

CHEMOTHERAPEUTIC DRUGS

GENERAL PRINCIPLES OF ANTIMICROBIAL THERAPY

Lesson objectives

by the end of this lesson, students are expected to;

- ▮ define what chemotherapy, antimicrobial, and antibiotics means
- ▮ list the goals of chemotherapy
- list the factors to consider in the selection of chemotherapeutic agents
- classify chemotherapeutic agents based on mechanisms of action.
- describe mechanisms of action of chemotherapeutic agents

PRINCIPLES OF ANTIMICROBIAL THERAPY

Definition:

a) Chemotherapy

- Use of drugs against invading organisms as well as cancerous cells.

b) Antimicrobial agent

- Use of chemicals against invading organisms.

c) Antibiotic

- A drug that is produced by one microorganism and has the ability to harm other microbes.

GENERAL PRINCIPLES...

Goal: Selective toxicity

- Ability to injure or kill an invading microorganism without harming the cells of the host.
- Relative rather than absolute
- How is selective toxicity achieved?
 - Biochemical differences that exist between microorganisms and human beings.
 - Examples:
 - A. inhibition of an enzyme required to synthesize folic acid

GENERAL PRINCIPLES...

- B. Disruption of bacterial cell wall synthesis by penicillins
- C. Inhibition of microbial protein synthesis by erythromycin
- D. Inhibition of microbial nucleic acid synthesis by rifampicin

Problems associated with the use of antimicrobial agents

1. Toxicity

- a) Local irritancy: TTC, erythromycin, chloramphenicol
- b) Systemic toxicity (Therapeutic index high V_s low)

2. Hypersensitivity reactions (from rash to anaphylactic shock)

3. Drug resistance

4. Superinfection (alteration in normal flora)

Conditions predisposing to super-infection

Corticosteroid therapy

Chemotherapy

Immunosuppressant & decreased WBC count

AIDS, agranulocytosis, DM, SLE

5. Nutritional deficiencies (Vit B & k)

Prolonged use of antimicrobial agents ...Vitamin deficiencies

Problems associated.....

6. Masking an infection

A short course of antimicrobial therapy may be sufficient to treat one infection but only briefly suppress the other infection

- a) Syphilis masked by the use a single dose of penicillin which is sufficient to cure gonorrhea
- b) TB masked by a short course of streptomycin given for trivial respiratory infection

Choice of antimicrobial agents

Patient factor

1. Age (kinetics related)

Chloramphenicol (conjugation & excretion is insufficient in newborn). Gray baby syndrome

2. Renal & hepatic function

3. Local factors

presence of pus, secretions, necrotic material or foreign body make eradication practically impossible,

Haematomas foster bacterial growth (Penicillin & cephalosporins bound to degraded Hb)

Low P^H at site of infection reduce activity of macrolids & aminoglycosides

4. Drug allergy

Choice of antimicrobial agents

Host factor

5. Impaired host defense

Bactriostatic agents may be curative for patient with normal host defense.

Bactericidal intensive therapy may be required for patient with impaired host defense

6. Pregnancy

Better to avoid any antimicrobial agents

Otherwise see the label (category).

7. Genetic factors

Primaquine, nitrofurantoin, sulphonamides & fluoroquinolones are likely to produce hemolysis in G6PD deficient patients

Choice of antimicrobial agents

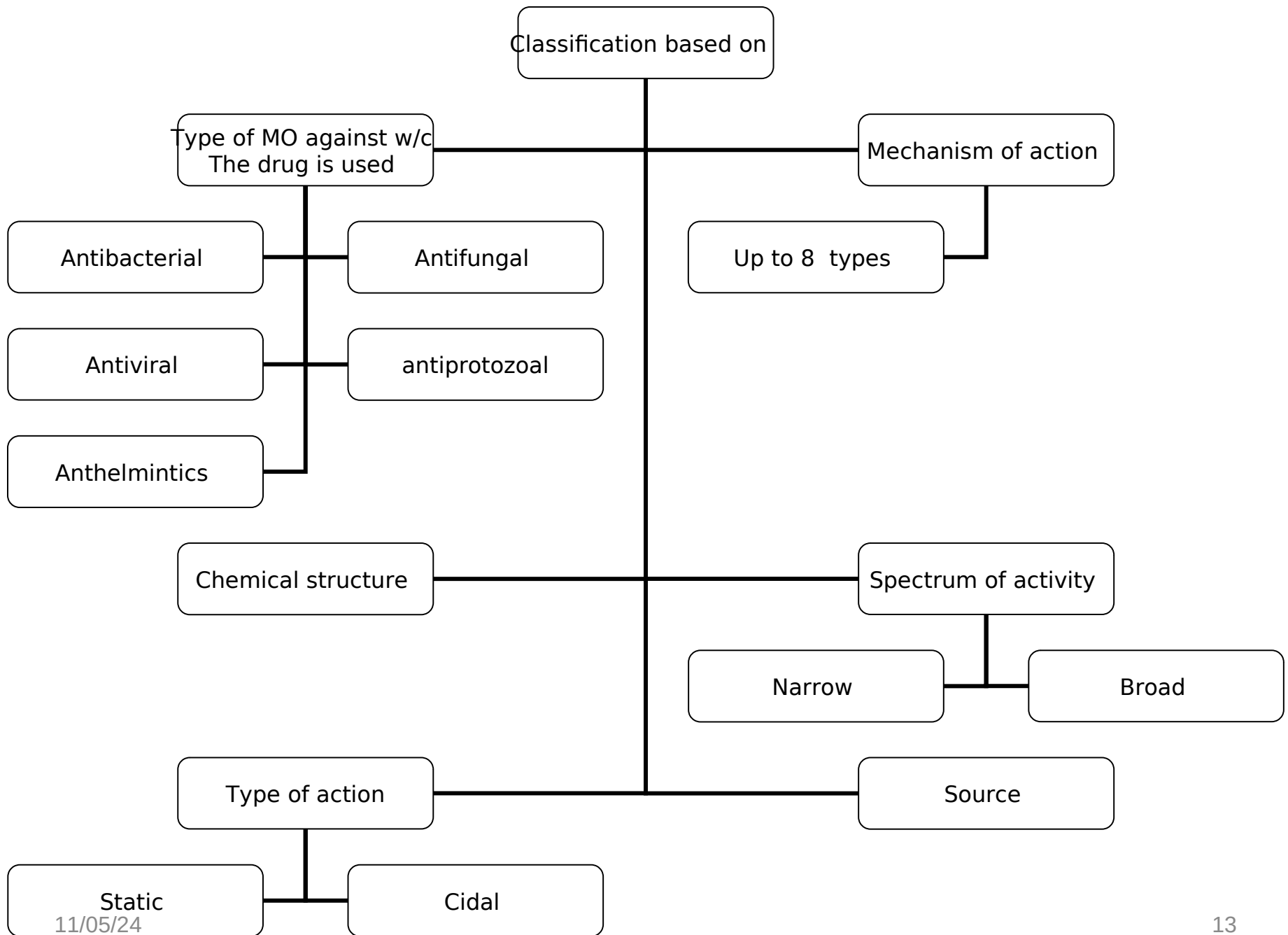
Drug factors

1. Spectrum of activity (Broad v_s narrow)
2. Type of activity (bacteriostatic v_s bactericidal)
3. Sensitivity of the organism: MIC, postantibiotic effect
4. Relative toxicity
5. Pharmacokinetic profile
6. Route of administration
7. Evidences of clinical efficacy
8. Cost

Classification of Antimicrobial Drugs

Type of organism against which the drug is used

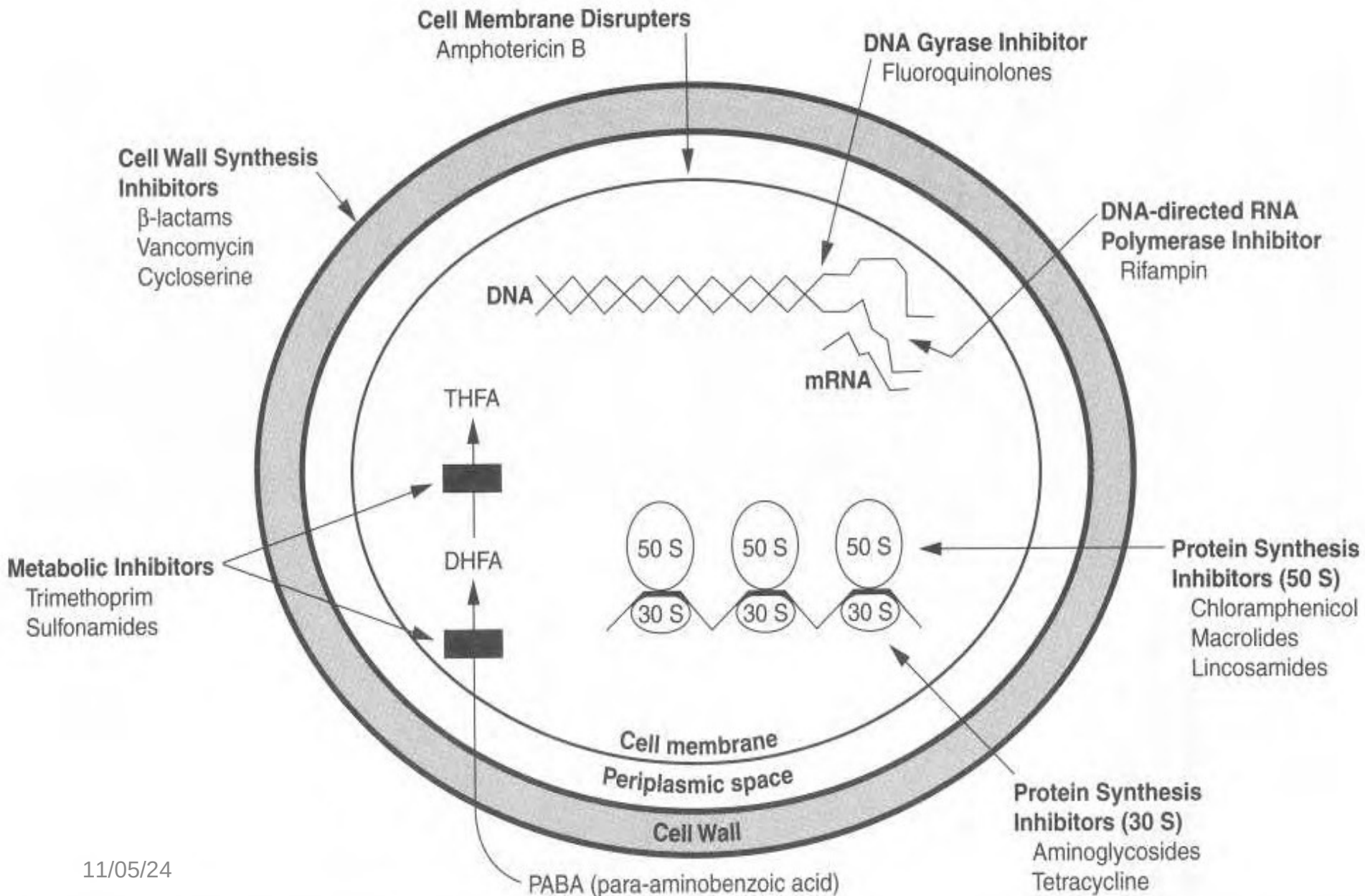
- 1) Antibacterial
- 2) Antifungal
- 3) Antiviral
- 4) Antiprotozoal
- 5) Anthelmintics



ANTIBACTERIAL AGENTS

A. Site of Antibacterial Actions

ANTIBACTERIAL AGENTS



GENERAL PRINCIPLES...

B. Mechanisms of Antibacterial Action

1) Inhibition of cell wall synthesis

- Penicillin, cephalosporin, cycloserine, vancomycin, Bacitracin, Carbapens

2) Increase in cell membrane permeability

- Polyene antibiotics, polymixins

3) Inhibition protein synthesis

- Aminoglycosides, chloramphenicol, tetracycline

4) Inhibition of nucleic acid synthesis

- Rifampicin, fluoroquinolones

5) Antimetabolites

- Sulphonamides, trimethoprim

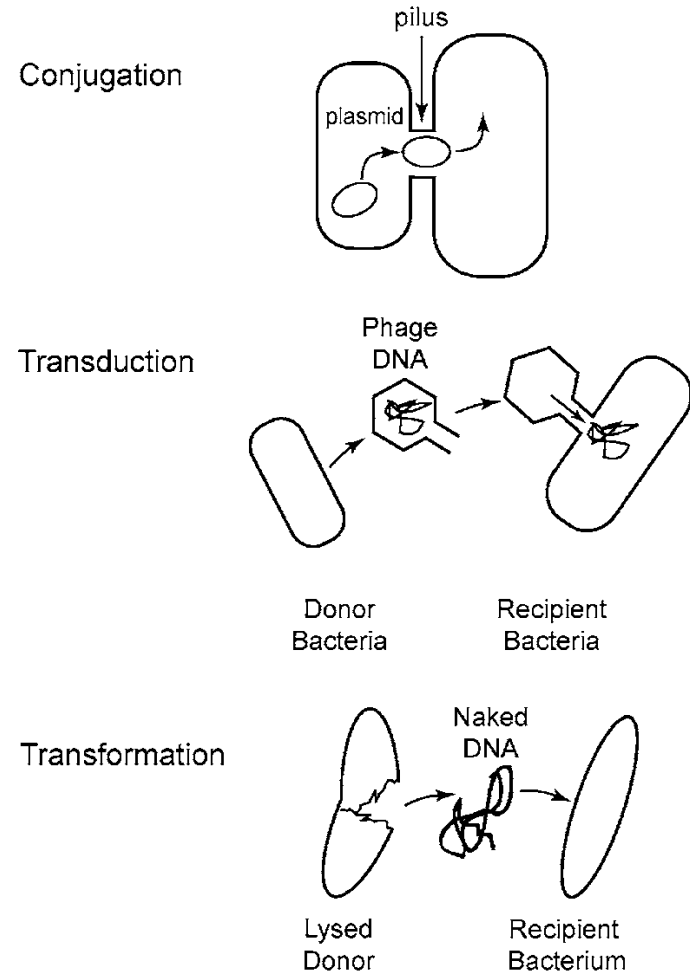
GENERAL PRINCIPLES...

C. Drug resistance

- Unresponsiveness of microorganism to antimicrobial agents

Mechanisms by which Resistance is acquired;

- A. Spontaneous mutation
- B. Gene transfer
 - Conjugation,
 - Transduction,
 - Transformation



GENERAL PRINCIPLES...

Biochemical alterations leading to antimicrobial resistance include:

- A. Destruction of the drug by the organism
 - B- lactamase inactivates penicillins
- B. Development of altered drug receptor
 - Aminoglycosides, erythromycin, penicillin
- C. Decreased drug entry
 - Tetracycline
- D. Development of alternate metabolic pathway
 - Sulphonamides

GENERAL PRINCIPLES...

- ***Relationship between antibiotic use and the emergence of drug resistant microbes***
 1. How do antibiotics promote resistance?—Microbes secrete compounds that are toxic to other microbes, and microbes compete with one another for nutrients
 2. Which antibiotics promote resistance?—Some more likely than others (e.g., broad-spectrum drugs)
 3. Does the amount of antibiotic use influence the emergence of resistance?—The more you use, the faster drug-resistance emerges; hospitals use many antibiotics, which then result in nosocomial infections that become hard to treat.

GENERAL PRINCIPLES...

- ***Delaying the emergence of resistance***
 - a) Antimicrobials should be employed only when actually needed
 - b) Narrow spectrum agents should be employed whenever possible
 - c) Newer antibiotics should be reserved
- ***Selection of antibacterial agents***
 - A. The identity of infecting organism
 - B. Drug sensitivity of the infecting organism
 - C. Host factor

GENERAL PRINCIPLES...

- A. The identity of infecting organism**
 - a. Direct microscopic visualization
 - b. Cultivation and identification
 - c. Detection of microbial antigens
 - d. Detection of microbial DNA or RNA
 - e. Detection of host immune response

- B. Drug sensitivity of the infecting organism**
 - 1) Disk diffusion method
 - 2) Serial dilution method: MIC

GENERAL PRINCIPLES...

- **Bacteriostatic V_s bactericidal**

- **Bacteriostatic**

- Arrest the growth and replication of bacteria at serum levels achievable in the patient

- **Bactericidal**

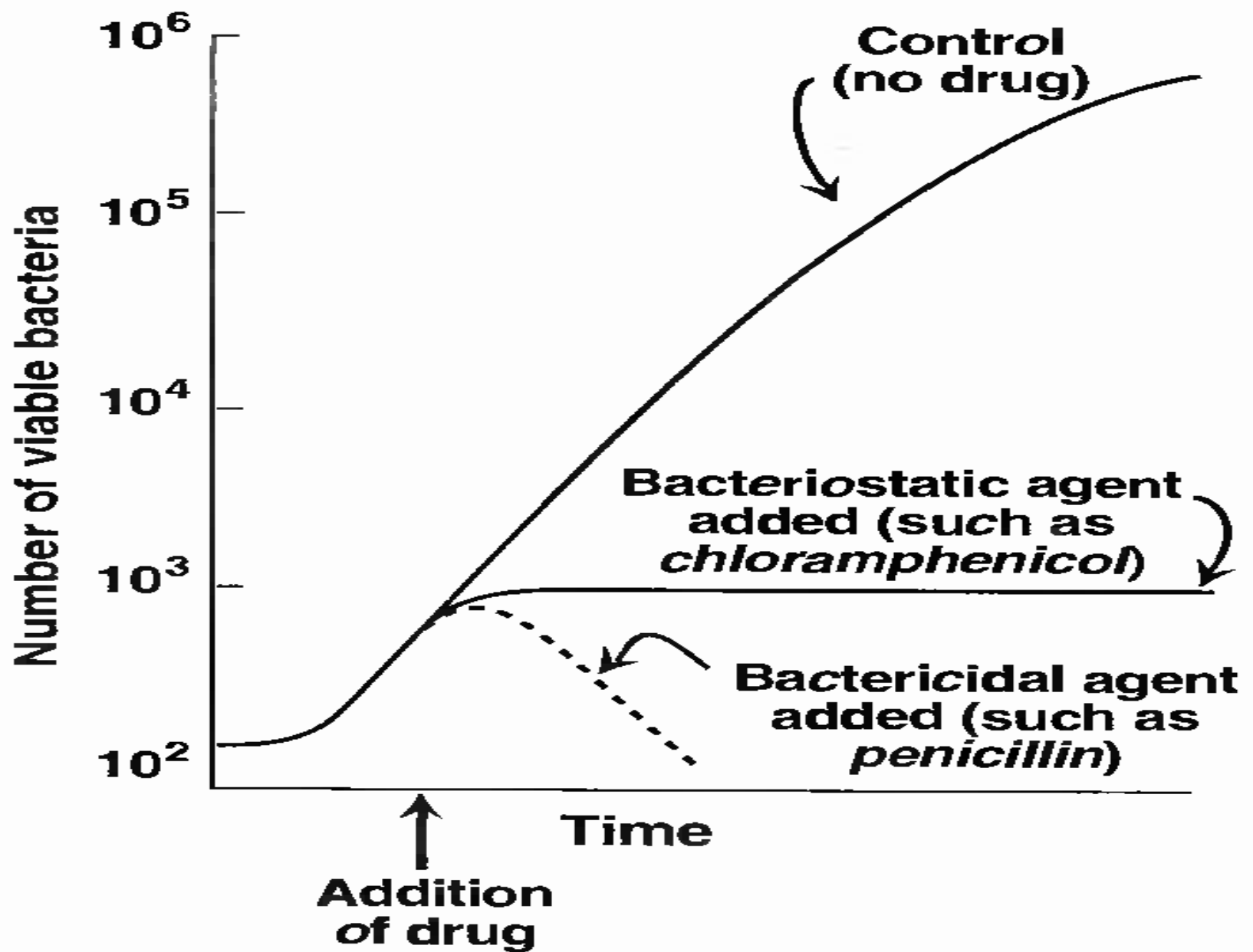
- kill bacteria at drug serum levels achievable in the patient

EXAMPLES:
Chloramphenicol
Erythromycin
Clindamycin
Sulfonamides
Trimethoprim
Tetracyclines



EXAMPLES:
Aminoglycosides
Beta-lactams
Vancomycin
Quinolones
Rifampin
Metronidazole





GENERAL PRINCIPLES...

C. Host factor

a) site of the infection

» BBB

» Abscess

b) Immunity of the host

c) *Age*

d) *Pregnancy*

e) *Kidney*

f) *Liver function*

g) *Lactation*

GENERAL PRINCIPLES...

Antimicrobial drug combinations

❖ Indication

- 1) Severe infection of unknown etiology
- 2) Mixed infection
- 3) Prevention of resistance
- 4) To reduce severity & incidence of adverse effects (↓_{ed} toxicity)
- 5) To achieve synergism [e.g., penicillin & aminoglycoside]

❖ Disadvantages of antimicrobial agents combination

- a) Increase risk of allergy
- b) Antagonism of antimicrobial effect
- c) Increase risk of superinfection
- d) Increased cost

GENERAL PRINCIPLES...

Prophylactic Use of Antimicrobial

- Approved use for the following:
 - A. Surgery—Decreased incidence of infection in certain surgeries
 - B. Prophylaxis against specific organisms (Bacterial Endocarditis—In patients with congenital or valvular heart disease)
 - C. Neutropenia—Patients are at high risk for infections
 - D. Other Indications for Antimicrobial Prophylaxis—For women with recurrent urinary tract infection, for prophylaxis against type A influenza, following exposure to organisms responsible for STDs

GENERAL PRINCIPLES...

Misuses of Antimicrobial Drugs

- A. Attempted Treatment of Untreatable Infection
- B. Treatment of Fever of Unknown Origin
- C. Improper Dosage—Too low or too high
- D. Treatment in the Absence of Adequate Bacteriologic Information
- E. Omission of Surgical Drainage—Have limited efficacy in presence of foreign material, necrotic tissue, or pus

GENERAL PRINCIPLES...

Determinants of Rational Dosing

Three important properties that have a significant influence on the frequency of dosing are:

- A. concentration-dependent killing,
- B. Time-dependent killing, and
- C. Postantibiotic effect.

A. Concentration-dependent killing

- a) show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism

GENERAL PRINCIPLES...

- b) include aminoglycosides, fluoroquinolones, and carbapenems
- c) by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

B. Time-dependent killing

- a. The clinical efficacy of antimicrobials that have a nonsignificant, dose-dependent killing effect is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC.
- b. Include beta-lactams, glycopeptides, macrolides, clindamycin, and linezolid

GENERAL PRINCIPLES...

- some severe infections are best treated by continuous infusion of these agents rather than by intermittent dosing.

C. Postantibiotic effect.

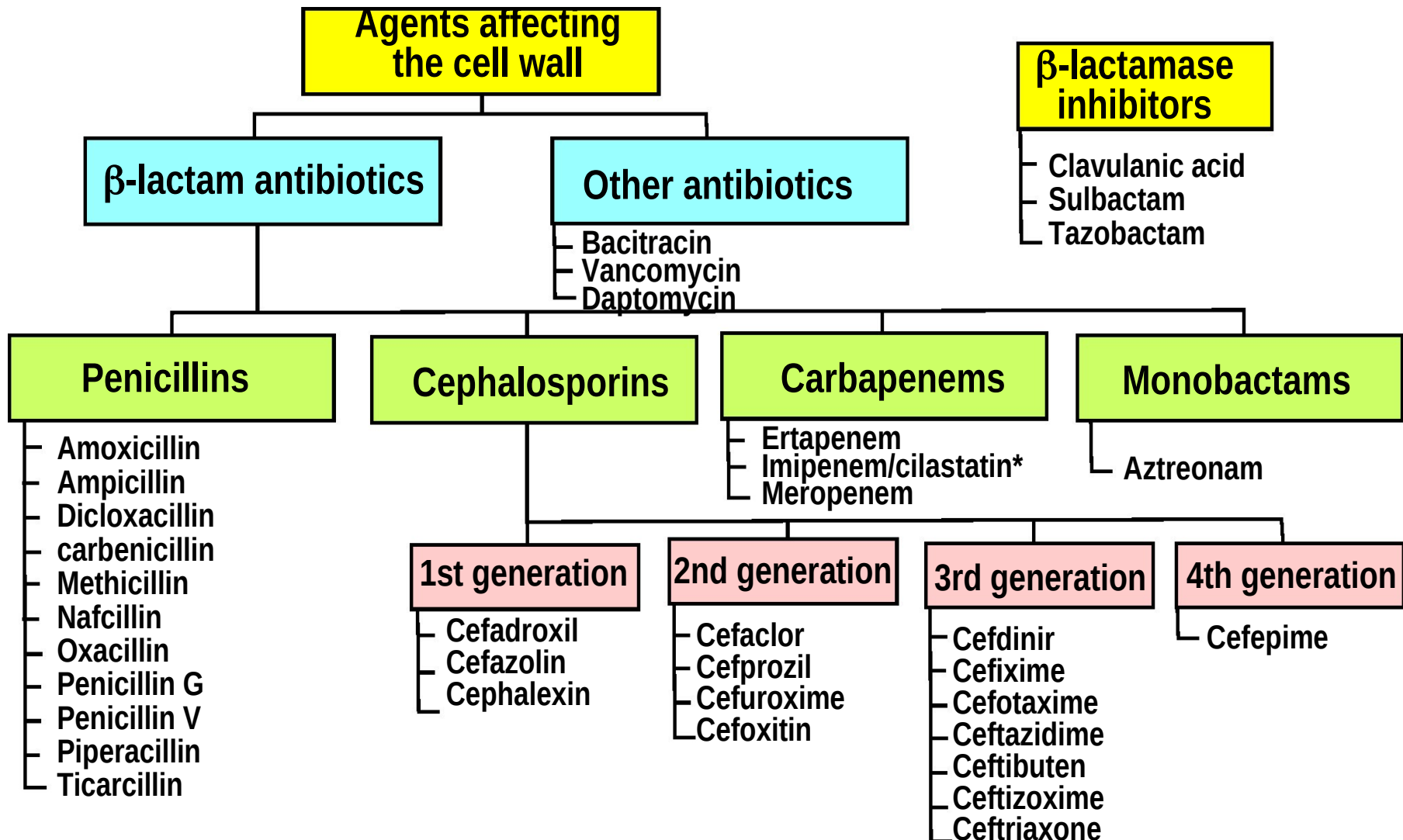
- Persistent suppression of bacterial growth after limited exposure to an antimicrobial agent is known as the postantibiotic effect (PAE).
- Antimicrobial drugs exhibiting a long PAE (several hours) often require only one dose per day. For example, antimicrobials, such as aminoglycosides and fluoroquinolones, exhibit a long PAE, particularly against gram-negative bacteria.

Beta-lactam Antibiotics And Other Inhibitors Of Cell Wall Synthesis

Lesson objectives;

- classify antibiotics acting on cell wall of bacteria
- describe mechanism of action of betalactam antibiotics
- explain mechanism of resistance to betalactam antibiotics
- list common clinical application of cell wall synthesis inhibitors
- list common adverse effects of betalactam antibiotics

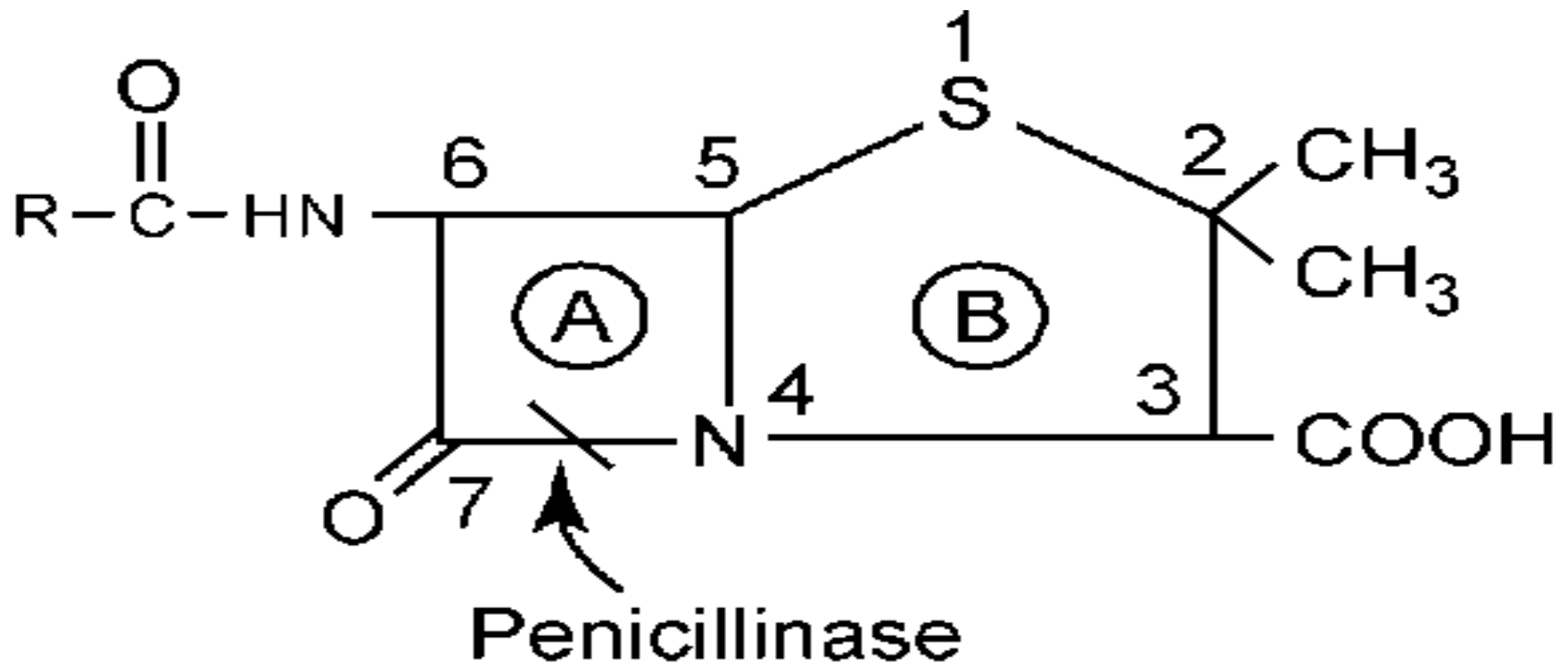
Beta-lactam Antibiotics And Other Inhibitors Of Cell Wall Synthesis



BETA-LACTAM ANTIBIOTICS...

PENICILLINS

➤ Chemistry



A = β -lactam ring

B = Thiazolidine ring

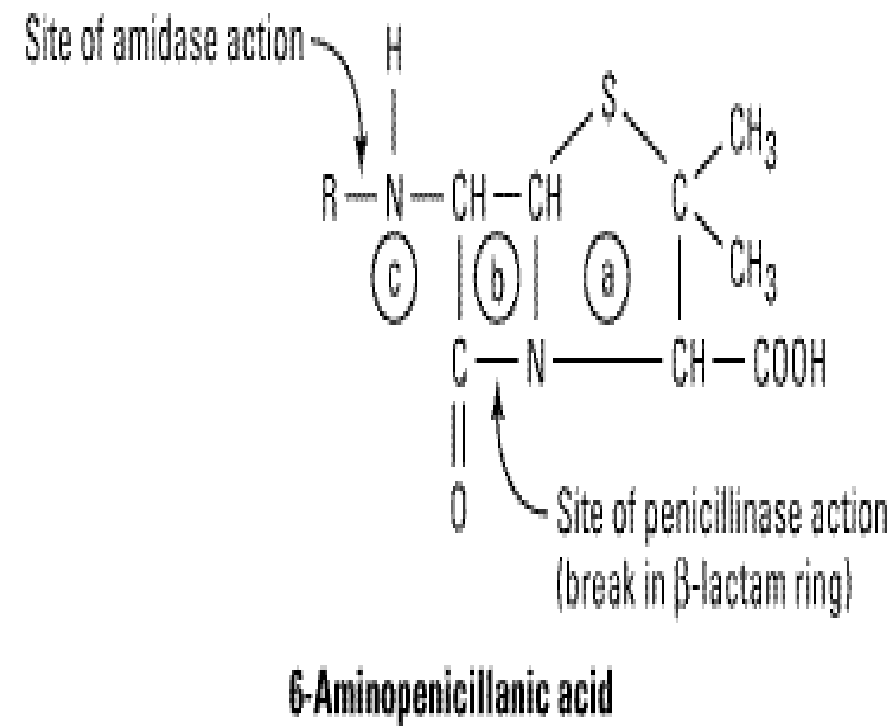
BETA-LACTAM...

Structural and Activity Relationships

- 1) The beta- lactam ring is essential for antibacterial actions
- 2) Properties of individual penicillin are determined by additions made to the basic nucleus

These modifications determine:

- a) Affinity for Penicillin binding proteins (PBPs)
- b) Resistance to penicillinase
- c) Ability to penetrate the gram negative cell envelope
- d) Resistance to stomach acid &
- e) Pharmacokinetic properties

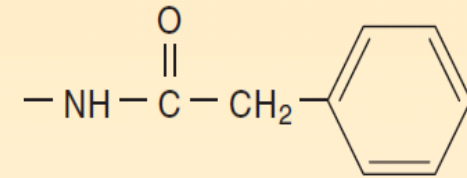


DRUG

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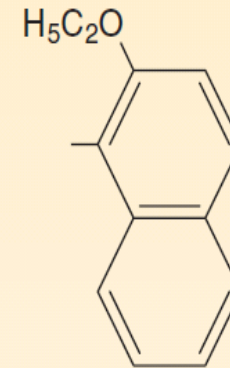
PENICILLIN G

A narrow-spectrum, penicillinase-sensitive penicillin



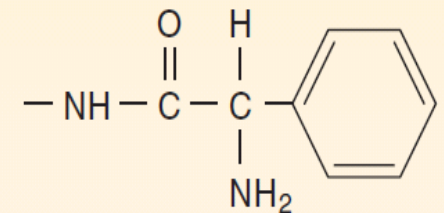
NAFCILLIN

A narrow-spectrum, penicillinase-resistant (antistaphylococcal) penicillin



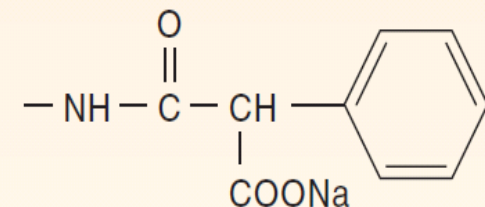
AMPICILLIN

A broad-spectrum penicillin



CARBENICILLIN

An extended-spectrum (antipseudomonal) penicillin

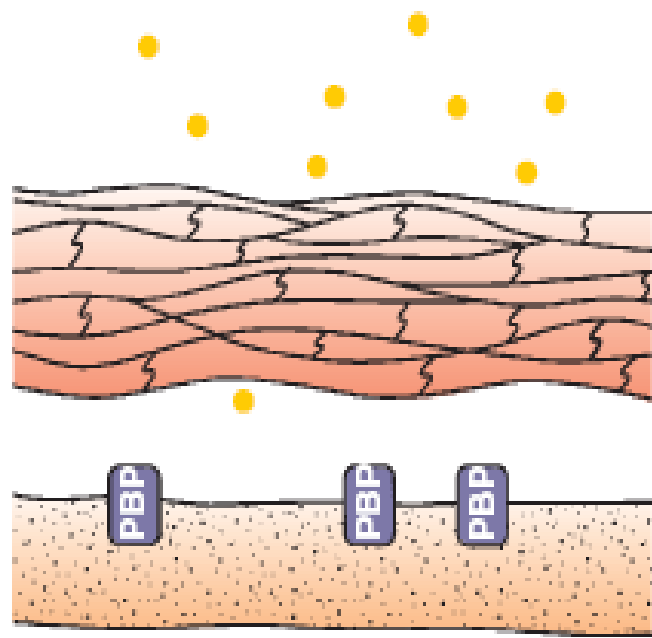


BETA-LACTAM ANTIBIOTICS...

