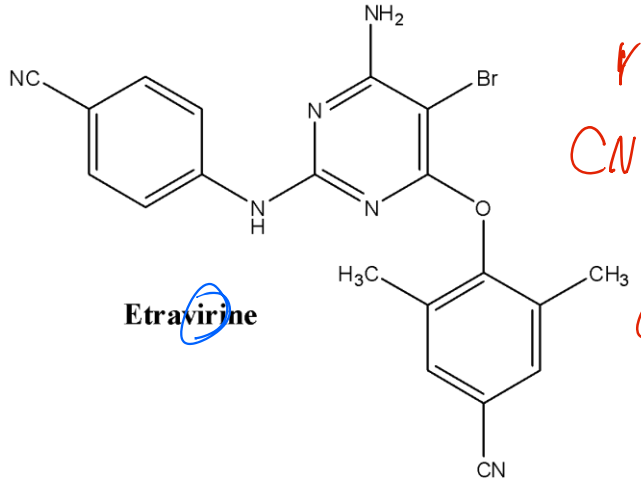
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)= (X- VIR-Y)



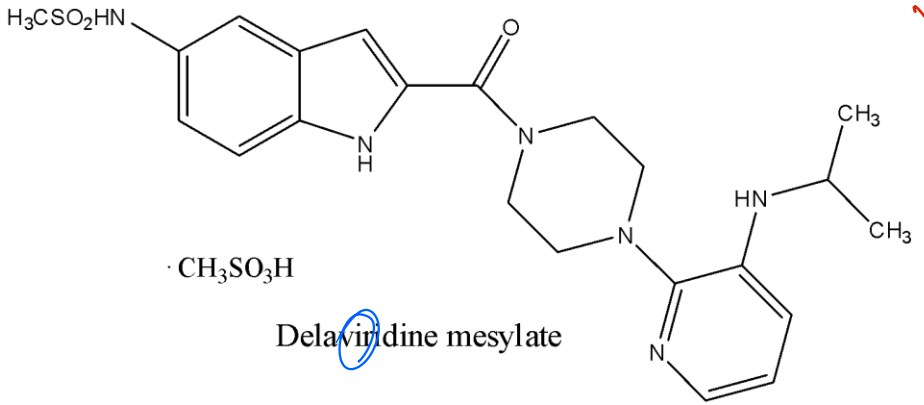
Efavirenz



Nevirapine



Etravirine



Delavirdine mesylate

These agents are allosteric inhibitors whose binding distorts the active site on the enzyme. Etavirine is the most recent and is not cross resistant with the others. Resistance develops very easily with these so they are seldom used alone.

Inhibitor Of HIV Integrase Strand Transfer (INSTI).(X- tegravir)

Raltegravir (Merck) is the first HIV integrase inhibitor to be approved (2007) by the FDA for marketing. This enzyme catalyzes the process that results in viral DNA insertion into the host cell genome. Raltegravir inhibits this activity thus inhibiting the progression of the infection.

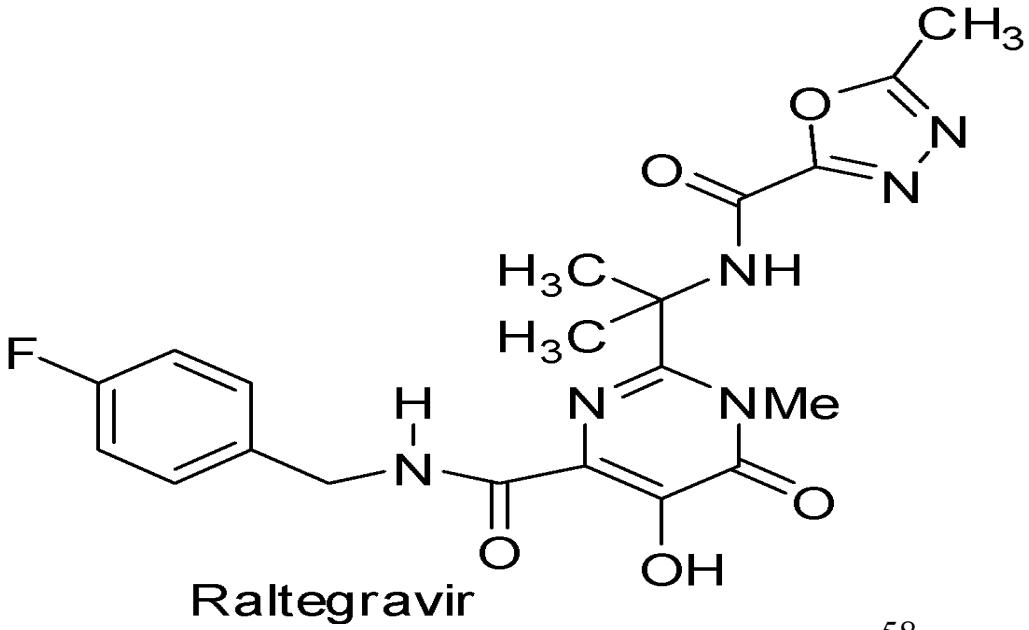
Raltegravir is active in clinical trials against HIV strains resistant to other antiretroviral drugs when included in combination therapy.

Raltegravir is orally active.

Doultegravir

Bictegravir

Elvitefravir

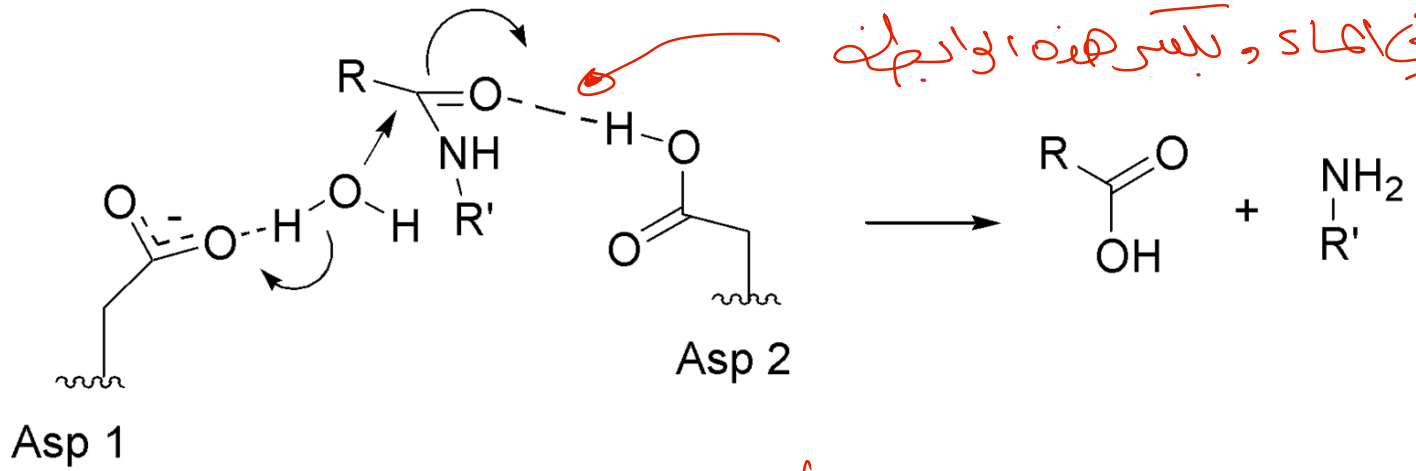


Raltegravir

Inhibition Of HIV Protease (PI)(X-navir)

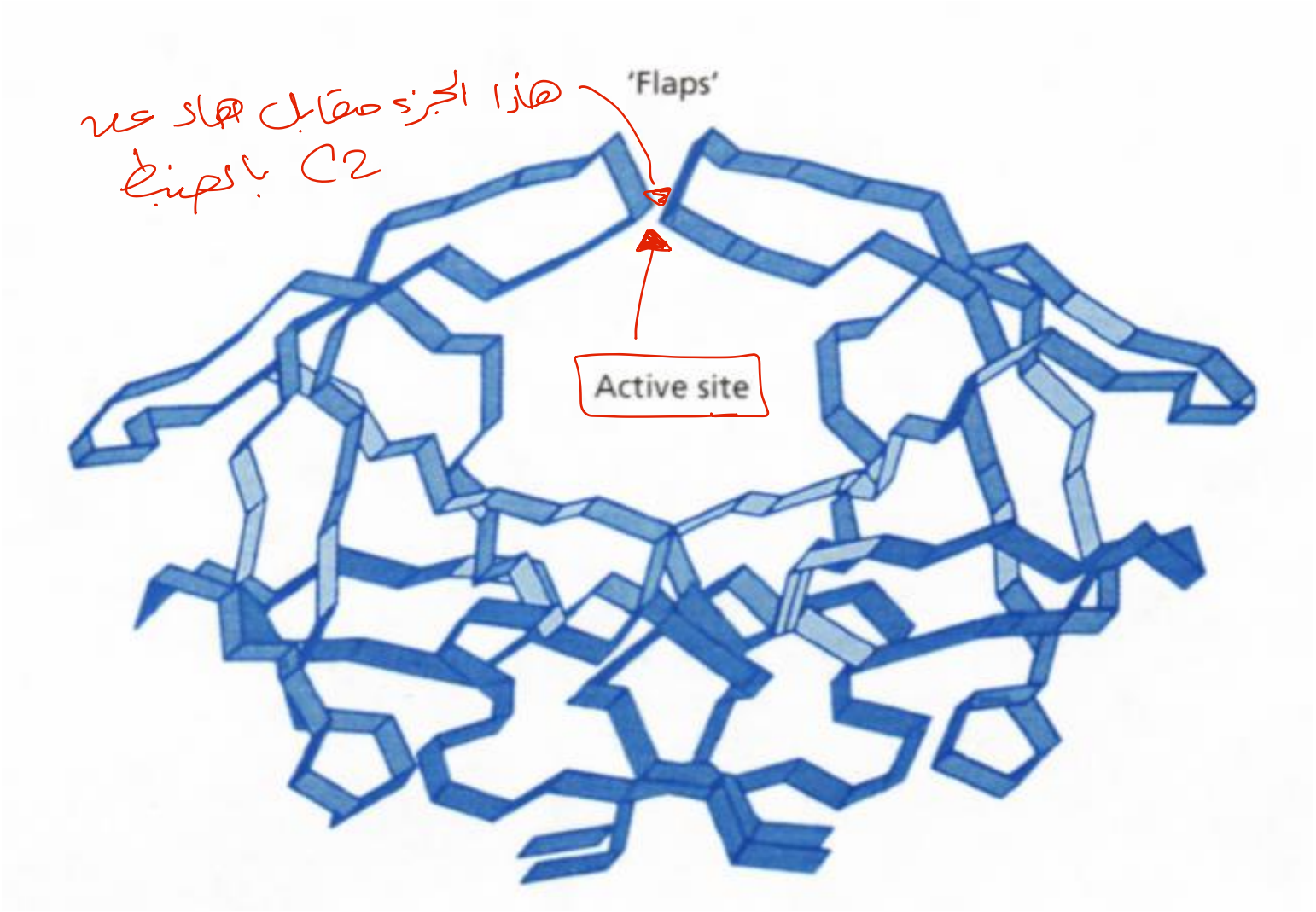
Proteases cleave specific peptide bonds by addition of water (hydrolysis).
They are classified by the specific mechanism by which they do this.

HIV protease is an aspartyl protease that activates water using two strategic aspartyl side chains in a push-pull manner.



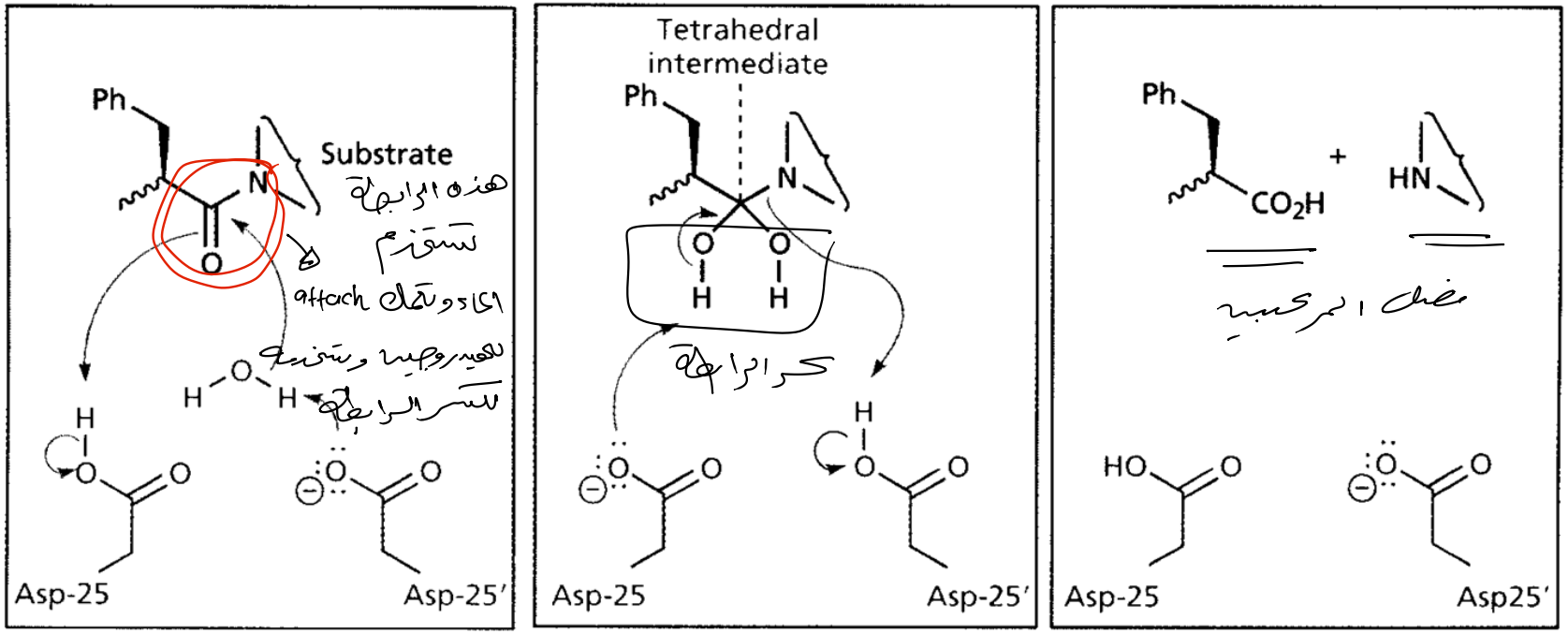
HIV protease is an enzyme crucial for post-translational modification of immature core proteins into structural proteins. The use of these agents is much more effective than use of inhibitors of RT.

THE STRUCTURE OF HIV PROTEASE



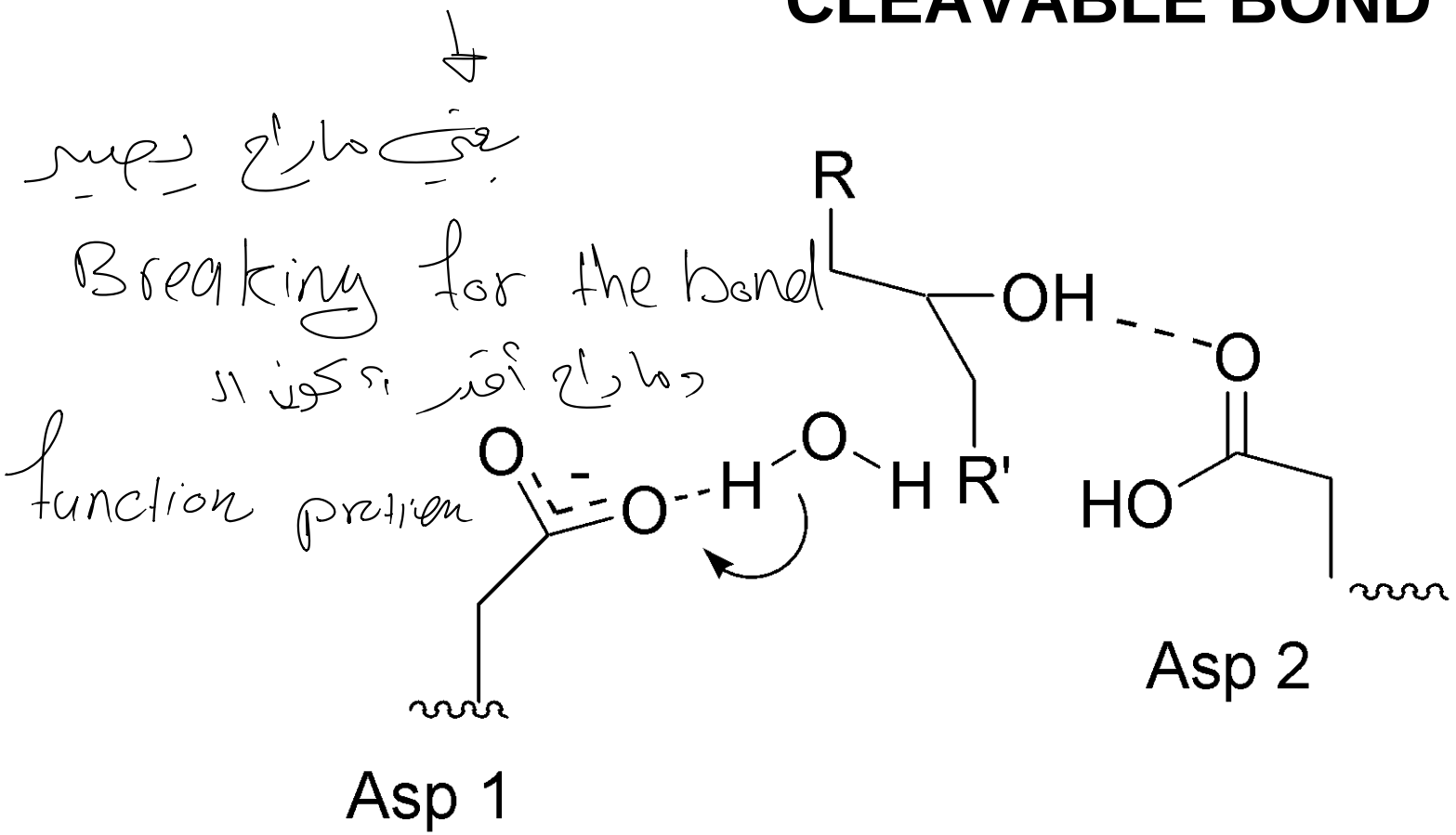
The enzyme is an aspartoyl protease dimer with C-2 symmetry.

