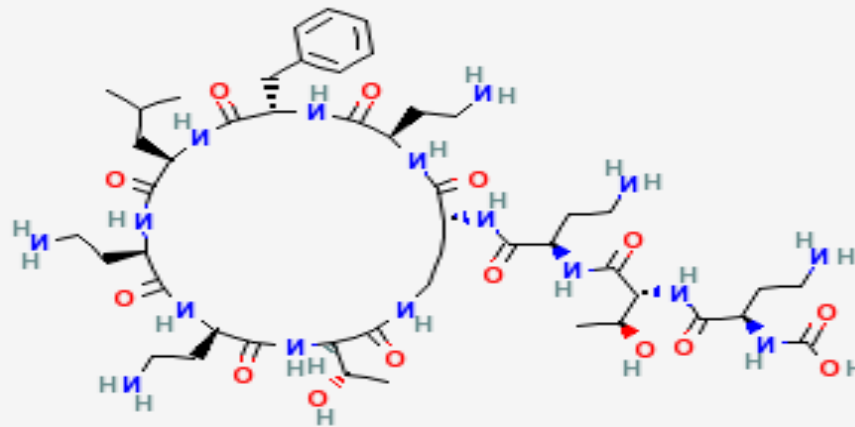




Antibiotics



Antibiotics

- Antibiotics are large group of the drugs,
- which can Inhibit **selectively** growth of **bacteria, fungi** or inhibit growth of tumor (**cancer**), without causing serious damage
- to the host.
- Antibiotics can inducing human defence mechanism'

Antibiotics

- The first observation of antibiotic effect was made in the 19th century by French chemist Louis Pasteur, who discovered that certain saprophytic bacteria can kill anthrax bacilli.



Antibiotics

- German physician and chemist Paul Ehrlich began experimenting with the synthesis of organic compounds that would selectively attack an infecting organism without causing serious damage to the host.



Antibiotics

- His experiments led to the development, in 1909, of salvarsan, a synthetic compound containing arsenic, which exhibited selective action against spirochetes, the bacteria that cause syphilis. Salvarsan remained the only effective treatment for syphilis until the purification of penicillin in the 1940s.

- **The first antibiotic to be discovered was penicillin. Its discoverer, Alexander Fleming, had been culturing bacteria on an agar plate with fungal contamination, and noticed that the culture medium around was free of bacteria. He had worked on the antibacterial properties of lysozyme, and make the correct interpretation of what he saw: that the mold was secreting something that stopped bacterial growth.**

Antibiotics



- The discoveries of ***penicillin*** by Fleming in 1929 open the era of chemotherapy.

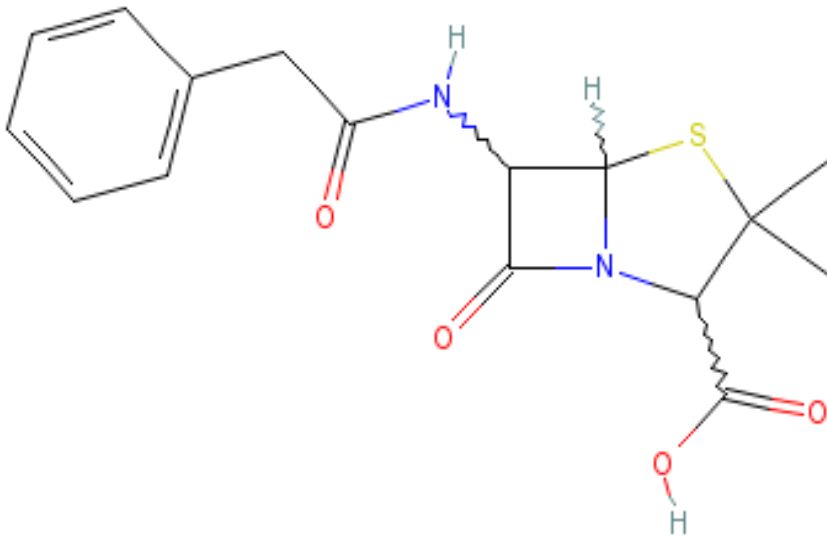
Antibiotics



- The ***B-lactam*** structure of penicillin was detected by Chain in 1942

Antibiotics

- **B-lactam ring**

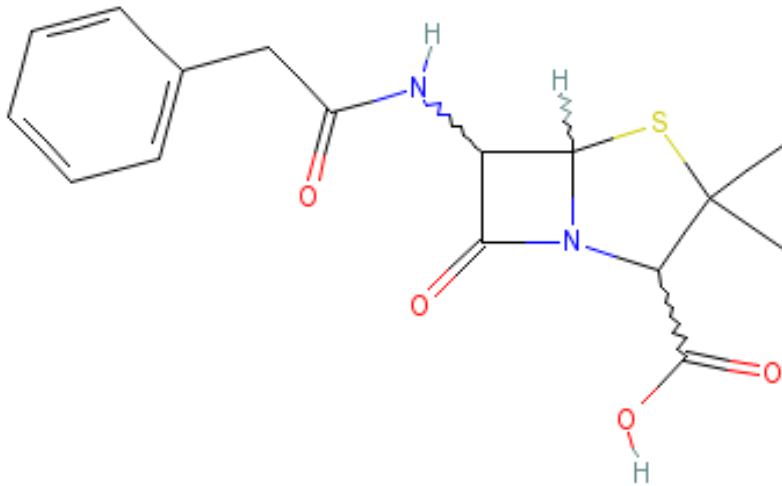


Antibiotics



- Z.V. Ermoleva in Russia.

Antibiotics



- Antibiotics are among the ***most frequently prescribed drugs*** for treatment and control of microbial infection
- In Russia use more than 31 groups of antibiotics and 200 drugs.

Antibiotics

The effectiveness of chemotherapeutic drug was dependent on the degree of its ***selective toxicity***, ie, selective inhibition of the growth of the microorganism without damage to the host.

Selective toxicity is achieved by exploiting the differences between the metabolism and structure of the microorganism and the human cell (penicillins can inhibiting the growth of bacterial but not human cells).

Antibiotics

- **Narrow(limited)-spectrum** antibiotics are active against one or few types of microorganisms (Vancomycin is primarily used against gram-positive cocci, namely, staphylococci and enterococci).
- **Broad-spectrum** antibiotics are active against several types of microorganism (tetracyclines are active against G-rods, mycoplasmas).
- ***Bacteriostatic*** drug inhibits their growth but does not kill them.
- ***Bacteriostatic antibiotics*** are dependent on the host 's defense
- A ***bactericidal*** drug kills bacteria.
- Bactericidal drug are usually independent in their actions and cause effects directly on disease agents.

Antibiotics

- Most ***Antibiotics*** originate in one of two ways:
- As ***natural products*** of microorganism
- Chemically modified (semisynthetic) forms of natural antibiotics.
- Synthetic forms
- ***The natural products of microorganism***
 - 1. Bacteria
 - From 2. Streptomycetaceae
 - 3. Fungi

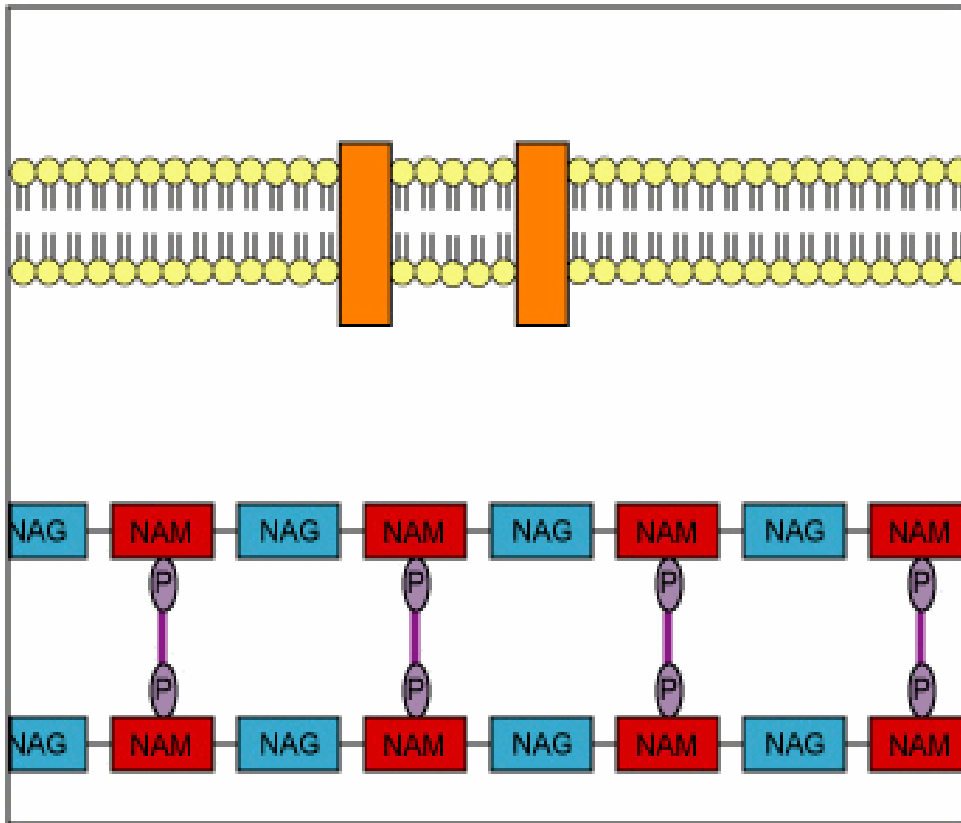
Antibiotics

- *Two important requirements:*
- 1. **Antibiotics** must be shown to be *relatively nontoxic* to the host.
- It must exhibit antimicrobial activity at *low* concentration

Mechanism of action of antibacterial drugs

- **1. Inhibition of bacterial cell wall synthesis .**
 - Penicillin's, cephalosporins, imipenem, aztreonam, vancomycin.
- **Inhibition of protein synthesis**
 - Action of 50S ribosomal subunit.
 - Action of 30S ribosomal subunit.
 - Chloramphenicol, erythromycin, clindamycin, Linezolid.
 - Tetracyclins, aminoglycosides.
- **Inhibition of nucleic acid synthesis.**
 - Inhibition of DNA synthesis .
 - Inhibition of RNA synthesis .
 - Quinolones
 - Rifampin
- **Alteration of cell membrane synthesis**
 - Polymyxin

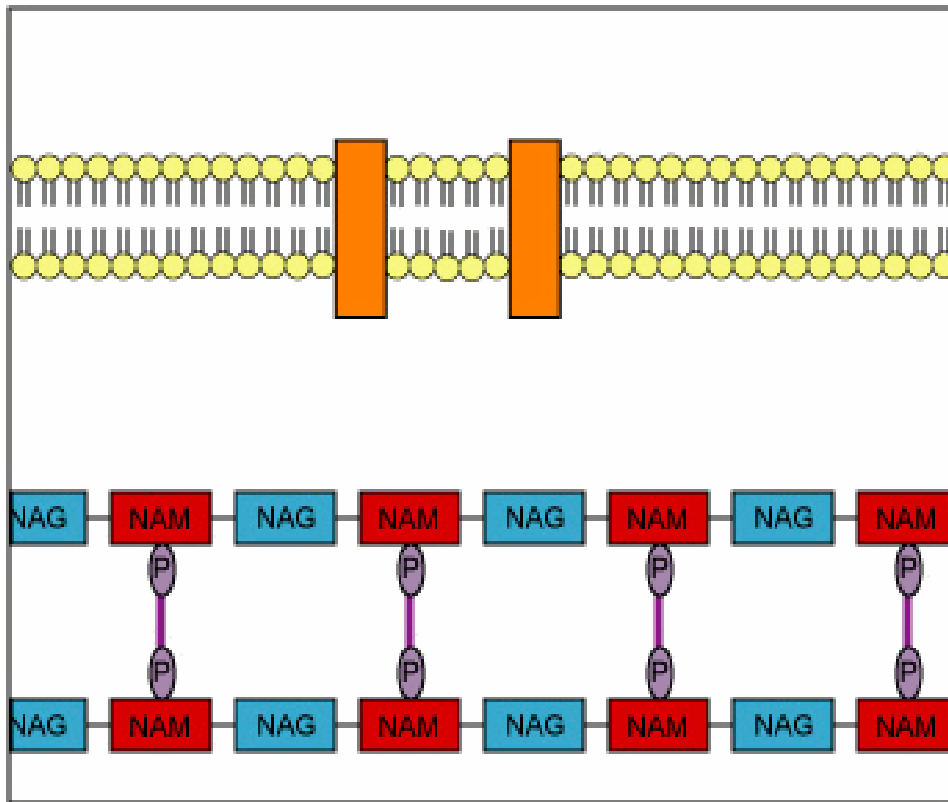
Mechanism of action of antibacterial drugs



- Target of B-lactam drugs is *transpeptidase*, the enzyme that connects the peptides of the peptidoglycan. B-lactam is effective during the the growth stage. Since fully formed are not sensitive to its action.

Inhibition of cell wall synthesis

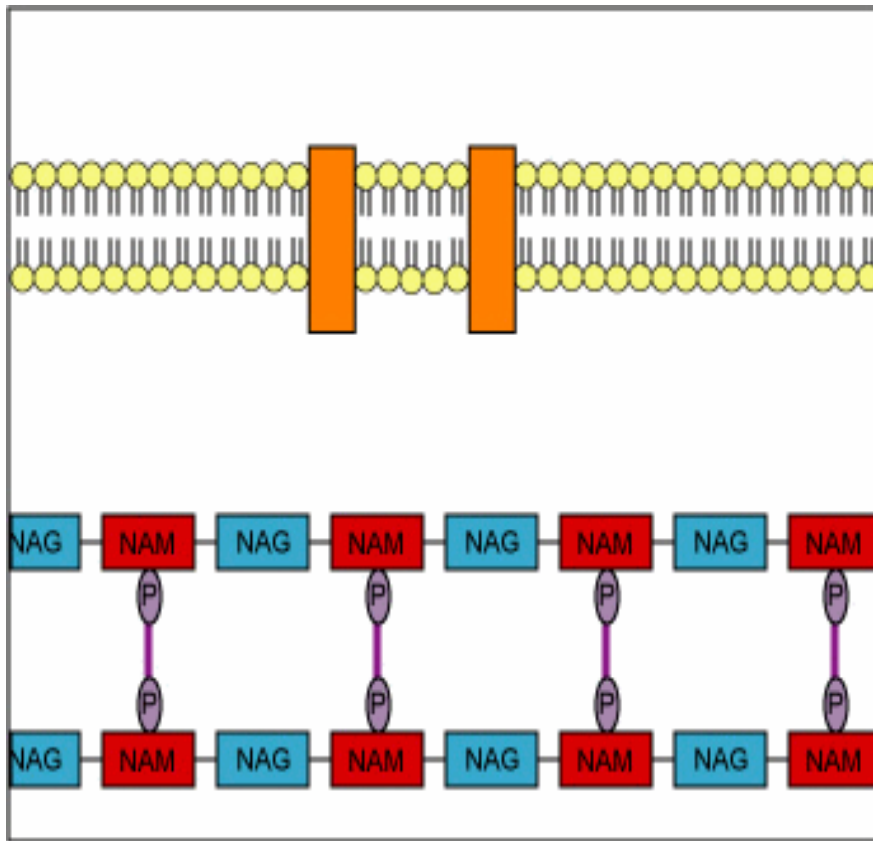
B-lactam antibiotics



- Two additional factors are involved in the action of penicillin.
- 1. Penicillin binds to a variety of receptors in the bacterial cell membrane called PBPs. Some PBPs are *transpeptidase*, the function of other is unknown.
- 2. **Autolytic enzymes** called murein hydrolase's are activated in P-treated cell, degrade the peptidoglycan.