➤ Mechanism of action

- Inhibition of bacterial cell wall synthesis
- Interfere with the last step of bacterial cell wall synthesis
 - Inhibition of transpeptidase
- Resulting in exposure of the osmotically less stable membrane.
- Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins.
 - Bactericidal

GRAM-POSITIVE ENVELOPE

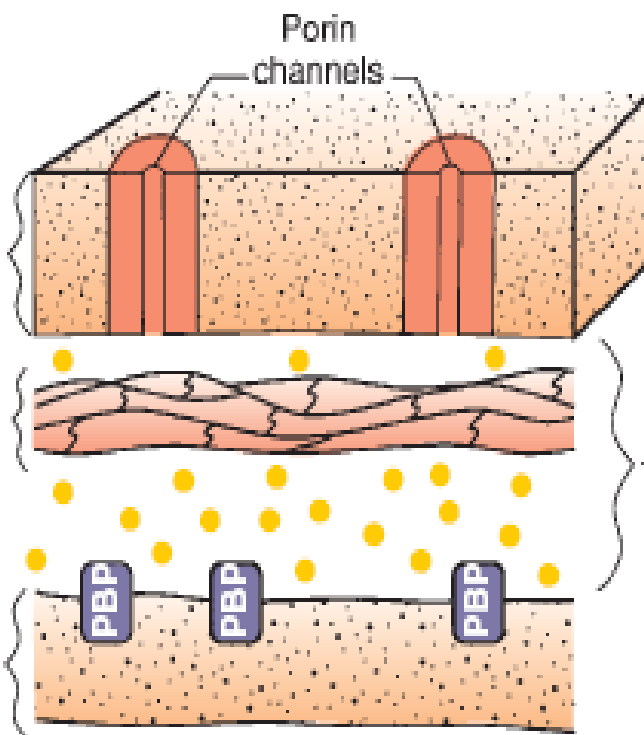


Outer membrane –

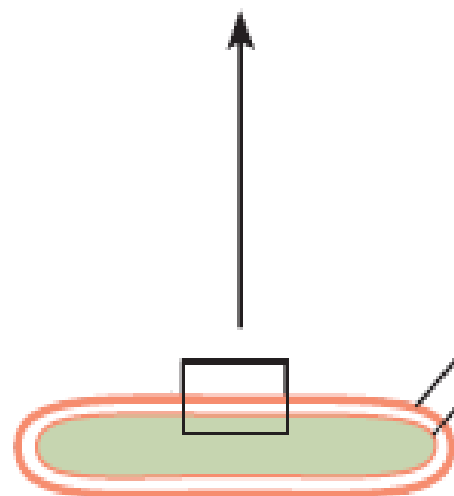
Cell wall
(peptidoglycan
matrix)

Cytoplasmic
membrane

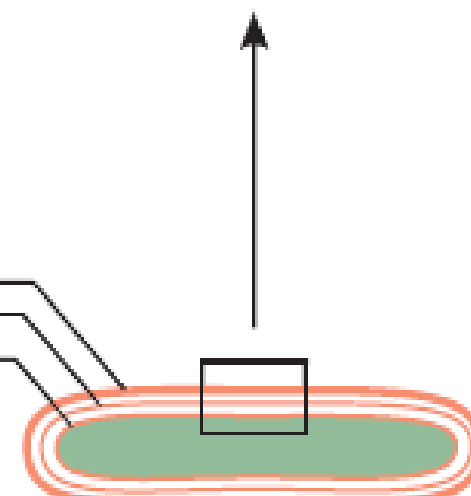
GRAM-NEGATIVE ENVELOPE

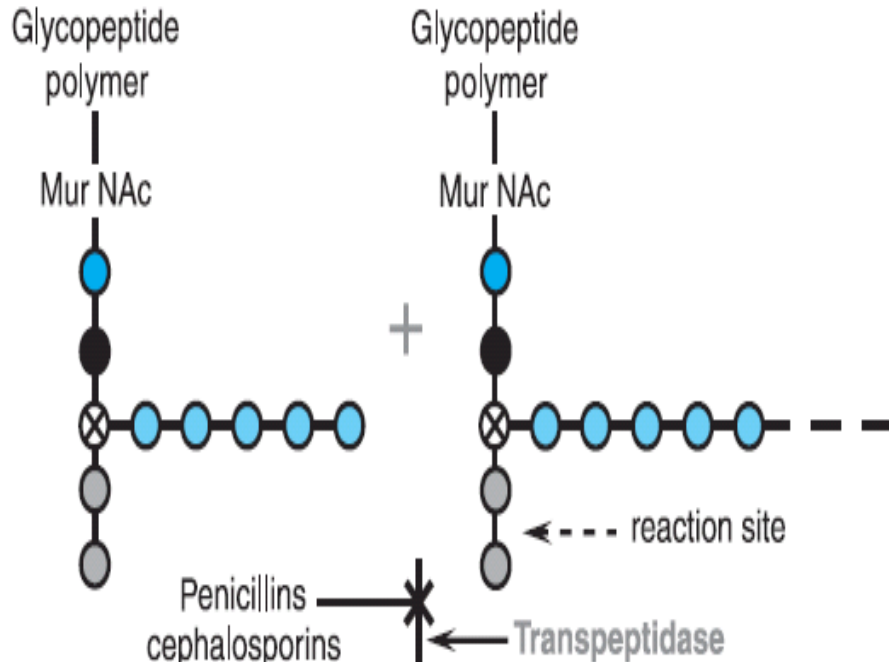
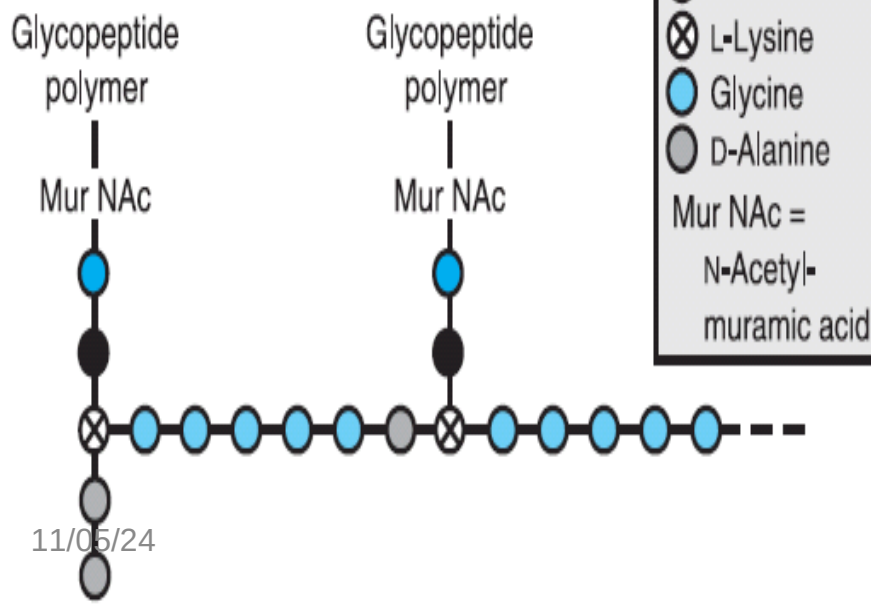
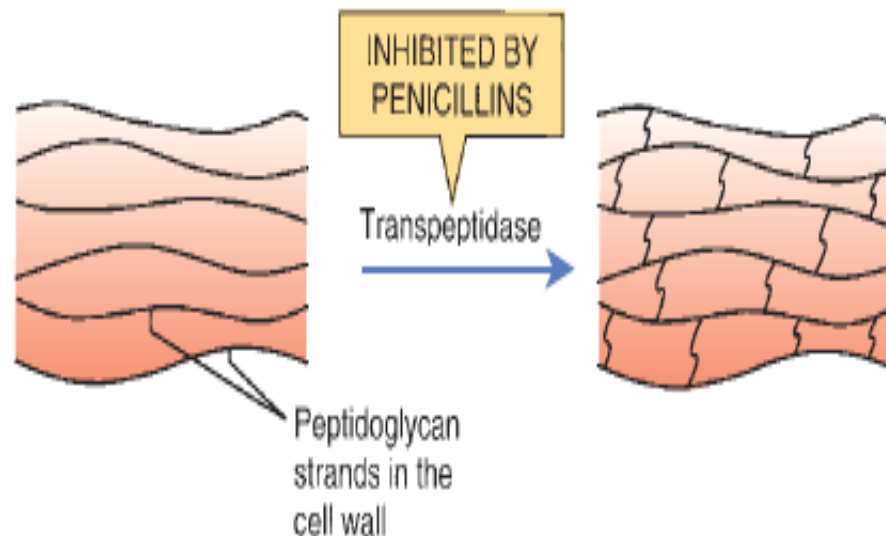
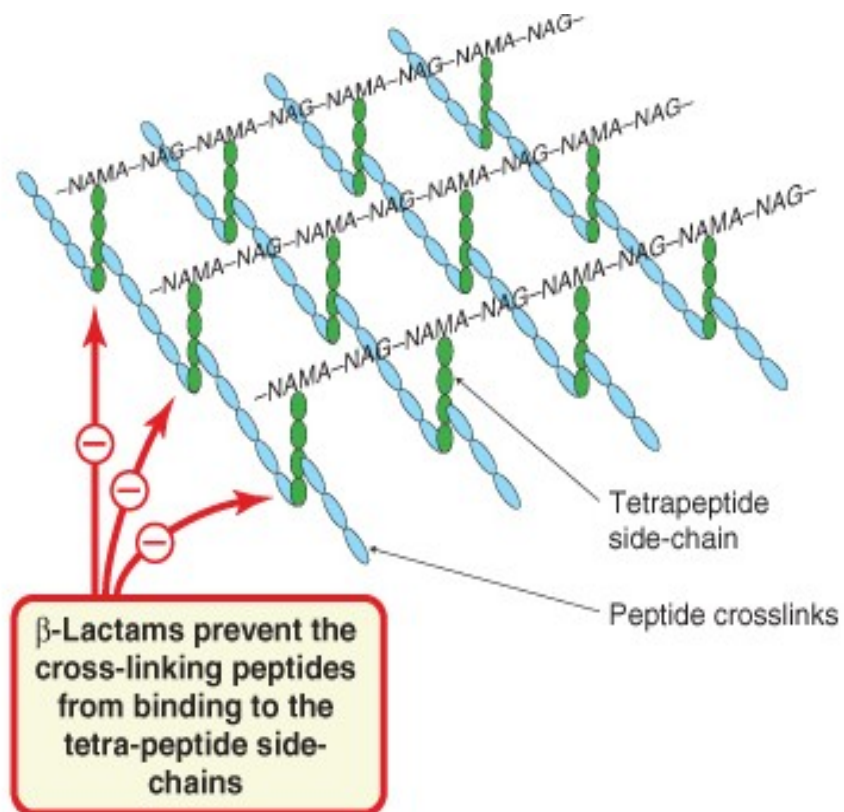


Periplasmic
space



Outer membrane
Cell wall
Cytoplasmic membrane





BETA-LACTAM ANTIBIOTICS...

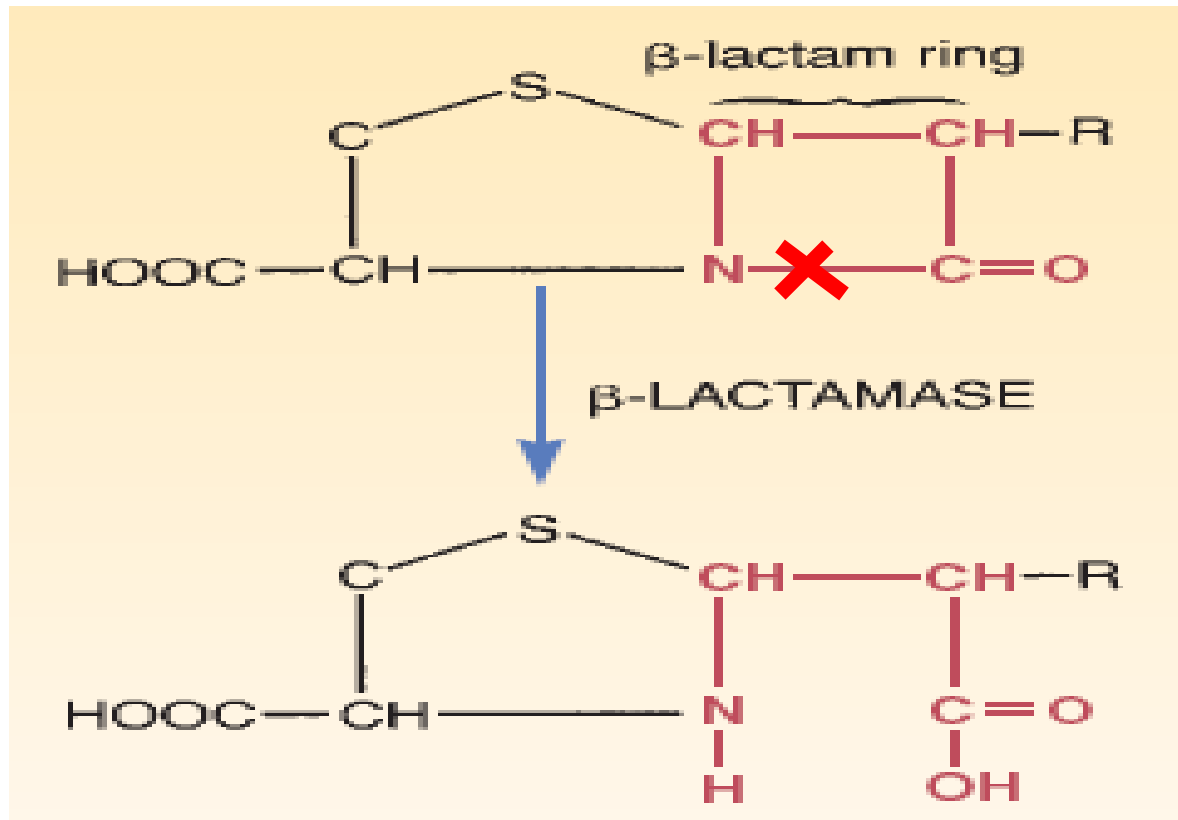
Classification

Penicillin class	Drug	Antimicrobial spectrum
Natural Penicillins	Penicillin G Penicillin V	gram+ cocci and bacilli, some gram– cocci (<i>Neisseria</i>)
Penicillinase-resistant	Nafcillin (Nafcil) Cloxacillin Dicloxacillin Oxacillin	<i>Staphylococcus aureus</i>
Broad-spectrum (Aminopenicillins)	Ampicillin Amoxicillin Bacampicillin	Same as Pen G plus some gram– organisms
Extended spectrum	Ticarcillin (Ticar) Piperacillin (Pipracil) Carbenicillin (Geocillin) Mezlocillin (Mezlin)	Same as broad spectrum plus additional gram– coverage, including <i>Pseudomonas</i>

BETA-LACTAM ANTIBIOTICS...

Mechanism of bacterial resistance

- 1) Inactivation of antibiotic by β -lactamase



BETA-LACTAM ANTIBIOTICS...

2. Impaired penetration: from G-ves, absence of porins
3. Modification of target penicillin binding sites
4. Presence of efflux pump

BETA-LACTAM ANTIBIOTICS...

NATURAL PENICILLINS

Penicillin G

- a) Active against: G+ve cocci except penicillinase producing staphylococci
- b) Active against: some G+ve bacilli
- c) G -ve cocci [N. meningitidis, N. gonorrhea]
- d) Spirochetes [Borrelia, Leptospira]

BETA-LACTAM ANTIBIOTICS...

➤ *Therapeutic uses*

A. Drug of choice for

- a) pneumonia or meningitis by *Streptococcus pneumoniae*
- b) Pharyngitis by *Streptococcus pyogenes*
- c) Infectious endocarditis by *Streptococcus viridans*

B. Infection caused by G+ve bacilli

- a) Gangrene by *Cl. Perfringens*
- b) Tetanus by *Cl. Tetani*
- c) Anthrax by *B. anthracis*

BETA-LACTAM ANTIBIOTICS...

- C. First choice for meningitis by *N. meningitidis*
- D. Drug of choice for the treatment of syphilis
- E. Prophylactic applications
 - a) Syphilis in sexual partners
 - b) Benzathine penicillin G monthly for life in recurrent rheumatic fever
 - c) Bacterial endocarditis

BETA-LACTAM ANTIBIOTICS...

- **Pharmacokinetics**
 - Penicillin G is available as salts [Na^+ , K^+ , Procaine, Benzathine penicillin G]
 - Penicillin G: orally ineffective due to gastric acid
 - Distributes well to most tissues; Inflammation increases distribution into CSF, joints & eye
 - Penicillin G is eliminated by tubular secretion [90%]
 - Excretion delayed by probenecid

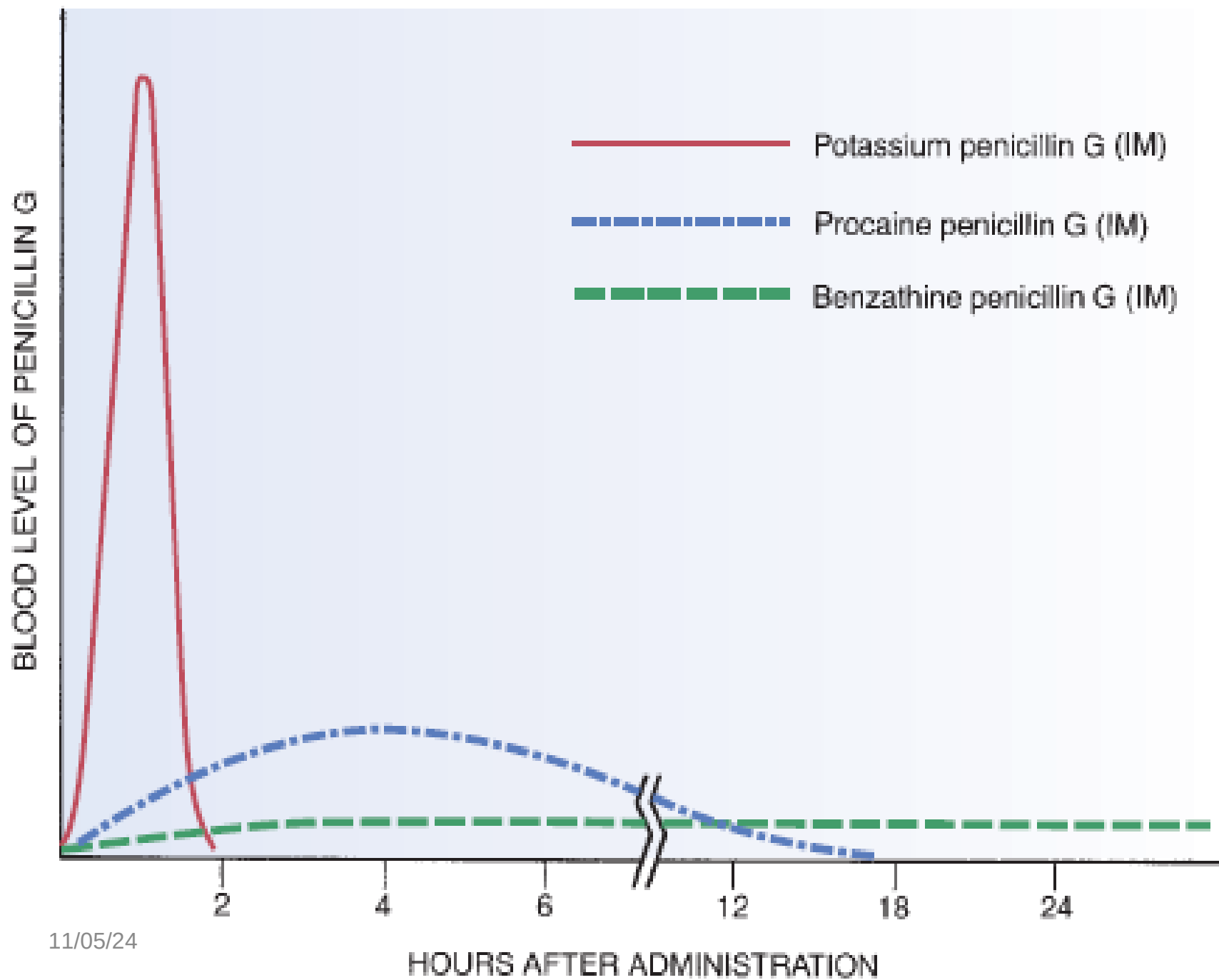


TABLE 45.1 Pharmacokinetic Parameters of Selected Penicillins

Drug	Route	Half-life (hr)	Renal Excretion (%)	Dose Adjustment in Renal Failure
Natural penicillins				
Penicillin G	IM, IV	0.5	79–85	Yes
Penicillin V	Oral	0.5	20–40	Yes
Antistaphylococcal penicillins (penicillinase resistant)				
Nafcillin	IM, IV	0.8–1.2	31–38	No
Oxacillin	IM, IV	0.4–0.7	39–66	No
Cloxacillin	Oral	0.5–0.6	40–70	No
Dicloxacillin	Oral	0.6–0.8	35–90	No
Aminopenicillins				
Ampicillin	Oral, IM, IV	1.1–1.5	40–92	Yes
Amoxicillin	Oral	1.4–2.0	86	Yes
Antipseudomonal penicillins				
Carbenicillin	Oral	0.8–1.2	85	Yes
Mezlocillin	IM, IV	0.9–1.7	61–69	Yes
Piperacillin	IM, IV	0.8–1.1	74–89	Yes
Ticarcillin	IM, IV	1.0–1.4	95	Yes

BETA-LACTAM ANTIBIOTICS...

- **PHENOXYMETHYL PENICILLIN [PENICILLIN V]**
 - Acid stable: given orally
 - Used for streptococcal pharyngitis, prophylaxis of rheumatic fever
 - Not for serious infections

BETA-LACTAM ANTIBIOTICS...

- **PENICILLINASE RESISTANT PENICILLINS**

Cloxacillin

Dicloxacillin

Oxacillin

Methicillin

Nafcillin

- They have chains that protect the β -lactam ring
- Used against penicillinase producing strains of staph.aureus and staph.epidermidis
- Emergence of staphylococcal strains [methicillin resistant]: Vancomycin

BETA-LACTAM ANTIBIOTICS...

Methicillin

- Acid labile; allergic reaction; interstitial nephritis

Nafcillin

- Erratic & incomplete absorption from P.O.
- Given i.m. or i.v.

Isoxazolyl penicillins [cloxacillin, dicloxacillin, oxacillin]

- Acid stable; orally & parentally administered
- Absorption affected by food

BETA-LACTAM ANTIBIOTICS...

AMINOPENICILLINS

- [ampicillin, amoxicillin, bacampicillin]

Antimicrobial spectrum

- as penicillin G;
- plus G-ve bacilli [H.influenza, E.coli, Salmonella, Shigella]
- Ineffective against β lactamase producing bacteria

BETA-LACTAM ANTIBIOTICS...

A. Ampicillin

Therapeutic use

1. UTI, RTI
2. Shigellosis [but not amoxicillin]
3. Typhoid fever: less efficacious than ciprofloxacin
4. Meningitis combined with 3rd generation

Adverse effects

- a. Diarrhea [incompletely absorbed- irritate; alteration of bacterial flora]
- b. Rashes

BETA-LACTAM ANTIBIOTICS...

B. Amoxicillin

- Oral absorption is better
- Incidence of diarrhea is less
- Less active against shigella

C. Bacampicillin: prodrug of ampicillin

BETA-LACTAM ANTIBIOTICS...

ANTIPSEUDOMONAL PENICILLINS

- **Carboxypenicillins**
 - **Carbenicillin**
 - active against *pseudomonas aeruginosa*
 - Neither penicillinase resistant nor acid resistant
 - **Ticarcillin**
 - 2-4 times more potent against *pseudomonas*
- **Ureidopenicillins**
 - **piperacillin, mezlocillin, Azlocillin**
 - active against *pseudomonas*, *Klebsiella pneumoniae*

BETA-LACTAM ANTIBIOTICS...

- ***BETA-LACTAMASE INHIBITORS***

- Clavulinic acid, sulbactam, tazobactam

- Inhibits bacterial β -lactamases; have weak antibacterial

- Most active against β -lactamase produced by:

- S.aureus, H.influenza, some

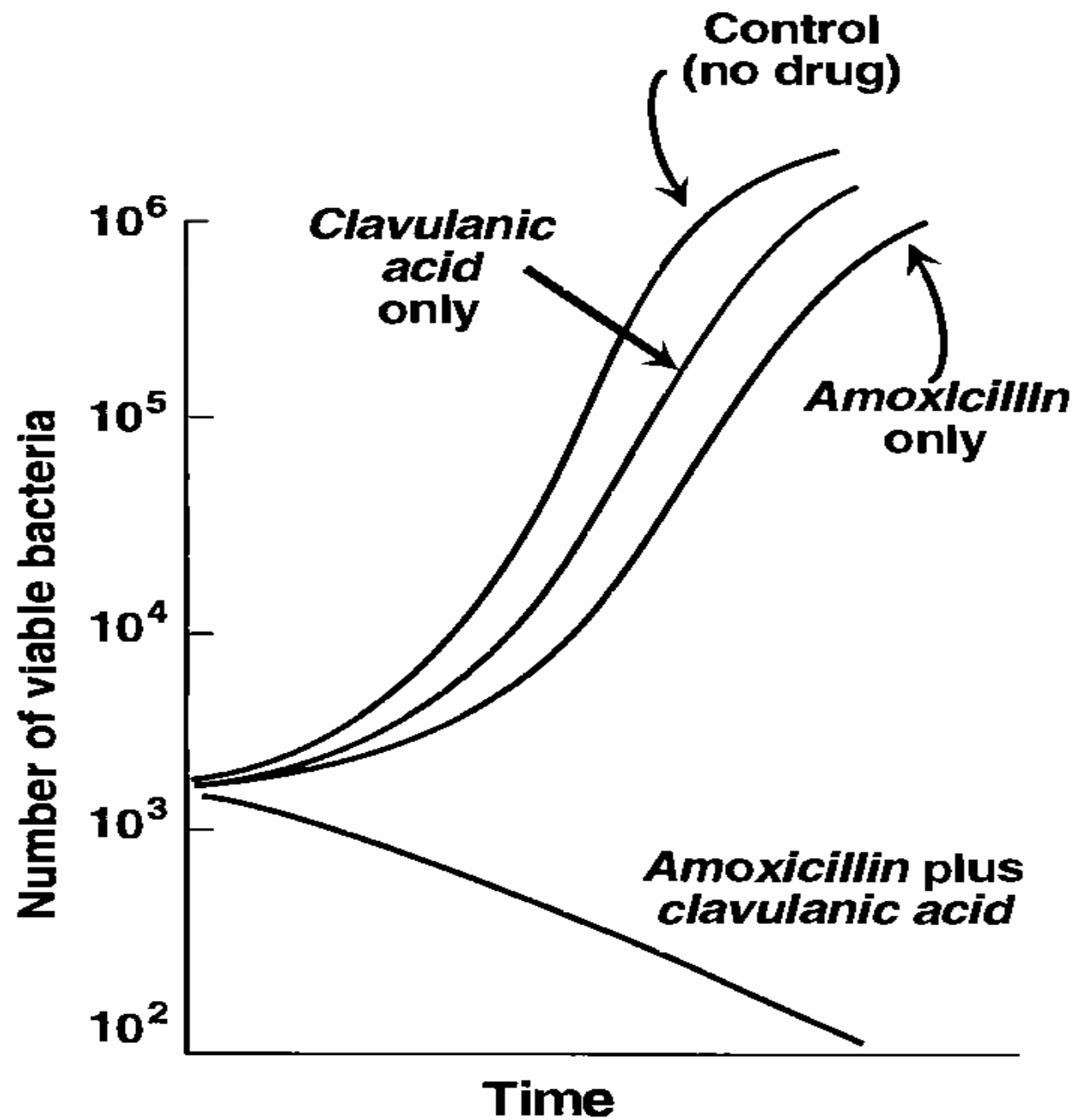
- enterobacteriaceae, Bacteroid spp

- Chromosomal β -lactamases of Serratia spp, Enterobacter spp, P.aeruginosa are not inhibited

- Restore antibacterial activity of amoxicillin, ampicillin, piperacillin, mezlocillin

BETA-LACTAM ANTIBIOTICS...

- **Amoxicillin-clavulinic acid [augmentin®]**
- **Used in:**
 - Acute otitis media [H.influenza; B.catarrhalis];
 - Sinusitis
 - Lower RTI
 - Skin infection [streptococci, staphylococci]
 - Diabetic foot infection [staphylococci, aerobic & anaerobic G^{-ve}]

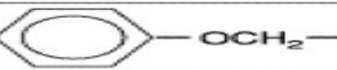
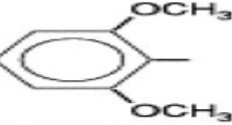
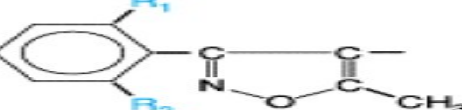
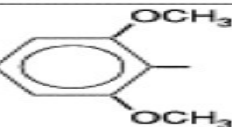
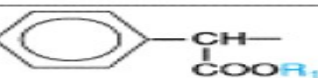
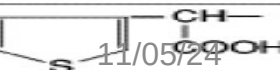


BETA-LACTAM ANTIBIOTICS...

- **Ampicillin-Sulbactam [Unasym[®]]**
 - Sulbactam is less potent than clavulnic acid
 - Combination is available 1:0.5
 - Same spectrum of augmentin: used in mixed infection
- **Piperacillin-tozabactam (Zosyn)**
 - Equivalent or superior to 3rd generation cephalosporin

Penicillins are substituted 6-aminopenicillanic acids



$\begin{array}{c} \text{CH}_3 \\ \\ \text{O}=\text{C}-\text{N}-\text{CH}-\text{COOH} \\ \\ \text{R} \end{array}$		MAJOR PROPERTIES	
R	NONPROPRIETARY NAME	Absorption Oral after Administration	Resistance to Penicillinase
	Penicillin G	Variable (poor)	No
	Penicillin V	Good	No
	Methicillin	Poor (not given orally)	Yes
	Oxacillin ($R_1 = R_2 = \text{H}$)		
	Cloxacillin ($R_1 = \text{Cl}; R_2 = \text{H}$)	Good	Yes
	Dicloxacillin ($R_1 = R_2 = \text{Cl}$)		
	Nafcillin	Variable	Yes
	Ampicillin [†] ($R_1 = \text{H}$)	Good	No
	Amoxicillin ($R_1 = \text{OH}$)	Excellent	
	Carbenicillin ($R_1 = \text{H}$)	Poor (not given orally)	
	Carbenicillin indanyl ($R_1 = 5\text{-indanol}$)	Good	No
	Ticarcillin	Poor (not given orally)	No
	Mezlocillin	Poor (not given orally)	No

BETA-LACTAM ANTIBIOTICS...

- ***DRUG INTERACTION PENICILLINS***
 - Aminoglycosides
 - Probenecid
 - Bacteriostatic antibiotics
 - Ampicillin and oral contraceptives [decreased enterohepatic circulation]

BETA-LACTAM ANTIBIOTICS...

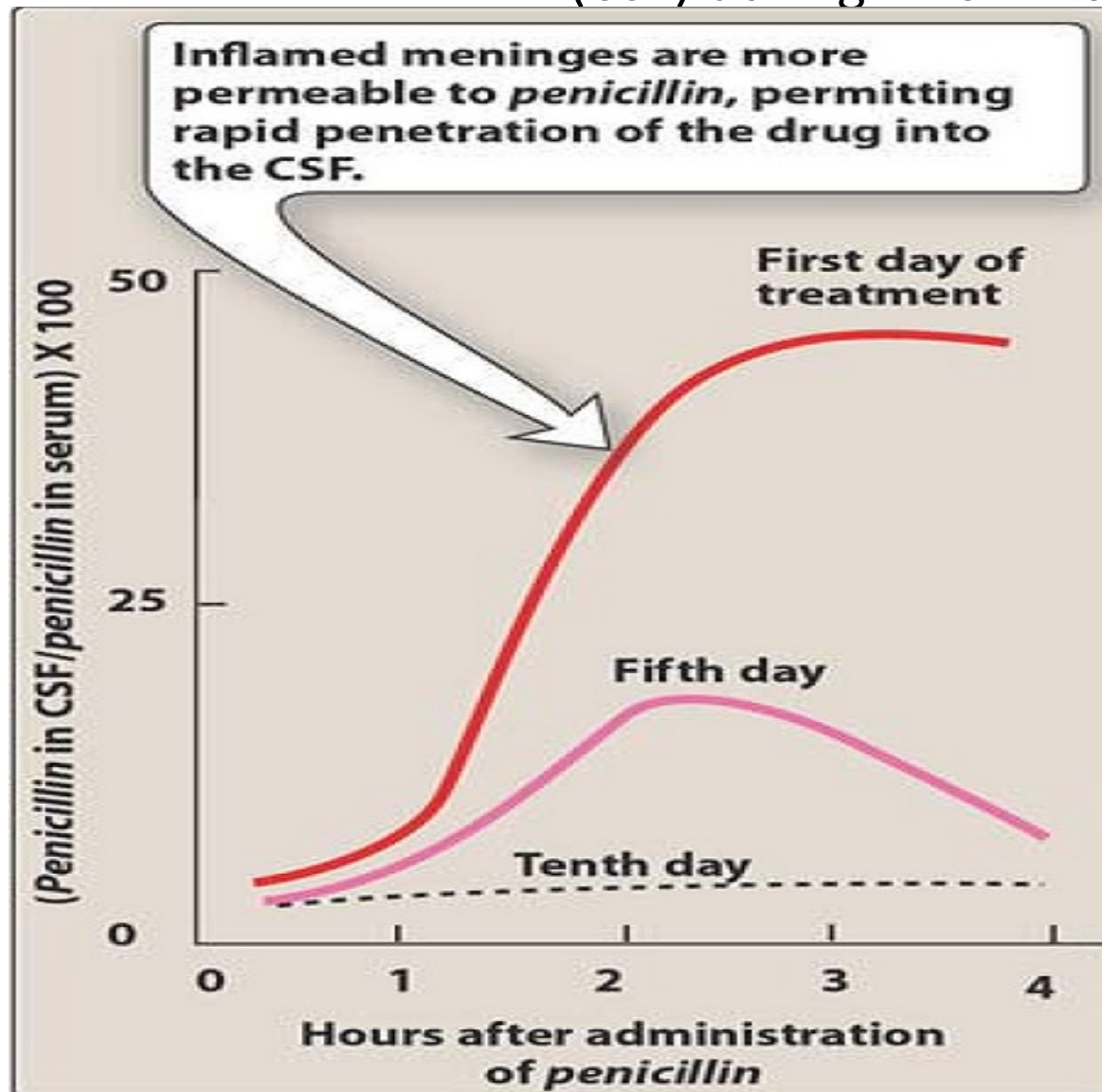
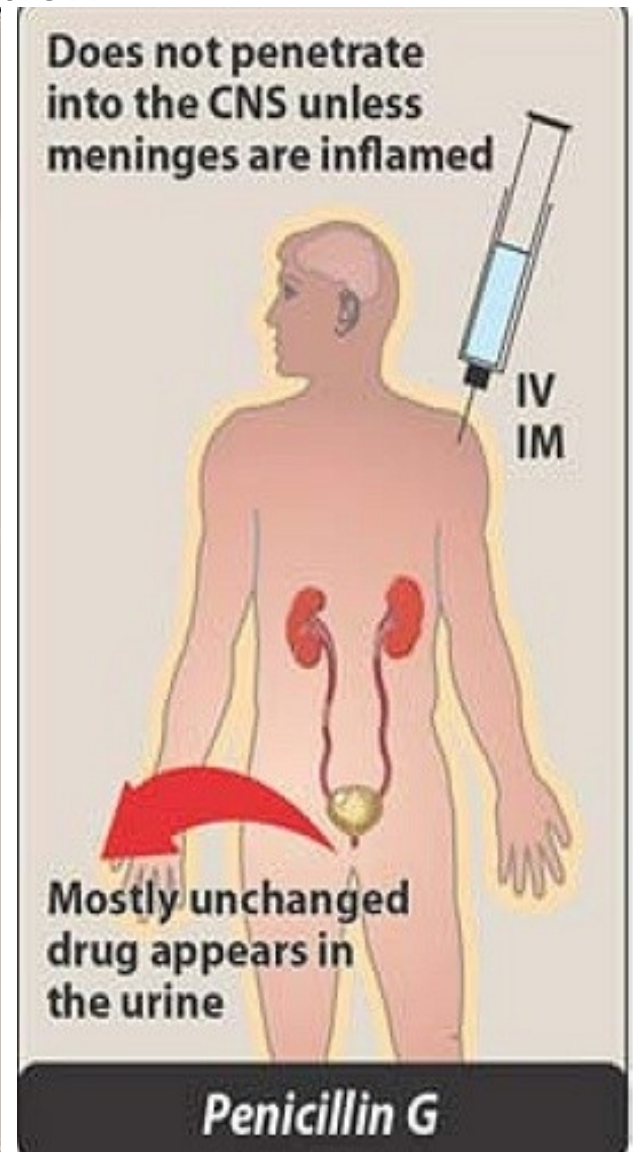
ADVERSE EFFECTS OF PENICILLINS

- ☐ Diarrhea
- ☐ Nephritis
- ☐ Neurotoxicity
- ☐ Hematologic toxicities
- ☐ Cation toxicity (sodium overload)
- ☐ Hypersensitivity/allergy
 - ☐ All penicillins are cross-sensitizing & cross-reacting
 - ☐ The antigenic determinants are degradation products of penicillins (penicilloic acid & products of alkaline hydrolysis bound to host protein)

- Allergic reactions include anaphylactic shock, serum sickness-type reactions (urticaria, fever, joint swelling, intense pruritus, etc),
 - skin rash, oral lesions, fever, interstitial nephritis (an autoimmune reaction to a penicillin-protein complex), eosinophilia, hemolytic anemia & other hematologic disturbances
- Most patients allergic to penicillins can be treated with alternative drugs.
 - if it necessary to use penicillins in a highly penicillin-allergic patient (eg, treatment of enterococcal endocarditis or neurosyphilis)

- In patients with renal failure penicillin in high doses can cause seizures.
- Nafcillin is associated with neutropenia
- Oxacillin can cause hepatitis
- Methicillin causes interstitial nephritis
- Large doses of penicillins given orally may lead to gastrointestinal upset, particularly nausea, vomiting, and diarrhea.
 - Ampicillin has been associated with pseudomembranous colitis.

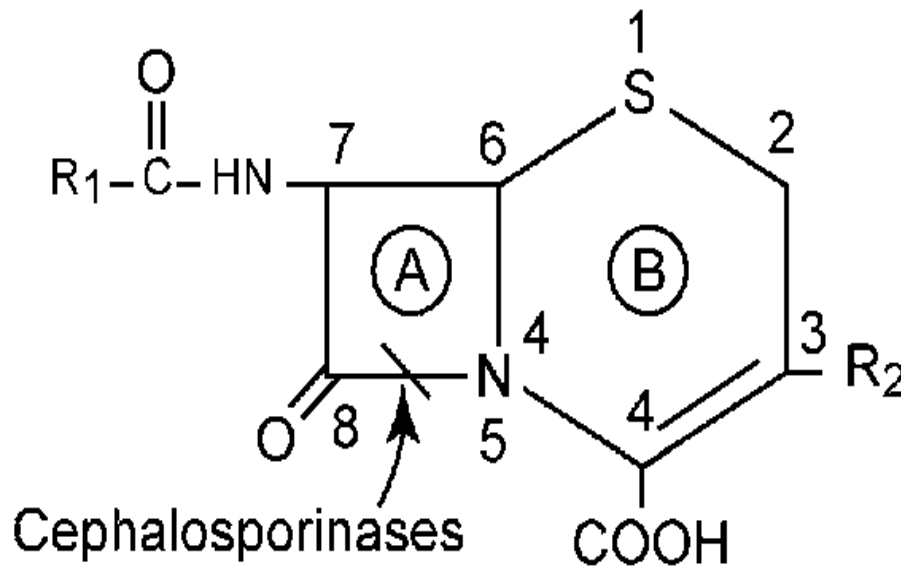
Enhanced penetration of penicillin into the cerebral spinal fluid (CSF) during inflammation



BETA-LACTAM ANTIBIOTICS...