Mechanism of Aspartoyl Protease Cleavage



The protease inhibitors are transition-state directed and their absolute configuration is vital to their action.

INHIBITION OF HIV PROTEASE BY A LIGAND WITH A NON-CLEAVABLE BOND



SOME HIV PROTEASE INHIBITORS

X—navir

These agents are metabolized by CYP 3A4 which leads to many drug-drug interactions.

A combination including ritonavir treatment of AIDS as ritonavir inhibits CYP3A4 so acts as a "booster" of the activity of the other PIs.

Most PIs cause GI distress and potentially cause liver toxicity.

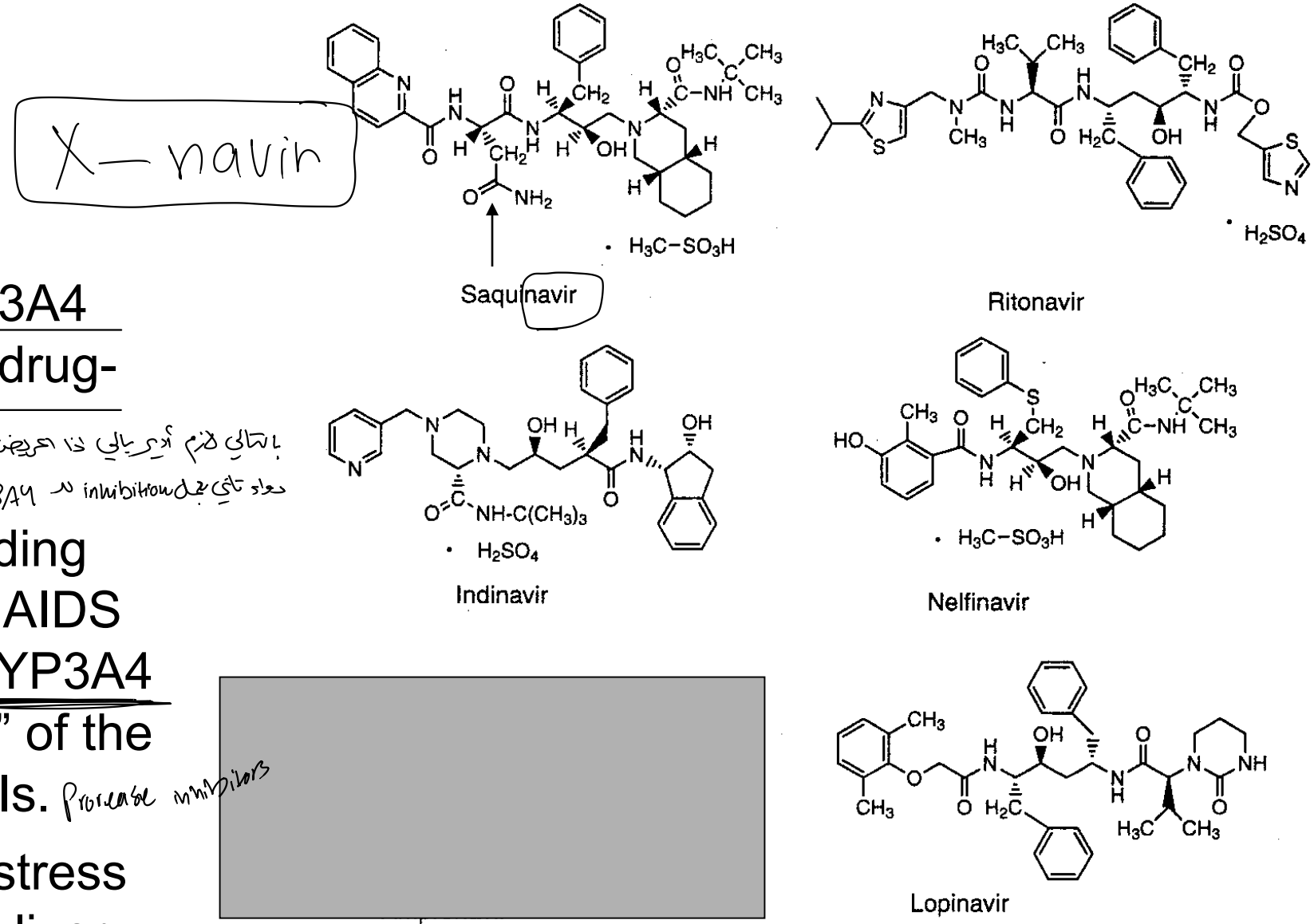
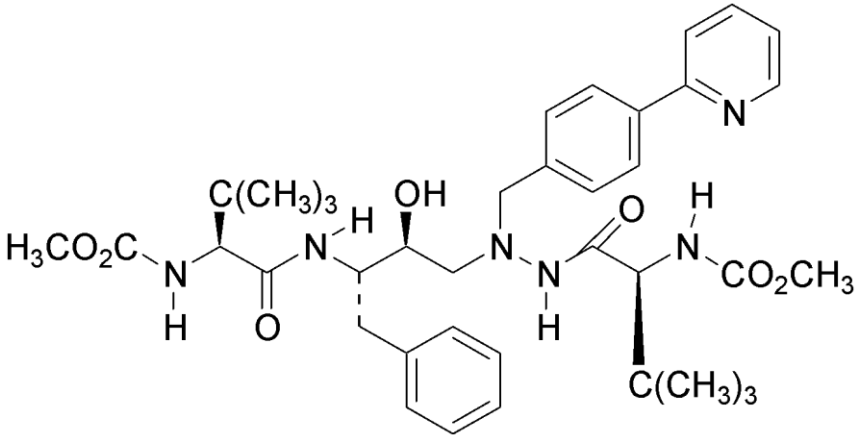
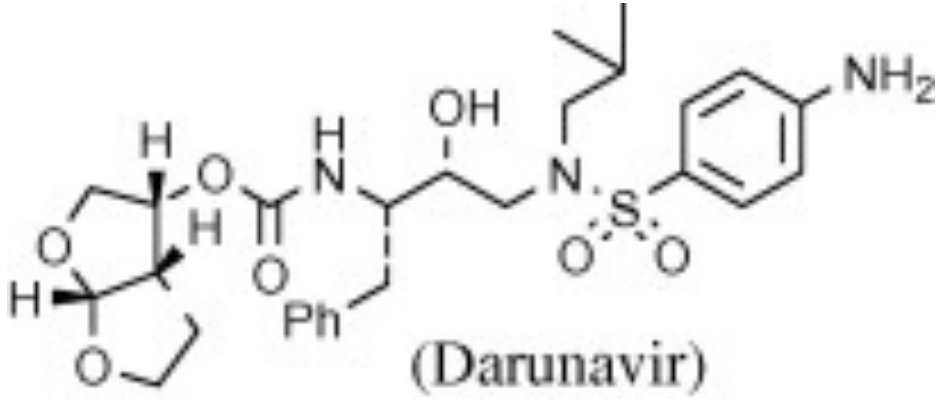


Fig. 39.10. Structures of FDA approved HIV protease inhibitors (PIs).

Additional Examples of HIV Protease Inhibitors

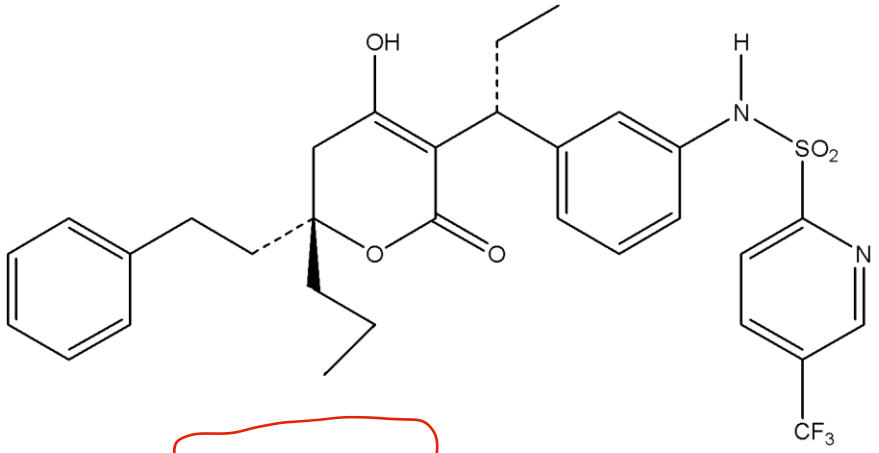


ATAZANAVIR (BMS), A viral protease inhibitor) was approved by the FDA in June, 2003. It is taken once a day orally. Along with the other protease inhibitors, it is not curative and has many side effects/drug interactions.



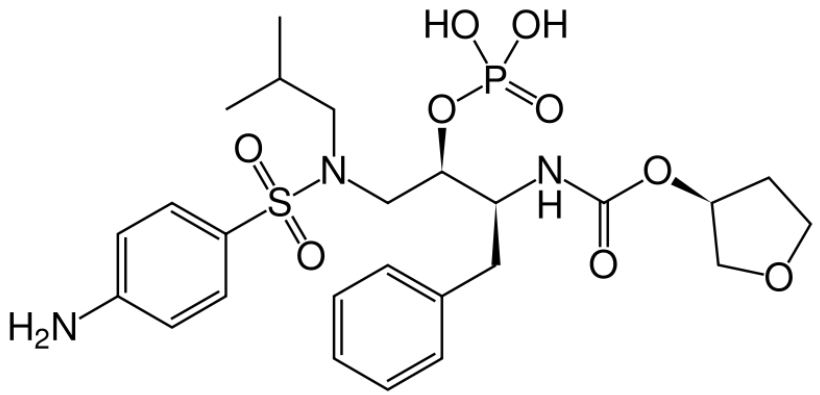
This drug is given along with ritonavir in order to achieve adequate blood levels.

Additional Examples of HIV Protease Inhibitors



Note that TIPRANAVIR has a rather different structure than the other protease inhibitors.

Tipranavir has recently been introduced as an HIV protease inhibitor. It is co-administered with ritonavir to suppress metabolism of tipranavir. It is a comparatively flexible molecule that is active against resistant strains of HIV and in advanced cases. It is associated with hepatic toxicity. Fatty meals increase blood levels of tipranavir.



FOSAMPRENAVIR is a water soluble phosphate prodrug of amprenavir

X- tegravir وبتوقف على إنزيم ال integrase وبتطوا بتقطع integrase inhibitors في مجموعة أخرى اسمها less drug interaction وأهم

COMBINATION DRUG THERAPY OF AIDS

Because of the ease with which resistance develops to AIDS chemotherapy, it has become commonplace to treat sufferers with combinations of antiviral drugs. This is expensive but greatly decreases the rate of drug resistance development and so it is life prolonging. Some such currently favored combinations are:

NNRTI combo: Etavirenz + tenofovir/emtricitabine

PI combo: Atazanevir/ritonavir + tenofovir/ antricitabine

INSTI combo: Raltegravir + tenofovir/amtricitabine

CCR5I combo: Maraviroc + zidovudine/lamivudine

* tegravir

1- Nausea

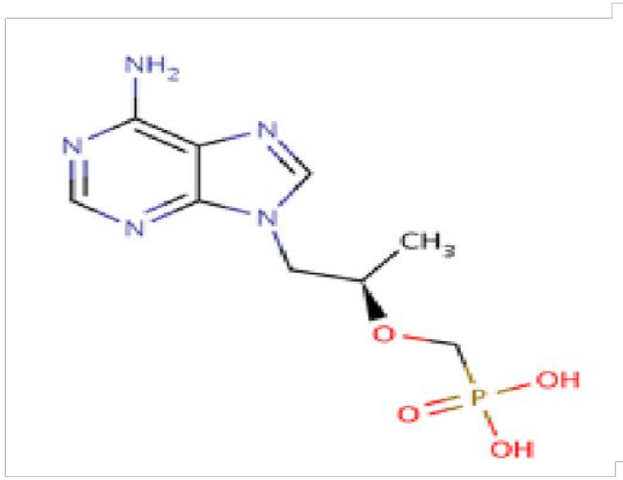
2- rash

3- dizziness

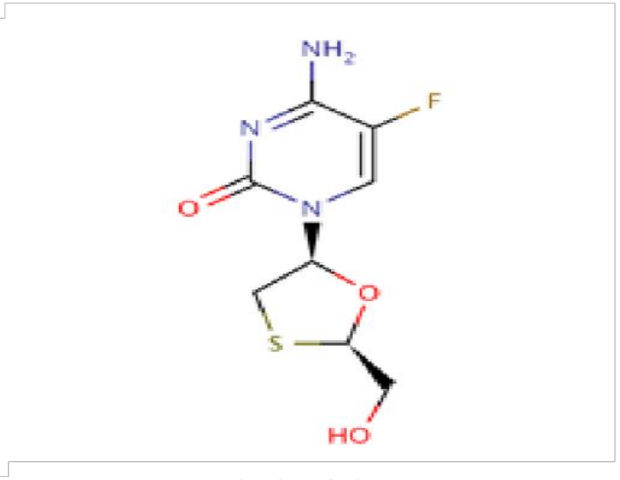
4- weight gain

Atripla

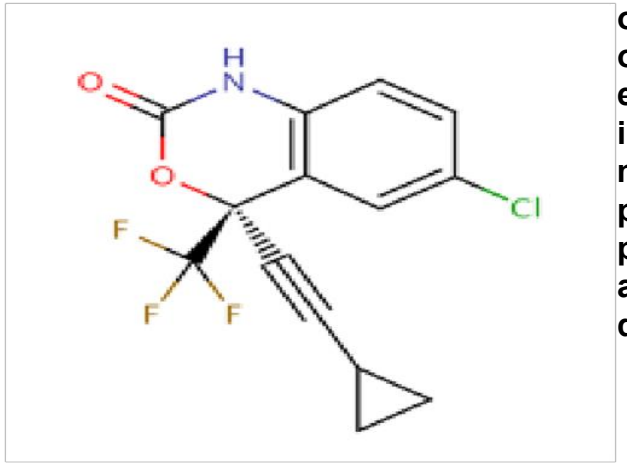
The successful combination of tenofovir, emtricitabine and efavirens in a single tablet (Atripla) represents AIDS monotherapy and has greatly simplified therapy and compliance. Resistance so far is not serious.



Tenofovir
(NRTI inhibitor)



Emtricitabin
(NRTI inhibitor)



Efavirenz
(NNRTI inhibitor)

The stereochemistry of the Me of tenofovir and of the anomeric carbon of the sugar of emtricitabin decrease inhibition of mitochondrial polymerase thus preventing toxic lactic acidosis and lipid dyscrasia.

كل الأنواع عبارة عن RNA ماعدا الـ B هو DNA بس

Viral Hepatitis

Hepatitis is a severe, chronic (hepatitis B, D and E) or acute, inflammatory disease of the liver. There are several hepatitis-causing viruses.

simple سببت فقط الإسهال

Hepatitis virus A is spread mainly by ingestion of water or food contaminated with fecal material.

Hepatitis B virus is spread mainly by contact with infected blood or unprotected sex with an infected individual.

Hepatitis virus C is mainly spread by contact with infected blood. It is poorly treated with existing drugs and potential therapies are an intense research objective in industry.

يعني لو B بتقوم لازم مصاب فيD تلقائي

Hepatitis virus D is contracted by hepatitis virus B sufferers who come in contact with infected blood. Hepatitis virus E is mainly spread by ingestion of water or food contacted with fecal material.

Prevention by avoidance of high risk behavior is best but there is a preventive vaccine for hepatitis A and B, but not for the others.

Ca. 1.25M suffer from HBV infections in the USA.

Interferon alfa-2b and lamivudine have limited utility.

Common Symptoms of Viral Hepatitis

Jaundice (yellowing of the skin and eyes)
Fatigue
Abdominal pain
Loss of appetite
Nausea
Vomiting
Diarrhea
Low grade fever
Headache

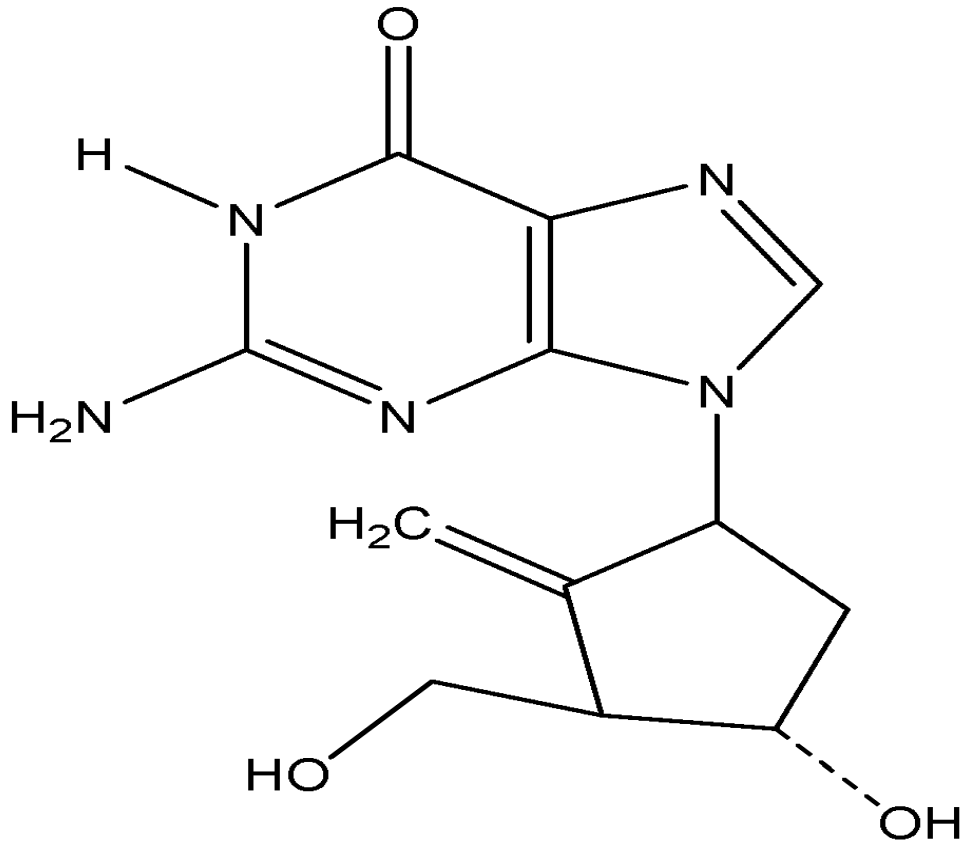
However, some people do not have symptoms.

