Microbiology

Antimicrobial Drug Therapy

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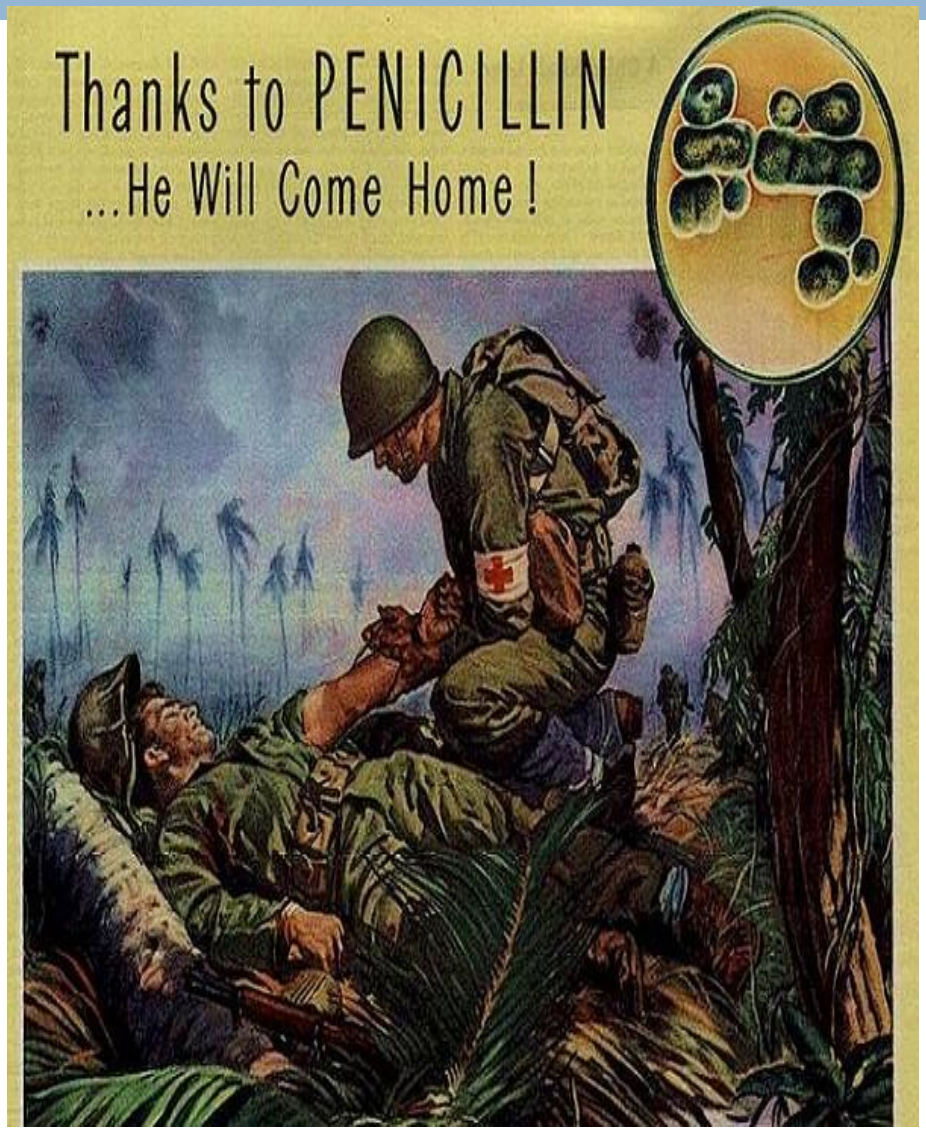
(1st) semester

5th lecture

Antimicrobial Drug Therapy

1928 – Fleming discovered penicillin, produced by ***Penicillium.***



History

1928- Alexander Fleming discovers a mold which inhibits the growth of staphylococcus bacteria

1940- penicillin is isolated and tested on mice by researchers at Oxford

1941- penicillin mass produced by fermentation for use by US soldiers in WWII

1950's- 6-APA (6-aminopenicillanic acid) is discovered and semi-synthetic penicillins are developed.

1960's to today- novel β-lactams/ β-lactamase inhibitors are discovered and modified from the natural products of bacteria

Antibiotic versus chemotherapeutic agent

Antibiotic strictly refers to substances that are of biological origin.

Chemotherapeutic agent refers to a synthetic chemical.

The distinction between these terms has been blurred because many of our newer "antibiotics" are actually chemically modified biological products or even chemically synthesized biological products. However, the term antibiotic is often used to refer to all types of antimicrobial agents.

Empiric therapy

- Often an **antibiotic is given to a patient before the organism infecting the patient is identified. This is known as empiric therapy**. The choice of drug is guided by knowing which organisms are likely to be causing the specific infection.
- Empiric therapy should be followed as much as possible by **directed narrow spectrum therapy** once the organism's identity and sensitivity to different antibiotics are established.

Selection of antimicrobial agents:

Selection of the most appropriate antimicrobial agent requires knowledge of:

1) The organism's identity,

2) The organism's susceptibility to a particular agent,

3) The site of the infection,

4) Patient factors, (age, drug allergy, pregnancy & lactation, renal & Hepatic function,…..)

5) The safety of the agent.

6) The cost of therapy.

Features of Antimicrobial Drugs:

1. Selective Toxicity

- **Cause greater harm to microorganisms than to host**

Clinicaly antimicrobial agents all exhibit selective toxicity toward the bacterium rather than the host. It is this characteristic that distinguishes antibiotics from disinfectants. When selectivity is high the antibiotics are normally not toxic. However, even highly selective antibiotics can have side effects.. Penicillins are a classic example of excellent selective toxicity. This class of antibiotic interferes with bacterial cell wall synthesis and repair. Euokaryotic cells do not have a cell wall and penicillins have remarkably low direct toxicity to humans

2. Antimicrobial Action

- **Bacteriostatic:** inhibit growth of microorganisms

Bacterostatic Some antibiotics do not kill bacteria at achievable serum concentrations but inhibit bactrerial growth, but growth is resumed upon drug withdrawal. Bacterostatic drugs are appropriate when the host's immune system is able to finish the job. Tetracyclines and sulfonamides are bacterostatic.