Inhibition of cell wall synthesis

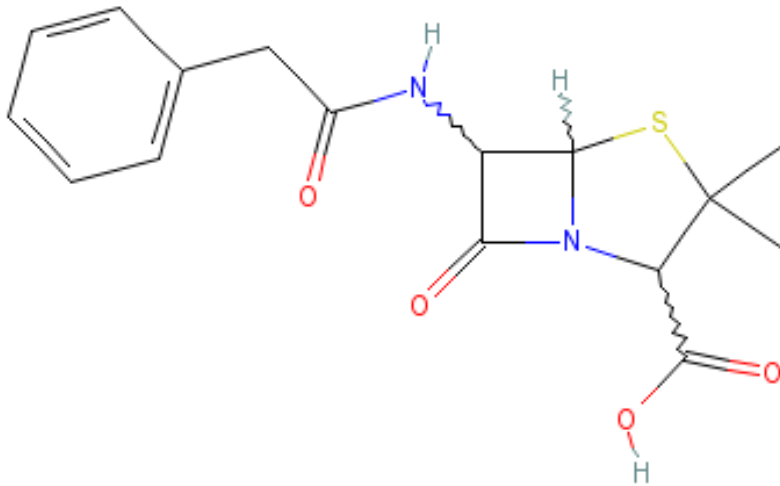
B-lactam antibiotics



- Sensitive bacterial cell growing in the presence of penicillin possesses modified forms - unusual shapes and abnormal internal organization.

Inhibition of cell wall synthesis

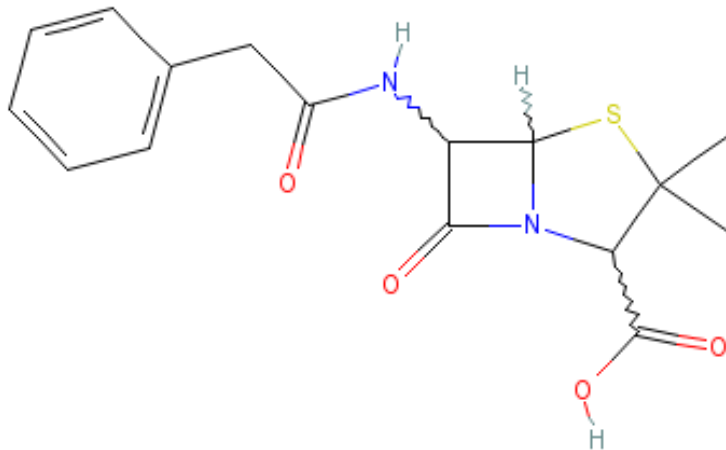
B-lactam antibiotics.



- The basic structure of penicillin – B-lactam ring
- Penicillin have a five – membered ring.

Inhibition of cell wall synthesis

B-lactam antibiotics



- **Penicillin** is one of the widely used and effective antibiotics.
- **Penicillin** is highly active against **G⁺** and **G⁻** cocci, Bacilli, Clostridium.
- **Limited** effectiveness against **G⁻** rods.
- **hydrolysis by gastric acid**
- **Inactivation by B-lactamases(cleavage of the ring by penicillinases)**

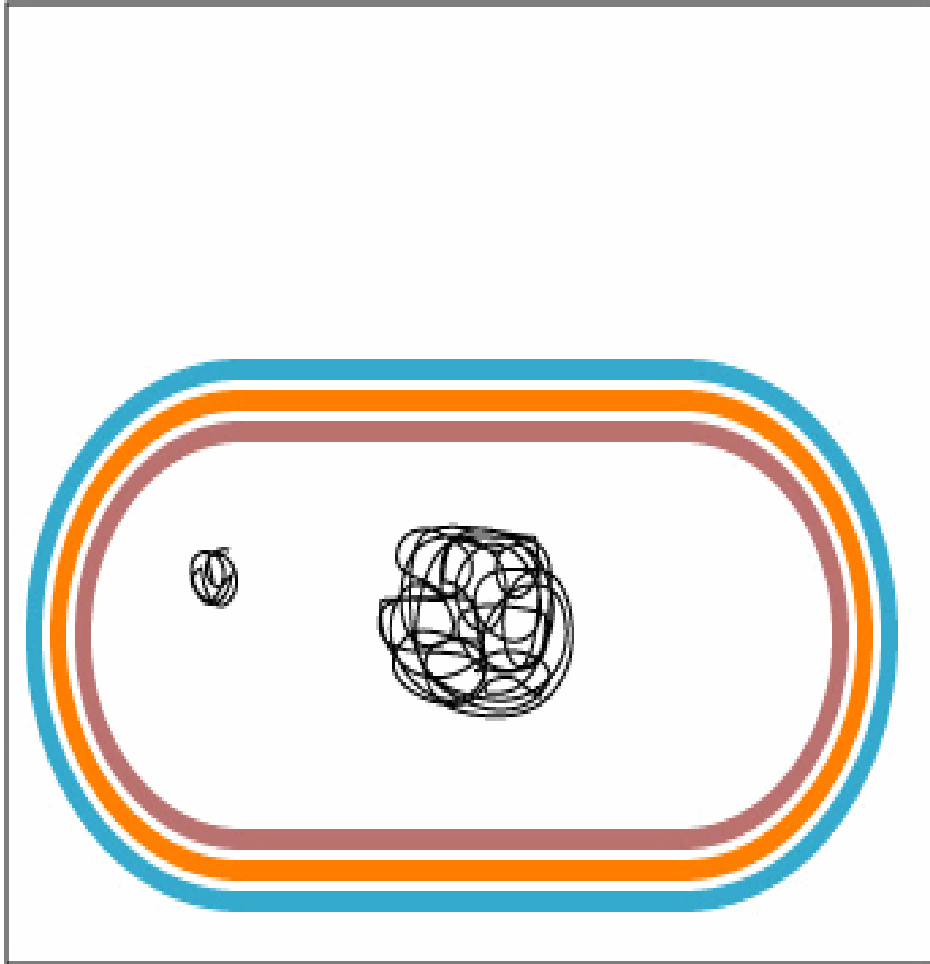
The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

- 1. Drug inactivation or modification: e.g. enzymatic deactivation of *Penicillin G* in some penicillin-resistant bacteria through the production of β -lactamases.
- 2. Alteration of target site: e.g. alteration of **PBP**—the binding target site of penicillins—in **MRSA** and other penicillin-resistant bacteria.

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

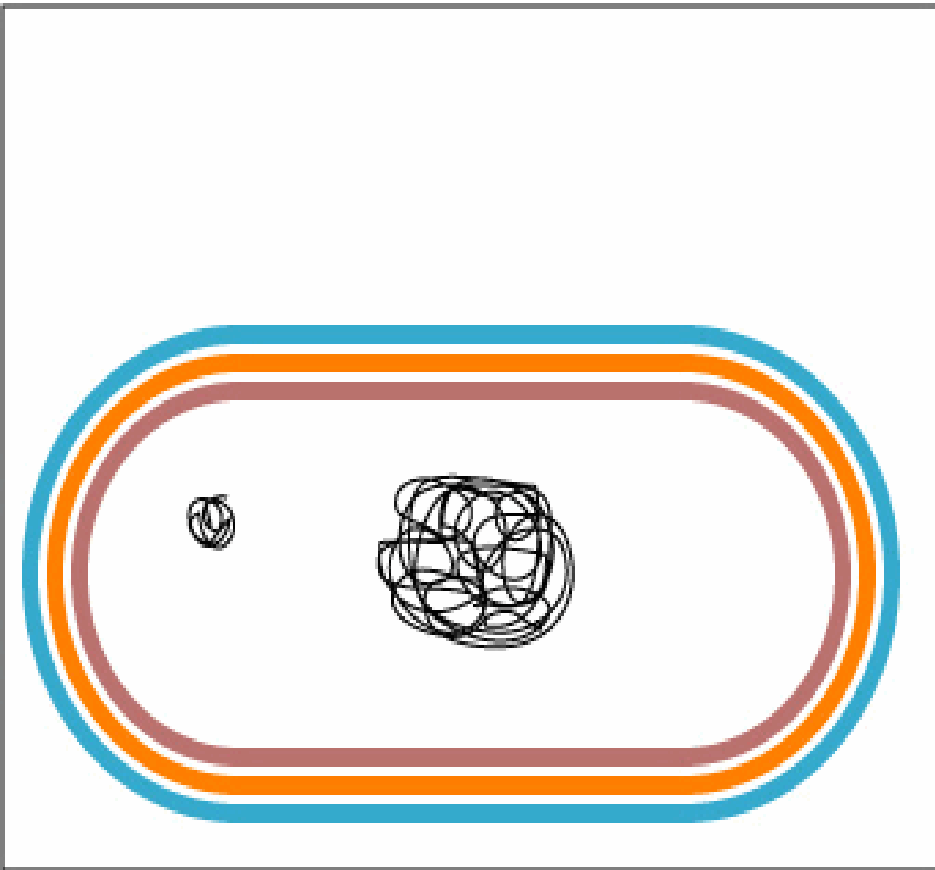
- **3. *Bacterial resistance to antibiotic - producing an altered porin in the outer membrane of G- cell wall***
- **4. Reduced drug accumulation: by decreasing drug permeability and/or increasing active efflux (pumping out) of the drugs across the cell surface**

Mechanisms of bacterial resistance



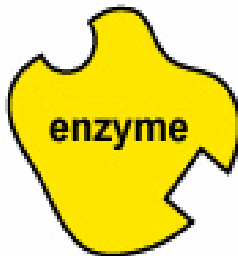
- Bacteria may resist an antimicrobial agent that **destroy or inactivate the antibiotic.**
- Example –production of **B-lactamases.**
- **B-lactamases break the beta-lactam ring of the antibiotic, thus destroying the drug.**
- The first enzyme was named ***penicillinase***

Mechanisms of bacterial resistance



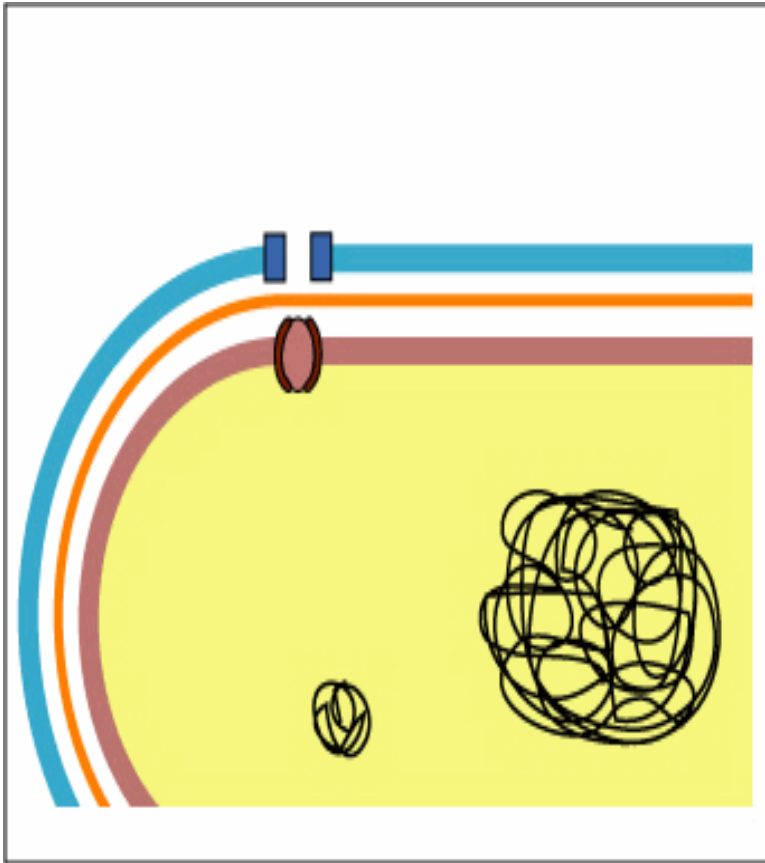
- The synthesis of β -lactamas may be regulated by genes on the ***bacterial chromosomes*** or on ***plasmids***.
- In G-bacteria antibiotic inactivating – enzyme are located in the periplasmic space.
- In G⁺ antibiotic inactivating – enzyme are typically secreted from the bacteria and interact with the antibiotic extracellularly.

Mechanisms of bacterial resistance



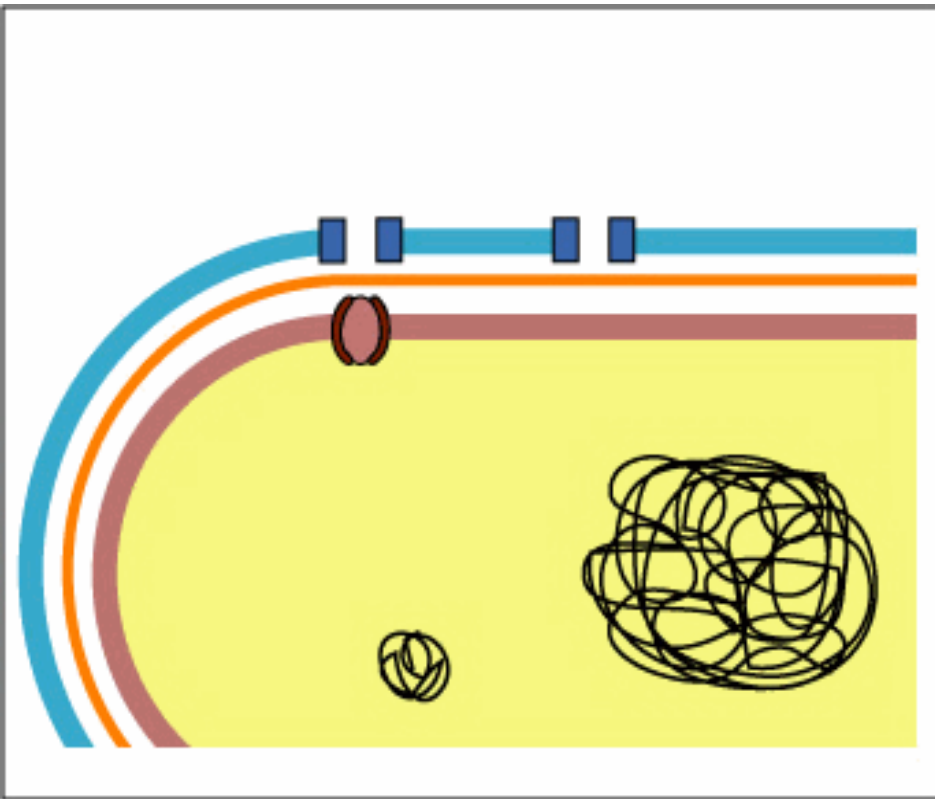
- Bacteria may become resistant to B-lactam antibiotic, by producing *altered transpeptidases (penicillin-binding proteins)*
- With reduced affinity for the binding of B-lactam antibiotic.
- **MRSA.**

Mechanisms of bacterial resistance



- ***Bacterial resistance to antibiotic producing an altered porin in the outer membrane of G- cell wall.***
- Altered porin preventing passage of the antibiotic.