Entecavir

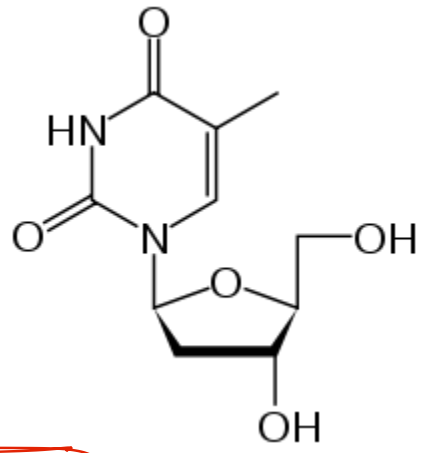
Entecavir *(Baraclude)* has been approved recently for the treatment of chronic hepatitis B infections.

It is a nucleoside-based inhibitor of reverse transcriptase.

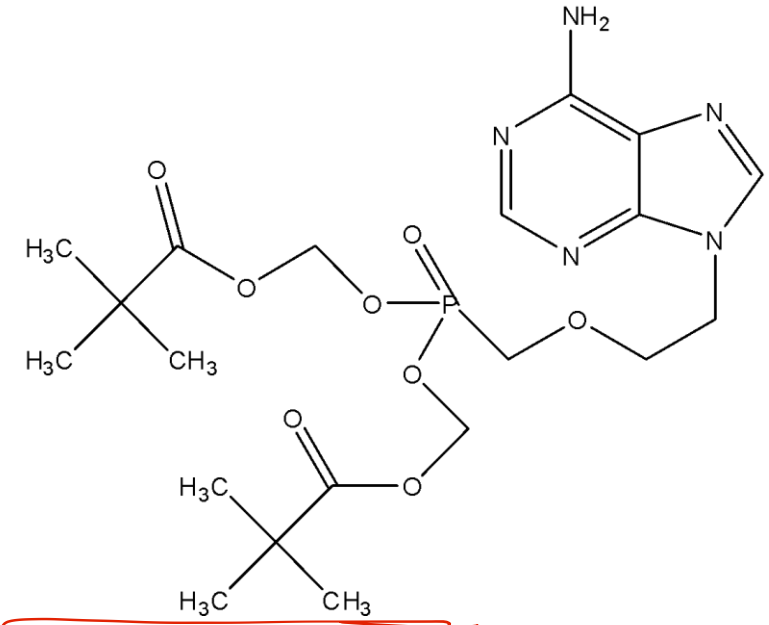
Care must be taken to avoid drug-related liver damage and lactic acidosis.



Additional Anti-hepatitis B Agents



TELBIVUDINE is used for the treatment of hepatitis B. It is reported to be more active than entecavir and less likely to elicit resistance.



ADEFOVIR DIPIVOXIL is an orally available prodrug of adefovir used against hepatitis B (and herpes simplex) by blocking the action of reverse transcriptase. Resistance develops against it more slowly than against lamivudine (which was previously employed).

Recapitulation

Important anti herpes and anti varicella zoster drugs = Valacyclovir, Valganciclovir, Foscarnet

Important anti cytomegalovirus drugs = Valganciclovir, Cidofovir, Foscarnet

Important anti influenza drugs = Amantadine, Zanamivir, Oseltamivir

Important anti HBV and HCV drugs = INF-α, Lamivudine, Ribavirin, Adefovir dipivoxil, Entrecavir,

Important anti AIDS drugs:

Fusion inhibitor =

Reverse transcriptase inhibitor:

Nucleosides =

Nonnucleosides =

Protease inhibitor =





Thank you




"Tell me and I forget; teach me and I may remember; but involve me and I learn."
Benjamin Franklin
UMKC
School of Pharmacy

General Pharmacology

GENERAL PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY

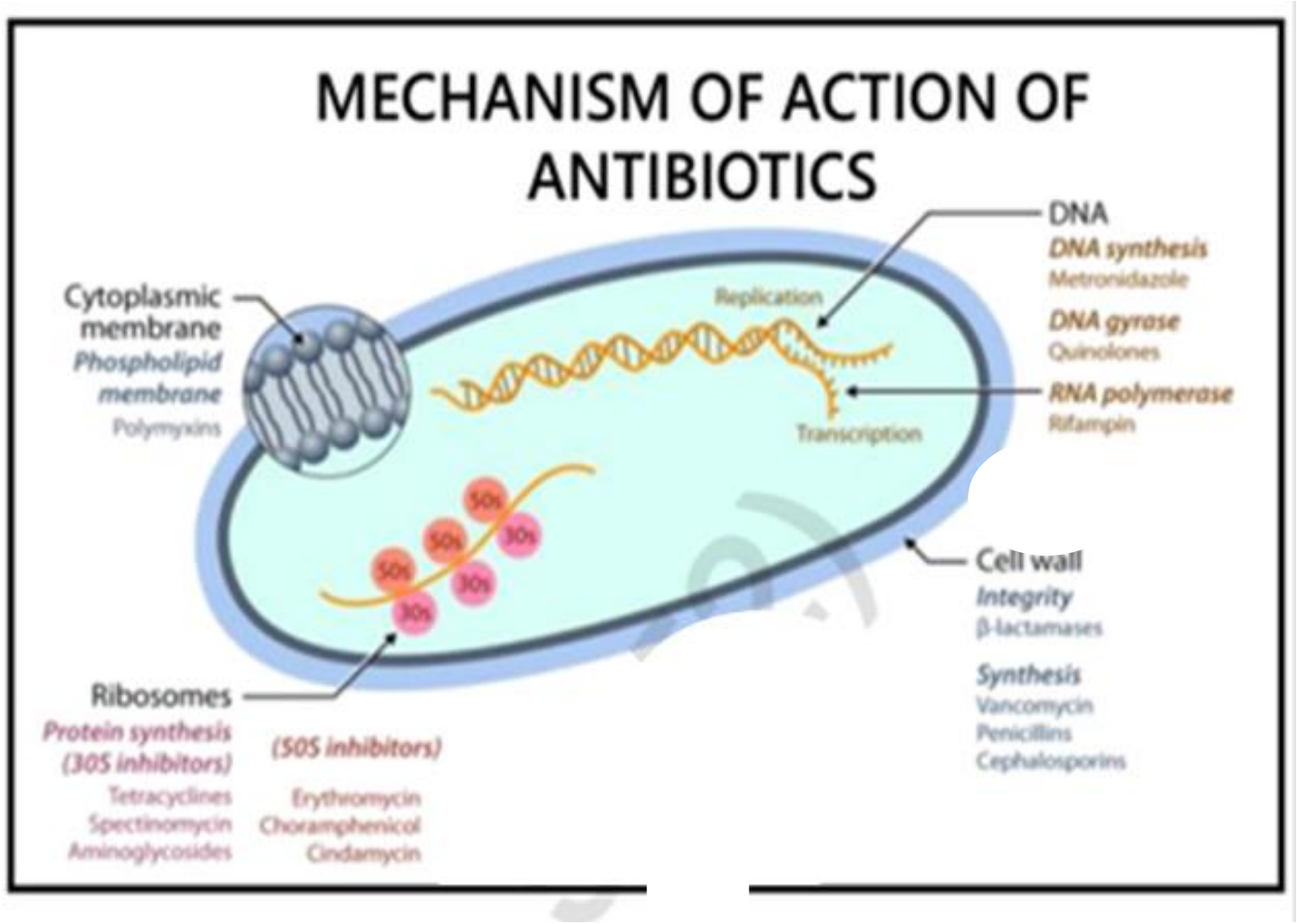
2025

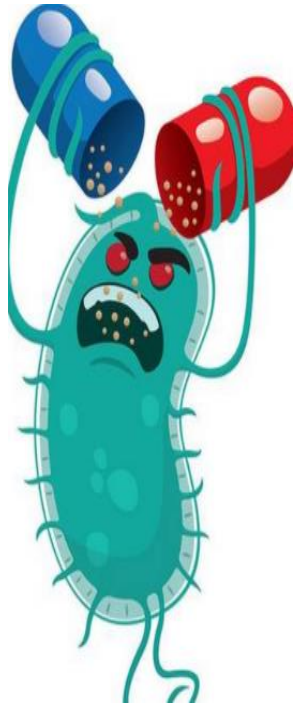
Esmaa Motawe

interdisciplinary PhD in Pharmacology &Toxicology/ Pharmaceutical Sciences

Antibiotic Therapy: Mechanism of Action

- Interference with cell wall synthesis
- Interference with protein synthesis
- **Interference with DNA replication**
- Acting as a metabolite to disrupt critical metabolic reactions inside the bacterial cell



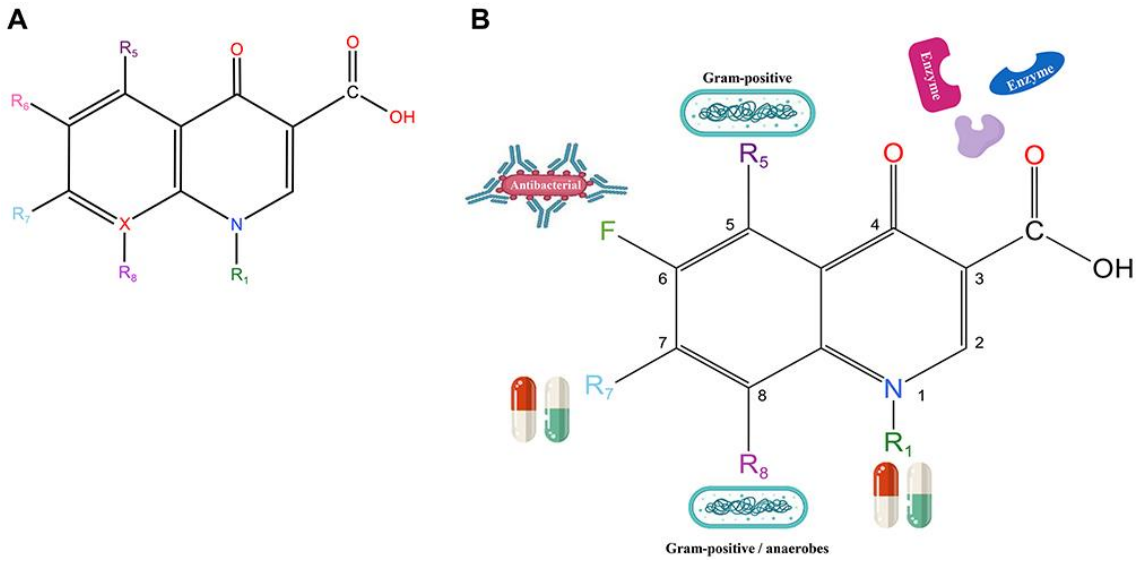


Nucleic acid inhibitors (DNA inhibitors)

FMN

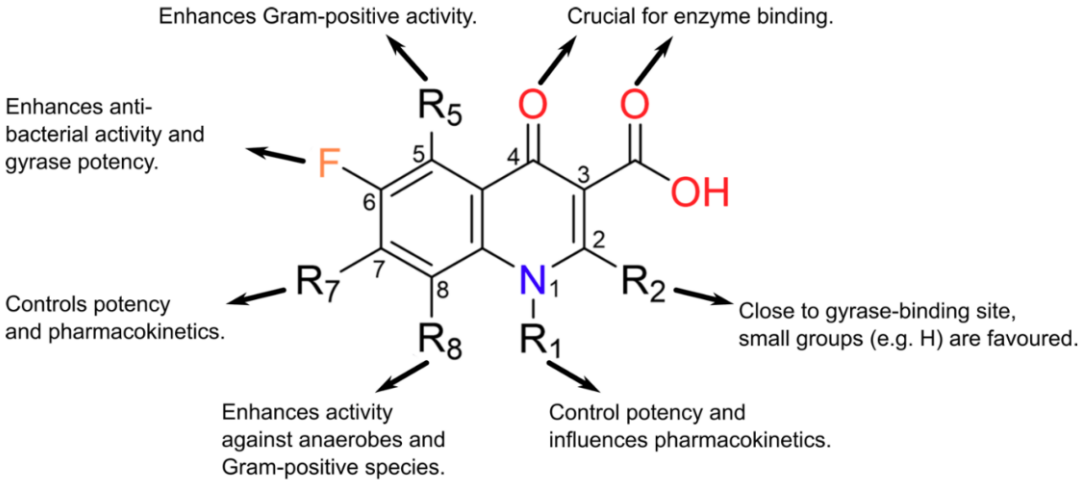
Fluoroquinolones

- Following synthesis of *nalidixic acid* in the early 1960s, continued modification of the quinolone nucleus expanded the spectrum of activity, improved pharmacokinetics, and stabilized compounds against common mechanisms of resistance.
- Overuse resulted in rising rates of resistance in gram-negative and gram-positive organisms, increased frequency of Clostridium difficile infections, and identification of numerous untoward adverse effects

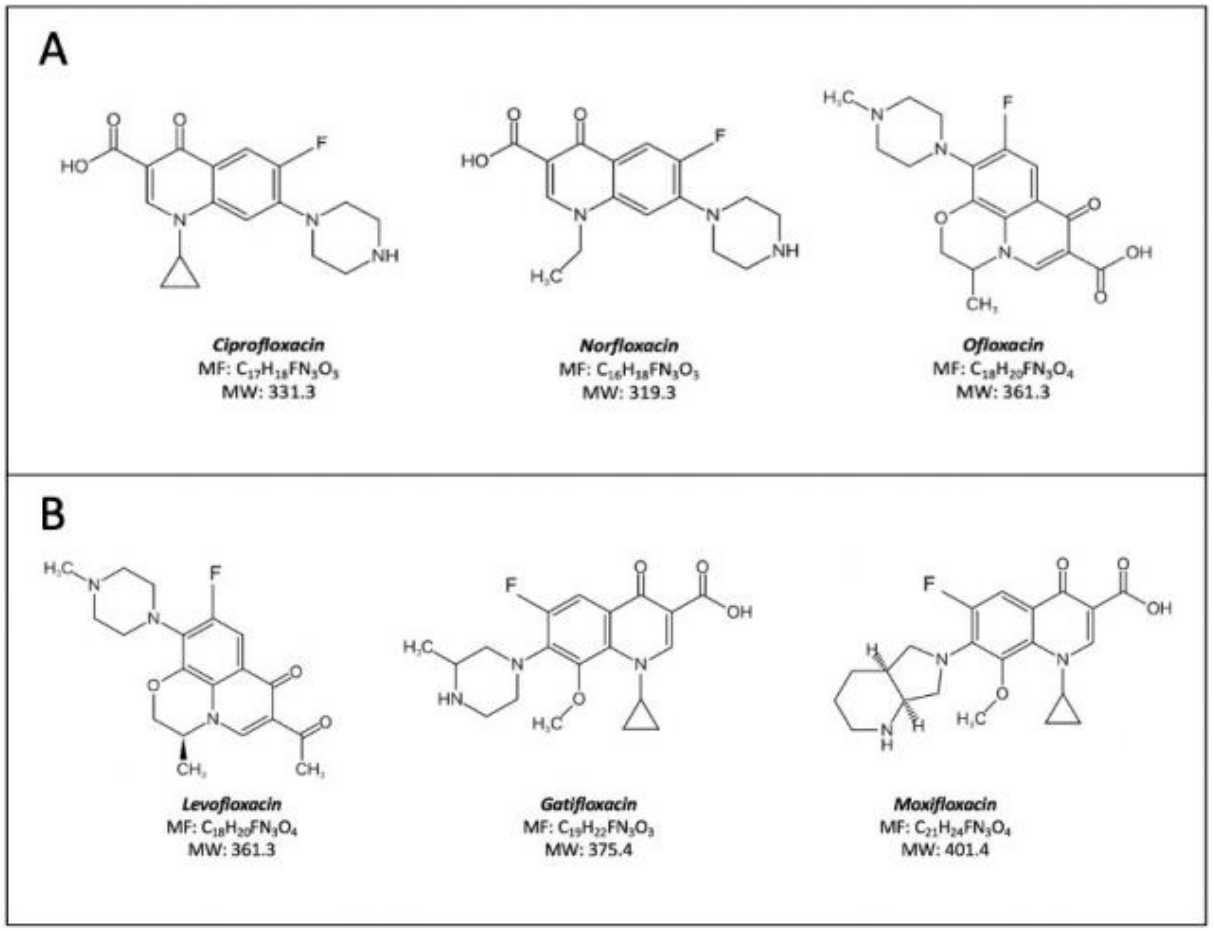


FLOROQUINOLONES(FQ)