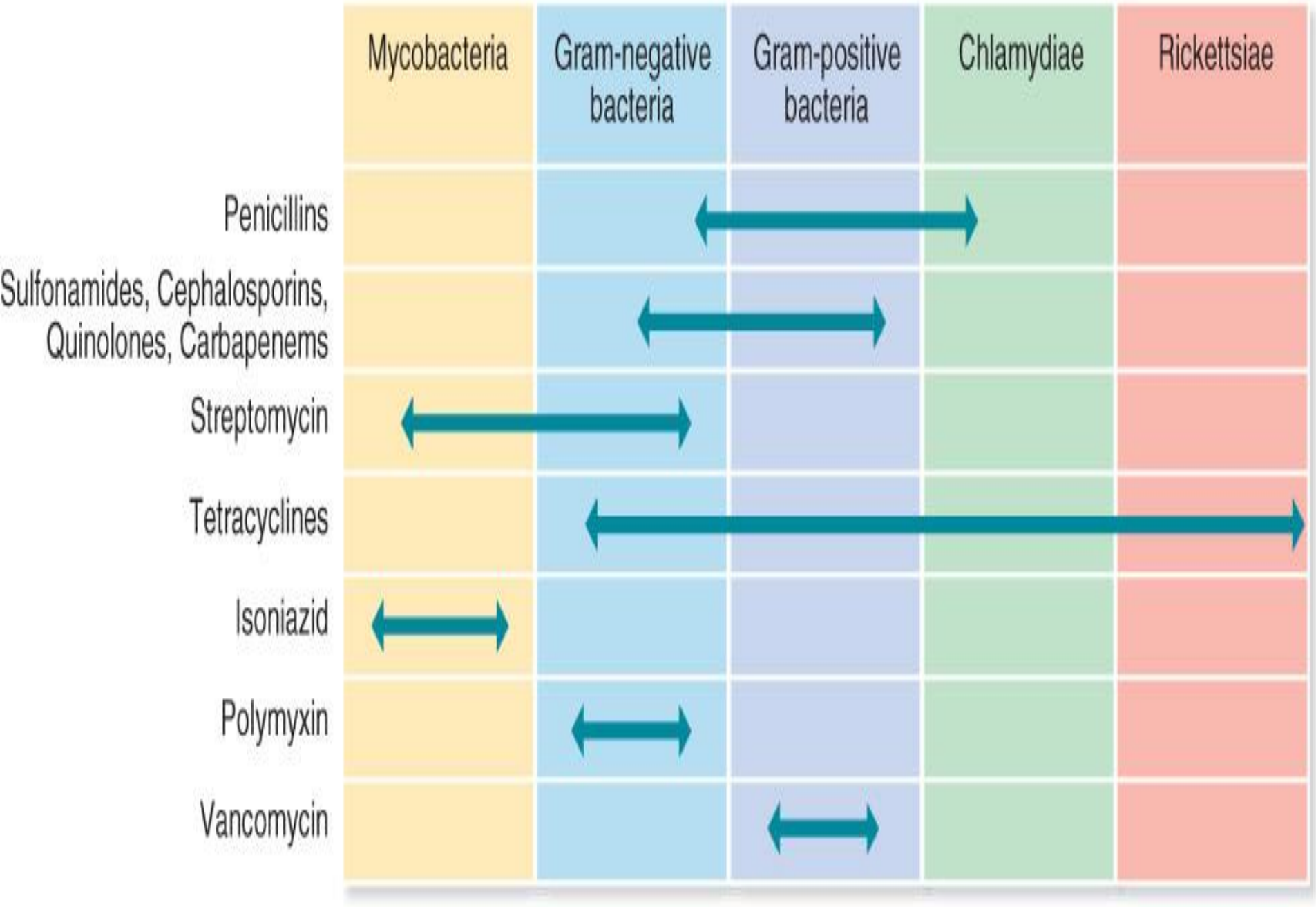
- **Bactericidal:** Kill microorganisms

Bactericidal Drugs that kill bacteria. In patients with immunologic compromise or life-threatening infection a bactericidal antibiotic should be given. Bactericidal drugs are also highly desirable in infections characterized by poor regional host defenses, such as endocarditis and meningitis. Penicillins and the other beta-lactam are examples of bactericidal drugs.

3. Spectrum of Activity

- Antimicrobial medications vary with respect to the range of microorganisms they kill or inhibit
- Some kill only limited range : Narrow-spectrum antimicrobial
- While others kill wide range of microorganisms: Broad-spectrum antimicrobial

- Some sites in the body are **'privileged'** like the central nervous system, prostate, joints and eyes. Infection in these sites must be treated with antibiotics that can penetrate them.
- In patients with renal or hepatic failure, it is often necessary to readjust drug dosing if the antibiotic is metabolized or excreted by one of these organs.


Mycobacteria
Gram-negative bacteria
Gram-positive bacteria
Chlamydiae
Rickettsiae
Penicillins
Sulfonamides, Cephalosporins, Quinolones, Carbapenems
Streptomycin
Tetracyclines
Isoniazid
Polymyxin
Vancomycin

4. Effects of Combining Drugs (synergy and antagonism)

- **synergy** When one drug's mechanism of action makes another drug more effective, they are said to work in synergy. For instance, penicillins by making the bacterial cell wall more permeable facilitate the action of aminoglycosides that work intracellularly and must gain entry into the cell.

- **Antagonism** occurs when one antibiotic, usually the one with the least effect, interferes with the effects of another antibiotic.

Combination therapy

Antibiotic synergism occurs when the effects of a combination of antibiotics is greater than the effects of the individual antibiotics.

Combination therapy with two or more antibiotics is used in special cases

- To prevent the emergence of resistant strains
- To treat emergency cases during the period when an etiological diagnosis is still in progress
- To take advantage of antibiotic synergism.
- To treat mixed infection such as following massive trauma.

5. Adverse Effects

1. **Allergic Reactions:** some people develop hypersensitivities to antimicrobials
2. **Toxic Effects:** some antimicrobials toxic at high concentrations or cause adverse effects
3. **Suppression of normal flora:** when normal flora killed, other pathogens may be able to grow to high numbers

6. Resistance to Antimicrobials

- Some microorganisms inherently resistant to effects of a particular drug
- Other previously sensitive microorganisms can develop resistance through spontaneous mutations or acquisition of new genes

Mechanisms of action of Antibacterial Drugs

1. Inhibit cell wall synthesis
2. Inhibit protein synthesis
3. Inhibit nucleic acid synthesis
4. Injury to plasma membrane
5. Inhibit synthesis of essential metabolites

Cell Wall (peptidoglycan synthesis)

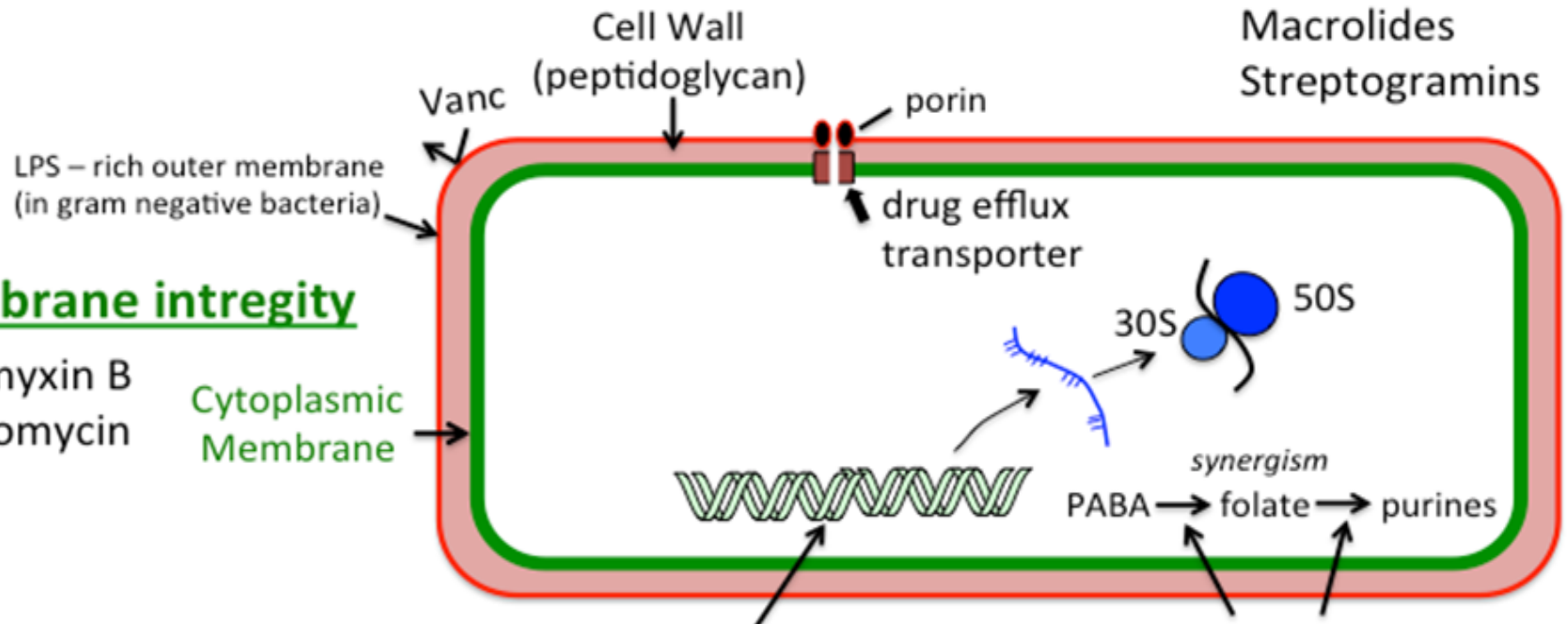
β-lactams
- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams

Bacitracin
Glycopeptides

Protein synthesis

30S inhibitors
- Aminoglycosides
- Tetracyclines
- Tigecycline

50S inhibitors
- Chloramphenicol
- Clindamycin
- Linezolid
- Macrolides
- Streptogramins



Membrane intregity

Polymyxin B
Daptomycin

Cytoplasmic Membrane

Nucleic acid synthesis

Fluoroquinolones
Metronidazole
Rifamycins

Metabolic pathways (folate)

