جامعة بغداد

كلية العلوم

قسم علوم الحياة

المرحلة الثالثة

Antibiotics

المضادات النظري

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Antibiotics

Introduction

Most microbiologist distinguish two groups of antimicrobial agents used in the treatment of infectious disease: **antibiotics**, which are natural substances produced by certain groups of microorganisms, and **chemotherapeutic agents**, which are chemically synthesized. A hybrid substance is a **semisynthetic antibiotic**, wherein a molecular version produced by the microbe is subsequently modified by the chemist to achieve desired properties. Furthermore, some antimicrobial compounds, originally discovered as products of microorganisms, can be synthesized entirely by chemical means. They might be referred to as **synthetic antibiotics** to distinguish them from the chemotherapeutic agents.

History of antibiotics

- More than 3,000 years ago ancient people discovered that some molds could be used as a cure. The Egyptians, the Chinese, and Indians of central America would use molds to treat rashes and infected wounds.

- In the late **1880s Synthetic antibiotic chemotherapy** as a science and development of antibacterials **began** in Germany **with Paul Ehrlich**. Ehrlich noted that certain dyes would color human, animal, or bacterial cells, while others did not. He then proposed the idea that it might be possible to create chemicals that would act as a selective drug that would bind to and kill bacteria without harming the human host. After screening hundreds of dyes and chemicals against various organisms, he discovered that **compound number 606** , arsphenamine , was active against syphilis spirochete . Arsphenamine was made available in 1910 under trade name Salvarsan. Ehrlich coined the phrase '**magic bullet'** to describe this new wonder drug. The diluted yellow Salvarsan treatment was difficult and painful to inject. As it was an arsenic based compound, it was also toxic. Salvarsan would later be replaced by antibiotics such as penicillin.

- In the **1890's Rudolf Emmerich and Oscar Low**(two German doctors, who were the first to make an effective medication from microbes. They proved that

the germs that caused one disease may be the cure for another, the two men created a medication from Bacillus pyocyaneus (now called *Pseudomonas aeruginosa*, it produces pyocyanin, a characteristic green-blue phenazine pigment), that they called **pyocyanase**.* Pyocyanase was the first antibiotic drug to be used in hospitals. It was able to destroy other strains of bacteria. Among the bacteria that it killed were those that caused cholera, typhoid, diphtheria, and anthrax. Unfortunately, its effectiveness was sporadic, did not work equally on all patients, and the presence of large amounts of phenazines such as pyocyanin made it quite toxic to humans . It is no longer used today.

The modern era of antimicrobial chemotherapy began in 1929 with Fleming's discovery of penicillin, and Domagk's discovery in 1935 of synthetic chemicals (sulfonamides) with broad antimicrobial activity.

- **Alexander Fleming** made a crucial discovery that lead to the production of the **"Wonder Drug", penicillin**. After leaving some used culture plates unattended for several weeks, he arrived back from his vacation to find fungus growing on them. On one plate, the S*taphylococcus aureus* bacteria that had been cultured there appeared to be inhibited by the fungus that had appeared. This fungus was found to be *Penicillium notatum* and everywhere it appeared on the plate, the bacterial growth was inhibited. * Later, other scientists discovered that penicillin could cure certain infections in mice and rabbits. In turn, it did not harm the animals in any way.

- **Gerhard Domagk(**who received the 1939 Nobel Prize) in Germany developed **Prontosil**, the **first sulfa drugs**.* Prontosil had a relatively broad effect against Gram-positive cocci, but not against enterobacteria.

- **In 1939, Rene Dubos** reported discovery of the first naturally derived antibiotic, **gramicidin** from *B. brevis*. It was one of the **first commercially manufactured antibiotics** in use during World War II to prove highly effective in treating wounds and ulcers.

- With the help of Howard **Florey** [a pathologist] and Ernst **Chain** [a biochemist], the β-lactam antibiotic, penicillin, was purified and produced on an industrial scale for widespread use for the first time in the early 1940's. *For their discovery and development of penicillin as a therapeutic drug, Ernst Chain, Howard Florey, and Alexander Fleming shared the 1945 Nobel Prize.

- The word "antibiotics" comes from the Greek anti ("against") and bios ("life"). The noun "antibiotic" was suggested in 1942 by Dr. Selman A. Waksman. In 1943, an American, Dr. Selman A. **Waksman,** discovered a drug called **streptomycin**. It originated from microbes found in soil and was a cure for many intestinal diseases. He discovered 20 other antibiotics, includ Neomycin, Actinomycin (Nobel prize 1952).

Characteristics of Antibiotics

Antibiotic are chemical substances (low-molecular weight substances)that can inhibit the growth of, and even destroy, harmful microorganisms. They are derived from special microorganisms or other living systems. Antibiotics are produced as secondary metabolites by certain groups of microorganisms, especially *Streptomyces*, *Bacillus*, and a few molds (*Penicillium* and *Cephalosporium*) that are inhabitants of soils on an industrial scale using a fermentation process.

Several hundreds of compounds with antibiotic activity have been isolated from microorganisms over the years, but only a few of them are clinically-useful. The reason for this is that only compounds with selective toxicity can be used clinically. The **selective toxicity** of antibiotics means that they must be highly effective against the microbe but have minimal or no toxicity to humans. In practice, this is expressed by a drug's **therapeutic index (TI)** : - the ratio of the **toxic dose** {The dose at which the antibiotic becomes too toxic to the patient(host)} to the **therapeutic dose** (The dose required to eliminate the infection). The larger the index is the safer drug (antibiotic) for human use(the better) .

$$\textbf{Chemotherapeutic Index} = \frac{\text{Toxic Concentration (DTM)}}{\text{Effective Concentration (DCM)}}$$

• DTM = dosis tolerata maxima (toxic)

• DCM = dosis curativa minima (effective)

- Antibiotics may have **a cidal (killing) effect** or **static(inhibitory) effect** on a range of microbes. The range of bacteria or other microorganisms that is affected by a certain antibiotic is expressed as its **spectrum of action**. Antibiotics effective against procaryotes that kill or inhibit a wide range of Gram-positive and Gram-negative bacteria are said to **be broad spectrum.** If effective mainly against Gram-positive or Gram-negative bacteria, they are narrow spectrum. If effective against a single organism or disease, they are referred to as **limited spectrum**.

- **Semi-synthetic antibiotics**: chemically modified natural antibiotics

Antibiotics are modified in an attempt to

-enhance the beneficial effects

- minimize the undesirable effects

- increase solubility

- increase stability

- improve pharmacokinetics (i.e., wider distribution and longer half-life)

A clinically-useful antibiotic should have as many of these characteristics as possible.

-It should have a wide spectrum of activity with the ability to destroy or inhibit many different species of pathogenic organisms.

-It should be nontoxic to the host and without undesirable side effects(selective toxicity with minimal side effects to host**).**

- bactericidal rather than bacteriostatic.

-It should be nonallergenic to the host.

-It should not eliminate the normal flora of the host.

-It should be able to reach the part of the human body where the infection is occurring.

-It should be inexpensive and easy to produce.

-It should be chemically-stable (have a long shelf-life).

-Microbial resistance is uncommon and unlikely to develop.

Words to Know

-**Bactericidal drugs** : Act by killing bacteria.

-**Bacteriostatic drugs** : Act to suppress or inhibit bacterial replication sufficiently until the immune system can eliminate the organisms

-**Prophylactic drugs** : Drugs taken to **prevent** a disease rather than treat an established infection

-**Synergism** : Certain drugs work better together in combination compared to being used individually.

-**Antagonism** : Certain drugs may decrease the effectiveness of others, or prove toxic when taken in combination.

-**Mono therapy** : Taking a single agent to treat an infection

-**Combination therapy** or **polytherapy** : Taking more than one drug to treat an infection. Conditions treated with combination therapy include tuberculosis, leprosy, cancer, malaria, and HIV/AIDS. One major benefit of combination therapies is that they reduce development of drug resistance, since a pathogen or tumor is less likely to have resistance to multiple drugs simultaneously.

Antibiotic classes

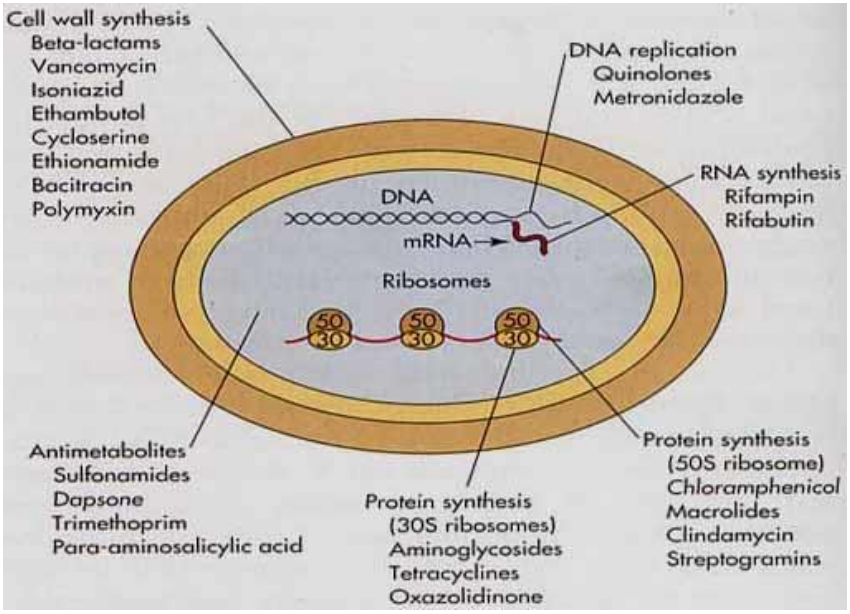
An '**antibiotic class'** refers to a group of antibiotics with a very similar chemical structure. Because of their similar chemical structure members of an antibiotic class have the same basic mechanism of action. Generally, within a class, there is the same core nucleus critical to function, while differing side chains modify the drug's toxicity, spectrum, pharmacokinetics, etc.

The main classes of antibiotics are:

- Beta-Lactams (Penicillins & Cephalosporins)

- Macrolides
- Quinolones
- Tetracyclines
- Aminoglycosides
- Glycopeptides
- Lincomycin

Below, the different antibiotic classes are grouped by their mechanism of action:



Antibiotics and their mechanisms of action:

An antibiotic is a type of antimicrobial substance active against bacteria and is the most important type of antibacterial agent for fighting bacterial infections.

There are several major ways by which antibiotics kill microbes or inhibit their growth. Antibiotics generally target basic bacterial structures/functions necessary for life and/or replication.

Different **mechanisms of action** include:

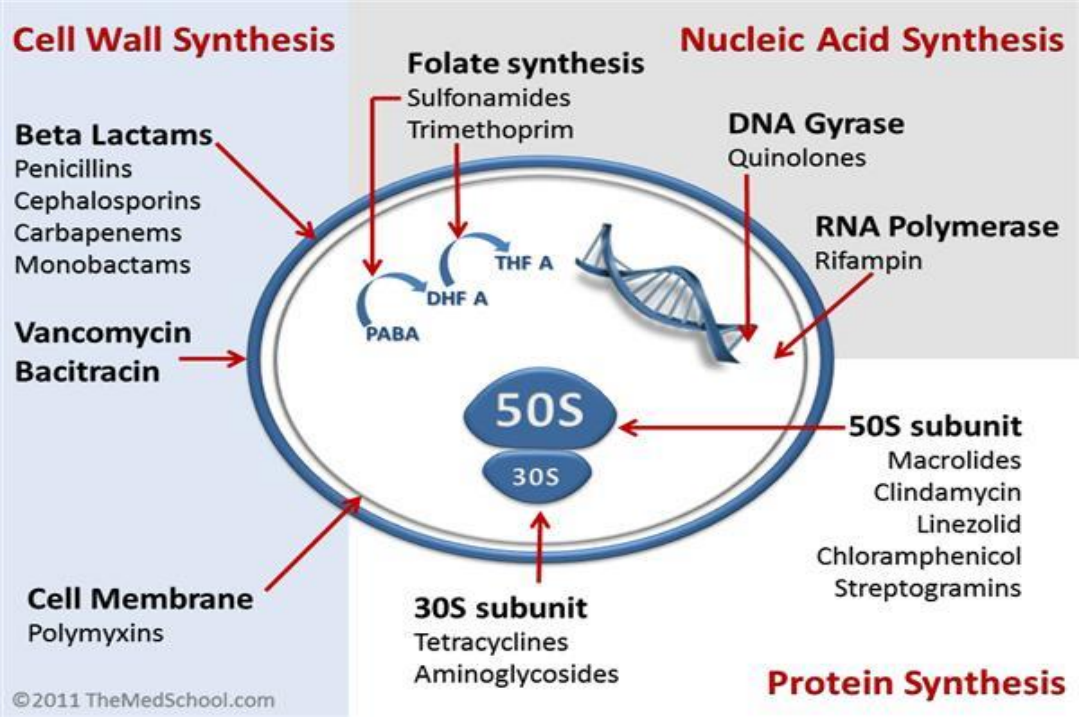
1) **Inhibition of cell wall synthesis**

2) **Inhibition of protein synthesis**

3)**Inhibitionof nucleic acid synthesis**

4) **Inhibition of folate metabolism**

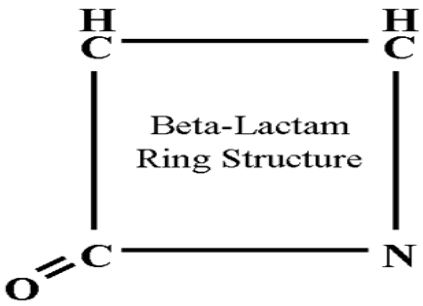
5) Miscellaneous mechanisms.



Antibiotics and their mechanisms of action

Beta-Lactam Antibiotics

Beta-Lactam Antibiotics : are a broad class of antibiotics, consisting of all antibiotic agents that contains a β-lactam nucleus in its molecular structure. β-lactam ring consisting of 3 carbon atoms and 1 nitrogen atom.



-beta-lactam antibiotics are characterized by three fundamental structural requirements:

1-the beta-lactam structure

2-a free carboxyl acid group

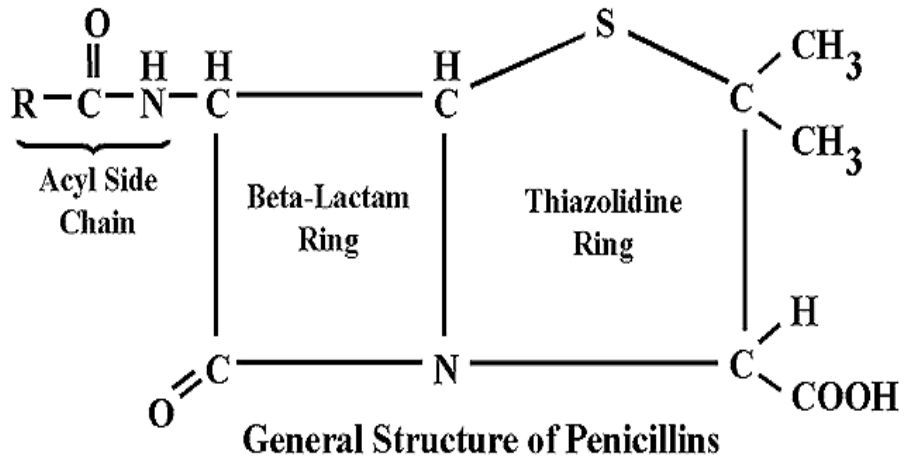
3-one or more substituted amino acid side chains

These antibiotics contain a 4-membered beta lactam ring includes penicillin ,cephalosporins, monobactams, and carbapenems .They are the products of two groups of fungi, *Penicillium* and *Cephalosporium* molds. The beta lactam antibiotics are stereochemically related to D-alanyl-D-alanine which is a substrate for the last step in peptidoglycan synthesis, the final cross-linking between peptide side chains. Beta lactam antibiotics are normally bactericidal and require that cells be actively growing in order to exert their toxicity.

Different beta lactams differ in their spectrum of activity and their effect on Gram-negative rods, as well as their toxicity, stability in the human body, rate of clearance from blood, whether they can be taken orally, ability to cross the blood-brain barrier, and susceptibility to bacterial beta-lactamases.

The Penicillins

The penicillins all share a beta-lactam ring attached to a thiazolidine ring.