Nucleic acid inhibitors (DNA inhibitors)



FLUOROQUINOLONES
Ciprofloxacin CIPRO
Delafloxacin BAXDELA
Gemifloxacin FACTIVE
Levofloxacin LEVAQUIN
Moxifloxacin AVELOX, MOXEZA, VIGAMOX
Ofloxacin GENERIC ONLY



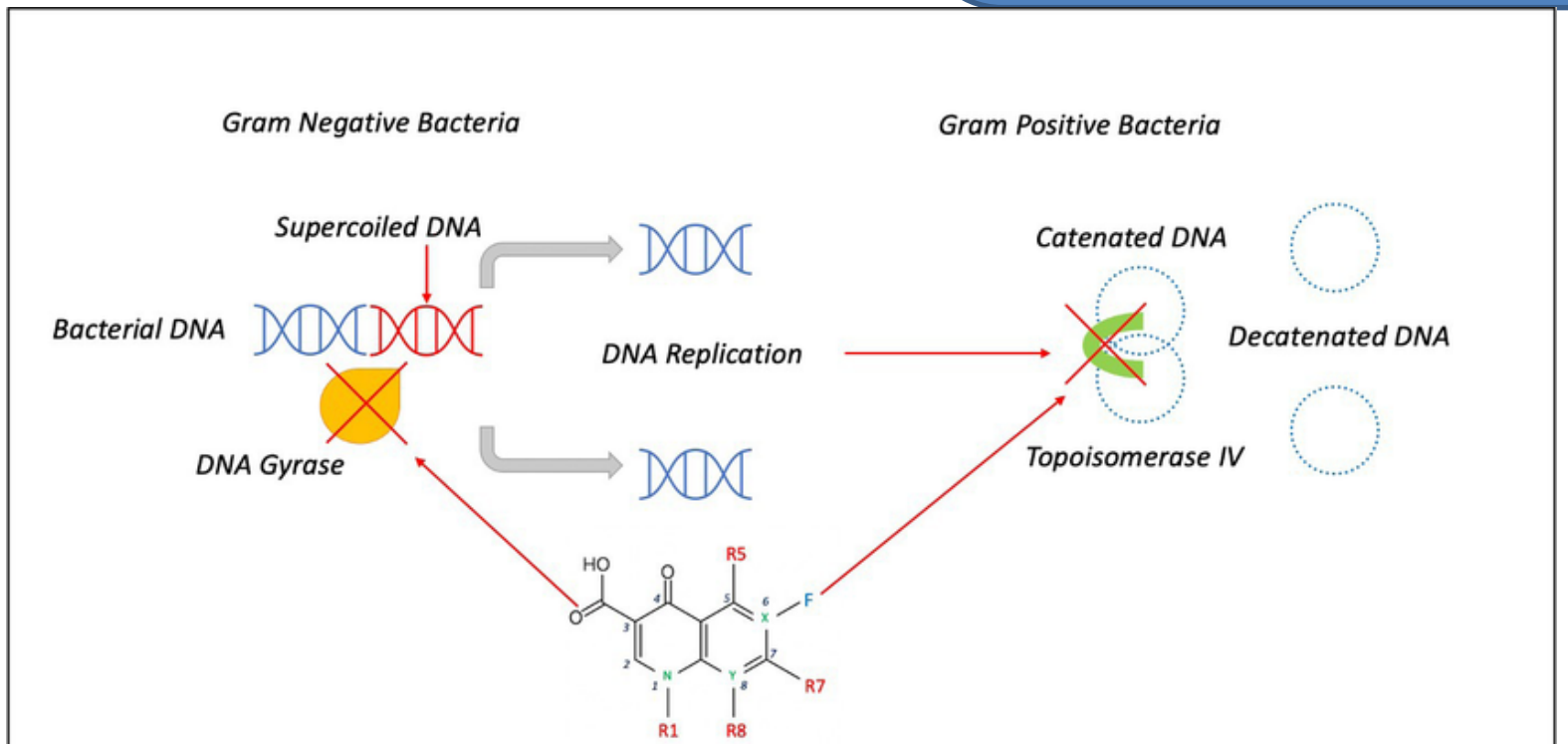
Mechanism of action

DNA gyrase (DNA helicase)=(Topoisomerase II : is the primary target

Gram-negative bacteria

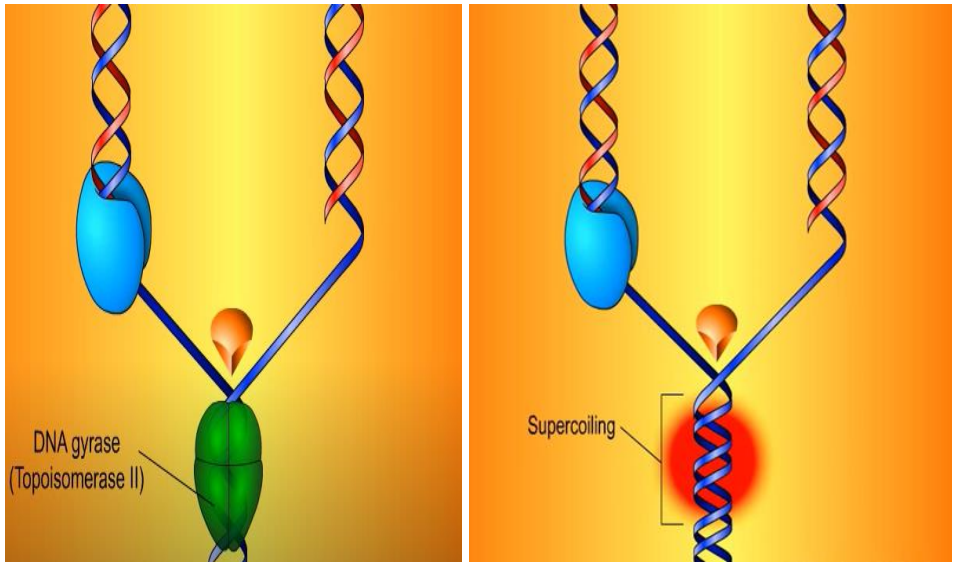
Topoisomerase IV : the more sensitive target

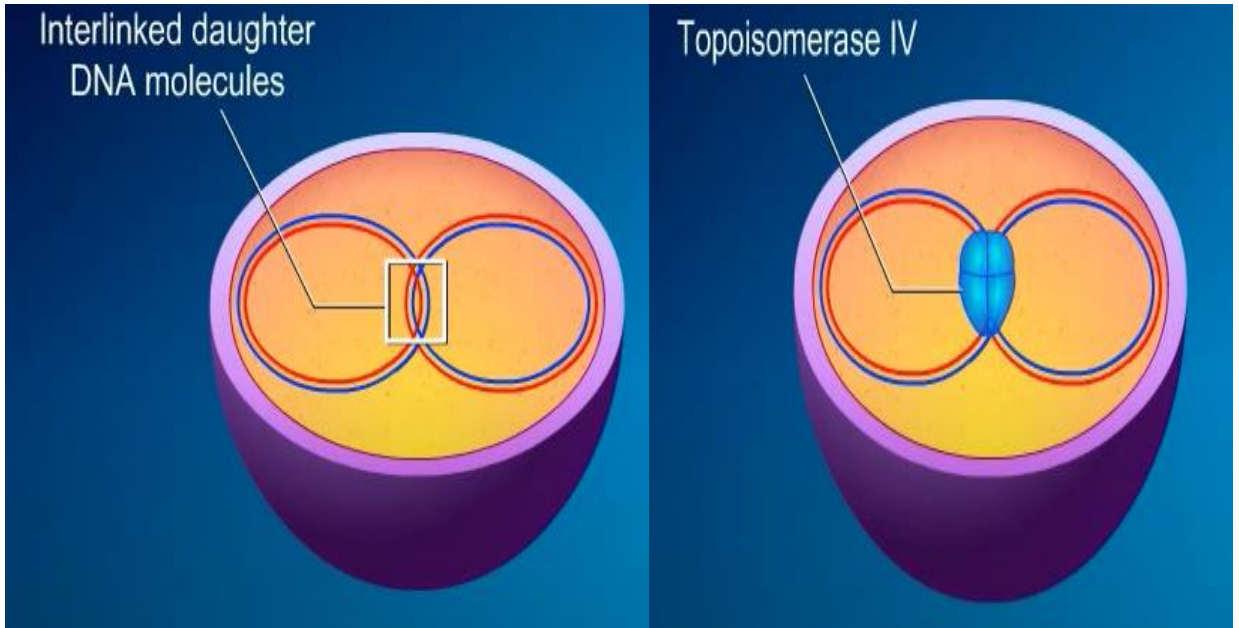
Gram-positive organisms



Mechanism of action

- DNA gyrase is responsible for reducing torsional stress ahead of replicating forks by breaking double-strand DNA. Inhibition of gyrase prevents negative supercoiling in replicating DNA
- Topoisomerase IV assists in separating daughter chromosomes once replication is completed. Inhibition of topoisomerase IV prevents separation of DNA strands
- Following cell wall entry through porin channels, fluoroquinolones bind to these enzymes and interfere with DNA ligation



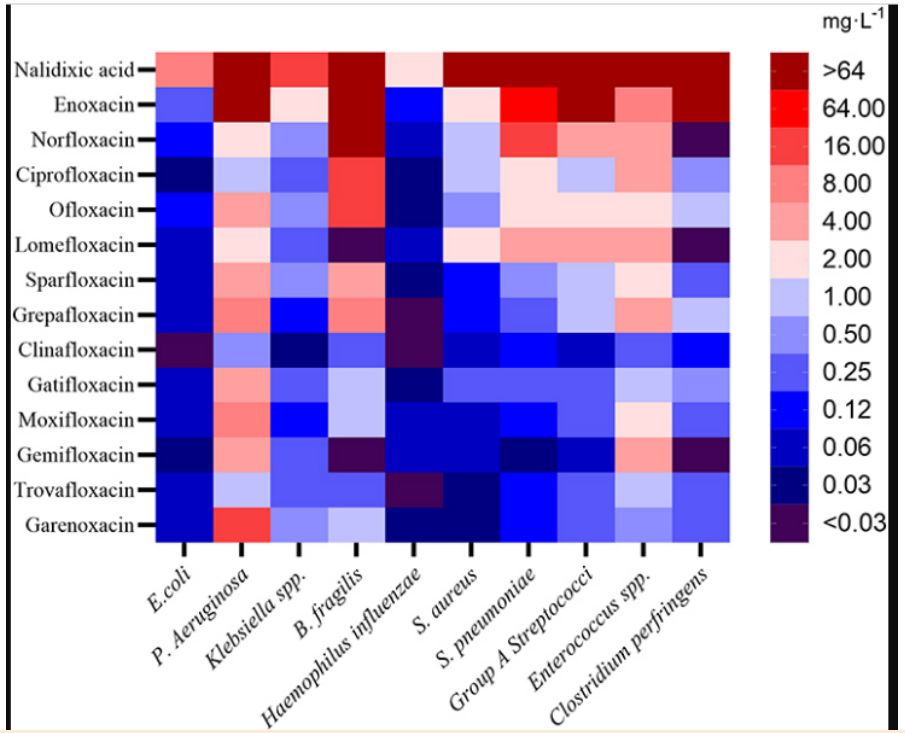


Spectrum

Quinolones are divided into first, second, third, and fourth generations according to their discovery history and their antibacterial properties.

At present, third-generation antibiotics are most commonly used in clinical practice

First-generation Nalidixic acid	• Narrow spectrum • Aerobic Gram-negative bacilli, mostly Enterobacteriaceae.
Second-generation **Ciprofloxacin**	• Gram-negative • Gram-postive • Pseudomonas aeruginosa
Third-generation **levofloxacin** **Moxifloxacin**	• Maintain the spectrum of second G (+/-) • Improved activity against Streptococcus spp., including S. pneumoniae, MRSA • Atypical
Fourth-generation Gemifloxacin, Delafloxacin	• Enhanced Gram-positive activity, including Staphylo and Streptococcus spp • Atypical • Anaerobes • Delafloxacin active against (MRSA) and Enterococcus faecalis.



Moxifloxacin: higher affinity for topoisomerase IV (ex; G +ve S.pneumoniae)

Ciprofloxacin: higher affinity for DNA gyrase (ex; G-ve P.aeruginosa)

Bactericidal : Killing is concentration dependent: AUC/MIC

Poor anaerobic activity

Excellent against atypical bacteria (legionella, mycoplasma, chlamydia

Pharmacokinetics

Absorption

- Well absorbed after oral administration, with levofloxacin and Moxifloxacin having a bioavailability that exceeds 90% - leads to serum levels that are very comparable to IV dosing
- Calcium and other divalent cations also interfere with the absorption of these agents

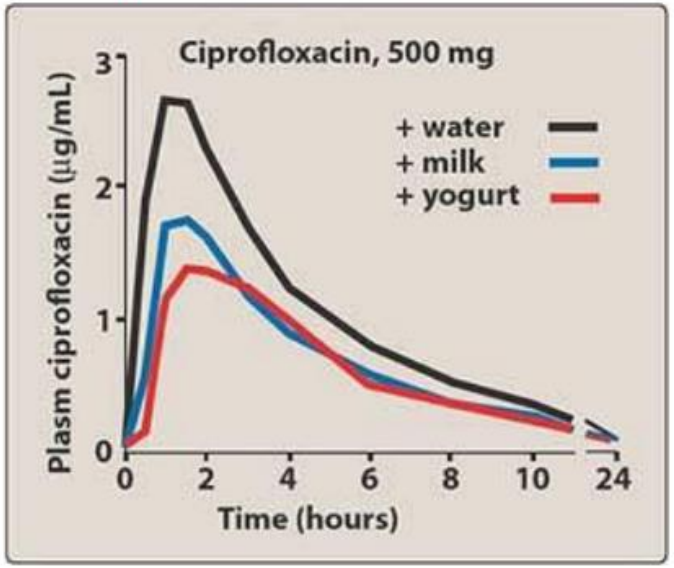
Distribution

- Fluoroquinolones distribute well into all tissues and body fluids.
- Concentrations are high in bone, urine (**except *Moxifloxacin***), kidney, prostatic tissue (but not prostatic fluid), and lungs as compared to serum.
- Penetration into CSF is good

Elimination

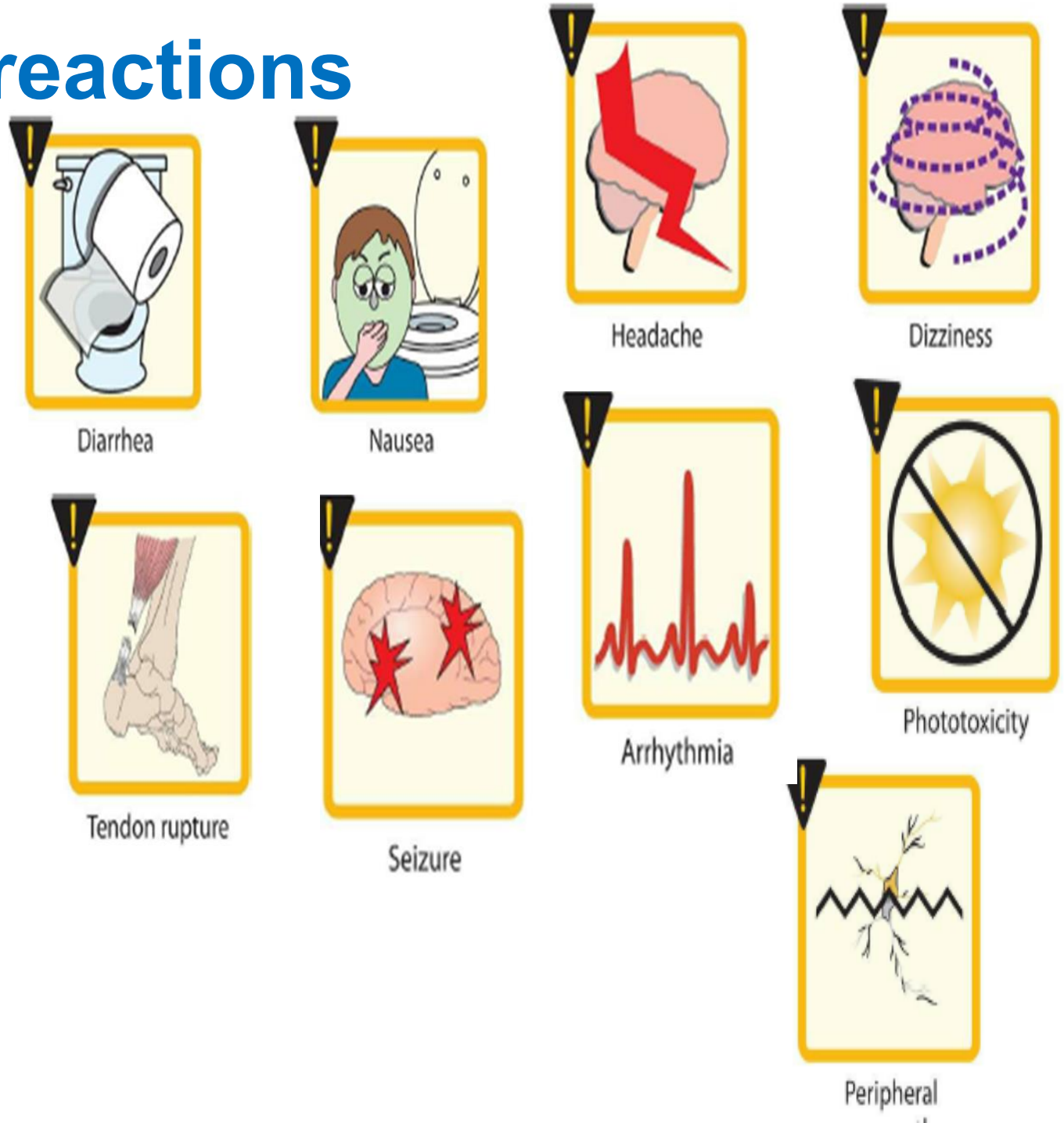
- Most fluoroquinolones are excreted renally.
- Dosage adjustments are needed in renal dysfunction Except Moxifloxacin (:)?