Sulfonamides
Trimethoprim

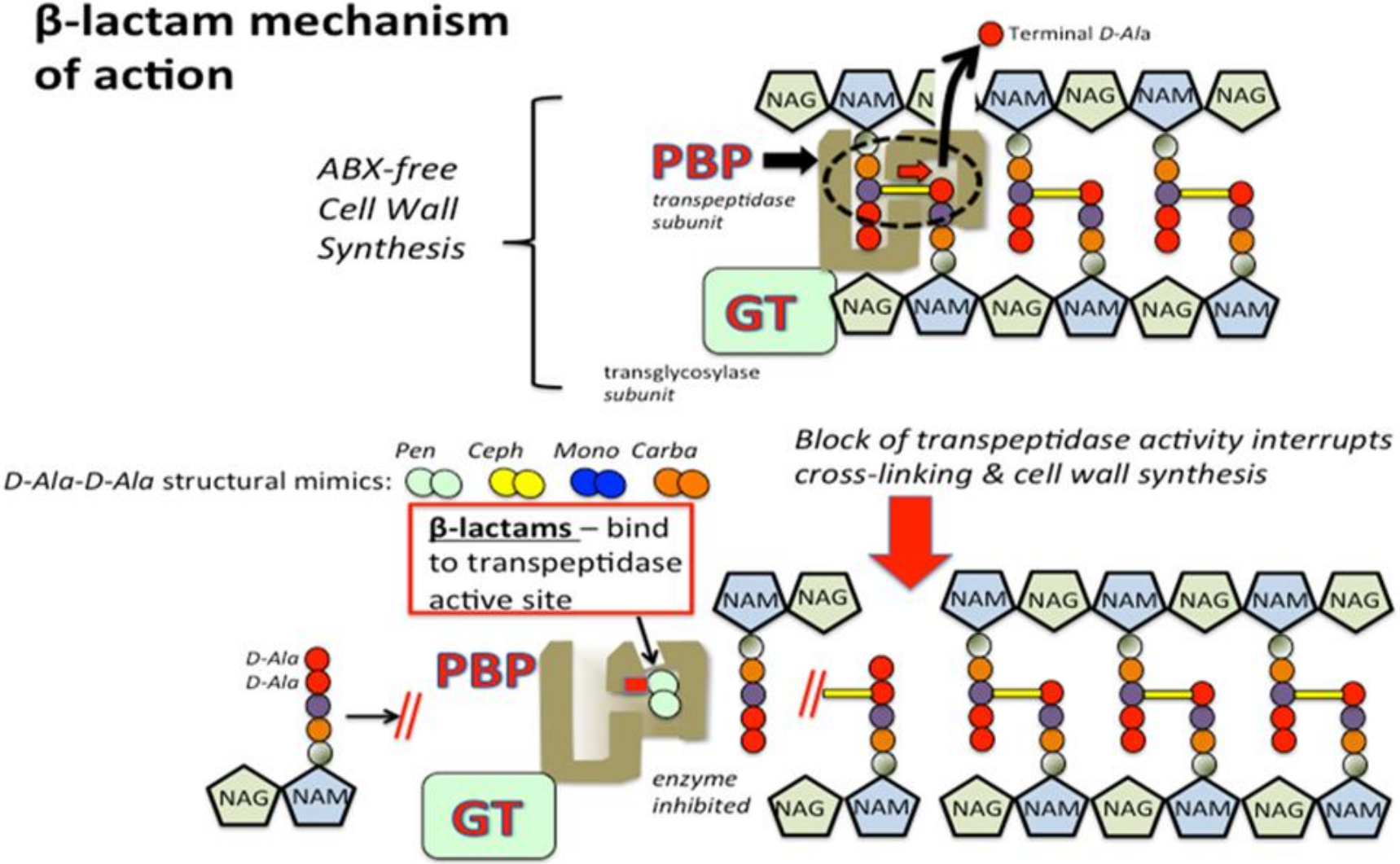
β-Lactam Drugs- inhibit cell wall synthesis

- Irreversibly inhibit enzymes involved in the final steps of cell wall synthesis
- These enzymes mediate formation of peptide bridges between adjacent stands of peptidoglycan
- β -lactam ring similar in structure to normal substrate of enzyme
- Drug binds to enzyme, competitively inhibit enzymatic activity

β-Lactams are divided into several classes based on their structure and function; and are often named by their origin, but all classes have a common β-Lactam ring structure.

β-lactams disrupt the synthesis of the bacterial cell wall by interfering with the transpeptidase which catalyzes the cross linking process.

Mechanism


β-lactam mechanism of action
ABX-free Cell Wall Synthesis
Terminal D-Ala
NAG
NAM
PBP
transpeptidase subunit
GT
transglycosylase subunit
D-Ala-D-Ala structural mimics:
Pen
Ceph
Mono
Carba
β-lactams – bind to transpeptidase active site
Block of transpeptidase activity interrupts cross-linking & cell wall synthesis
D-Ala
D-Ala
enzyme inhibited

Transpeptidase- PBP

- Peptidoglycan is a carbohydrate composed of alternating units of NAMA and NAGA.
- The NAMA units have a peptide side chain which can be cross linked from the L-Lys residue to the terminal D-Ala-D-Ala link on a neighboring NAMA unit.
- The cross linking reaction is catalyzed by a class of transpeptidases known as penicillin binding proteins
- A critical part of the process is the recognition of the D-Ala-D-Ala sequence of the NAMA peptide side chain by the PBP. Interfering with this recognition disrupts the cell wall synthesis.
- β-lactams mimic the structure of the D-Ala-D-Ala link and bind to the active site of PBPs, disrupting the cross-linking process.

Range of Activity

β-Lactams can easily penetrate Gram (+) bacteria, but the outer cell membrane of Gram (-) bacteria prevents diffusion of the drug. β-Lactams can be modified to make use of import porins in the cell membrane.

β-Lactams also have difficulty penetrating human cell membranes, making them ineffective against atypical bacteria which inhabit human cells.

Any bacteria which lack peptidoglycan in their cell wall will not be affected by β-lactams.

Toxicity

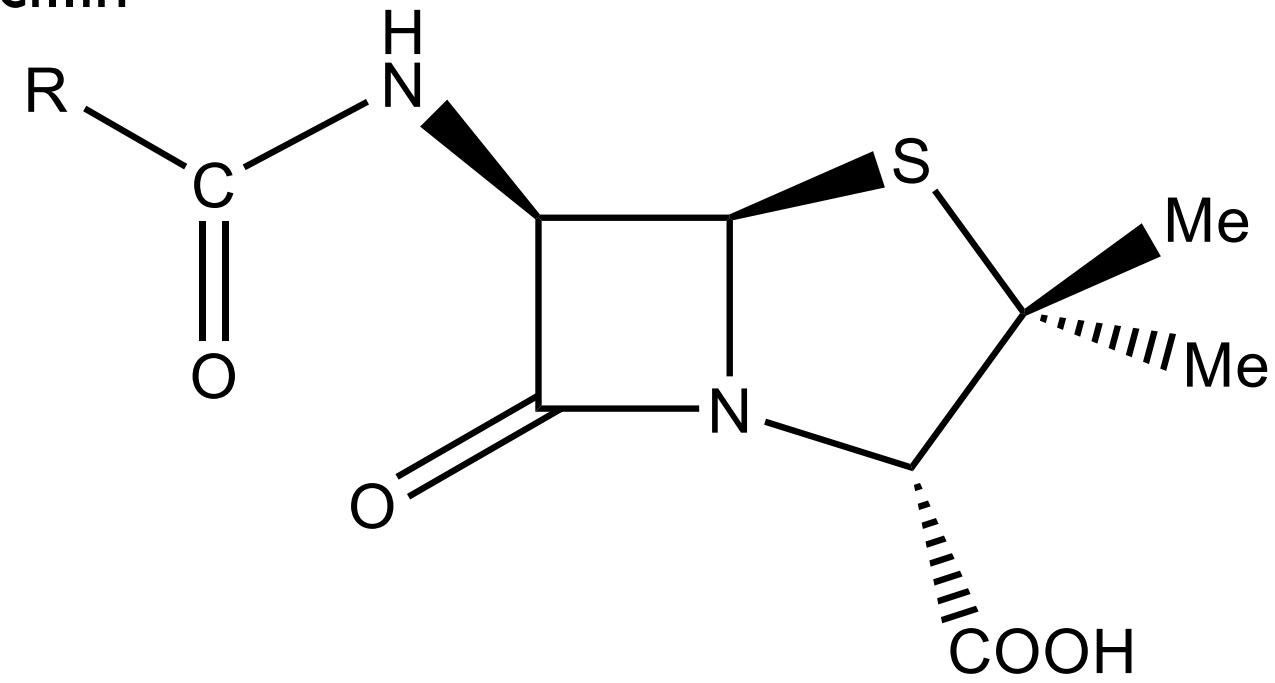
β-Lactams target PBPs exclusively, and because human cell membranes do not have this type of protein β-lactams are relatively non toxic compared to other drugs which target common structures such as ribosomes.