CEPHALOSPORINS

Related both structurally and functionally to the penicillins



Derivatives of 7-aminocephalosporanic acid

Act in the same manner as penicillins

Are relatively stable in dilute acid and are highly resistant to penicillinase

A = β -lactamase ring

B = Dihydrothiazine ring

General Features

- Many are absorbed readily after oral administration while some are administered parenterally
- Excretion primarily by the kidney (dosage adjustment in renal insufficiency)
 - ✓ Probenecid slows tubular secretion
- Several cephalosporins penetrate into CSF in sufficient concentration, cross the placenta, relatively good penetration into the aqueous humor but is poor into the vitreous humor

Classification

Classified into four based on their spectrum (general features) of antimicrobial activity

- First generation
 - ✓ Cefadroxil, cefazolin, cephalixin, Cephalothin
- Second generation
 - ✓ Cefaclor, Cefprozil, Cefuroxime, Cefoxitin (a cephamycin)
- Third generation
 - ✓ Cefdinir, Cefixime, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftriaxone, Cefditoren
- Fourth generation
 - ✓ Cefepime, Cefpirome

BETA-LACTAM ANTIBIOTICS...CEPHALOSPORINS

Drug	Route	Half-life (hr)	Renal Excretion (%)
First generation			
Cefadroxil	Oral	1.2–2.5	70–90
Cefazolin	IM, IV	1.5–2.5	70–95
Cephalexin	Oral	1.0	95
Cephapirin	IM, IV	0.6	50–70
Cephradine	Oral	0.7	75–100
Second generation			
Cefaclor	Oral	0.6–0.9	60–85
Cefamandole	IM, IV	0.5–1.2	100
Cefmetazole	IV	1.2–1.5	85
Cefonicid	IM, IV	3.5–4.5	95–99
Cefotetan	IM, IV	2.8–4.6	60–91
Cefoxitin	IM, IV	0.7–1.0	85
Cefprozil	Oral	1.2–1.4	64
Cefuroxime	IM, IV	1.1–1.3	95
Cefuroxime axetil	Oral	1.1–1.3	52
Loracarbef ^a	Oral	1.0	87–97
Third generation			
Cefdinir	Oral	1.7	18
Cefepime	IM, IV	2.0	70–99
Cefixime	Oral	2.3–3.7	50
Cefoperazone	IM, IV	2.0	20–30
Cefotaxime	IM, IV	1.0	40–60
Cefpodoxime proxetil	Oral	1.9–3.7	40
Ceftazidime	IM, IV	1.9	80–90
Ceftibuten	Oral	1.5–2.8	57–75
Ceftizoxime	IM, IV	1.4–1.8	57–100
Ceftriaxone	IM, IV	5.8–8.7	33–67

Mechanism of action

- Inhibition of cell wall synthesis
- ***Bactericidal***

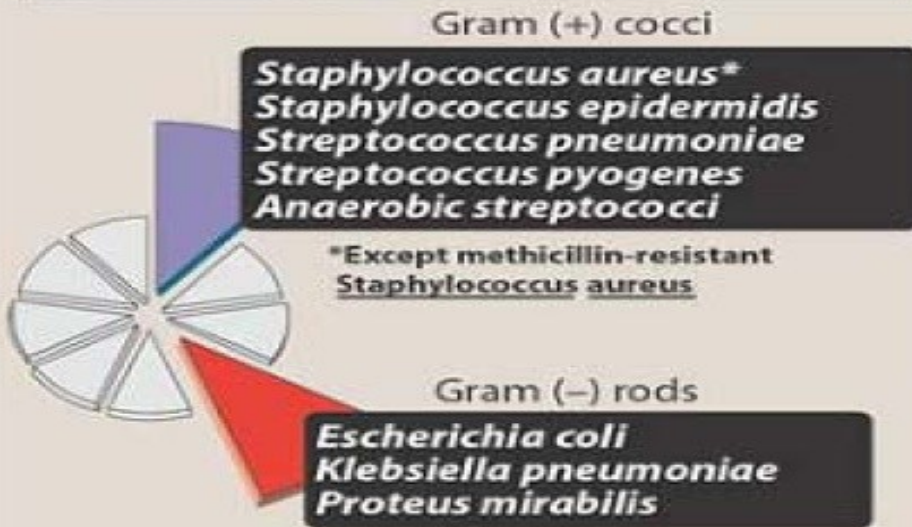
Mechanisms of Bacterial Resistance

- Production of β -lactamases (cephalosporinases)
- Altered penicillin binding proteins (PBPs)
- From 1st generation to 3rd generation
 - Increasing activity against G^{-ve} & anaerobes
 - Increasing resistance to destruction by β -lactamase
 - Increasing ability to reach CSF

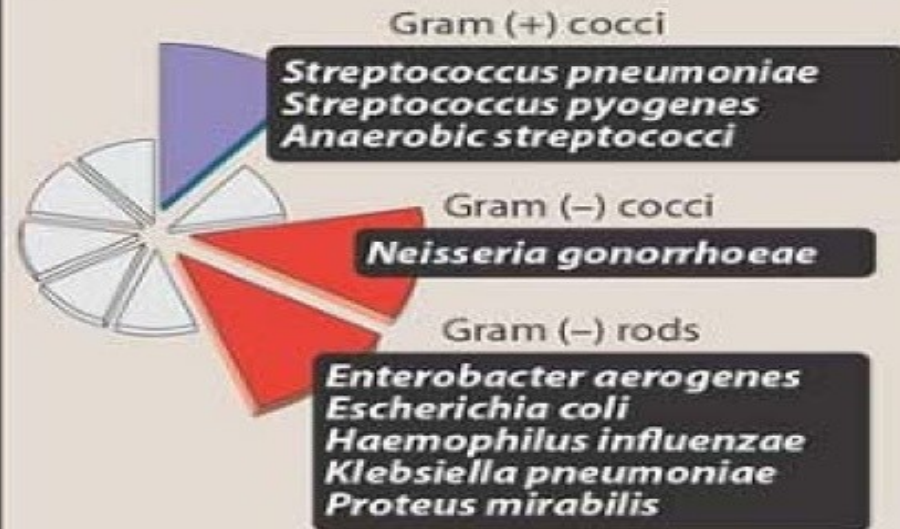
Table 1.6. Organisms That May Be Susceptible to Cephalosporins

1st generation (cefazolin)	2nd generation (cefoxitin, cefotetan)	3rd generation (ceftriaxone, cefotaxime)	4th generation (cefepime)
Methicillin-sensitive <i>Staphylococcus aureus</i> (best activity) <i>Streptococcus pyogenes</i>	Covers same organisms as cefazolin, but weaker gram-positive activity.	Covers same organisms as cefazolin, but often weaker gram- positive and stronger gram-negative activity.	Covers same organisms as cefazolin and ceftriaxone. Excellent gram-positive and gram-negative activity.
Penicillin (PCN)–sensitive <i>S. pneumoniae</i> <i>Escherichia coli</i> (some species) <i>Klebsiella pneumoniae</i> (some species) <i>Proteus mirabilis</i> (some species)	Also covers: <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Neisseria gonorrhoeae</i> <i>N. meningitidis</i> <i>Bacteroides fragilis</i> (some strains)	Also covers: <i>H. influenzae</i> <i>M. catarrhalis</i> <i>N. gonorrhoeae</i> <i>N. meningitidis</i> <i>Citrobacter freundii</i> <i>Morganella</i> spp. <i>Salmonella</i> spp. <i>Shigella</i> spp.	Also covers: Intermediate PCN-resistant <i>S. pneumoniae</i> <i>Enterobacter</i> spp. <i>Pseudomonas aeruginosa</i> <i>Serratia</i> spp.

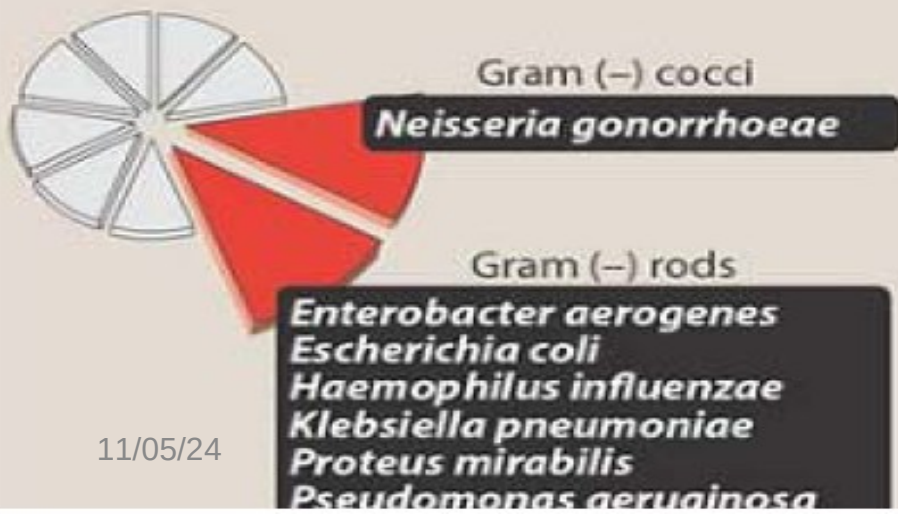
First-generation cephalosporins



Second-generation cephalosporins



Third-generation cephalosporins



Therapeutic applications of cephalosporins

	Effect against G +ve	Effect against G-ve
1 st GC	+++	+
2 nd GC	++	++
3 rd GC	+	+++

FIRST GENERATION CEPHALOSPORINS

1. Excellent gram (+)coverage with some gram (-)
 - Gram(+) cocci including Penicillinase-producing & nonpenicillinase producing Staphylococcal strains, streptococcus pyogens, S. pneumonia
 - limited activity against gram(-) bacteria (some strains of E. coli, Klebsiella, Shigella are inhibited *in vitro*)
 - Inactive against Enterococci, MRSA, Listeria monocytogenes
2. Do not cross the blood–brain barrier.
3. Inexpensive
4. Useful for treating soft-tissue infections & for surgical prophylaxis
5. Can often be used as an alternative to penicillin G

Selected 1st generation cephalosporins

Generic	Route	Half life(h)	Properties
Cephalexin	oral	0.9	<ul style="list-style-type: none"> - Active against G+ve - Less active against penicillinase producing staph
Cefadroxil	oral	1.2	Used in t/t of UTI
Cephradine	Oral, iv/ im	0.7	Similar to cephalexin
Cefazolin*	Iv/ im	1.8	<ul style="list-style-type: none"> - Good penetration to bone - preferred due to $t_{1/2}$
Cephalothin	iv	0.6	Used in severe staph infection. E.g. endocarditis

BETA-LACTAM ANTIBIOTICS...

SECOND GENERATION CEPHALOSPORINS

- 1) Improved activity against *Haemophilus influenzae*, *Neisseria* species, and *Moraxella catarrhalis*.
- 2) Cefoxitin and cefotetan have anaerobic activity and are used in mixed soft-tissue infections and pelvic inflammatory disease.
- 3) Cefotetan and cefamandole have a methylthiotetrazole ring that decreases prothrombin production. Vitamin K prophylaxis is recommended in malnourished patients.
- 4) Cefuroxime–axetil is a popular oral cephalosporin;
Cefuroxime (iv)

BETA-LACTAM ANTIBIOTICS...

SECOND GENERATION CEPHALOSPORINS

- Have greater stability against β -lactamase
- Active, *in vitro*, against
 - Bacteria susceptible to 1st GC
 - Most strains of Haemophilus influenza (anaerobes)
 - Gram (-) bacteria (2nd GC are more active than 1st GC)
 - May be active against Enterobacter, E.coli, Klebsiella, Neisseria that are resistant to 1st GC
- Inactive against
 - Enterococci, MRSA, & Pseudomonas

BETA-LACTAM ANTIBIOTICS...

THIRD GENERATION CEPHALOSPORINS

- Improved gram-negative coverage.
- Excellent activity against *Neisseria gonorrhoeae*, *N. meningitidis*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.
- Higher β -lactamase stability
- Less active in vitro against susceptible staphylococci than 1st GC
- Expanded spectrum of activity against gram (-)
- Recommended for community-acquired pneumonia and bacterial meningitis
- Active in vitro against
 - Gram (-) susceptible to 1st & 2nd GCs
 - Most are active against enterobacter, *E. coli*, *Klebsiella*, *Neisseria*.. That may be resistant to 1st and 2nd GC, Some are active against *Pseudomonas*
- Inactive against MRSA and generally are inactive against enterococci & *Listeria monocytogenes*

BETA-LACTAM ANTIBIOTICS...

THIRD GENERATION CEPHALOSPORINS

- Ceftriaxone has a long half-life that allows for once-daily dosing. In children, acalculous cholecystitis can occur with large doses.
- Cefotaxime has a shorter half-life but activity identical to that of ceftriaxone; does not cause biliary sludging.
- Ceftazidime has excellent activity against most *Pseudomonas aeruginosa* strains, but reduced activity against *Staphylococcus aureus*.

BETA-LACTAM ANTIBIOTICS...

THIRD GENERATION CEPHALOSPORINS

CEFTRIAXONE*

- Most potent; $t_{1/2}$ 8hrs
- High efficacy in bacterial meningitis, multiresistant typhoid fever,
- complicated UTI, Abdominal sepsis, septicaemias

CEFTAZIDIME

- Excellent activity against G^{-ve} including p.aeruginosa
- Penetrate CSF & t/t of choice in meningitis due to p. aeruginosa; given parenterally

CEFOPERAZONE

- Strong activity against pseudomonas; high PPB
- Do not reliably penetrate into CSF
- Primarily indicated in severe urinary, respiratory, biliary infection and septicaemia

BETA-LACTAM ANTIBIOTICS...

Fourth generation cephalosporins

Cefepime & cefpirome

- Expanded spectrum of activity against gram(-)
- More resistant to inactivation by β -lactamases
- Excellent gram-positive (including methicillin sensitive *Staphylococcus aureus*) and gram negative coverage (including *Pseudomonas aeruginosa*, certain *Enterobacteriaceae*, that are generally resistant to 3rd GC).
- More active against gram(+) than most 3rd GCs
- Inactive against MRSA, enterococci, and *Listeria monocytogenes*
- Excellent broad-spectrum empiric therapy
- Useful in nosocomial infections

BETA-LACTAM ANTIBIOTICS...

ADVERSE EFFECTS OF CEPHALOSPORINS

- Allergic reactions
- Antibiotic-associated colitis: superinfection
- Bleeding tendency: hypoprothrombinemia
[methylthiotetrazole/MTT containing group
Cefoperazone, cefotetan, cefmandole, cefmetazole
- Local effects: thrombophlebitis from iv injection

BETA-LACTAM ANTIBIOTICS...

DRUG INTERACTION

- a) Probenecid
- b) Alcohol: disulfiram like rxn
- c) Drugs that promote bleeding

Therapeutic Uses

- Skin and soft tissue infections due to *S. aureus* and *S. pyogenes* (1st GCs)
- Colorectal surgery, where prophylaxis for intestinal anaerobes is desired (2nd GCs)
- Generally 2nd GCs displaced by 3rd GCs
 - Oral 2nd GCs can be used to treat RTI
 - In situations where facultative gram(-) & anaerobes are involved (intra-abdominal infections, pelvic inflammatory disease, and diabetic foot infection)

Therapeutic Uses (cont'd)

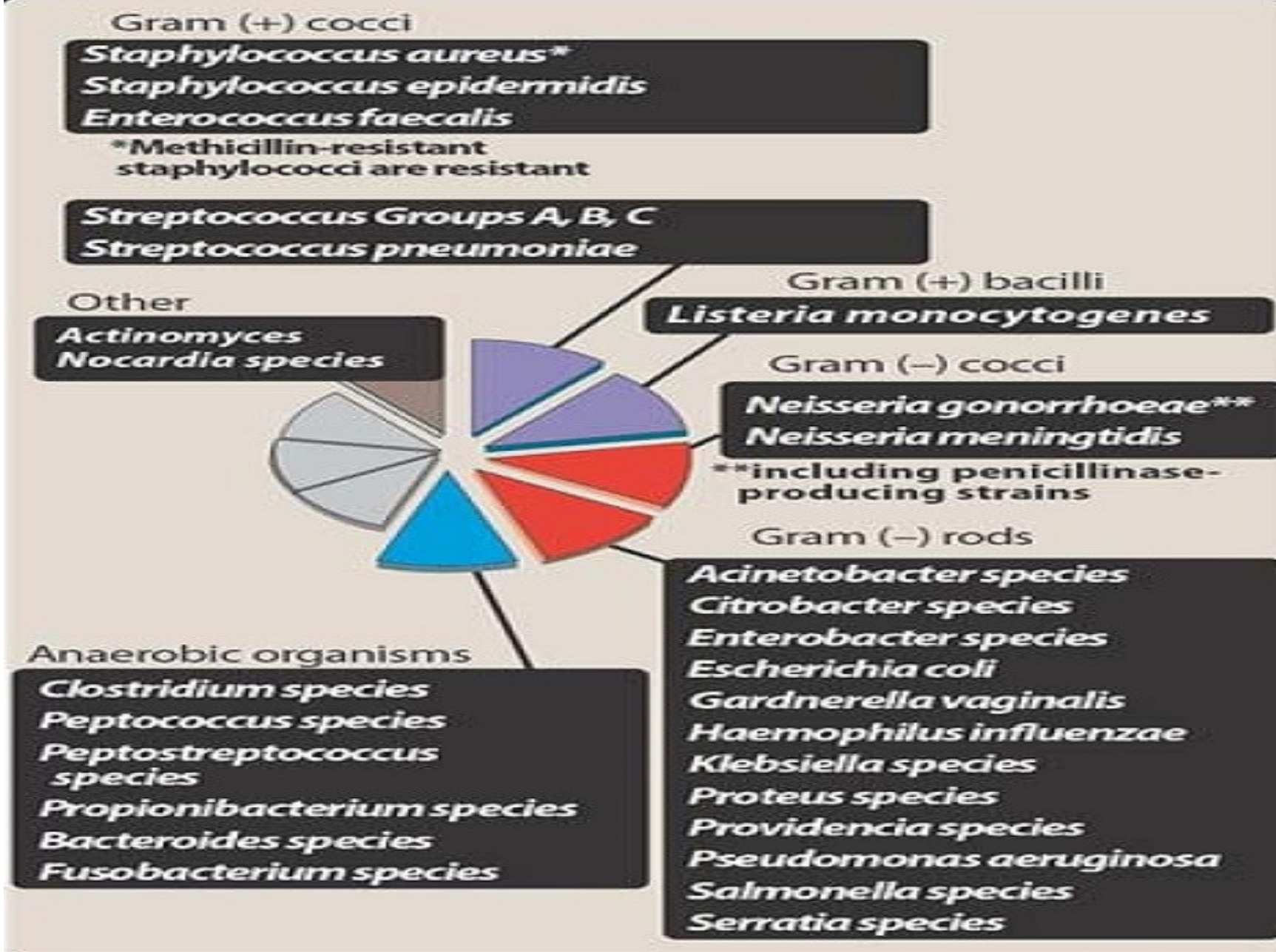
3rd GCs (with or without aminoglycosides)

- Drugs of choice for serious infections caused by *Klebsiella*, *Enterobacter*, *Proteus*, *Serratia*, & *Haemophilus* spp
- Ceftriaxone is the therapy of choice for all forms of gonorrhea and for severe forms of Lyme disease.
- Drugs of choice for the treatment of meningitis caused by *H. influenzae*, sensitive *S. pneumoniae*, *N. meningitidis*, and gram-negative enteric bacteria
- Treatment of *Pseudomonas* meningitis infection
- Treatment of community-acquired pneumonia

Therapeutic Uses (cont'd)

➤ 4th GCs

- Empirical treatment of nosocomial infections where antibiotic resistance owing to extended-spectrum β -lactamases or chromosomally induced β -lactamases are anticipated



Antimicrobial spectrum of imipenem

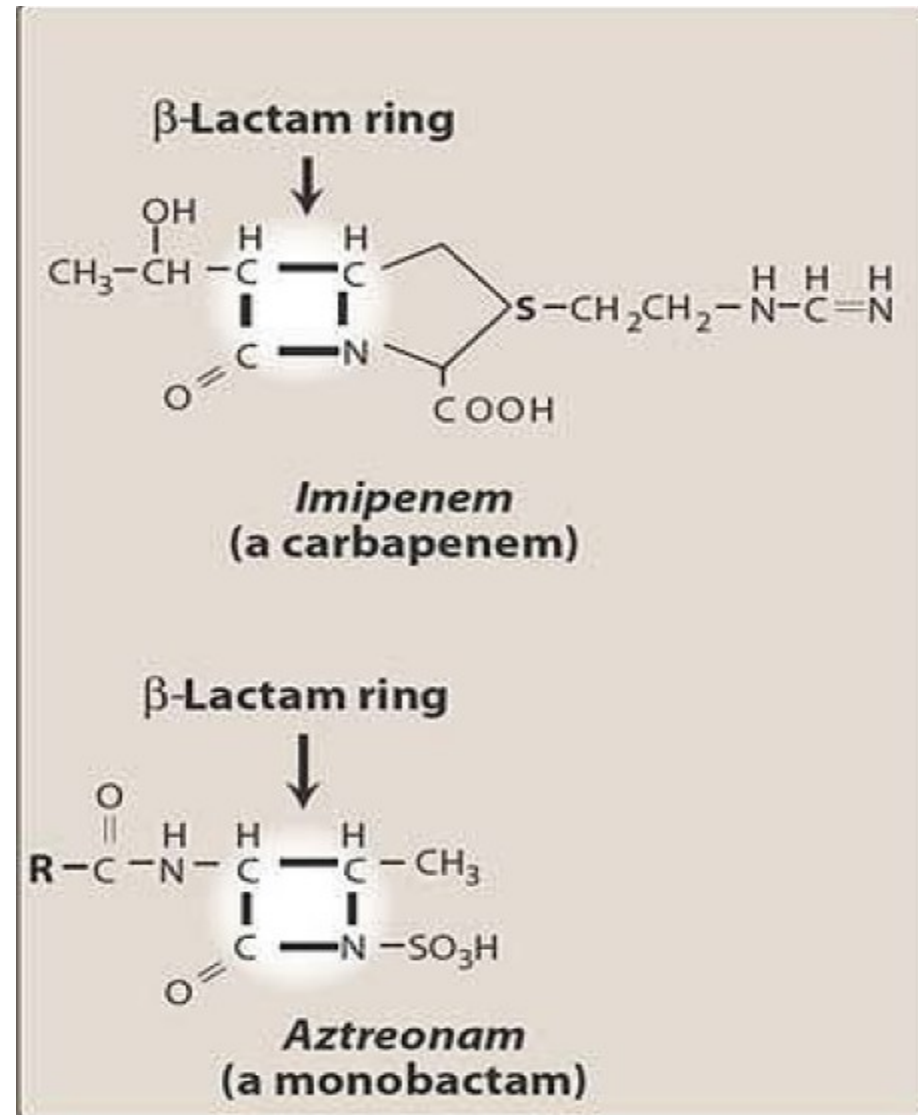
OTHER B-LACTAM ANTIBIOTICS

I. CARBAPENEMS

- *Mechanism of action*
 - bind to PBP $\Rightarrow$ inhibit bacterial cell wall synthesis
 - β -lactamase resistant
- *Specific agents* [Imipenem with cilastatin ; Meropenem]

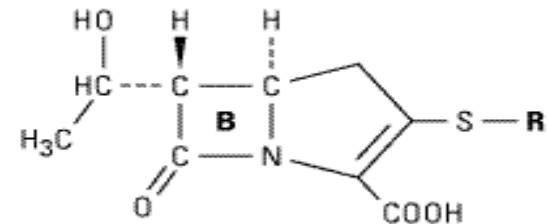
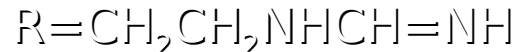
II. MONOBACTAMS- Aztreonam

Mechanism: bind to PBP
 $\Rightarrow$ Inhibit bacterial cell wall synthesis



Imipenem

- Marketed in combination with *cilastatin*, a drug that inhibits the degradation of imipenem by a renal tubular dipeptidase
- Derived from a compound produced by *Streptomyces cattleya*.
- Distributed in CSF; metabolized in renal tubule by dehydropeptidases which can be inhibited by cilastatin
- Given by iv/not absorbed orally



Imipenem

Antimicrobial Activity

- Active against
 - Streptococci (including pen-resistant), enterococci (excluding *E. faecium* and non- β -lactamase-producing pen-resistant strains), staphylococci (including penicillinase-producing strains), and *Listeria*
- Most MRSA strains are resistant
- Excellent Activity against the Enterobacteriaceae, including organisms that are cephalosporin-resistant
- Most strains of *Pseudomonas* and *Acinetobacter* are inhibited.
- Anaerobes, including *B. fragilis*, are highly susceptible.

Imipenem

Therapeutic Uses

- Especially useful for the treatment of infections caused by cephalosporin-resistant nosocomial bacteria
- For empirical treatment of serious infections in hospitalized patients who have recently received other β -lactam
- Imipenem should not be used as monotherapy for infections caused by *P. aeruginosa* because of the risk of resistance developing during therapy

Imipenem

Adverse effect

- 1) GIT: NVD in rapid iv infusion
- 2) CNS: Seizure
- 3) Hypersensitivity reaction

OTHER B-LACTAM...

II. MONOBACTAMS- Aztreonam

- Mechanism: bind to PBP $\Rightarrow$ Inhibit cell wall synthesis
- Antimicrobial spectrum: narrow [G-ve aerobic bacteria: H. influenza, N. meningitides, & Pseudomonas]
- β -lactamase resistant; no cross sensitivity with other β -lactam
- used as substitute to aminoglycosides in UT, Lower RT, skin & soft tissue infection

OTHER INHIBITOR OF CELL WALL SYNTHESIS

VANCOMYCIN:

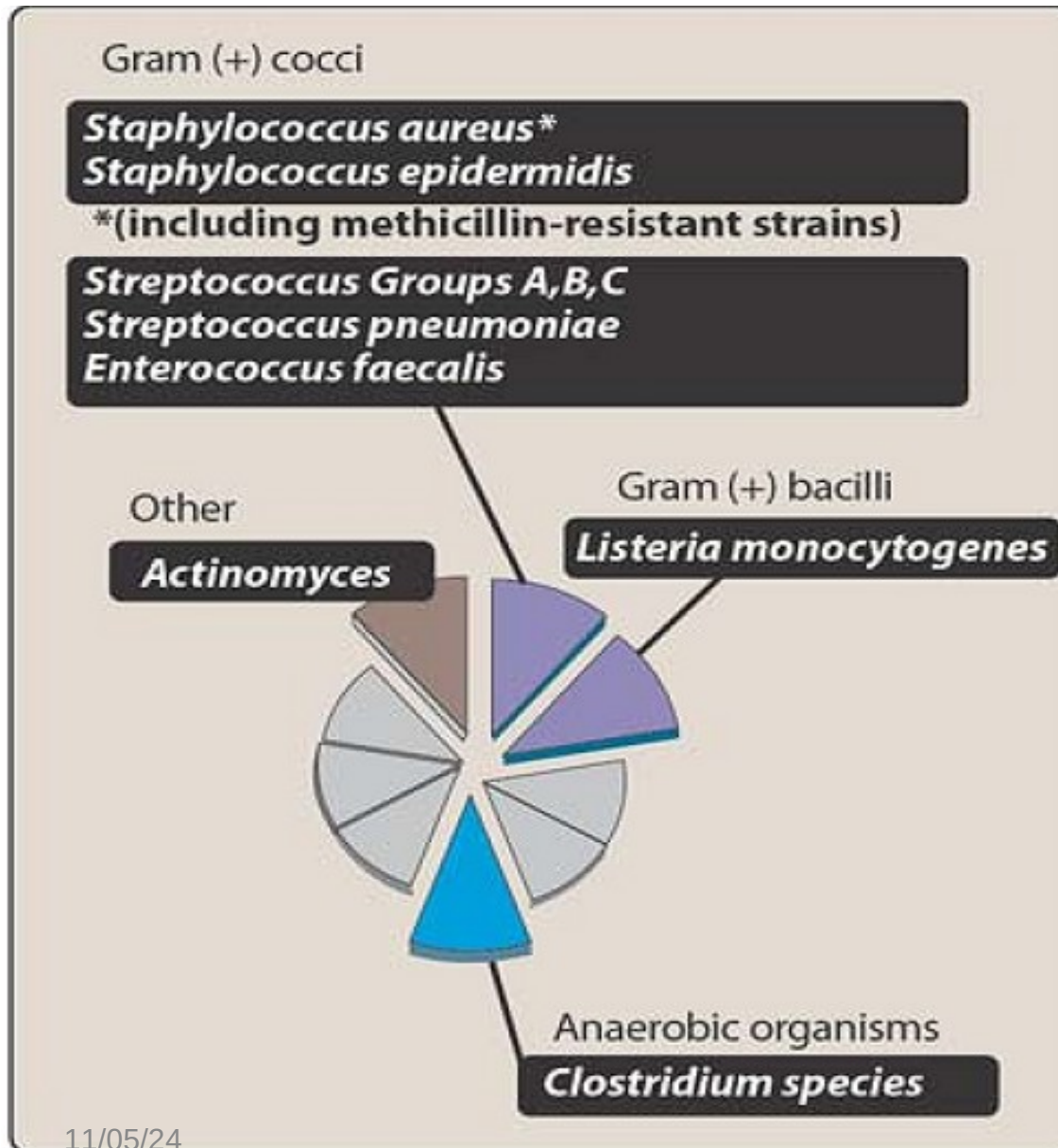
- Glycopeptide, Produced by *Streptococcus orientalis*
- MoA
 - Inhibit bacterial cell wall synthesis by binding to peptidoglycan pentapeptide $\Rightarrow$ Transglycosylase inhibition $\Rightarrow$ inhibition of elongation of peptidoglycan & cross linking.
- Spectrum
 - Effective against multiple drug-resistant organisms, such as MRSA & enterococci.
 - Against G^{+ve} [staphylococcus aureus & staph epidermidis including methicillin resistant, & Cl.difficile]
- P_k
 - Not absorbed orally; given iv except antibiotic induced colitis

Mechanism of Action

➤ Cell wall synthesis inhibitor

- Binds firmly to the D-Ala-D-Ala terminus of nascent peptidoglycan pentapeptide .
- This inhibits the transglycosylase, preventing further elongation of peptidoglycan and cross-linking.
- The peptidoglycan is thus weakened and the cell becomes susceptible to lysis.
- The cell membrane is also damaged, which contributes to the antibacterial effect.

Antimicrobial spectrum of *vancomycin*



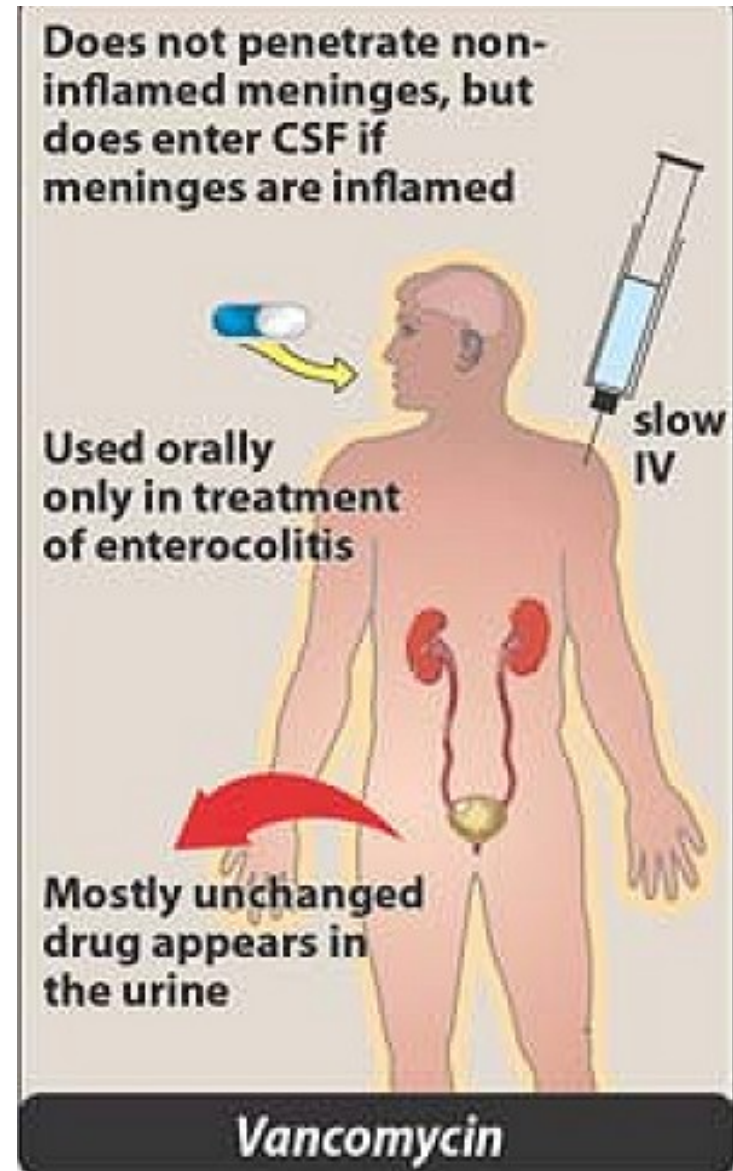
- It is effective primarily against gram-positive organisms
- It has been lifesaving in the treatment of MRSA & methicillin-resistant *Staphylococcus epidermidis* (MRSE) infections

Mechanism of Resistance

- Resistance to vancomycin in enterococci and vancomycin-resistant *S aureus strains* is due to modification of the D-Ala-D-Ala binding site of the peptidoglycan building block in which the terminal D-Ala is replaced by D-lactate.

Pharmacokinetics

- Poorly absorbed from the GIT& should be orally administered only for the treatment of antibiotic-associated enterocolitis caused by *Clostridium difficile*
- Parenteral doses must be administered IV The drug has a serum elimination half-life of about 6 hours.
- Appears in various body fluids, including the CSF when the meninges are inflamed
- About 90% is excreted by glomerular filtration (dosage adjustments in renal impairment)



Clinical Uses

- It should be used only to treat serious infections & is particularly useful in the management of infections due to MRSA, & in severe staphylococcal infections in patients who are allergic to penicillins and cephalosporins.
- Effective & convenient when there is disseminated staphylococcal infection or localized infection of a shunt in a patient with irreversible renal disease who is being maintained by hemodialysis or peritoneal dialysis
- Treatment of infections caused by *Corynebacterium* spp.
- Important in the management of known or suspected penicillin-resistant pneumococcal infections

Adverse effects

- Adverse reactions are encountered in about 10% of cases.
- Most reactions are minor
- Vancomycin is irritating to tissue, resulting in phlebitis at the site of injection.
- Chills & fever may occur.
- Ototoxicity is rare and nephrotoxicity uncommon with current preparations.
 - However, administration with another ototoxic or nephrotoxic drug, such as an aminoglycoside, increases the risk of these toxicities.
- Ototoxicity can be minimized by maintaining peak serum concentrations below 60 mcg/mL.
- Among the more common reactions is the so-called "red man" or "red neck" syndrome.
 - This infusion-related flushing is caused by release of histamine.
 - It can be largely prevented by prolonging the infusion period to 1–2 hours or increasing the dosing interval

Newer glycopeptide antibiotics

- **Teicoplanin**
 - very similar to vancomycin in mechanism of action and antibacterial spectrum
 - It can be given by IM and IV
- **Dalbavancin**
 - Derived from teicoplanin
 - Effective on methicillin-resistant and vancomycin-intermediate *S aureus*
- **Telavancin**
 - Derived from vancomycin
 - active versus gram-positive bacteria

Other Cell Wall- Active Agents

- **Daptomycin**
 - Novel cyclic lipopeptide
 - Similar to that of vancomycin
 - Active against vancomycin-resistant strains of enterococci and *S aureus*
- **Fosfomycin**
 - Analog of phosphoenolpyruvate
 - It inhibits the cytoplasmic enzyme enolpyruvate transferase and block the addition of phosphoenolpyruvate to UDP-NAG
 - Active against both gram-positive and gram-negative
 - A single 3 g dose for tt of uncomplicated lower UTI in women

- **Cycloserine**

- Produced by *Streptomyces orchidaceus*
- Inhibits many g-ve and g+ve organisms, MTB
- Structural analog of D-alanine and inhibiting alanine racemase and D-alanyl-D-alanine ligase

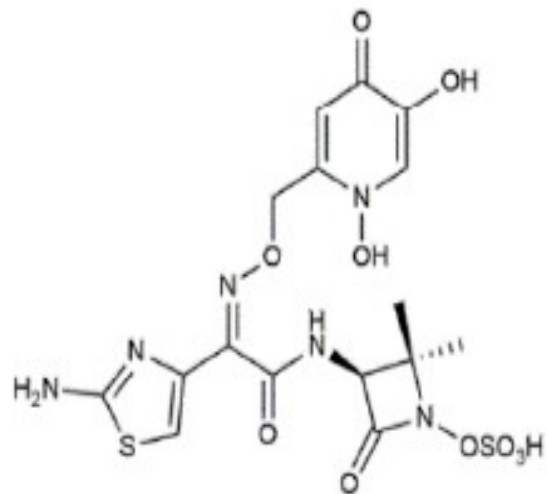
- **Bacitracin**

- Bacitracin inhibits cell wall synthesis by interfering with dephosphorylation in cycling of the lipid carrier
- Effective against Gram positive microorganisms
- Topical application due to nephrotoxicity
- Often used for traumatic abrasions

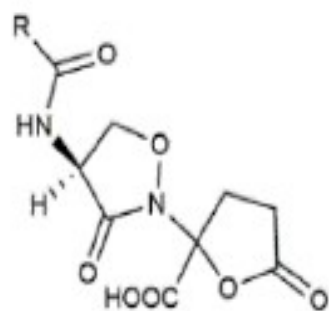
Recent Developments in Transpeptidase Inhibitors

- Antibiotics review, 2016 by Eric Sauvage and Mohammed Terrak
- Except for penicillin derivatives, research continues in an ongoing process to find new compounds active against the most harmful bacteria
- **Carbapenems**
 - Are last resort β -lactam antibiotics
 - Due to binding to bind B2-PBPs as well as B3-PBPs they are broad spectrum highly potent
 - Inhibit LD-transpeptidases catalyze the formation of a 3,3 peptidoglycan cross-link
 - The latest news makes the future rather bleak

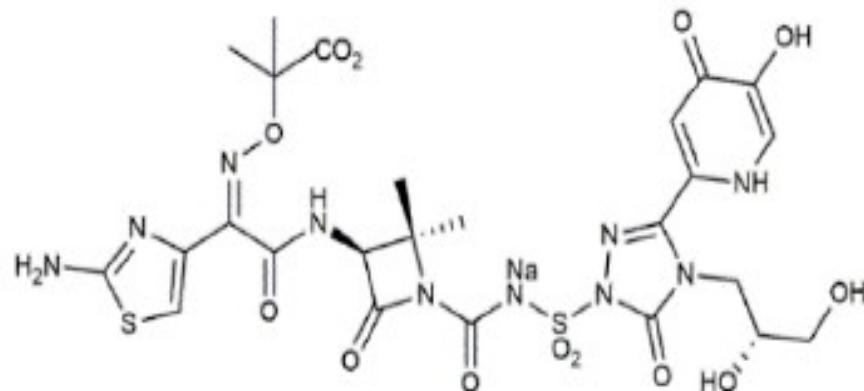
- Some new carbapenems in development
 - ME1036, biapenem, panipenem, razupenem, tebipenem and tomopenem
- Doripenem
 - FDA approval in 2007 for complicated urinary tract infections and intra-abdominal infections
 - Is stable to hydrolysis by many β -lactamases but is hydrolyzed by class B metallo- β -lactamases and serine carbapenemases
- **Monobactams**
 - BAL30072
 - ✓ Active against *P. aeruginosa*, *A. baumannii* and *Klebsiella pneumoniae*, with an enhanced activity when combined with meropenem or colistin
 - ✓ Has a high affinity for PBP3 but also for PBP1a and PBP1b
 - Monocarbam MC-1
 - ✓ Highly active against *P. aeruginosa* clinical isolates
 - ✓ Resistance could rapidly appear



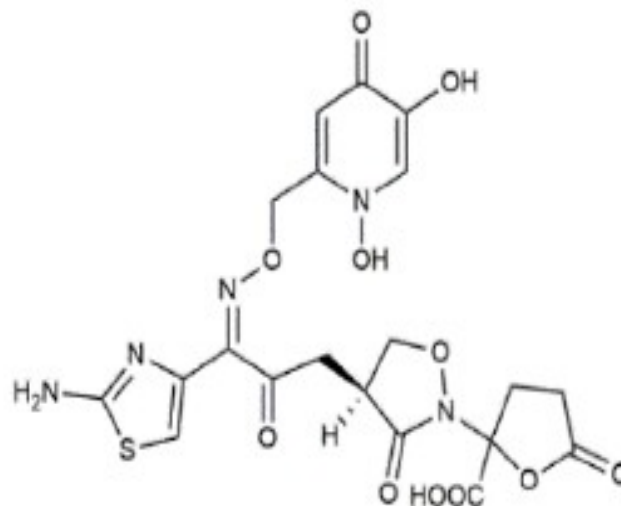
BAL30072



Lactivicin



Monocarbam MC-1



Siderophore-conjugated lactivicin

Protein synthesis inhibitor antibiotics;

Objectives;

- Classify antibiotics acting on protein synthesis
- Explain the detail mechanism of action of protein synthesis inhibitors
- Describe mechanism of resistance
- List clinical uses and SEs.