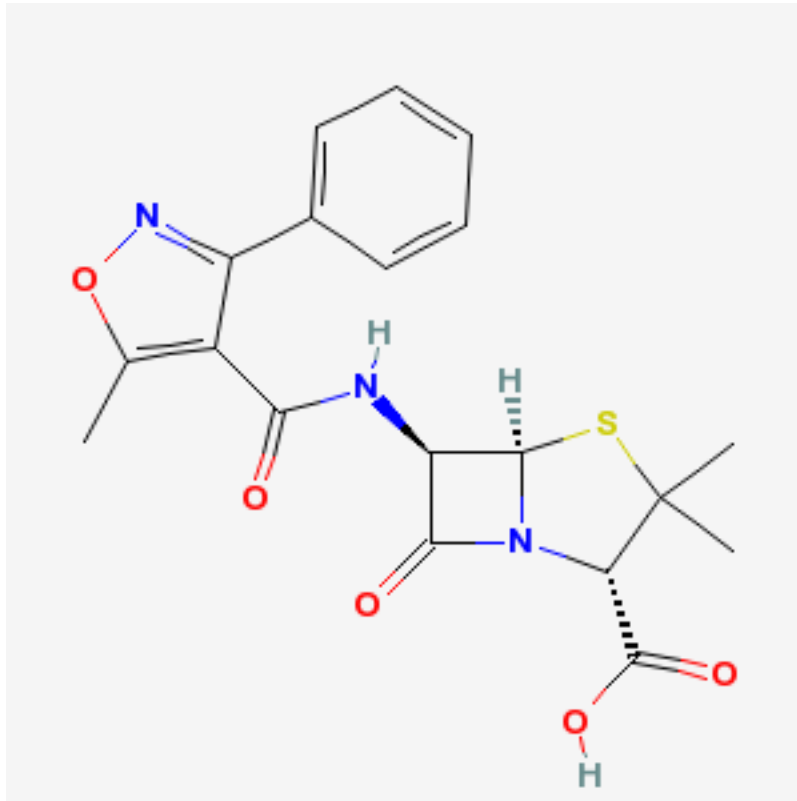
Mechanisms of bacterial resistance



- Bacterial resistance to antibiotic - producing *an altered transport (carrier) protein in the cytoplasmic membrane*. It blocking transport into the cytoplasm.
- This mechanism applies to both G⁺ and G⁻ bacteria.

Inhibition of cell wall synthesis

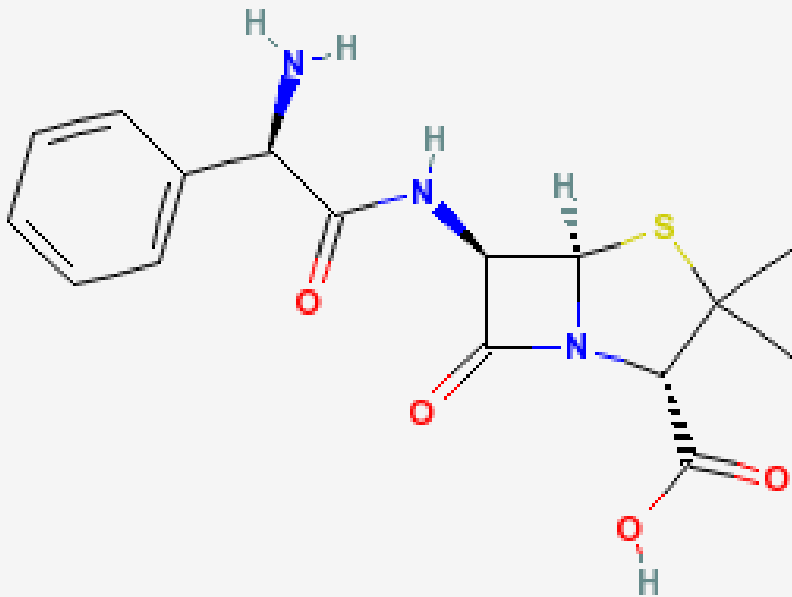
B-lactam antibiotics



- **Semisynthetic penicillin** **active against Staphylococcus.**
- **OXACILLIN** **active against G⁺ and G⁻ cocci, Bacilli, Clostridium.**
- **Limited effectiveness against G⁻ rods.**
- **That drug is resistant to *penicillinase*.**

Inhibition of cell wall synthesis

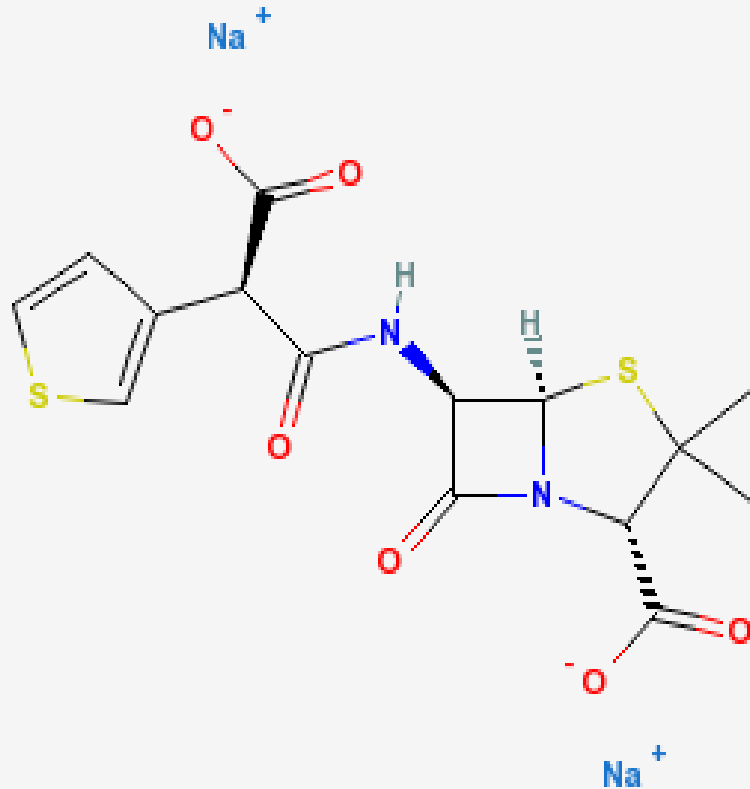
B-lactam antibiotics



- **AMINOPENICILLINS**
- **(Ampicillin, amoxicillin) are**
- **the slight modification of the molecule by the addition of amino group (NH₂) converts penicillin into a *broader-spectrum* chemotherapeutic agents.**
- **Ampicillin active against G - rods(E.coli,Proteus,Shigella , Salmonella,H.influenza)**
- **No active against *P.aeruginosa*.**
- **Leads to disbacteriosis.**

Inhibition of cell wall synthesis

B-lactam antibiotics



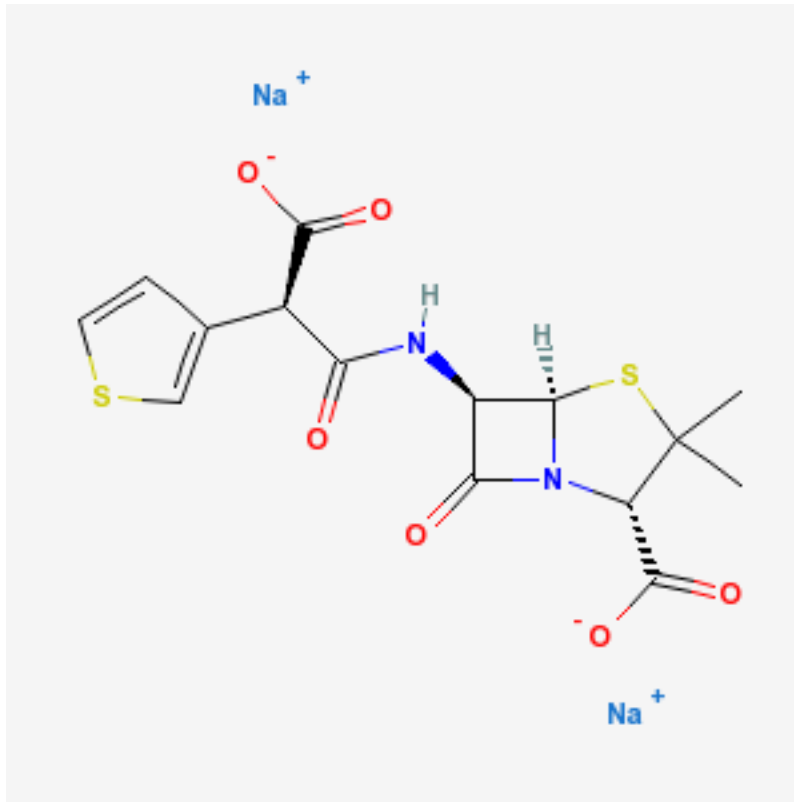
Semisynthetic penicillin active against Pseudomonas.

Carboxipenicillins

Carbenicillin, ticarcillin is highly active against G-bacteria and primarily Pseudomonas and certain strains of Proteus, Especially when used in combination with an aminoglycoside.

Inhibition of cell wall synthesis

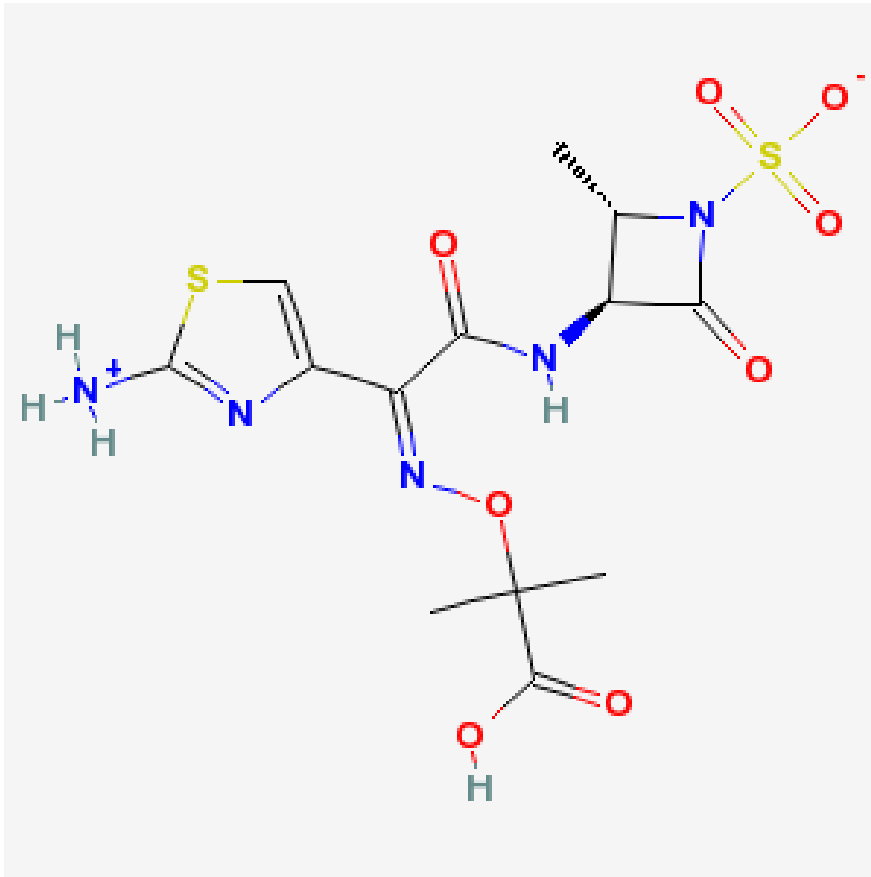
B-lactam antibiotics



- *Ureidopenicillins*
- Azlocillin, Mezlocillin have active against *Pseudomonas*
- Even higher then Carbenicillin and higher active then non sporforming G- anaerobic bacteria (B.fragilis).

Inhibition of cell wall synthesis

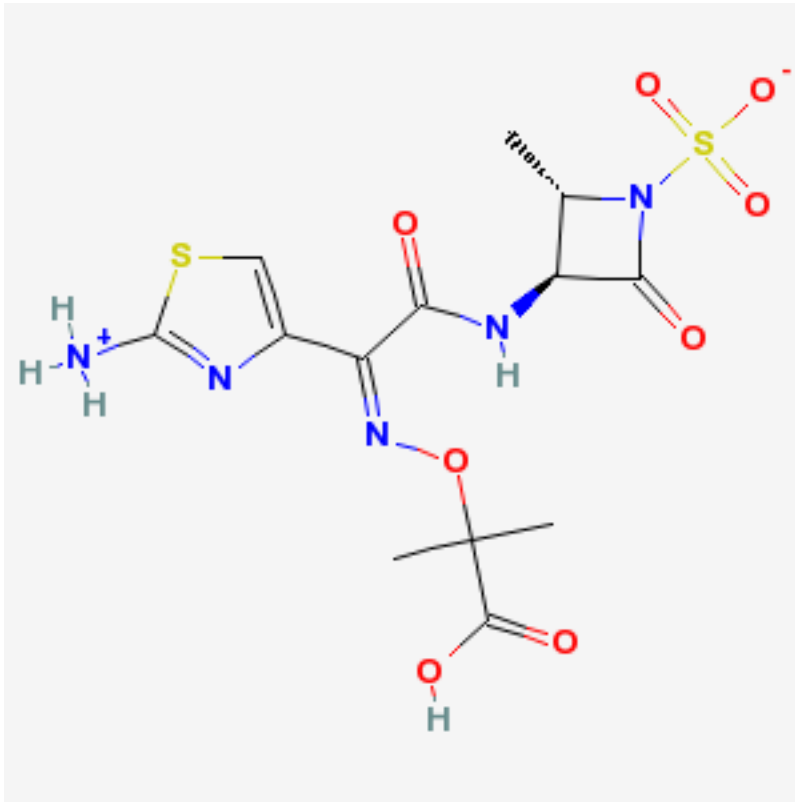
B-lactam antibiotics



- **Monobactams**
- **Aztreonam** - represent a group of monocycle, function like other **B-lactam antibiotics**
- Remarkable activity against aerobic G-bacteria, including species of **Pseudomonas, Klebsiella, Enterobacter, Serratia.**
- Have no activity against G⁺ anaerobes
- Aztreonam is stable to most B-lactamas.
- Is a means of controlling B-lactamas-producing.

Inhibition of cell wall synthesis

B-lactam antibiotics

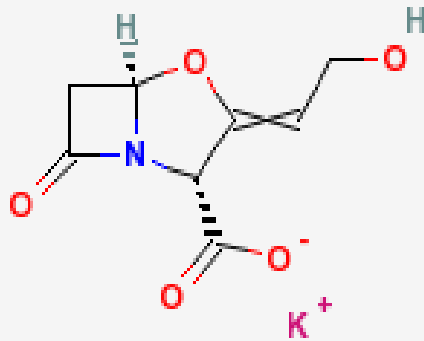
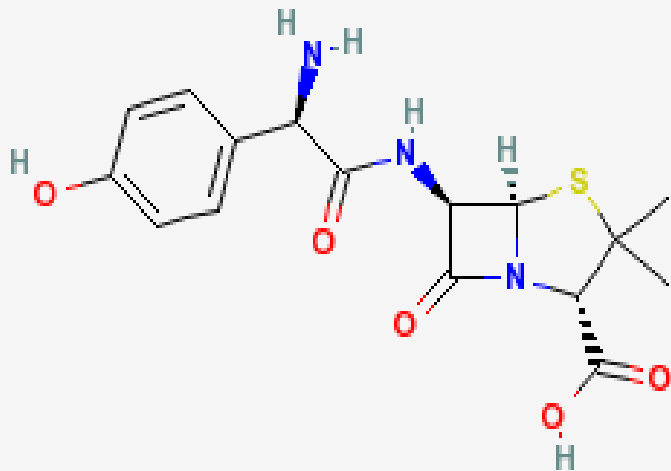


- **Monobactams**
- **Aztreonam** have selective antibacterial action microbiota of the host.
- **Aztreonam** is also able to penetrate the outer membrane of G-bacteria.
- **No** active **against** MRSA.