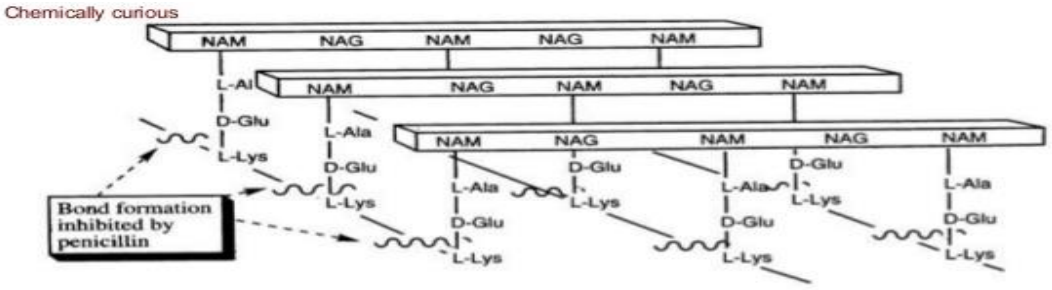
General Structure of Penicillins

The ring is very strained and the bond between the carbonyl and the nitrogen in the β-lactam ring is very labile(site of cleavage by bacterial penicillinase or by acid) and responsible for the molecule reactivity. The penicillin nucleus(6-aminopenicillanic acid) itself is the chief structural requirement for biological activity; metabolic transformation or chemical alteration of this portion of the molecule causes loss of all significant antibacterial activity. The nature of R-group determines the antibiotic's stability to enzymatic or acidic hydrolysis and affects its antibacterial spectrum so that the R - group substituent of the penicillin

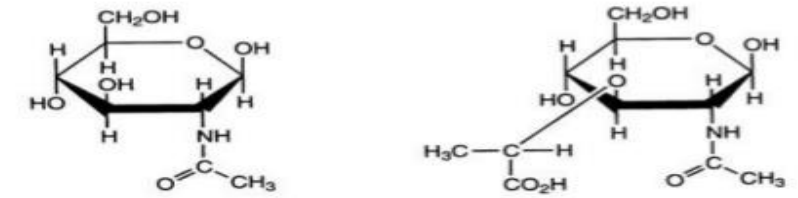
nucleus can be changed to give the molecule different antibacterial properties, change its pharmakokinetic properties, ability to get through porins of gram negatives, stability to beta-lactamases, etc.

Mode of action

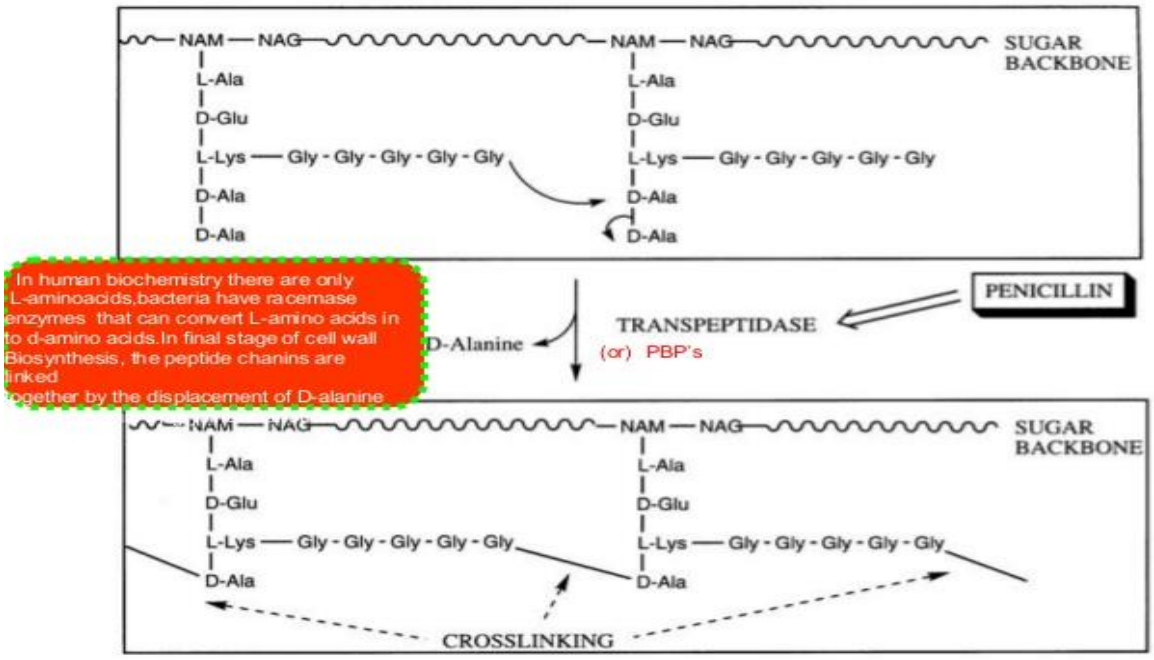
The targets of the penicillins are enzymes(transpeptidase) which called penicillin binding proteins (PBPs) ,the transpeptidase is involved in synthesis of the cell wall. Penicillin attacks bacterial cells by inactivating this enzyme which is essential for bacterial growth(peptidoglycan transpeptidase catalyses the cross-linking of the peptidoglycan, which forms the cell wall of the bacteria). The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive organisms. The peptidoglycan transpeptidase enzyme is not needed in animals as their cells do not have cell walls. Therefore, the penicillin can safely disrupt the bacterial cell wall biosynthesis without harming existing cells in the body. The penicillin stops the growth of the bacterial cell wall, causing the pressure inside the cell to rise considerably until the cell lyses and thus the cell is destroyed (in other words, the antibiotic causes cytolysis or death due to osmotic pressure). In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the bacteria's existing peptidoglycan.



Peptidoglycan structure.



Sugars contained in cell wall structure of bacteria.



Cross-linking of bacteria cell walls inhibited by penicillin.

The activity of antibiotics depends on 3 things:

1-Affinity for the target (e.g.how well penicillin binds PBPs)

2-Permeability properties (e.g. through capsule, peptidoglycan)

3-Stability to bacterial enzymatic degradation (e.g. beta-lactamases)

Classification

The penicillins can be classified according to their antibacterial activity:

Natural penicillins , Antistaphylococcal penicillins , Aminopenicillins,

Extended spectrum penicillins: carboxypenicillins and ureidopenicillins

1- Natural penicillins (Narrow spectrum – penicillinase (lactamase) sensitive)

Natural penicillins, including **penicillin G** & **penicillin V**, are produced by fermentation of *Penicillium chrysogenum*. They are are active against non β-lactamase–producing gram-positive cocci (*Pneumococci*, *Staphylococci*, *Streptococci*), few gram-negative cocci (*meningococci* and *gonococci*), gram-positive bacilli (*Bacillus anthracis*, *Bacillus perfringens*, *Bacillus diphtheriae*), anaerobes (*Clostridum perfringens*, *C. tetani*), and spirochetes (*Treponema pallidum*, *T. pertenue* and *Leptospira*).They are considered narrow spectrum since they are not effective against Gram-negative rods. The natural penicillins are very susceptible to inactivation by beta-lactamases.

a-Penicillin G (Benzylpenicillin) is the prototype of the class and the most potent of all penicillins against susceptible gram-positive bacteria. It is sensitive to stomach acids and requires intravenous or intramuscular administration. Penicillin G (intravenous use) is short acting, but its salts, procaine and benzathine (intramuscular use) , have extended duration of action because they can distribute into storage tissues to be released slowly.

- **Procaine Penicillin G**: after intramuscular injection, T ½ - 12 hrs, used for uncomplicated pneumococcal pneumonia or gonorrhea .

-penicillin G benzathine: duration of antimicrobial activity in the plasma is about 26 days,It is slowly absorbed into the circulation, after intramuscular injection, **and hydrolysed to benzylpenicillin *in vivo***. It is the drug-of-choice when prolonged low concentrations of benzylpenicillin are required and appropriate,

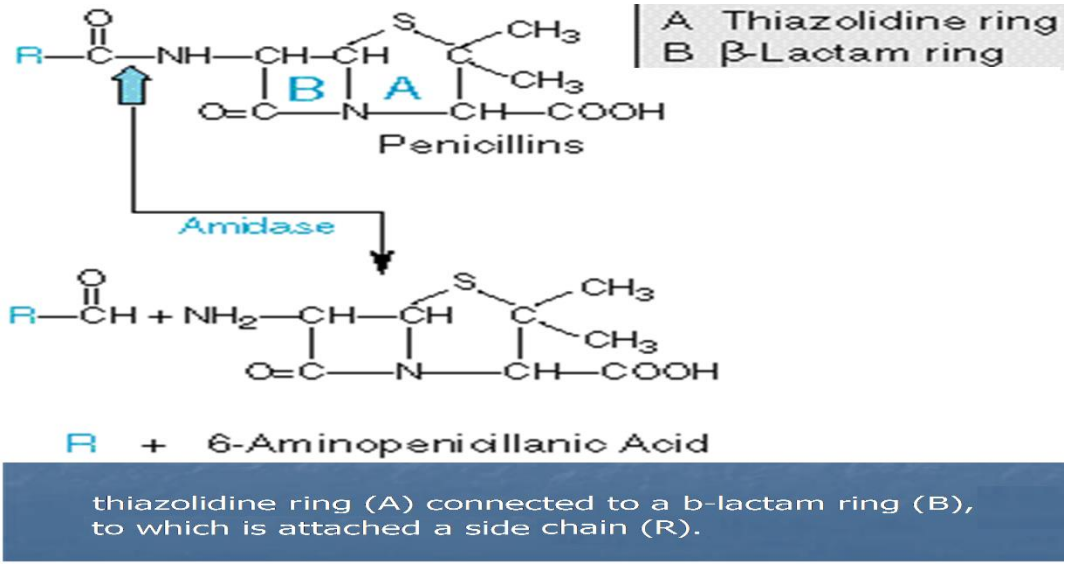
allowing prolonged antibiotic action over 2–4 weeks after a single IM dose used for prophylaxis of rheumatic fever , Early or latent syphilis

b- Phenoxymethylpenicillin (penicillin V)

– Better oral availability (acid resistant) , Stable to stomach acid (has methoxy-linkage), but not broad spectrum , its Gram (+) aerobic activities similar to Penicillin G and it is 5-10x less active against gram (-) microbes, esp. Neisseria and certain anaerobes, dose 4x a day .

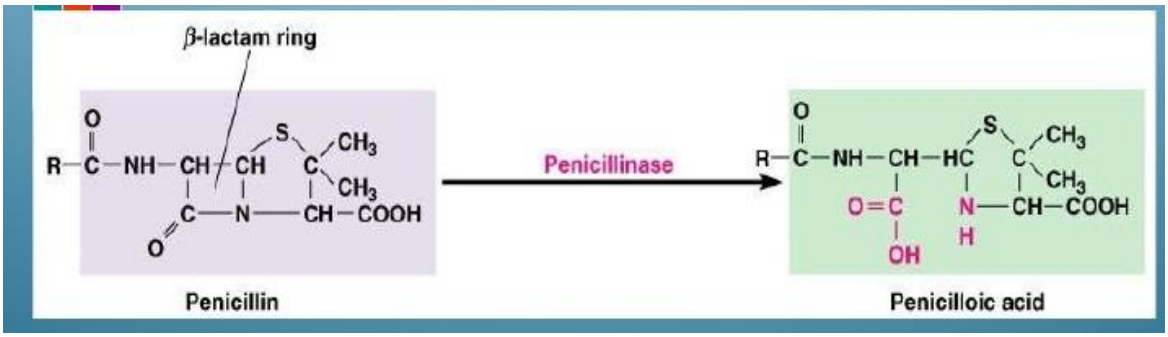
Semisynthetic penicillins

Semisynthetic penicillins first appeared in 1959. A mold produces the main part of the molecule (6-aminopenicillanic acid), which can be modified chemically by the addition of side chains. Many of these compounds have been developed to have distinct benefits or advantages over penicillin G, such as increased spectrum of activity (effectiveness against Gram-negative rods), resistance to penicillinase, effectiveness when administered orally, etc.



2- Narrow spectrum – penicillinase (lactamase) resistant (Anti-Staphylococcal Penicillins)

These drugs were created in response to the problem in the 1950's, staphylococcal infections in hospitals were resistant to penicillin due to production of beta-lactamases.



Anti-Staphylococcal Penicillins are ***semi-synthetic,*** and have big bulky side chains that provide steric hindrance to protect the beta-lactam from cleavage by the beta lactamases. This group of penicillin drugs includes:

a- Methicillin(Poor oral availability) **, b- Nafcillin**

c. Isoxazolyl penicillins (Good oral availability**) (Oxacillin, Cloxacillin , Dicloxacillin , Flucloxacillin).**

There are slight differences in each of these, i.e. administration, pharmacokinetics, etc.

Methicillin was the first member of this group, followed by oxacillin, nafcillin, cloxacillin and dicloxacillin. Methicillin was the first penicillin developed through rational drug modification. Since then all bacteria which are resistant to methicillin are designated as methicillin resistant (e.g MRSA - methicillin-resistant S. aureus).

Due to the bulky side group, all of the antistaphylococcals have difficulty penetrating the cell membrane and have a poor range(less potent) of activity compared to other penicillins.

Spectrum*:* Antistaphylococcals have a very narrow spectrum as they were developed solely for killing β-lactamase producing staphylococci. Their major clinical indications are susceptible *S. aureus* and *S. epidermidis* infections.

Note: Antistaphylococcals are the only penicillins that by themselves are resistant to penicillinases. Their rank order of resistance is methicillin > cloxacillin = dicloxacillin > oxacillin.

3- Broad spectrum – penicillinase (lactamase) sensitive(Aminopenicillins)

Ampicillin, amoxicillin, bacampicillin, Pivampicillin ,Talampicillin.

The aminopenicillins have a wider range of activity than natural or antistaphylococcal penicillins. However, they lack the bulky side groups and are susceptible to inactivation by beta-lactamases. Aminopenicillins have additional hydrophilic groups, allowing the drug to penetrate into Gram-negative bacteria via the porins.

Advantages of aminopenicillins include higher oral absorption, higher serum levels, and longer half-lives. Aminopenicillins are resistant to gastric acids so can be administered orally.

Spectrum*:* Aminopenicillins are similar to penicillin G in the activity against Gram-positive organisms but are slightly weaker than the latter. Aminopenicillins are more active against *enterococci* and *Listeria monocytogenes* compared to penicillin G.

Gram-negative spectrum includes *Haemophilus influenzae*, *Salmonella*, *Shigella, Escherichia coli*, *Proteus mirabilis*, *N. gonorrhoeae*, *N. meningitidis*.

a- Ampicillin :– Good oral availability**,** has an amino group that allows it to get through porins of easily-killed gram negatives (*E. coli, Neisseria, Hemophilus),* but not stable to beta-lactamase **.**Very widely used so 75-80%, *E. coli* are resistant **,** destroyed by stomach acid**.**

b- Amoxicillin : – Excellent oral availability **,** has a hydroxy group, quite stable to stomach acid **.**This is what everyone gets from the pediatrician even when they don’t need it, like for upper respiratory infections.

Amoxicillin is usually the drug of choice within the class because it is better absorbed following oral administration than other beta-lactam antibiotics.

c-Esters of Ampicillin (Bacampicillin, Pivampicillin ,Talampicillin)

No inherent antimicrobial activity as esters, but pharmacologically active following hydrolysis to ampicillin, 50% higher blood concentration than Ampicillin and Amoxicillin **.**

4- Extended spectrum – penicillinase (lactamase) sensitive (Anti-pseudomonal penicillins)

Extended-spectrum penicillins (also called antipseudomonals) include both **carboxypenicillins (carbenicillin and ticarcillin)** and **ureidopenicillins (piperacillin, azlocillin, and mezlocillin).** Antipseudomonal penicillins are similar to the aminopenicillins in structure but have either a carboxyl group or urea group instead of the amine.

In general, the antipseudomonal penicillins have greater activity than do other penicillins against gram-negative bacteria (especially *Pseudomonas* and *Proteus*) due to enhanced penetration through the cell wall of these bacteria.

The major advantage of carboxypenicillins is their activity against *Pseudomonas aeruginosa* (one of the major pathogens responsible for nosocomial pneumonia) and certain indole-positive *Proteus* species that are resistant to aminopenicillins. Ticarcillin is stronger against *P. aeruginosa* and *Enterobacter* species than carbenicillin.

Against anaerobes and Gram-positive organisms, carboxypenicillins generally have the same spectrum of activity as penicillin G. However, they are substantially weaker in comparison with penicillin G.

Ureidopenicillins have greater activity against *P. aeruginosa* compared to carbenicillin and ticarcillin. Piperacillin is the most potent of the extended-spectrum penicillins against *Pseudomonas*. The spectrum of piperacillin and mezlocillin is extended to include *Klebsiella*, *Enterobacter*, *Citrobacter*.

All antipseudomonals are destroyed by β-lactamases. The extended-spectrum penicillins are not used in the treatment of infections caused by Gram-positive

bacteria because penicillin G and aminopenicillins are more potent against these organisms.

Adverse effects

The penicillins have minimal toxicity and are among the safest antibiotics. The most serious side effect of penicillins is allergy.

- Penicillin Hypersensitivity: penicillins are the most common cause of drug allergy. Allergic reactions occur in 0.7% – 8% of treatments ,10% of allergic reactions are life-threatening and 10% of these are fatal,manifestations of allergy to penicillins include rash, fever, bronchospasm, , serum sickness, exfoliative dermatitis.