About 10% of the population is allergic (sometimes severely) to some penicillin type β-lactams.

Classes of β-Lactams

The classes of β-lactams are distinguished by the variation in the ring adjoining the β-lactam ring and the side chain at the α position.

Penicillin



Modification of β-Lactams

β-Lactam type antibiotics can be modified at various positions to improve their ability to:

-be administered orally (survive acidic conditions)

-be tolerated by the patient (allergies)

-penetrate the outer membrane of Gram (-) bacteria

-prevent hydrolysis by β-lactamases

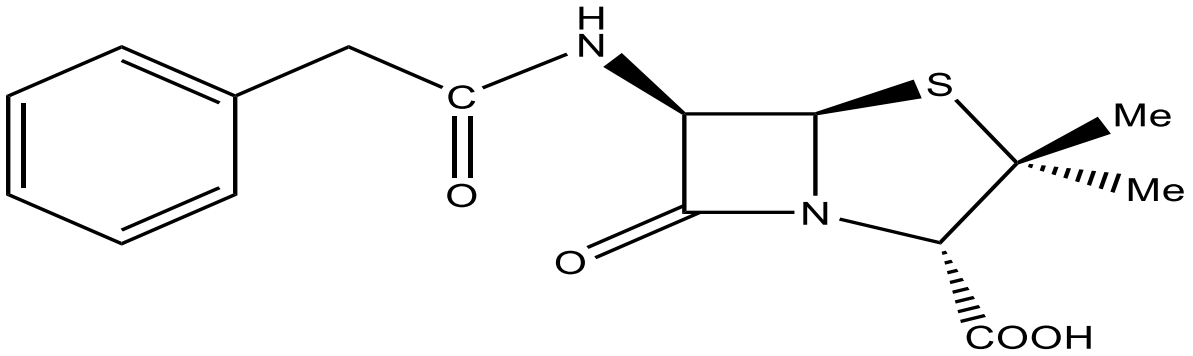
-acylate the PBPs of resistant species (there are many different PBPs)

Penicillins- Natural

Natural penicillins are those which can be obtained directly from the penicillium mold and do not require further modification. Many species of bacteria are now resistant to these penicillins.

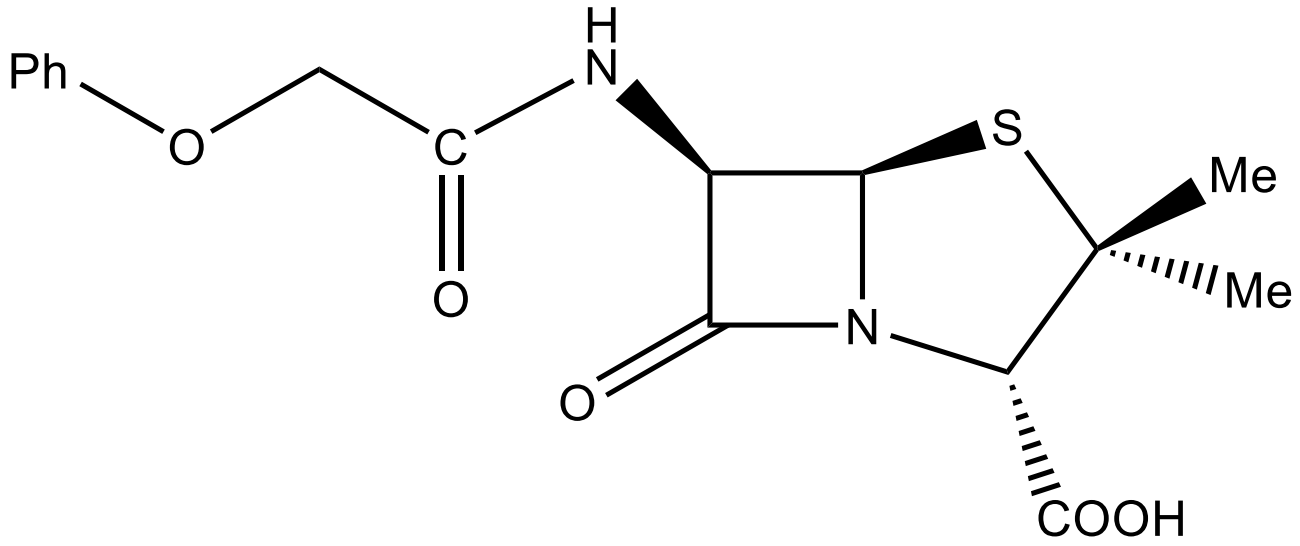
Penicillin G (not orally active)

Penicillin G could not be administered orally due to the acidic conditions of the stomach.



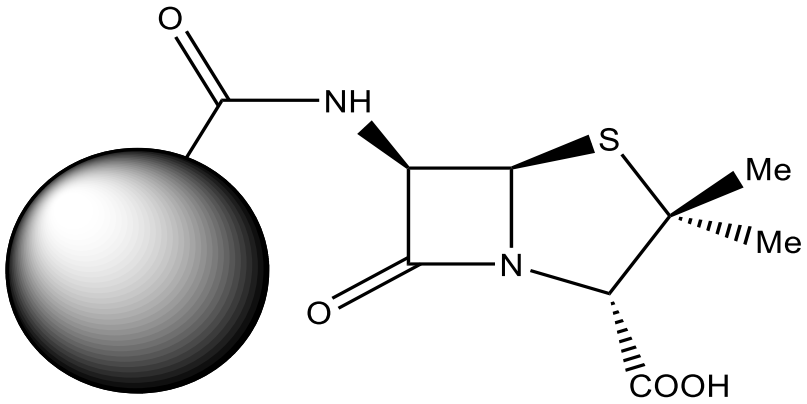
Penicillin V

penicillin V acid stable and orally viable.



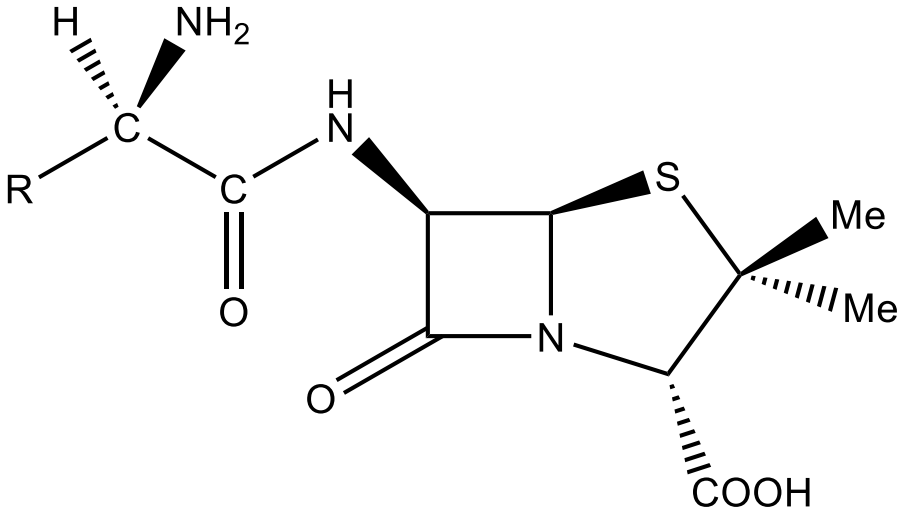
Penicillins- Antistaphylococcal

- Penicillins which have **bulky side groups** can block the β-Lactamases which hydrolyze the lactam ring.
- These lactamases are prevalent in *S. aureus* and *S. epidermidis*, and render them resistant to Penicillin G and V. This necessitated the development of semi-synthetic penicillins through rational drug design.
- Methicillin was the first penicillin developed with this type of modification, and since then all bacteria which are resistant to any type of penicillin are designated as methicillin resistant. (MRSA-methicillin-resistant *S. aureus*)



Penicillins- Aminopenicillins

- In order to increase the range of activity, the penicillin has been modified to have more hydrophilic groups, allowing the drug to penetrate into Gram (-) bacteria via the porins.
- These penicillins have a wider range of activity than natural or antistaphylococcal drugs
- The additional hydrophilic groups make penetration of the gut wall difficult, and can lead to infections of the intestinal tract **by *H. pylori***

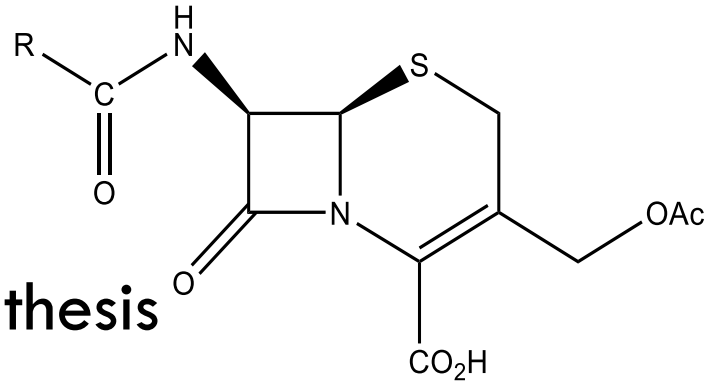


Penicillins Adverse effects

- Allergy (in 0.7% to 1.0% patients). Patient should be always asked about a history of previous exposure and adverse effects
- Super infections(e.g. caused by *Candida*)
- Diarrhea : especially with ampicillin, less common with amoxicillin
- Rare: hemolysis, nephritis

Cephalosporins

Unlike penicillin, cephalosporins have two side chains which can be easily modified. Cephalosporins are also more difficult for β-lactamases to hydrolyze.