Inhibition of cell wall synthesis

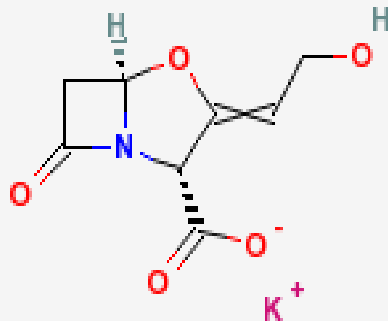
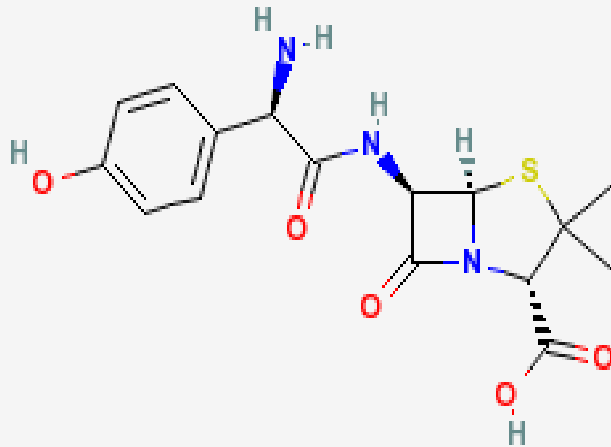
B-lactam antibiotics

Inhibitor B-lactamase.



- *Augmentin* is combination of amoxicillin and clavulanate (clavulanate has a structure similar to penicilline) it is B-lactamase inhibitor.
- Sulbactam – another B-lactamase Inhibitor.
- Combination Sulbactam + Ampicillin = Unasyn.

Inhibitor B-lactamase.



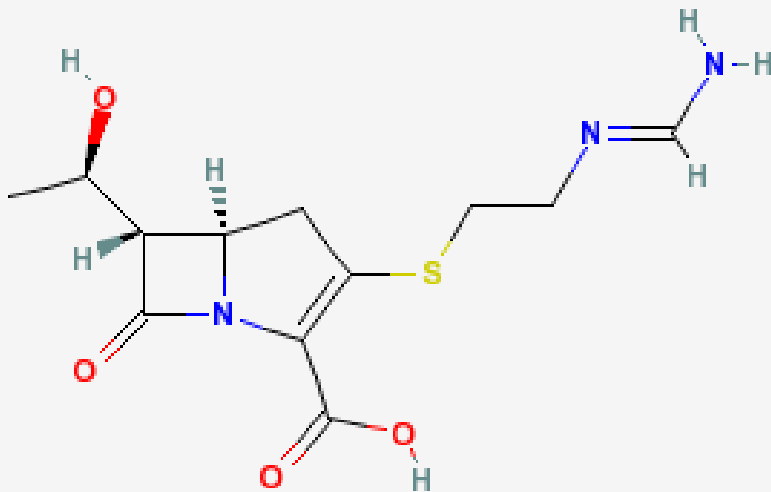
- ***Inhibitor B-lactamase.***
- **Combination antibiotic containing amoxicillin and clavulanic**
- **Spectrum of activity.**
- **Against all microorganism, which also sensitive ampicilline.**
- **More active against **enterococcus****
- **It has high activity against non sporforming G- anaerobic bacteria (B.fragilis).**
- **Have not activity against ***Pseudomonas***,**

Inhibitor B-lactamase.

- **Addition of clavulanate (a beta-lactam) increases drug's resistance to beta-lactamase (an enzyme produced by bacteria that may inactivate amoxicillin).**

Inhibition of cell wall synthesis

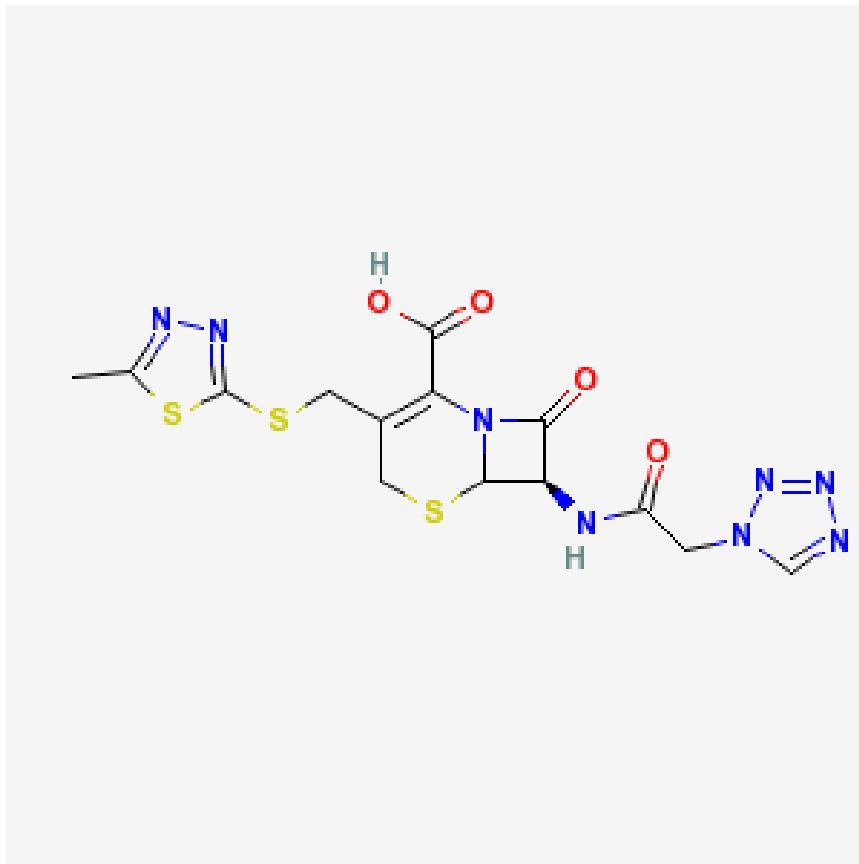
B-lactam antibiotics



- **Carbapenems (imipenem)** are the antibiotics with broader spectrum of activity, **Carbapenems** are effective than other B-lactam .
- **Carbapenems** are active against G⁺ and G⁻ and enterococci, G⁻ anaerobic bacteria (B.fragilis).
- **No** active against **MRSA**.

Inhibition of cell wall synthesis

B-lactam antibiotics



- **Cephalosporins** have a sixmembered ring adjacent to **B-lactam** ring.
- **Common properies of Cephalosporins**
- **Bactericidal effects.**
- **Low toxicity**
- **A broad spectrum of activity.**
- **No active against MRSA, enterococcus.**
- **Sinergism with AG.**

B-lactam antibiotics Cephalosporins

- I generation of Cephalosporins (cefazolin, cephalotin).
- I generation of Cephalosporins are active primarily **against G+ and G-cocci**.
- **G- specrum is limited.**
- **Pseudomonas is resistant**
- I generation of Cephalosporins are resistant for
- B-lactamase which produced by staphylococcus.
- Sensitive for B-lactamase of G- bacteria

B-lactam antibiotics Cephalosporins

- II generation of Cephalosporins (cefamandol, cefuroxime)
- They are effective against G+ and G-cocci
- and anaerobes similar I generation.
- They have elevated activity against G- bacteria (E.coli, Proteus, Shigella, Salmonella)
- No active against P.aeruginosa.

B-lactam antibiotics Cephalosporins

- **III generation of Cephalosporins (Cefoperazone, Cefotaxime).**
- **They have elevated activity against G-bacteria (E.coli, Proteus, Shigella, Salmonella)**
- **Variable activity against P.aeruginosa.**
- **Variable activity against non sporforming G- anaerobic bacteria (B.fragilis).**

B-lactam antibiotics Cephalosporins

- **IV generation of Cephalosporins**
- **(Cefpiron, Cefitim).**
- **A broad spectrum of activity.**
- Active **against P.aeruginosa.**
- **No** active **against MRSA, enterococcus**

Side reactions to antimicrobial agents (B-lactam antibiotics)

- Produce **hypersensitivity** reaction.
- The most serious reaction to penicillin **anaphylactic shock** is extremely rare.
- Skin test with dilute solution of penicillin G.
- **AMINOPENICILLINS** leads to **disbacteriosis**-antibiotic-associated colitis.

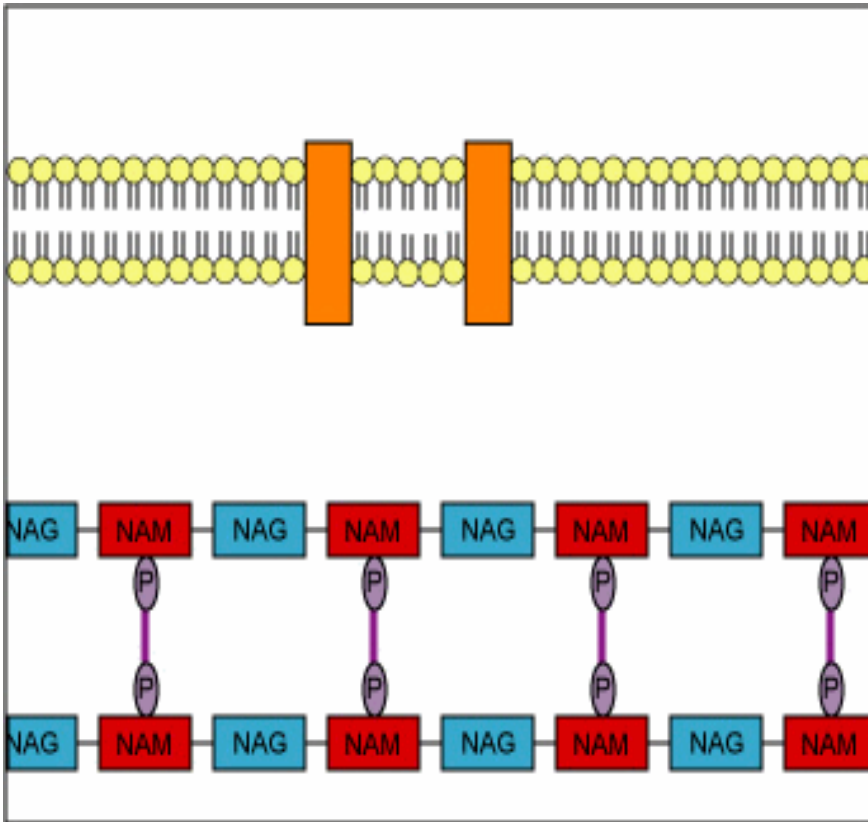
Side reactions to antimicrobial agents

- Antibiotic-associated colitis is caused by toxins produced by the bacterium *Clostridium difficile* after treatment with antibiotics. When most of the other intestinal bacteria have been killed, *Clostridium difficile* grows rapidly and releases 2 toxins that damage the intestinal wall. The disease and symptoms are caused by these toxins, not by the bacterium itself.

Side reactions to antimicrobial agents

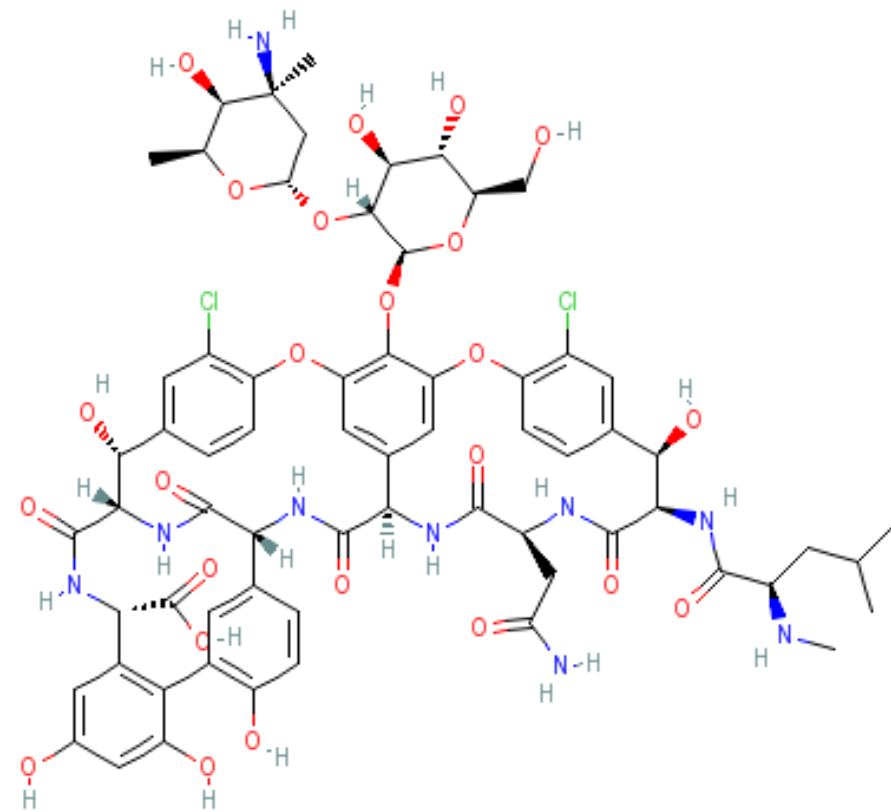
- **Pancitopenia is rare and reversible.**

Inhibition of cell wall synthesis



- Vancomycin is glycopeptides that inhibit of cell wall synthesis by blocking transpeptidation but by a mechanism different from that of B-lactam antibiotics.
- Vancomycin interact with the D-alanine-D-alanine portion of the pentapeptide which blocks transpeptidase.
- Vancomycin transglycosylase Inhibit too.

Inhibition of cell wall synthesis



- Vancomycin is bactericidal agent effective against certain **G+** bacteria-
- **MRSA, enterococcus**
- **No active against G-** bacteria.
- It applies for treatment a series staphylococcus – resistance infections.
- Can cause phlebitis
- ototoxicity, nephrotoxicity.
- Red man syndrome.

Inhibition of cell wall synthesis

- It applies for treatment a serious staphylococcus –resistance infections, including endocarditis, peritonitis, oral treatment of Clostridium difficile-associated pseudomembranous colitis.
- Can cause phlebitis
- ototoxicity, nephrotoxicity.
- Red man syndrome.