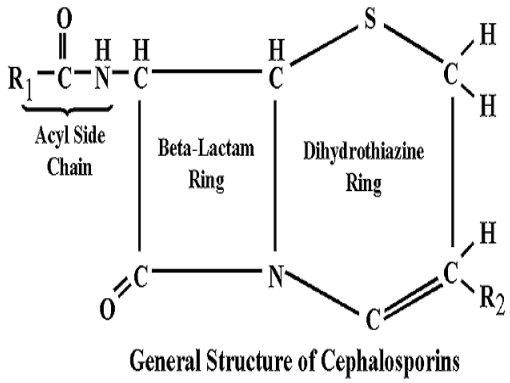
- Common side effects: Many persons who take penicillins experience diarrhea, nausea, and vomiting.

Hepatotoxicity (cholestatic hepatitis) most commonly occurs with oxacillin, nafcillin, and flucloxacillin

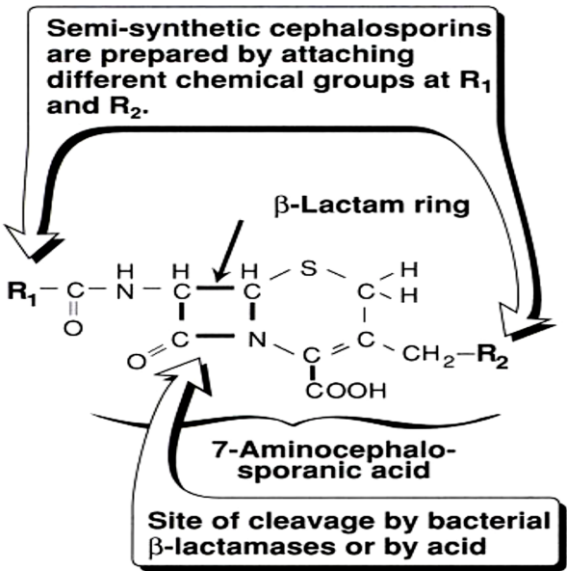
- Other side effects are less common : Very high doses of penicillin G can cause kidney failure. Methicillin famous for interstitial nephritis

The Cephalosporins

Cephalosporins are structurally and pharmacologically related to the penicillins. Cephalosporins are beta-lactam compounds in which the beta-lactam ring is fused to a 6-membered dihydrothiazine ring, thus forming the cephem nucleus. **Side chain modifications to the cephem nucleus confers 1) an improved spectrum of antibacterial activity, 2) pharmacokinetic advantages, and 3) additional side effects.**



General Structure of Cephalosporins



Cephalosporin compounds were first isolated from cultures of *Cephalosporium* in 1948.They have a low toxicity and a somewhat broader spectrum than natural penicillins. They are often used as penicillin substitutes against Gram-negative bacteria and in surgical prophylaxis. They are subject to degradation by some bacterial beta-lactamases, but they tend to be resistant to beta-lactamases from *S. aureus.* Cephalosporin(**Bactericidal**) prevents cell wall synthesis by binding to enzymes called penicillin binding proteins (PBPs). These enzymes are essential for the synthesis of the bacterial cell wall.

Cephalosporins are derived from cephalosporin C(natural cephalosporins) which is an acid-stable molecule with antibacterial activity and is produced from *Cephalosporium acremonium*. All of them are semi- synthetic .The first agent cephalothin (cefalotin) was used in 1964.

Cephalosporins are grouped into "generations" based on their spectrum of antimicrobial activity.

Major differences between generations :increased activity against Gram-negative bacteria & increased resistance to class C β-lactamases = cephalosporinase**.** The first cephalosporins were designated first generation while later, more extended spectrum cephalosporins were classified as second generation cephalosporins. Each newer generation of cephalosporins has significantly greater gram-negative antimicrobial properties than the preceding generation, in most cases with decreased activity against gram-positive organisms. Fourth generation cephalosporins, however, have true broad spectrum activity. The newer agents have much longer half-lives resulting in the decrease of dosing frequency.

Classification

١- First Generatio

First generation cephalosporins are moderate spectrum agents. They are effective alternatives for treating staphylococcal and streptococcal infections and therefore are alternatives for skin and soft-tissue infections, as well as for streptococcal pharyngitis.

Cefazolin, Cephalothin (parenteral) , Cephalexin, Cefadroxil, Cephradine (oral)

- cephalothin, cefazolin, cephalexin. have good activity against most Gram positive cocci *(Streptococcus, pneumococcus* but not or methicillin-resistant *Staphylococcus).* They are more active against Gram negative organisms *(Escherichia co1i Kiebsiella pneumoniae,* and the **indole negative** *Proteus mirabilis)* than are the natural penicillins. They are effective against some anaerobic cocci *(Peptococcus* and *Peptosteptococcus,* but NOT *Bacteroides fragilis).*

*They are ineffective against *Pseudomonas aeruginosa, Enterobacter*, and indole-positive *Proteus* species.

*These drugs do not cross the blood-brain barrier.

cefazolin and cephalexin used for surgical prophylaxis, URIs, otitis media**.**

٢- Second Generation

The second generation cephalosporins have a greater gram-negative spectrum while retaining some activity against gram-positive bacteria. They are also more resistant to beta-lactamase. They are useful agents for treating upper and lower respiratory tract infections, sinusitis and otitis media. These agents are also active against *E. coli, Klebsiella and Proteus*, which makes them potential alternatives for treating urinary tract infections caused by these organisms. Cefoxitin is a second generation cephalosporin with anaerobic activity .

• Cefaclor, Cefuroxime (Oral)

•Cefamandole, Cefonicid, Cefuroxime, Cefoxitin , Cefotetan , Ceforanide (Parenteral)

* **cefuroxime ,cefamandole, cefaclor** are effective against *Haemophilus influenza*

* **cefoxitin** is **effective against *Bacteroides fragilis***

*These drugs do not achieve adequate levels in the CSF. **Cefoxitin , cefuroxime** used prophylactically for Surgical prophylaxis abdominal or colorectal surgeries

٣- Third Generation

Third generation cephalosporins have a broad spectrum of activity and further increased activity against gram-negative organisms. Some members of this group (particularly those available in an oral formulation) have decreased activity against gram-positive organisms. The spectrum is extended to include: *Enterobacter E. coli*, *Proteus mirabilis, Klebsiella, Pseudomonas* (**ceftazidime and cefaperazone only**), *Serratia,* β -lactamase producing *Haemophillus influenza* and *Neisseria* species.

The parenteral third generation cephalosporins (ceftriaxone and cefotaxime) have excellent activity against most strains of *Streptococcus pneumoniae,* including those with intermediate and high level resistance to penicillin.

- Only **cetizoxime and moxalactam** retain good **activity against *Bacteroides fragilis.***

-**Ceftazidime** IV and IM , excellent gram-negative coverage

*Used for difficult-to-treat organisms such as Pseudomonas spp.

- Cefotaxime

* Active against gram-negative bacteria , enterobacteria, gonococcus . Active against *Pseudomonas aeruginosa.*

* Penetrates the CNS => used for meningitis.

- **Ceftriaxone** IV and IM, long half-life, once-a-day dosing, is effective as a **single dose therapy for uncomplicated Neisseria gonorrhea**

*Easily passes meninges and diffused into CSF to treat CNS infections.

- **Cefixime** Only oral third-generation agent(Tablet and suspension**)** *Best of available oral cephalosporins against gram-negative

4- Fourth Generation

– cefpirome, cefepime

Fourth generation cephalosporins are extended spectrum agents with similar activity against gram-positive organisms as first generation cephalosporins. They also have a greater resistance to beta-lactamases than the third generation cephalosporins. Many can cross blood brain barrier and are effective in meningitis.

- Cefepime has broad gram-negative coverage with somewhat enhanced activity against pseudomonas but slightly lesser activity against pneumococci. - Cefpirome is more active against pneumococci and has somewhat lesser activity against pseudomonas. Cefepime and cefpirome are highly active against

nosocomial pathogens such as Enterobacter and Acinetobacter and their use should therefore be restricted to the setting of nosocomial sepsis.

- Both antibiotics had good activity against *Staphylococcus aureus* and coagulase-negative staphylococci except for methicillin-resistant strains and *Staphylococcus haemolyticus* which were of borderline sensitivity.
- Both antibiotics had little useful activity against the *Bacteroides fragilis* group or *Bacteroides oralis* group but were active against most other anaerobes. *Clostridium difficile* and some other *Clostridium* species were resistant.

A cephalosporin Uses:

A cephalosporin with or without an aminoglycoside is first-line treatment of *Klebsiella*(Cephalosporins demonstrate synergistic activity when combined with an aminoglycoside to treat *Klebsiella*).

-First generation cephalosporins are used for surgical prophylaxis of wound infection.

-Third generation cephalosporins are used to treat meningitis due to *pneumococci, meningococci, and Haemophillus influenza.*

-Ceftriaxone is the drug of choice for treating beta-lactamase producing *Neisseria gonorrhea.*

Adverse effects

-Hypersensitivity reactions very similar to those that occur with penicillins may be seen.

-Nephrotoxicity has been reported. (cefamandole, cefotetan, moxalactam, cefoperazone).

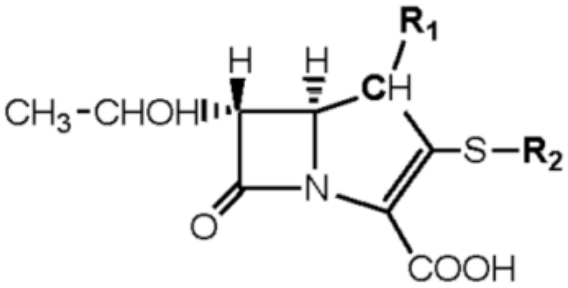
-Diarrhea may occur with oral forms. Many second and particularly third generation cephalosporins are ineffective against Gram-positive organisms, especially methicillin resistant Staphylococci and Enterococci.

-During treatment with such drugs, these resistant organisms as well as fungi, often proliferate and may induce **superinfection.**

-Hyperprothrombinemia, Thrombocytopenia, Platelet dysfunction. Administration of vitamin K (10mg) twice a week can prevent this.

Other beta lactams

1-Carbepenems: are a new class of drugs which are structurallv similar to the penicillins. These drugs are derived from *Streptomyces* species and developed to deal with beta-lactamase producing Gram-negative organisms, which were resistant to broad spectrum and extended spectrum penicillins.



CARBAPENEMS

* The semisynthetic Carbapenems are **imipenem, meropenem, ertapenem** which act in the same way as the other beta-lactams. Widest spectrum, but may inactivated by class B β–lactamase = carbapenemase.

- Imipenem:

* Imipenem, like other β -lactams, binds to penicillin binding proteins , it is bactericidal. Imipenem differs from the penicillins in its antimicrobial spectrum. It is a broad-spectrum antibiotic with excellent activity against a variety of gram positive and gram negative organism (both aerobic and anaerobic). It is resistant to most forms of b β -lactamase, including that produced by *Staphylococcus*. However, methicillin-resistant *Staphylococcus* is usually resistant to imipenem .Susceptible organisms include: *Streptococci, Enterococci. Staphylococci, Listeria, Enterobacteriaceae, Pseudomonas, Bacteroides*, and *Clostridium.*

***** Imipenem is rapidly hydrolyzed by the enzyme, dihydropeptidase, which is found in the brush border of the proximal renal tubule. It is always administered with **cilastatin**, an inhibitor of dipeptidase.

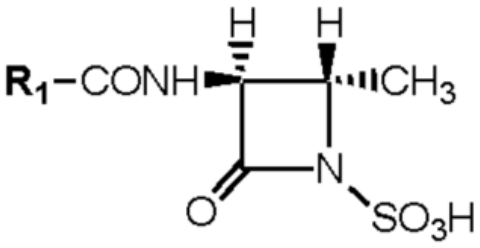
***Side efects:** Individuals who are allergic to the penicillins may demonstrate cross-reactivity with imipenem .Imipemem may produce nausea and vomiting.

- Meropenem

*It is similar to imipenem.It is not degraded by dehydropeptidase, thus no cilastatin is needed.Excessive levels in kidney failure can cause seizures with imipenem but not with meropenem.

2- Monobactam (Aztreonam):

***Aztreonam:** This drug is a synthetic monocyclic beta-lactam (a monobactam) , originally isolated from the bacterium *Chromobacterium violaceum*. Its given IV/IM, Aztreonam interacts with penicillin binding proteins and induces the formation of long filamentous bacteria **, monobactams** are useful for the treatment of allergic individuals. A person who becomes allergic to penicillin usually becomes allergic to the cephalosporins and the carbapenems as well. Such individuals can still be treated with the monobactams, which are structurally different so as not to induce allergy.



MONOBACTAMS

***** The antimicrobial spectrum of aztreonam differs from that of other beta-lactams. It more closely resembles the spectrum of the aminoglycosides. Gram positive and anaerobic bacteria are resistant. Susceptible organisms include: (It has an unusual spectrum being active only against Gram-negative aerobic rods) Enterobacteriaceae, Pseudomonas, Hemophillus and Neisseria. Aztreonam is resistant to the beta-lactamase produced by gram negative organisms.

***Side effects:** Generally, the drug is well tolerated. Patients who are allergic to penicillins do not exhibit cross-reactions with aztreonam.

Beta-lactamases

Beta-lactamases are enzymes produced by some bacteria and are responsible for their resistance to beta-lactam antibiotics. The lactamase enzyme breaks beta-lactam ring , deactivating the molecule's antibacterial properties.

*Penicillinase is a specific type of β-lactamase, showing specificity for penicillins.

*Cephalosporinases that can also hydrolyse cephalosporins.

*Broad-spectrum {beta}-lactamases, meaning that they are capable of inactivating penicillins and cephalosporins at the same rate.

*Extended spectrum of activity, represents the ESBLs, which are capable of inactivating third-generation cephalosporins (ceftazidime, cefotaxime, and cefpodoxime) as well as monobactams (aztreonam)

*carbenicillinase, these enzymes inactivate carbenicillin more than benzylpenicillin, with some effect on cloxacillin.

*cloxacillinases, enzymes inactivate cloxacillin more than benzylpenicillin, with some activity against carbenicillin .The correct term is "OXACILLINASE". These enzymes are able to inactivate the oxazolylpenicillins like oxacillin, cloxacillin, dicloxacillin.

*Carbapenemases, are able to hydrolyse carbapenems.

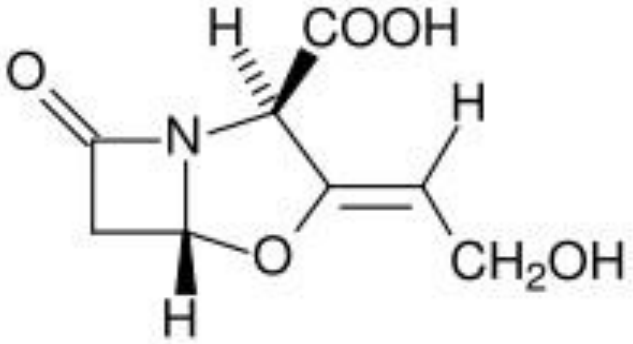
Beta-lactamase inhibitors

clavulanic acid, tazobactam, sulbactam

-poor antimicrobial activity on their own. They are potent inhibitors of many bacterial beta-lactamases and can protect hydrolyzable penicillins from inactivation by these enzymes, but poor activity for chromosomal cephalosporinases.

-they are beta-lactam structures , beta-lactamases inhibitor because they are β–lactam analogue.

Clavulanic acid is not an antibiotic. It is a beta-lactamase inhibitor sometimes combined with semisynthetic beta lactam antibiotics to overcome resistance in bacteria that produce beta-lactamase enzymes, which otherwise inactivate the antibiotic, clavulanic acid is an irreversible, "suicide" inhibitor of beta-lactamase. Most commonly it is combined with amoxicillin is **clavamox** or **augmentin**. **(trade name)** .



The structure of calvulanic acid.