Ciprofloxacin-food interactions



Adverse reactions

- Most common adverse effects are nausea, vomiting and diarrhea.
- Headache, and dizziness
- Tendinitis, tendon rupture, peripheral neuropathy, and CNS effects (hallucinations, anxiety, insomnia, confusion, and seizures).
- Phototoxicity
- Hepatotoxicity
- Blood glucose disturbances (Gatifloxacin) (usually in diabetic patients receiving oral hypoglycemic agents or insulin).
- Fluoroquinolones may prolong the QTc interval, and these agents should be avoided in patients predisposed to arrhythmias or taking medication associated with QT prolongation. (Gatifloxacin, levofloxacin, Gemifloxacin)



Contraindications

- Not approved in children<18 years : in animal models, fluoroquinolones may damage growing cartilage and cause an arthropathy. May be used in children if needed (eg, for treatment of pseudomonal infections in patients with cystic fibrosis
- Pregnancy and lactation
- Arrhythmic patients

Generic/TRADE	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitor M / Comments	Dosing (Pediatric, Adult, Usual Max)	$/10d
Fluoroquinolones: Inhibit DNA-gyrase, causing breakdown of bacterial DNA. Bactericidal. Concentration dependent killing (aim for high peak concentrations). PK: ciprofloxacin, levofloxacin, moxifloxacin = **excellent bioavailability**. • AE: GI upset (N/V/D); headache; dizziness; rash/photosensitivity; ↑ QTc (risk highest with moxifloxacin); confusion/psychosis; ↓/↑ blood glucose (including reports of coma); ↑ *C. difficile*; seizure; tendinopathy/tendon rupture (↑ risk if concomitant corticosteroid, ≥60yrs, & women, onset highest within 1st month post exposure and managed with supportive measures); ↑? retinal detachment; ↑ weakness in myasthenia gravis; articular damage in kids; hepatotoxicity; nephrotoxicity; peripheral neuropathy NNH~150,000/10 day course, ↑ risk >60yrs, ↑BMI, ♂; ?↑ aortic aneurysm; ?↑ pseudotumor cerebri syndrome, ?heart valve regurgitation. • DI: CYP1A2 inhibition → ↑ levels of clozapine, duloxetine, methotrexate, quinapril, rasagiline, ropinirole, theophylline, tizanidine, varenicline, ↑ INR with warfarin. QTc prolongation (watch for other QTc-prolonging agents). • ↓ absorption via chelation with Ca^{++}, Fe^{++}, Al^{+++}, Mg^{++} (may **space calcium, iron, multivitamins**, etc. by giving >2 hours after fluoroquinolone, or hold for duration of fluoroquinolone therapy). Binds to enteral tube feeds (due to cations in feed - calcium, iron, etc.). May have less absorption via jejunostomy tube since fluroquinolones are likely absorbed in the duodenum. Increased risk of tendon rupture with corticosteroids use. ↓ BG with SUs, insulin. • CI: see adverse effects. Caution: ≥ 60 yrs, renal impairment, solid organ transplant, <18 yrs (safety not proven, but ciprofloxacin in particular often used). M: joint pain, blood glucose if DM, if prolonged therapy: CBC, SCr, LFTs. • PK: ciprofloxacin, levofloxacin, moxifloxacin = **excellent bioavailability**. Penetrates into bone/joint. • Moxifloxacin and levofloxacin → anaerobic, atypical, *Streptococci*, & gram-negative coverage has lead to designation as "respiratory fluoroquinolones"; effective in pneumonia and AECOPD, **but reserve use** where possible. **Reserve fluoroquinolones whenever possible.** (***FDA 2016: not for sinusitis, bronchitis, or uncomplicated UTIs as harms outweighed potential benefits and other antibiotics usually available***) • Ciprofloxacin has fairly reliable antipseudomonal activity (agents that kill *Pseudomonas* are uncommon). If Pseudomonas suspected in serious infection with risk factors for MDR, may use combo therapy empirically in some cases (consult ID). • These are broad-spectrum agents, with particularly good coverage against gram-negative pathogens. Preventing resistance, by limiting fluoroquinolone use, is important. **When might use be necessary?** Those with contraindications to other therapies (e.g. true penicillin allergy), infections resistant or likely to be resistant to other therapies.		Use discouraged in <18yrs.
Ciprofloxacin CIPRO, g 250, 500, 750mg tab ☎ ▼ 500mg XL tab, g ☎ ⊗; 1000mg XL tab ☎ ⊗ 100mg/mL susp ☎ ▼ strawberry; 2mg/mL IV (200 & 400mg bags) ⊗ $P_1P_{2.3}L$	• **Coverage**: Primarily gram-negative coverage → *Pseudomonas*; *Enterobacterales*; ?*Neisseria*; *Haemophilus*; *Moraxella*; *Pasteurella*; many atypicals. Essentially no anaerobic coverage. But shigella resistance is increasing. • **Useful in**: Pseudomonal inf; complicated UTIs; pyelonephritis; intra-abdominal infections & if neutropenia. • Cipro XL may not be best choice → does not create high peak important in concentration-dependent killing. • A lower ciprofloxacin dose may be indicated in elderly females with a high total bilirubin.	**Kids:** 20-30mg/kg/day po divided q12h **Adult:** 500mg **po** q12h (or 1000mg XL daily) 400mg **IV** q12h x 5 days **Max:** 1500mg/day (e.g. 750mg BID known Psudomonas infection)	$48 $20 $325 $28
LevoFLOXacin LEVAQUIN, g 250, 500, 750mg tab ☎ ▼ 5mg/mL IV (250, 500 & 750mg bags) NIHB x 30 days maximum $P_1P_{2.3}L$	• **Coverage**: *Strep pneumoniae*; MSSA; *Enterobacterales*; *Neisseria*; *Haemophilus*; *Moraxella*; *Pasteurella*; many atypicals; some anaerobes. Sometimes has activity against *Pseudomonas*. • **Useful in**: high-risk AECOPD; pneumonia (usually as alternative to 1st-line agents); intra-abdominal infections; pyelonephritis or complicated UTIs & if neutropenia. (**Quinsair** 240mg/2.4ml ☎ ▼$565/amp inhalation solution for chronic *Pseudomonas aeruginosa* in adult cystic fibrosis pts)	**Kids:** 8-10mg/kg po q24h **Adult:** **250-500**-750mg po q24h **250-500**-750mg IV q24h x 5 days **Max:** 750mg/day	$31 $27-29 $170-272 $63
Moxifloxacin AVELOX, g 400mg tab ☎ ▼; 400mg/250mL IV NIHB x 14 days maximum $P_1P_{2.3}L$	• **Coverage**: *Strep pneumoniae*; MSSA; *Enterobacterales*; *Neisseria*; *Haemophilus*; *Moraxella*; *Pasteurella*; many atypicals; anaerobes. • **Useful in**: high-risk AECOPD; pneumonia (usually as alternative to 1st-line agents); ?appendicitis.[CODA] & if neutropenia. Does not penetrate urine – do not use to treat UTIs.	**Kids:** not indicated **Adult:** 400mg po q24h (or IV x 5 days) **Max:** 400mg/day	- $28(190) $28
Norfloxacin NOROXIN, g 400mg tab ☎ ▼ $P_1P_{2.3}L$	• **Coverage**: *Strep pneumoniae*; MSSA; *Enterobacterales*. • **Useful in**: UTIs; prophylaxis of spontaneous bacterial peritonitis (prophylactic dose is 400mg po daily). • Appears equivalent to ciprofloxacin in treatment of UTI.[8-10]	**Kids:** not indicated **Adult:** 400mg po q12h **Max:** 800mg/day	- $51 $51

Metronidazole (*Flagyl*)

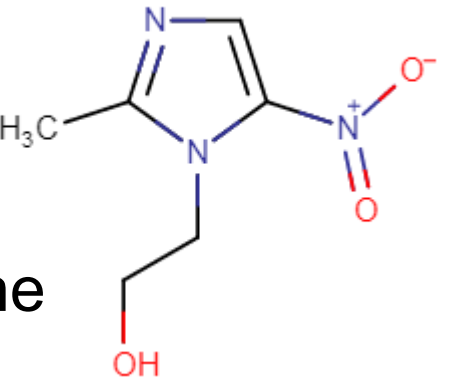


Metronidazole is a commonly used antibiotic, belonging to the nitroimidazole class of antibiotics

Used as an antibiotic for several decades, with added antiparasitic properties that set it apart from many other antibacterial drugs, allowing it to treat a wide variety of infections

Indicated for the treatment of confirmed trichomoniasis caused by Trichomonas vaginalis (except for in the first trimester of pregnancy), bacterial vaginosis.

certain types of amebiasis, and **various anaerobic infections.**



Anaerobic infections may occur on the skin and skin structures, the abdomen, the heart, reproductive organs, central nervous system, and the respiratory system

Used off-label in the treatment of Crohn's disease, as a prophylactic agent after surgery, and in the treatment of Helicobacter pylori infection.It has also been studied in the prevention of preterm births and to treat periodontal disease

Mechanism of action

- The exact mechanism of action of metronidazole is NOT fully established.

- An intermediate in the reduction of metronidazole which is only made by anaerobic bacteria and protozoa, binds deoxyribonucleic acid and electron-transport proteins of organisms, **blocking nucleic acid synthesis**

Metabolism

- Metronidazole undergoes hepatic metabolism via hydroxylation, oxidation, and glucuronidation. The metabolism of metronidazole yields 5 metabolites

- Only 20% of the dose found in the urine is accounted for by unchanged metronidazole

- Metronidazole and metabolites are 60 to 80% eliminated in the urine, and 6-15% excreted in the feces

Adverse effects

- Include peripheral neuropathy, central nervous system toxicity,
- Seizures,
- Disulfiram-like effect (if combined with alcohol) dark urine,
- Metallic taste in the mouth, nausea, epigastric discomfort, and vertigo
- Neutropenia.

Urinary Tract Antiseptics : Nitrofurantoin

- First-line therapy for uncomplicated cystitis
- It acts by Inhibiting DNA and RNA synthesis.
- Spectrum: Susceptible organisms include E. coli, Klebsiella spp.(Gram negative)- Enterococcus spp., and Staphylococcus spp(Gram positive)
- Patients with impaired renal function should not receive *nitrofurantoin* due to an increased risk of adverse events.

Adverse effects include:

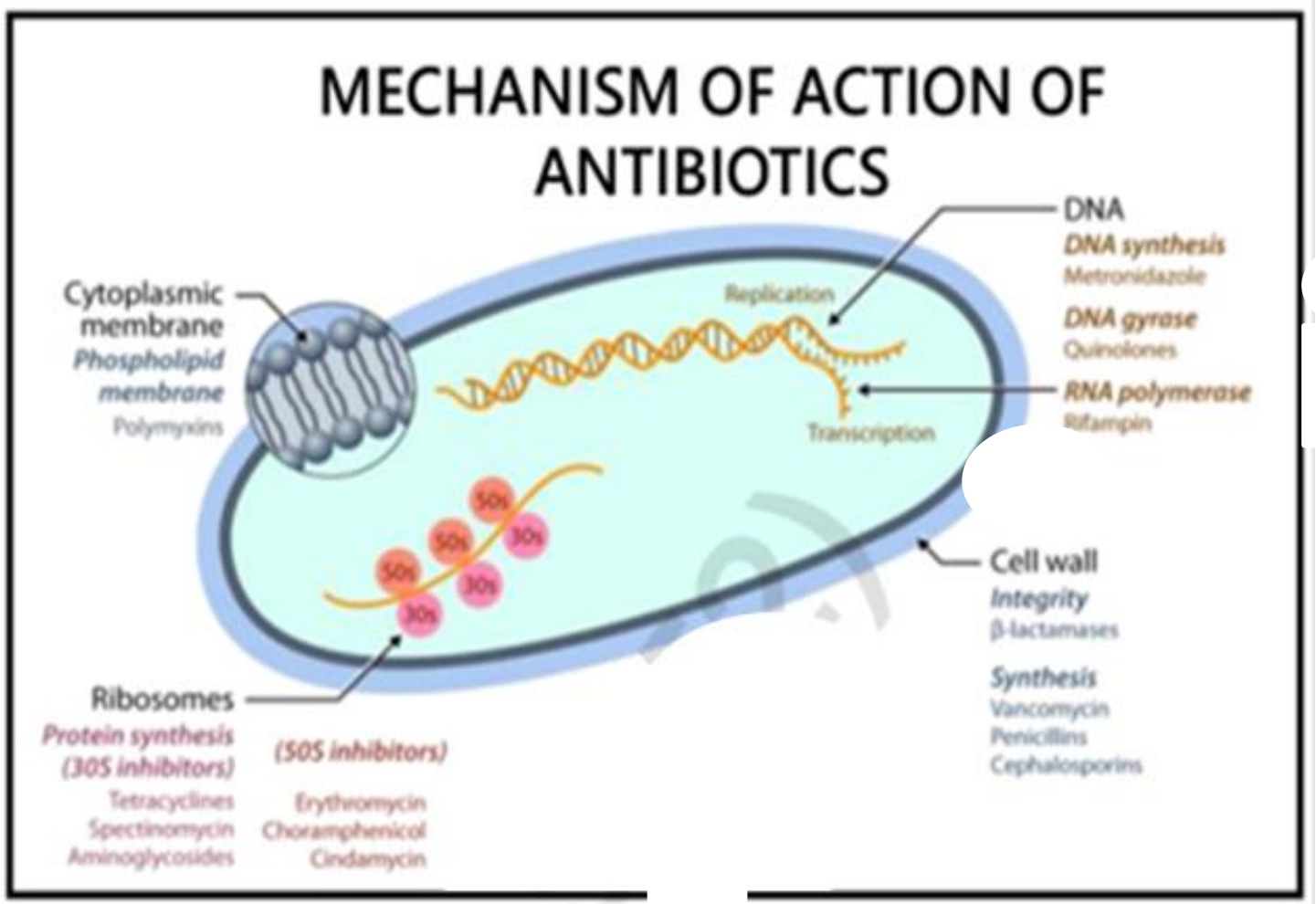
- Gastrointestinal disturbances
- Acute pneumonitis
- Neurologic problems
- Pulmonary fibrosis
- Hemolytic anemia in patients with G6PD deficiency

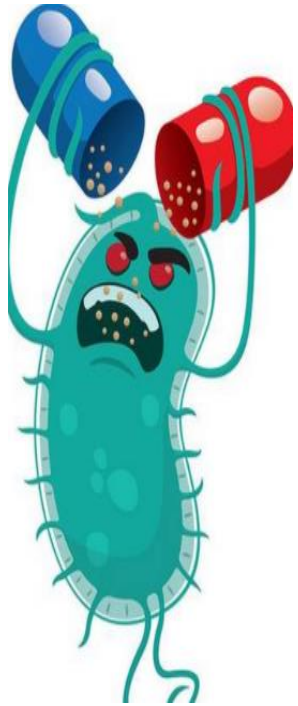
Contraindications:

- Renal impairment
- Pregnancy (3 rd trimester)

Antibiotic Therapy: Mechanism of Action

- Interference with cell wall synthesis
- Interference with protein synthesis
- Interference with DNA replication
- **Acting as a metabolite to disrupt critical metabolic reactions inside the bacterial cell**





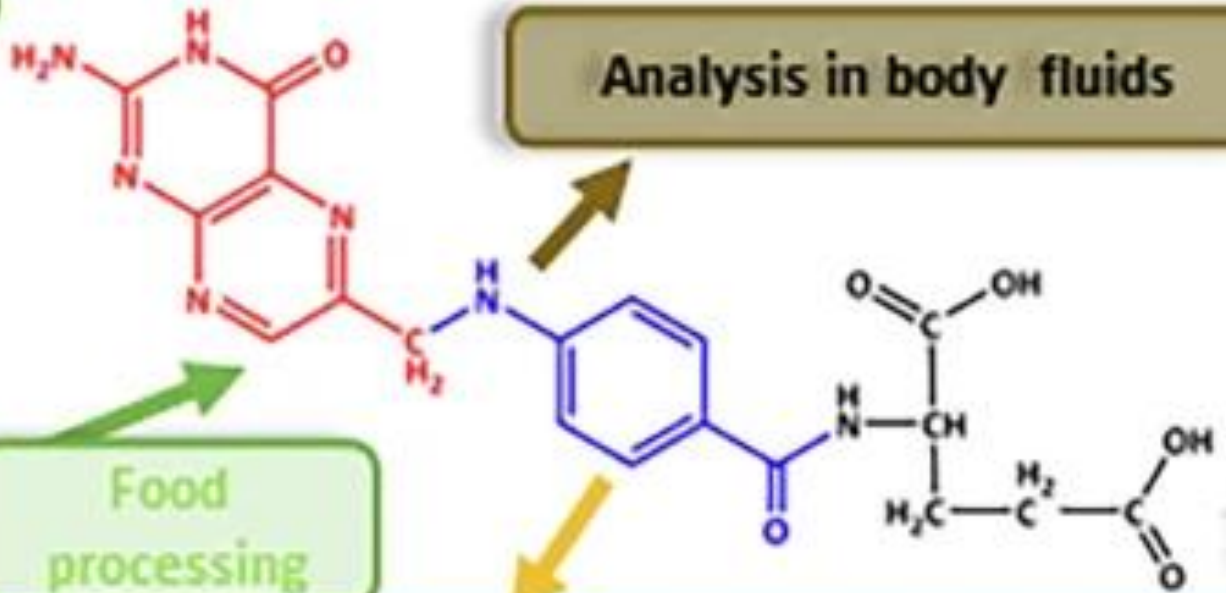
ANTIMETABOLITES

(Folic Acid Antagonists)