- **Bactercidial**- modify cell wall synthesis
- first generation are early compounds
- Second generation- resistant to β-lactamases
- Third generation- resistant to β-lactamases & increased spectrum of activity
- Fourth generation- increased spectrum of activity

Cephalosporins

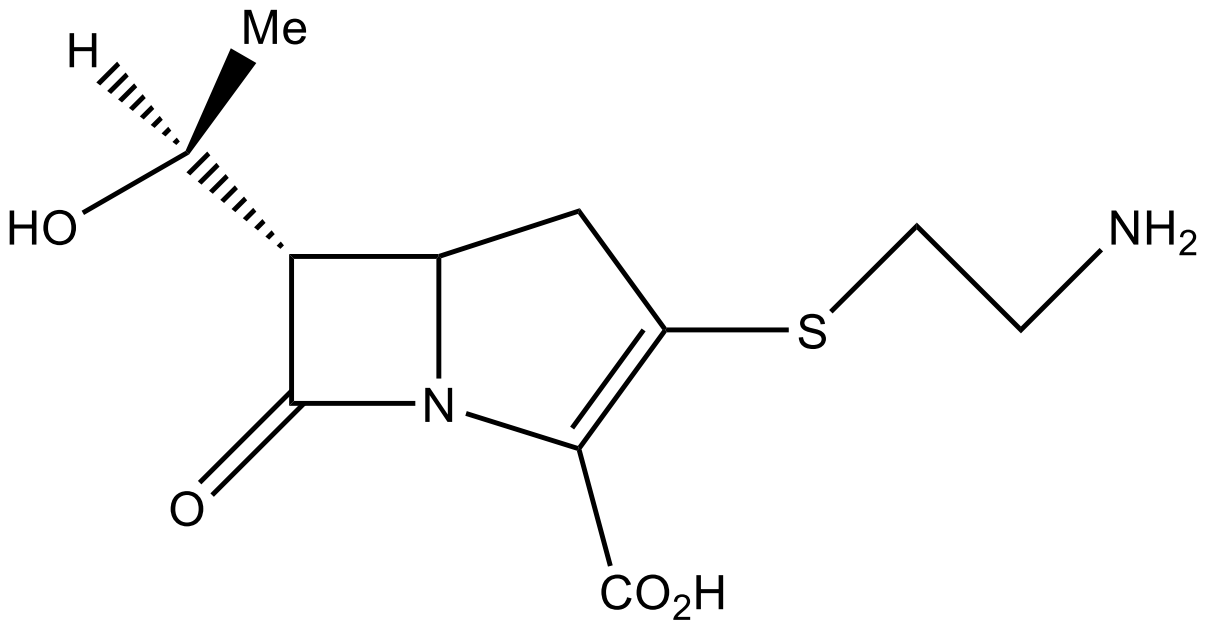
- **FIRST GENERATION-** eg cefadroxil, cefalexin, Cefadrine - most active vs gram +ve cocci. An alternative to penicillins for staph and strep infections; useful in UTIs
- **SECOND GENERATION-** eg cefaclor and cefuroxime. Active vs enerobacteriaceae eg *E. coli*, *Klebsiella spp*,*proteus spp*. May be active vs *H influenzae and N meningtidis*
- **THIRD GENERATION-** eg cefixime and other I.V.s cefotaxime,ceftriaxone,ceftazidine. Very broad spectrum of activity in gram -ve rods, less activity vs gram +ve organisms.
- **FOURTH GENERATION-** cefpirome better vs gram +ve than 3rd generation. Also better vs gram -ve esp enterobacteriaceae & *pseudomonas aerugenosa*. I.V. route only

Cephalosporins Adverse effects

- Allergy (10-20% of patients with penicillin allergy are also allergic to cephalosporins)
- Nephritis and acute renal failure
- Superinfections
- Gastrointestinal upsets when given orally

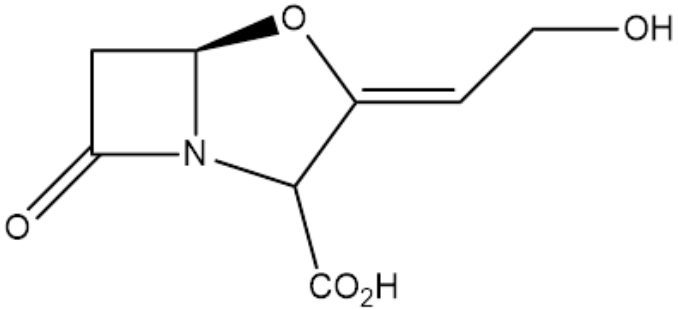
Carbapenems

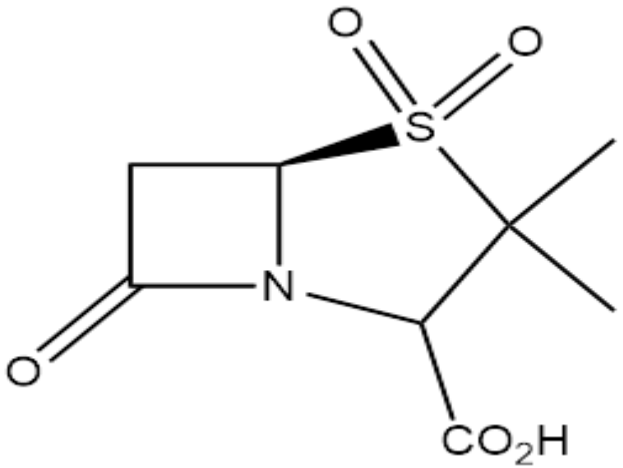
Carbapenems are a potent class of β-lactams which attack a wide range of PBPs, have low toxicity, and are much more resistant to β-lactamases than the penicillins or cephalosporins.



β-Lactamases

- β-Lactamases were first discovered in 1940 and originally named penicillinases.
- These enzymes hydrolyze the β-lactam ring, deactivating the drug, but are not covalently bound to the drug as PBPs are.
- Especially prevalent in Gram (-) bacteria.
- These molecules bind irreversibly to β-lactamases but do not have good activity against PBPs. The rings are modified to break open after acylating the enzyme.





Aminoglycosides (bactericidal)

Streptomycin, kanamycin, gentamicin, tobramycin, amikacin, neomycin (topical)

- **Mode of action - The aminoglycosides irreversibly bind to the 16S ribosomal RNA and freeze the 30S initiation complex (30S-mRNA-tRNA) so that no further initiation can occur. They also slow down protein synthesis that has already initiated and induce misreading of the mRNA. By binding to the 16 S r-RNA the aminoglycosides increase the affinity of the A site for t-RNA regardless of the anticodon specificity. May also destabilize bacterial membranes.**
- **Spectrum of Activity-Many gram-negative and some gram-positive bacteria**
- **Resistance - Common**
- **Synergy - The aminoglycosides synergize with β-lactam antibiotics. The β-lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.**

Tetracyclines (bacteriostatic)

tetracycline, minocycline and doxycycline

- **Mode of action** - The tetracyclines reversibly bind to the 30S ribosome and inhibit binding of aminoacyl-t-RNA to the acceptor site on the 70S ribosome.
- **Spectrum of activity** - Broad spectrum; Useful against intracellular bacteria
- **Resistance** - Common
- **Adverse effects** - Destruction of normal intestinal flora resulting in increased secondary infections; staining and impairment of the structure of bone and teeth.