They are available only in fixed combinations with specific penicillins:

Ampicillin + sulbactam= Unasyn

Amoxicillin + clavulanic acid= Augmentin

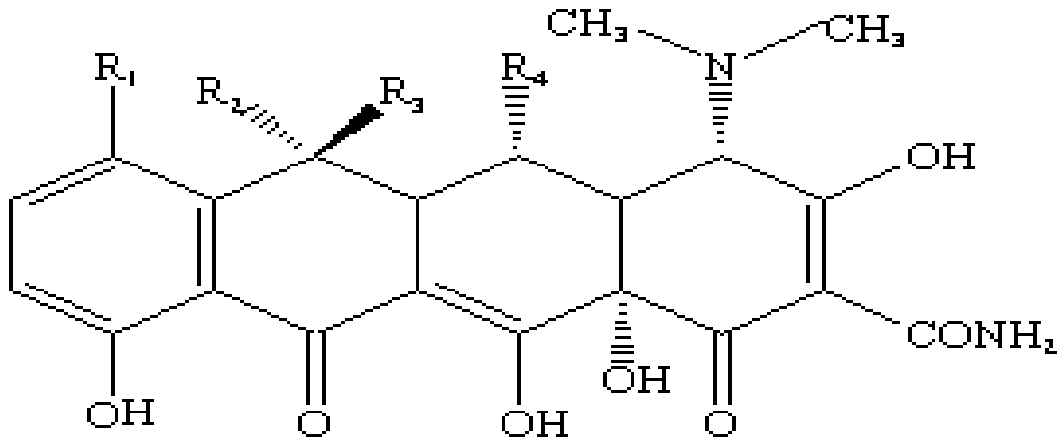
Ticarcillin + clavulanate potassium=Timentin

Piperacillin + tazobactam sodium= Tazocin (Zosyn)

Tetracyclines

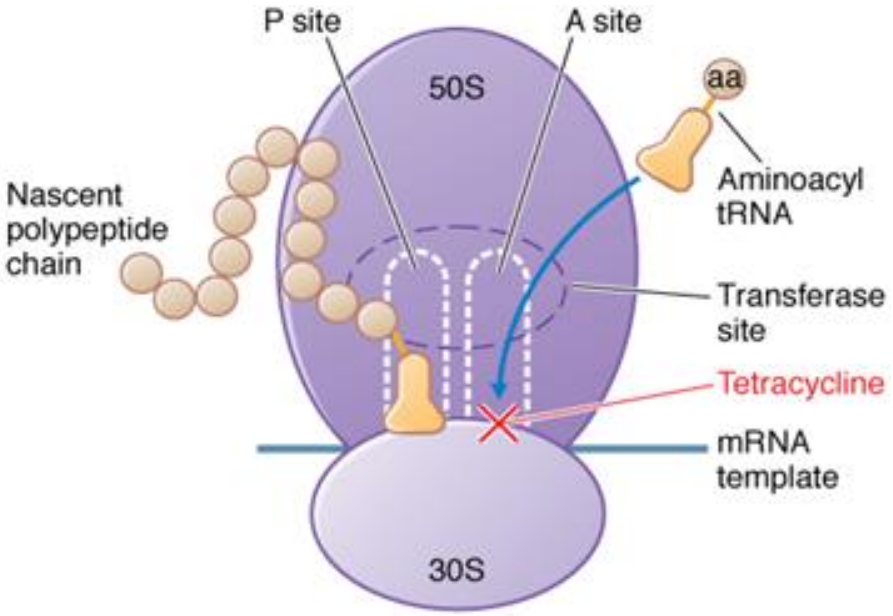
The **tetracyclines** consist of eight related antibiotics which are all natural products of *Streptomyces*, although some can now be produced semisynthetically or synthetically.

The basic tetracycline structure consists of four benzene rings with various constituents on each ring.The crystalline bases are faintly yellow, odorless, slightly bitter compounds. They are only slightly soluble in water at pH 7 but they can form soluble sodium salts and hydrochloride.



The tetracycline core structure

The tetracyclines are broad-spectrum antibiotics with a wide range of activity against both Gram-positive and Gram-negative bacteria. *Pseudomonas aeruginosa* is less sensitive but is generally susceptible to tetracycline concentrations that are obtainable in the bladder. The tetracyclines are bacteriostatic compounds. They inhibit protein synthesis by blocking the binding of aminoacyl tRNA to the A site on the ribosome (act on 30S ribosomal subunit).



However, most bacteria possess an active transport system for tetracycline that will allow intracellular accumulation of the antibiotic at concentrations 50 times as great as that in the medium. This greatly enhances its antibacterial effectiveness and accounts for its specificity of action, since an effective concentration cannot be accumulated in animal cells (Penetration into cell requires an energy-dependent transport not present in mammals). Thus a blood level of tetracycline which is harmless to animal tissues can halt protein synthesis in invading bacteria. The tetracyclines have a remarkably low toxicity and minimal side effects when taken by animals. The combination of their broad spectrum and low toxicity has led to their overuse and misuse by the medical community and the wide-spread development of resistance has reduced their effectiveness.

The tetracyclines have activity against spirochetes and atypical bacteria, such as *Mycoplasma* and *Chlamydia* species, Rickettsia. It is first-line therapy for Chlamydia, Q fever and some protozoa. It is commonly used to treat acne today.

Chlortetracycline, the first tetracycline, was developed in 1948 as a product of *Streptomyces aureofaciens*. Followed by oxytetracycline and tetracyclines in 1950 ,1952 respectively . Chlortetracycline was altered to produce tetracycline. Doxycycline and minocycline are semisynthetic derivatives.

Despite the success of the early tetracyclines, analogs were developed to improved water solubility either to allow parenteral administration or to enhance oral absorption. These approaches resulted in the development of the semisynthetic compounds rolitetracycline and lymecycline.

Resistance – Common: Although tetracycline antibiotics have some roles in human and veterinary medicine, the widespread emergence of microbial resistance due to efflux and ribosomal protection mechanisms has severely limited their effectiveness**,** bacterial resistance is typically the result of mutations that either prevent entrance of tetracyclines into the cell or increase the export of tetracycline out of the cell. The resistance may be transmitted by plasmids. This

plasmid mediates the production of a number of proteins that appear to affect transport of the drug into the cell, thereby preventing binding to the ribosomes.

The tetracyclines may be divided according to source into:

- **Naturally occurring** : Tetracycline, Chlortetracycline, Oxytetracycline
- **Semi-synthetic** : Doxycycline, Lymecycline, Meclocycline, Methacycline, Minocycline, Rolitetracycline

The tetracyclines may be divided into three groups based on their pharmacokinetic traits. These groups are the short-acting group, intermediate-acting group, and long-acting group. The varying half-lives are the result of different rates of renal excretion .

Short-Acting Tetracyclines

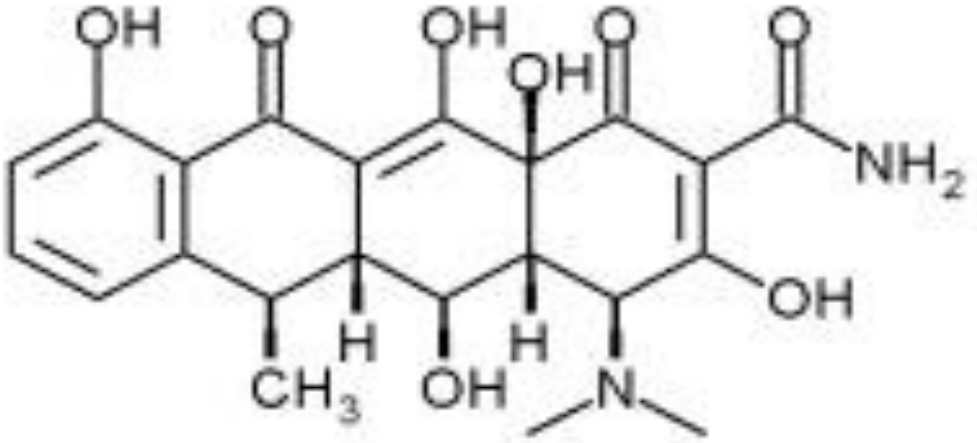
The short-acting **tetracyclines** (Half-life is 6-8 hrs) include **oxytetracycline** and tetracycline, the namesake of the class. Frequent dosing is needed because of the very short half-life of these agents. Oxytetracycline is no longer available in the United States. Tetracycline has a broad spectrum of activity, with coverage of many aerobic gram-negative bacilli, atypical bacteria (such as *Chlamydia trachomatis*, *Chlamydia psittaci*, and *Mycoplasma pneumoniae*), and spirochetes, Tetracycline is also a second-line agent for *T. pallidum*. It is used for treatment of rickettsial infections, typhus, , trachoma, nongonococcal urethritis,. It is also commonly used for the treatment of acne.

Intermediate-Acting Tetracyclines (Half-life is ~12 hrs)

The only intermediate-acting agent available in the U.S. is meclocycline. Meclocycline is no longer used as an antibiotic.

Long-Acting Tetracyclines

The long-acting tetracycline agents (Half-life is 16 hrs or more), allowing to be used one or twice daily only, **doxycycline and minocycline**, are the more recently developed drugs. The main difference between these and the short-acting agents is that these may be dosed less frequently. Minocycline is usually the most active followed by doxycycline.



Doxycyclineis frequently used to treat chronic prostatitis, sinusitis, syphilis, chlamydia and acne. In addition, it is used in the treatment and prophylaxis of anthrax and in prophylaxis against malaria. It is also effective against *Yersinia pestis* and is prescribed for the treatment of Lyme disease and Rocky Mountain spotted fever. Because doxycycline is one of the few medications that is effective in treating Rocky Mountain spotted fever (with the next best alternative being chloramphenicol), it is indicated even for use in children for this illness. Doxycycline is also one (of many) recommended drugs for chemoprophylatic treatment of Malaria in travels to areas of the world where malaria is endemic.

Glycylcyclines(Tigecycline)

Glycylcycline antibiotics are a new generation of antibiotics derived from tetracyclines. They were developed to overcome the bacterial resistance to tetracyclines. They are the semisynthetic group e.g., 9-*(N,N*-dimethylglycylamido)-6-demethyl-6-deoxytetracycline, 9-(*N,N*-dimethylglycylamido)-minocycline, and 9-*t*-(butylglycylamido)-minocycline. These compounds possess a 9-glycylamido substituent.

Glycylcycline antibiotics long-acting tetracycline, inhibit bacterial reproduction by blocking bacterial protein synthesis. They have broad spectrum of activity against gram-negative and gram-positive bacteria, but are more potent against bacteria that is resistance to tetracyclines. Glycylcycline antibiotics are active against resistant organisms such as methicillin resistant staphylocci, penicillin-

resistant streptococcus pneumoniae and vancomycin resistant enterococci. The drug is licenced for the treatment of skin and soft tissue infections as well as intra-abdominal infections.

Side effects

- Pregnant women are particularly sensitive to tetracycline -induced hepatic damage. Jaundice (increased UREA) , liver failure, kidney failure (In pregnant women experiencing pyelonephritis can be fatal).

-Children receiving long-or short term therapy with TET may develop brown discoloration of the teeth. The drug deposits in the teeth and bones probably due to its chelating property and the formation of a TET -calcium orthophosphate complex. This discoloration is permanent.

-Skeletal growth can be depressed when the drug is given to premature infants. Tetracycline crosses the placental barrier and can accumulate in fetal bones, thus delaying bone growth. They are also excreted in breast milk. Although bone and tooth defects are associated with the total dose of tetracycline given and occur more often after repeated courses so that must avoid giving to pregnant women and children under the age of 8.

- Allergic reactions and skin toxicity . Cause skin photosensitivity, so exposure to the Sun or intense light is not recommended, (Photoxicity) darkening of skin & sunburn when patient exposed to sunlight.

- Be inactivated by Ca^{2+} ion, so are not to be taken with milk, yogurt, and other dairy products.

-Drug-induced severe diarrhea, mucosal inflammation lupus, and hepatitis. Should not be given to patient with severe liver disease.

Aminoglycosides

Aminoglycosides are a group of drugs sharing chemical, antimicrobial, pharmacologic, and toxic characteristics .They are potent bactericidal antibiotics include several natural and semisynthetic compounds that are used to treat bacterial diseases. They are particularly active against aerobic, gram-negative bacteria and act synergistically against certain gram-positive organisms. The first aminoglycoside, streptomycin, was isolated from *Streptomyces griseus* in 1943. Neomycin, isolated from *Streptomyces fradiae*, had better activity than streptomycin against aerobic gram-negative bacilli but, because of its toxicity, could not safely be used systemically. Gentamicin, isolated from Micromonospora in 1963, was a breakthrough in the treatment of gram-negative bacillary infections, including those caused by *Pseudomonas aeruginosa*. In the following decades, natural aminoglycosides, such as tobramycin, and semisynthetic aminoglycosides, such as netilmicin and amikacin, were identified and developed. At present, the group includes streptomycin, neomycin, kanamycin, amikacin, gentamicin, tobramycin, sisomicin, netilmicin, and others. Aminoglycosides that are derived from bacteria of the *Streptomyces* genus are named with the suffix *mycin*, whereas those that are derived from *Micromonospora* are named with the suffix *micin*.

Gentamicin is the most commonly used aminoglycoside, but amikacin may be particularly effective against resistant organisms. Aminoglycosides are used in the treatment of severe infections of the abdomen and urinary tract, as well as bacteremia and endocarditis. They are also used for prophylaxis, especially against endocarditis. All are potentially ototoxic and nephro toxic, though to different degrees. All can accumulate in renal failure. Single daily dosing of aminoglycosides is possible because of their rapid concentration-dependent killing and post-antibiotic effect in which bacterial cell killing continues for a brief period of time after the blood plasma concentration of the antibiotic has fallen below the so-called minimal inhibitory concentration . Single daily dosing

of aminoglycosides appears to be safe, efficacious and cost effective. In certain clinical situations, such as patients with endocarditis or pediatric patients, traditional multiple dosing is still usually recommended.

Initially aminoglycosides penetrate bacterial cell wall, to reach periplasmic space through porin channels (passive diffusion). **Further transport across cytoplasmic membrane takes place by active transport by proton pump; an oxygen-dependent process**.That is why beta lactum antibiotics which weaken or inhibit bacterial cell wall synthesis facilitate passive diffusion of aminoglycosides if given together(synergistic action). Subsequently further transport of aminoglycosides across the cytoplasmic membrane takes place by energy dependent and oxygen dependent active transport . As such transport cannot take place in anaerobic conditions and anaerobic bacteria have less energy available for aminoglycoside uptake into the bacterial cell, so aminoglycosides are inactive against anaerobic bacteria(Anaerobic bacteria are often resistant to aminoglycosides).

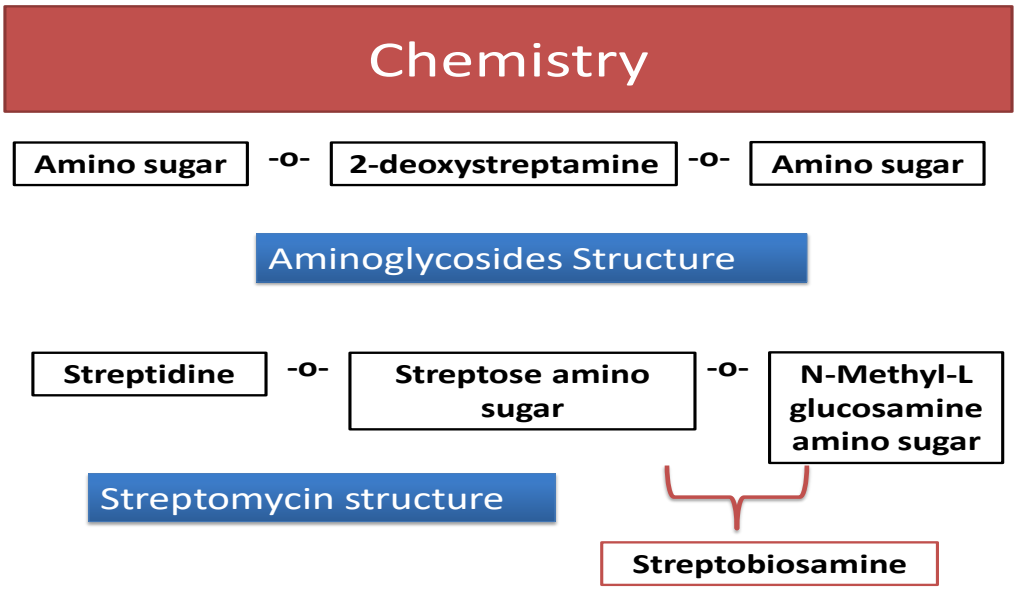
Under certain circumstances, aminoglycoside and *β*-lactam antibiotics exert a synergistic action in vivo against some bacterial strains when the two are administered jointly. For example, carbenicillin and gentamicin are synergistic against gentamicin-sensitive strains of *P. aeruginosa* and several other species of Gram-negative bacilli, and penicillin G and streptomycin (or gentamicin or kanamycin) tend to be more effective than either agent alone in the treatment of enterococcal endocarditis. The two antibiotic types should not be combined in the same solution because they are chemically incompatible. Damage to the cell wall caused by the *β*-lactam antibiotic interfere with cell wall syntheses so it increase penetration of the aminoglycoside into the bacterial cell. So we can decrease the dose due to synergistic effect.

Traditionally, the antibacterial properties of aminoglycosides were believed to result from inhibition of bacterial protein synthesis through irreversible binding to the 30S bacterial ribosome. This explanation, however, does not account for

the potent bactericidal properties of these agents, since other antibiotics that inhibit the synthesis of proteins (such as tetracycline) are not bactericidal. Recent experimental studies show that the initial site of action is the outer bacterial membrane. The cationic antibiotic molecules create fissures in the outer cell membrane, resulting in leakage of intracellular contents and enhanced antibiotic uptake. This rapid action at the outer membrane probably accounts for most of the bactericidal activity.

Structure Chemistry

Term aminoglycoside stems from there structure characterized by two amino sugars joined to a non sugar aminocyclitol by –o- glycosidic bond. In majority of aminoglycosides this aminocyclitol or non sugar moeity is 2-deoxystrepamine , however in streptomycin, the aminocyclitol is streptidine which is not placed centrally as in other aminoglycosides. Rather it is placed laterally to the amino sugar streptose which is joined by other aminosugar, (N-Methyl L glucosamine, these 2 amino sugars are jointly called Streptobiosamine.