VITAMIN B_9 (FOLATE)

Sources of vitamin B_9

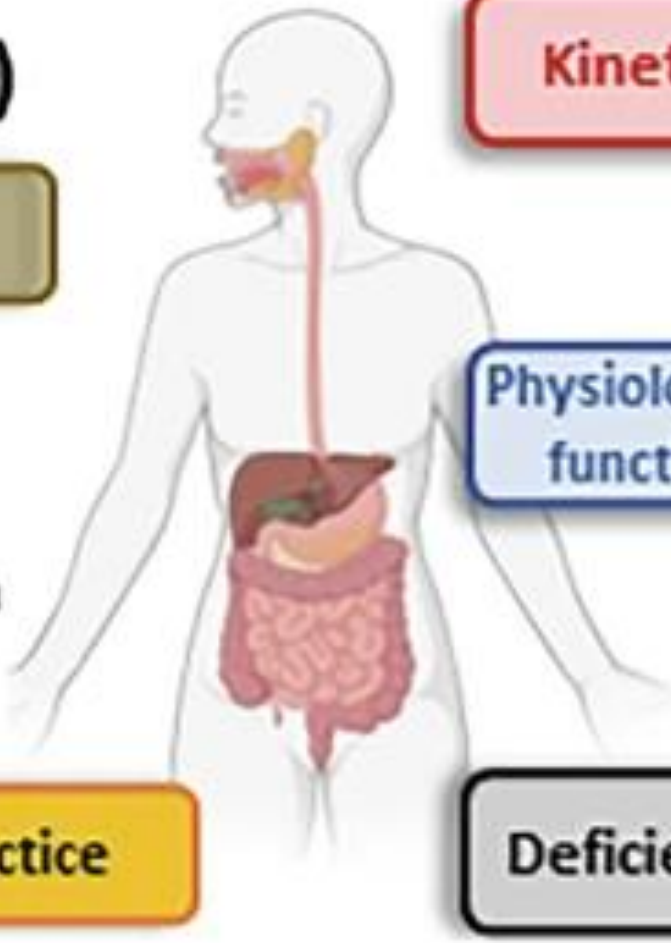




Analysis in body fluids

Food processing

Structure modification → drugs in clinical practice



Kinetics

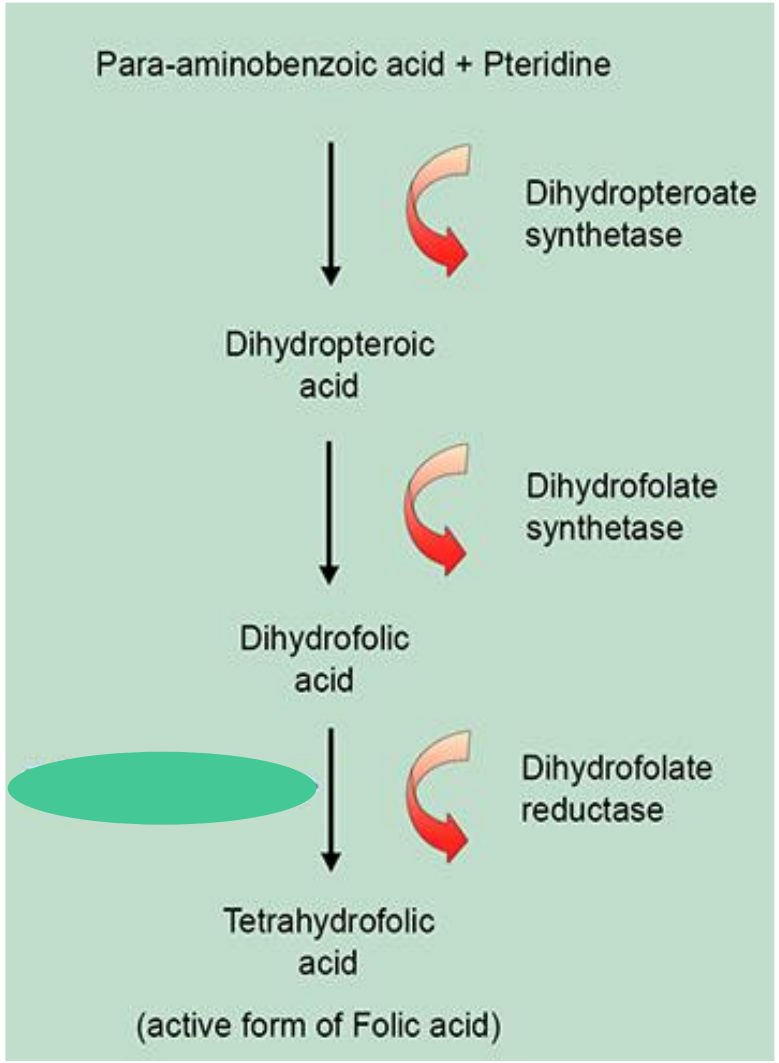
Physiological function

Deficiency

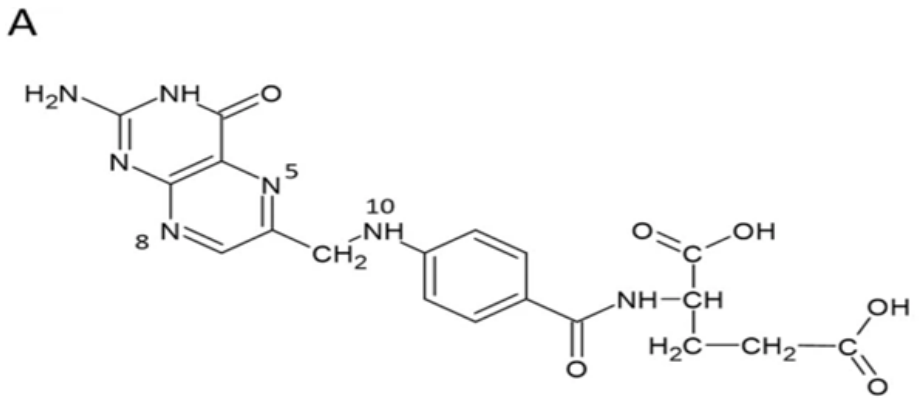
Folic acid synthesis differs significantly between bacteria and humans.

Bacteria synthesize folic acid (known as folate = **Vitamin B9**) de novo (from scratch).

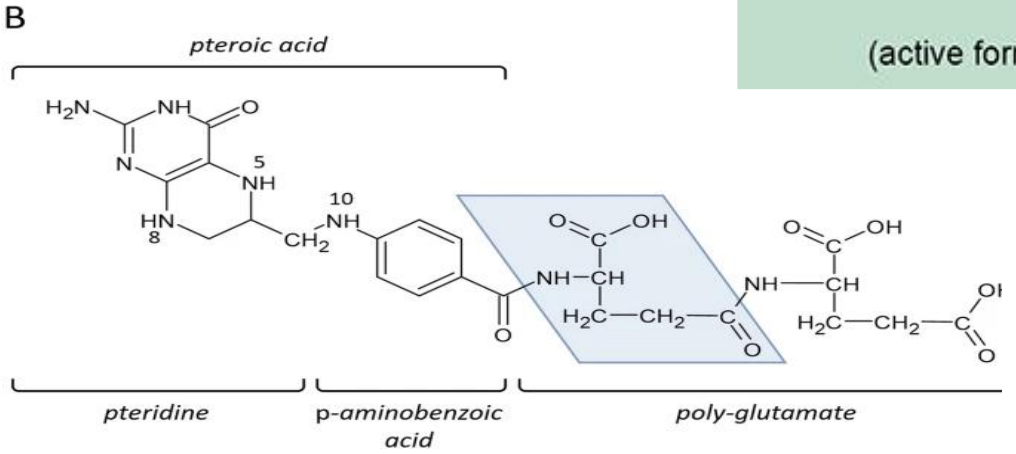
Bacteria possess the necessary enzymes (dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR) to produce folic acid from simpler precursor molecules



A Folic acid



B Tetrahydrofolate.

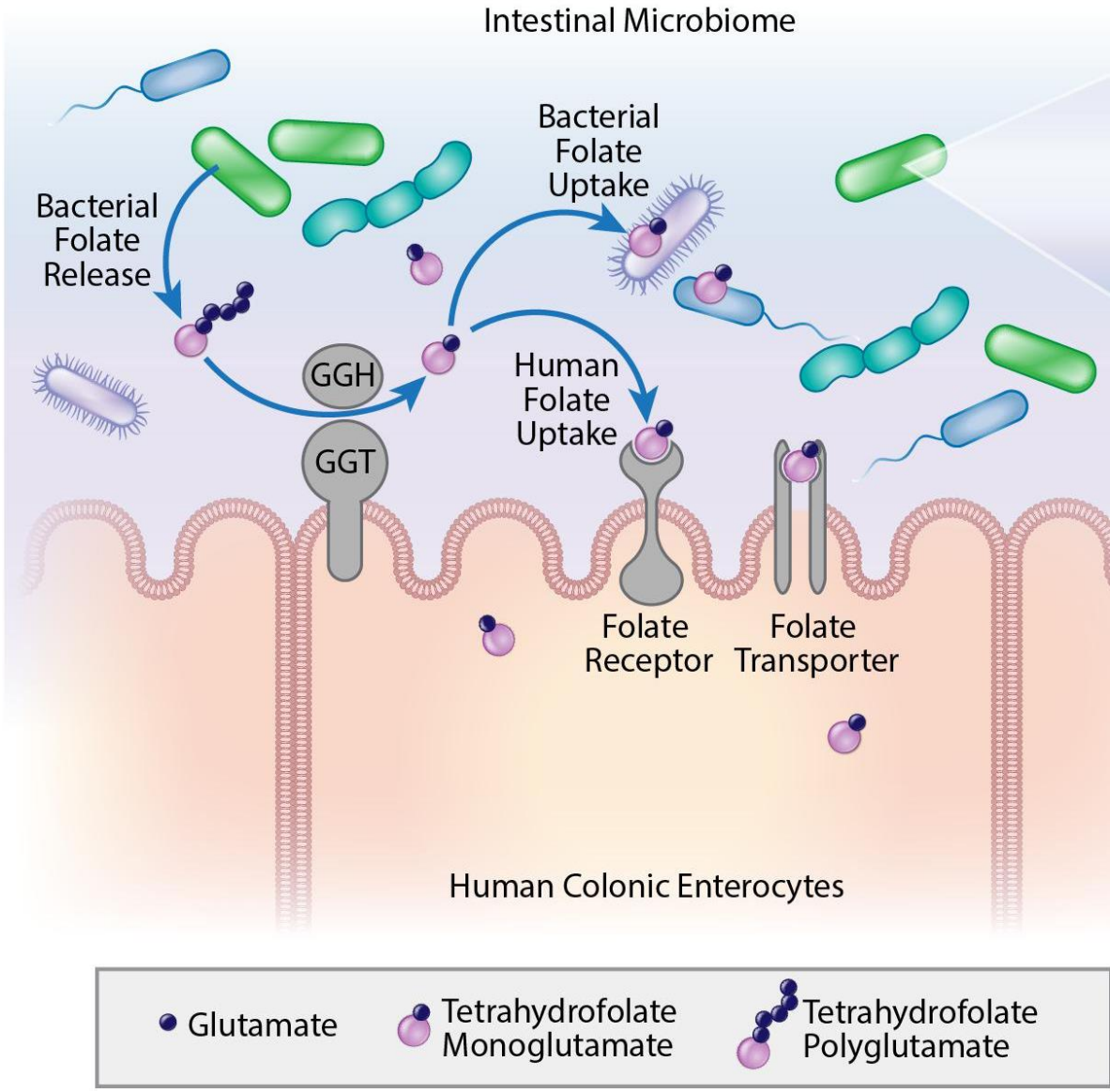


Humans cannot and must obtain it through diet.

Humans have specialized transport systems for folate uptake into cells and tissues.

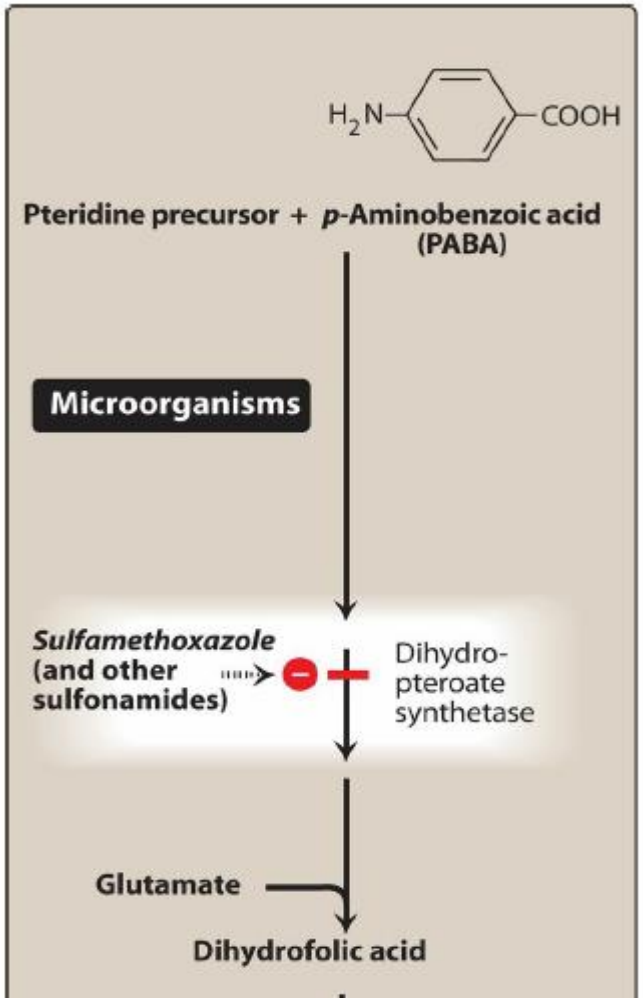
Studies suggest that bacteria in the human gut (Anaerobic) may synthesize folate, potentially contributing to the host's folate levels. The human host absorbs and uses some of these folates

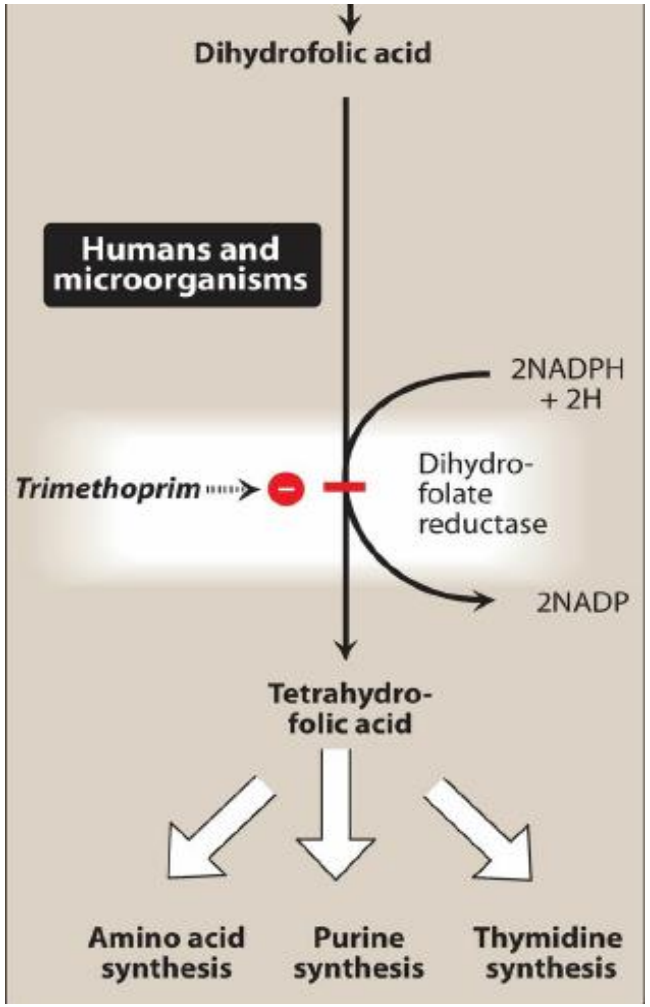
This difference is crucial for the development of antibiotics, which target bacterial folic acid synthesis pathways without affecting human cells



Folic acid antagonists (Mechanism of action)

- Folic acid is a coenzyme essential in the synthesis of ribonucleic acid (RNA), DNA, and certain amino acids. In absence of folate, cells cannot grow or divide