Macrolides (bacteriostatic)

Erythromycin, azithromycin

- **Mode of action -** The macrolides inhibit translocation by binding to **50 S ribosomal** subunit
- **Spectrum of activity -** Gram-positive bacteria, *Mycoplasma*, *Legionella* (intracellular bacterias)
- **Resistance –** Common
- Macrolides are widely distributed in the body except to the brain and cerebrospinal fluid

Chloramphenicol, Lincomycin, Clindamycin (bacteriostatic)

- **Mode of action** - These antimicrobials bind to the 50S ribosome and inhibit peptidyl transferase activity.
- **Spectrum of activity** - Chloramphenicol - Broad range;
  Lincomycin and clindamycin - Restricted range
- **Resistance** - Common
- **Adverse effects** - Chloramphenicol is toxic (bone marrow suppression) but is used in the treatment of bacterial meningitis.

Sulfonamides and Trimethoprim

Mode of action

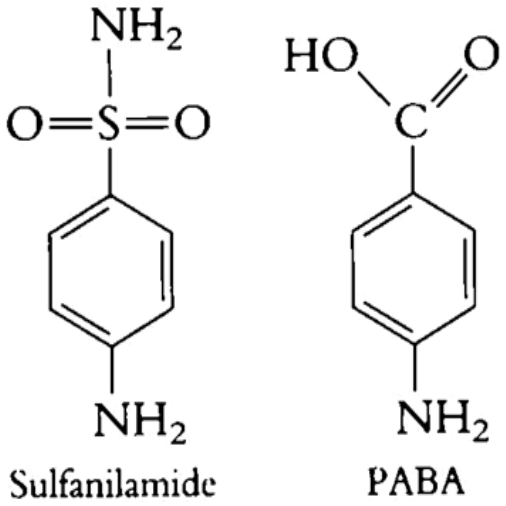
- Folate is metabolized by enzyme dihydrofolate reductase to the active tetrahydrofolic acid.
- Most sulfonamides are well absorbed orally and they are widely distributed including to the CNS.
- Most are excreted by the kidney unchanged.

Sulfonamides (bacteriostatic)

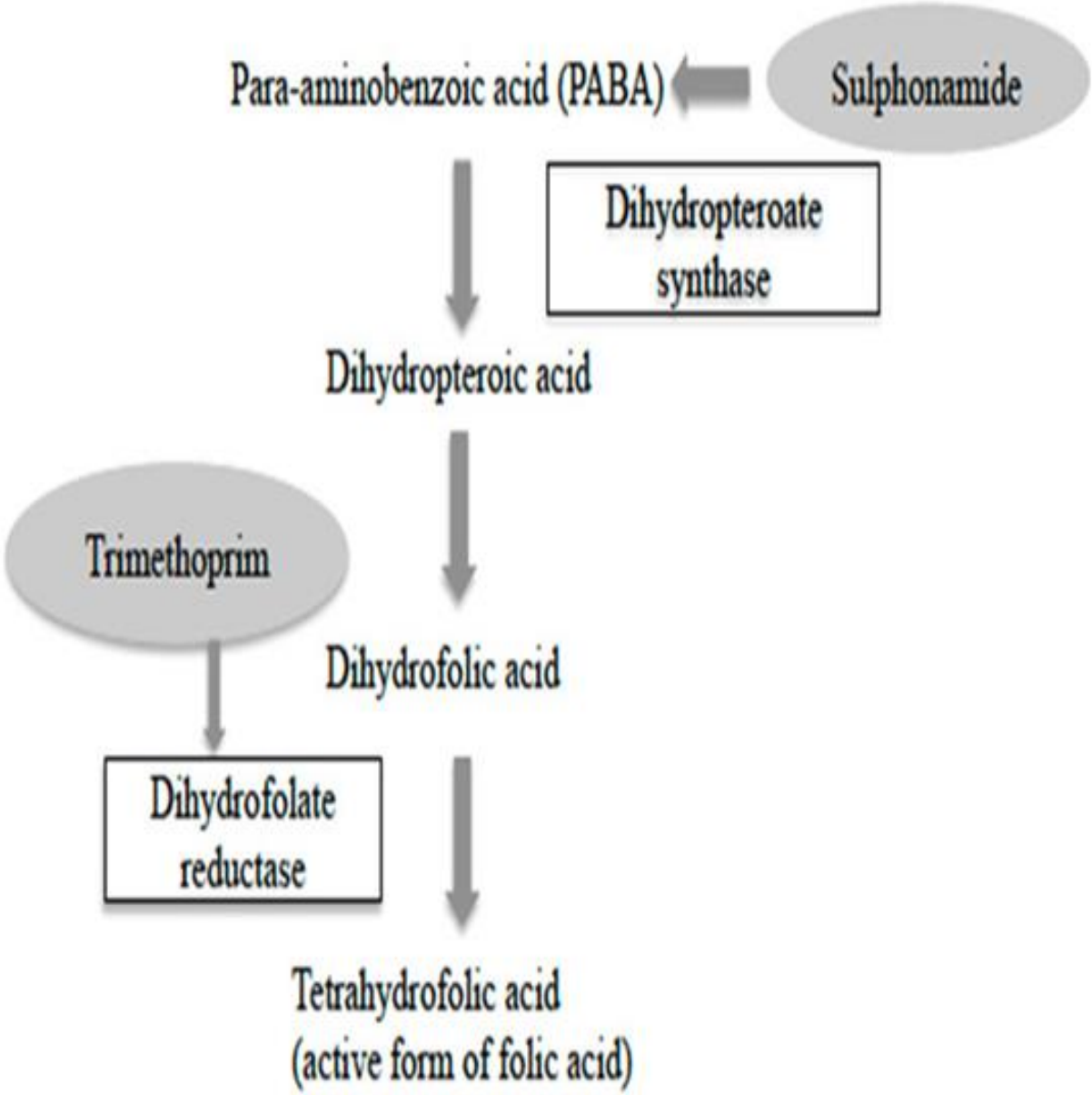
- **Mode of action** - These antimicrobials are analogues of para-aminobenzoic acid and competitively inhibit formation of dihydropteroic acid.
- **Spectrum of activity** - Broad range activity against gram-positive and gram-negative bacteria; used primarily in urinary tract and *Nocardia* infections.
- **Resistance** - Common
- **Combination therapy** - The sulfonamides are used in combination with trimethoprim; this combination blocks two distinct steps in folic acid metabolism and prevents the emergence of resistant strains.

Trimethoprim (bacteriostatic)

- **Mode of action** - These antimicrobials binds to dihydrofolate reductase and inhibit formation of tetrahydrofolic acid.
- **Spectrum of activity** - Broad range activity against gram-positive and gram-negative bacteria; used primarily in urinary tract and *Nocardia* infections.
- **Resistance** - Common
- **Combination therapy** - These antimicrobials are used in combination with the sulfonamides; this combination blocks two distinct steps in folic acid metabolism and prevents the emergence of resistant strains.



Structural similarity of sulfonamide and PABA.



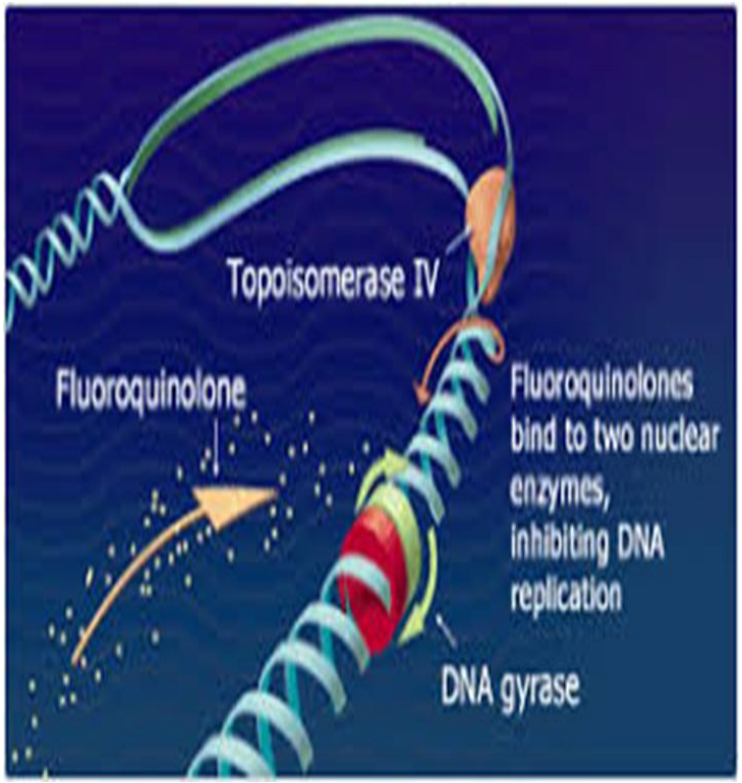
DNA synthesis inhibitors

- Rifampin binds strongly to the DNA-dependent RNA polymerase, inhibiting RNA synthesis. This drug covers gram-positive cocci, many gram-negative bacilli, and most mycobacterium species.
- Quinolones and fluoroquinolones block the action of DNA gyrase. They cover enteric gram-negative bacilli, some gram positives, and have unreliable activity against *Streptococcus pneumoniae*. They have no anaerobic coverage.