Inhibition of cell wall synthesis

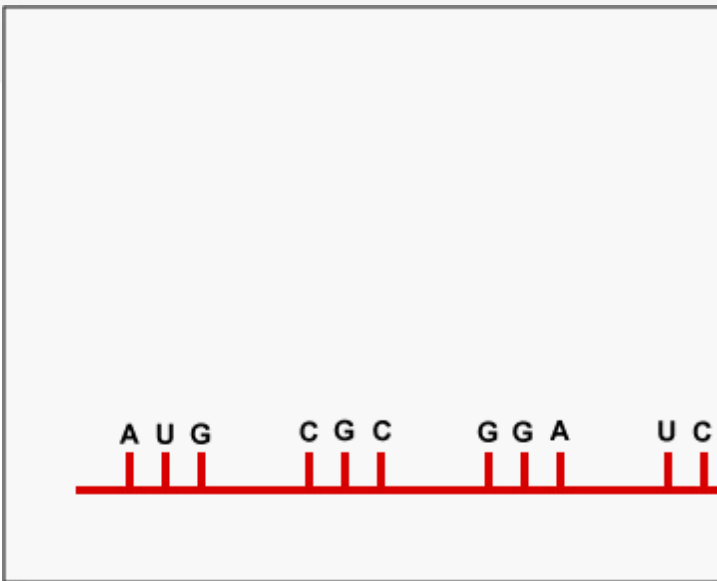
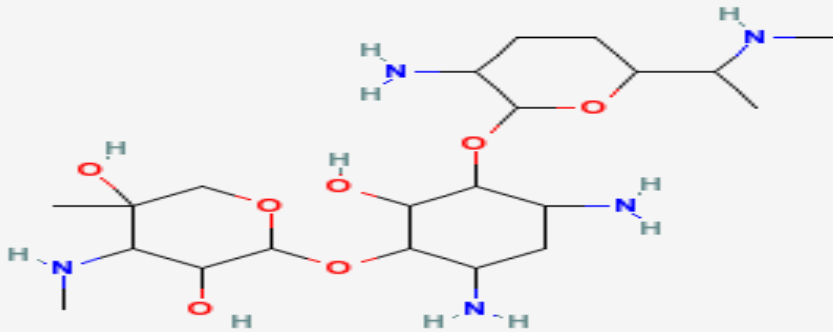
- **Not absorbed from the gastrointestinal tract.**
- **Largely excreted by the renal route;**
- **Poor penetration into cerebrospinal fluid (CSF).**
- **Resistance – occasionally seen in enterococci.**

Inhibition of protein synthesis

- ***Aminoglycosides** are one of the oldest and most functional groups of broad-spectrum antibiotics. The name of this group of antibiotics is derived from its complex structure, which includes the connection of two or three components by glycosidic bonds.*

Inhibition of protein synthesis

- All *aminoglycosides* are bactericidal and interfere with protein synthesis. They appear to act by combining with *subunit of the ribosome*, causing a misreading of genetic code.



Inhibition of protein synthesis

- *The aminoglycosides are divided into 3 groups or generations.*
- *I generation:*
- Streptomycin
- Kanamycin
- Neomycin
- Streptomycin's primary activity is ***against G- bacteria, enterococci, M.tuberculosis.***
- Kanamycin is active against ***G+ and G- bacteria, M.tuberculosis.***
- ***It is not effective against Pseudomonas***

Inhibition of protein synthesis

- *II generation of aminoglycosides:*
- gentamicin
- Tobramycin
- They have a *broad-spectrum antimicrobiol* activity, but it is *primary active against infections from G-* bacteria and it drugs of choice for *P.aeruginosa* infections.
- It have activity *against Staphylococcus* on combination with *B-lactam antibiotics*

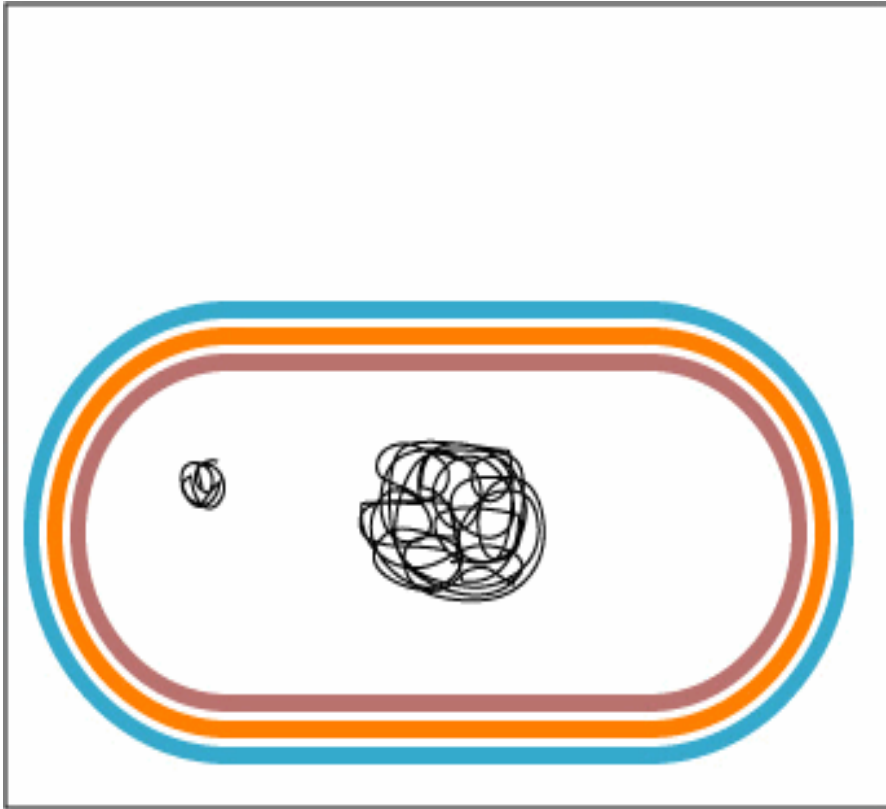
Inhibition of protein synthesis

- *III generation of aminoglycosides:*
- Gentamicin
- Amikacin, netilmicin.
- They have *elevated activity against resistance G- bacteria (Pseudomonas, Proteus, Klebsiella)*.
- All aminoglycosides are not effective against anaerobes, because their transport into the bacterial cell requires oxygen.

Inhibition of protein synthesis

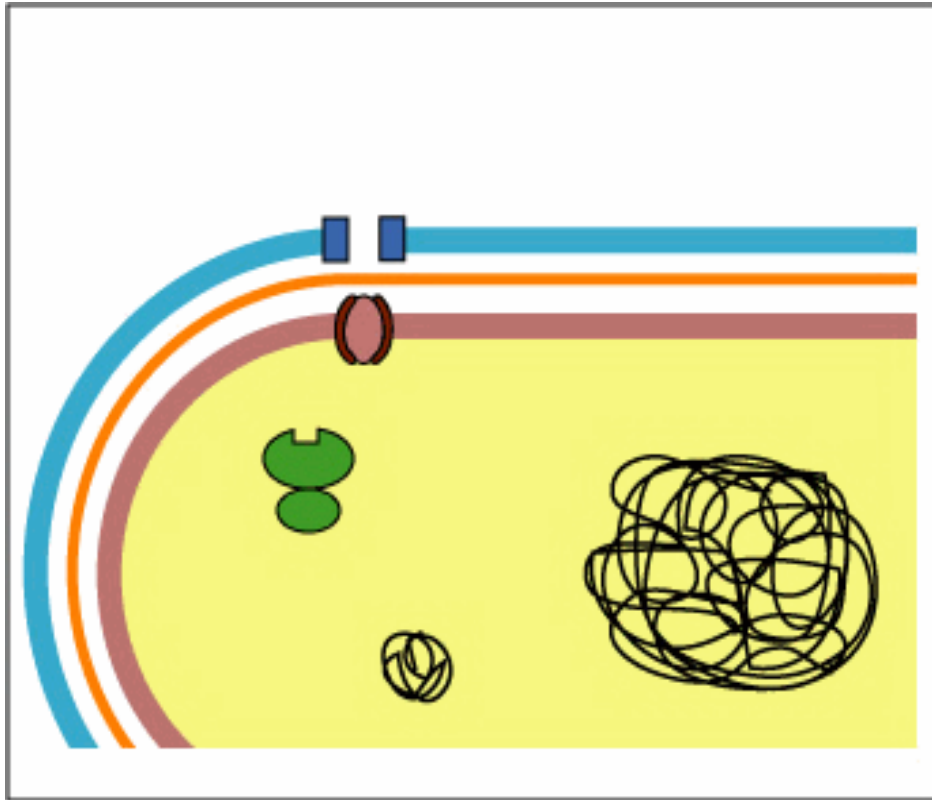
- **Poorly absorbed from the gut; they have poor penetration into tissue and fluids;**
- **Excretion is almost entirely by the kidneys.**
- **Serum levels require monitoring with careful dosage adjustment particularly in renal failure.**

Mechanism of resistance



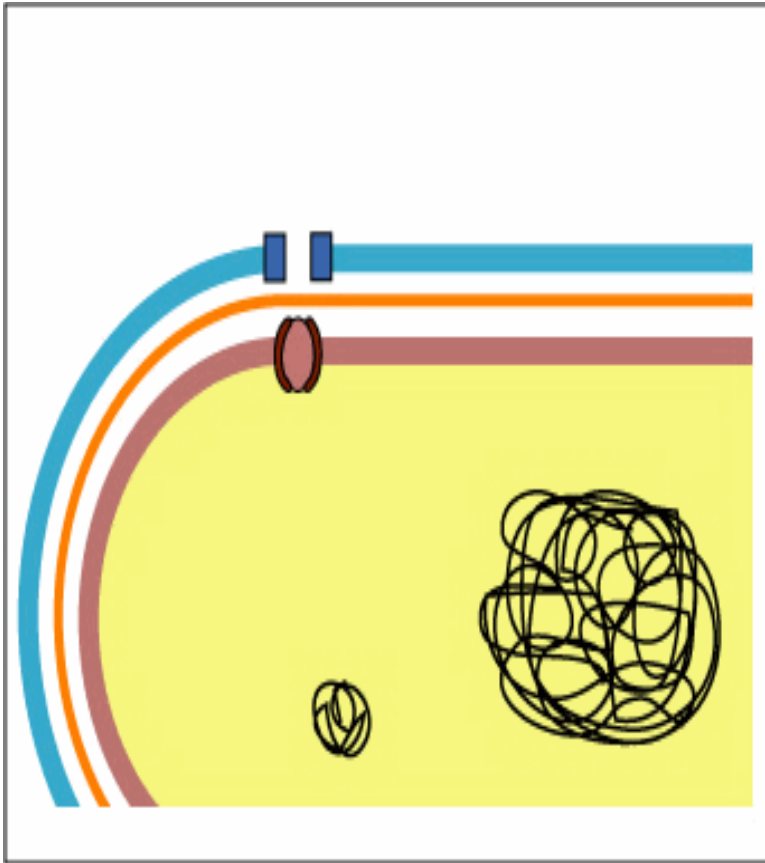
- Resistance to aminoglycosides occurs by 3 mechanisms:
- 1. The important - modification of the drugs by plasmid encoded
- Adenylating,
- Acetylating
- Phosphorylating

Mechanism of resistance



- **2. Chromosomal mutation in the gene that codes for the target protein in the 30S subunit of bacterial ribosome.**

Mechanism of resistance



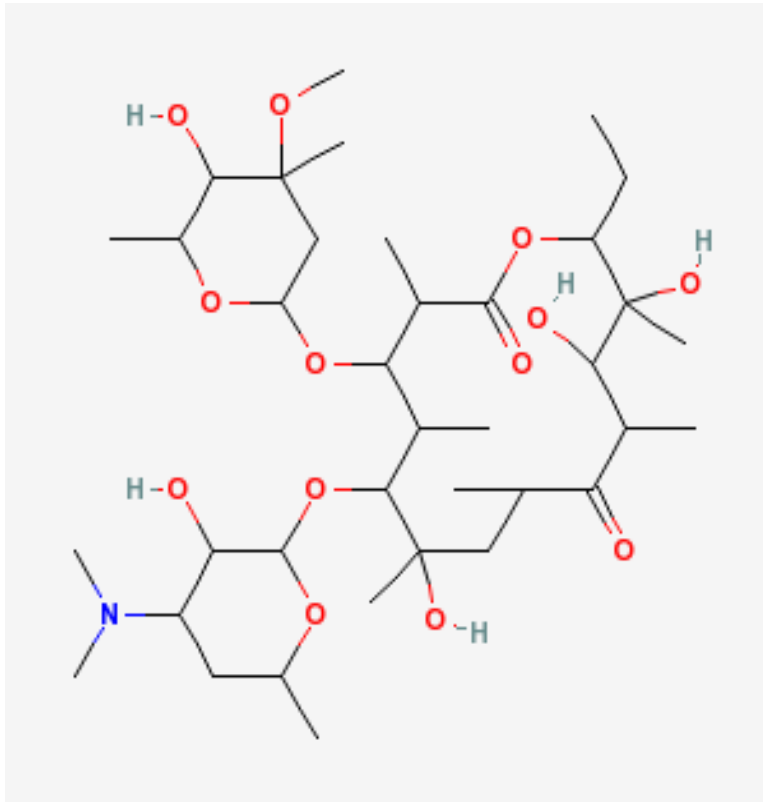
- **Decreased permeability of the bacterium to the drug.**

Adverse reaction to aminoglycosides:

- Most of **aminoglycosides** can be toxic to **kidneys and auditory nerves** (Streptomycin, Kanamycin can cause serious ototoxicity, *gentamicin have Nephrotoxicity effect*).
- **The newer aminoglycosides are generally safe.**
- **Aminoglycosides do not cause allergies or interfere with immunology processes.**
- **They are poorly absorbed from the gastrointestinal tract.**

Inhibition of protein synthesis

Macrolides



- **Macrolides** –the name of this group of antibiotics is derived from its complex structure, which includes in the molecules
- ***Macrocyclic lactone ring,***
- **one or more deoxysugars. The lactone rings are usually 14, 15 or 16-membered.**

Inhibition of protein synthesis

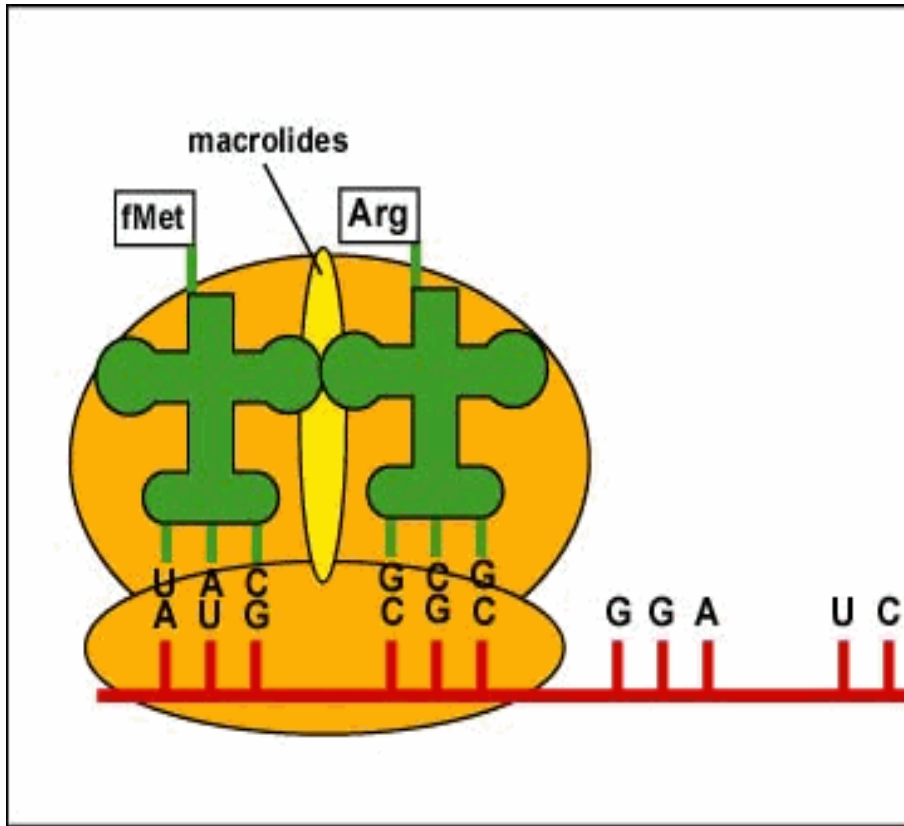
Macrolides

- **Nature Macrolides.**
- **Erythromycin**
- **Oleandomycin**
- **Roxythromycin**
- **Semisynthetic Macrolides**
- **Dirithromycin,**
- **Azithromycin**