Classification of inhibitors of bacterial protein synthesis

- Drugs That Affect The 30S Ribosomal Subunit

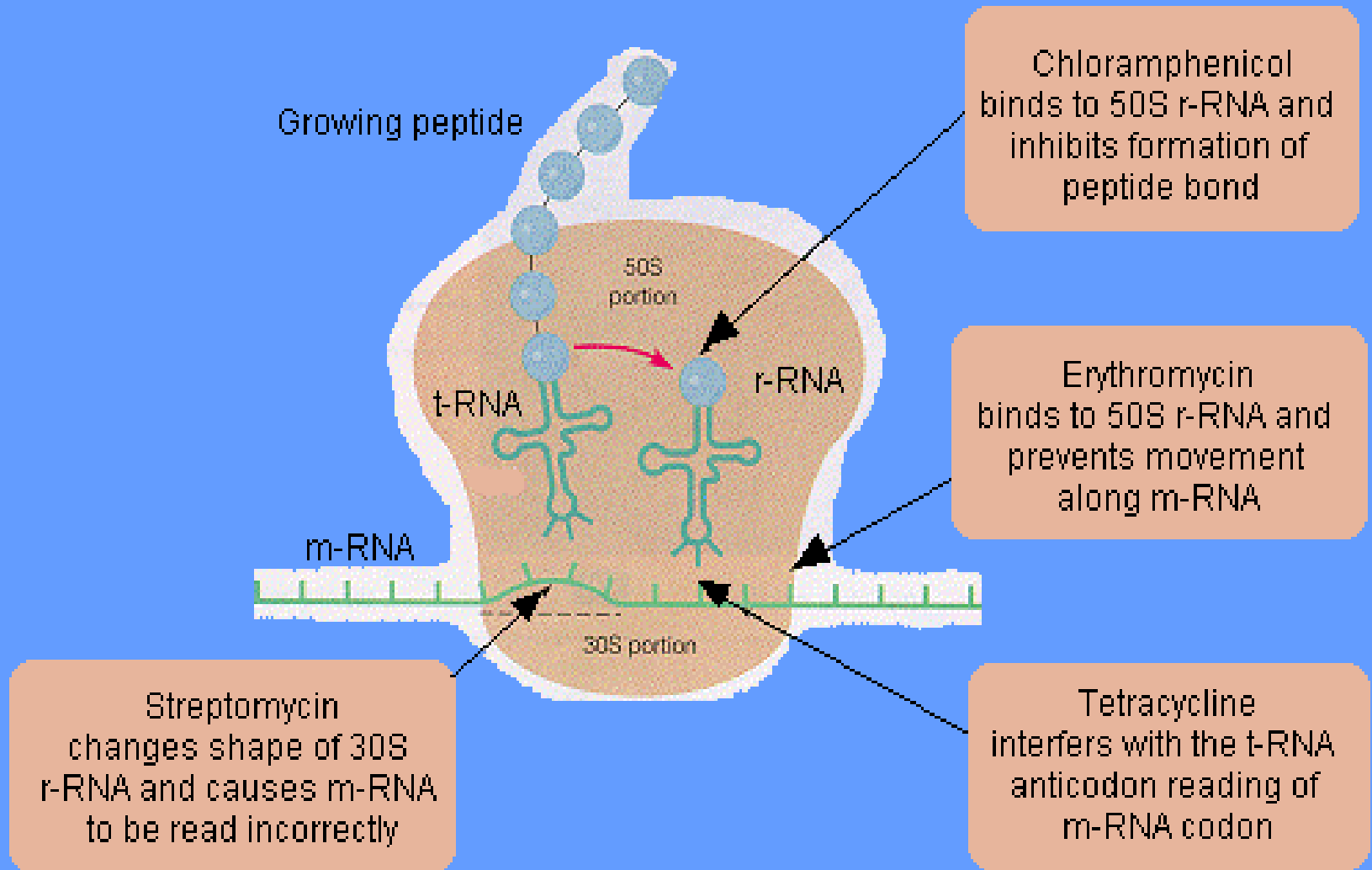
➤ Aminoglycosides	-Tetracyclines	- Other Antibiotics
✓ Gentamicin	Doxycycline	-Spectinomycin
✓ Neomycin	Minocycline	
✓ Streptomycin	Tetracycline	

- Drugs That Affect The 50s Ribosomal Subunit

➤ Macrolides	- Ketolide	-Other Antibiotics	- Other Inhibitors
✓ Azithromycin	Telithromycin	Chloramphenicol	Mupirocin
✓ Clarithromycin		Clindamycin	Linezolid
✓ Erythromycin		Quinupristin-dalfopristin	

Protein Synthesis Inhibition

Inhibition of Protein Synthesis by Antibiotics



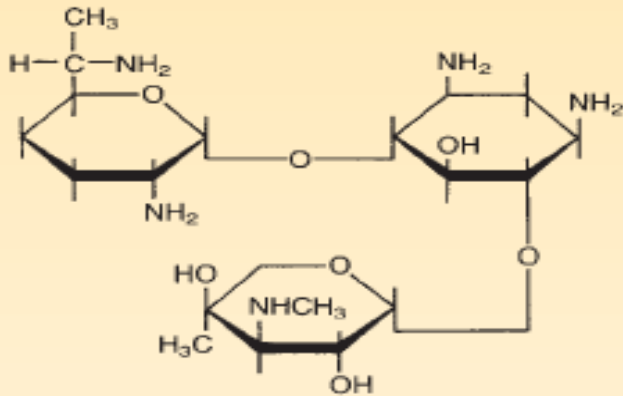
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Table V-1-3. Summary of Mechanisms of Protein Synthesis Inhibition

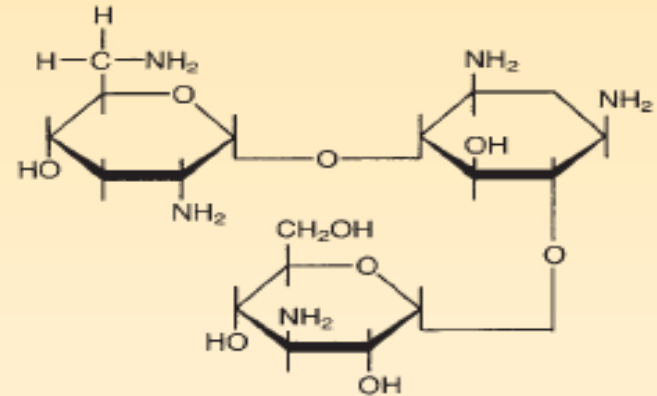
Event	Antibiotic(s) and Binding Site(s)	Mechanism(s)
1 Formation of initiation complex	Aminoglycosides (30S)	Interfere with initiation codon functions — block association of 50S ribosomal subunit with mRNA-30S (static); misreading of code — incorporation of wrong AA (-cidal)
2 Amino-acid incorporation	Tetracyclines (30S)	Block the attachment of aminoacyl tRNA to acceptor site (-static)
3 Formation of peptide bond	Chloramphenicol (50S)	Inhibit the activity of peptidyltransferase (-static)
4 Translocation	Macrolides and clindamycin (50S)	Inhibit translocation of peptidyl-tRNA from acceptor to donor site (-static)

AMINOGLYCOSIDES

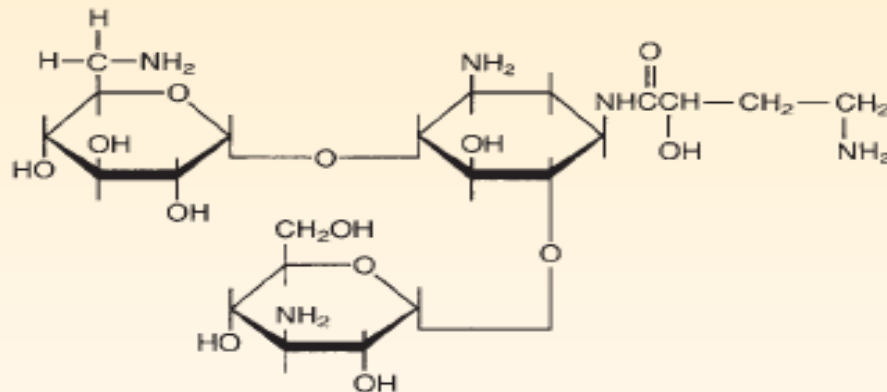
- Includes: Streptomycin, Gentamicin, Kanamycin, Amikacin, Tobramycin, Sisomicin, Netilmicin & others



GENTAMICIN (C₄)



TOBRAMYCIN



AMIKACIN

BACTERIOCIDAL...

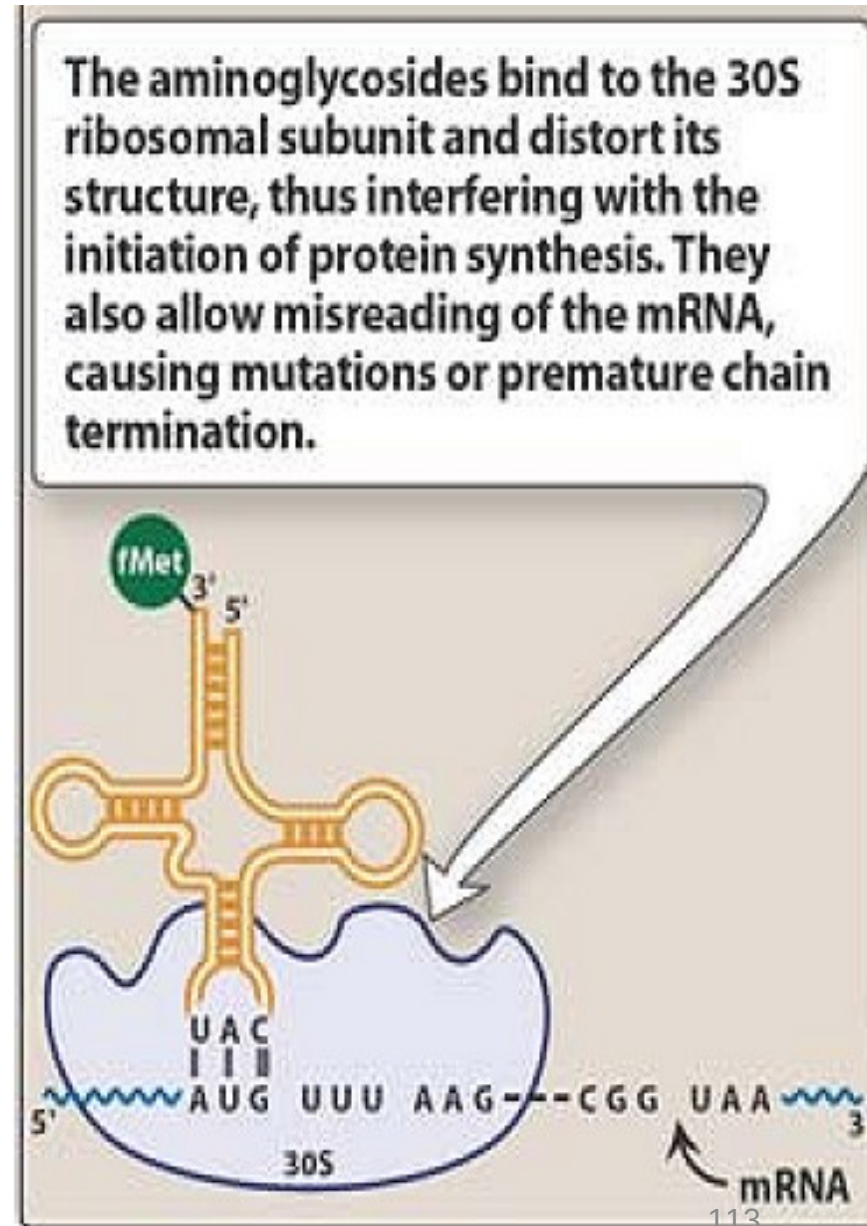
- ***General properties:***
 - Composed of two or more aminosugars connected by a glycoside linkage
 - At physiological pH, they are polycations
 - Are water soluble, stable in solution
 - Interact chemically with β -lactam antibiotic
- ***Mechanism of action***
 - Transport of aminoglycosides through outer membrane by passive diffusion via porins; then they are actively transported across the cell membrane

BACTERIOCIDAL...

- The drug binds to 30s ribosomal subunit $\Rightarrow$ Protein synthesis inhibition
 - Block initiation complex of peptide formation
 - Induce misreading of mRNA
 - Promote polysome instability

Mechanism of action

- Aminoglycosides
 - Are rapidly bactericidal
 - Post-antibiotic effect
- Penetration through the outer bacterial membrane
 - Outer membrane disruption
 - Diffusion through outer membrane porins.



Mechanism of action (cont'd)

- Transport across the cytoplasmic membrane depends on electron transport
 - Requirement for a membrane electrical potential (interior negative) to drive permeation
 - Rate-limiting & can be blocked or inhibited by divalent cations (e.g., Ca^{2+} & Mg^{2+}), hyperosmolarity, a reduction in pH & anaerobic conditions.
 - Antimicrobial activity reduced in the anaerobic environment of an abscess

Mechanism of action (cont'd)

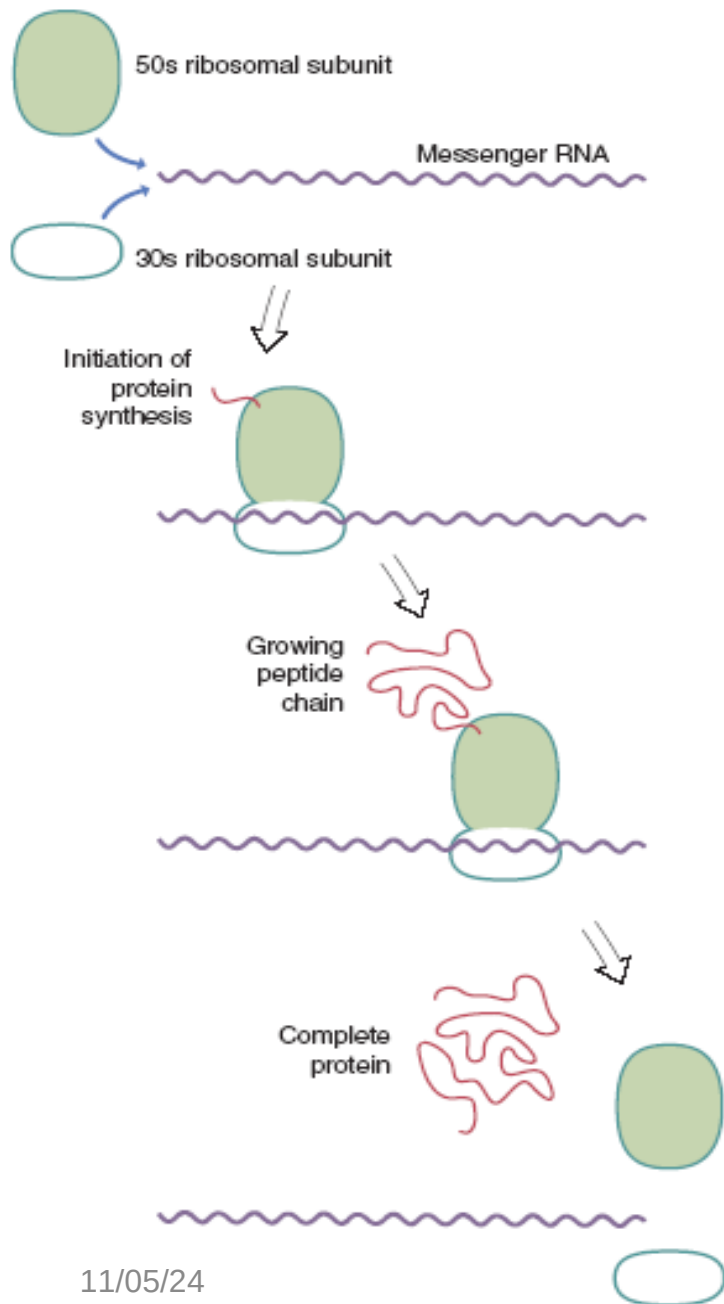
➤ Inside the cell

- Aminoglycosides bind to ribosomes and interfere with protein synthesis
 - ✓ misreading and premature termination of mRNA translation
- Hence, aberrant proteins produced and may be inserted into the cell membrane, leading to altered permeability

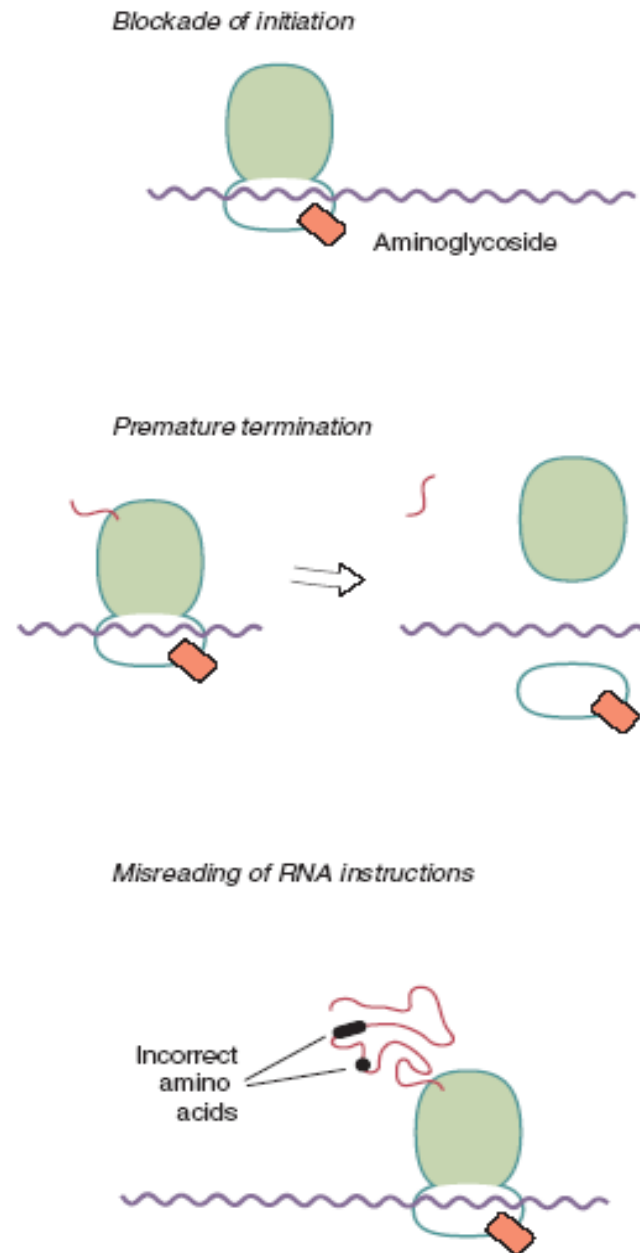
➤ Bind to 30S ribosomal subunit and disrupt the normal cycle of ribosomal function by interfering.

- With the initiation of protein synthesis
- Misreading of the mRNA template
- Incorporation of incorrect amino acids into growing polypeptide chains

A Normal Protein Synthesis



B Effects of Aminoglycosides



Mechanism of Resistance

Resistance could be due to

1. Inactivation of the drug by microbial enzymes
 - ✓ Aminoglycoside-modifying enzymes phosphorylate, adenylate, or acetylate specific hydroxyl or amino groups
 - ✓ The metabolites may compete with the parent drug for transport across the inner membrane, but are incapable of binding to ribosomes
2. Alteration of drug target site /low affinity of the drug for the bacterial ribosome
3. Altered drug transport /failure to penetrate intracellularly

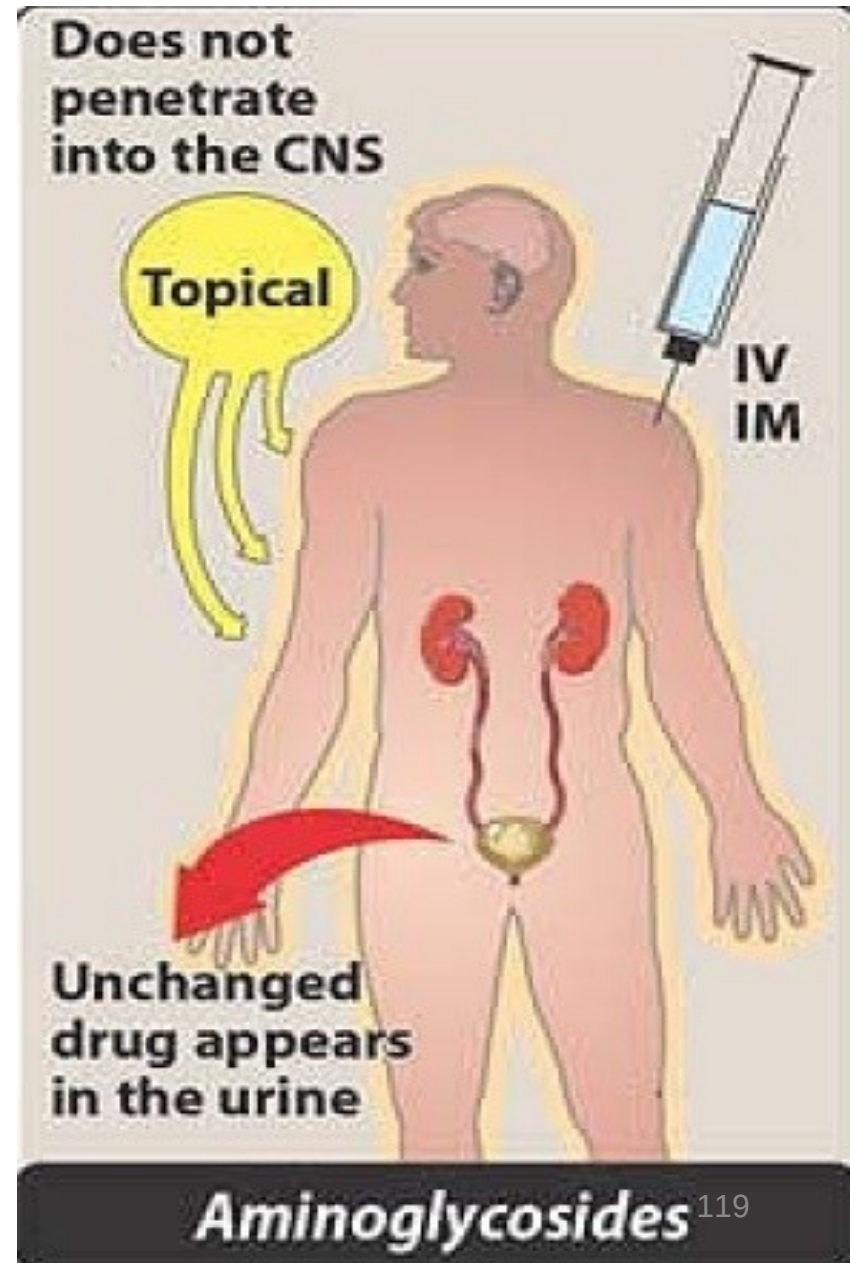
Antibacterial Spectrum

- Primarily active against aerobic gram (-) bacilli
- Little activity against anaerobic microorganisms or facultative bacteria under anaerobic conditions.
- Limited action against most gram (+) bacteria
 - Produce synergistic bactericidal effect *in vitro* (against enterococci, streptococci & staphylococci) when combined with a cell wall-active agent

Pharmacokinetics

➤ Absorption

- Very poorly absorbed from GIT.
- Absorbed rapidly from i.m. sites of injection.
 - ✓ In critically ill patients, especially those in shock, absorption of drug may be reduced from intramuscular sites because of poor perfusion



Pharmacokinetics

Distribution

- Do not penetrate into most cells & has negligible plasma albumin binding (except for streptomycin)
- $V_d \cong$ the volume of extracellular fluid
- High concentrations are found in renal cortex and inner ear (likely contributor to the nephrotoxicity & ototoxicity)
- Streptomycin and tobramycin can cause hearing loss in children born to women who receive the drug during pregnancy.
 - ✓ Recommendation: use with caution during pregnancy and only for strong clinical indications in the absence of suitable alternatives.

Elimination

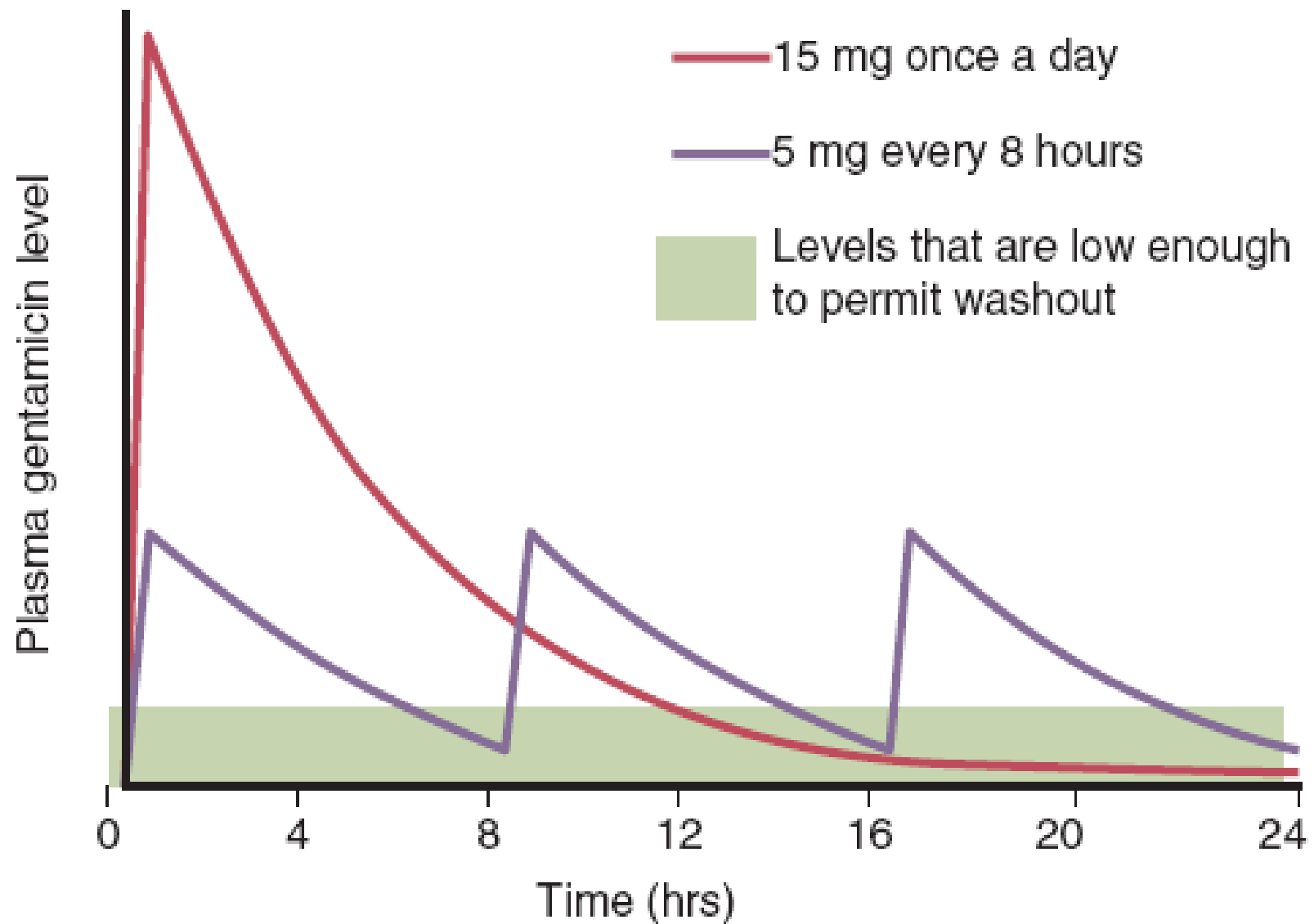
- The aminoglycosides are excreted almost entirely by glomerular filtration,

Dosing

- Total daily dose as a single injection or 2-3 equally divided doses (traditional)
- Numerous clinical studies demonstrate that a single daily dose of aminoglycoside is just as effective &/no more (& often less) toxic than multiple smaller doses.

(Total daily dose as a single injection is associated with less toxicity & is just as effective as multiple-dose regimens)

- ✓ More drug accumulates with higher plasma concentrations



Specific Indications for antimicrobials

<i>Pathogens</i>	<i>Aminoglycoside</i>
<i>Aerobic G-ve bacilli</i> <i>Klebsella species</i> <i>p. aeruginosa</i> <i>Francisella tuberculosis</i> <i>Brucella abortus</i> <i>Yersinia pestis</i> <i>Serratia marcesceus</i>	<i>A, G, NT</i> <i>T</i> <i>St, G</i> <i>St, G</i> <i>St, G</i> <i>G</i>
<i>Aerobic G+ve cocci</i> <i>Streptococci viridans</i> <i>Staphylococcus aureus</i> <i>Enterococcus faecalis</i>	<i>G</i> <i>G</i> <i>G</i>
<i>Others</i> <i>M. avium</i> <i>M. tuberculosis</i>	<i>A</i> <i>St</i>

BACTERIOCIDAL...

- **Adverse Effects of Aminoglycosides**
 - 1) Ototoxicity
 - a) Cochlear toxicity: tinnitus, high frequency hearing loss
 - Neomycin, kanamycin, amikacin,
 - b) Vestibular toxicity: vertigo, ataxia, loss of balance
 - Streptomycin and Gentamicin
- ♣ **Toxicity can be minimized by:**
 - Short duration of therapy
 - Periodic assessments of renal function
 - Avoiding concurrent use of ototoxic drugs

BACTERIOCIDAL...

2) Nephrotoxicity

- a) Injure cells of proximal renal tubules
- b) Acute tubular necrosis and prominent symptoms include: Proteinuria, production of dilute urine, elevation of creatinine
- c) Risk factors: older pts, renal disease, large doses, frequent dosing interval, Concomitant drugs[vancomycin, frusemide, clindamycin, piperacillin, cephalothin, foscarnet]

BACTERIOCIDAL...

3) Rarely neuromuscular blockade

- weakness of respiratory musculature
- flaccid paralysis, dilated pupil
- Risk is amplified in pts with tubocurarine, succinylcholine
- Aminoglycosides prevent internalization of Ca^{2+} in presynaptic axon $\Rightarrow$ decrease release of acetylcholine

BACTERIOSTATIC INHIBITORS OF PROTEIN SYNTHESIS

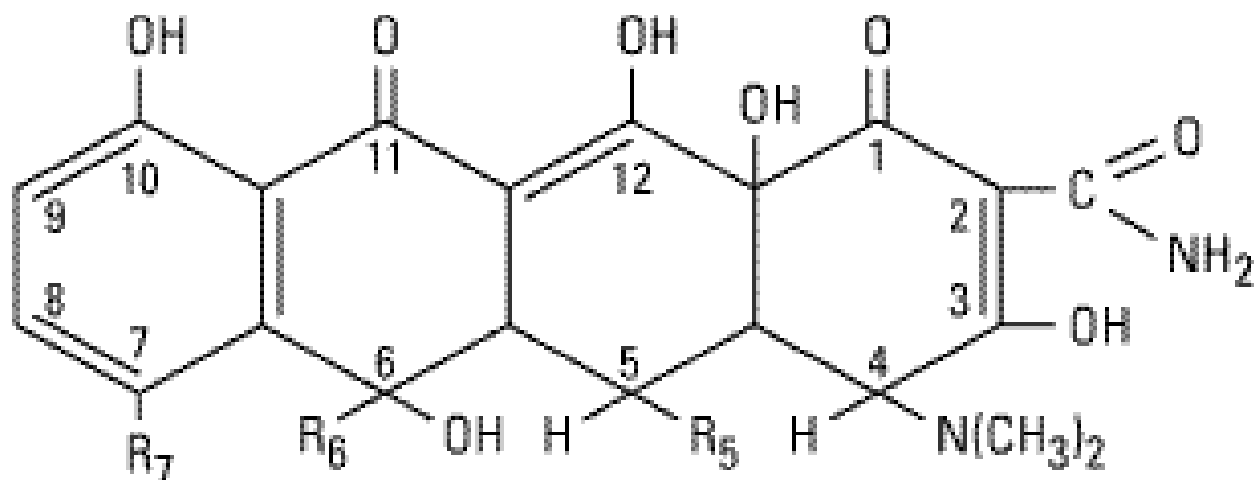
- **Tetracyclines**
- **Macrolides**
- **Lincosamides**
- **Chloramphenicol**
- **Spectinomycin**

BACTERIOstatic...

Tetracycline (TTC)

- Produced by different species of *Streptomyces*
 - OxyTTC is a natural product elaborated by *Streptomyces rimosus*
 - TTC is a semisynthetic derivative of chlorTTC
 - Demeclocycline is the product of a mutant strain of *Strep. Aureofaciens*
 - Methacycline, doxycycline, and minocycline are semisynthetic derivatives.
- Chlortetracycline, the prototype of the class, was introduced in 1948

BACTERIOstatic...



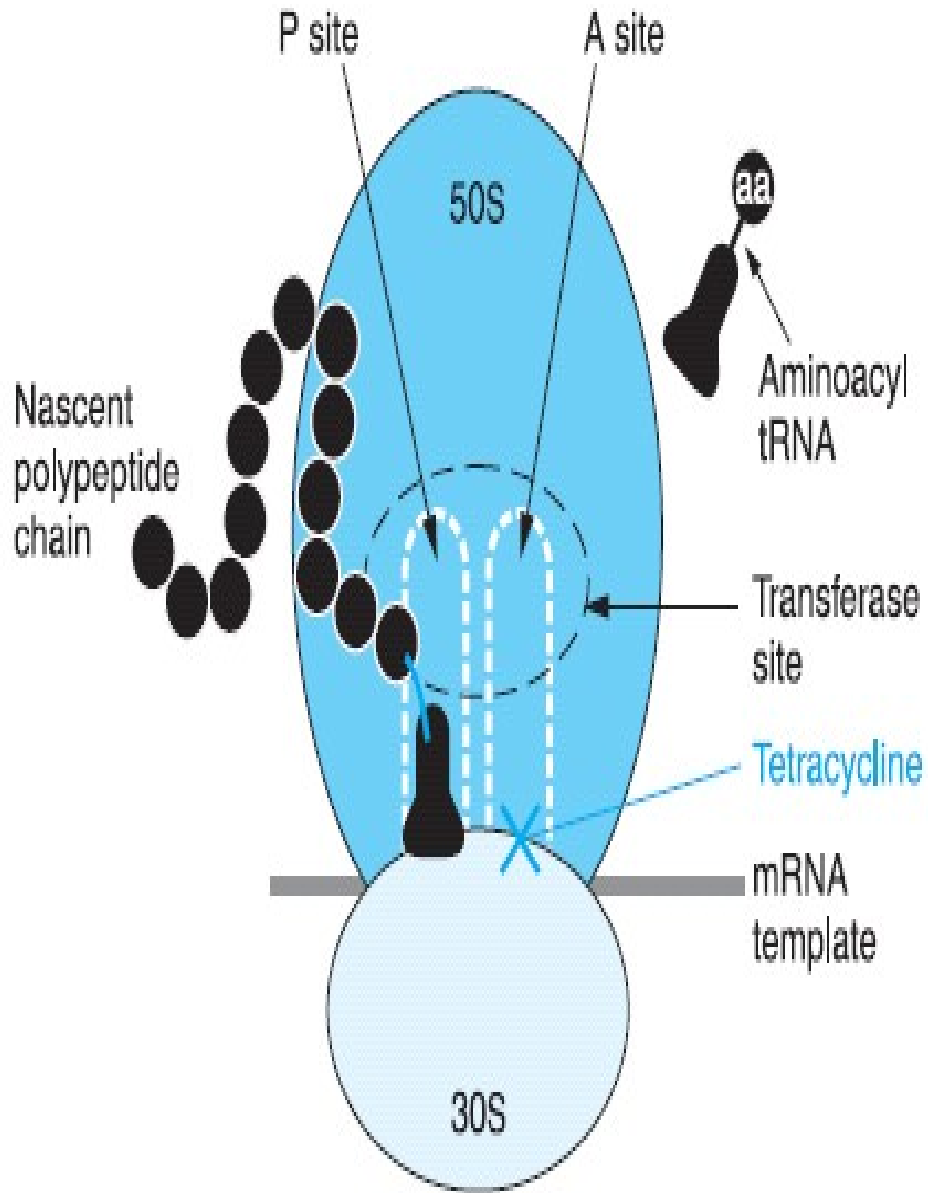
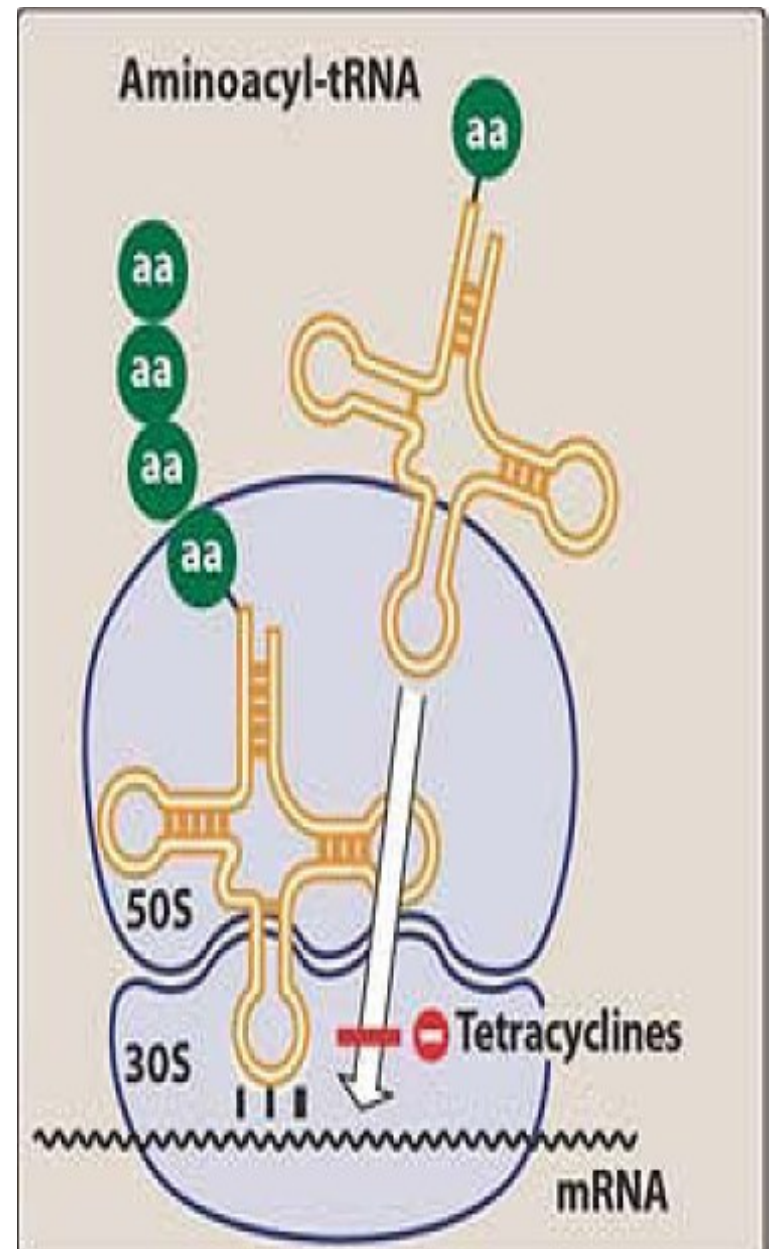
	R ₇	R ₆	R ₅	Renal Clearance (mL/min)
Chlortetracycline	— Cl	— CH ₃	— H	35
Oxytetracycline	— H	— CH ₃	— OH	90
Tetracycline	— H	— CH ₃	— H	65
Demeclocycline	— Cl	— H	— H	35
Methacycline	— H	≡ CH ₂ *	— OH	31
Doxycycline	— H	— CH ₃ *	— OH	16
Minocycline	— N(CH ₃) ₂	— H	— H	10

*There is no — OH at position 6 on methacycline and doxycycline.