The aminoglycosides are thus strongly basic compounds that exist as polycations at physiological pH. Their inorganic acid salts are very soluble in water. All are available as sulfates. Solutions of the aminoglycoside salts are stable to autoclaving. The high water solubility of the aminoglycosides contributes to their

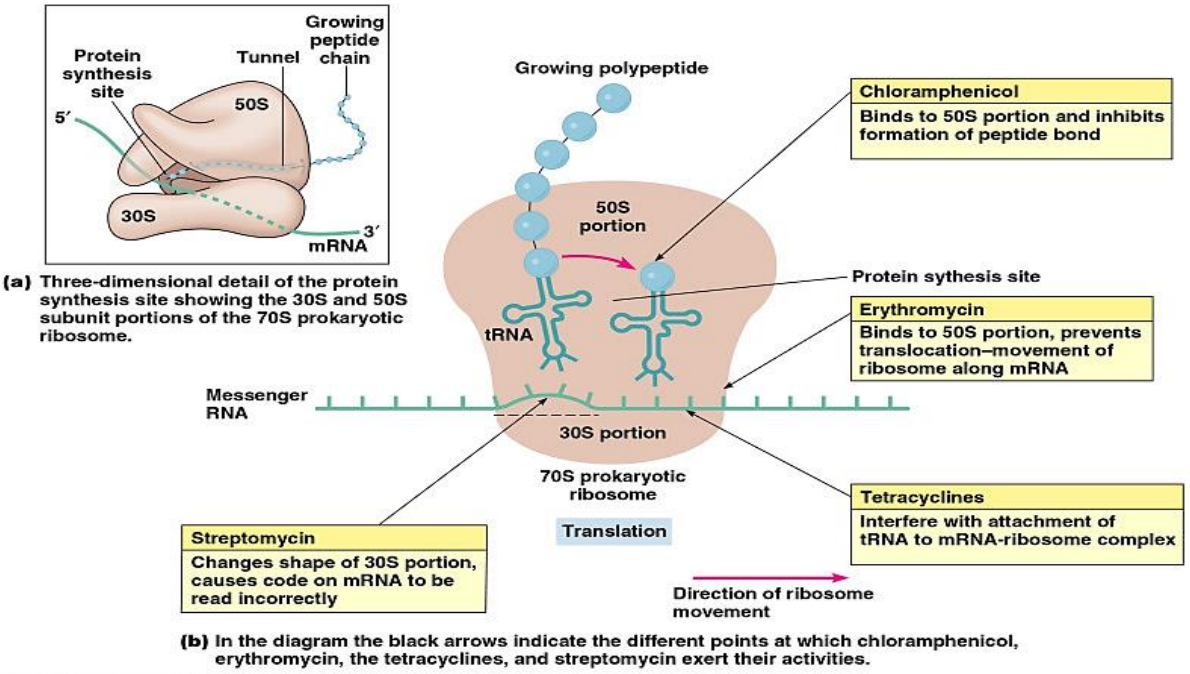
pharmacokinetic properties. All aminoglycosides are more active at alkaline pH than at acid pH.

Aminoglycosides are poorly absorbed from the gastrointestinal tract. After parenteral administration, aminoglycosides are primarily distributed within the extracellular fluid. They distribute well into most body fluids but not into the central nervous system, bone, or fatty or connective tissues. They tend to concentrate in the kidneys and are excreted by glomerular filtration. Aminoglycosides are apparently not metabolized in vivo.

Mechanism of Action

The aminoglycosides act directly on the bacterial ribosome to inhibit the initiation of protein synthesis and to interfere with the fidelity of translation of the genetic message. They bind to the 30S ribosomal subunit to form a complex that cannot initiate proper amino acid polymerization. Difference in ribosomal units (Eukaryotes : 60S and 40 S subunit) is the basis of selectivity of antimicrobial drugs against bacteria(this is why antibiotic drugs do not inhibit mammalian protein synthesis).

The binding of streptomycin and other aminoglycosides to ribosomes also causes misreading mutations of the genetic code ,apparently resulting from failure of specific aminoacyl RNAs to recognize the proper codons on messenger RNA (mRNA) and hence incorporation of improper amino acids into the peptide chain .All of the commercially available aminoglycoside antibiotics are bactericidal, except spectinomycin.



(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S prokaryotic ribosome.

(b) In the diagram the black arrows indicate the different points at which chloramphenicol, erythromycin, the tetracyclines, and streptomycin exert their activities.

Resistance to aminoglycosides is based on

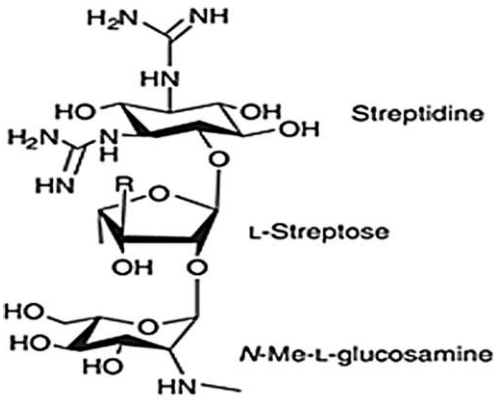
(1) a deficiency of the ribosomal receptor (chromosomal mutant).

(2) enzymatic destruction of the drug (plasmid-mediated transmissible resistance of clinical importance).

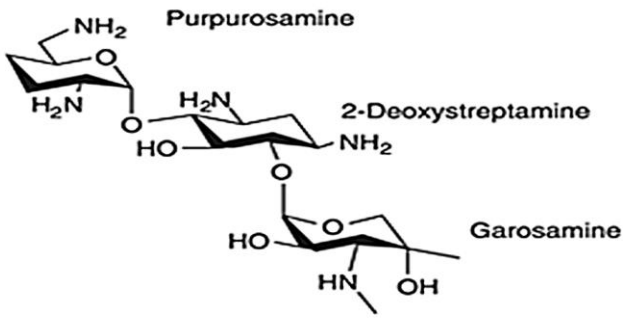
(3) lack of permeability to the drug molecule and lack of active transport into the cell. The last can be chromosomal (eg, streptococci are relatively impermeable to aminoglycosides), or it can be plasmid-mediated (eg, in gram-negative enteric bacteria).

Streptomycin

Streptomycin was the first aminoglycoside—it was discovered in the 1940s as a product of *Streptomyces griseus.* It was studied in great detail and became the prototype of this class of drugs. After intramuscular injection, streptomycin is rapidly absorbed and widely distributed in tissues except the central nervous system. Only 5% of the extracellular concentration of streptomycin reaches the interior of the cell. Absorbed streptomycin is excreted by glomerular filtration into the urine. After oral administration, it is poorly absorbed from the gut; most of it is excreted in feces.



1 Streptomycin R=CHO
2 Dihydrostreptomycin R=CH_2OH



3 Gentamycin A

Streptomycin may be bactericidal for enterococci (eg, in endocarditis) when combined with a penicillin. In tularemia and plague, it may be given with a tetracycline. In tuberculosis, it is used in combination with other anti tuberculosis drugs (isoniazid, rifampin).

The therapeutic effectiveness of streptomycin is limited by the rapid emergence of resistant mutants. All microbial strains produce streptomycin-resistant chromosomal mutants with relatively high frequency. Chromosomal mutants have an alteration in the P 12 receptor on the 30S ribosomal subunit. Plasmid-mediated resistance results in enzymatic destruction of the drug.

Fever, skin rashes, and other allergic manifestations may result from hypersensitivity to streptomycin. This occurs most frequently upon prolonged contact with the drug, in patients receiving a protracted course of treatment (eg, for tuberculosis), or in personnel preparing and handling the drug.

Streptomycin is ototoxic (particularly for the auditory portion of the eighth nerve) causing tinnitus, vertigo, and ataxia, which are often irreversible. It is moderately nephrotoxic.

Gentamicin

In concentrations of 0.5–5 μg/mL, gentamicin is bactericidal for many gram-positive and gram-negative bacteria, including many strains of proteus, serratia, and pseudomonas. Gentamicin is ineffective against streptococci and bacteroides.

Gentamicin has been used in serious infections caused by gram-negative bacteria resistant to other drugs. Penicillins may precipitate gentamicin in vitro (and thus must not be mixed), but in vivo they may facilitate the aminoglycoside entrance into streptococci and gram-negative rods and result in bactericidal synergism, beneficial in sepsis and endocarditis.

Gentamicin is toxic, particularly in the presence of impaired renal function. Gentamicin sulfate, 0.1%, has been used topically in creams or solutions for infected burns or skin lesions.

Tobramycin

This aminoglycoside closely resembles gentamicin, and there is some cross-resistance between them. Separate susceptibility tests are desirable. Tobramycin has slightly enhanced activity against *Pseudomonas aeruginosa* when compared with gentamicin.

The pharmacologic properties of tobramycin are virtually identical to those of gentamicin. Most of the drug is excreted by glomerular filtration. In renal failure, the drug dosage must be reduced, and monitoring of blood levels is desirable.

Like other aminoglycosides, tobramycin is ototoxic but perhaps less nephrotoxic than gentamicin. It should not be used concurrently with other drugs having similar adverse effects or with diuretics, which tend to
enhance aminoglycoside tissue concentrations.

Sisomicin

Identical to gentamicin , more potent on pseudomonas and β-hemolytic streptococci (2-4 times more active against pseudomonas and proteus even those which are resistant to gentamicin) .

Netilmicin

Semisynthetic derivative of sisomicin , relatively resistant to aminoglycoside inactivating enzymes .More active against klebsiella, enterobacter & staphylococci , less active against pseudomonas aeruginosa .Doses and

pharmacokinetics similar to gentamicin. Less ototoxic than gentamicin and tobramycin.

Neomycin

wide spectrum active against Gm-ve bacilli and some gm+ve cocci ,Pseudomonas and strep.pyogenes not sensitive .Too toxic for parenteral use , limited to topical use . Highly toxic for internal ear mainly auditory and also kidney . Oral and topical administration does not cause systemic toxicity

Topically used in skin, eye and external ear infections combined with bacitracin or polymyxin-B to widen antibacterial spectrum and to prevent emergence of resistant strains.

Orally used for preparation of bowel before surgery and Hepatic coma(Supresses ammonia forming coliforms prevents encephalopathy) .

Kanamycin

is a close relative of neomycin, with similar activity and complete cross-resistance. Paromomycin is also closely related and is used in amebiasis. These drugs are stable and poorly absorbed from the intestinal tract and other surfaces. Neither drug is used systemically because of ototoxicity and neurotoxicity. Oral doses of both neomycin and kanamycin are used for reduction of intestinal flora before large bowel surgery, often in combination with erythromycin. Otherwise, these drugs are mainly limited to topical application on infected surfaces (skin and wounds).

Framycetin

Very similar to neomycin .Too toxic for systemic administration .Used topically on skin, eye (Soframycin eye drops 0.5 % and cream 1 %) and ear .

Amikacin

Amikacin is a semisynthetic derivative of kanamycin. It is relatively resistant to several of the enzymes that inactivate gentamicin and tobramycin and therefore can be employed against some microorganisms resistant to the latter drugs.

However, bacterial resistance due to impermeability to amikacin is slowly increasing. Many gram negative enteric bacteria are inhibited by amikacin in concentrations obtained after injection. Like all aminoglycosides, amikacin is nephrotoxic and ototoxic . Its level should be monitored in patients with renal failure.

Spectinomycin

Spectinomycin is an aminocyclitol antibiotic (related to aminoglycosides) for intramuscular administration. Its sole application is in the single-dose treatment of gonorrhea caused by β-lactamase-producing gonococci or occurring in individuals hypersensitive to penicillin. About 5–10% of gonococci are probably resistant. There is usually pain at the injection site, and there may be nausea and fever.

- Advantages and disadvantiges of aminoglycosides

Advantages	Dis advantages
Rapid bactericidal action	Inactivity against anaerobes
Relatively low cost	Narrow therapeutic index
Chemical stability	Toxicities : ototoxicity, nephro toxicity
Broad spectrum activity	
No allergic reaction	Lack of oral absorption
Synergistic action with other antibiotics	
Post antibiotic effect	

Inhibition of bacterial protein synthesis

Macrolides :

- **Macrolides** were first discovered in the 1950s, when scientists isolated from the soil bacterium *Streptomyces erythraeus*.
- Macrolides represent a large family of protein synthesis inhibitors of great clinical interest due to their applicability to human medicine.
- Macrolide antibiotics are classified according to the size of the macrocyclic lactone ring as being either 12-, 14-, 15- or 16-membered ring macrolides, the majority of macrolides contain amino sugar and/or neutral sugar moieties connected to the lactone ring via a glycosylic bond
- Macrolides act as antibiotics by binding to bacterial 50S ribosomal subunit and interfering with protein synthesis, they have growth-inhibiting (bacteriostatic) effects on bacteria (broad-spectrum activity).
- Macrolides include :
- Erythromycin
- Azithromycin
- Carbomycin
- Cethromycin
- Clarithromycin
- Dirithromycin
- Mitemcinal
- Oleandomycin
- Roxithromycin
- Spiramycin

Antimicrobial activity and chemical derivatives:

In general, macrolide antibiotics are active mainly against Gram-positive bacteria and have only limited activity against Gram-negative bacteria, Macrolides are very active against *Staphylococcus*, *Streptococcus* and *Diplococcus* Gram-positive bacteria, and among Gram-negative cocci, *Neisseria gonorrhoea*, *Haemophilus influenzae*,

Bordetella pertussis and *Neisseria meningitis*. Additionally, they are also extremely active against various Mycoplasmas.

Although macrolides display excellent antibacterial activity, their generally poor bioavailability, unpredictable pharmacokinetics and low stability in the acidic pH of the stomach prompted early searches for new derivatives with improved properties. This resulted in the second generation of macrolides, which were semisynthetic derivatives of the first, natural product, generation. derivatives of erythromycin were developed and marketed, namely, clarithromycin, roxithromycin, azithromycin.

Erythromycin

*It has an antimicrobial spectrum similar to or slightly wider than that of penicillin, and is often used for people who are allergic to penicillins.

*For respiratory tract infections caused by gram positive bacteria including streptococci, pneumococci, and corynebacteria it has better coverage of atypical organisms, includng*Chlamydia* ,*Mycoplasma* and *Legionella.*

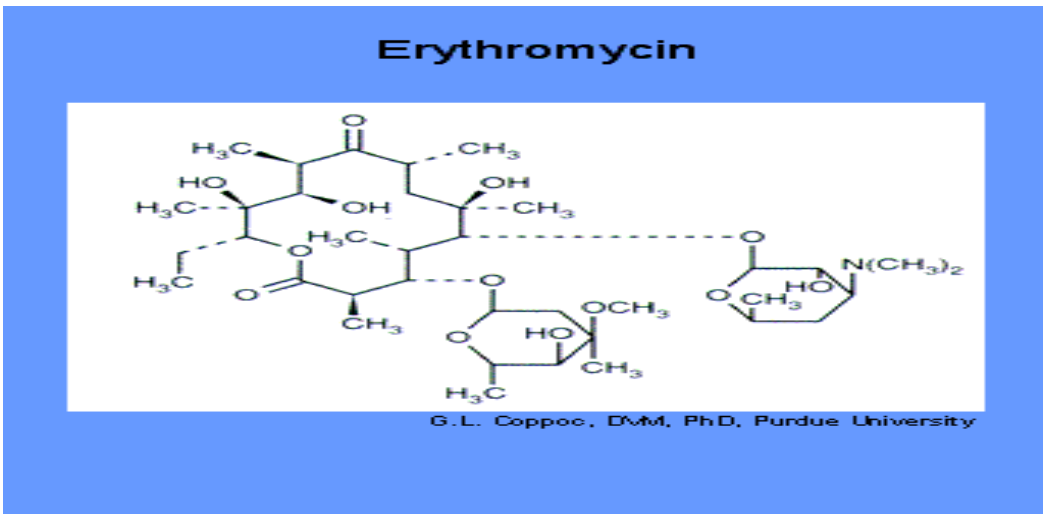
*For urinary tract infections including bronchitis, pneumonia.

*For skin and soft tissue infections.

*For urinary tract infections.

- Common side effects include abdominal cramps, vomiting, and diarrhea.

*Erythromycin tend to accumulate within phagocytes, therefore, during active Phagocytosis, large concentration of erythromycin are released in the site of infection.



Erythromycin: The macrolide ring is the lactone (cyclic ester) at upper-left; Desosamine ring at upper right while the Cladinose ring at lower right.

The newer members of this family:

- **Azithromycin** :

is an antibiotic useful for the treatment of a number of bacterial infections. This includes :

*middle ear infections, strep throat.

* pneumonia.

*Traveler's diarrhea, and certain other intestinal infections.

*It may also be used for a number of sexually transmitted infections including chlamydia and gonorrhea infections. Along with other medications, it may also be used for malaria.

*Although less active against staphylococci and streptococci than erythromycin , azithromycin is more active against respiratory infections due to *Haemophilus influenzae*and *Moraxella catarrhalis*.