Inhibition of protein synthesis

Macrolides



- ***Mechanism of action.***
- **Macrolides act by inhibition protein synthesis in the bacterial cell, binds to 50s subunit and block the translocation steps.**

Inhibition of protein synthesis

Macrolides

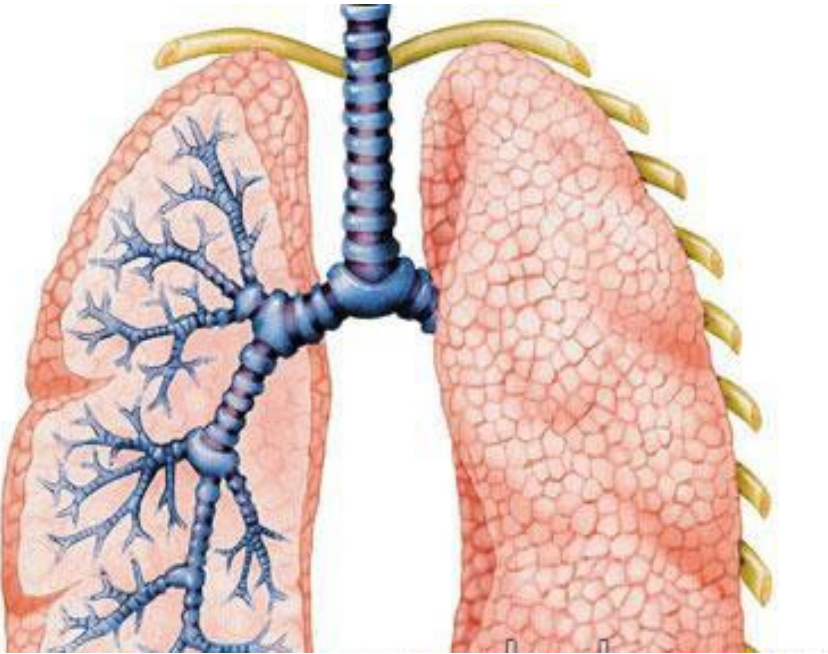
- The common properties of *Macrolides*
- **Bacteriostatic effect**, can also be bactericidal in high concentrations
- They have a very low toxicity.
- They have activity against *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia*, G+ cocci, Mycoplasma, Legionella.
- Azithromycin has a broadest range of antimicrobial activity, even against *E.coli*, *Proteus*, *Shigella*, *Salmonella*.
- Erythromycin has poor gastrointestinal tolerance.
- This is less of a problem with the newer drugs.

Macrolides

- **Macrolides tend to accumulate within leukocytes, and are therefore actually transported into the site of infection.**
- **The Macrolides are apicates for treatment of respiratory tract disease, is one of safest drugs.**

Macrolides

- **Antibiotic macrolides** are used to treat infections such as respiratory tract and soft tissue infections

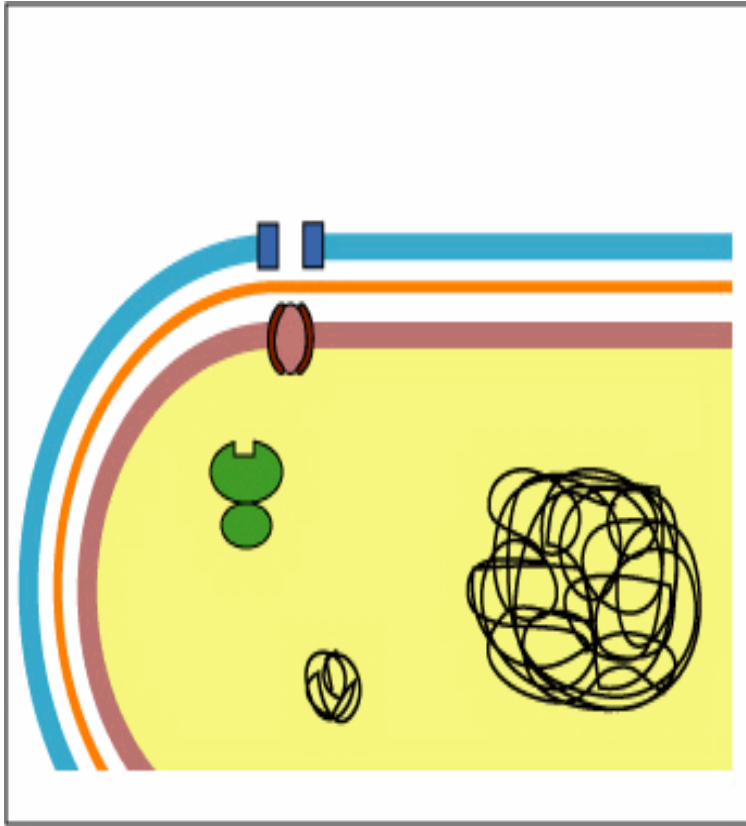


Inhibition of protein synthesis

Macrolides

- The antimicrobial spectrum of macrolides is slightly wider than that of penicillin, and therefore macrolides are **applied for** patients with a penicillin allergy. Beta-hemolytic streptococci, pneumococci staphylococci and are susceptible to macrolides. Unlike penicillin, macrolides are effective against mycoplasma, mycobacteria some rickettsia, and chlamydia.

Mechanism of resistance



Resistance is due to a plasmid-encoded or chromosomal enzyme that methylates the 23s rRNA and blocking binding of drugs.

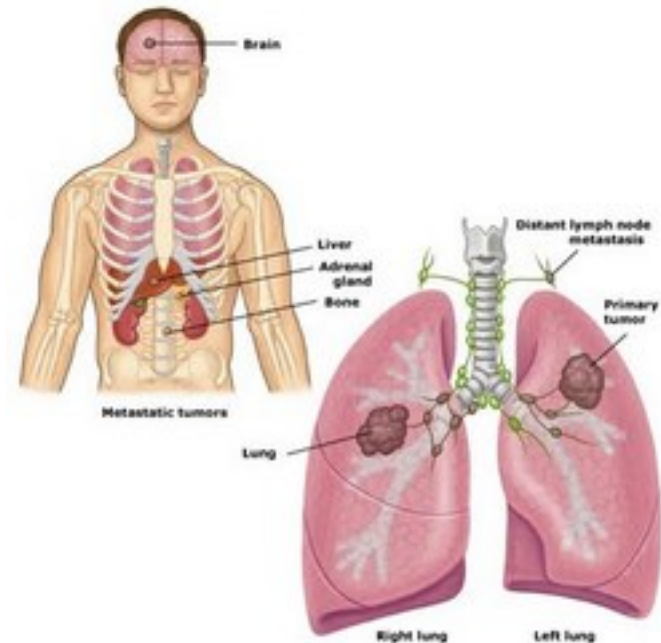
Through mutation, and results in cross-resistance to macrolides, lincosamides.

Mechanism of resistance

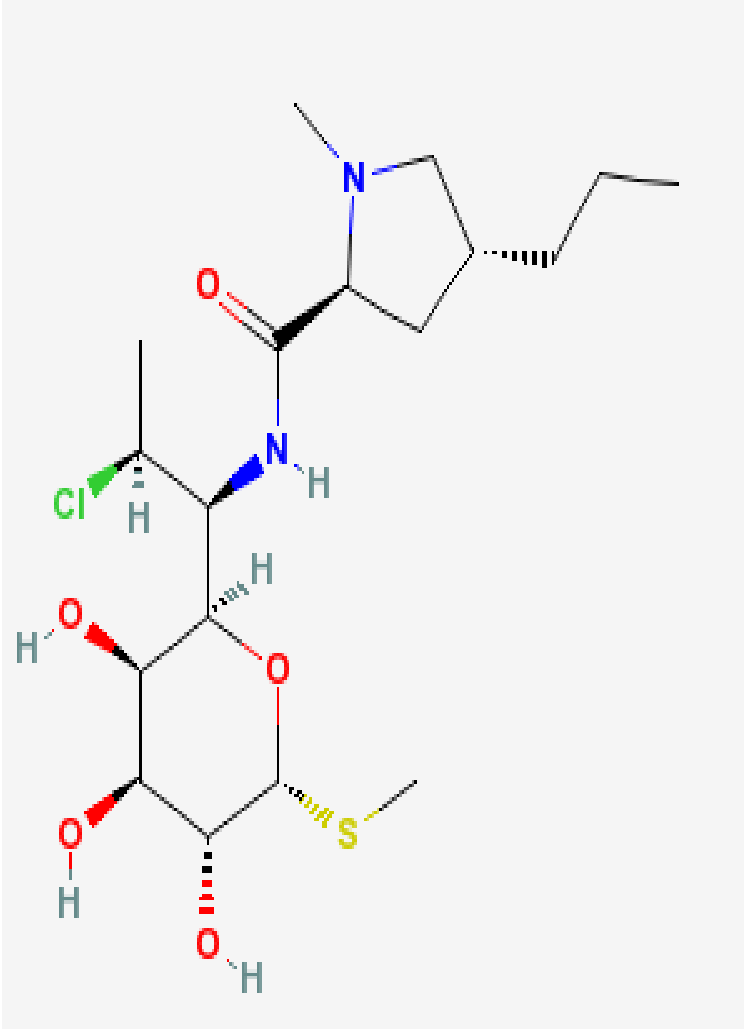
- Two other types of resistance rarely seen include the production of drug-inactivating enzymes (*esterases or kinases*) as well as the production of active *ATP-dependent efflux proteins* that transport the drug outside of the cell.

Side effects

- They have a very low toxicity.
- Macrolides exhibit enterohepatic recycling; that is the drug is absorbed in the gut and sent to the liver, only to be excreted into the duodenum in bile from the liver. This can lead to a build up of the product in the system, and so causing nausea.



Inhibition of protein synthesis



- *Clyndamycin and lincomycin act on 50s* subunit by binding to the 23S subunit of the bacterial ribosome and blocks peptide bond formation.
- Bacteriostatic effect.
- Active mainly against **G+** *cocci*.
- Activity against anaerobes, both: non sporforming **G-anaerobic** bacteria (*B.fragilis*) and G+ such as *Clostridium perfringens*.
- Active against protozoan agent

Clyndamycin and lincomycin

- Clyndamycin and lincomycin *can exist in macrophages.*
- May induce changes in the surface structure of bacteria that make them more sensitive to immune system attack (opsonization and phagocytosis).

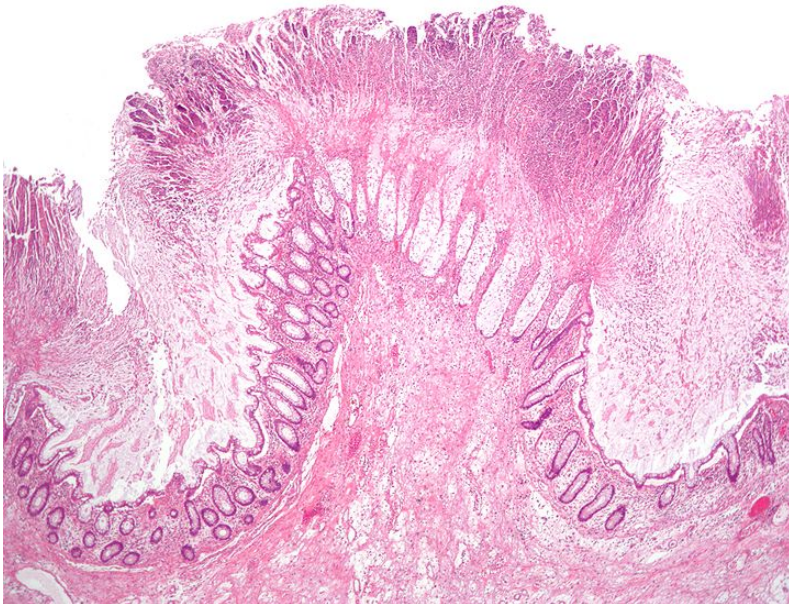
Clyndamycin and lincomycin



- Clyndamycin and lincomycin are *deposited in bones* and aplicates for treatment osteomyelites.

side effect

- The most side effect is ***pseudomembranous colitis*** (suppression of normal flora of the bowel and overgrowth of a drug resistant strain of *Clostridium difficile*).



Adverse effects

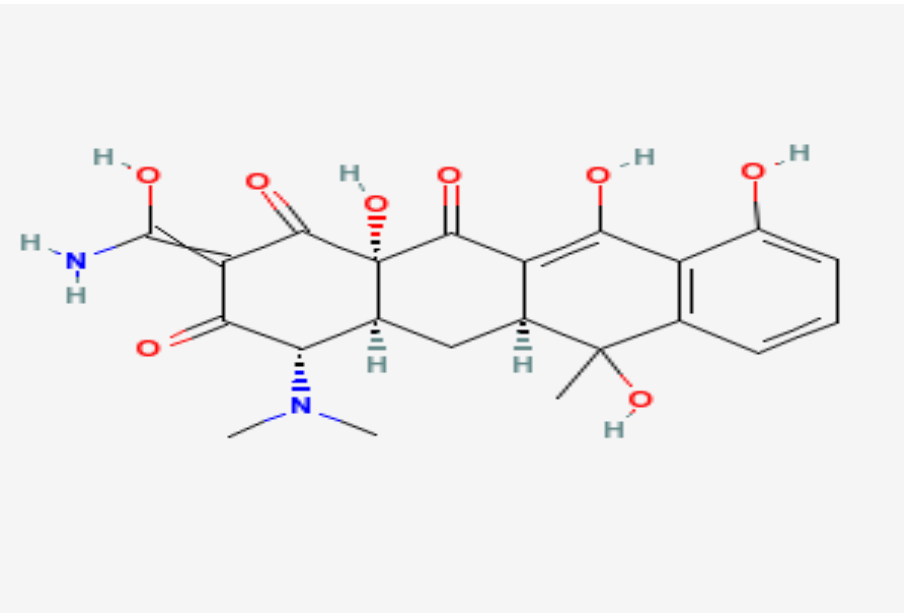
- Overgrowth of *Clostridium difficile*, which is resistant to clindamycin, results in the production of a toxin that causes a range of adverse effects, from diarrhea to colitis and toxic megacolon.

Inhibition of protein synthesis

- **Tetracyclines** are produced by species of streptomyces and have four cycle rings with different R groups. **Inhibit protein synthesis by binding to the 30s ribosomal subunit.**

Bacteriostatic effect.

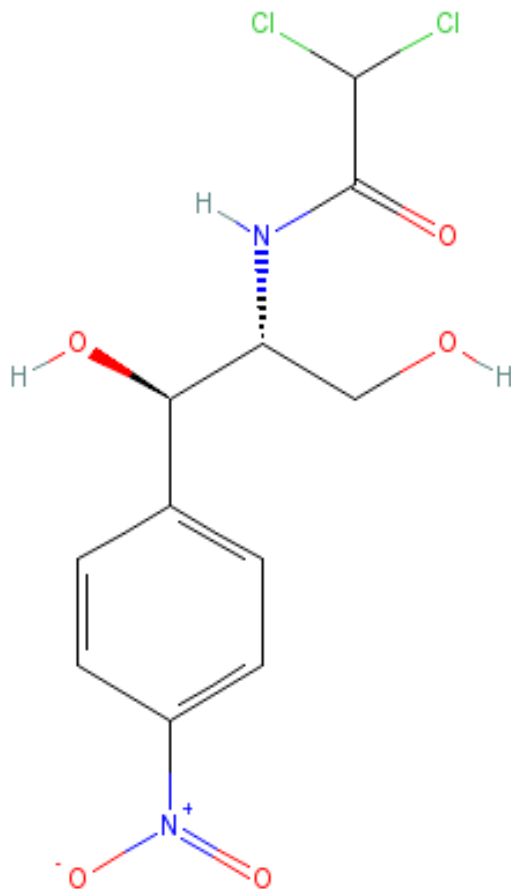
They have a broad-spectrum antimicrobial activity against G+, G-, Chlamydia, Mycoplasma, Legionella.