BACTERIOstatic...

TETRACYCLINES

- G+ve & G-ve aerobic & anerobic bacteria
- Spirochetes, Mycoplasma, Rickettsia, Chlamydia & some protozoa
- Includes: Oxytetracycline, Tetracycline, Demelocycline, Doxycycline, Minocycline
- **Mechanism:**
 - Enter microorganism by passive & active transport



BACTERIOstatic...

- Act by binding 30s ribosome ⇒
block aminoacyl-tRNA to acceptor
site on mRNA ribosome complex⇒
prevent addition of aminoacid to
growing peptide

Resistance to the Tetracyclines

➤ The main resistance mechanisms

1. Decreased accumulation of tetracycline as a result of either decreased antibiotic influx or acquisition of an energy-dependent efflux pathway;
2. Production of a ribosomal protection protein that displaces tetracycline from its target
3. Enzymatic inactivation of tetracyclines

Pharmacokinetics

<i>Class</i>	<i>Drug</i>	<i>Lipid solubility</i>	<i>% p. o. absorbed</i>	<i>Effect of food on absorption</i>	<i>elimination</i>
<i>Short acting</i>	<u><i>TTC</i></u>	<i>Low</i>	<i>76</i>	↓	<i>Renal</i>
	<i>OxyTTC</i>	<i>Low</i>	<i>58</i>	↓	<i>Renal</i>
<i>Intermediate</i>	<i>Demeclocycline</i>	<i>Moderate</i>	<i>66</i>	↓	<i>Renal</i>
<i>Long acting</i>	<u><i>Doxycycline</i></u>	<i>High</i>	<i>93</i>	<i>No change</i>	<i>Hepatic</i>
	<i>Minocycline</i>	<i>High</i>	<i>95</i>	<i>No change</i>	<i>Hepatic</i>

Pharmacokinetics

➤ Absorption

- Partially absorbed from the stomach and upper GIT
- Impaired by Food (*all except doxycycline and minocycline*)
- *TTCs form insoluble chelates with calcium, magnesium, and other metal ions* ⇒ interfere with absorption

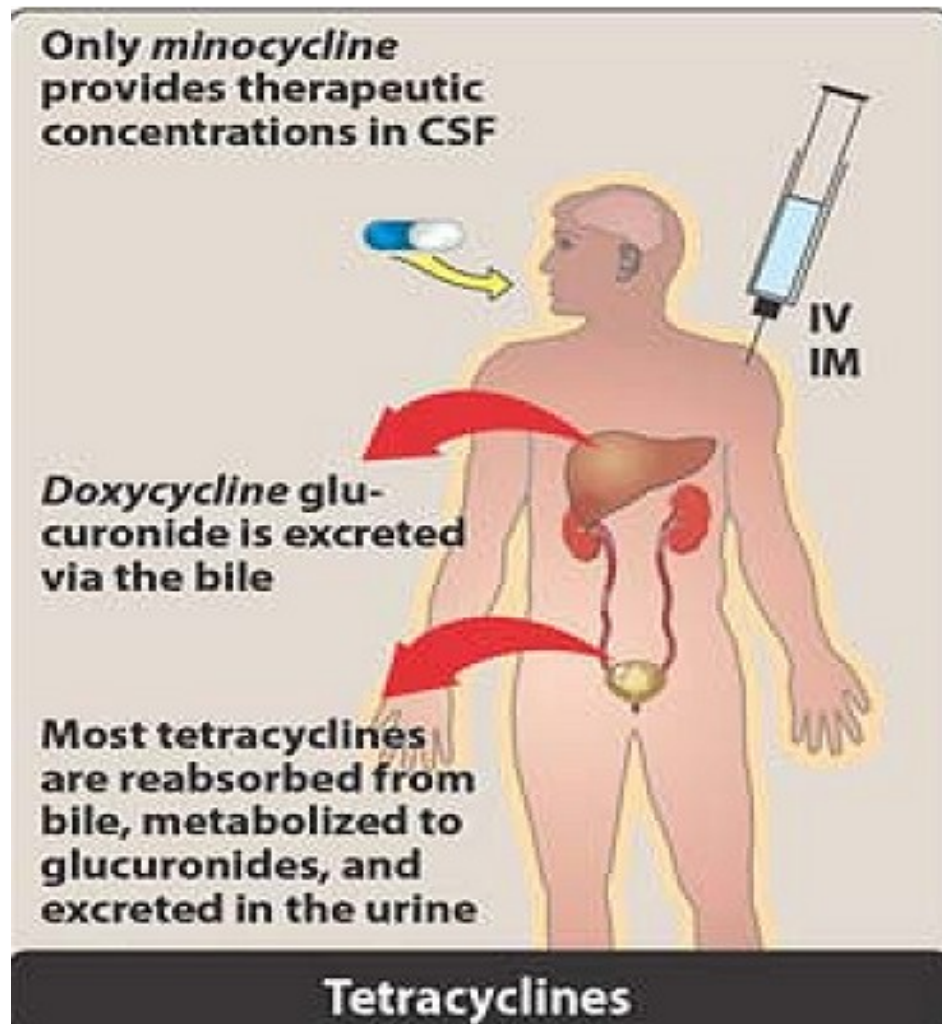
➤ Distribution

- Distributed throughout body tissues and fluids
 - ✓ Minocycline and doxycycline (highest lipid solubility), oxyTTC (the least)

➤ Elimination

- TTCs are excreted mainly in bile and urine
- Ten to 50 % of various TTCs is excreted into the urine.
- Doxycycline is eliminated by nonrenal mechanisms ⇒ TTC of choice in renal insufficiency.

Cont...



<i>Major Indications</i>	<i>Effective alternative</i>
<i>1. Chlamydial Infections</i>	<i>- Acne, severe</i>
<i>Lymphogranuloma venereum</i>	<i>- M. pneumoniae</i>
<i>Conjunctivitis</i>	<i>- Nocardia</i>
<i>Trachoma</i>	<i>- Rat-bite fever</i>
<i>Acute epididymitis</i>	<i>- Syphilis</i>
<i>2. Rickettsial infections</i>	<i>- Amebiasis</i>
<i>Typhus fever</i>	<i>- P. falciparum</i>
<i>Rocky mountain spotted fever</i>	<i>- Meningococcal disease</i>
<i>3. Other infections</i> }	<i>Prevention [minocycline]</i>
<i>Plague</i> }	<i>- Oral bowel preparations for</i>
<i>Tularemia In combination with aminglyco.</i>	<i>Intestinal surgery</i>
<i>Brucellosis</i>	<i>[TTC+ Neomycin]</i>
<i>Relapsing fever</i>	<i>- tXt of inappropriate secretion</i>
<i>Cholera</i>	<i>Of ADH [Demeclocycline]</i>
<i>Urethritis</i>	

Typical therapeutic applications of tetracyclines.

CHLAMYDIAL INFECTIONS

- Chlamydia trachomatis is the major cause of sexually transmitted disease in the United States. It causes nongonococcal urethritis, pelvic inflammatory disease, and lymphogranuloma venereum.
- Chlamydia psittaci causes psittacosis, which usually takes the form of pneumonia. Other clinical forms include hepatitis, myocarditis, and coma.
- Doxycycline or azithromycin is used to treat chlamydial infections.

ROCKY MOUNTAIN SPOTTED FEVER

- This disease, caused by Rickettsia rickettsii, is characterized by fever, chills, and aches in bones and joints.
- Response to tetracyclines is prompt if the drug is started early in the disease process.

MYCOPLASMA PNEUMONIA

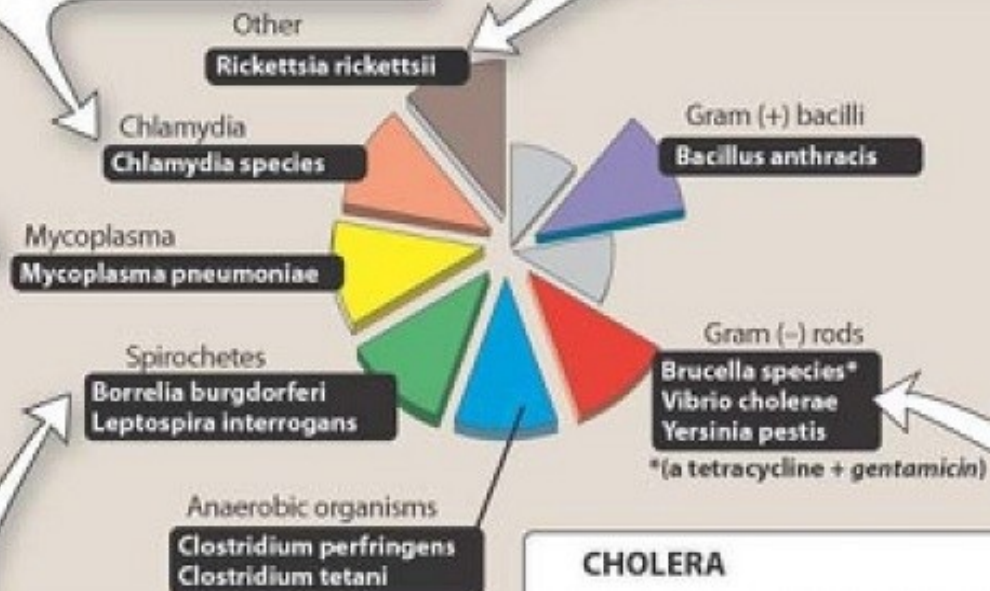
- Mycoplasma pneumoniae is a common cause of pneumonia in young adults and in people who live in close confines, such as in military camps.
- Treatment leads to a shorter duration of fever, cough, and malaise.
- Treatment with macrolides is also effective.

LYME DISEASE

- This is a spirochetal infection caused by Borrelia burgdorferi. The disease is transmitted by the bite of infected ticks.
- Infection results in skin lesions, headache, and fever, followed by meningoencephalitis and, eventually, arthritis.
- A single, 200-mg dose of doxycycline, given within 72 hours after a tick bite, can prevent development of the disease.

CHOLERA

- Cholera is caused by Vibrio cholerae ingested as part of fecally contaminated food or water.
- The organism multiplies in the gastrointestinal tract, where it secretes an enterotoxin that produces diarrhea.
- Treatment includes doxycycline, which reduces the number of intestinal vibrios, and fluid replacement.



Therapeutic Uses

- ***Rickettsial Infections***
 - Doxycycline is the drug of choice
- ***Mycoplasma Infections***
- ***Chlamydial infections***
- ***Trachoma***
- ***Sexually Transmitted Diseases***
 - Because of resistance, doxycycline no longer is recommended for gonococcal infections
- ***Anthrax***
 - Doxycycline: for prevention or treatment of anthrax

Therapeutic Uses (cont'd)

➤ ***Bacillary Infections***

- Brucellosis
 - ✓ Tetracyclines in combination with rifampin or streptomycin
- Tularemia
 - ✓ TTCs are effective, though streptomycin is preferable
- Cholera
 - ✓ Doxycycline

➤ ***Other Bacillary Infections***

- Ineffective in infections caused by *Shigella*, *Salmonella*, or other Enterobacteriaceae

Therapeutic Uses (cont'd)

➤ *Coccal Infections*

- Resistance restricts their use in staphylococcal, streptococcal, or meningococcal infections.
- Community strains of MRSA often are susceptible to TTC, doxycycline, or minocycline
- Doxycycline effective for empirical therapy of community-acquired pneumonia

➤ Are generally drugs of choice in infections with *Mycoplasma pneumoniae*, *chlamydiae*, *rickettsiae*, and some spirochetes

➤ Are sometimes employed in the treatment of protozoal infections (*Entamoeba histolytica*, *Plasmodium falciparum*)

Adverse effects

❖ Gastrointestinal Adverse Effects

- NVD

- Administration of food with doxycycline or minocycline ameliorate some of the symptoms

- Normal flora alteration

❖ Effect on bone & teeth

- Deposition in calcium deposited in newly formed bone or teeth

- Yellow or brown discoloration of teeth

- Suppression of long bone growth in infants

- ✓ Doxycycline bind less with Ca^{2+} $\Rightarrow$ less frequent dental changes

Adverse effects (cont'd)

- Liver Toxicity
 - Especially during pregnancy
- Kidney Toxicity
 - Aggravate azotemia in patients with renal disease
- Photosensitization
- Vestibular Reactions
 - Dizziness, vertigo, nausea, and vomiting

C/Is

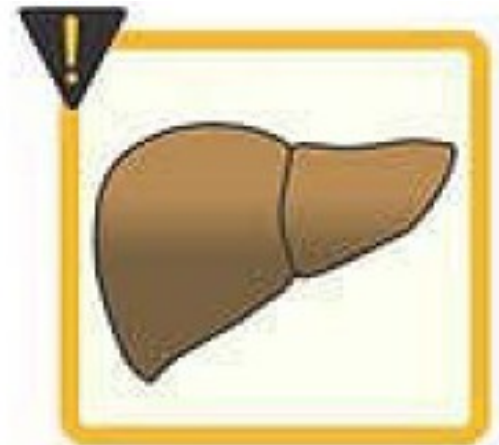
- In pregnant women
- Children under the age of 8 years



GI disturbance



Deposition of
drug in bones
and teeth



Liver failure



Phototoxiciv



Vertigo



Avoid in pregnancy

Macrolide antibiotic

- erythromycin, *telithromycin*, *azithromycin*, *clarithromycin*
- ERYTHROMYCIN
 - few indications where it is a drug of first choice,
 - mostly as an alternative to penicillin in allergy to beta-lactam ATBs.
- binding irreversibly to a 50S subunit of the bacterial ribosome - inhibition of the translocation step of protein synthesis - bacteriostatic

Macrolide antibiotic

- ERY
 - as PNC G - especially G + bacteria and spirochaetes, N.gonorrhoeae
 - used in patients allergic to the PNCs
 - intracellular - Chlamydia, Mycoplasma, Legionella, Corynebacterium diphtherie
 - Antistaphylococcal antibiotic – not MRSA
- Clarithromycin:
 - similar to erythromycin, but it is also effective against Haemophilus influenzae.
 - higher activity than ERY against intracellular pathogens (e.g., Chlamydia, Legionella, Moraxella, Urea plasma species) and Helicobacter pylori
- Azithromycin:
 - Less active against streptococci and staphylococci than erythromycin;
 - more active against respiratory infections due to H. influenzae and Moraxella catarrhalis.
 - The preferred therapy for urethritis caused by Chlamydia trachomatis.
- Telithromycin:
 - spectrum similar to azithromycin, less vulnerable to resistance

Macrolide antibiotic

- Resistance to erythromycin - a serious clinical problem.
 - Most strains of staphylococci in hospital isolates are resistant to this drug.
- Several mechanisms:
 - the inability of the organism to take up ATB or the presence of an efflux pump (it limits the amount of intracellular drug);
 - a decreased affinity of the 50S ribosomal subunit for ATB;
 - plasmid-associated erythromycin esterase.
- Clarithromycin and azithromycin show cross-resistance with erythromycin,
 - telithromycin can be effective against macrolide-resistant organisms.
- Food interferes with absorption of Erythro and Azithromycin but can increase that of clarithromycin.

Macrolide antibiotic

- Metabolism:
 - are extensively metabolized with exception of AZI.
 - inhibit the oxidation of CYP-450 system.
- Excretion:
 - Erythromycin and azithromycin
 - concentrated and excreted in an active form in the bile. Partial reabsorption occurs via enterohepatic circulation.
 - Inactive metabolites are excreted into the urine.
 - clarithromycin and its metabolites
 - are eliminated by the kidney as well as the liver (adjust dosage in compromised renal function!).

ADR

- Epigastric distress:
 - common - it can lead to poor compliance for erythromycin.
 - Clarithromycin and azithromycin - better tolerated by the patient, but GIT problems are also most common side effects.
- Cholestatic jaundice:
 - especially with the estolate form of erythromycin, presumably as the result of a hypersensitivity reaction
 - the lauryl salt of the propionyl ester of erythromycin
- Ototoxicity:
 - Transient deafness - erythromycin, especially at high dosages.
- Telithromycin – hepatotoxicity, prolongation of QTc interval, may worsen myasthenia gravis

Macrolide antibiotic - interactions

- Erythromycin, telithromycin, and clarithromycin inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulations of these compounds.
- E.g., theophylline, warfarin, carbamazepine, cyclosporine and statins
- Interaction with digoxin may occur in some patients - ATB eliminates a species of intestinal flora that ordinarily inactivates digoxin
 - greater reabsorption and lower secretion

linezolid

- New ATB; against resistant G+ organisms
 - (e.g., methicillin- and vancomycin-resistant *S. aureus*, vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis*, and PNC-resistant streptococci).
- Bacteriostatic - Inhibits of bacterial protein synthesis
 - binding to the P site of the 50S ribosomal subunit
 - block the formation of the 70S initiation complex

Antibacterial spectrum

- Primarily against G+ organisms
 - e.g., staphylococci, streptococci, and enterococci, as well as *Corynebacterium* species and *Listeria monocytogenes*) - its main clinical use.
 - Moderately active against *Mycobacterium tuberculosis*.
- Bacteriostatic (cidal against the streptococci and *Clostridium perfringens*).

Pharmacokinetics

- Completely absorbed on oral administration. I.v. is also available.
- Widely distributed in the body.
- CYP450 enzymes are not involved in their formation.
- Excretion - both by renal and nonrenal routes.

Chloramphenicol

- Broad-spectrum
 - wide range of G+ and gram- organisms;
 - also some intracellular - e.g. rickettsiae.
 - P. aeruginosa is not affected, nor are the chlamydiae.
 - Excellent activity against anaerobes.
- use is restricted to life-threatening infections
 - because of its toxicity –
- mostly bacteriostatic
 - depending on the organism.
 - bactericidal - to H. influenzae
- bacterial 50S ribosomal subunit
 - inhibit protein synthesis at the peptidyl transferase reaction.
 - Toxicity? - similarity of mammalian mitochondrial ribosomes to those of bacteria,
 - protein synthesis in these organelles may be inhibited at high circulating chloramphenicol levels - producing bone marrow toxicity!!

Chloramphenicol - ADR

- Hemolytic anemia
 - in patients with low levels of glucose 6-phosphate dehydrogenase.
- Reversible anemia
 - (is dose-related and occurs concomitantly with therapy) and
- Aplastic anemia (pancytopenia),
 - idiosyncratic and usually fatal !!!
 - is independent of dose and may occur after therapy has ceased !!!
- Potential teratogenic effects
- GIT
 - Dysmicrobia, GIT disturbances, diarrhea, hypovitaminosis B and K
- Gray baby syndrome:
 - in neonates if the dosage is not properly adjusted
 - Low capacity to glucuronate chloramphenicol
 - drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes
 - Adults who have received very high doses – may also exhibit this toxicity.
- Interactions
 - inhibits some hepatic P450 and blocks the metabolism of drugs (warfarin, phenytoin, tolbutamide).

Clindamycin

- mechanism as macrolides
 - antagonism when co-administered.
- infections caused by anaerobic bacteria (e.g. Bacteroides fragilis). Also active against non-enterococcal, gram-positive cocci.
 - Note: Clostridium difficile is resistant to clindamycin.
- orally (well absorbed) or parenterally.
 - Distributes well into all body fluids except the CSF.
- Penetration into bone occurs even in the absence of inflammation.
- It undergoes extensive oxidative metabolism (to inactive products),
 - excreted into the bile or urine by glomerular filtration.
 - Therapeutic levels of the drug are not achieved in the urine.
- Accumulation
 - in patients with either severely compromised renal function or hepatic failure.

ADR:

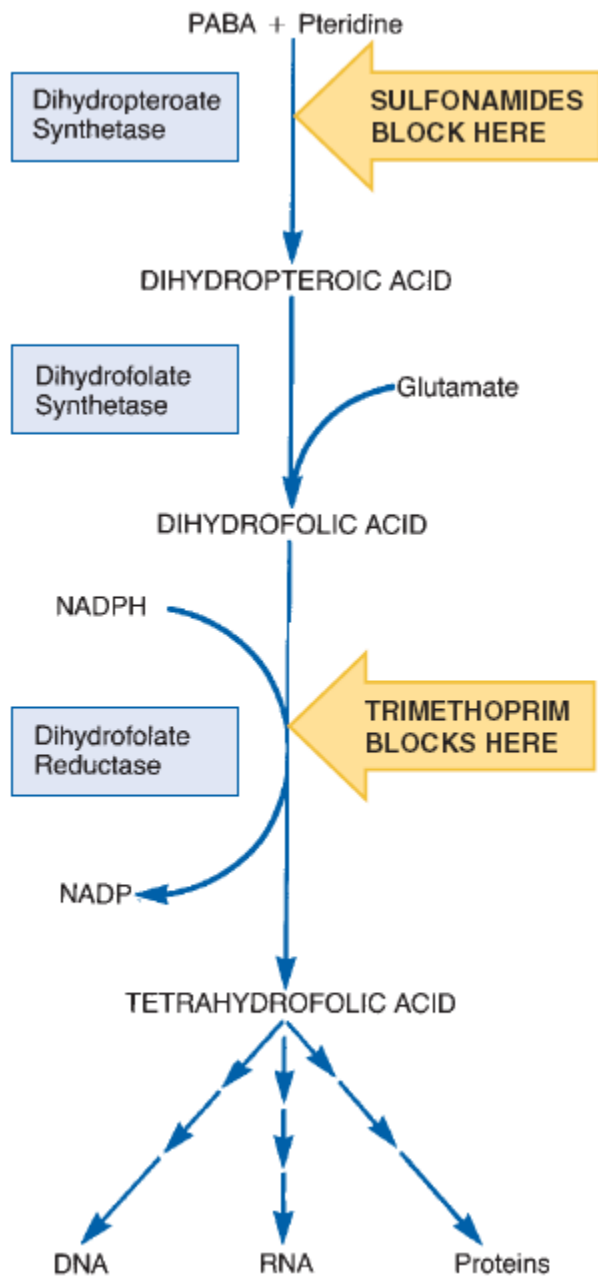
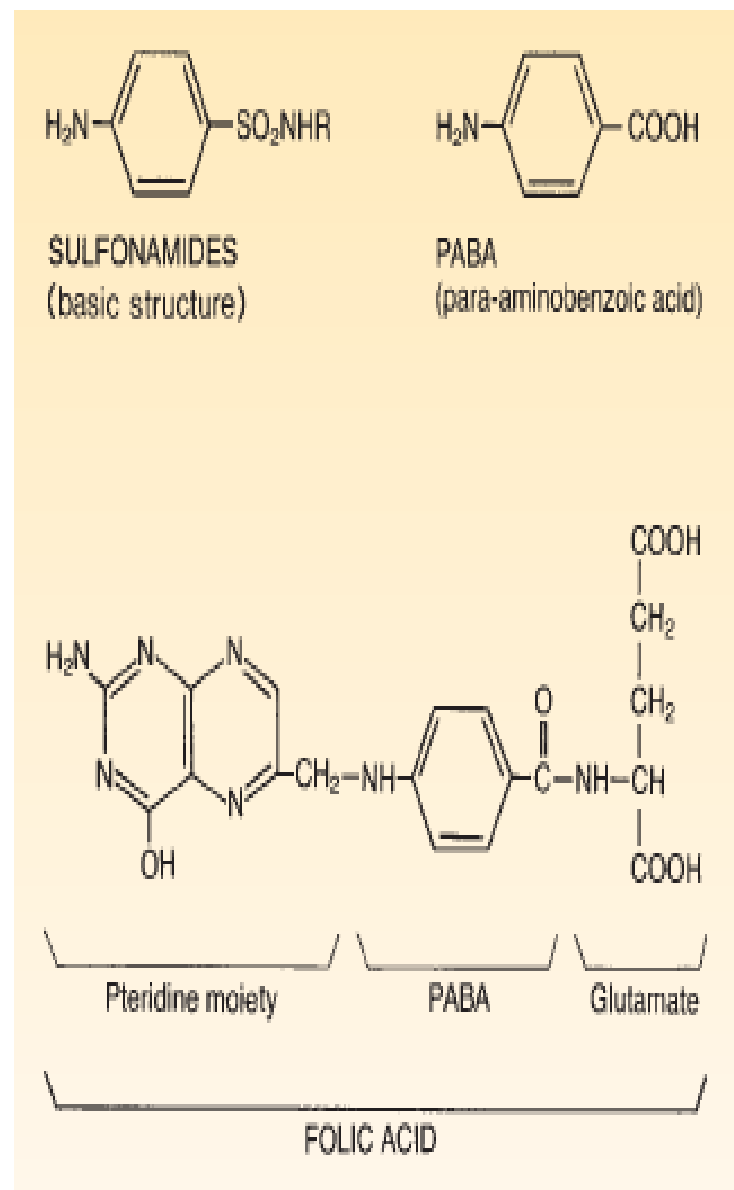
the most serious adverse effect is potentially fatal pseudomembranous colitis !! (caused by overgrowth of Clostridium difficile) - vancomycin

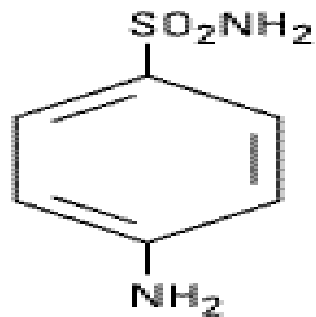
SULPHONAMIDES & TRIMETHOPRIM

Lesson objectives;

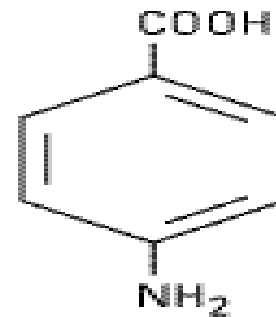
- **list clinically useful sulphonamides**
- **Explain the mechanism of action of sulphonamides and trimethoprim**
- **Describe the mechanism of resistance**
- **List common adverse effects**

- **Sulphonamides;**
 - First antimicrobial drugs w/c paved the way for antibiotic revolution in medicine.
 - Mechanism: Inhibit bacterial growth by interfering with microbial folic acid synthesis
 - Inhibit competitively incorporation of PABA into tetrahydropteroate
 - act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS)
 - As such, microorganisms will be "starved" of folate and die.
 - *Mammalian cells require preformed folic acid and are not affected by sulfonamides.*

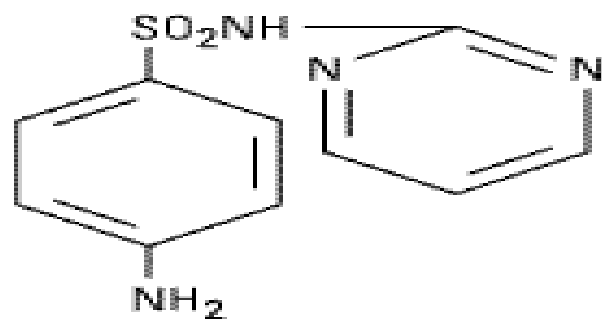




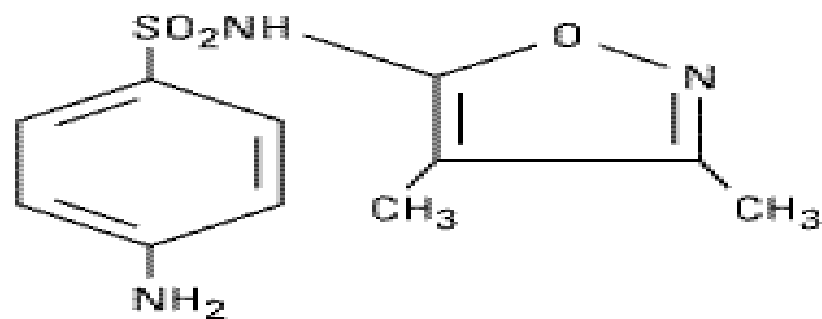
Sulfanilamide



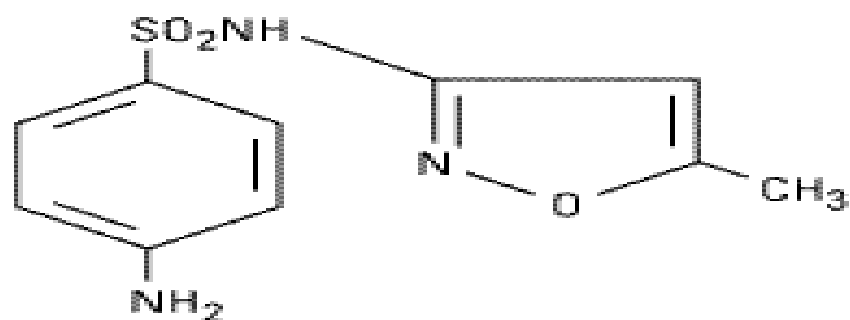
***p*-Aminobenzoic acid (PABA)**



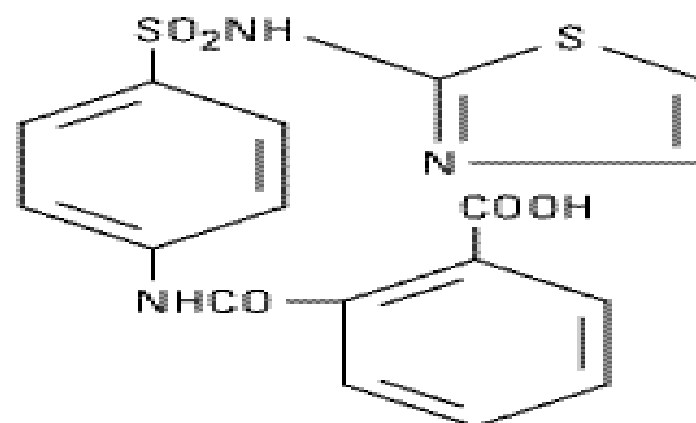
Sulfadiazine



Sulfisoxazole



Sulfamethoxazole



**Sulfathalidine
(phthalylsulfathiazole)**

SULPHONAMIDES...

– Microbial resistance

- Synthesis of PABA in amounts sufficient to overcome sulphonamide mediated inhibition
- Dehydropetroate synthetase $\Rightarrow$ $\downarrow$ affinity to sulphonamide
- $\downarrow$ Sulphonamide uptake

– Classification of sulphonamides

- systemic sulphonamides
 - short acting agents: sulfisoxazole & sulfadiazine.
 - Intermediate acting: sulphamethoxazole
 - Long acting : sulphadiazine

SULPHONAMIDES...

- Sulphonamide limited to GIT
 - » Succinylsulfathiazole & sulfasalazine
- Topical sulphonamide:
 - » Mafenide acetate
 - » Silver sulfadiazine
 - » Sulfacetamide

Therapeutic uses

- Declined due to introduction of cidal antibiotic with lower toxicity & development of resistance
 - 1) UTI [Sulfisoxazole: high solubility, achieve effective concentration & less expensive]

SULPHONAMIDES...

2) Other uses

- a) Nocardiasis-infection of the lung or the whole body
- b) Trachoma [sulfacetamide]
- c) Sulphadiazine / sulphadoxine + pyrimethamine: to treat toxoplasmosis & malaria
- d) Ulcerative colitis: sulfasalazine

Adverse effects

- 1) hypersensitivity reactions
 - a) Mild [rash, fever, photosensitivity]
 - b) Severe [Stevens-Johnson syndrome: lesion of skin & mucus membrane, fever, malaise & toxemia]



When used in large doses, they may cause a strong allergic reaction such as [Stevens–Johnson syndrome](#)

SULPHONAMIDES...

- 2) Haematologic effect
 - a) Hemolytic anemia [Glucose 6 phosphate dehydrogenase deficiency]
 - b) Agranulocytosis: leucopenia & thrombocytopenia
- 3) Kernicterus: by displacing bilirubin from plasma protein⇒ crosses the BBB; Not given in <2 Months age
- 4) Renal damage from crystalurea- In acid urine, older sulfonamides are insoluble and crystalluria may result.

SULPHONAMIDES...

- **COTRIMOXAZOLE**

- Trimethoprim + sulphamethoxazole
- Shows synergism
- Selected because of similarity in pharmacokinetics

Mechanism: Inhibition of two sequential steps

- *Trimethoprim is a highly selective inhibitor of dihydrofolate reductase of lower organisms; ~100,000 times more drug is required to inhibit human reductase.*
- *This relative selectivity is vital because the enzyme is essential to all species.*

ANTIBACTERIAL SPECTRUM

- *Spectrum of trimethoprim resembles that of sulfamethoxazole.*
- *Most gram-negative and gram-positive microorganisms are sensitive to trimethoprim.*

Efficacy of Trimethoprim–Sulfamethoxazole in Combination

- *A synergistic interaction between these drugs is apparent even when microorganisms are resistant to sulfonamide,*
- *But maximal synergism occurs when microorganisms are sensitive to both drugs.*

SULPHONAMIDES...

Therapeutic Uses

- a) UTI: Caused by *E.coli*, *Klebsiella*, *Enterobacter*, PCP: t/t of choice
- b) Drug of choice for shigellosis
- c) **Other infections**
 - Acute otitis media & chronic bronchitis [*H. influenza*, *streptococcus pneumonia*]
 - Urethritis & pharyngitis due to penicillinase producing *N. gonorrhoe*
 - Alternative to CAF for typhoid fever

Pharmacokinetics

- TMP concentrates in the relatively acidic milieu of prostate & vaginal fluids $\Rightarrow$ effective
- Trimethoprim[1 part] & sulphamethoxazole [5 part]

-Tablet 100mg + 20mg (pediatric)

- 400+80mg , 800 + 160mg, 120mg /5ml suspension.
- Injection, 400mg+80mg/5ml

SULPHONAMIDES...

- **Adverse effects**
 - Dermatologic
 - GI: NV & stomatitis
 - Hematologic:
 - » megaloblastic anemia; Leukopenia; thrombocytopenia
 - HIV pts with PCP: drug induced fever, rashes, diarrhea

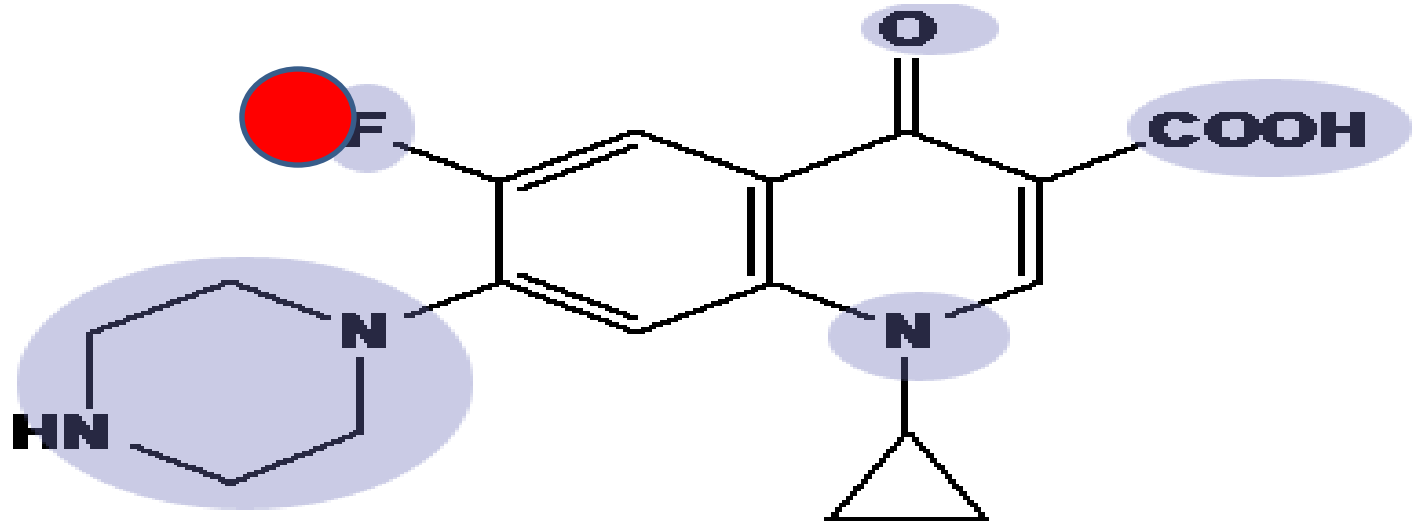
Quiz ;

Write your answer on a piece of paper;

- 1.What are the mechanism of action of sulphnamides
- 2.Write in short the mechanisms of resistance
- 3.Write three clinical applications of sulphonamides
- 4.Write three ADRs for sulphonamides

Quinolones and Fluoroquinolones

- Have Quinolone structure



- Nalidixic acid is first member

- Fluorination of Quinolones -

Fluoroquinolones

- Gram negative mainly (Plus gram positive New FQs)

- **DNA replication: conservative, semiconservative and dispersive**



Couple of
dancers gyrating.



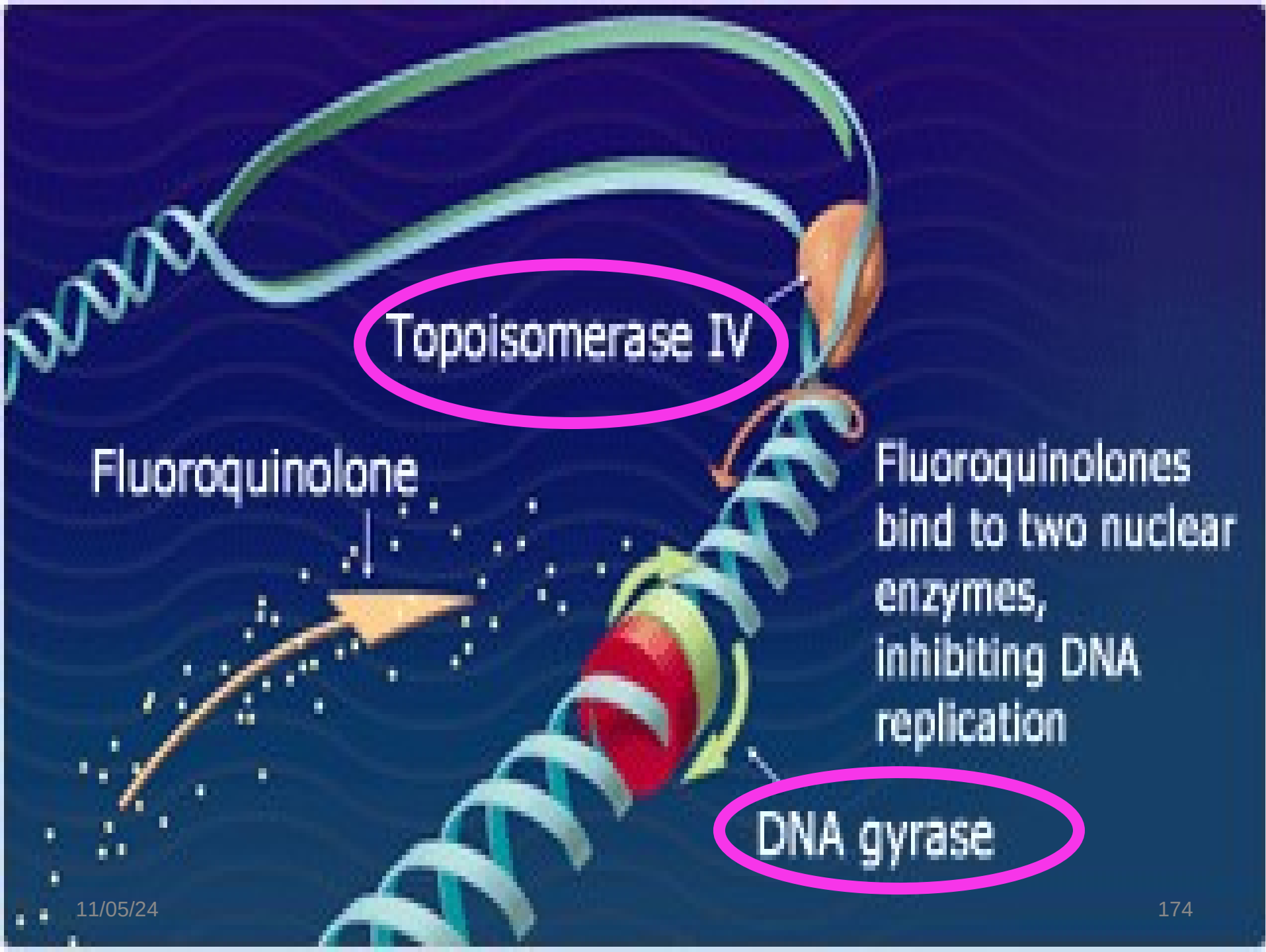
The Queen stops the
gyrating dancers.