Quinolones (bactericidal)

nalidixic acid, ciprofloxacin, norfloxacin, levofloxacin

- **Mode of action** - These antimicrobials bind to the A subunit of DNA gyrase (topoisomerase) and prevent supercoiling of DNA, thereby inhibiting DNA synthesis.
- **Spectrum of activity** - Gram-positive cocci and urinary tract infections
- **Resistance** - Common for nalidixic acid; developing for ciprofloxacin



DNA-gyrase or Topoisomerase IV with DNA

↑ ↓

Complex topoisomerases-DNA

↑ ↓ Fluoroquinolones

Complex fluoroquinolones-topoisomerases-DNA

↓ Blocking of DNA synthesis and cell growing

Appearance of free extremes
(Death cell)

Antibacterial medications injure plasma membrane

- Polymyxin B: binds to membrane of G- bacteria and alters permeability
- This leads to leakage of cellular contents and cell death
- These drugs also bind to eukaryotic cells to some extent, which limits their use to topical applications
- Polymyxin B
  - Topical
  - Combined with bacitracin and neomycin in over-the-counter preparation

Metronidazole

- Metronidazole binds to DNA and blocks replication
- It is well absorbed after oral or rectal administration and can be also given i.v.
- It is metabolized by the liver.
- Metronidazole is active against anaerobic organisms (e.g. *Bacteroides, Clostridia*), which are encountered particularly in abdominal surgery.
- It is also used against *Trichomonas, Giardia and Entamoeba* infections and can be used to treat pseudomembranous colitis.
- Increasingly, it is used as part of treatment of *Helicobacter pyloris* infestion of the stomach and duodenum associated with peptic ulcer disease.
- It is used also to treat a variety of dental infections, particularly dental abscess.

Nitrofurantoin

- This is used as a urinary antiseptic and to treat Gram-negative infections in the lower urinary tract.
- It is taken orally and is well absorbed and is excreted unchanged in the urine.
- It only exerts its antimicrobial effect when it is concentrated in the urine and so has no systemic antibacterial effect.

Fucidin

- Fucidin is active only against *Staphylococcus aureus* (by inhibiting bacterial protein synthesis) and is not affected β-lactamase.
- It is usually only used with flucloxacillin to reduce the development of resistance.
- It is well absorbed and widely distributed, including to bone
- It can be given orally or parenterally.
- It is metabolized in the liver.

Vancomycin

- This interferes with bacterial cell wall formation and is not absorbed after oral administration and must be given parenterally.
- It is excreted by the kidney.
- It is used i.v. to treat serious or resistant *Staph. aureus* infections and for prophylaxis of endocarditis in penicillin-allergic people.

Antibiotics for leprosy

- Leprosy is caused by infection with *Mycobacteria leprae*.
- A mixture of drugs are used to treat leprosy, depending on the type and severity of the infection and the local resistance patterns.
- *Rifampicin* is used and *dapsone*, which is related to the sulphonamides.

Safety Concerns with the Use of Antimicrobials:

Toxicity

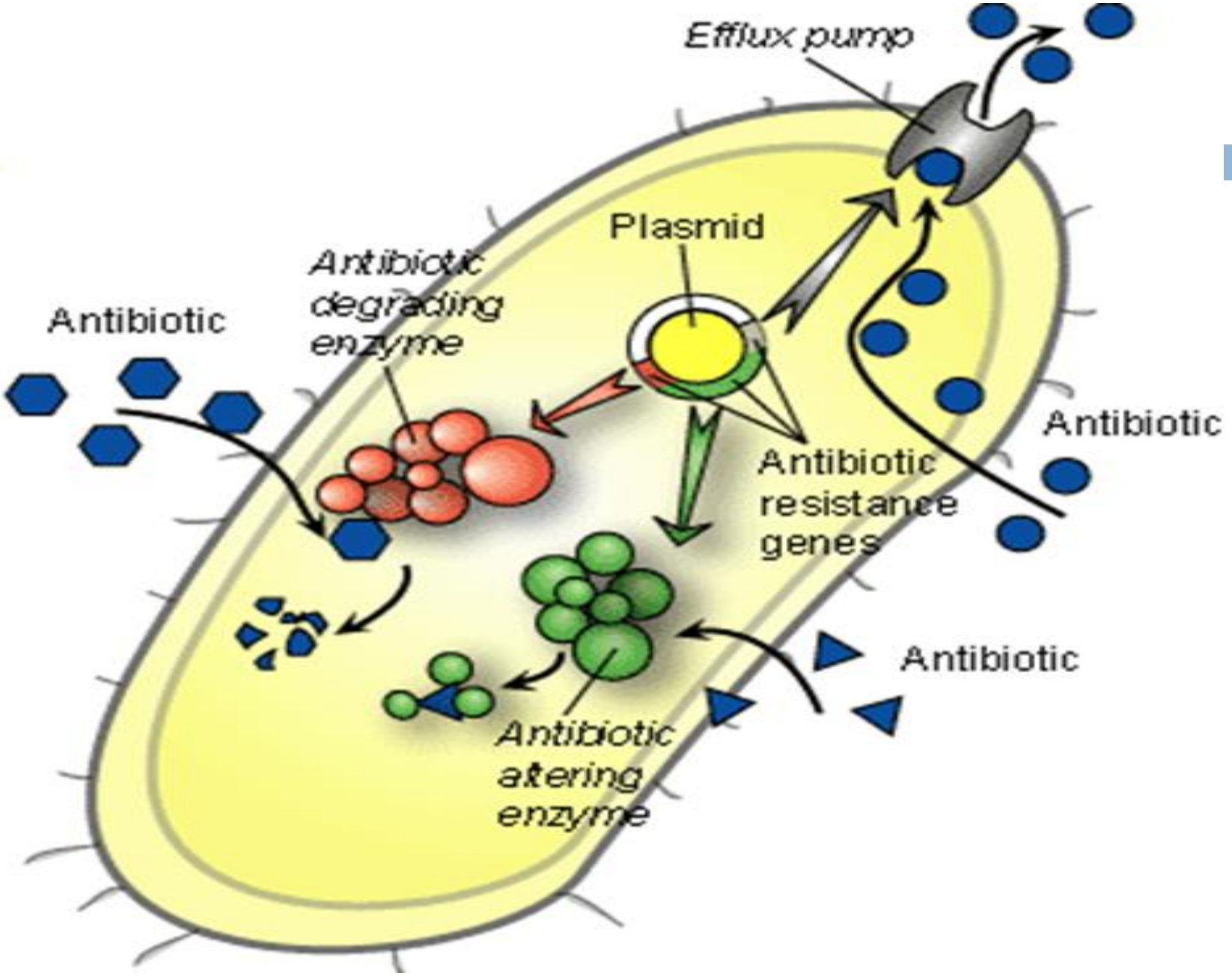
- Kidney damage
- Liver damage

- **Interactions with other medications**
  - May neutralize effectiveness of contraceptive pills
- **Hypersensitivity reactions**
  - Anaphylactic reactions to penicillin
- **Fetal damage/risk to pregnant women**
  - Tetracycline causes discoloration of teeth in children and may cause liver damage in pregnant women
  - Fluoroquinolones may cause cartilage damage.
- **Antibiotic Resistance**

ANTIBIOTIC RESISTANCE

Mechanisms of Resistance

- Enzymatic Inactivation**
- Decreased permeability
- Efflux
- Alteration of target site
- Overproduction of target
- Bypassing drug's action


Efflux pump
Plasmid
Antibiotic degrading enzyme
Antibiotic
Antibiotic resistance genes
Antibiotic
Antibiotic
Antibiotic altering enzyme

Decreased Permeability

- Outer membrane permeability (Gram negative bacteria)
- Impedes the entry of hydrophobic antibiotics (erythromycin)
- Porins: Loss of porins leads to increased resistance to β-lactams
- Inner membrane permeability
- Altered proton motive force leading to Aminoglycoside resistance after long term use

- Prevention of antibiotic entry into the cell by reduce the permeability - In gram negative bacteria porins are transmembrane proteins that allow for the diffusion of antibiotics through their highly impermeable outer membrane. Modification of the porins can bring about antibiotic resistance, as is the case of ***Pseudomonas aeruginosa*** resistance to **imipenem**.