Inhibition of protein synthesis

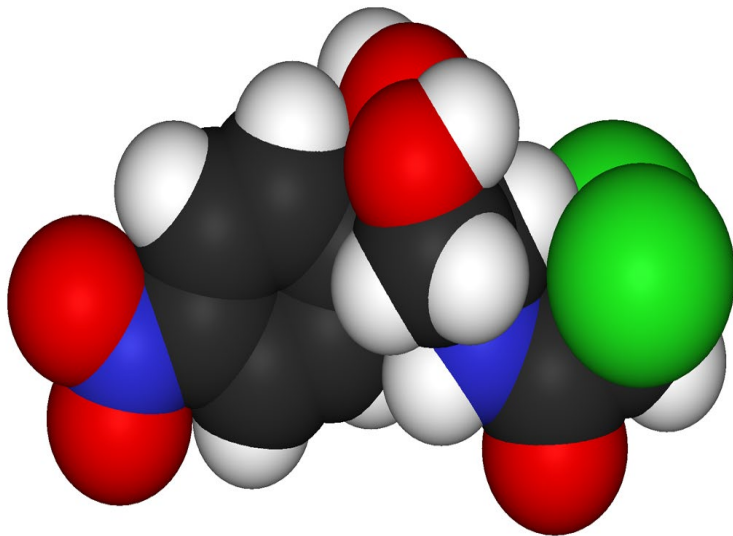
- Tetracycline's are deposited in *growing bones and teeth* with depression of linear bone growth.
- Not given *during pregnancy or to young children.*
- *Suppression of normal flora* of the bowel.

Inhibition of protein synthesis



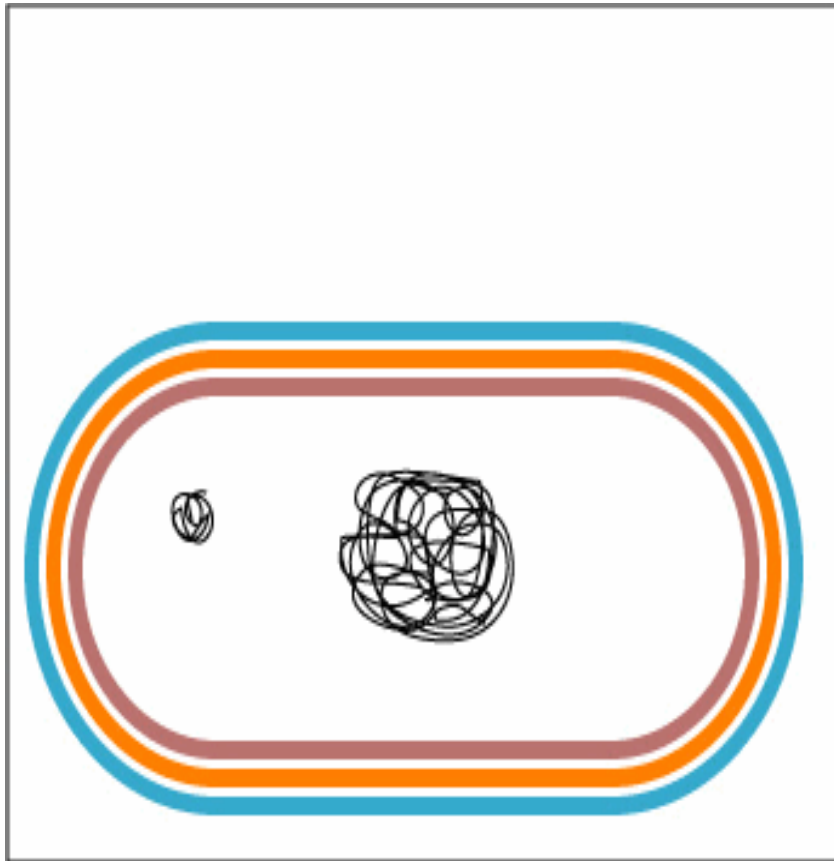
- **Chloramphenicol (Laevomycin)** Inhibit protein synthesis by binding to the 50s ribosomal subunit and blocking the action of peptidyltransferase, this prevent the synthesis of new peptide bonds.

Chloramphenicol (Laevomisetin)



- They have a **broad-spectrum antimicrobial activity against G+, G- (including anaerobes) Chlamydia.**

Resistance to Chloramphenicol

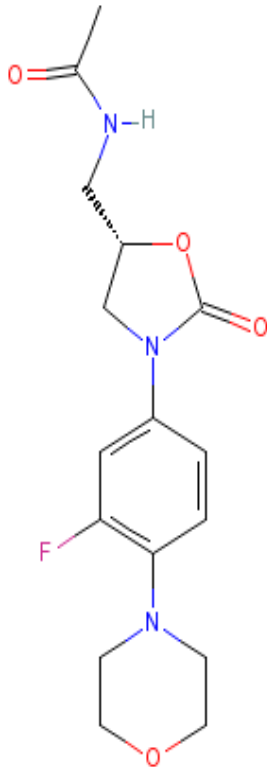


- Resistance to Chloramphenicol is due by two mechanism:
- 1. Enzyme acetyl transferase acetylates in to acetyl ester.
- 2. reduce nitro group on the molecule.

Inhibition of protein synthesis

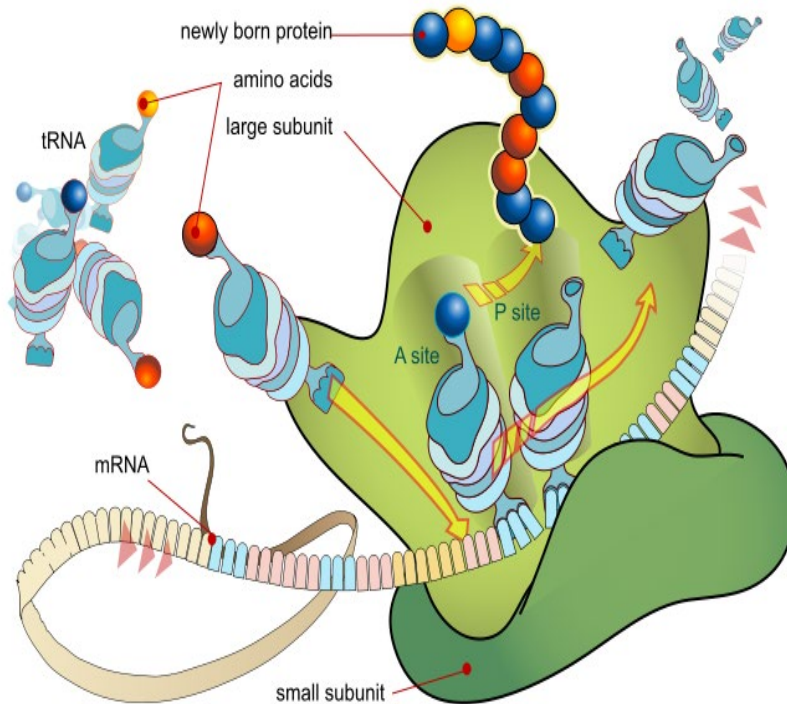
- **Chloramphenicol (Laevoamicetin) toxicity -**
- **Irreversible aplastic anemia.**
- **Transient bone marrow depression**
- **(these hematologic changes reverse rapidly when the drug is stopped).**

Inhibition of protein synthesis



- ***Linezolid*** is a synthetic antibiotic binds to the 23S ribosomal RNA in the 50S, they stop the growth and reproduction of bacteria by disrupting translation of messenger RNA(mRNA) into proteins in the ribosome.

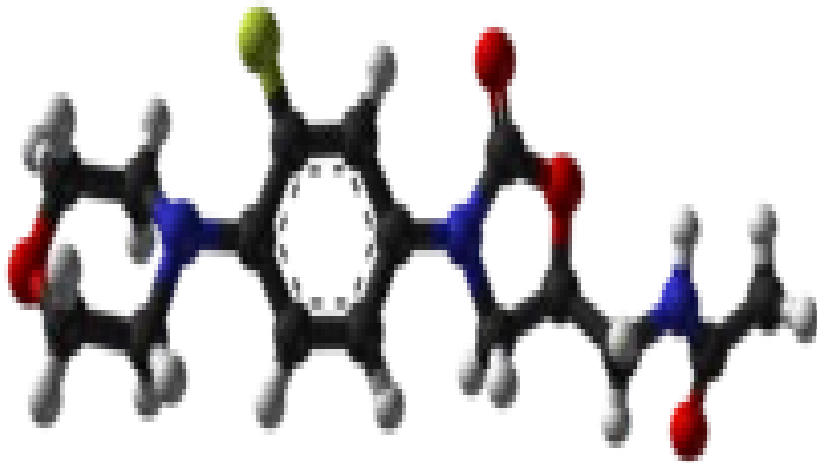
Linezolid



Simplified schematic of mRNA translation. Linezolid occupies the A site (at center) and prevents tRNA from binding.

- Mechanism of action is not fully understood, linezolid appears to work on the **first step of protein synthesis, initiation**, unlike most other protein synthesis inhibitors, which inhibit **elongation**

Inhibition of protein synthesis - Linezolid



- ***Linezolid*** used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics (**vancomycin-resistant enterococcus, MRSA, penicillin-resistant pneumococci**)

Spectrum of activity

- Linezolid is effective against all clinically important Gram-positive bacteria—those whose cell wall contains a thick layer of peptidoglycan and no outer membrane— *Enterococcus faecium* and *Enterococcus faecalis*(including vancomycin-resistant enterococci, *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus*, MRSA), *Streptococcus agalactiae* , *Streptococcus pneumoniae*, *Streptococcus pyogenes* the *viridans* group streptococci, and *Listeria*

Inhibition of protein synthesis - Linezolid

- Linezolid's spectrum of activity against Gram-positive bacteria is similar to that of the glycopeptide antibiotic vancomycin
- Linezolid has no clinically significant effect on most Gram-negative bacteria *Pseudomonas* and the Enterobacteriaceae.

linezolid

- Indications for linezolid use are:
vancomycin-resistant *Enterococcus* infection, with or without bacterial invasion of the bloodstream; hospital- and community-acquired pneumonia caused by *S. aureus* or *S. pneumoniae*; complicated skin and skin structure infection (cSSSI) caused by susceptible bacteria, including diabetic foot infection

linezolid

- Linezolid is better than vancomycin against nosocomial pneumonia, particularly ventilator-associated pneumonia caused by MRSA, perhaps because the penetration of linezolid into bronchial fluids is much higher than that of vancomycin

linezolid

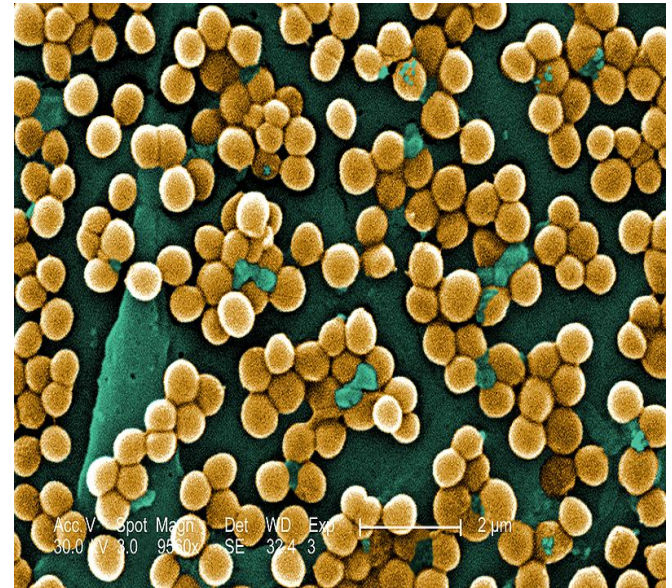
- *Staphylococcus aureus* is one of the most important pathogens that cause infections in hospitalized patients. Treatment of infections caused by methicillin-resistant strains of *S. aureus* (MRSA) is one of the main problems of antimicrobial therapy in term of resistance of this pathogen to all -lactams and to many other classes of antimicrobials. Such resistance leads to increased mortality and to decrease in cost-effectiveness of treatment. Glycopeptide antibiotic vancomycin has been the drug of choice for the treatment of the serious staphylococcal infections

Adverse effects

- Linezolid is a relatively safe drug.
- Common side effects of linezolid use (those occurring in more than 1% of people taking linezolid) include diarrhea (reported by 3–11% of clinical trial participants), headache (1–11%), nausea (3–10%), vomiting (1–4%), rash (2%),
- linezolid has been associated with *Clostridium difficile*-associated diarrhea (CDAD) and pseudomembranous colitis, occurring in about one in two thousand patients in clinical trials.

Mechanism of Resistance

- The resistance of most Gram-negative bacteria to linezolid is due to the activity of efflux pumps, which actively "pump" linezolid out of the cell faster than it can accumulate.
- Gram-positive bacteria usually develop resistance to linezolid as the result of a point mutation



**Methicillin-resistant
Staphylococcus
aureus (bottom; false
colors)**

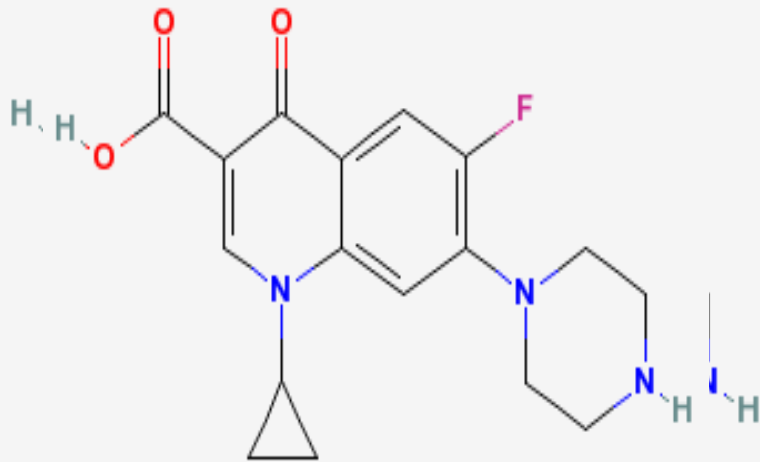
Inhibition of DNA synthesis

- **Quinolones.**

The quinolones are a family of synthetic broad-spectrum antibiotics. The first important class is nalidixic acid, had limited spectrum of antimicrobial active against G-, than against G+bacteria.