"The DNA gyrase
was inhibited".

Quinolones

- MOA- (Queen stops gyrating dancers)
 - In gram negative –
 - ✓ Inhibition of DNA gyrase enzyme (Inhibit negative super coiling)
 - In gram positive –
 - ✓ Inhibition of Topoisomerase IV – Inhibition of nicking and separation of daughter DNA strands after DNA replication (Inhibition of Decatenation)
 - ✓ The malformed DNA is digested by Exonucleases
- Why not human cells affected ?
 - Mammalian cells have Topoisomerase II (serve as inhibiting positive



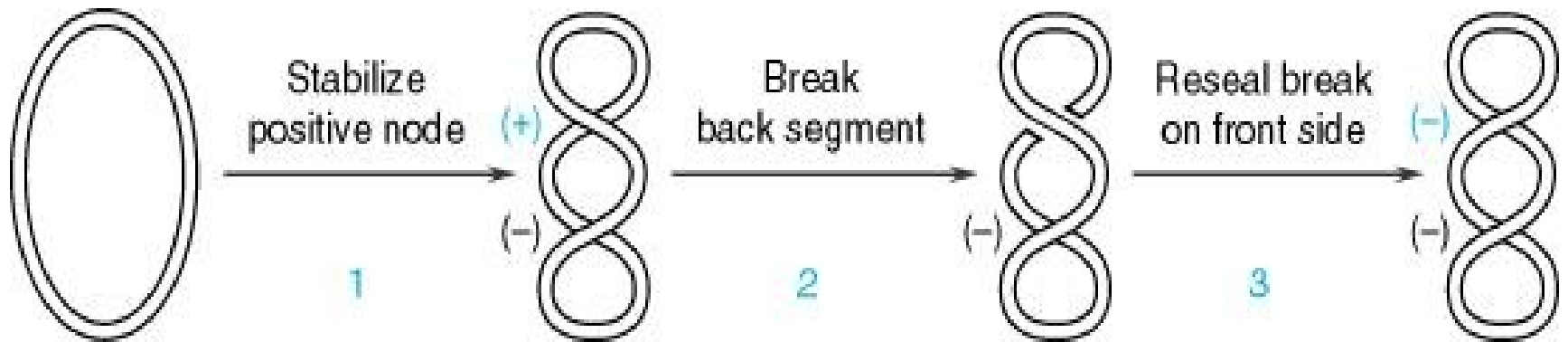
Topoisomerase IV

Fluoroquinolone

Fluoroquinolones
bind to two nuclear
enzymes,
inhibiting DNA
replication

DNA gyrase

- Double-helical DNA separation...."overwinding" (excessive +ve supercoiling) of the DNA in front of the point of separation
- DNA gyrase continuously introduce negative supercoils into DNA to overcome this mechanical obstacle
- Both strands of the DNA be cut to permit passage of a segment of DNA through the break, the break then is resealed



- Quinolones inhibit the nicking and closing activity of the gyrase and also block the decatenating activity of topoisomerase IV

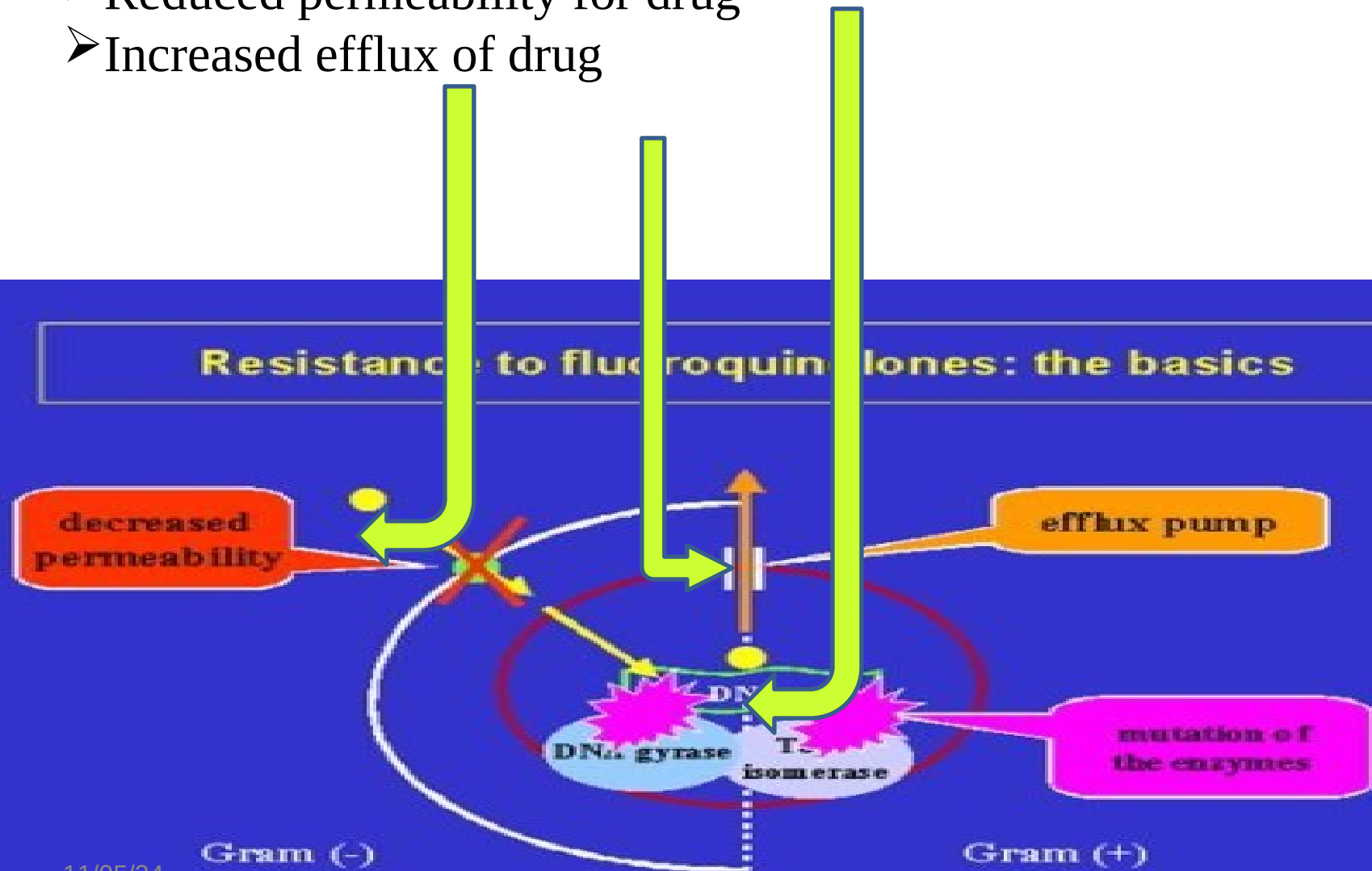
- The DNA gyrase of *E. coli* is composed of two A subunits and two B subunits
- The A subunits carry out the strand-cutting function of the gyrase (site of action of the quinolones)
- Mutations of the gene that encodes the A subunit polypeptide ... resistance
- Topoisomerase IV also is composed of four subunits in *E. coli*
- Topoisomerase IV separates interlinked (catenated) daughter DNA molecules that are the product of DNA replication
- Eukaryotic cells do not contain DNA gyrase

Antibacterial Spectrum of quinolones

- Fluoroquinolones are potent bactericidal agents against
 - *E. coli*, *Salmonella*, *Shigella*, *Enterobacter*, *Campylobacter*, *staphylococci*, *P. aeruginosa* and *Neisseria*
 - Streptococci (levofloxacin, gatifloxacin, moxifloxacin)
 - Intracellular bacteria such as *Chlamydia*, *Mycoplasma*, *Legionella*, *Brucella*, and *Mycobacterium* (including MTB)
 - Ciprofloxacin, ofloxacin and pefloxacin have MIC₉₀ values from 0.5 to 3 mg/ml for *M. fortuitum*, *M. kansasii*, and *M. tuberculosis*
 - Anaerobic bacteria (garenoxacin, Moxifloxacin, trovafloxacin and gemifloxacin)
- Fluoroquinolones are inactive against MRSA
- Ciprofloxacin is the most active agent of this group against G-ves, *P. aeruginosa* in particular

Resistance-

- Due to mutation in chromosomes
 - Altered DNA gyrase and Topoisomerase IV
 - Reduced permeability for drug
 - Increased efflux of drug



Quinolones (Narrow spectrum)

- Nalidixic acid
- Acrosoxacin
- Cinoxacin
- Flumequine
- Oxolinic acid
- Pipemidic acid
- Piromidic acid

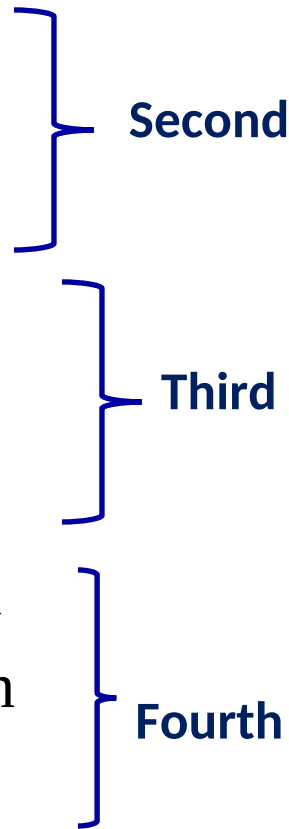
Fluoroquinolones
First Generation

- Ciprofloxacin
- Norfloxacin
- Pefloxacin
- Ofloxacin

Members

Fluoroquinolones
New Generations

- Lomefloxacin
- Levofloxacin
- Prulifoxacin
- Sparfloxacin
- Gatifloxacin
- Gemifloxacin
- Moxifloxacin
- Trovafloxacin
- Alatrofloxacin
- Finafloxacin



improved spectrum

- Clinafloxacin
- Gatifloxacin
- Gemifloxacin
- Moxifloxacin
- Pazufloxacin
- Sparfloxacin
- Tosufloxacin
- Trovafloxacin

Therapeutic Uses and ADRs

•UTIs:

➤Nalidixic Acid

- Fluoroquinolones are significantly more potent (broad spectrum)
- More efficacious than co-trimoxazole

• **Prostatitis:**

- Norfloxacin, ciprofloxacin and ofloxacin
- Used for patients not responding to co-trimoxazole

• **Sexually Transmitted Diseases:**

- The quinolones are contraindicated in pregnancy
- Chancroid (infection by *H. ducreyi*): treated with 3 days of cipro
- Gonorrhea tt - Single dose Ciprofloxacin 500mg

•Chlamydia trachomatis- Ciprofloxacin one week or single dose

Azithromycin

- **Respiratory Tract Infections**
 - Ciprofloxacin, ofloxacin and norfloxacin are poor in tt of community-acquired pneumonia and bronchitis (*S. pneumonia* and anaerobic bacteria)
- Levofloxacin, Moxifloxacin, Gemifloxacin, Gatifloxacin, Sparfloxacin have good activity against *S. pneumonia* and also called Respiratory FQs (good activity against anaerobes)
- **Bone, Joint and Soft Tissue Infections**
 - Caused by *S. aureus* and gram-negative rods
 - Ciprofloxacin should not be given to children or pregnant women
- Ciprofloxacin received wide usage for the prophylaxis of anthrax (treatment of tularemia)
- Neutropenic cancer patients with fever
 - 11/05/24 Quinolone + aminoglycoside = β -lactam + aminoglycoside

- **Ciprofloxacin-**
 - Long Post Antibiotic Effect (PAE)
 - Less active at acidic pH
 - Interacts with food and calcium
 - High tissue penetrability (Except BBB)
 - High conc. in urine and bile
 - CNS SE and tendonitis and tendon rupture and damage growing cartilage and cause an arthropathy are FQs SES
 - **Uses**
 - CNSI, OI, ENTI, RTI, GITI, UTI, PID, STDs
 - Nosocomial infections and septicaemia
 - Tuberculosis- MDR TB and XDR TB

▪ Typhoid

➤ Treatment 2 weeks

➤ Prevention of carrier state 2 months

➤ Other drugs- Other FQs

✓ Cephalosporins ,Ceftriaxone (Fastest)

✓ Chloramphenicol, Cotrimoxazole and Ampicillin

- Less potent, primarily used for UTI and GIT infections –

Norfloxacin

- No FQs effective against spirochaetes
- Ofloxacin and Pefloxacin are effective against *M. leprae*
- Moxifloxacin is the only FQ not used in UTI as its concentration is poor in urine
- 11/05/24 Chronic Prostatitis tt - Ciprofloxacin for 1 to 2 months

Elimination of Fluoroquinolones

■ Renal

- Norfloxacin
- Ofloxacin
- Ciprofloxacin
- Lomefloxacin
- Levofloxacin
- Gatifloxacin

■ Hepatic

- Pefloxacin
- Moxifloxacin
- Trovafloxacin
- Sparfloxacin
- Gemifloxacin

Fluoroquinolones safe in renal failure

Pefloxacin

Moxifloxacin

Trovafloxacin

- Broad spectrum antimicrobials
 - Nitroimidazoles: Anaerobic infections only
 - As a group cover bacteria, fungi, viruses, protozoa, and helminths
 - Include metronidazole, tinidazole, ornidazole, secnidazole and nimorazole
 - Metronidazole possesses potent antibacterial activity against
 - ✓ Strict anaerobes
 - ✓ Some micro-aerophilic bacteria (*Gardnerella vaginalis* and *H. pylori*)
 - Bacterial resistance is uncommon against metronidazole
 - ✓ Now it is the drug of choice for the treatment of anaerobic infections
 - ✓ Used for prophylaxis in some surgical procedures (anaerobes are likely infective bacteria)
 - Reduced form of metronidazole is thought to induce strand breakage in DNA
 - These compounds are best avoided in pregnancy

ANTIMYCOBACTERIAL AGENTS:

DRUGS FOR TUBERCULOSIS & LEPROSY

- TB is a chronic bacterial infection caused by a group of bacteria, *Mycobacteriaceae*,
- Common of which is *Mycobacterium tuberculosis*.
- Less frequently, it can be caused by *Mycobacterium bovis* and *Mycobacterium africanum*.
- The clinical picture is quite variable and depends on the specific organ affected by the disease.

- Although the lung is the most commonly affected organ, almost all parts of the body can be infected with this bacterium.
- HIV infection has now become one of the most important risk factors for the development of active tuberculosis.
- Patients with TB usually present with the symptom complex of low grade fever with sweating, loss of appetite and weight loss.

- Treating mycobacterial infection present problems:
- mycobacteria are slow growing microbes
 - can also be dormant; resistant to many drugs
 - lipid rich cell wall is impermeable to many agents
 - a substantial portion is intracellular
 - Needs prolonged treatment
 - Drug toxicity & poor patient compliance
 - High risk of emergence of resistant bacteria

ANTIMYCOBACTERIAL...

OVERVIEW OF ANTITUBERCULOUS THERAPY

- **Basic principles of treatment**
 - The objective of therapy is: to eliminate symptoms & prevent relapse
 - To accomplish this goal, t/t must kill actively dividing & resting mycobacteria
 - Since the response of mycobacterial infections to chemotherapy is slow, t/t is prolonged
 - Combination of drugs are required to prevent the emergence of resistance

ANTIMYCOBACTERIAL...

Individual Antituberculous Agents

- 1st line drugs: superior efficacy & acceptable toxicity
 - Isoniazide (H)
 - Rifampin (R)
 - Pyrazinamide (Z)
 - Ethambutol (E)
 - Streptomycin (S)
- 2nd line drugs: less efficacy, greater toxicity or both.
 - Used in combination with 1st line drugs to treat disseminated TB & TB caused by resistant organism
 - PAS
 - Kanamycin
 - Capreomycin
 - Ethionamide
 - Cycloserine
 - Gatifloxacin
 - Levofloxacin
 - Moxifloxacin

Mechanism of Action and Recognized Mutational Resistance in Commonly Used Anti-TB Agents

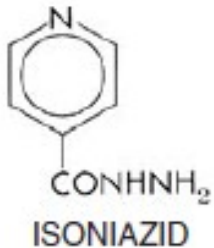
<i>Drug</i>	<i>Mechanism of Action</i>	<i>Site of Mutational Resistance (gene)</i>
Isoniazid	Inhibits mycolic acid synthesis	<i>inhA</i> (regulatory region) (mycolic acid gene)
	Catalase/peroxidase enzyme	<i>katG</i> (catalase/peroxidase gene)
Rifampin	Inhibits RNA polymerization	β -subunit <i>rpoB</i> (RNA polymerase gene)
Pyrazinamide	Unknown	<i>pncA</i> (pyrazinamidase gene)
Ethambutol	Inhibits cell wall synthesis (blocks arabinosyl transferase)	<i>embB</i> (gene for arabinosyl transferase enzyme)
Streptomycin	Inhibits protein synthesis	<i>rpsL</i> (gene for ribosomal S12 protein); 16S ribosomal RNA gene
Amikacin	Inhibits protein synthesis	16S ribosomal RNA gene (? amikacin binding site)
Capreomycin	Inhibits cell wall synthesis	Unknown
Quinolones	Inhibits DNA structure	<i>gyrA</i> (gyrase A gene)

ANTIMYCOBACTERIAL...

- **ISONIAZID (INH/Isonicotinic hydrazide)**

Synthetic analog of pyridoxine (Vit B₆)

MoA



- Activated by mycobacteria catalase peroxidase
- Active metabolite: form covalent complex with acyl carrier protein (AcpM) & KasA (β -ketoacyl carrier protein synthase) $\Rightarrow$ inhibits bacterial mycolic acid synthesis
- Mycolic acid is a unique class of very-long-chain, hydroxylated fatty acids found in mycobacterial cell walls

ANTIMYCOBACTERIAL...

- **Resistance**
 - Mutation of the catalase peroxidase gene
 - May also involve mutation in target inhA gene
 - Combined with other drugs, INH has good resistance preventing action; no cross resistance with other antiTB
- **Pharmacokinetics**
 - Well absorbed p.o. or i.m.
 - Distributed widely: CSF $\approx$ 20% of plasma conc. Increased in meningeal inflammation
 - Metabolised by acetylation
 - » Fast acetylation $t_{1/2} \approx 1\text{hr}$
 - » Slow acetylation $t_{1/2} \approx 3\text{hr}$

ANTIMYCOBACTERIAL...

- **Therapeutic Uses**

- component of all TB chemotherapeutic regimens
- Alone is used to prevent
 - transmission to close contact at high risk of disease
- Progression of infection in recently infected, asymptomatic individuals
- Development of active TB in immunodeficient individuals

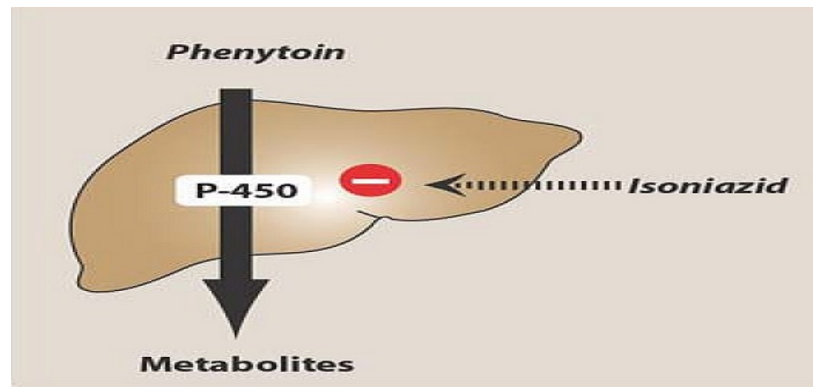
ANTIMYCOBACTERIAL...

- **Adverse effects**
 - Allergic reactions (fever, skin rashes)
 - Direct toxicities
 - Drug induced hepatitis: high risk age, rifampin, alcohol
 - Peripheral neuropathy
 - due to relative pyridoxine deficiency: increased vit B6 excretion & interference with vit B6 utilization
 - Likely to occur in slow acetylators & pts with predisposing factor [malnutrition, alcoholism, diabetes, AIDS & Uremia]
 - Reversed by administration of vit B6

ANTIMYCOBACTERIAL...

- Other adverse effect
 - Convulsion
 - Optic neuritis
 - Psychosis

} reversed by vit. B6
- **Drug interaction**
 - » reduces metabolism of phenytoin
 - » absorption of INH is impaired by $\text{Al}(\text{OH})_3$



ANTIMYCOBACTERIAL...

- **RIFAMPICIN**

- Semisynthetic derivative of rifamycin B produced from *streptomyces mediterranei*
- Mechanism: binds to the β -subunit of bacterial DNA dependent RNA polymerase $\Rightarrow$ inhibits RNA synthesis
- Resistance- point mutation or deletion within an 81bp region of the gene encoding the β subunit of RNA polymerase

ANTIMYCOBACTERIAL...

Pharmacokinetics

- well absorbed; distributed throughout the body
- excreted mainly through liver into bile

Therapeutic uses

- a) Mycobacterial infection
- b) TB: Bacteriocidal for intra & extracellular bacteria
- c) Leprosy
- d) Atypical mycobacteria
- e) Prophylaxis of meningococcal carriers

ANTIMYCOBACTERIAL...

- f) In combination therapy for serious staphylococcal infection [osteomyelitis, endocarditis]
- g) With ceftriaxone or vancomycin in t/t of meningitis

Adverse effects

- 1) Hepatitis in pts with
 - » Preexisting liver disease
 - » High dose
 - » Alcoholics
 - » Elderly
- 2) Hypersensitivity reactions
 - » Fever
 - » Pruritis
 - » Interstitial nephritis
 - Flushing
 - Thrombocytopenia

ANTIMYCOBACTERIAL...

3. Miscellaneous adverse reaction

- Harmless orange color appearing in urine, saliva, tears, sweat & soft contact lenses GI upset

- **Drug interaction**

- is a microsomal enzyme inducer; enhances its own metabolism as well as other drugs [warfarin, Steroids, HIV protease inhibitors & ketoconazole]

ANTIMYCOBACTERIAL...

- **ETHAMBUTOL**

- **Mechanism:** Inhibits cell wall synthesis by blocking arabinosyl transferase $\Rightarrow$ bacteriostatic
- **Therapeutic use:** TB
- **Adverse effects**
 - Retrobulbar neuritis (optic neuritis)
 - Loss of visual acuity & red-green color blindness
 - GI intolerance
 - Hyperuricemia due to decreased uric acid excretion

ANTIMYCOBACTERIAL...

- **PYRAZINAMIDE**

- Synthetic pyrazine analogue of nicotinamide
- Converted to pyrazinoic acid, active form of drug
- However the drugs target & mechanism are unknown

– **Therapeutic use: TB**

– **Adverse effects**

- GI intolerance
- Hepatotoxicity
- Hyperuricemia

ANTIMYCOBACTERIAL...

- **TB TREATMENT REGIMENS**

- initial phase: rapid killing of actively growing bacilli
 - Infectious pts become noninfectious ($\approx$ 2wks)
 - DOT is essential in the initial phase to ensure that pts take every single dose
 - Protects against the development of resistance
- Continuation phase
 - Elimination of bacilli that are still multiplying & reduces failure & relapse

ANTIMYCOBACTERIAL...

DRUG REGIMENS & TREATMENT FAILURE

– Category I

- New (untreated) smear positive pulmonary TB
- New smear negative pulmonary & extrapulmonary TB
- R_x regiment: 2S(RHZ)/6(EH) or 2(ERHZ)/6(EH)

– Category II

- Who relapsed after being treated & declared free from the disease
- Those patient who are previously treated for more than one month & smear positive up on return
- Who still remain smear positive while under treatment, at month five and beyond
- Interrupted treatment case
- R_x regimen: 2SE(RHZ)/1E(RHZ)/5E₃

– Category III

- New cases of smear negative pulmonary TB with parenchymal involvement or less severe forms of extrapulmonary TB, lymphnode TB, unilateral pleural effusion, bone, skin TB
- R_x 2HRE/ 6(EH)

– Category IV

- Chronic case who remained or have become smear – positive after completing fully supervised retreatment (category II)
- They are most likely MDR
- MDR: resistant to both H & R, & may be to other antiTB too
- The actual treatment regimen is designed according to the individual patient
- R_x For H resistant – 12 RZE

- TB in pregnant mother
 - (2HRZ + 4HR) recommended regimen
 - H, R & Z safe drugs
 - E can be added in the late stage but not on early pregnancy period
 - S contraindicated
 - Z ?????? Not recommended ...no sufficient data available for its teratogenicity
- TB treatment in breast feeding mother
 - All Anti TB drugs are compatible
 - Infant carefully watched
 - Infant should receive BCG vaccine & INH prophylaxis

- TB in AIDS patients
 - TB-HIV co infection is serious problem
 - HIV +V cases have more severe and infectious TB
 - HIV infection is the strongest risk factor for making latent TB overt
 - Adverse effects to anti TB drugs is more common in HIV patients
 - Rx is same as non HIV patient but duration is longer & at least 4 drugs has to be used
- Corticosteroids
 - In general they should not be used for TB patients

- Chemophylaxis

Indicated only in

- Contact of open cases
- Children with +Ve Mantoux test & a TB patient in the family
- Neonate of tubercular mother
- Patient with leukemia, DM, HIV +ve but not anergic, patients on corticosteroid therapy with +Ve Mantoux test

Important information about the first line antitubercular drugs

Drug	S/Es	C/Is	D/Is	Dosage forms
Isoniazid (H)	Peripheral neuritis, numbness, mental disturbance, rash, fever, arthralgia, hepatitis		Al(OH) ₃ decreases absorption, Inhibits metabolism of phenytoin, diazepam, warfarin	Tablet, 100 mg, 300 mg;
Rifampicin (R)	Hepatitis, renal failure, hemolysis, pupurea, rash, nausea, vomiting, anorexia, orange/green urine		Increase metabolism of warfarin, corticosteroids, Protease Inhibitors, sulfonyl ureas, oral contraceptives	Capsule, 150 mg, 300mg, 600mg; Syrup, 20mg/5ml
Ethambutol (E)	Optic neuritis, nausea, rashes, fever, neurological changes, hyperurecemia	Children <6 years old		Tablet, 100g, 400 mg
Pyrazinamide (Z)	Hepatotoxicity, nausea, vomiting, hyperuricemia, arthralgia, flushing, rashes, fever	Liver disease		Tablet, 500 mg

Fixed dose combination antiTB drugs and their dosage forms

Fixed Dose combination antiTB drugs	Dosage forms
Rifampicin, Isoniazid and Pyrazinamide (RHZ)	Tablet, 150/75/400 mg
Ethambutol and Isoniazid (EH)	Tablet, 400 /150 mg
Rifampicin and Isoniazid (RH)	Capsule, 150 /100 mg; tablet, 150/100mg, 300/150mg
Rifampicin and Isoniazide and Pyrazinamide and	Tablet, 150/75/400/275mg

Symptom-based approach to management of anti TB drug side effects

Side-effects		Drugs	Management
a. Minor [Continue anti TB drugs]	Anorexia, nausea, abdominal pain.	Rifampicin	Give tablets as last thing at night.
	Joint pains	Pyrazinamide	Aspirin
	Burning sensation in feet.	Isoniazid	Pyridoxine 100mg daily.
	Orange/red urine	Rifampicin	Reassurance
b. Major [Stop drug(s) responsible]	Deafness	Streptomycin	Stop streptomycin, use ethambutol instead.
	Dizziness	Streptomycin	Stop S, use ethambutol <i>instead</i> .
	Jaundice	Most anti-TB drugs	Stop all anti-TB drugs, jaundice clears.
	Vomiting and confusion.	Most anti-TB drugs	Stop all anti-TB drugs until the situation improves.
	Visual impairment.	Ethambutol	Stop E and do proper ophthalmic evaluation.
	Shock, purpura	Rifampicin	Stop Rifampicin and supportive

ANTILEPROTIC DRUGS

- Leprosy (Hansen's disease) caused by *M. leprae*
 - There are two types of leprosy
 1. Lepromatous leprosy
 - » Severe
 - » Rapidly progress
 - » Marked ulceration
 - » Tissue destruction & nerve damage
 - » t/t lasts at least 2yrs with (Dapsone, Rifampicin, Clofazimine)

ANTILEPROTIC...

2. Tuberculoid leprosy

- Mild infection
- slow in progress & loss of sensation
- T/t lasts 6months (Dapsone + rifampicin)

Treatment of leprosy has three objectives:

- a) conversion of pts to noninfectious state
 - b) prevention of bacterial multiplication
 - c) avoidance or reduction of complication
- To achieve these objectives, WHO recommends that all pts receive t/t with multiple drugs [dapsone, rifampicin, clofazimine, ethionamide]

ANTILEPROTIC...

DAPSONE/SULFONES

- The primary drug [effective, low in toxicity & inexpensive]

Mechanism: inhibition of folate synthesis

Pharmacokinetics:

- given orally, well absorbed
- Widely distributed [$t_{1/2} \approx 24-48\text{hrs}$]
- Enterohepatic recycling
- Excreted as metabolites renally

Adverse effects

- GI disturbance - headache
- Rashes - show erythema nodosum
(↑ Inflammatory rxn)

ANTILEPROTIC...

CLOFAZIMINE

- weakly bactericidal
- mechanism: not known
- used together with dapsone
- has anti-inflammatory action
- $t_{1/2} \approx 8\text{wks}$
- Adverse effects
 - Redbrown color to the skin & conjunctiva
 - GI disturbances

Antiviral Drugs

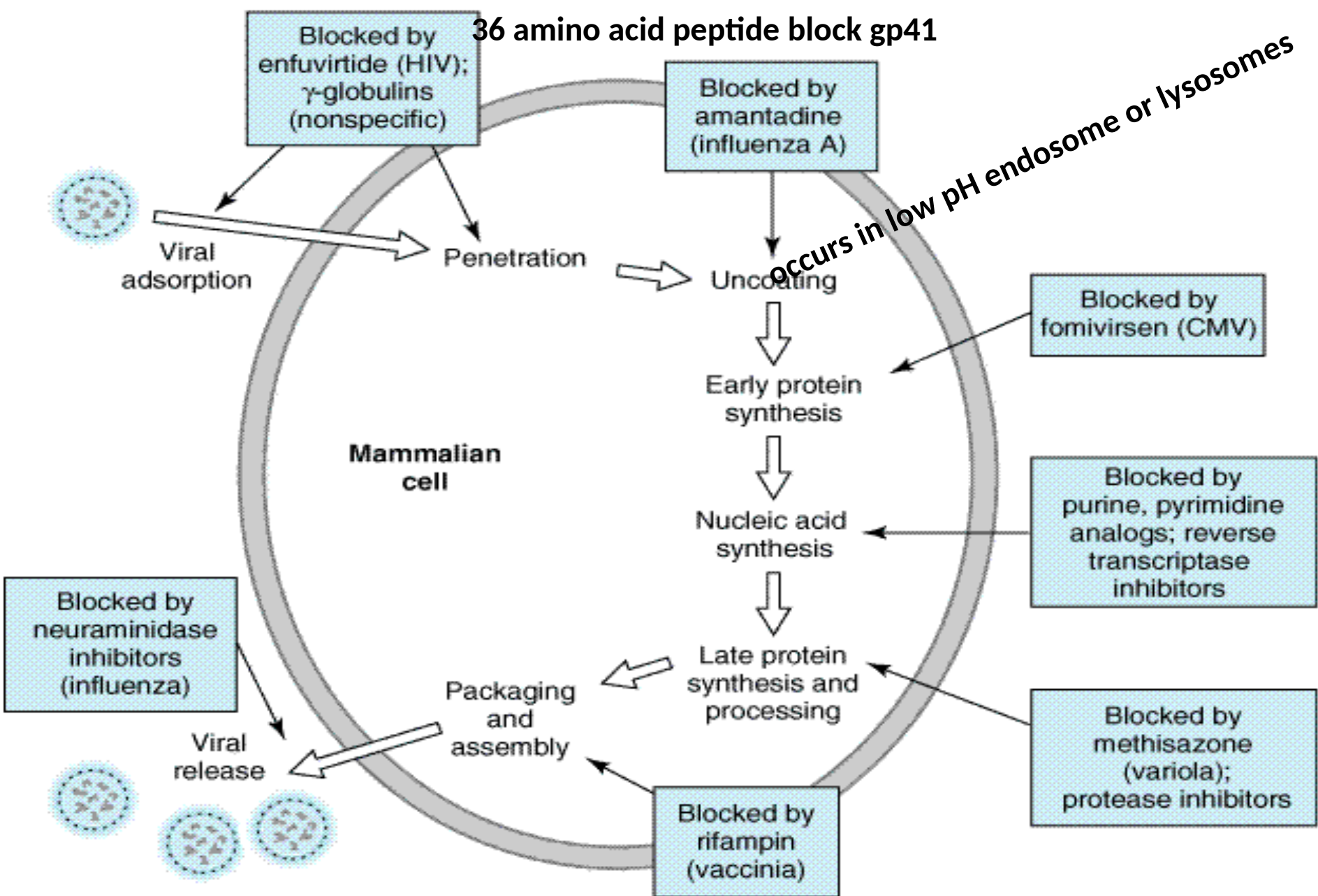
Overview

- Viruses are obligate intracellular parasites
 - Few drugs are selective enough to prevent viral replication without injury to the host.
 - Clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated.

Summary of Antiviral Drugs

FOR RESPIRATORY VIRUS INFECTIONS	FOR HEPATIC VIRAL INFECTIONS	FOR HIV INFECTIONS	
<ul style="list-style-type: none">AmantadineOseltamivirRibavirinRimantadineZanamivir	<ul style="list-style-type: none">AdefovirEntecavirInterferonLamivudineTelbivudine	<ul style="list-style-type: none">AbacavirAtazanavirDarunavirDelavirdineDidanosineEmtricitabineEnfuvirtideEfavirenzEtravirineFosamprenavirIndinavirLamivudine	<ul style="list-style-type: none">LopinavirMaravirocNelfinavirNevirapineRaltegravirRitonavirSaquinavirStavudineTenofovirTipranavirZidovudine
FOR HERPES AND CYTO-MEGALOVIRUS INFECTIONS			
<ul style="list-style-type: none">AcyclovirCidofovirFamciclovirFomivirsenFoscarnet	<ul style="list-style-type: none">GanciclovirPenciclovirValacyclovirValganciclovirVidarabine		

36 amino acid peptide block gp41



The major sites of antiviral drug action

I. Treatment of Respiratory Virus Infections

- Viral respiratory tract infections for which treatments exist include those of influenza A and B

A. Neuraminidase inhibitors

- Orthomyxoviruses that cause influenza (A and B) contain neuraminidase, is essential to the life cycle of the virus.
- Viral neuraminidase can be selectively inhibited by the sialic acid analogs, oseltamivir and zanamivir (which prevent the release of new virions and their spread)
- Administered
 - prior to exposure, they prevent infection
 - within the first 24 to 48 hours after the onset of infection, they have a modest effect on the intensity and duration of symptoms

Pharmacokinetics

- **Oseltamivir** an orally active prodrug that is rapidly hydrolyzed by the liver to its active form
- **Zanamivir** not active orally and is either inhaled or administered intranasally.

Adverse effects:

- GI discomfort and nausea (Oseltamivir), take with food
- respiratory tract irritation (Zanamivir); C/I: asthma/COPD

Resistance:

- Mutations of the neuraminidase have been identified in adults treated with neuraminidase inhibitors.
- These mutants, however, are often less infective and virulent than the wild type.

B. Inhibitors of viral uncoating (adamantine derivatives)

- Therapeutic spectrum of amantadine & rimantadine is limited to influenza A (treatment & prevention)
- Treatment is particularly useful in high-risk patients who have not been vaccinated and during epidemics.

Mode of action:

- Amantadine and rimantadine block the viral membrane matrix protein, which functions as a channel for H⁺
 - This channel is required for the fusion of the viral membrane with the cell membrane that ultimately forms the endosome [The acidic environment of the endosome is required for viral uncoating]
- These drugs may also interfere with the release of new virions.

Pharmacokinetics

- Both drugs are well absorbed orally Amantadine distributes throughout the body and readily penetrates into the CNS whereas rimantadine does not cross BBB

Adverse Effects:

- SEs of Amantadine (not Rimantadine) are mainly associated with the CNS.
- Minor neurologic symptoms: insomnia, dizziness & ataxia
- More serious SE's (hallucinations and seizures) have been reported
- Both drugs cause GI intolerance.
- Used with caution in pregnant and nursing mothers, (embryotoxic and teratogenic in rats)

Resistance: develop rapidly in up to 50% of individuals

- Resistance has been shown to result from a change in one amino acid of the M2 matrix protein.
- Cross-resistance occurs between the two drugs.

C. Ribavirin

- Ribavirin is a synthetic guanosine analog effective against a broad spectrum of RNA and DNA viruses (also in chronic hepatitis C when used with interferon)

Mode of action:

- The major metabolic product ribavirin-triphosphate, inhibits GTP formation, preventing viral mRNA capping, and blocking RNA-dependent RNA polymerase

Pharmacokinetics:

- Ribavirin is effective orally and intravenously.
- An aerosol is used in certain respiratory viral conditions
- The drug and its metabolites are eliminated in the urine

Adverse effects:

- Dose-dependent transient anemia
- teratogenic in animals, contraindicated in pregnancy

III. Treatment of Hepatic Viral Infections

- The hepatitis viruses identified as "A, B, C, D, and E"
- Pathogenesis: replication in & destruction of hepatocytes
- Hepatitis B & C (the only hepatic viral infections with currently available therapy) are the most common causes of chronic hepatitis, cirrhosis, & hepatocellular carcinoma
- Chronic hepatitis B is usually treated with peginterferon α -2a (subcutaneous); not for pts coinfecting with AIDS
 - Interferon is a family of inducible glycoproteins that interfere with the ability of viruses to infect cells
- Oral therapy includes lamivudine, adefovir, telbivudine...
- In the treatment of chronic hepatitis C, the preferred treatment is the combination of peginterferon α -2a or α -2b plus ribavirin

IV. Treatment of Herpesvirus Infections

- Herpesviruses are associated with a broad spectrum of diseases: cold sores, viral encephalitis, and genital infections (a hazard to the newborn during parturition)
- Drugs that are effective against these viruses exert their actions only during the acute phase of viral infections
- Except for foscarnet and fomivirsen, all are purine or pyrimidine analogs that inhibit viral DNA synthesis.