* Has a long serum half- life with a better tolerability and ease of administration (once daily dosing).

* Common side effects include nausea, vomiting, diarrhea and upset stomach.

- **Clarithromycin:**
- Is an antibiotic used to treat various bacterial infections, including strep throat, pneumonia, skin infections, *H. pylori* infection, and Lyme disease,

* This antibiotic has a spectrum similar to that of erythromycin but it is also effective against *Haemophillus influenza.*

* Its activity against intracellular pathogens, such as *Chlamydia, Legionella, Moraxella* higher than that of erythromycin.

* For upper and lower respiratory tract infections.

* For skin and soft tissue infections.

- **Dirithromycin:**

  It has a spectrum of antimicrobial activity similar to that of erythromycin. It is no longer available in United States; however it is still available in many European countries.

- **Telithromycin :**

  Which is the first "**Ketolide**" antimicrobial agent that has been approved and is now in clinical use.

  * For community acquired pneumonia.

  * Chronic bronchitis.

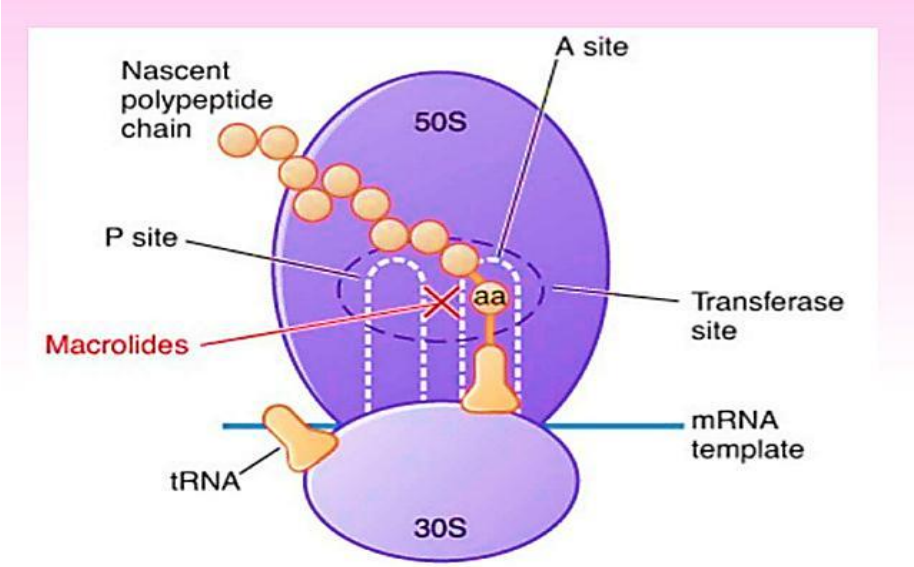
  * Acute sinusitis.

  * Tonsillitis and pharyngitis.

  Ketolides and macrolides have very similar antimicrobial coverage. However, the ketolides are active against many macrolide – resistant gram positive strains.

  .M**echanism of action of macrolides:**

  Macrolides prevent bacteria from growing by interfering with their protein synthesis., macrolide acts by penetrating the bacterial cell membrane and reversibly binding to the 50 S subunit of bacterial ribosomes or near the “P” or donor site so that binding of tRNA (transfer RNA) to the donor site is blocked. Translocation of peptides from the “A” or acceptor site to the “P” or donor site is prevented, and subsequent protein synthesis is inhibited. This action is mainly bacteriostatic, but can also bebactericidal in high concentrations.



Bacterial resistance to macrolides results from:

- An alteration (methylation) of the rRNA receptor.
- Production of drug-inactivating enzymes (esterases or kinases)
- Production of active ATP-dependent efflux proteins that transport the drug outside of the cell(efflux pumps).

Lincosamides:

*Lincosamides constitute a relatively small group of antibiotics with a chemical structure consisting of amino acid and sugar moieties. * Many semi-synthetic derivatives of **lincomycin** have been prepared. Of these, only the chlorinated derivative **clindamycin** is highly biologically active and is applied practically.

*Natural lincosamides are produced by several *Streptomyces* species, mainly by *Streptomyces lincolnensis and S. roseolus* .

***Therapeutic Effects**: Bactericidal or bacteriostatic, depending on susceptibility and concentration.

***Spectrum of activity**: active against most gram-positive aerobic cocci, including: *Streptococcus pneumoniae*, and *Streptococcus pyogenes* infections. but not enterococci.

*Clindamycin is used for staphylococcal bone,joint infections, dental infections and serious intra-abdominal sepsis ,in the last, it is usually combined

with an agent active against Gram-negative pathogens such as gentamicin because of its ability to inhibit production of bacterial protein toxins.

* Has good activity against those anaerobic bacteria that cause bacterial vaginosis, including *Bacteroides fragilis* and *Gardnerella vaginalis.*

Mechanism of action:

Mechanism of action is via inhibition of protein synthesis in sensitive microorganisms, Lincosamides act on the 50S ribosomal subunit of the bacterial ribosome. The binding sites are similar to those for erythromycin . The lincosamides prevent transpeptidation during the formation of the nascent peptide chain by inhibiting peptidyltransferase.

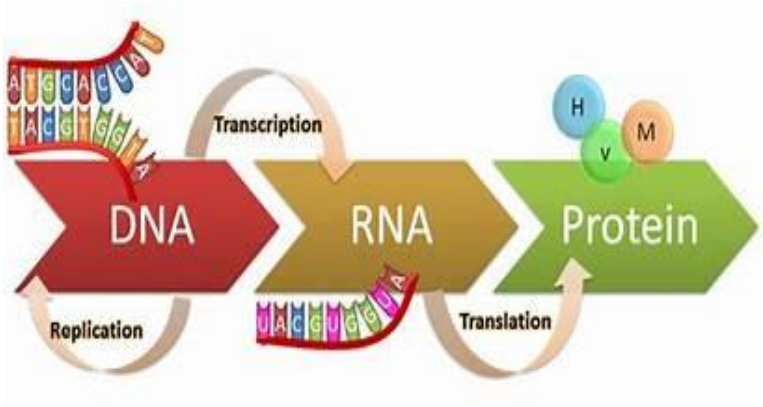
*Acquired **resistance** to lincosamides may be due to modification of the bacterial target, modification of the antibiotics and reduced permeability.

***The most serious** adverse effect **is antibiotic-associated pseudomembranous colitis, clindamycin should be stopped if any diarrhoea occurs.antibiotics associated colitis , most commonly with lincomycin or clindamycin, but also with o ther broadsectrum antibiotics, such as ampicillin and tetracycline. It can range fr om mild nonspecific colitis and diarrhea to severe fulminant pseudomembranous colitis with profuse watery diarrhea, abdominal cramps, and fever. The inflamma tion may be caused by a toxin produced by *Clostridium difficile*, a microorganism t hat is normally present in the resident bowel flora of infants, but is rarely found in adults, the disruption of the normal flora allows the growth of *C. difficile*.**

Inhibition of Bacterial Nucleic Acid Synthesis

In a bacterial cell, or any kind of cell for that matter, the nucleic acids DNA and RNA are incredibly important molecules. When a cell divides, it must first replicate its DNA to give the new cell what basically amounts to its instruction manual for life, and in the daily life of a cell, transcription of DNA into RNA is a major step in the assembly line that creates proteins. It's easy to see that if DNA or RNA synthesis are inhibited, a cell won't be able to get anything done at all!

So, inhibiting nucleic acid synthesis consider a great strategy for an antibiotic, and luckily for us, the enzymes that carry out DNA and RNA synthesis are different enough between eukaryotic and prokaryotic cells that selective toxicity can be achieved.



From DNA to protein

A/ Antibiotics which inhibit bacterial DNA synthesis:

**Quinolons*:*

Quinolones are a group of antibiotics that interfere with DNA synthesis by inhibiting topoisomerase, most frequently topoisomerase II (DNA gyrase), an enzyme involved in DNA replication. DNA gyrase relaxes supercoiled DNA molecules and initiates transient breakages and rejoins phosphodiester bonds in superhelical turns of closed-circular DNA. This allows the DNA strand to be replicated by DNA or RNA polymerases. The fluoroquinolones, second-generation quinolones that

include ***levofloxacin, norfloxacin****, and ciprofloxacin, are active against both Gram-negative and Gram-positive bacteria.*

Antimicrobial Activity:

The quinolones can be classified into four generations based on antimicrobial activity : ***First-generation:*** *agents, which are used less often today, have moderate gram negative activity and minimal systemic distribution.*

Second-generation: *quinolones have expanded gram-negative activity and atypical pathogen coverage, but limited gram-positive activity. These agents are most active against aerobic gram-negative bacilli. Ciprofloxacin remains the quinolone most active against* Pseudomonas aeruginosa.

Third-generation*: quinolones retain expanded gram-negative and atypical intracellular activity but have improved gram-positive coverage. Finally,* ***fourth-generation*** *agents improve gram-positive coverage, maintain gram-negative coverage, and gain anaerobic coverage*

Mechanism of action :

Quinolones and fluoroquinolones are chemotherapeutic bactericidal drugs, eradicating bacteria by interfering with DNA replication,Quinolones exert their antibacterial effect by preventing bacterial DNA from unwinding and duplicating , by inhibit the bacterial DNA gyrase or the topoisomerase IV enzyme, thereby inhibiting DNA replication and transcription.

Examples: Ciprofloxacin , levofloxacin, sparfloxacin, norfloxacin **,** ***m****oxifloxacin****,*** *Nalidixic acid.*

Therapeutic Uses of Quinolones

1-Gnetourinary infections:

Because of their extensive gram-negative coverage, quinolone antibiotics were initially used to treat urinary tract infections. The higher genitourinary drug

concentrations that occur with renally cleared quinolones promote their effectiveness in the treatment of genitourinary infections. Given in three- to 10-day courses

2- Prostatitis

Quinolones are effective in the treatment of prostatitis because of their excellent penetration into prostatic tissue. When taken for four to six weeks, Levofloxacin is an excellent first-line agent in the treatment of prostatitis. Ciprofloxacin should be reserved for use in patients with resistant gram-negative, pseudomonal, and enterococcal prostatitis, because of its superior activity against P. aeruginosa *and enterococci.*

3-Respirtory diseases:

Acute bacterial sinusitis may be the complication of an initial viral illness. The primary bacterial isolates are S. aureus, S. pneumoniae, Haemophilus influenzae, *and* Moraxella catarrhalis. *The U.S. Food and Drug Administration (FDA) has labeled gatifloxacin, moxifloxacin, sparfloxacin, and levofloxacin for use in the treatment of acute bacterial sinusitis. Clinical trials comparing fluoroquinolones with amoxicillin–clavulanate potassium (Augmentin), cefuroxime axetil (Ceftin), and clarithromycin have demonstrated the efficacy of the quinolone antibiotics. However, we believe that quinolones should not be used as first-line agents in the treatment of acute bacterial sinusitis because of the potential for development of bacterial resistance.*

4-Sexually transmited diseases*: A single dose of ciprofloxacin or ofloxacin should be considered as alternative treatment in, for example, patients with penicillin allergy.Recently, gatifloxacin was reported to be as effective as ofloxacin against N. gonorrhoeae. ciprofloxacin has been reported to be as effective as trimethoprim-sulfamethoxazole for treating chancroid caused by* Haemophilus ducreyi.

5-Gastroenteritis:

Norfloxacin or ciprofloxacin has been found to be comparable in the treatment of traveler's diarrhea caused by Shigella species, enterotoxigenic E. coli, *or* Campylobacter jejuni. *Ciprofloxacin and ofloxacin are the agents of choice for*

treatment of enteric typhoid fever. Norfloxacin has been found to be drug of choice in the treatment of Vibrio cholerae *infection.*

Ciprofloxacin

Ciprofloxacin is a broad-spectrum antibiotic of the **fluoroquinolone class. It is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, and a type II topoisomerase, topoisomerase IV which necessary to separate bacterial DNA, thereby inhibiting cell division.*

**This antibiotic used to treat a number of bacterial infections includes bone and joint infections, intra abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections, among others.*

Adverse Effects of Quinolones

Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain

CNS: headache, dizziness, drowsiness, confusion, depression

Dermatologic: rash, photosensitivity reactions, pruritus

*B//**Antibiotics which inhibit bacterial RNA:***

Rifamycins

* The rifamycins are a group of antibiotics that are synthesized either naturally by the bacterium *Amycolatopsis rifamycinica* or artificially. They are a subclass of the larger family of ansamycins. Rifamycins are particularly effective against mycobacteria, and are therefore used to treat tuberculosis and leprosy, .Rifamycins work by binding to the bacterial DNA-dependent RNA polymerase, the enzyme that is responsible for transcription of DNA into RNA. The antibiotic molecule is thought to bind to the polymerase in such a way that it creates a wall that prevents the chain of RNA from elongating. Rifamycins are bactericidal antibiotics. In the presence of rifamycins, bacteria can't transcribe any genes that they need to carry out their normal functions, so they die.

*Rifamycins are broad-spectrum antibiotics, meaning they're effective against many types of bacteria, including Gram-negative, Gram-positive, and obligate

intracellular bacteria. There are two main reasons for this. First, the rifamycin molecule can penetrate well into cells and tissues. This means that, unlike some antibiotics that can't cross certain types of bacterial cell walls, the rifamycins can almost always get in and gain access to their target enzyme. And second, the bacterial RNA polymerase is well-conserved even among very different bacteria. This means that the enzyme's structure is similar enough that the rifamycins can bind well to their target in diverse types of bacteria.

Currently available rifamycins:

Rifampicin or Rifampin ,Rifabutin ,Rifapentine ,Rifaximin .

Adverse effects

- *Digestive system: nausea, vomiting, diarrhea, gastritis, hepatitis.*
- *Allergic reactions: urticaria, eosinophilia.*
- *Nervous system: headache, decreased visual acuity, ataxia.*
- *Urinary system: interstitial nephritis*

Antimetabolite

* Antimetabolites are drugs that interfere with one or more enzymes or their reactions that are necessary for DNA synthesis. They affect DNA synthesis by acting as a substitute to the actual metabolites that would be used in the normal metabolism (for example antifolates interfere with the use of folic acid).. The presence of antimetabolites can have toxic effects on cells, such as halting cell growth and cell division.

*Antimetabolites are drugs used in cancer chemotherapy. Cancer cells divide more rapidly compared to normal cells so antimetabolites affect cancer cell replication more than they affect normal cell replication. Antimetabolite drugs are commonly used to treat leukemia, cancers of the breast, ovary, and the gastrointestinal tract, as well as other types of cancers.ex: Fluorouracil (5-FU) and 6-Mercaptopurine (6-MP).

* Antimetabolites generally impair DNA replication machinery, either by incorporation of chemically altered nucleotides or by depleting the supply of deoxynucleotides needed for DNA replication and cell proliferation.

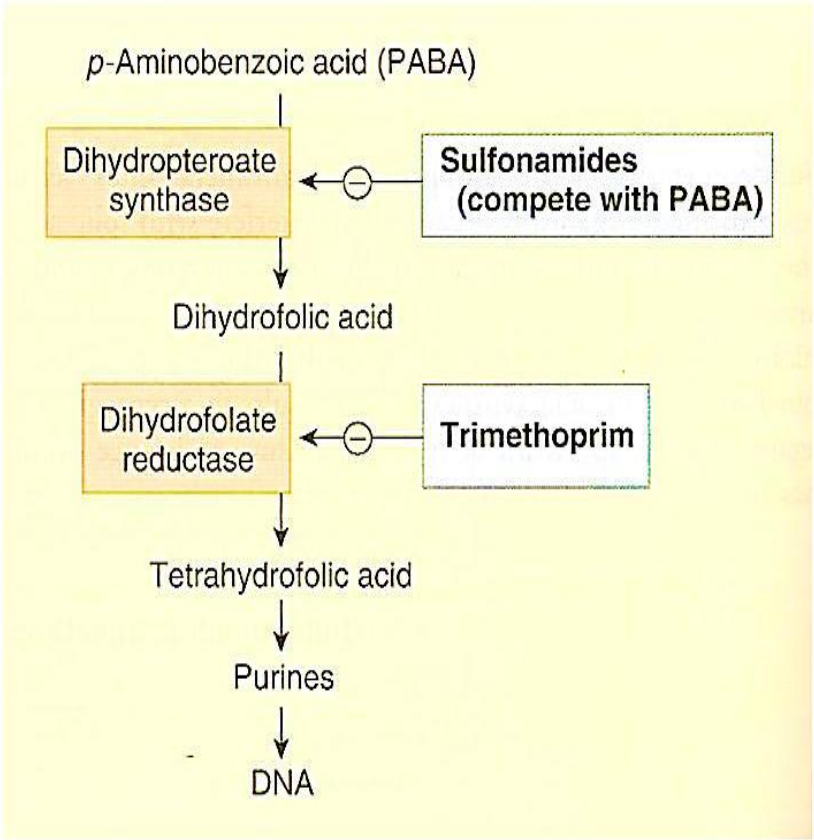
There are two types of antifolate drugs used in chemotherapy. Members of the first group, the sulfonamides, inhibit the synthesis of dihydrofolate in some bacteria and parasites. Members of the second group, the folate reductase inhibitors, block the action of dihydrofolate reductase and the formation of tetrahydrofolate in various organisms.