New class of **Quinolones**

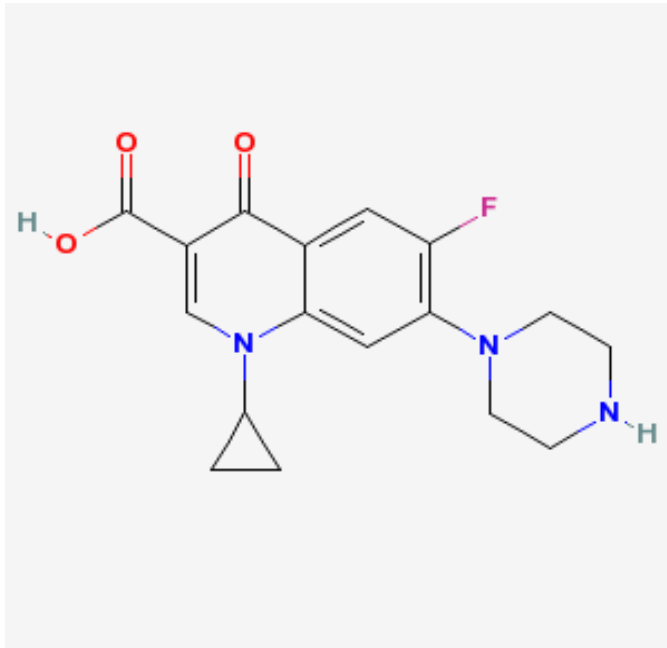
Ftorquinolones consist of *Ciprofloxacin, norfloxacin, perfloxacin, ofloxacin.*



Quinolones.



Inhibition of DNA synthesis

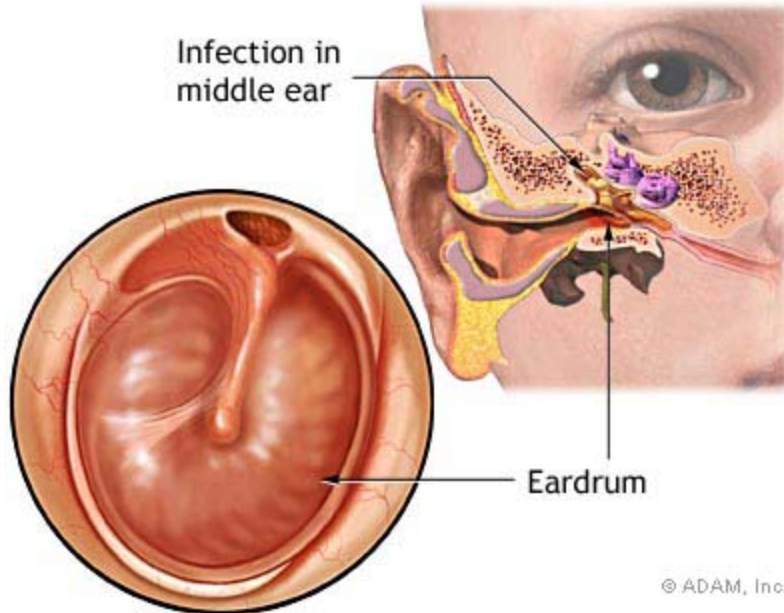


- **Antimicrobial activity**
- **Primary activity is against G- bacteria, even against Pseudomonas, Legionella, Chlamydiae, poor activity against pneumococci.**

The common positive properties of quinolones

- The *broad spectrum* **activity**
- *Bactericidal* **effect.**
- A *low toxicity.*
- They *don not influence on for anaerobes.*
- Possess a *selective antibacterial activity* **on the microbiota of the host.**
- Possess a *high intracellulare activity.*
- Can be *spread in all tissue* **of the host.**
- Can *exist in macrophages.*

quinolones



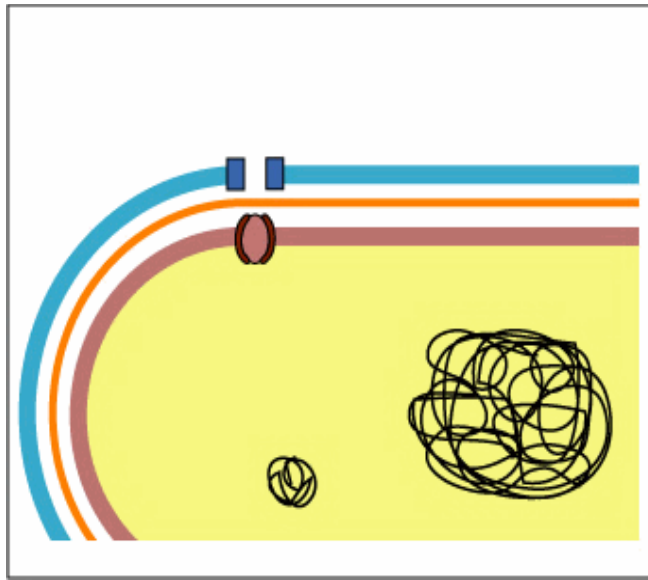
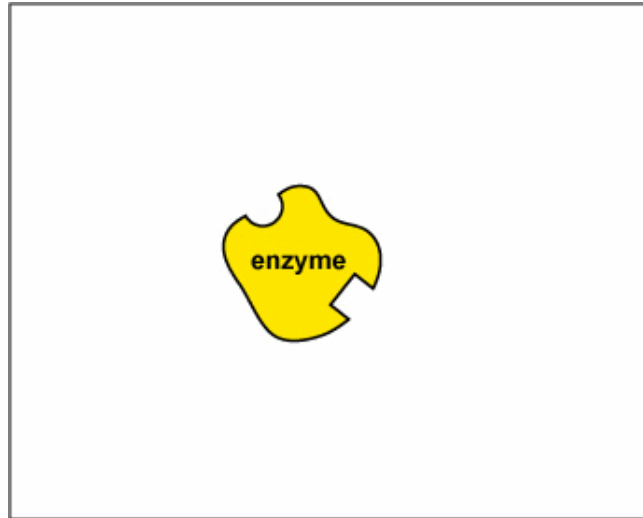
- Can be applied *per os* for *treatment of* serious diseases.
- Fluoroquinolones are not recommended as first-line antibiotics for acute sinusitis

Inhibition of DNA synthesis



- **Mechanism of action**
Quinolones –inhibit function of enzymes DNA-gyrase. That enzyme are essential to DNA-replication.
- **New Quinolones**
- **Levofloxacin** –
"respiratory Quinolones activity against Streptococcus pneumonia.
- **Quinolones** are bactericidedal drugs.
- **Quinolones** possess a high Intracellular activity.

Inhibition of DNA synthesis



- **Resistance to Quinolones**
- **Is due primarily to chromosomal mutations that modify the bacterial DNA gyrase.**
- **Altered porin preventing passage of the antibiotic.**

Inhibition of DNA synthesis

- **Toxicity and side effects.**
- In general, fluoroquinolones are well tolerated.
- **Gastrointestinal disturbances, photosensitivity, neurological disturbances, possible effect on growing cartilage relatively contraindicates use of Quinolones**
- in children.

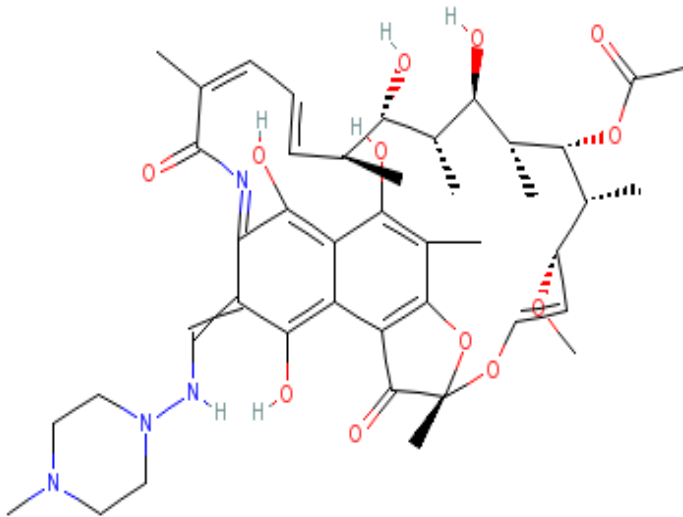
Toxicity and side effects.

- **Fluoroquinolones are sometimes associated with an QTc interval prolongation and cardiac arrhythmias.**
- **The central nervous system is an important target for fluoroquinolone-mediated neurotoxicity.**

Inhibition of DNA synthesis

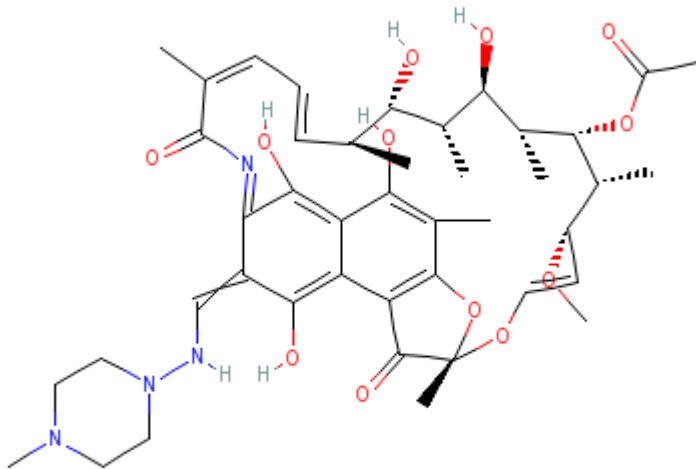
- **Metronidazoles.**
- **Mechanism of action.**
- **Metabolized by nitroreductases to active intermediates which result in DNA breakages.**
- **It is active against bacteroides, other anaerobes, Trichomonas vaginalis.**
- **Resistance –rare.**

Inhibition of RNA synthesis



- **Rifampicin** is relatively new semisynthetic derivation of rifamycin.
- Action of **Rifampicin** is based on blocking mRNA synthesis by bacterial RNA polymerase.. (inhibition of DNA-dependent RNA synthesis).
- **Rifampicin** is used primarily for the treatment of tuberculosis, leprosy, mycobacterium avium complex infection
- **They have a** broad-spectrum antimicrobial activity against G+, G-

Rifampicin

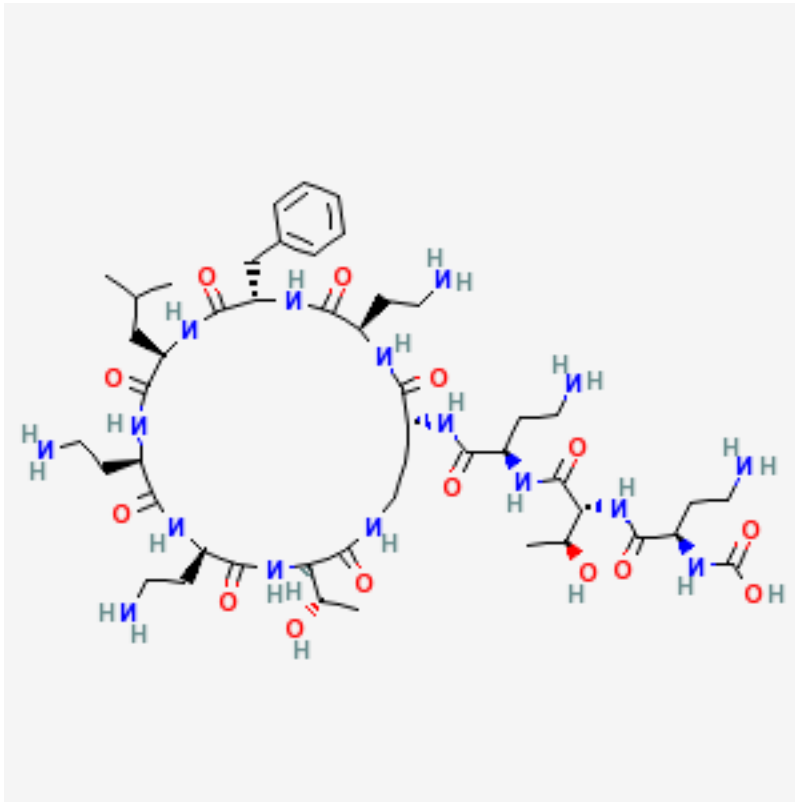


- They have a broad-spectrum antimicrobial activity against G⁺, G⁻
- In addition, rifamycins showed potency towards HIV. This is due to their inhibition of the enzyme reverse transcriptase, which is essential for tumor persistence.

Inhibition of RNA synthesis - Rifampicin

- **Toxicity.**
- **Adverse reactions include skin and transient liver function abnormalities,**
- **A rare cause of hepatic failure.**

Alteration of cell membrane function

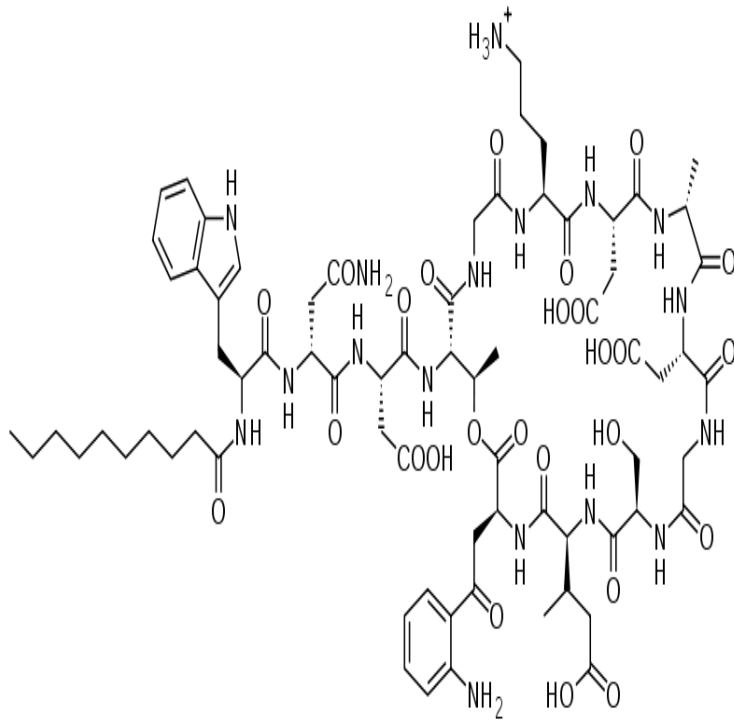


- **Polymyxins** are cyclic peptides composed of 10 amino acid. The positively charged free amino act like a cationic **detergent** to disrupt the phospholipid structure of cell membrane.
- **Polymyxin E** Primary activity is against G-bacteria,
- especial **Pseudomonas**

Alteration of cell membrane function

- **Polymyxins** may be bacteriostatic or bactericidal, depending upon the dosage
- Kidney damage and nerve injury are usually reversible.

Alteration of cell membrane function



- **Daptomycin** is a novel lipopeptide antibiotic
- It is a naturally-occurring compound found in the soil saprotroph *Streptomyces roseosporus*

Mechanism of action

- Daptomycin has a distinct mechanism of action, disrupting multiple aspects of bacterial cell membrane function. It appears to bind to the membrane and cause rapid depolarization, resulting in a loss of membrane potential leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death.

Daptomycin

- Daptomycin is active against Gram-positive bacteria only. It has proven *in vitro* activity against enterococci (including glycopeptide-resistant Enterococci (GRE)), staphylococci (including methicillin-resistant Staphylococcus aureus, and corynebacteria.
- Its special niche is currently for highly resistant organisms such as VISA and VRSA (vancomycin resistant Staphylococcus aureus)
- The bactericidal activity of daptomycin is concentration-dependent.

Indications

- **Daptomycin** is approved in the United States for skin structure infections caused by Gram-positive infections, *Staphylococcus aureus* bacteraemia and right-sided *S. aureus* endocarditis. It binds avidly to pulmonary surfactant, and therefore cannot be used in the treatment of pneumonia.

Antifungal agents

- *1. Polyenes* drugs, which *bind* to the *ergosterol* in the membranes
- of fungi (Amphotericin B, nystatin).
- *2. Azoles* act by inhibiting *ergosterol synthesis*(they block cytochrome P-450-depedent demethylation of lanosterol, precursor of ergosterol)-*fluconazol, ketonazol.*