A. Acyclovir

- Acyclovir is the prototypic antiherpetic therapeutic agent.
- HSV (1 & 2) & VZV infections are sensitive to acyclovir
- The most common use of acyclovir is in therapy for genital herpes infections.
- It is also given prophylactically to seropositive patients before bone marrow and after heart transplants; Why?

- **Mode of action:** Acyclovir is monophosphorylated in the cell by the herpes virus thymidine kinase, virus-infected cells are most susceptible. The monophosphate analog is converted to the di & triphosphate forms by the host cells.
- Acyclovir triphosphate competes with dGTP as substrate for the viral DNA polymerase and itself incorporated into viral DNA causing premature DNA-chain termination
- **Pharmacokinetics:** Routes: IV, oral, or topical route.
- The drug distributes well throughout the body, including the CSF. The valyl ester prodrug, valacyclovir, has greater oral bioavailability than acyclovir.
- **Adverse effects:** SEs depend on the route (topical → local irritation; oral → headache, diarrhea, nausea, & vomiting)
- **Resistance:** Altered or deficient thymidine kinase & DNA polymerases found in some resistant viral strains

B. Cidofovir

- Cidofovir is a nucleotide analog of cytosine, its phosphorylation is not dependent on viral enzymes
- Cidofovir is approved for treatment of CMV-induced retinitis in patients with AIDS.
- Cidofovir is available for intravenous, intravitreal and topical administration.
- Neutropenia, metabolic acidosis, and ocular hypotony occur. It produces significant toxicity to the kidney (contraindicated in renal impairment or in those who are taking nephrotoxic drugs, including NSAIDs)
- Probenecid must be coadministered with cidofovir to reduce the risk of nephrotoxicity
- Since the introduction of HAART, importance of cidofovir has diminished.

C. Fomivirsen

- Fomivirsen is an antisense oligonucleotide directed against CMV mRNA.
- Its use is limited to those who cannot tolerate or have failed other therapies for CMV retinitis.
- The drug is administered intravitreally.
- The common adverse effects include iritis, vitritis...

D. Foscarnet

- Foscarnet is not a purine or pyrimidine analog.
- It is phosphonoformate, a pyrophosphate derivative, and does not require activation by viral (or human) kinases.
- Foscarnet has broad in vitro antiviral activity.
- Approved for CMV retinitis & for acyclovir-resistant HSV
- It reversibly inhibits viral DNA & RNA polymerases, & interferes with viral DNA & RNA synthesis.

- Mutation of the polymerase structure is responsible for resistant viruses.
- Foscarnet is poorly absorbed orally and must be taken IV
- It is dispersed throughout the body, and greater than 10 % enters the bone matrix, from which it slowly leaves.
- ***Adverse effects:*** nephrotoxicity, anemia, nausea, and fever

E. Ganciclovir

- Ganciclovir is an analog of acyclovir that has 8-20 times greater activity against CMV (only approved for this)
- It is currently available for treatment of CMV retinitis and for CMV prophylaxis in transplant patients.
- **Pharmacokinetics:** Ganciclovir is administered IV and distributes throughout the body, including the CSF
- Valganciclovir is the valyl ester of ganciclovir. Like valacyclovir, valganciclovir has high oral bioavailability

- **Adverse effects:** severe, dose-dependent neutropenia. Ganciclovir is carcinogenic as well as embryotoxic and teratogenic in experimental animals.
- **Resistance:** Resistant CMV strains have been detected that have lower levels of ganciclovir triphosphate.

F. Penciclovir and famciclovir

- Penciclovir is an acyclic guanosine nucleoside derivative active against HSV-1, HSV-2, and VZV. Only topical
- Monophosphorylated by viral thymidine kinase, triphosphate by cells, which inhibits HSV DNA polymerase
- Famciclovir, acyclic analog of 2'-deoxyguanosine, is a prodrug that is metabolized to the active penciclovir.
- The drug is effective orally
- **Adverse effects:** headaches and nausea

Other drugs Herpesvirus Infections: Vidarabine (ara-A), Trifluridine...

V. Overview of the Treatment for HIV Infection

- Prior to approval of zidovudine in 1987, treatment of HIV infections focused on OIs rather than on inhibiting HIV
- Today, the viral life cycle is understood and a highly active regimen of combinations of drugs is employed to:-
 - suppress replication of HIV and
 - restore number of CD4+ cells & host immunocompetency
- This multi drug regimen is referred to as HAART
- There are five classes of antiretroviral drugs which targets one of four viral processes:-
 - nucleoside & nucleotide reverse transcriptase inhibitors (NRTIs)
 - non-nucleoside reverse transcriptase inhibitors (NNRTIs)
 - protease inhibitors
 - entry inhibitors and
 - integrase inhibitors

- The current recommendation: is to administer two NRTIs with either a protease inhibitor or an NNRTI.
- Selection of the appropriate combination is based on
 1. avoiding the use of two agents of the same nucleoside analog
 2. avoiding overlapping toxicities and genotypic and phenotypic characteristics of the virus
 3. patient factors such as disease symptoms & concurrent illnesses
 4. impact of drug interactions, and
 5. ease of adherence to a frequently complex administration regimen
- The goals of therapy :-
 - to maximally and durably suppress viral load replication
 - to restore and preserve immunologic function
 - to reduce HIV-related morbidity and mortality, and
 - to improve quality of life.

Potential targets for antiviral agents excluding HIV

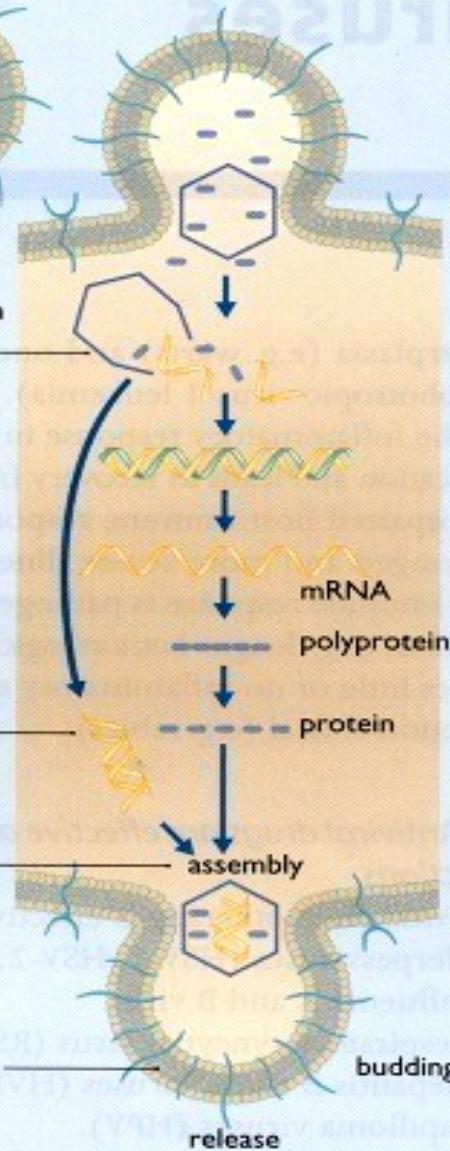
1. Block binding
2. Fusion and penetration
3. Inhibit uncoating

5. Inhibit translation

6. Inhibit genome replication

7. Inhibit assembly

8. Interfere with budding



NRTIs Used to Treat HIV Infection

- NRTIs are analogs of native ribosides (nucleosides or nucleotides containing ribose), which lack a 3'-OH group
- **Mechanism of action:** They are phosphorylated by cellular enzymes to corresponding triphosphates which are incorporated into viral DNA by virus reverse transcriptase.
- Because the 3'-hydroxyl group is not present, a 3'-5'-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated
- The drugs have lower affinities for host cell DNA polymerases (although mitochondrial DNA polymerase appears to be susceptible at therapeutic concentrations)

- **Pharmacokinetics:** primarily renally excreted, & require dosage adjustment in renal insufficiency
- **Adverse effects:** Many of the toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in certain tissues.
- Dideoxynucleosides (zalcitabine, didanosine, & stavudine) have a greater affinity for mitochondrial DNA polymerase
 - leading to peripheral neuropathy, pancreatitis, and lipoatrophy
- Avoid overlapping toxicities when > one NRTI is given
- **Drug interactions:** Not many; renal excretion of NRTIs?
- **Resistance:** resistance is well characterized, and common mutation at viral codon 184
- Cross-resistance occurs between agents of the same analog class (thymidine, cytosine, guanosine and adenosine)
 - so concomitant use of agents in the same class is contraindicated (for example, zidovudine plus stavudine).

A. Zidovudine (AZT)

- the first agent available for treatment of HIV infection
- approved for use in children and adults and to prevent prenatal infection in pregnancy
- recommended for prophylaxis in those exposed to HIV
- The drug is well absorbed after oral administration.
- Penetration across the BBB is excellent, and the drug has a half-life of 1 hour.
- Most of the AZT is glucuronylated by the liver and then excreted in the urine
 - The toxicity is potentiated if glucuronylation is decreased by probenecid, acetaminophen, indomethacin, & cimetidine.
- AZT is toxic to bone marrow. Headaches are common.
- Both stavudine and ribavirin are activated by the same intracellular pathways and should not be given with AZT.

B. Stavudine (d4T)

- d4T is an analog of thymidine, in which a double bond joins the 2' and 3' carbons of the sugar.
- strong inhibitor of cellular enzymes (DNA polymerases), ↓ing mitochondrial DNA synthesis, resulting in toxicity
- The drug is almost completely absorbed on oral ingestion
- Stavudine penetrates the BBB.
- Renal impairment interferes with clearance. The major and most common clinical toxicity is peripheral neuropathy along with lipoatrophy and hyperlipidemia.

C. Didanosine (ddI)

- The second drug approved to treat HIV-1 infection
- Upon entry into host cell, ddI is biotransformed to ddATP
- Like AZT, the resulting ddATP is incorporated into the DNA chain, causing termination of chain elongation.

D. Tenofovir (TDF)

- It is converted by cellular enzymes to the diphosphate, which is the inhibitor of HIV reverse transcriptase.
- Cross-resistance with other NRTIs may occur, but some AZT-resistant strains retain susceptibility to tenofovir.
- Taken with a meal to increase bioavailability.
- Tenofovir has a long half-life, allowing once-daily dosing.
- Most of the drug is recovered unchanged in the urine
- Serum creatinine must be monitored and doses adjusted in renal insufficiency.
- GI complaints are frequent and include N/V
- The only NRTI with significant drug interactions.
- Tenofovir decreases the concentrations of atazanavir such that atazanavir must be boosted with ritonavir

E. Lamivudine (3TC)

- 3TC is approved for treatment of HIV in combination with AZT
- 3TC terminates the synthesis of the proviral DNA chain, and inhibits the reverse transcriptase of both HIV & HBV.
- However, it does not affect mitochondrial DNA synthesis or bone marrow precursor cells.
- It has good bioavailability on oral administration, depends on the kidney for excretion, and is well tolerated.

F. Emtricitabine (FTC)

- FTC, a fluoro-derivative of lamivudine, inhibits both HIV and HBV reverse transcriptase.
- FTC is orally active, with a mean bioavailability of 93 %
- It is eliminated essentially unchanged in the urine
- Headache, diarrhea, nausea, rash: common adverse effects

G. Zalcitabine (ddC)

- the first cytosine analog developed; however, due to severe toxicity, it was removed from the market.

H. Abacavir (ABC)

- ABC a guanosine analog. There may be some cross-resistance with strains resistant to AZT and lamivudine.
- It is well absorbed orally, & metabolites appear in the urine
- Common side effects include gastrointestinal disturbances, headache, and dizziness.
- Approximately 5% of patients exhibit hypersensitivity reaction which is characterized by drug fever, plus one or more of the following symptoms of:
 - Rash
 - gastrointestinal symptoms
 - malaise, and
 - respiratory distress

NNRTIs Used to Treat AIDS

- NNRTIs are highly selective, noncompetitive inhibitors of HIV-1 reverse transcriptase.
- Bind to HIV reverse transcriptase adjacent to the active site, induce conformational change and enzyme inhibition.
- They do not require activation by cellular enzymes.
- Major advantage: their lack of effect on the host blood-forming elements and cross-resistance with NRTIs.
- These drugs, however, do have common characteristics that include:
 - cross-resistance within the NNRTI class
 - drug interactions, and
 - a high incidence of hypersensitivity reactions, including rash.

A. Nevirapine (NVP)

- Used in combination with other antiretroviral drugs for the treatment of HIV-1 infections in adults and children.
- Severe hepatotoxicity
 - NVP should not be initiated with CD4+ T-cell counts greater than: in ♀ 250 cells/mm³ or in ♂ 400 cells/mm³.
- NVP is well absorbed orally
- The lipophilic nature of NVP accounts for its entrance into the fetus and mother's milk and wide tissue distribution
- NVP is an inducer of the CYP3A4 increasing metabolism of oral contraceptives, ketoconazole, methadone, metronidazole, quinidine, theophylline, and warfarin.
- SE's: rash, fever, headache, and fatal hepatotoxicity, Stevens-Johnson syndrome & toxic epidermal necrolysis.
- A 14-day titration period at half the dose is mandatory

B. Efavirenz (EFV)

- EFV treatment results in ↑in CD4+ and a ↓in viral load comparable to that achieved by protease inhibitors when used in combination with NRTIs; (it is preferred NNRTI)
- Following oral administration, efavirenz is well distributed, including to the CNS
- Bioavailability is ↑when taken with a high-fat meal.
- A half-life of more than 40 hours accounts for its recommended once-a-day dosing.
- Efavirenz is extensively metabolized to inactive products.
- Most adverse effects are associated with CNS: dizziness, headache, vivid dreams, and loss of concentration
- Rash is the other most common side effect, with an incidence of approximately 25 percent.
- Severe, life-threatening reactions are rare.

HIV Protease Inhibitors

- Inhibitors of HIV protease have significantly altered the course of this devastating viral disease
- Within a year of their introduction in 1995, the number of deaths in the United States due to AIDS declined
- These potent agents have several common features that characterize their pharmacology.
- **Mechanism of action:** reversibly inhibit the HIV aspartyl protease, responsible for cleavage of the viral polyprotein into a number of essential enzymes (reverse transcriptase, protease, and integrase) and several structural proteins.
- Exhibit at least a thousand-fold greater affinity for HIV-1 and HIV-2 enzymes than for comparable human proteases, such as renin and cathepsin (selective toxicity)

- Treatment of antiretrovirally naïve patients with a PI and two NRTIs results in a decrease in the plasma viral load to undetectable levels in 60 to 95 percent of patients.
- Treatment failures under these conditions are most likely due to a lack of patient adherence.
- **Pharmacokinetics**: have poor oral bioavailability.
- Extensive metabolism, little excreted unchanged in urine
- PI's are substrates for the P-glycoprotein multidrug efflux pump (presence of PgP in BBB may limit access to CNS)
- **Adverse effects**: PI's commonly cause parathesias, NVD
- Disturbances in glucose & lipid metabolism (diabetes, hypertriglyceridemia, and hypercholesterolemia) occur
- Chronic administration results in fat redistribution, including loss of fat from the extremities and its accumulation in the abdomen and the base of the neck

- **Drug interactions:** a common problem for all PI's; they are substrates and potent inhibitors of CYP isozymes.
- Drugs that rely on metabolism & contraindicated:-
 - rhabdomyolysis from simvastatin or lovastatin
 - excessive sedation from midazolam and
 - respiratory depression from fentanyl
- Drug interactions that require dosage modification and cautious use with PI's :warfarin, sildenafil and phenytoin
- CYP Inducers → (may) lower [PI] → treatment failures
- Thus, drugs such as rifampin and St. John's wort are also contraindicated with protease inhibitors.
- **Resistance:** Resistance occurs as an accumulation of stepwise mutations of the protease gene.

A. Ritonavir (RTV)

- RTV is no longer used as a single PI but, instead, is used as a pharmacokinetic enhancer or booster of other PI's.
- Ritonavir is a potent inhibitor of CYP3A, and concomitant ritonavir administration (at low doses) increases the bioavailability of the second PI
→ longer dosing intervals
- Ritonavir is also a self-inducer of its own metabolism
- NVD, headache, and paresthesias are adverse effects.

B. Saquinavir (SQV)

- To maximize bioavailability, SQV can be given along with a low dose of RTV.
- High-fat meals also enhance absorption.
- Drugs that enhance the metabolism of SQV , such as rifampin, rifabutin, NVP, EFV...avoided if possible
- Adverse effects:headache, fatigue, ND & GI disturbances.

C. Indinavir (IDV)

- IDV is well absorbed orally and, of all the PI's, is the least protein-bound, at 60 %.
- Acidic gastric conditions are necessary for absorption
- Absorption is decreased when administered with meals (RTV overcomes this and permits twice-a-day dosing)
- Hepatic clearance account for elimination of indinavir (dosage reduction in hepatic insufficiency)
- Indinavir has the shortest half-life of the PI's, at 1.8 hours.
- It is well tolerated, with usual GI symptoms & headache)
- Indinavir characteristically causes nephrolithiasis (adequate hydration is important) and hyperbilirubinemia.
- Fat redistribution is particularly troublesome with this drug.

E. Nelfinavir (NFV)

- NFV is well absorbed and does not require strict food or fluid conditions; however, it is usually given with food.
- NFV undergoes metabolism by several CYP isozyme (The major metabolite has equal antiviral activity)
- NFV is the only PI that cannot be boosted by RTV, because it is not extensively metabolized by CYP3A.
- Most common SE, Diarrhea; controlled by loperamide

F. Fosamprenavir (fAPV)

- fAPV is a prodrug metabolized to amprenavir following oral absorption.
- Its long plasma half-life permits twice-a-day dosing, and ritonavir boosting increases plasma levels of amprenavir
- adverse effects: NVD, fatigue, paresthesias, and headache.

G. Lopinavir (LPVr)

- LPVr is a peptidomimetic protease inhibitor.
- LPVr has poor bioavailability, enhanced by low dose RTV
- Common side effects: GI effects & hypertriglyceridemia
- Enzyme inducers lower concentrations; should be avoided.
- The oral solution contains alcohol; disulfiram or metronidazole can cause unpleasant reactions.

**Other PI's include: Atazanavir (ATV), Tipranavir(TPV),
Darunavir (DRV)**

Entry Inhibitors

A. Enfuvirtide

- HIV fuses its membrane with that of the host cell to gain entry into the host cell; accomplished by conformational changes in the viral transmembrane glycoprotein gp41
- Enfuvirtide is a 36-amino-acid peptide that binds to gp41, preventing the conformational change.
- Enfuvirtide, in combination with other ARVs, is approved for therapy of treatment-experienced patients with evidence of viral replication despite ongoing ART
- As a peptide, it must be given subcutaneously.
- adverse effects: pain, erythema, induration, and nodules are related to the injection (3 % discontinue treatment)
- Enfuvirtide must be reconstituted prior to administration. It is an expensive medication.

B. Maraviroc

- Maraviroc is the second entry inhibitor, because it is well absorbed orally, it is formulated as an oral tablet.
- Maraviroc blocks the CCR5 coreceptor that works together with gp41 of the virus to facilitate HIV entry through the membrane into the cell.
- HIV may display tropism either to CCR5 coreceptor or to CXCR4 coreceptor, or to both.
- Maraviroc is metabolized by cytochromeP450 liver enzymes, and the dose must be reduced when given with the protease inhibitors.

Integrase Inhibitors

A. Raltegravir (RAL)

- RAL is the first of new class of antiretroviral drugs known as integrase inhibitors.
- RAL specifically inhibits the final step in integration of strand transfer of the viral DNA into host cell DNA.
- RAL has a half-life of approximately 9 hours and is therefore dosed twice daily.
- common side effects: nausea, headache and diarrhea
- as the most.
- RAL, in combination with other ARVs, is approved for therapy of treatment-experienced patients with evidence of viral replication despite ongoing ART

Post Exposure prophylaxis (PEP)

- To be effective treatment has to commence as soon as possible (within 1 to 2 hours, post-exposure).
- In most developed countries, PEP is commenced within 2 - 4 hours post exposure.
- Prophylaxis is sometimes given empirically up to 2 weeks in case of severe exposure when the delay has been unavoidable.
- Prophylaxis is to be given for 28 days.

Prevention of Mother To Child Transmission (PMTCT)

- Several antiretroviral regimens - using zidovudine plus lamivudine, nevirapine, or HAART have been shown to reduce perinatal transmission.
- In contrast to treating established infection, the short-term use of monotherapy is effective in this setting.
- Combination therapy is more effective and may delay the emergence of resistance.
- Non-drug measures that reduce transmission (including elective caesarean section and avoiding breast feeding) add to the benefit of antiretroviral therapy.

- HAART, ideally initiated in the second trimester, is the most effective in MTCT prophylaxis, and is recommended if the viral load is more than 1000 copies/ml, together with elective caesarean section.
- A zidovudine - containing regimen is recommended.
- Efavirenz is teratogenic and must be avoided in early pregnancy.
- The combination of didanosine and stavudine should be avoided in pregnancy due to the high risk of lactic acidosis.
- Only if the mother fulfils the adult criteria for initiation of HAART should she continue antiretroviral therapy after delivery.

- 3TC inhibits the reverse transcriptase of both HIV & HBV(Although this is not a retrovirus (it has a DNA genome), there is a step in the viral replication cycle in which a viral DNA polymerase converts RNA into a DNA copy by reverse transcription)
 - ...The polymerase of hepadnaviruses possesses reverse transcriptase activity...(GG-812)
- ...Most infected individuals harbor predominantly the CCR5-tropic virus; it is believed that the first cells infected in sexual transmission express this coreceptor...(GG-837)
- ...Reduced CNS penetration of PI's (with the attendant risk of facilitating viral replication in a sanctuary site) appears attributable to P-glycoprotein; thus inhibition of P-glycoprotein has been proposed as a therapeutic approach to enhance drug entry to the CNS...(Harrison-Par1-Topic3-INTERACTIONS BETWEEN DRUGS)

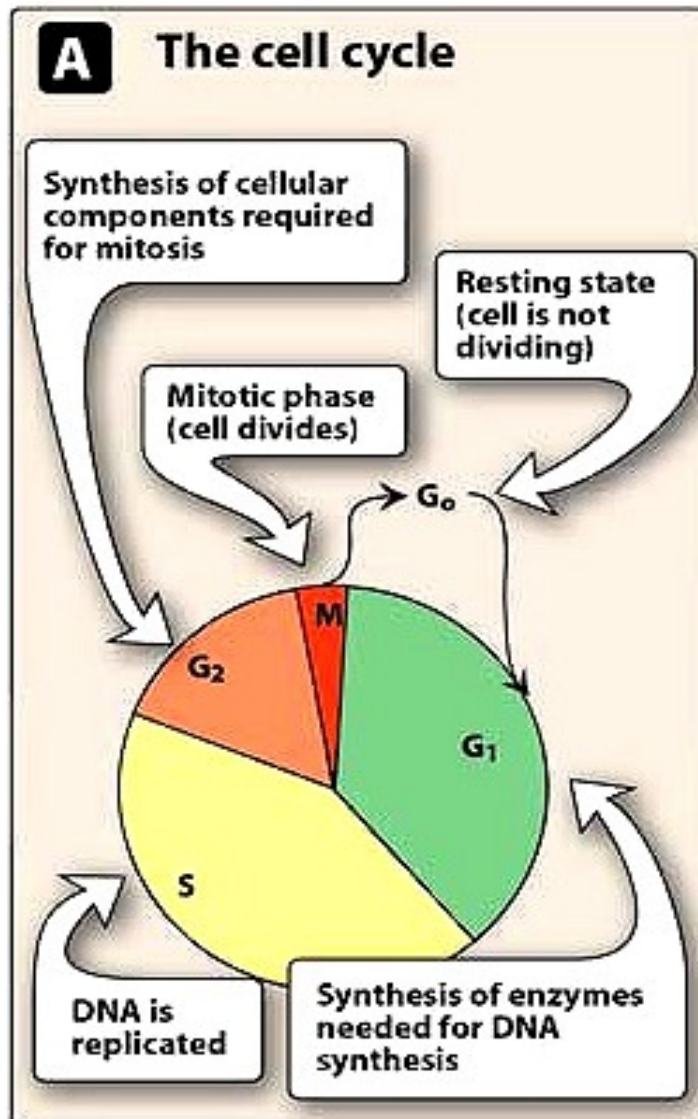
Anticancer drugs

Rational basis for cancer chemotherapy

- Approximately 10 types of human cancer have 40 to 80% “cure” rates using chemotherapy alone or chemotherapy plus surgery or radiation
- For many others chemotherapy gives palliative care
 - Prolongation of life, shrinkage of tumor, and improvement in symptoms
 - ovarian epithelial and breast carcinomas, oat cell carcinoma of the lung, and acute myelocytic leukemia

The normal cell cycle

- Definable sequence of events that characterize the growth and division of cells observed by morphological and biochemical means
- *M-phase, or mitosis, ($\Rightarrow$ using light microscopy)*
 - because of chromosomal condensation, spindle formation, and cell division.
- *S-phase $\Rightarrow$ DNA synthesis ($\Rightarrow$ incorporation of tritiated thymidine into cell nuclei)*
- The ***mitotic index*** and the ***thymidine labeling index*** represent cells in M-phase and S-phase respectively and define the proliferative characteristics of normal and tumor cells.



B Cell-cycle specific drugs

Antimetabolites
Bleomycin peptide antibiotics
Vinca alkaloids
Etoposide



Effective for high-growth-fraction malignancies, such as hematologic cancers

C Cell-cycle non-specific drugs

Alkylating agents
Antibiotics
Cisplatin
Nitrosoureas



Effective for both low-growth-fraction malignancies, such as solid tumors, as well as high-growth-fraction malignancies

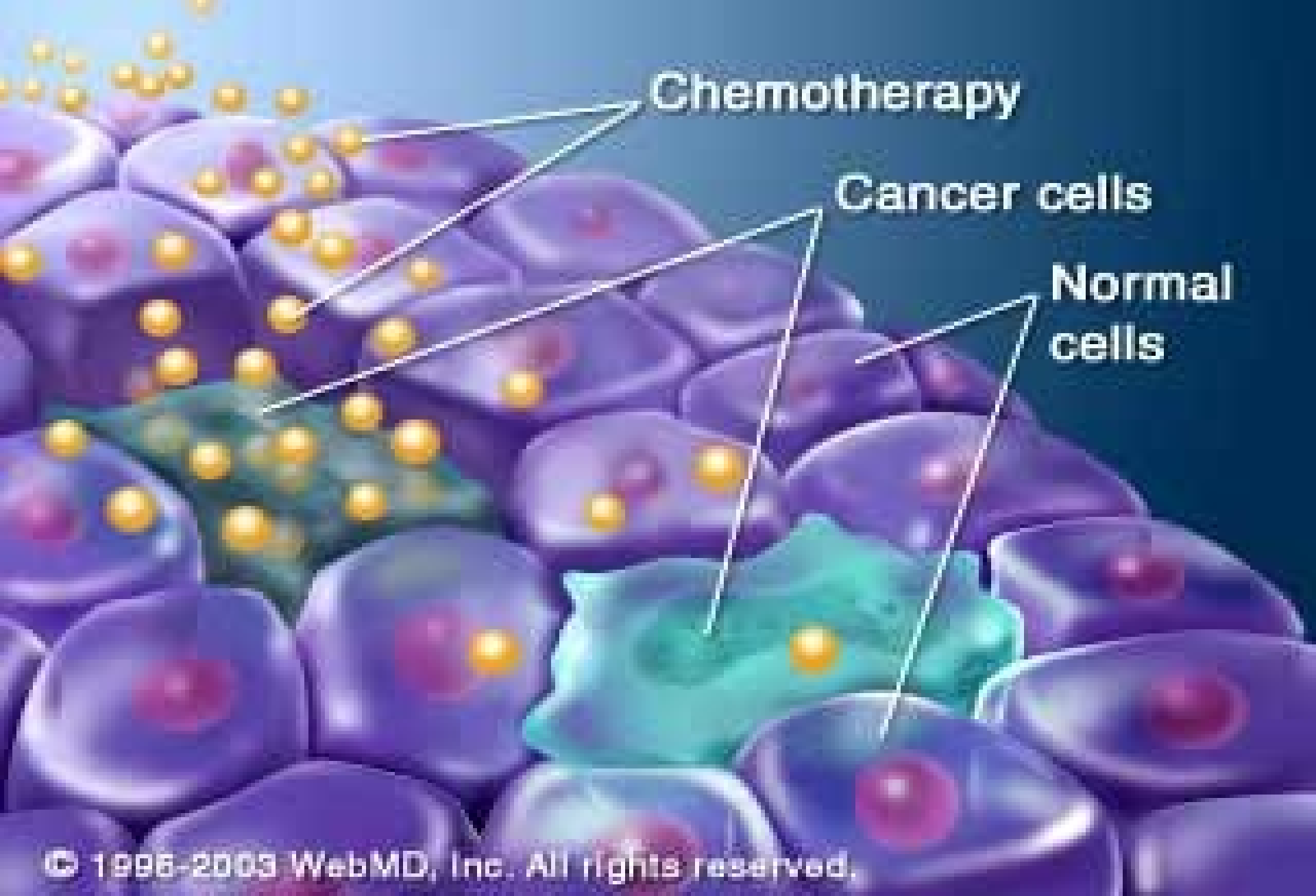
Drugs and the cell cycle

- **Class 1 agents (e.g., radiation, mechlorethamine, and carmustine)**
 - Exert their cytotoxicity in a nonspecific (i.e., non–proliferation dependent) manner.
 - kill both normal and malignant cells to the same extent.
- **Class 2 agents are phase specific**
 - Only a certain proportion of cells are sensitive
 - ✓ Hydroxyurea and cytarabine (cells in the S-phase).
 - ✓ bleomycin (G2- and early M-phases)
 - ✓ Should be given either by continuous infusion or in frequent small doses

Drugs and the cell cycle (cont'd)

➤ **Class 3 agents**

- kill proliferating cells in preference to resting cells.
- Recommended that these proliferation-dependent but non–phase-specific agents be administered in single large doses to take advantage of their sparing effect on normal cells that may be in G_0 .



Tumor Growth and Growth Fraction

- The rate of growth of cancers is initially quite rapid (exponential) and then **slows until a plateau is reached**
- The decrease in growth rate with increasing tumor size is related to
 - ✓ a decrease in the proportion actively proliferating cells(the growth fraction).
 - ✓ increase in cell loss due to hypoxic necrosis, poor nutrient supply, immunological defense mechanisms....

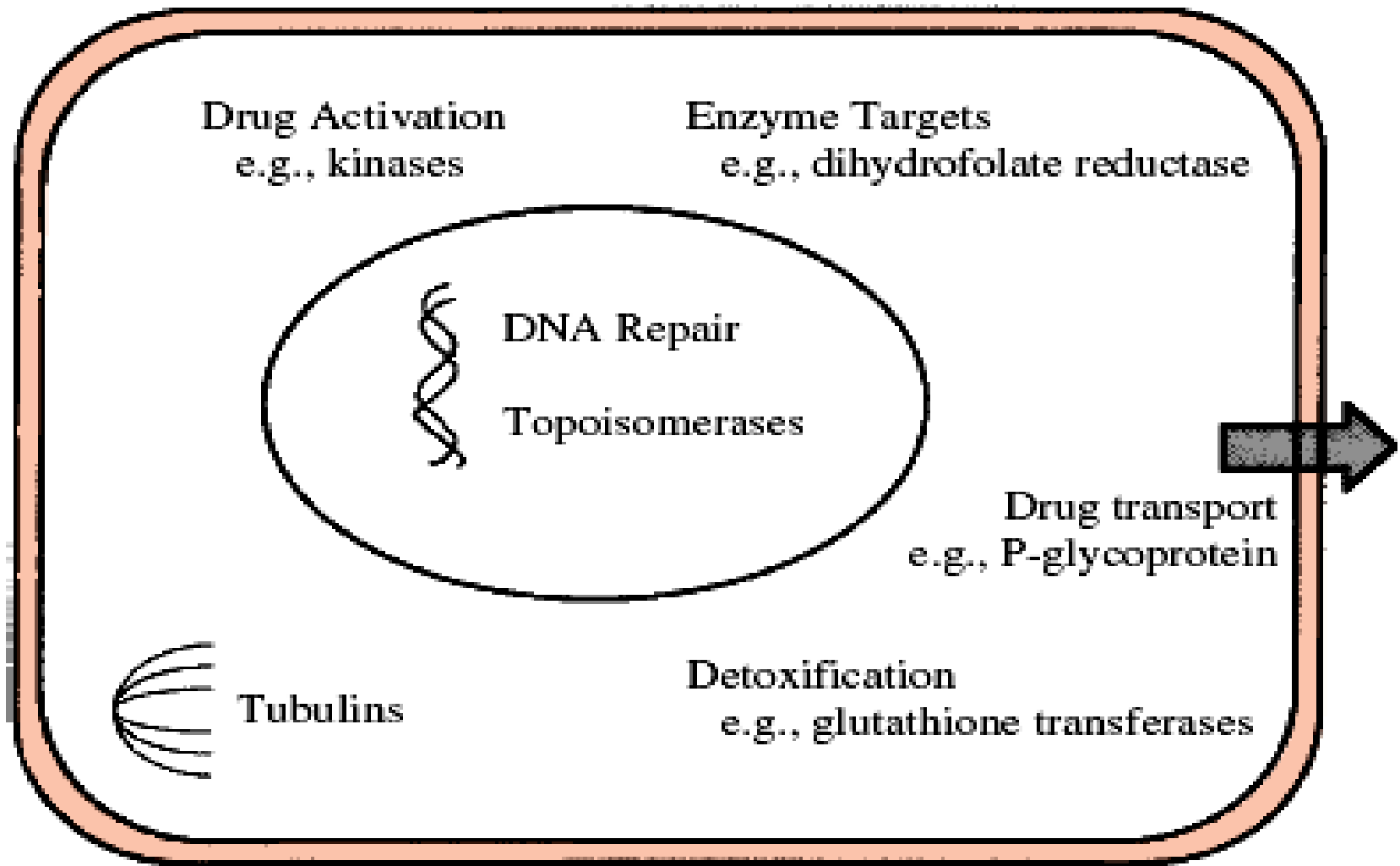
Tumor Growth and Growth Fraction (cont'd)

- The growth fraction indicates dividing cells that are potentially sensitive to chemotherapy
 - Tumors with high growth fractions are easily curable by drugs
 - ✓ Burkitt's lymphoma and trophoblastic choriocarcinoma are curable by single-agent chemotherapy (both have growth fractions close to 100%)
 - As tumors grow larger, the GF decreases, and the greater the distance of cells from nutrient blood vessels, the more likely they are to be in the G_0 , or resting, phase.

Tumor Growth and Growth Fraction (cont'd)

- Factors to consider before chemotherapy of a tumor with low GF is initiated
 - the earlier chemotherapy is instituted, the greater the chance of a favorable response
 - Debulking of tumors by surgery or radiation may be a means of stimulating the remaining cells into active proliferation.
 - Small metastases may respond to drugs more dramatically than will large primary tumors or a larger metastasis in the same patient.

Drug Resistance



General Toxicological Properties

- Most of the drugs used in cancer treatment have a therapeutic index that approaches unity
- lack of ***selective toxicity*** is the major limiting factor in the chemotherapy of cancer.
- Rapidly proliferating normal tissues, such as bone marrow, GIT, and hair follicles, are the major sites of acute toxicity

General Toxicological Properties (cont'd)

➤ Bone marrow toxicity

- Destruction of actively proliferating hematopoietic precursor cells ⇒ decreased WBC and platelet counts
 - ✓ Increased incidence of infections and hemorrhage.

➤ GIT Toxicity

- Nausea and vomiting ⇒ indirect effect
- stomatitis, dysphagia, diarrhea, Oral ulcerations, esophagitis

General Toxicological Properties (cont'd)

➤ *Hair Follicle Toxicity*

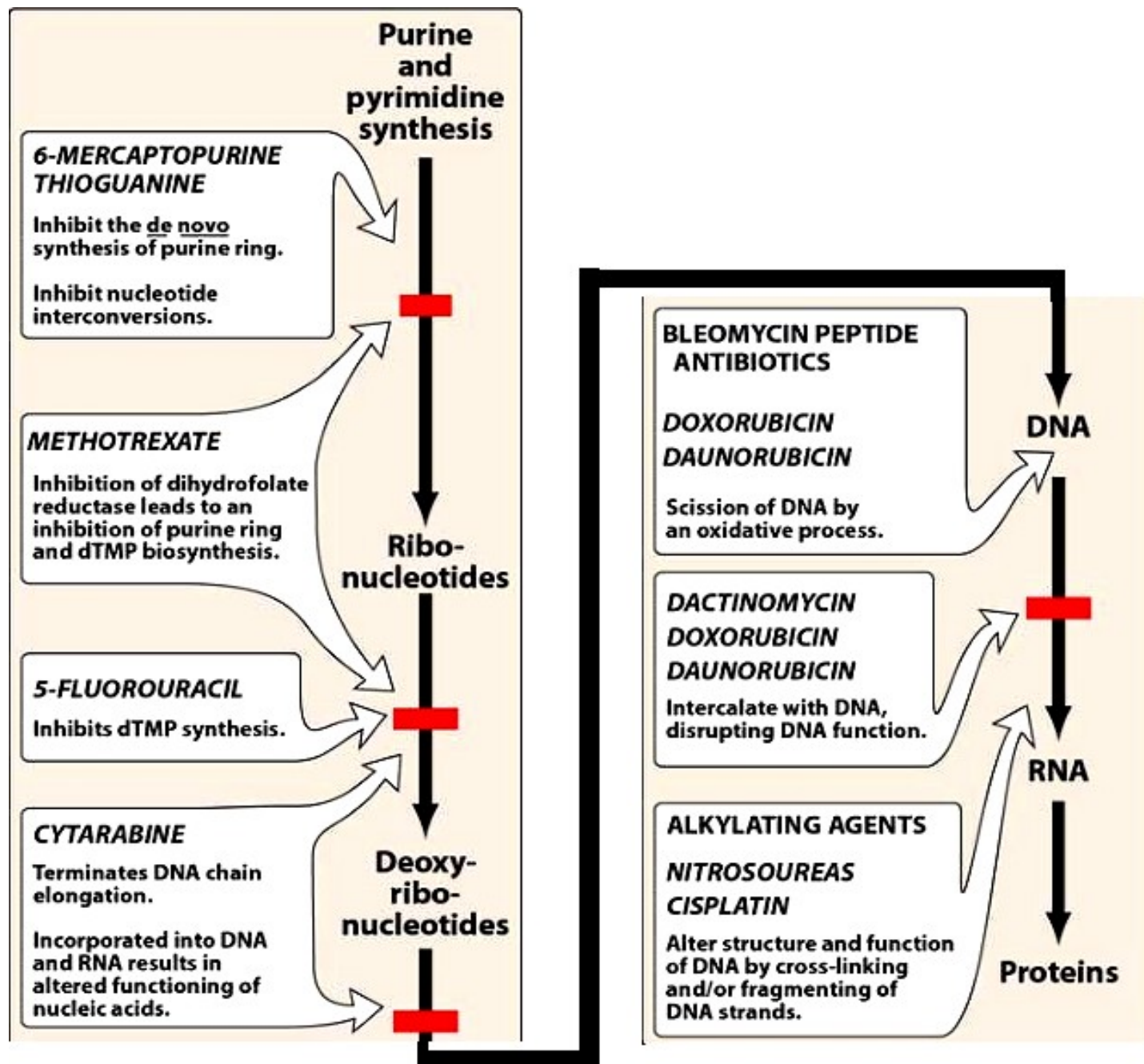
- Most anticancer drugs damage hair follicles and produce partial or complete alopecia.
- Patients should be warned, especially if paclitaxel, cyclophosphamide, doxorubicin, vincristine, methotrexate, or dactinomycin is used.
- Hair usually regrows normally after completion of chemotherapy.