Mechanism of action:

*Bacterial synthesis of folate begins with the fusion of pteridine and *p*-aminobenzoic acid (PABA) to form dihydrofolate. This step involves the enzyme dihydropteroate synthase. Dihydrofolate is then converted to tetrahydrofolate by folate reductase.

*In bacteria, the sulfonamides and trimethoprim inhibit sequential steps in the synthesis of folate. The sulfonamides are structural analogues of PABA and competitively inhibit dihydropteroate synthase, trimethoprim inhibits bacterial folate reductase .

Inhibitory effects of sulfonamides and trimethoprim on folic acid synthesis



Miscellaneous antibiotics:

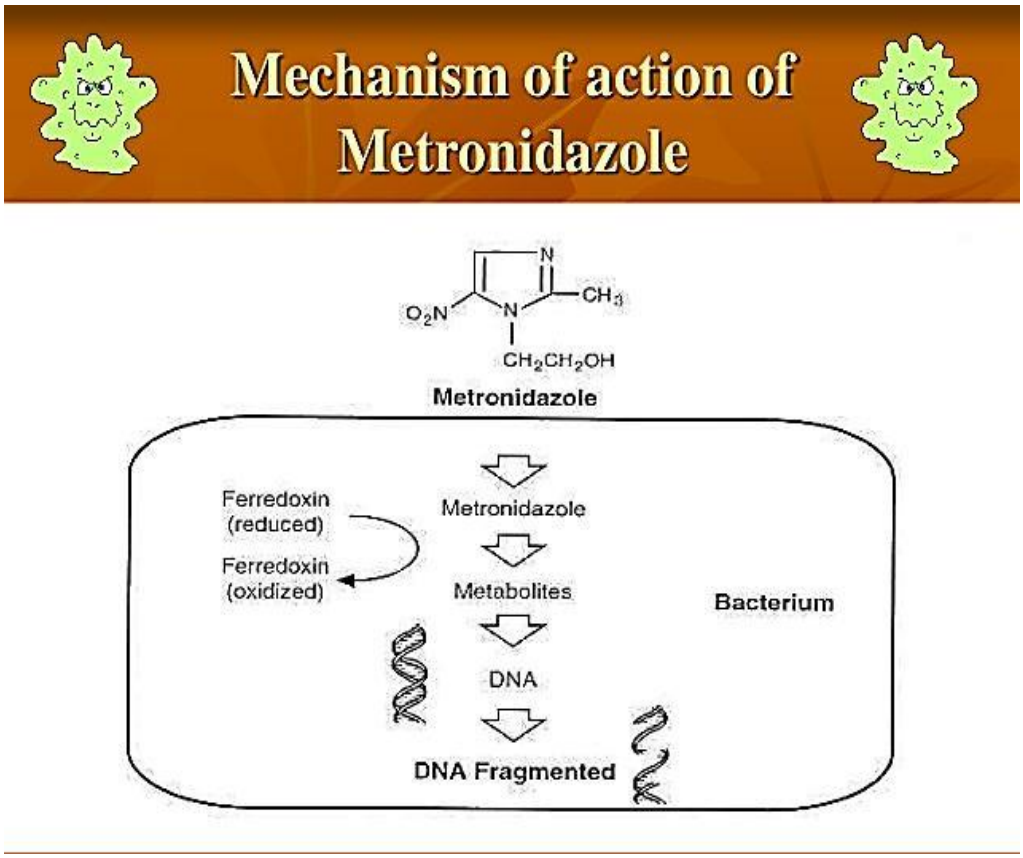
*Miscellaneous antibiotics are antibiotics which are the only agent available in their class. This means that they are unique in their action and not comparable to other antibiotics, although their spectrum of activity or certain side effects may be similar to other antibiotics.

*Miscellaneous antibiotics are used to treat infections caused by bacteria or other organisms, usually when other more common agents are not effective or not tolerated. There is not a single antibiotic that will treat all infectious disease scenarios.

1- Metronidazole (Flagyl):

* Metronidazole, marketed under the brand name Flagyl among others, is an antibiotic and antiprotozoal medication, It is used either alone or with other antibiotics to treat pelvic inflammatory disease , endocarditis , and bacterial vaginosis . It is effective for dracunculiasis , giardiasis, trichomoniasis , and amebiasis.

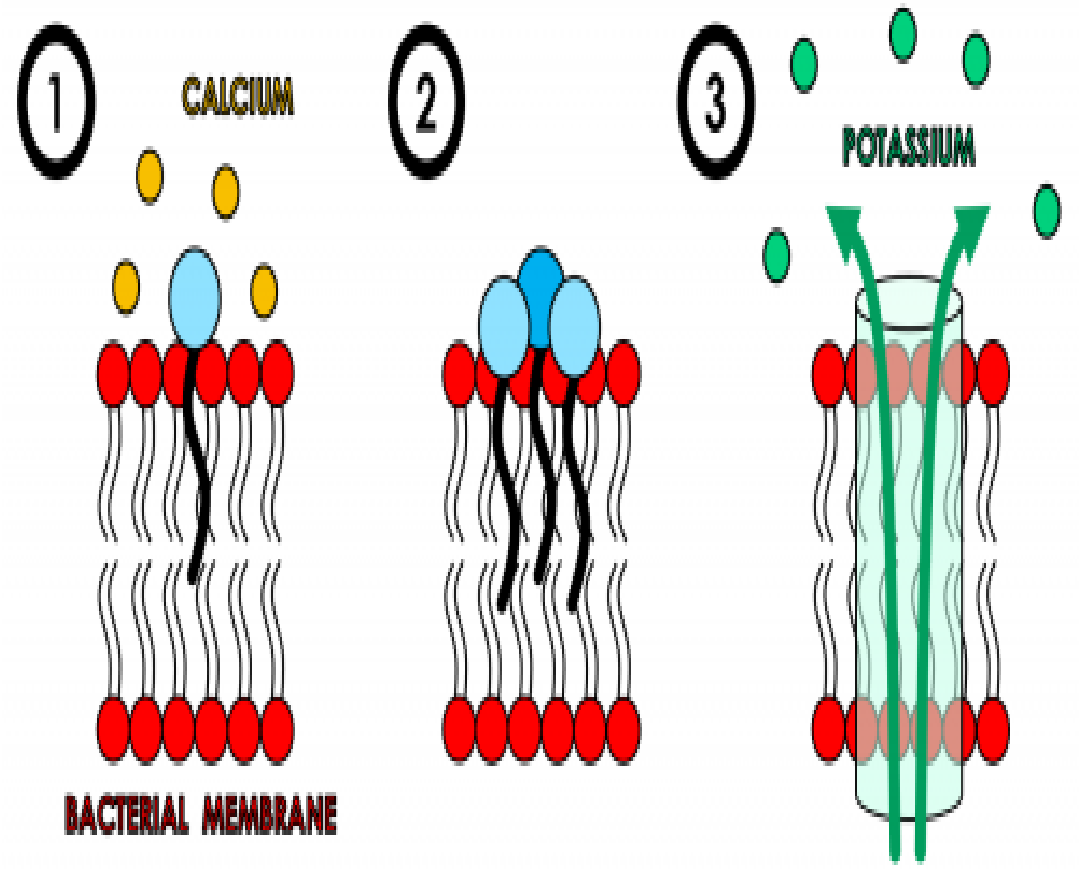
* Metronidazole is of the Nitroimidazole class. It inhibits nucleic acid synthesis by disrupting the DNA of microbial cells. This function only occurs when metronidazole is partially reduced, and because this reduction usually happens only in anaerobic bacteria and protozoans, it has relatively little effect upon human cells or aerobic bacteria.



2-Bacitracin : **is a mixture of related cyclic peptides produced by *Bacillus subtilis.* Bacitracin inhibits the synthesis of the bacterial cell wall by preventing the transport of peptidoglycan precursors through the cytoplasmic membrane. Bacitracin is primarily used as a topical preparation (as it can cause kidney damage when used internally). Bacitracin is a narrow spectrum antibiotic. It targets Gram-positive organisms, especially those that cause skin infections**.**

3- **Daptomycin**: is derived from the actinobacteria *Streptomyces roseosporus*, daptomycin is the only member of the cyclic lipopeptide class of antibiotics. This antibiotic has a distinct mechanism of action due to its unique structure: it has been proposed that its tail inserts into the bacterial membrane and when a group of daptomycin molecules come together, a pore is formed that leaks ions and causes a destructive loss of membrane potential that kills the bacterial cell. This unique mechanism of action has made daptomycin an extremely useful asset in treating infections caused by drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci

(VRE). In fact, daptomycin has been proven to be effective against all clinically-relevant Gram-positive bacteria and its bacterial resistance is very low.



Mechanism of action for daptomycin. 1) Daptomycin's tail binds to and inserts into the bacterial membrane in the presence of calcium ions. 2) Daptomycin groups together to form aggregated structures. 3) These aggregates form ion channels, or pores, at which point intracellular potassium is released, membrane potential is disrupted and therefore causes cell death.

4-Polymyxin:

***Effective mainly against gram**

negativeorganisms and is especially effective against *Pseudomonas aeruginosa*, which may cause septicemia, meningitis, urinary tract infections, and middle ear infections. Toxicity is low but there is sometimes damage to kidney and nerve cells*ex erts its antimicrobial effect through its cationic detergent action on cell membranes. Specifically, this antibiotic binds to the negatively charged site in

the lipopolysaccharide layer of the bacterial cell membrane via electrostatic affinity with the positively charged amino groups in the cyclic peptide portion. Subsequently, the fatty acid portion of polymyxin B dissolves in the hydrophobic region of the bacterial cell membrane. This results in an alteration in cell membrane structure, disruption of cell wall integrity and an increase in permeability for water and molecules. This will eventually lead to bacterial cell death.

Antibiotic Resistance

*Antimicrobial resistance or antibiotic resistance (AMR or AR): is the ability of a microbe to resist (withstand) the effects of medication that once could successfully treat the microbe. The term antibiotic resistance (AR or ABR) is a subset of AMR, as it applies only to bacteria becoming resistant to antibiotics. Resistant microbes are more difficult to treat, requiring alternative medications or higher doses of antimicrobials. These approaches may be more expensive, more toxic or both. Microbes resistant to multiple antimicrobials are called multidrug resistant(MDR). Antibiotic resistance can be either plasmid mediated or maintained on the bacterial chromosome.

Mechanisms:

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 which destroy the B-lactam ring of penicillins through hydrolysis, and without a B-lactam ring, penicillins are ineffective against the bacteria.

2-Alteration of target site: e.g. alteration of PBP—the binding target site of penicillins—in MRSA and other penicillin-resistant bacteria.

3-Alteration of metabolic pathway: e.g. some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides. Instead, like mammalian cells, they turn to utilizing preformed folic acid.

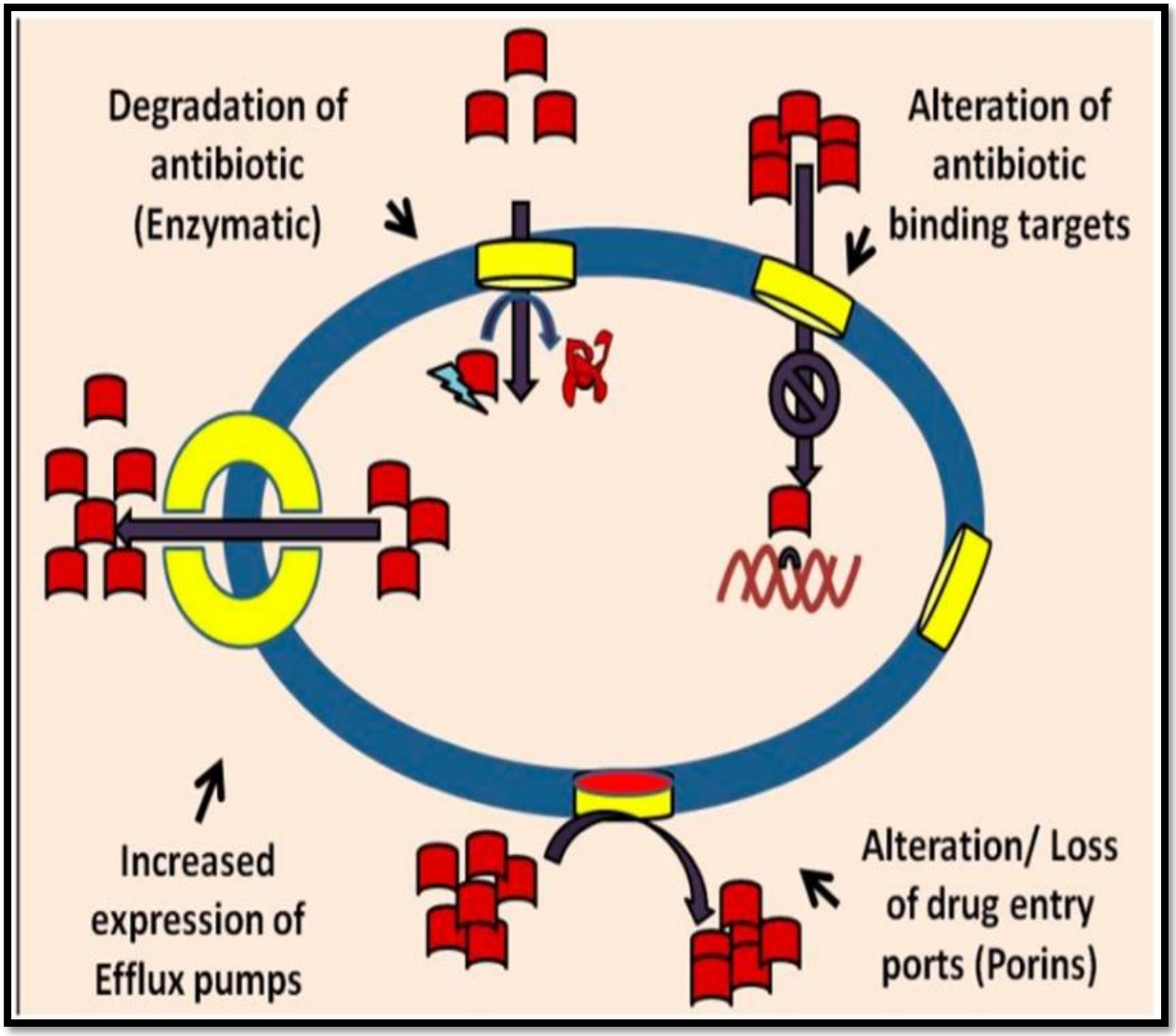
4-Reduced drug accumulation: by decreasing drug permeability and/or increasing active efflux(pumping out) of the drugs across the cell surface.

Examples:

1-*S.aureus* resistant to penicillin, methicillin, tetracycline ,erythromycin , methicillin and vancomycin.

2-Resistance of *Streptococcus pneumoniae* to penicillin and other beta-lactams.

3- Clindamycin-resistant *Clostridium difficile* is a nosocomial pathogen that causes diarrheal disease in hospitals world wide.



Antibiotic resistance mechanisms in bacteria

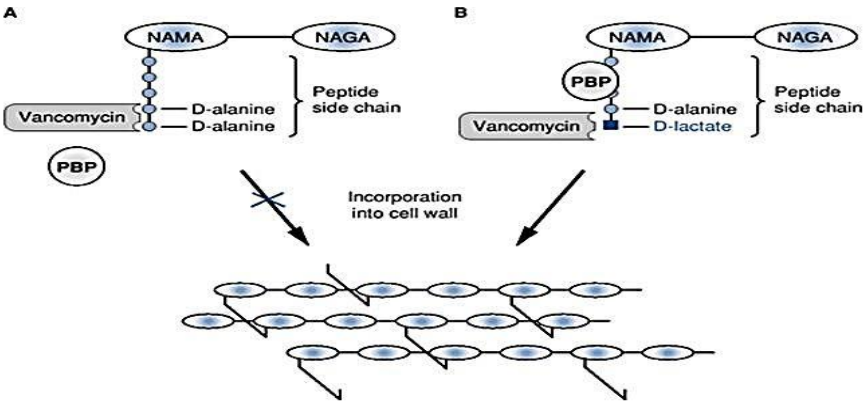
Glycopeptide antibiotics

Glycopeptide antibiotics are type of antibiotics that inhibit bacterial cell wall formation by inhibiting peptidoglycan synthesis. Glycopeptides such as vancomycin and teicoplanin are often used for the treatment of severe infections caused by Gram-positive pathogens, such as enterococci, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Clostridium difficile*. , which are resistant to beta-lactams and other antibiotics. They are also used in cases where there is an allergy to beta-lactams.