Efflux

- Active efflux of antibiotic (active export drugs) - Bacteria can actively pump out the antibiotic from the cell by using multidrug pump or efflux pump. An example would be the **energy dependent efflux** of tetracycline widely seen in enterobacteriaceae.

Antibiotic inactivation

- In this case the bacteria avoids the antibiotics by inactivating them. An example is the production of β-lactamases by bacteria, which destroys the beta lactam ring of penicillins and cephalosporins.

Altered target sites

- Bacteria synthesize modified targets (alteration of drug target) - Bacteria can also evade antibiotic action through the alteration of the compound's target. For instance, ***Streptococcus pneumonia*** modified **Penicillin-binding protein (PBP)** which renders them resistant to penicillin.

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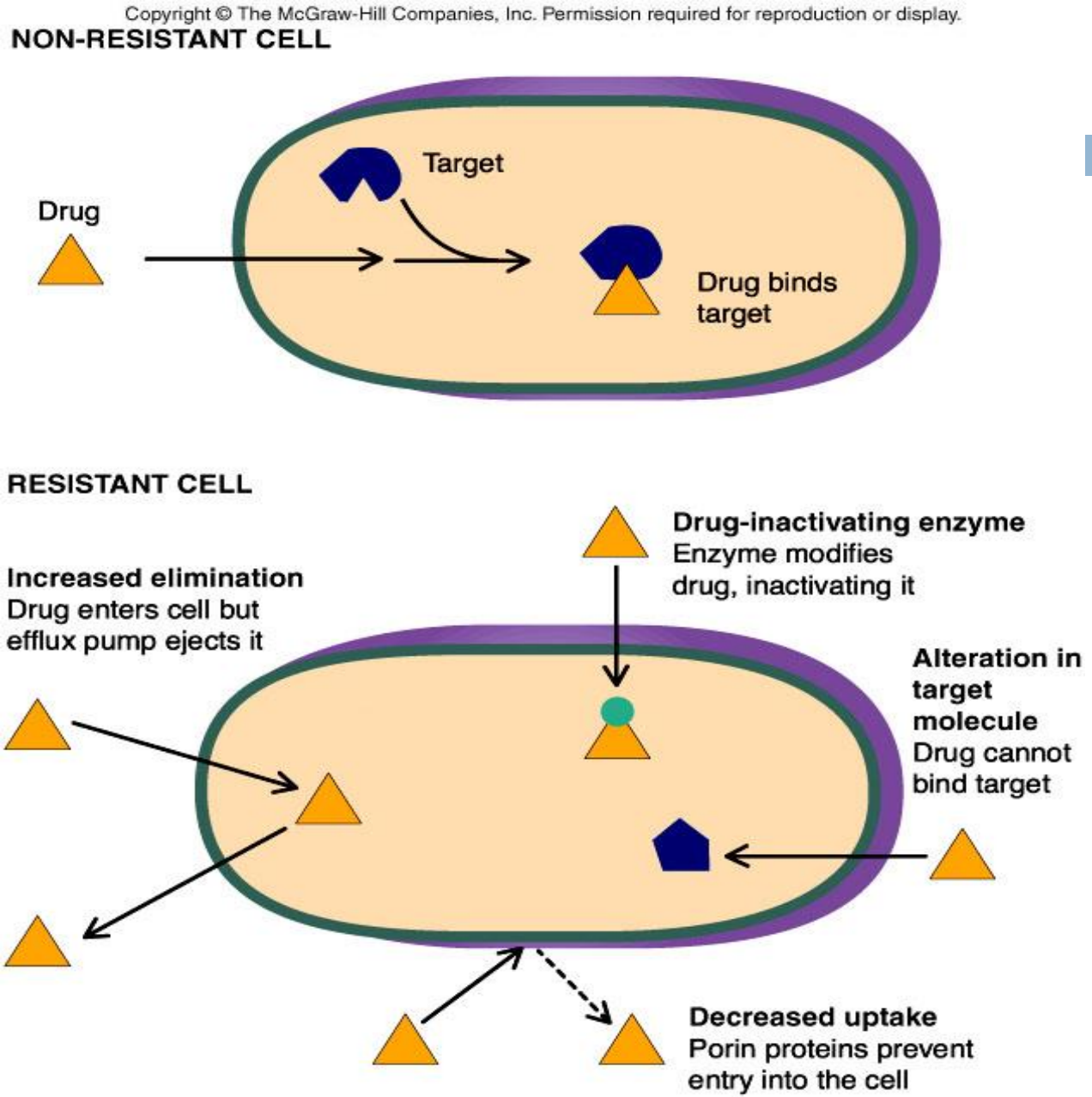

High level and Low level resistance

- High level resistance refers to resistance that cannot be overcome by increasing the dose of the antibiotics .resistance mediated by enzymes such as β-lactamase result in high level resistance.

- Low level resistance refers to resistance that can be overcome by increasing the dose of the antibiotics. Resistance mediated by mutation in the gene encoding a drug target is often low, as the altered target can still bind some of the drug but with reduces strength

Origin of Antibiotic Resistance

1- Genetic origin.

2-Non-genetic change.

Non-genetic antibiotic resistance

- Bacteria can be walled off within an abscess cavity that the drugs not penetrate effectively. Surgical drainage is therefore necessary.
- Bacteria can be in resting state e.g not growing they are therefore insensitive to cell wall inhibitors such penicillin and cephalosporin .
- Under certain circumstances ,organisms under the effect of drugs such as penicillin loss their cell wall and survive as protoplasts and be insensitive to cell wall active drugs .
- Presence of foreign bodies makes successful treatment more difficult.
- Several artifact can make it appear that the organisms are resistance e.g administration of wrong drugs or wrong dose or the failure of drugs to reach the appropriate site in the body.

Genetic basis of antibiotic resistance

1-Chromosome

2-Extrachromosomal

Chromosome antibiotic resistance

- **Spontaneous mutation of the bacterial chromosome** affecting a 'susceptibility gene' which cod for either the target of the drugs or the transport system in the membrane that controls the uptake of drugs . Spontaneous mutations occur with a frequency of 10^{-7} to 10^{-9}. as in the case with rifampin chromosomal mutants that occur at a high frequency .Treatment of infections with rifampin as the sole medication usually results in resistance.
- **Transposition** refers to the recombination of genetic material through the action of transposons. Transposons are DNA segments which have specialized insertion sequences at each end. These insertion sequences enable transposons to migrate between DNA molecules within the same bacterium (e.g., from plasmid to chromosome, from chromosome to bacteriophage DNA). The DNA between the two insertion sequences of transposons can code for various genes, such as genes that facilitate transposition and antibiotic resistance genes.

Extrachromosomal antibiotic resistance

- Genetic resistance can also occur through the extrachromosomal genetic elements named **plasmids**. Some plasmids carry their own gene of replication and transfer. R or resistance plasmids carry genes for bacterial antimicrobial resistance, often these genes work by inactivating an antibiotic. Examples are β-lactamases
- Plasmids can be transferred among bacteria by various processes.
- **Transduction**
- **Conjugation**
- **Transformation**

Misuse of antibiotics selects for resistance mutants. Misuse includes:

- Using outdated, weakened antibiotics
- Using antibiotics for the common cold and other inappropriate conditions
- Failure to complete the prescribed regimen
- Using someone else's leftover prescription
- Some physicians prescribe multiple drugs when one would be sufficient
- in some countries antibiotics available on non-prescription basis

Slowing the emergence and spread of antimicrobial resistance

1. **Responsibilities of Physicians:** must work to identify microbe and prescribe suitable antimicrobials, must educate patients
2. **Responsibilities of Patients:** need to carefully follow instructions
3. **Educate Public:** must understand appropriateness and limitations of antibiotics ; antibiotics not effective against viruses
4. **Global Impacts:** organism that is resistant can quickly travel to another country