Combination Chemotherapy

- Principles in designing combination therapy
 - Each drug in the combination regimen should have some individual therapeutic activity against the particular tumor being treated.
 - Drugs that act by different mechanisms may have additive or synergistic therapeutic effects.
 - Drugs with different dose-limiting toxicities should be used to avoid cumulative damage to an organ.

➤ Adjuvant chemotherapy

- Use of antineoplastic drugs when surgery or radiation therapy has eradicated the primary tumor
- High risk of relapse due to micrometastases.
- Should employ drugs that are known to be effective in the treatment of advanced stages of the particular tumor being treated.



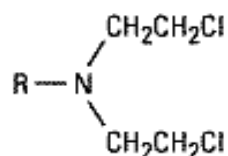
Hormone Antagonists

- **Some cancers such as breast cancer are initiated by hormones like estrogens to grow.**
- **Hence, hormone antagonists are considered to be effective**
- **E.g.;**
- **Tamoxifen**
 - **antagonist of estrogen receptor in breast tissue**
 - **Converted to its active metabolite, hydroxytamoxifen.**
 - **In endometrium, it behaves as mixed agonist/antagonist.**
 - **DOC for hormone receptor-positive breast cancer in pre-menopausal and post-menopausal women**
 - **Tamoxifene 20mg po /d for life for breast cancer.**

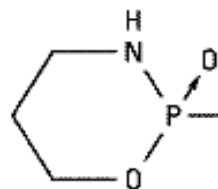
I. Alkylating Agents

➤ Chemistry

- Are strong electrophiles which form covalent linkages by alkylation of various nucleophilic moieties (phosphate, amino, sulfhydryl, hydroxyl, carboxyl gps)
- Chemotherapeutic and cytotoxic effects are directly related to the alkylation of DNA.
- five subtypes:
 - ✓ **nitrogen mustards**
 - ✓ **Alkyl sulfonates**
 - ✓ **Nitrosoureas**
 - ✓ **Ethyleneimine**
 - ✓ **Thiazines**

BIS(CHLOROETHYL)AMINES

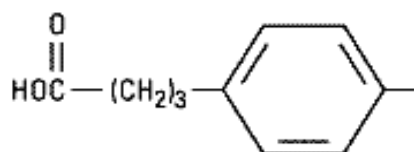
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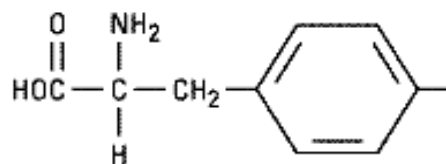
Cyclophosphamide



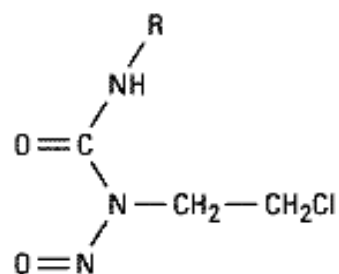
Mechlorethamine



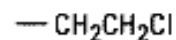
Chlorambucil



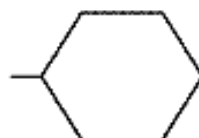
Melphalan

NITROSOUREAS

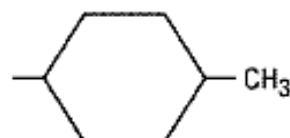
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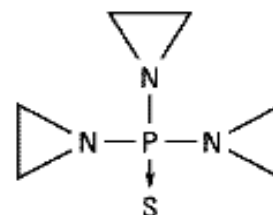
**BCNU
(carmustine)**



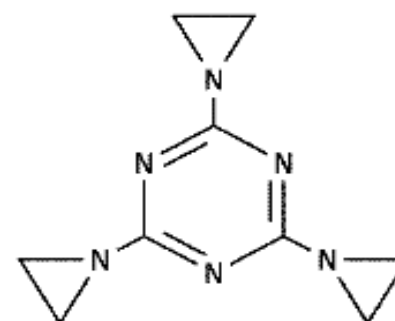
**CCNU
(lomustine)**



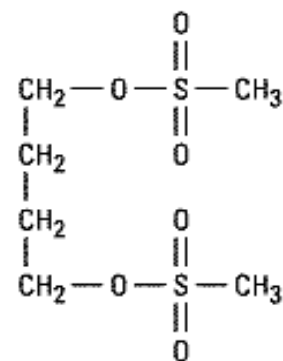
**Methyl-CCNU
(semustine)**

AZIRIDINES

Thiotepa



Triethylenemelamine

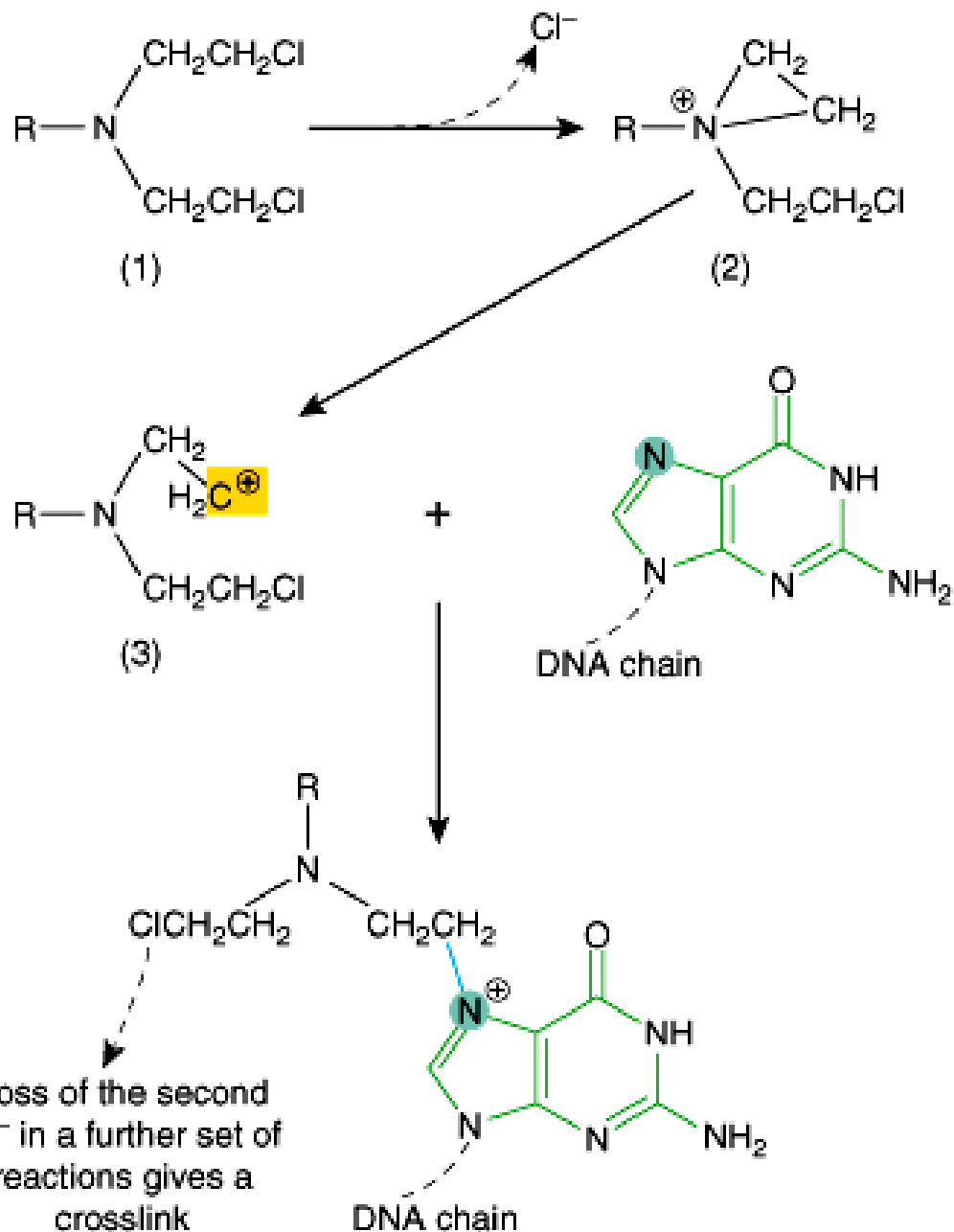
ALKYLSULFONATE

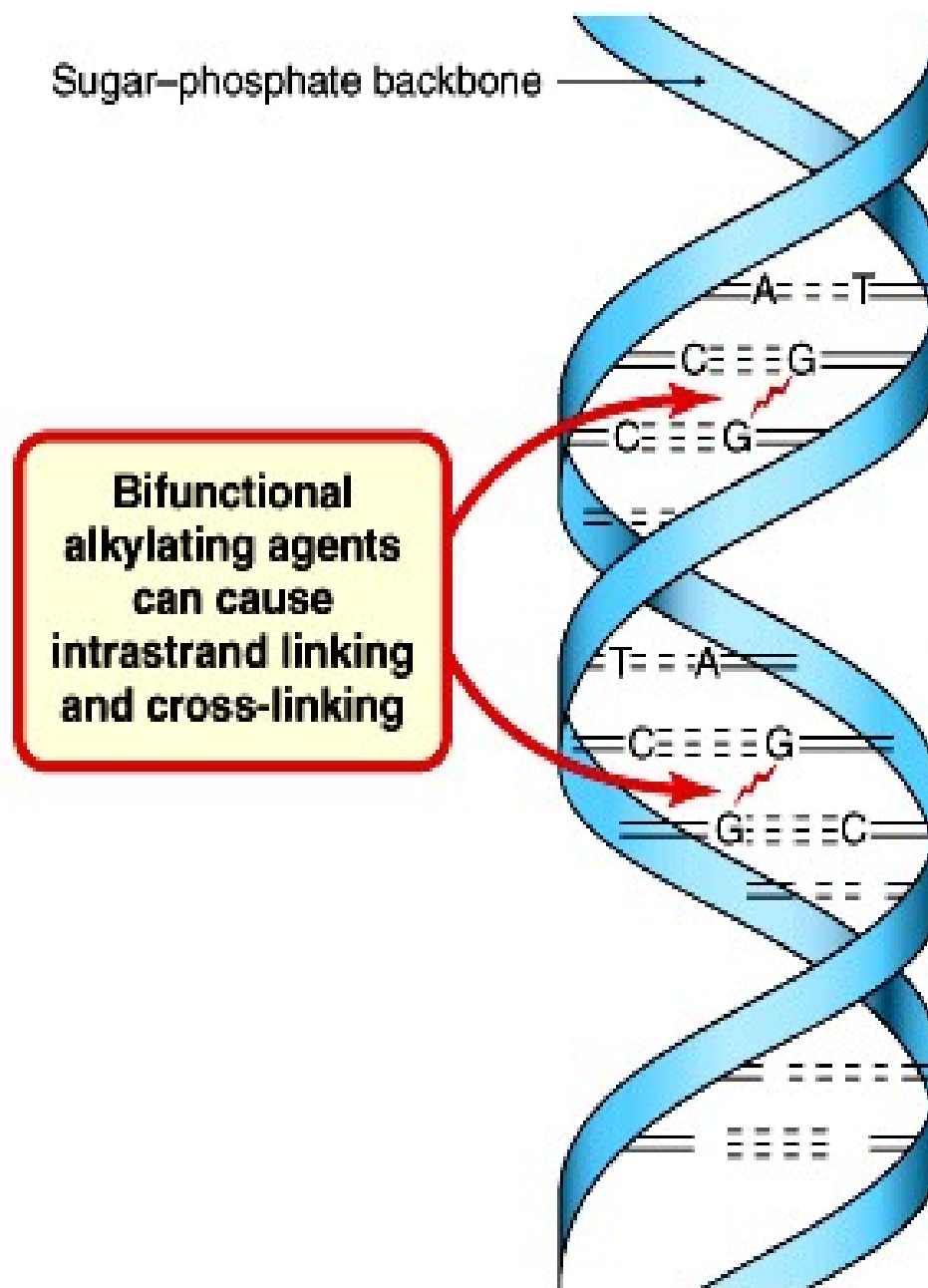
Busulfan

Nitrogen Mustards

➤ Mechlorethamine

- Considered the first modern anticancer drug
- In aqueous solution loses a chloride atom and forms a cyclic ethylenimmonium ion which interacts with nucleophilic groups, such as the N7 and O6 of guanine, and leads to an interstrand cross-linking of DNA.
- Generally more toxic to proliferating cells than to resting cells.
- Has a chemical and biological $t_{1/2}$ in plasma of less than 10 minutes after IV injection.





➤ Mechlorethamine (Cont'd)

■ Indication

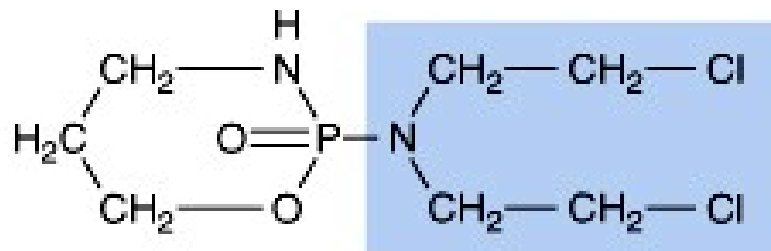
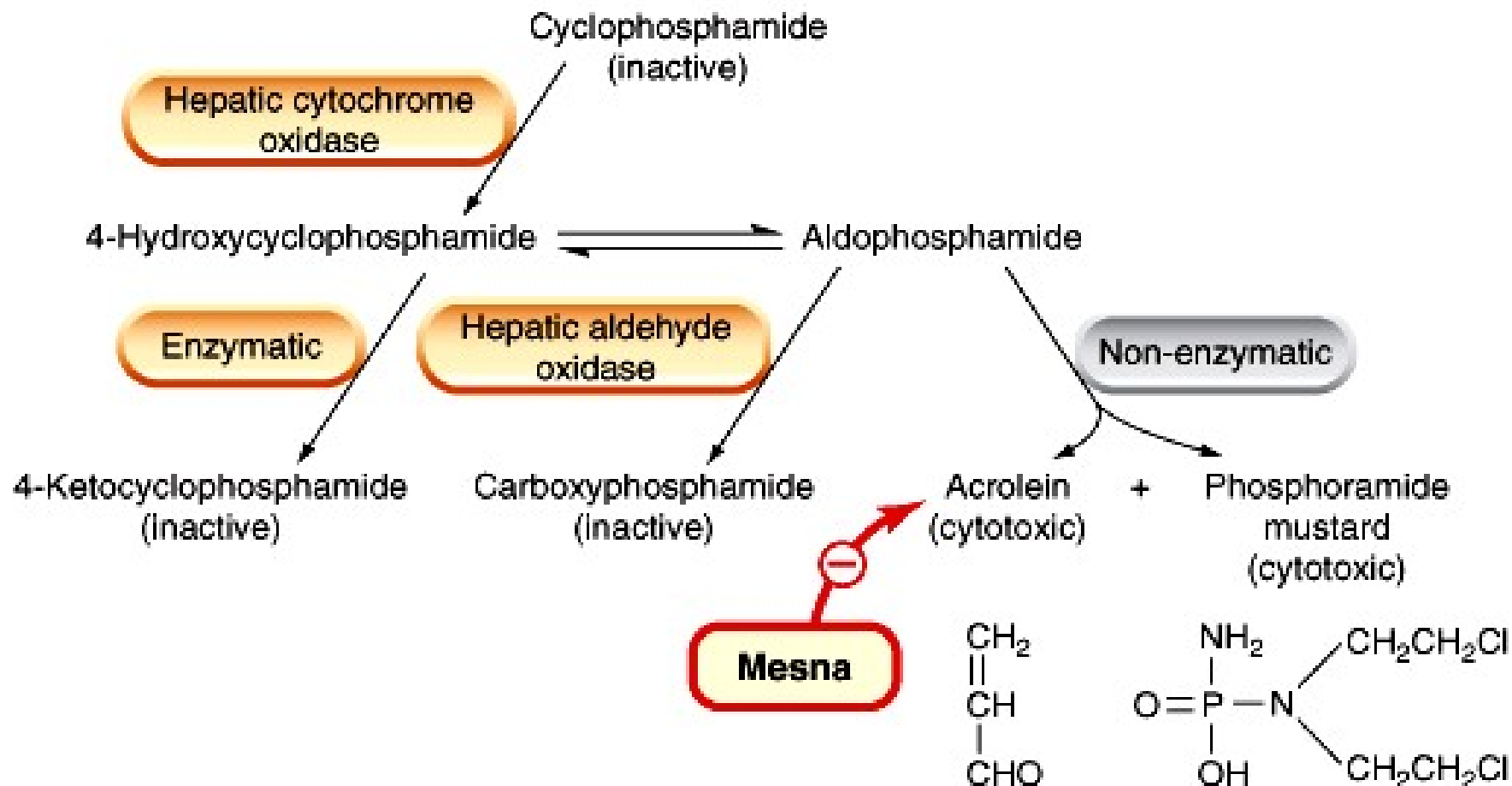
- ✓ Hodgkin's disease (as combination of mechlorethamine, vincristine, procarbazine, prednisone)

■ Adverse effects

- Dose-limiting toxicity : *myelosuppression (leukopenia and thrombocytopenia)*
- Affects rapidly proliferating normal tissues and cause alopecia, diarrhea, and oral ulcerations.
- *Nausea and vomiting may* occur 1 to 2 hours after injection
- Reproductive toxicity (amenorrhea and inhibition of oogenesis and spermatogenesis).
- Teratogenic and carcinogenic in experimental animals.

➤ Cyclophosphamide

- *The most versatile and* useful of the nitrogen mustards.
- Possess the broadest spectrum of antitumor activity of all alkylating agents.
- Same MOA
- Must be activated metabolically by microsomal enzymes of the cytochrome P450 system before ionization of the chloride atoms and formation of the cyclic ethylenimmonium ion can occur.
- The metabolites phosphoramidate mustard and acrolein are thought to be the ultimate active cytotoxic moiety derived from cyclophosphamide.



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➤ Cyclophosphamide (cont'd)

■ Indications

- In lymphomas (frequently used in combination with vincristine and prednisone)

- ✓ High IV dosages are often curative in Burkitt's lymphoma
- ✓ Oral daily dosages useful for less aggressive tumors (nodular lymphomas, myeloma, and chronic leukemias)

■ Breast cancer

- ✓ As a component of the combination: cyclophosphamide, methotrexate, 5-fluorouracil

■ Others

- ✓ Ovarian cancer, oat-cell and non-oat cell lung cancers, various sarcomas carcinomas of the testes, cervix, and bladder.
- ✓ in suppressing immunological rejection of transplant organs (alternative to azathioprine)

➤ Cyclophosphamide (cont'd)

■ Adverse effects

- ✓ Major dose limiting toxicity : bone marrow suppression
 - Reduces number of circulating lymphocytes and impairs the function of both humoral and cellular (i.e., B and T cell) immune system.
 - Chronic therapy increases the risk of infections.
- ✓ Nausea may occur a few hours after administration.
- ✓ Alopecia is more common than with other mustards.
- ✓ Cystitis (unique to cyclophosphamide and ifosfamide)
- ✓ Chronic drug treatment
 - Infertility, amenorrhea, possible mutagenesis and carcinogenesis.

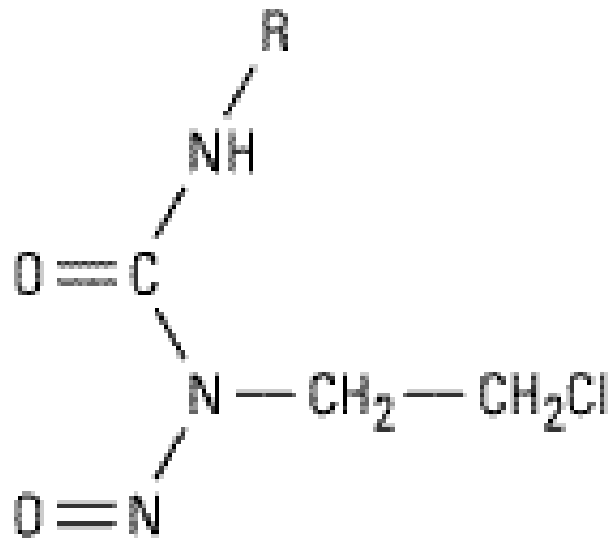
➤ Chlorambucil

- MOA and spectrum of activity similar
- Used primarily as daily palliative therapy for chronic lymphocytic leukemia, Waldenström's macroglobulinemia, myeloma, and other lymphomas.
- Bone marrow toxicity (major side effect)
- Nausea is uncommon or mild, and hair loss does not occur.
- immunosuppressive, teratogenic, and carcinogenic

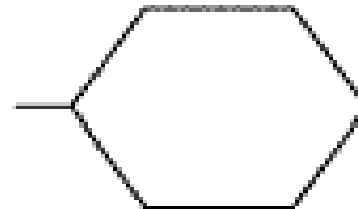
Nitrosoureas

- Include carmustine, lomustine, semustine
- Highly lipid soluble
 - Facilitates distribution into the brain and CSF
- Are chemically unstable, forming highly reactive decomposition products.
- The chemical half-life of these drugs in plasma is only 5 to 15 minutes.

NITROSOUREAS



BCNU
(carmustine)



CCNU
(lomustine)



Methyl-CCNU
(semustine)

Nitrosoureas (cont'd)

- Therapeutic and toxic effects are due to alkylation and carbamoylation
- Indication
 - Used as secondary treatment of Hodgkin's disease
 - Others: non-Hodgkin's lymphomas, multiple myeloma, melanoma, renal cell carcinoma, and colorectal cancer.

Nitrosoureas (cont'd)

➤ Adverse effects

- Severe nausea and vomiting
- The major site of dose-limiting toxicity is the bone marrow (leukopenia and thrombocytopenia)
- Less frequent side effects include alopecia, stomatitis, mild abnormalities of liver function.
- potentially mutagenic, teratogenic, and carcinogenic.

➤ Streptozocin

- A water-soluble nitrosourea
- Acts through methylation of nucleic acids and proteins.
- Streptozocin produces remission in 50 to 60% of patients with islet cell carcinomas of the pancreas.
- Almost all patients experience nausea and vomiting.
- Major toxicity: renal tubular damage
- Less severe toxicities include diarrhea, anemia, and mild alterations in glucose tolerance or liver function tests.

Alkyl Sulfonates

➤ Busulfan

- Forms intrastrand cross-linkages with DNA.
- Well absorbed after oral administration and has a plasma half-life of less than 5 minutes.
- Used in the palliative treatment of chronic granulocytic leukemia.
- Excessive uric acid production from rapid tumor cell lysis should be prevented by coadministration of **allopurinol**.
- Adverse effects
 - ✓ Thrombocytopenia and anemia and less commonly, nausea, alopecia, mucositis, and sterility also may occur

Ethylenimines

➤ Thiotepea

- Chemically less reactive than the nitrogen mustards, it is thought to act by similar mechanisms.
- Has antitumor activity against ovarian and breast cancers and lymphomas.
- largely supplanted by cyclophosphamide and other nitrogen
- **Major toxicities:** nausea and myelosuppression

Triazenes

➤ **Dacarbazine**

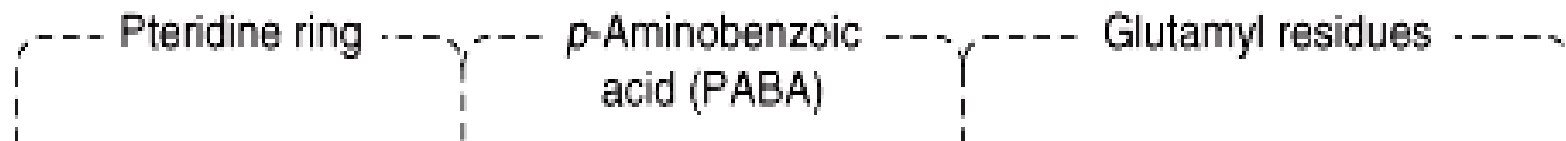
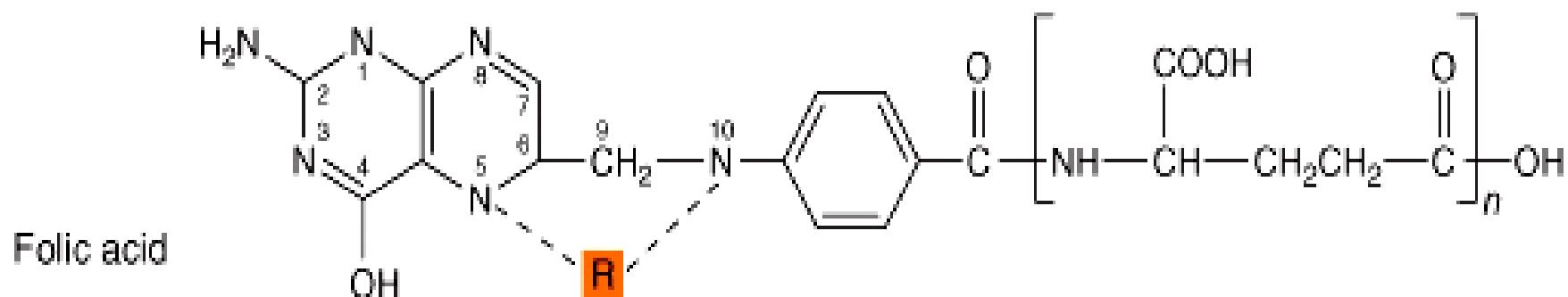
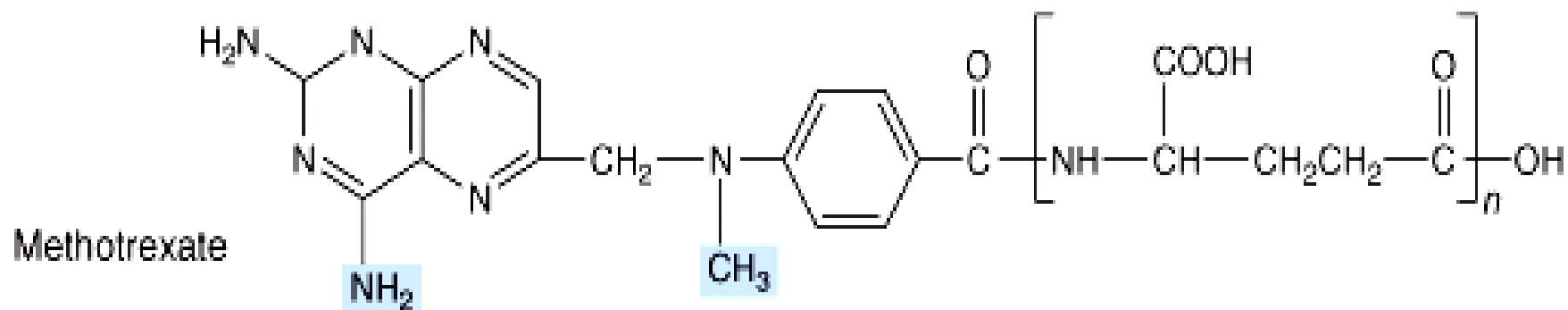
- Activated by photodecomposition and by enzymatic N-demethylation followed by methylation of DNA and RNA and inhibition of nucleic acid and protein synthesis.
- MOA: Same as with other alkylating agents
- Not appreciably protein bound, and it does not enter the CNS
- Dacarbazine is the most active agent used in metastatic melanoma, producing a 20% remission rate
- Adverse effects
 - ✓ May cause severe nausea and vomiting
 - ✓ Leukopenia and thrombocytopenia

II. Antimetabolites

Folate Antagonists

➤ **Methotrexate**

- Dihydrofolate reductase inhibitor
 - inhibition of DNA synthesis through a blockage of the biosynthesis of thymidylate and purines.
- Cells in S-phase are most sensitive
- Resistance
 - ✓ Increased intracellular DHFR levels
 - ✓ DHFR with decreased affinity for methotrexate
 - ✓ Decrease in methotrexate transport into cells



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➤ Methotrexate (Cont'd)

▪ **Clinical uses**

- ✓ Part of curative combination chemotherapy for acute lymphoblastic leukemias, Burkitt's lymphoma, and trophoblastic choriocarcinoma.
- ✓ Adjuvant therapy of breast carcinoma;
- ✓ High-dose methotrexate administration with leucovorin rescue has produced remissions in 30% of patients with metastatic osteogenic sarcoma.
- ✓ One of few anticancer drugs that can be safely administered intrathecally for the treatment of meningeal metastases.
- ✓ Immunosuppressive agent in severe rheumatoid arthritis.

➤ **Methotrexate (Cont'd)**

▪ **Adverse effects**

- ✓ Major dose-limiting toxicity: Myelosuppression
- ✓ GI toxicity (ulcerative mucositis and diarrhea).
- ✓ Nausea, alopecia, and dermatitis are common with high-dose methotrexate.
- ✓ renal toxicity (with high-dose due to precipitation of the drug in the renal tubules)
- ✓ Severe and progressive myelopathy or encephalopathy (neurological toxicity due to Intrathecal administration)
- ✓ A potent teratogen and abortifacient.

➤ **Methotrexate (Cont'd)**

- **Drug Interactions**

- ✓ Salicylates, probenecid, and sulfonamides inhibit the renal tubular secretion of methotrexate and may displace it from plasma proteins.
- ✓ Asparaginase inhibits protein synthesis and may protect cells from methotrexate cytotoxicity by delaying progression from G₁-phase to S-phase.

➤ Gemcitabine

- An antimetabolite, undergoes metabolic activation to difluorodeoxycytidine triphosphate, which interferes with DNA synthesis and repair.
- Single most active agent for the treatment of metastatic pancreatic cancer
- First-line agent for both pancreatic and small cell lung cancer.
- Dose-limiting toxicity: BMS

Purine Analogues

➤ Thioguanine (6-Thioguanine)

■ MOA

- ✓ Activated to 6-thioguanosine-5-monophosphate followed by
 - Incorporation of the thio nucleotide analogue into DNA or RNA
 - Feedback inhibition of purine nucleotide synthesis

■ Resistance

- ✓ Decreased activity of hypoxanthine guanine–phosphoribosyltransferase and
- ✓ Increased inactivation of the thio nucleotides by alkaline phosphatase.

➤ Thioguanine (cont'd)

- Clinical use
 - ✓ Part of a combined induction of chemotherapy in acute myelogenous leukemia.
- Adverse effects
 - ✓ Myelosuppression with leukopenia and thrombocytopenia (most common)
 - ✓ Liver toxicity with jaundice (less common than with mercaptopurine)

➤ **Mercaptopurine (6-Mercaptopurine)**

- An analogue of hypoxanthine
- Now used in the maintenance therapy of acute lymphoblastic leukemia.
- Activated by the enzyme HGPRTase, which inhibits the synthesis of the purines adenine and guanine and the conversion of inosinic acid to the nucleotides adenylylate and guanylate.
- Some mercaptopurine is also incorporated into DNA in the form of thioguanine.

➤ Mercaptopurine (cont'd)

- Resistance
 - ✓ Decreased drug activation by HGPRTase
 - ✓ Increased inactivation by alkaline phosphatase.
- **Major toxicities**: myelosuppression, nausea, vomiting, and hepatic toxicity.

Other purine analogs

➤ Fludarabine

- Fluorinated purine analogue

➤ Pentostatin

- Purine analogue
- MOA: inhibition of adenosine deaminase
- Effective in the therapy of hairy cell leukemia
- Adverse effects: myelosuppression, nausea, and skin rashes.

➤ Cladribine

- Synthetic purine nucleoside
- Relatively selective for both normal and malignant lymphoid cells and kills resting as well as dividing cells by mechanisms that are not completely understood.

Pyrimidine Analogues

➤ **Cytarabine (cytosine arabinoside)**

- An analogue of cytidine and deoxycytidine.
- kills cells in the S-phase of cell cycle by competitively inhibiting DNA polymerase
- Activated by pyrimidine nucleoside kinases to aracytosine triphosphate
- half-life in plasma of only 10 minutes after IV bolus
- Used in acute myelogenous leukemia (usually in + with an anthracycline agent, thioguanine, or both.
- Myelosuppression, severe BM hypoplasia (major)
- Nausea and mucositis also may occur.

➤ **Fluorouracil (5-Fluorouracil)**

- Halogenated pyrimidine analogue
- Activated to 5-fluoro-2-deoxyuridine-S'-phosphate (FdUMP) which inhibits thymidylate synthetase (that catalyzes conversion of dUMP to dTMP)
- 5-Fluorouracil is selectively toxic to proliferating rather than non-proliferating cells and is active in both the G₁-and S-phases.

➤ Fluorouracil (cont'd)

- Use

- ✓ In several combination regimens in the treatment of breast cancer.
- ✓ Palliative activity in GI adenocarcinomas

- Adverse effects

- ✓ Mild nausea if at all it occurs
- ✓ Myelosuppression (severe with IV bolus administration)

ANTIBIOTICS

➤ **Doxorubicin and Daunorubicin**

- Anthracycline antibiotics derived from *Streptomyces peucetius*.
- Daunorubicin is used to treat acute leukemias, while doxorubicin is extensively employed against a broad spectrum of cancers.
- MOA
 - ✓ Intercalates between base pairs
 - Results in steric hindrance, hence production of single-strand breaks in DNA and inhibition of DNA synthesis and DNA-dependent RNA synthesis
 - ✓ Generation of free radicals which contributes to
 - Anticancer activity
 - Cardiotoxic effects

➤ **Doxorubicin and Daunorubicin (cont'd)**

- Resistance

- ✓ Decreased drug accumulation due to enhanced active efflux of drug which shows high cross-resistance to other anthracyclines, vinca alkaloids, dactinomycin and podophylotoxins

- Doxorubicin is one of the most effective agents used in the treatment of carcinomas of the breast, ovary, endometrium, bladder, and thyroid and in oat cell cancer of the lung.

➤ **Doxorubicin and Daunorubicin (cont'd)**

- **Adverse effects**

- ✓ Acutely, doxorubicin may cause transient cardiac arrhythmias and depression of myocardial function.
- ✓ Bone marrow suppression

➤ **Other anticancer antibiotics**

- Idarubicin, Bleomycin, Mitomycin, Dactinomycin, Plicamycin.

PLANT-DERIVED PRODUCTS

- **Vinca alkaloids**
 - vincristine, vinblastine, and vinorelbine
- **Epipodophyllotoxins**
 - etoposide and teniposide
- **Taxanes**
 - paclitaxel and taxotere
- These classes differ in their structures and MOA but share the MDR mechanism, since they are all substrates for the multidrug transporter P-glycoprotein.

Vincristine

- mitotic inhibitor
- binds to tubulin dimers, inhibiting assembly of microtubule structures.
- Disruption of the microtubules arrests mitosis.
- affect all rapidly dividing cell.
- also affects intestinal epithelium and bone marrow.

- delivered via iv infusion for use in various types of chemotherapy regimens.
- Its main uses are in non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- in acute lymphoblastic leukemia, and in treatment for neuroblastoma.

SE; peripheral neuropathy, hyponatremia, constipation, and hair loss.

Vinca Alkaloids

➤ MOA

- Bind avidly to tubulin, proteins that form the mitotic spindle during cell division, and hence cause cellular arrest in metaphase during mitosis

➤ Resistance

- Decreased rate of drug uptake
- Increased drug efflux
- Cross-resistance usually occurs with anthracyclines, dactinomycin, and podophyllotoxins.

Vinca Alkaloids (Cont'd)

➤ Use

- Vincristine is an important component of the curative combination chemotherapy for acute lymphoblastic leukemia, Hodgkin's disease (mechlorethamine, vincristine, procarbazine, prednisone) and non-Hodgkin's lymphomas.
- Its relative lack of myelosuppression makes it more attractive than vinblastine for use in combination with myelotoxic drugs.

Vinca Alkaloids (Cont'd)

➤ Adverse effects

- Dose limiting toxicity
 - Neurological toxicity (vincristine)
 - Bone marrow toxicity (vinblastine)
- Severe leukopenia (major side effect of vinblastine)

Epipodophyllotoxins

➤ Etoposide

- A semisynthetic derivative of podophyllotoxin
- MOA
 - ✓ forms a complex with topoisomerase II, which results in a single-strand breakage of DNA.
 - ✓ It is most lethal to cells in the S- and G2-phases of the cell cycle
- Resistance
 - ✓ Decreased cellular drug accumulation.
- Use
 - ✓ most useful against testicular and ovarian germ cell cancers, lymphomas, small cell lung cancers, and acute myelogenous and lymphoblastic leukemia.
- Toxicities
 - ✓ include mild nausea, alopecia, allergic reaction, phlebitis at the injection site, and bone marrow toxicity.

Taxanes

➤ Paclitaxel (Taxol)

■ MOA

- ✓ Binds to tubulin dimers and microtubulin filaments, promoting the assembly of filaments and preventing their depolymerization.
- ✓ Results in disruption of mitosis and cytotoxicity and disrupts other normal microtubular functions, such as axonal transport in nerve fibers.

■ Resistance

- ✓ Efflux out (leads to decreased intracellular drug accumulation).

■ Use

- ✓ Is among the most active of all anticancer drugs (significant efficacy against carcinomas of breast, ovary, lung, head, neck)
- ✓ Combined with cisplatin in the therapy of ovarian and lung carcinomas and with doxorubicin in treating breast cancer.

Taxanes contd...

- Adverse effects
 - ✓ Myelosuppression (major)
 - ✓ Alopecia (common),
 - ✓ Reversible dose-related peripheral neuropathy.
 - ✓ Nausea is usually mild or absent.
 - ✓ Cardiovascular (mild hypotension and bradycardia)

ENZYMES

➤ **L-Asparaginase**

- Derived from *E. coli* and *Erwinia carotovora*.
- It catalyzes the hydrolysis of L-asparagine to aspartic acid and ammonia. L-Glutamine also can undergo hydrolysis by this enzyme
- Tumor cells sensitive to L-asparaginase are deficient in the enzyme asparagine synthetase and therefore cannot synthesize asparagine.
 - Depletion of exogenous asparagine and glutamine inhibits protein synthesis in cells lacking asparagine synthetase → inhibition of nucleic acid synthesis and cell death.

➤ L-Asparaginase (cont'd)

▪ **Use**

- ✓ Treatment of acute lymphoblastic leukemia (major)
- ✓ Particularly useful in combination chemotherapy
 - Lack of cross-resistance, bone marrow and GI toxicity
- ✓ Treatment of certain types of lymphoma

▪ **Adverse effects**

- ✓ Hypersensitivity reactions
- ✓ Nausea, anorexia, weight loss, and mild fever (1/3 of patients)
- ✓ Hepatic toxicity (severe in fewer than 5% of cases).
- ✓ CNS toxicity (drowsiness, confusion, impaired mentation, and even coma)
- ✓ Pancreatitis (in 5 to 10% of cases).
- ✓ Hyperglycemia, possibly due to inhibition of insulin synthesis

The end