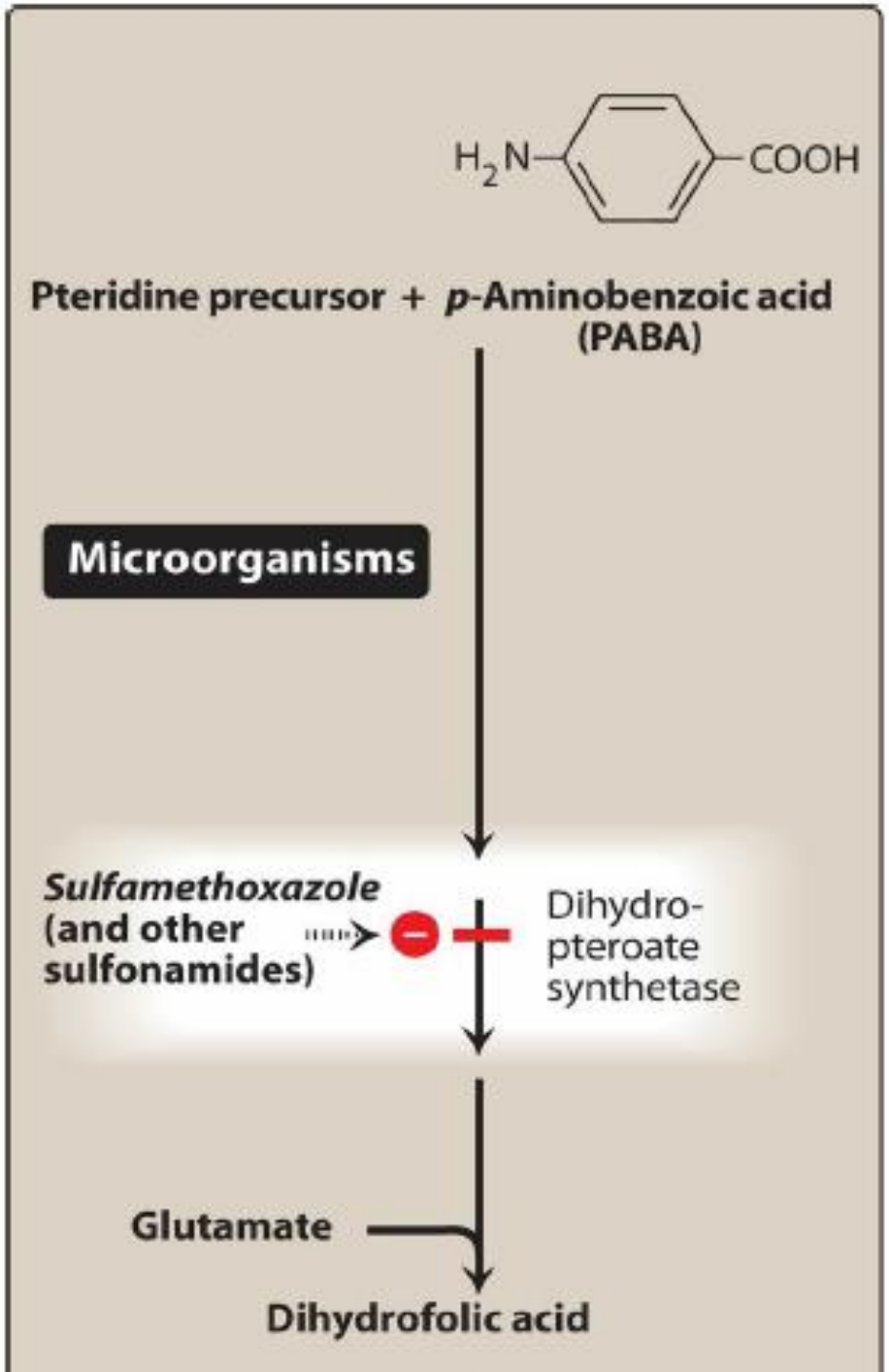


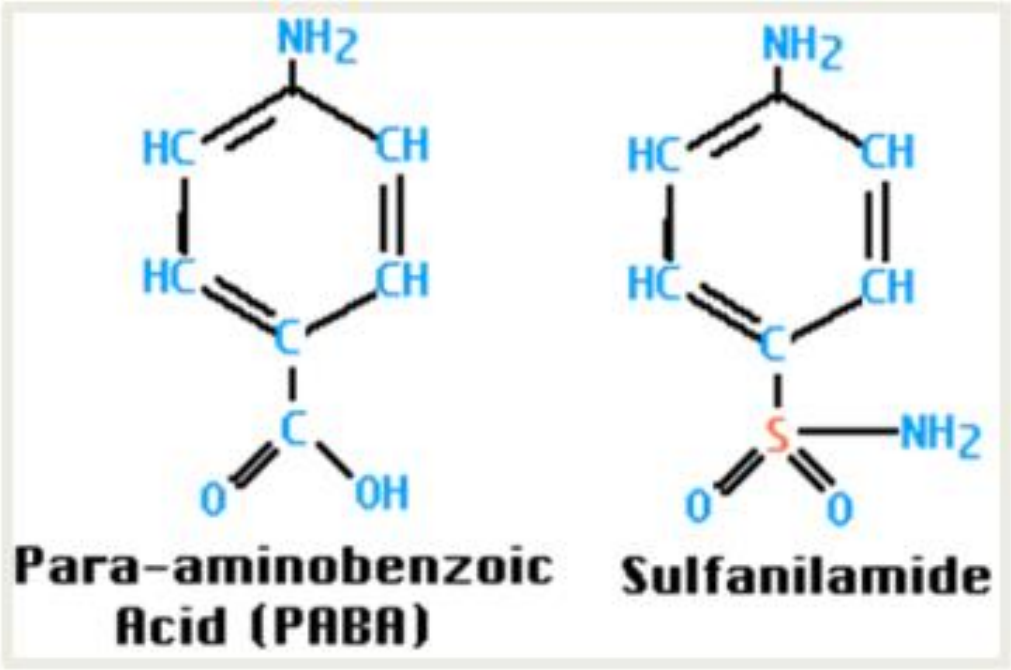


INHIBITORS OF FOLATE SYNTHESIS
Mafenide SULFAMYLON
Silver sulfadiazine SILVADENE, SSD, THERMAZENE
Sulfadiazine GENERIC ONLY
Sulfasalazine AZULFIDINE
INHIBITORS OF FOLATE REDUCTION
Pyrimethamine DARAPRIM
Trimethoprim PRIMSOL, TRIMPEX

Bacteriostatic

Both Sulfonamides and Trimethoprim provides a synergistic effect.





BACTERIOSTATIC

High concentration of PABA inhibits sulfa drugs activity

Sulfonamides are classified based on:

1. Chemical structure and pharmacological activity, primarily as antibacterial and non-antibacterial agents.

Antibacterial sulfonamides, like sulfamethoxazole, sulfanilamide, sulfapyridine, sulfadiazine, and sulfamethoxazole, are used to treat bacterial infections.

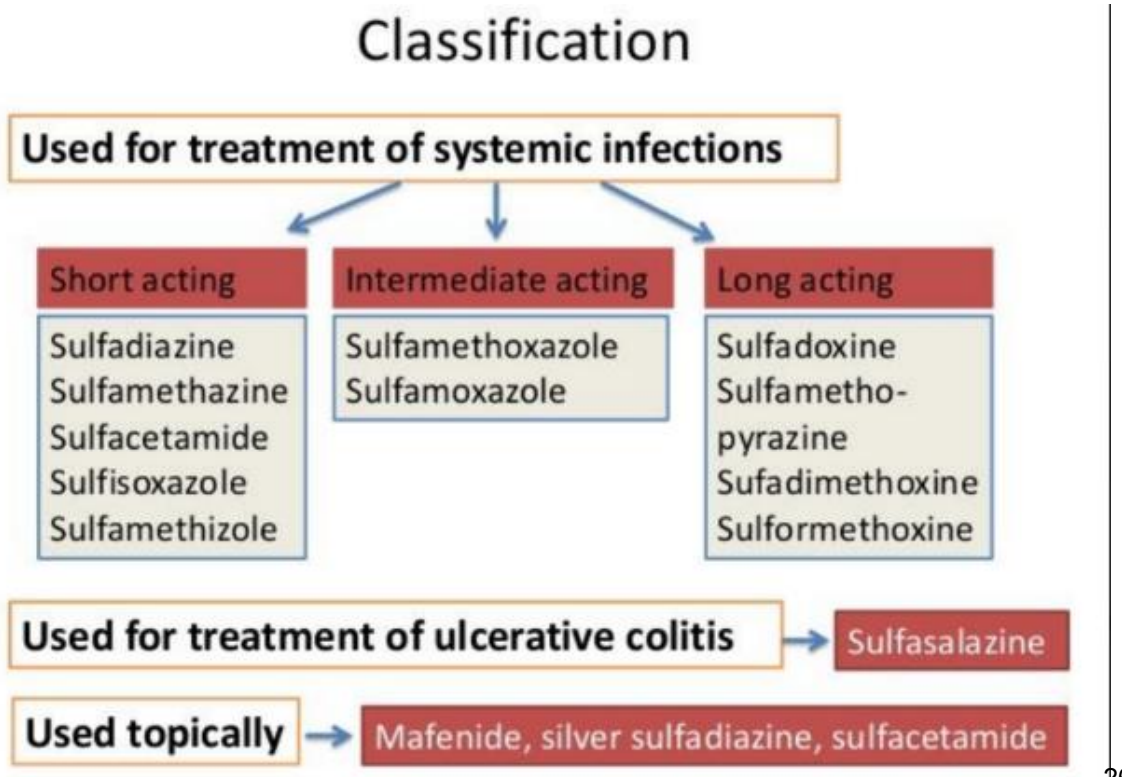
Non-antibacterial sulfonamides include carbonic anhydrase inhibitors (CAIs), sulfonylureas, and thiazide diuretics, among others.

2. Based on Duration of Action

3. Based on Pharmacokinetic Properties:

Poorly Absorbed (Locally Acting):
These are used for local effects in the gastrointestinal tract.

Rapidly Absorbed and Excreted (Systemic):
Used for systemic infections.



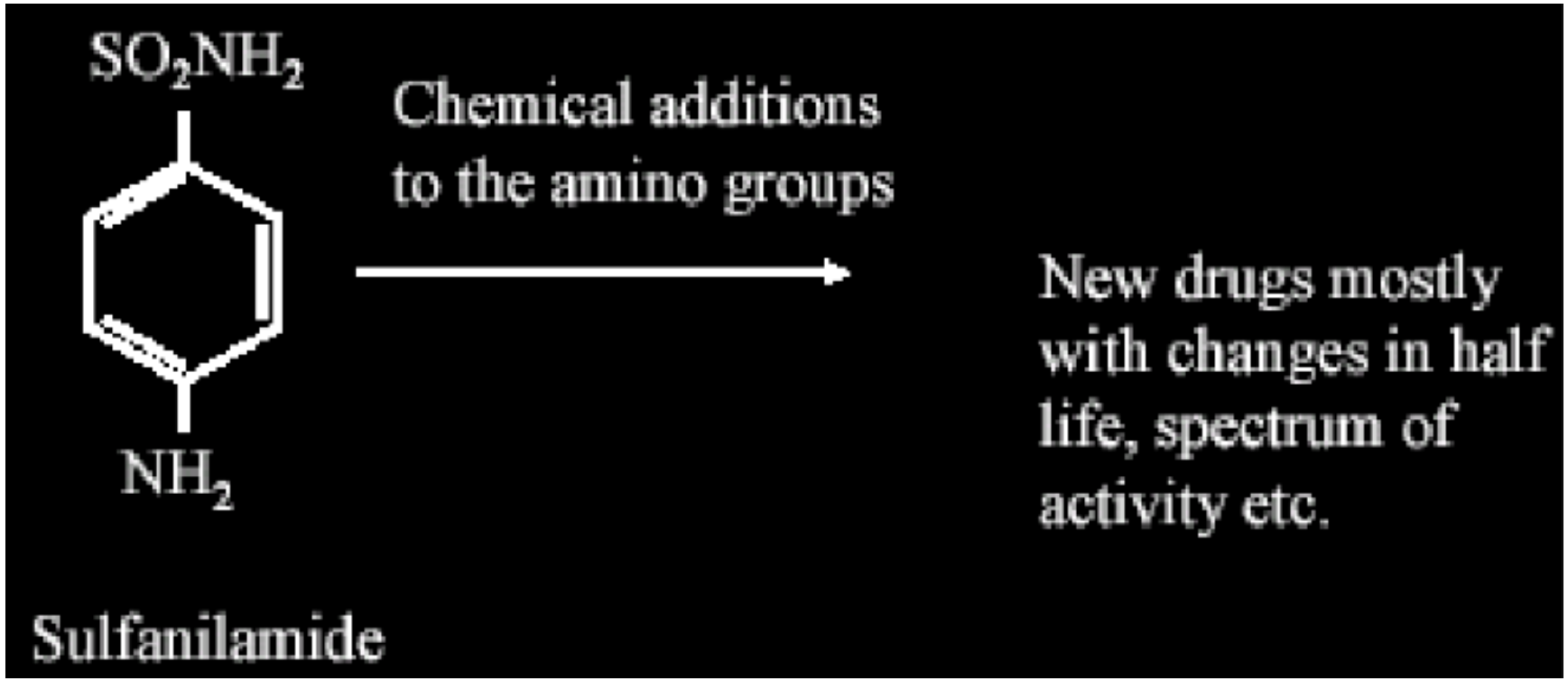
Antibacterial spectrum

- Broad Spectrum : Sulfa drugs active against Gram-negative and Gram-positive organisms such as Enterobacteriaceae, Haemophilus influenzae, Streptococcus spp., Staphylococcus spp
- Activity against some parasites : Plasmodium (malaria)- Toxoplasma gondii
- In burn units, *silver sulfadiazine* or *mafenide acetate* creams have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria.
- [Note: *Silver sulfadiazine* is preferred because *mafenide* produces pain on application and its absorption may contribute to acid–base disturbances.]

History

1932: Sulfa drugs noted to have antibacterial properties

First antibacterial agent used in the U.S.



Pharmacokinetics

Given orally, can be given I.V.

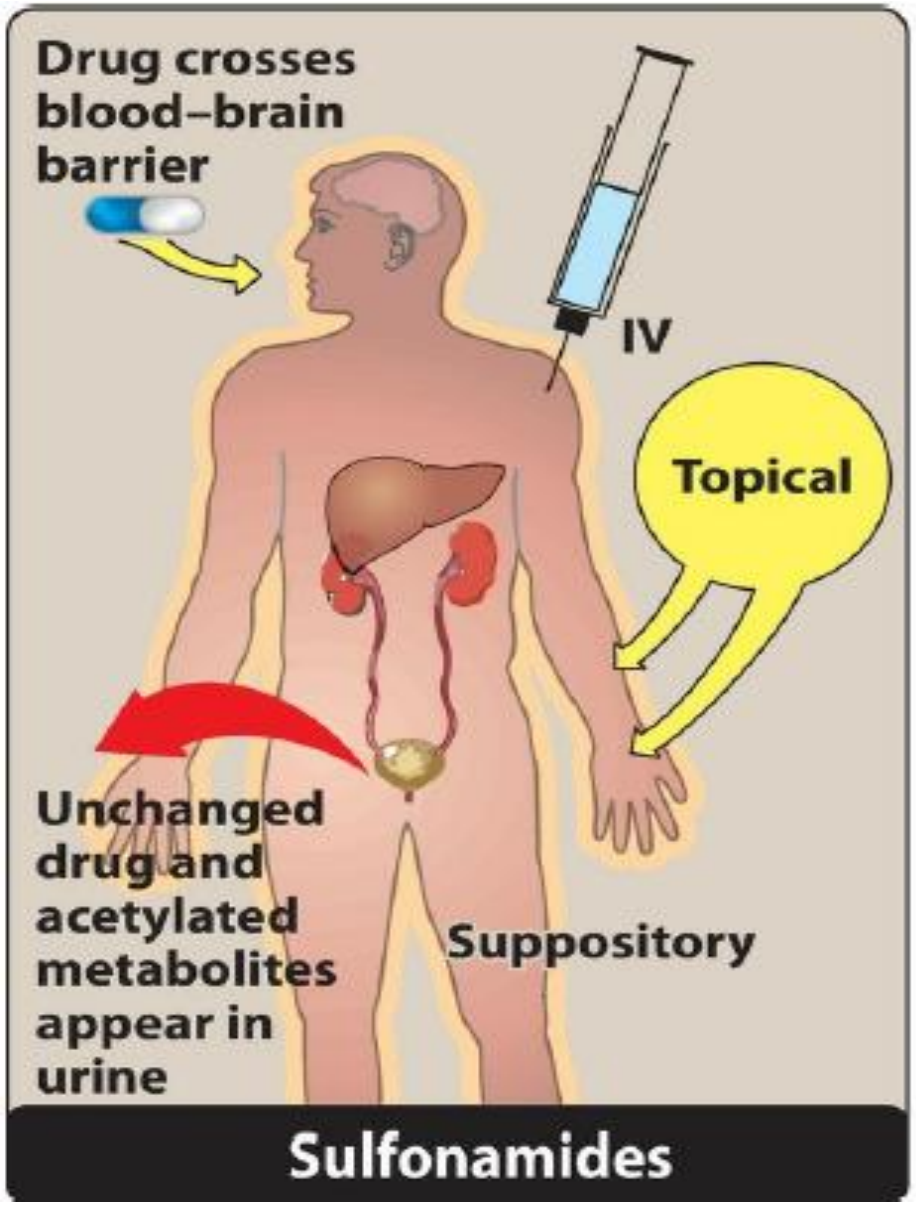
- ❑ Sulfasalazine: not absorbed orally, it is reserved for

treatment of chronic inflammatory bowel disease

- ❑ Distribution: Well distributed, including CSF

- ❑ Readily cross the placenta and reach fetal circulation (contraindicated in pregnancy)

- ❑ Metabolism: in the liver (acetylation)
- ❑ Excretion: by the kidney.
- ❑ Dose reduction is required in renal failure
- ❑ May be eliminated in breast milk

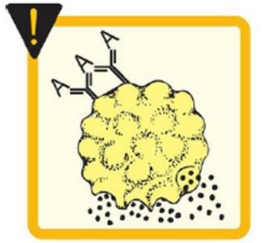


Adverse effects

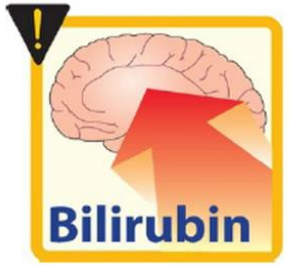
1. Crystalluria : Nephrotoxicity may develop as a result of crystalluria. Adequate hydration and alkalinization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.


Crystalluria

2. Photosensitivity &Hypersensitivity reactions, such as rashes, angioedema, or Stevens-Johnson syndrome, epidermal necrolysis, may occur.