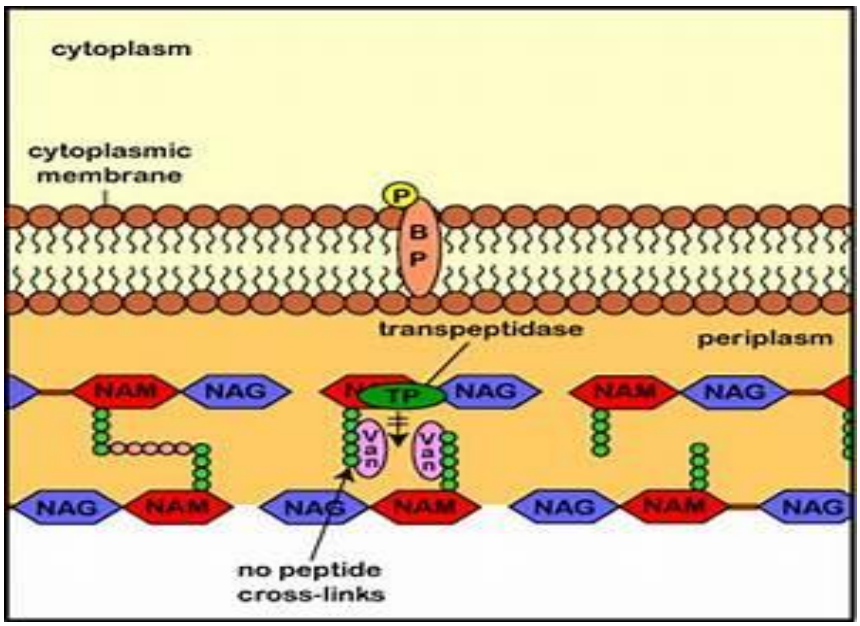
Structure and mechanism of action

Glycopeptides are glycosylated cyclic or polycyclic nonribosomal peptides produced by a various group of filamentous actinomycetes. **Vancomycin** acts by inhibiting cell wall synthesis of bacteria. Peptidoglycan layer of the cell wall is rigid due to its highly cross-linked structure. During the synthesis of the peptidoglycan layer of bacteria, new building blocks of peptidoglycan get inserted (i.e. monomers of N-acetylmuramic acid and N-acetylglucosamine) into the membrane. Reformation of the peptide cross links occurs by the enzyme transpeptidase. Vancomycin binds to the building blocks (i.e. NAG and NAM) of the peptidoglycan and prevents the transpeptidase from acting on these new formed blocks and thus prevents cross-linking of the peptidoglycan layer. By doing so, vancomycin makes the peptidoglycan layer less rigid and more permeable. This causes cellular contents of the bacteria to leak out and eventually death of the bacteria. Mutations in the transpeptidase enzyme can lead to increased resistance to vancomycin. These therapeutics target gram-positive bacteria by binding to the acyl-D-Ala-D-Ala terminus to the growing peptidoglycan and then cross-linking peptides within and between peptidoglycan on the outer surface of the cytoplasmic membrane . Glycopeptide-resistant bacteria avoid such a fate by replacing the D-Ala-D-Ala C-terminus of the pentapeptide with D-Ala-D-Lac or D-Ala-D-Ser, thus changing the glycopeptide-binding target and for removal of the high-affinity precursors that eliminating the glycopeptides binding target.

Mechanism of Action of Vancomycin



Vancomycin binds to the D-alanyl-D-alanine dipeptide on the peptide side chain of newly synthesized peptidoglycan subunits, preventing them from being incorporated into the cell wall by penicillin-binding proteins (PBPs). In many vancomycin-resistant strains of enterococci, the D-alanyl-D-alanine dipeptide is replaced with D-alanyl-D-lactate, which is not recognized by vancomycin. Thus, the peptidoglycan subunit is appropriately incorporated into the cell wall.



Polyene

Antimycotics:

Polyene antimycotics, sometimes referred to as polyene antibiotics, are a class of antimicrobial polyene compounds that target fungi. These polyene antimycotics are typically obtained from some species of Streptomyces bacteria. The polyenes bind to ergosterol in the fungal cell membrane and thus weakens it, causing leakage of K^+ and Na^+ ions, which may contribute to fungal cell death. Ergosterol serves as a bioregulator of membrane fluidity and asymmetry and

consequently of membrane integrity in fungal cell. Amphotericin B, nystatin, and natamycin are examples of polyene antimycotics. fungi are everywhere. There are millions of different fungal species on Earth, but only about 300 of those are known to make people sick. Fungal diseases are often caused by fungi that are common in the environment. Fungi live outdoors in soil and on plants and trees as well as on many indoor surfaces and on human skin. Most fungi are not dangerous, but some types can be harmful to health.

A Fungal Infection (mycosis) is an inflammatory infection in which fungi invade the skin or other body tissues. Some types of fungal infections can be mild, such as a rash on the skin, however they can be severe, such as fungal pneumonia.

An antifungal medication, also known as an antimycotic medication, is a pharmaceutical fungicide or fungistatic used to treat and prevent mycosis such as Aspergillosis ,Blastomycosis and Candidiasis etc,.

Structure:

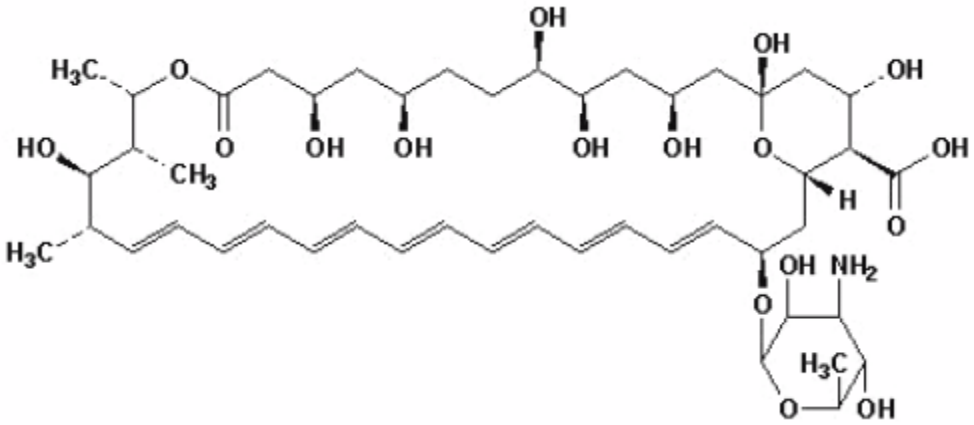
Their chemical structures feature a large ring of atoms (in essence, a cyclic ester ring) containing multiple conjugated carbon-carbon double bonds (hence polyene) on one side of the ring and multiple hydroxyl groups bonded to the other side of the ring.

Amphotericin B: is an antifungal medication used for serious fungal infections . The fungal infections it is used to treat include aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, and cryptococcosis.For certain infections it is given with flucytosine. It is typically given by injection into a vein.

Common side effects include a reaction with fever, chills, and headaches soon after the medication is given, as well as kidney problems. Allergic symptoms including anaphylaxis may occur. Other serious side effects include low blood potassium and inflammation of the heart. It appears to be relatively safe in pregnancy.

Amphotericin B was originally isolated from *Streptomyces nodosus* in 1955. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. It is available as a generic medication.

Amphotericin B binds with ergosterol, a component of fungal cell membranes, forming pores that cause rapid leakage of monovalent ions(K+, Na+, H+ and Cl−) and subsequent fungal cell death. This is amphotericin B primary effect as an antifungal agent Researchers have found evidence that amphotericin B also causes oxidative stress within the fungal cell, but it remains unclear to what extent this oxidative damage contributes to the drug's effectiveness. Two amphotericins, amphotericin A and amphotericin B, are known, but only B is used clinically, because it is significantly more active in vivo.

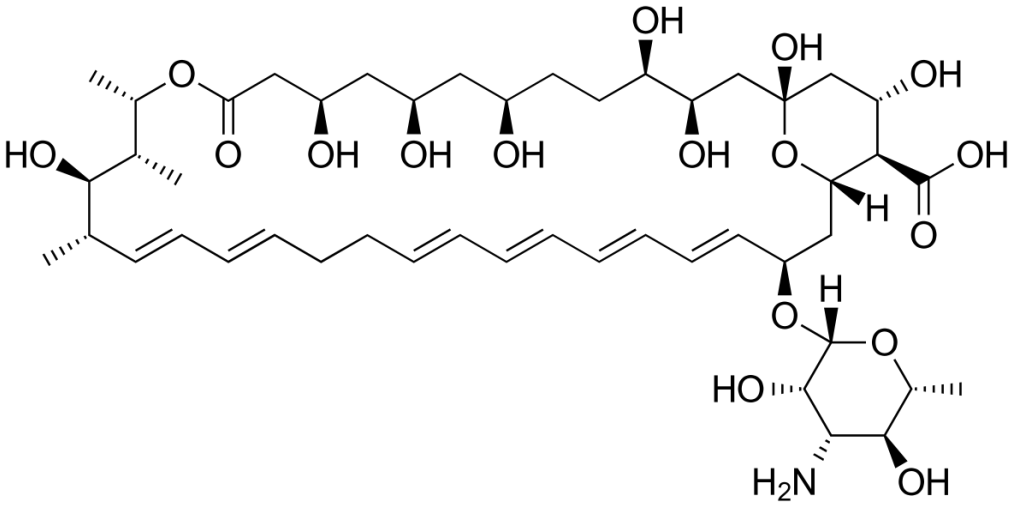


Chemical structure of Amphotericin B

Nystatin sold under the brand name Mycostatin among others, is a polyene antifungal medication. It is made from the bacterium, *Streptomyces noursei*. It is used to treat Candida infections of the skin including rash, thrush, esophageal candidiasis, and vaginal yeast infections. It may also be used to prevent candidiasis in those who are at high risk. Nystatin may be used by mouth, in the vagina, or applied to the skin.

Common side effects when applied to the skin include burning, itching, and a rash ,Common side effects when taken by mouth include vomiting and diarrhea. During pregnancy use in the vagina is safe while other formulations have not been studied in this group. It works by disrupting the cell membrane of the fungal cells.

Like amphotericin B , nystatin is an ionophore. It binds to ergosterol, a major component of the fungal cell membrane. When present in sufficient concentrations, it forms pores in the membrane that lead to K+ leakage, acidification, and death of the fungus. Ergosterol is a sterol unique to fungi, so the drug does not have such catastrophic effects on animals or plants. However, many of the systemic/toxic effects of nystatin in humans are attributable to its binding to mammalian sterols, namely cholesterol. This is the effect that accounts for the nephrotoxicity observed when high serum levels of nystatin are achieved

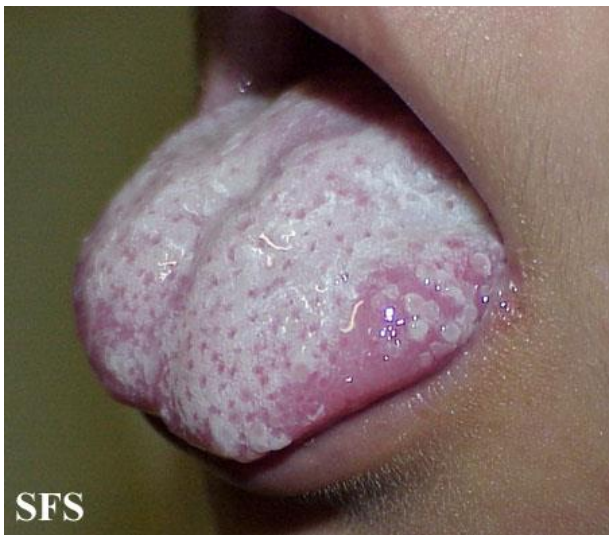


Chemical structure of Nystatin

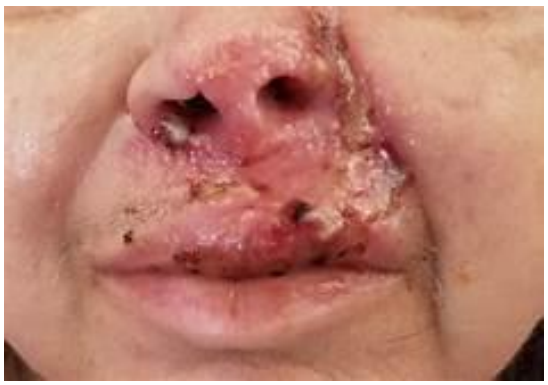
Flucytosine: also known as 5-fluorocytosine (5-FC), is an antifungal medication. It is specifically used, together with amphotericin B, for serious Candida infections and cryptococcosis. It may be used by itself or with other antifungals for chromomycosis. Flucytosine is used by mouth and by injection into a vein.

Mechanisms of action

- Flucytosine is intrafungally converted into the cytostatic fluorouracil which undergoes further steps of activation and finally interacts as 5-fluorouridinetriphosphate with RNA biosynthesis thus disturbing the building of certain essential proteins.
- Flucytosine also undergoes conversion into 5-fluorodeoxyuridinemonophosphate which inhibits fungal DNA synthesis.



Candidiasis



Blastomycosis

The acquisition and spread of antibiotic resistance in bacteria:

The development of resistance is inevitable following the introduction of a new antibiotic. Initial rates of resistance to new drugs are normally on the order of 1%. However, modern uses of antibiotics have caused a huge increase in the number of resistant bacteria. In fact, within 8-12 years after wide-spread use, strains resistant to multiple drugs become widespread. Multiple drug resistant strains of some bacteria have reached the proportion that virtually no antibiotics are available for treatment Antibiotic resistance in bacteria may be an **inherent** trait of the organism (e.g. a particular type of cell wall structure) that renders it naturally resistant, or it may be **acquired** by means of mutation in its own DNA or acquisition of resistance-conferring DNA from another source

Inherent (natural) resistance: Bacteria may be inherently resistant to an antibiotic. For example, an organism lacks a transport system for an antibiotic; or an organism lacks the target of the antibiotic molecule; or, as in the case of Gram-negative bacteria, the cell wall is covered with an outer membrane that establishes a permeability barrier against the antibiotic

Acquired resistance: Several mechanisms are developed by bacteria in order to acquire resistance to antibiotics. All require either the modification of existing genetic material or the acquisition of new genetic material from another source.

*Once the resistance genes have developed, they are transferred directly to all the bacteria's progeny during DNA replication. This is known as vertical gene transferor vertical evolution .

Vertical gene transfer

The spontaneous mutation frequency for antibiotic resistance is on the order of about 10^{-8}- 10^{-9}. This means that one in every 1^{08}- 1^{09} bacteria in an infection will develop resistance through the process of mutation. In *E. coli*, it has been estimated that streptomycin resistance is acquired at a rate of approximately 10^{-9} when exposed to high concentrations of streptomycin. Although mutation is a very rare event, the

very fast growth rate of bacteria and the absolute number of cells attained means that it doesn't take long before resistance is developed in a population.

Horizontal gene transfer

Another mechanism beyond spontaneous mutation is responsible for the acquisition of antibiotic resistance. Lateral or horizontal gene transfer (HGT) is a process whereby genetic material contained in small packets of DNA can be transferred between individual bacteria of the same species or even between different species. There are at least three possible mechanisms of HGT, equivalent to the three processes of genetic exchange in bacteria. These are transduction, transformation or conjugation.

Conjugation :occurs when there is direct cell-cell contact between two bacteria (which need not be closely related) and transfer of small pieces of DNA called plasmids takes place. This is thought to be the main mechanism of HGT.

Transformation :is a process where parts of DNA are taken up by the bacteria from the external environment. This DNA is normally present in the external environment due to the death and lysis of another bacterium.

Transduction:occurs when bacteria-specific viruses (bacteriophages) transfer DNA between two closely related bacteria.

Recommendation for use of antibiotics :

There are several advices that should be considered in order to reduce the resistance such as:-

١. Should be use the right antibiotic in an infectious situation as determined by antibiotic sensitivity testing.

٢.The patient should not ignoring the doctor's admonitions to take all of the antibiotics that he get, even if start to feel better, If patient stop taking antibiotics too early, the immune system may not be capable of killing off the stragglers, and any resistant bacteria left unscathed will be able to proliferate and spread to other people.

٣. patient should be give combination of antibiotics , when necessary , to minimize the development of resistance to a single antibiotic (as in case of T.B)and some

times given another antibiotic or combination of antibiotics if the first is not working but should be under the doctor see.

٤. Insisting on getting antibiotics to treat a cold or the flu. Antibiotics are completely ineffective against viruses. Worse yet, antibiotics can't discriminate between bacteria that are good for us and bacteria that cause disease. For example, our intestines are lined with bacteria that break down foods that we can't digest; take antibiotics lead to kill off some of these beneficial bugs. Using antibiotics indiscriminately can blow away most of the bacteria normally in your body.

Routes of administration

Oral antibiotics are simply ingested, this route is chosen for mild infections

While parenteral (intravenous (I.V.) and intramuscular(I.M.)) administration is used for treatment of patients with serious infections and it is used for drugs that are poorly absorbed from the gastrointestinal tract.

Cephalothin is the drug that administrated I.V only while ampicillin esters, Nalidixic acid, and Sulphonomide are taken orally only. Antibiotics may also sometimes be administered topically, as with eye drops or ointments.

I.M rout may be used, ex., Procain penicillin and benzathin penicillin G is only administrated by IM.