Hypersensitivity

3- Kernicterus : Bilirubin-associated brain damage occurs in newborns, when sulfa drugs competes for bilirubin binding sites on albumin and increases levels of unconjugated bilirubin. The bilirubin is then free to pass into the CNS



Kernicterus

4. : **Hemolytic anemia** in patients with G6PD

Drug potentiation

Sulfamethoxazole and warfarin??

- Inhibition of CYP2C9, resulting in reduced clearance of *warfarin*
- Sulfonamides may also displace *warfarin* from binding sites on serum albumin: Increase serum concentration of warfarin (increases
- INR) and methotrexate

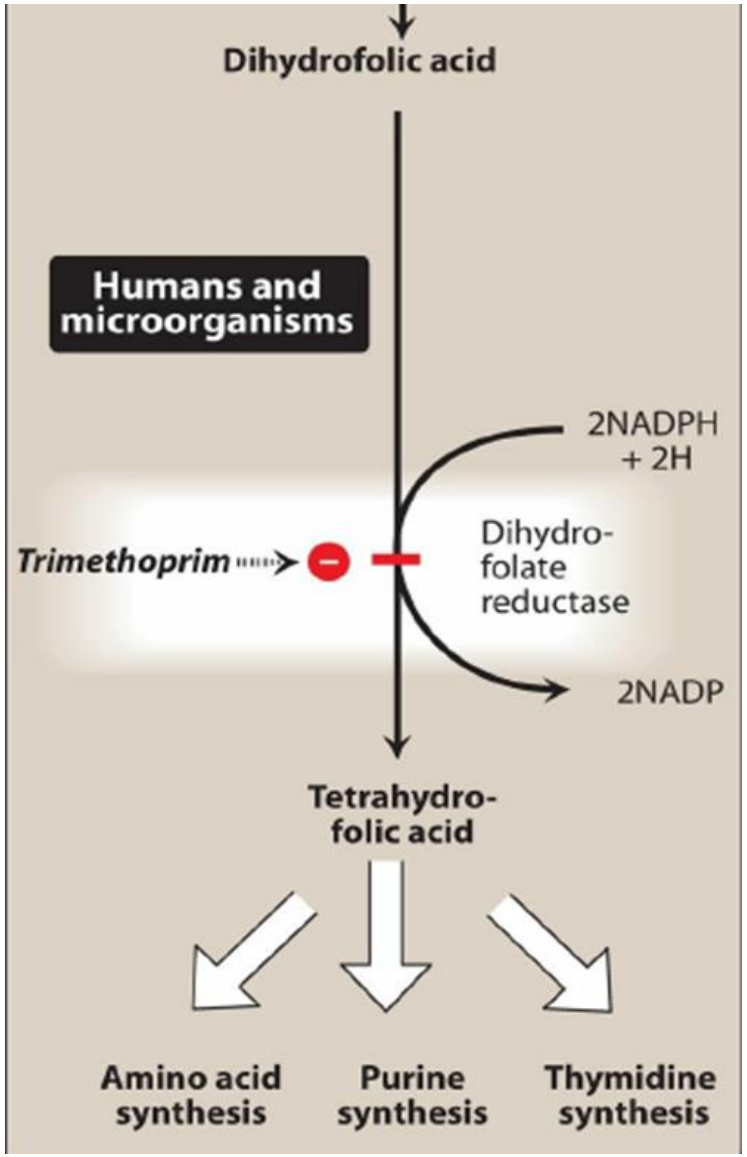
Contraindications

Newborns and infants less than 2 months due to risk of kernicterus.

Pregnant women at term

Trimethoprim

- Potent inhibitor of bacterial dihydrofolate reductase
- It binds to bacterial dihydrofolate reductase more readily than it does to human dihydrofolate reductase, which accounts for the selective toxicity of the drug.
- Available in combination with sulfamethoxazole



- Rapidly absorbed following oral administration
- The drug is a weak base, higher concentrations of trimethoprim are achieved in the relatively acidic prostatic and vaginal fluids
- It is distributed into body tissues and fluids, including penetration into the cerebrospinal fluid
- Spectrum : Similar to that of *sulfamethoxazole*.
- Trimethoprim is 20- to 50-fold more potent than the sulfonamides.
- Trimethoprim may be used alone in the treatment of urinary tract infections (UTIs) and in the treatment of bacterial prostatitis

Adverse effects

- Trimethoprim can produce the effects of folic acid deficiency.
- Megaloblastic anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those with nutrient-poor diets
- folinic acid (also known as leucovorin).
- Hyperkalemia especially when administered with other drugs

Mechanism of resistance (Trimethoprim)

1. Overproduction of DHFR

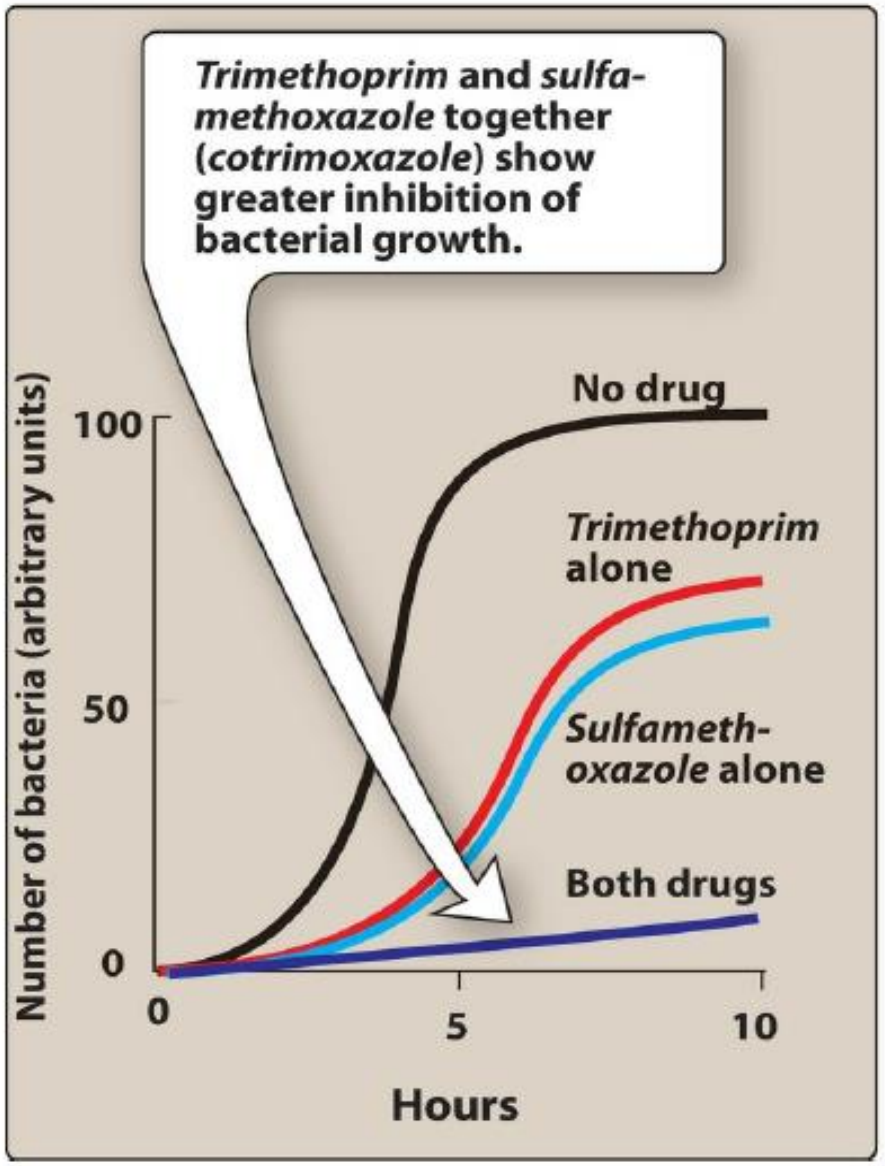
2. Production of a mutated DHFR that is resistant to trimethoprim (often plasmid mediated)

3. Resistance has been increasing >20% of E. coli are resistant in some regions

Trimethoprim-Sulfamethoxazole (Cotrimoxazole)

Cotrimoxazole is administered orally .
Intravenous administration may be in patients with severe pneumonia caused by Pneumocystis jirovecii

- Broad spectrum including MRSA
- Pneumocystis jirovecii
- Toxoplasmosis
- Listeria monocytogenes
- Salmonella infections.



Toxicity

1. Toxicities of sulfa
2. Bone marrow suppression

Megaloblastic anemia, leukopenia, thrombocytopenia

Reversed by administration of folinic acid

Common uses

UTIs (decreased efficacy with increasing E. coli resistance rates)

- Respiratory tract infections
- Pneumocystis pneumonia in AIDS/transplant
- Sinusitis, otitis media
- Concentrate in Vagina and Prostate fluids

USEFUL SLIDES

ABX against MRSA

CLean ur VaLiD Dox e Carolina Cotton Toy

CL = Clindamycin

Va = Vancomycin Li = Linezolid D = Daptpmycin

Dox = Doxycycline

Carolina = Ceftaroline

Co = Cotrimaxazole

T = tigacycline

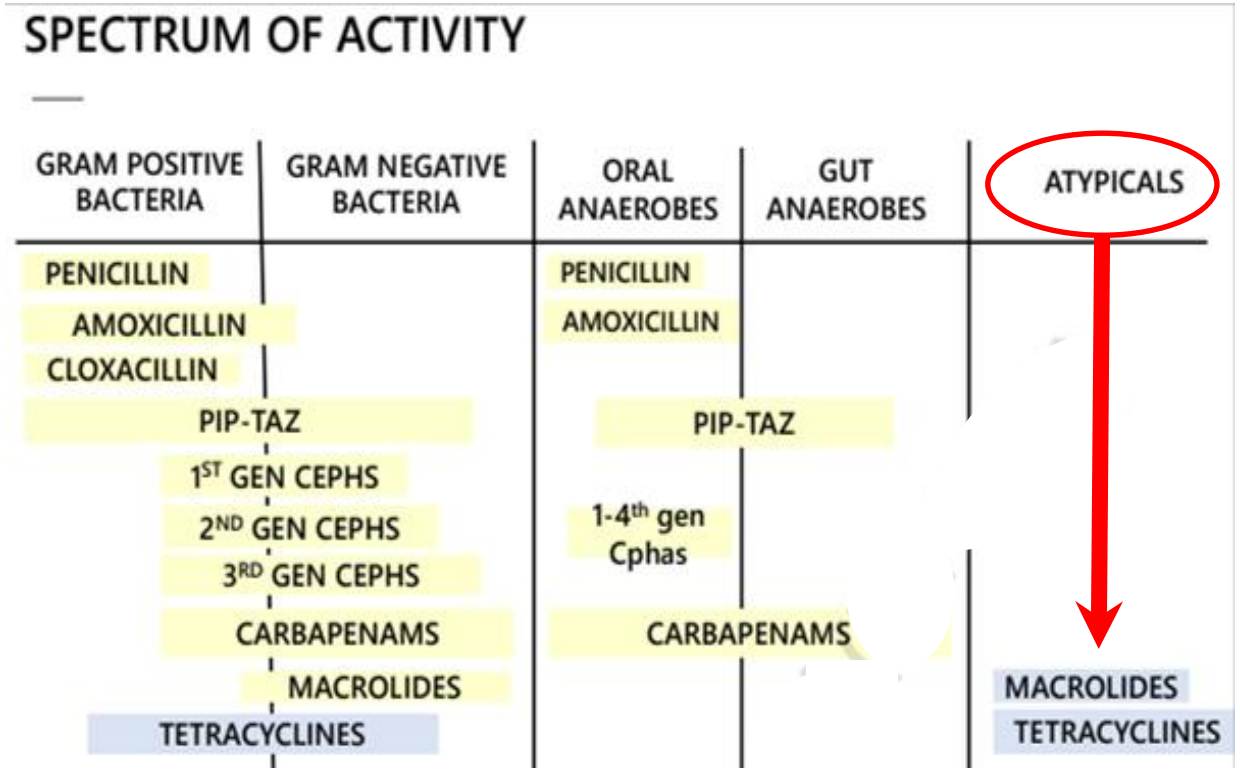
PREGNANCY AND BREASTFEEDING

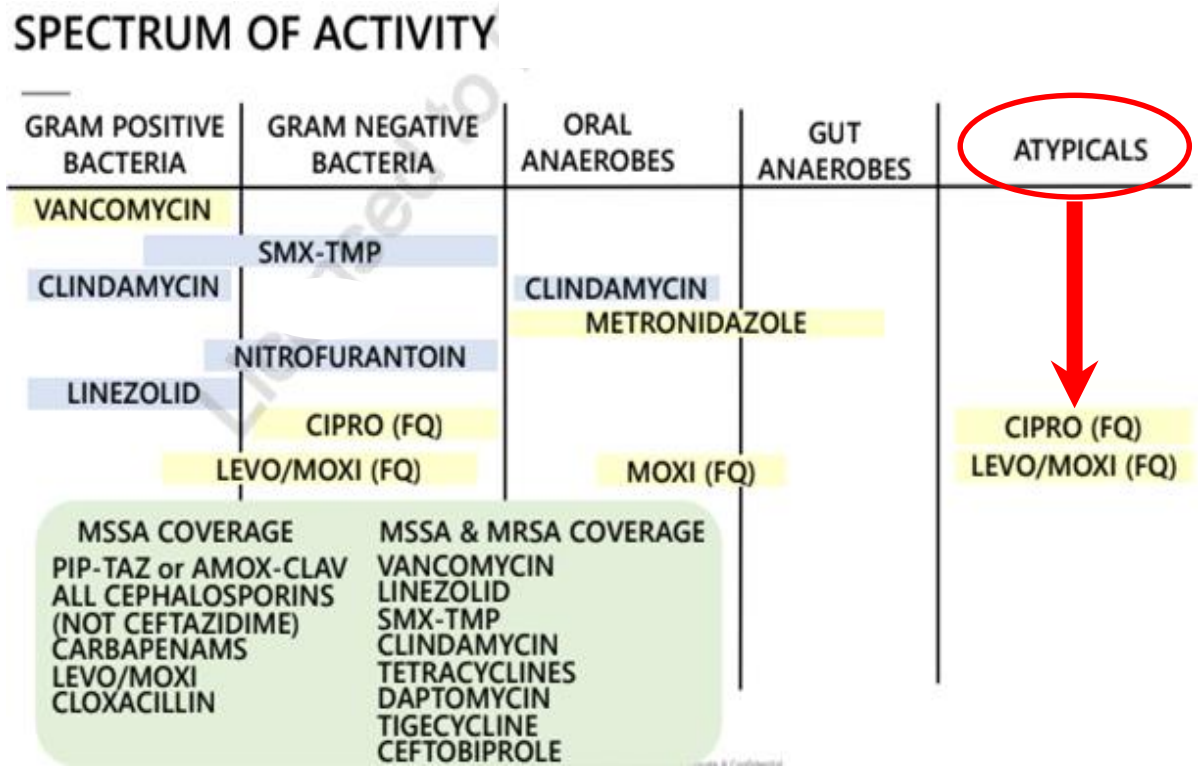
"Safe Fetus Means Avoid These Now"

Drugs to Avoid During Pregnancy	Clinical Pearls
Sulfamethoxazole/trimethoprim	Avoid during 1st and 3rd trimesters C/I near term
Fluoroquinolones*	C/I in all trimesters
Metronidazole (Macrolides – Clarithromycin should be avoided in pregnancy, esp. 1st trimester)	Avoid during 1 st trimester
Aminoglycosides*	Avoid in 1st, 2nd and 3rd trimesters
Tetracyclines	C/I in all 3 trimesters
Nitrofurantoin	C/I at term and during labour

BACTERICIDAL ABX	BACTERIOSTATIC ABX
B Lactams	Tetracyclines
Vancomycin	Macrolides
AMG	Clindamycin
Daptomycin	Linezolid
FQ	
Metronidazole	

SPECTRUM OF ACTIVITY





APPENDIX: WHAT'S NOT COVERED

* Amox/Amp does NOT cover *Klebsiella spp*

Atypical	*Gut Anaerobes*	*MSSA*	*MRSA*	*Entero-coccus*	*Group A/ S. pneumo*	*Enterobact /Serratia*	*H. influenzae*	*M. catarrhalis*	*PEcK*
Pen, Amp	Pen, Amp	Pen, Amp	Pen, Amp	Cloxacillin		Pen, Amp	Pen	Pen, Amp	Amp*
	1st /2nd /3rd /4th gen ceph		1st /2nd /3rd /4th gen ceph	1st/ 2nd /3rd /4th gen ceph		1st/2nd gen ceph	1st gen ceph	1st gen ceph	
Carbepen	~~X~~		Carbepen	~~X~~					
Pip/Taz	~~X~~		Pip/Taz	~~X~~					
	Macrolides	Macrolides	Macrolides	Macrolides		Macrolides			Macrolides
	Cipro	Cipro	FQ	FQ	Cipro	Cipro			
Metro	~~X~~	Metro	Metro	Metro	Metro	Metro	Metro	Metro	Metro
Linez	Linez			~~X~~		Linez	Linez	Linez	Linez
Dapto	Dapto			~~X~~		Dapto	Dapto	Dapto	Dapto
AMG	AMG	AMG	AMG	AMG	AMG				
Vanco	Vanco			~~X~~		Vanco	Vanco	Vanco	Vanco
	~~X~~			Clinda		Clinda	Clinda	Clinda	Clinda
SMX/TMP	SMX/TMP			SMX/TMP	SMX/TMP				
	Tetra			~~X~~		Tetra			

ATYPICAL
Legionella
Mycoplasma
Chlamydia

ANAEROBES
Oral anaerobes: *Peptostreptococcus, Fusobacterium, Prevotella*
Gut anaerobes: *Bacteroides fragilis, Clostridium* species





Thank you







Thank you

