Antibiotics
Lec 1

Antibiotics

Introduction

Most microbiologists 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 semi-synthetic 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 antibacterial 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 Arsphenamine was active against syphilis. Arsphenamine was made available in 1910 under trade name Salvarsan. As it was an arsenic-based compound, it was 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) 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 *Staphylococcus 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 the discovery of the first naturally derived antibiotic, gramicidin from *B. brevis*. It was one of the first commercially manufactured antibiotics used 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 1940s. 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, include Neomycin, Actinomycin (Nobel Prize 1952).

Characteristics of Antibiotics

Antibiotics 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).

$$\text{Chemotherapeutic Index} = \frac{\text{Toxic Concentration}}{\text{Effective Concentration}}$$

Antibiotics may have acidal (killing) effect or static (inhibitory) effect on a range of microbes. The range of bacteria or other microorganisms that are affected by a certain antibiotic is expressed as its spectrum of action. Antibiotics are effective against prokaryotes 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 a 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:

1. It should have a wide spectrum of activity with the ability to destroy or inhibit many different species of pathogenic organisms.
2. It should be nontoxic to the host and without undesirable side effects (selective toxicity with minimal side effects to host).
3. Bactericidal rather than bacteriostatic.
4. It should be non-allergenic to the host.
5. It should not eliminate the normal flora of the host.
6. It should be able to reach any part of the human body where the infection is occurring.
7. It should be inexpensive and easy to produce.
8. It should be chemically-stable (have a long shelf-life).
9. 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 be used individually.
- Antagonism: Certain drugs may decrease the effectiveness of others, or prove toxic when taken in combination.
- Monotherapy: Taking a single agent to treat an infection.
- Combination therapy or poly-therapy: Taking more than one drug to treat an infection. Conditions treated with combination therapy include tuberculosis, leprosy, malaria, and cancer. One major benefit of combination therapies is that they reduce the development of drug resistance since a pathogen or tumor is less likely to have resistance to multiple drugs simultaneously.

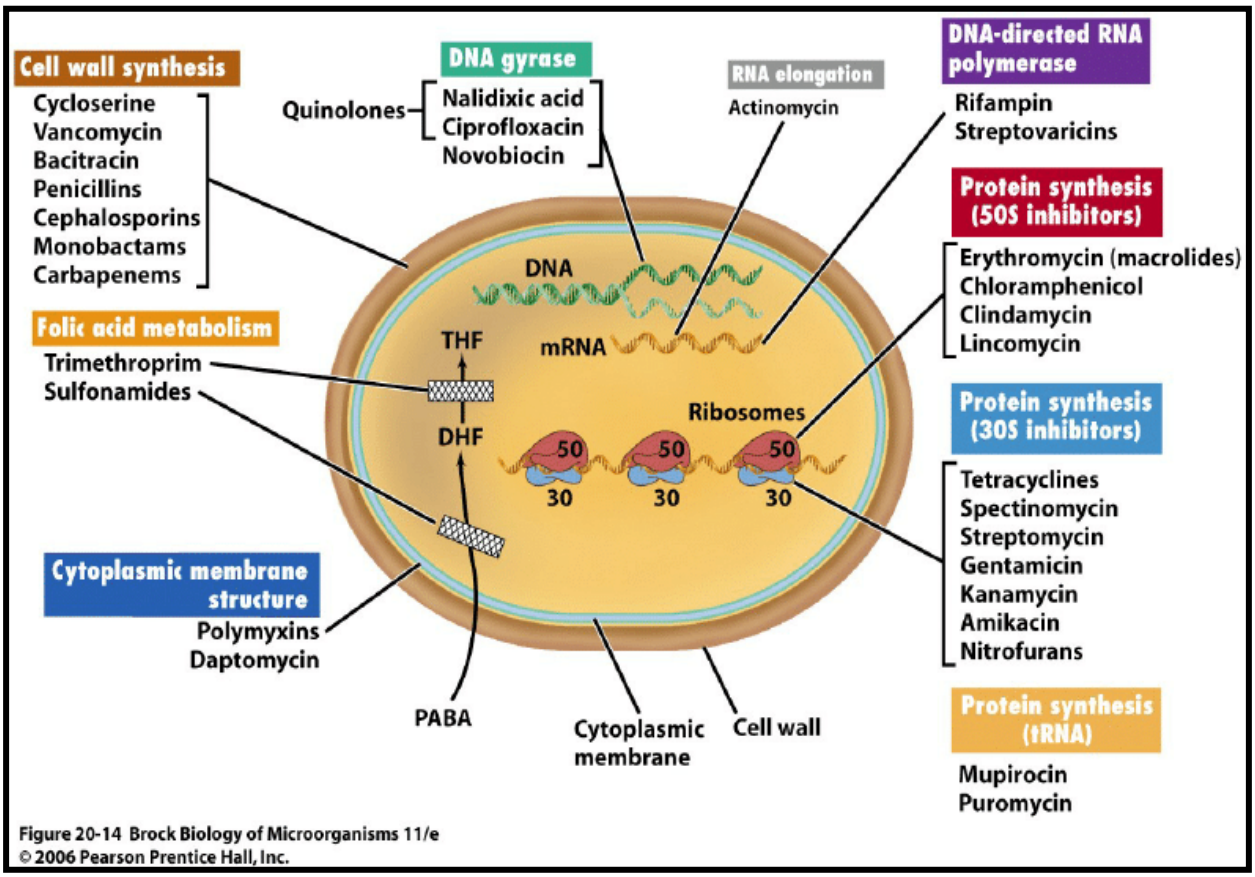
Antibiotic classes

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:

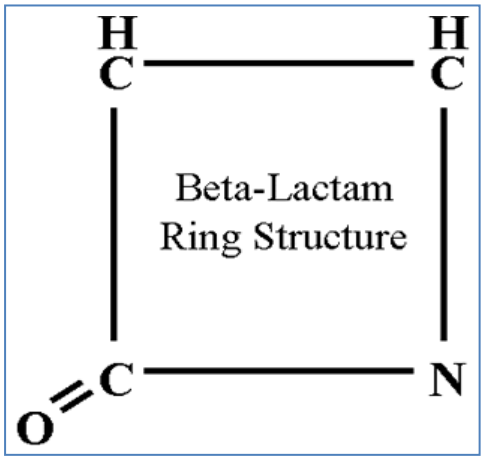
- β-Lactams (Penicillins & Cephalosporins)
- Macrolides
- Quinolones
- Tetracyclines
- Aminoglycosides
- Glycopeptides
- Lincomycin

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



Beta-Lactam Antibiotics

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



<u>β-lactam antibiotics are characterized by three fundamental structural requirements</u>:

1- the beta-lactam structure

2- a free carboxyl acid group

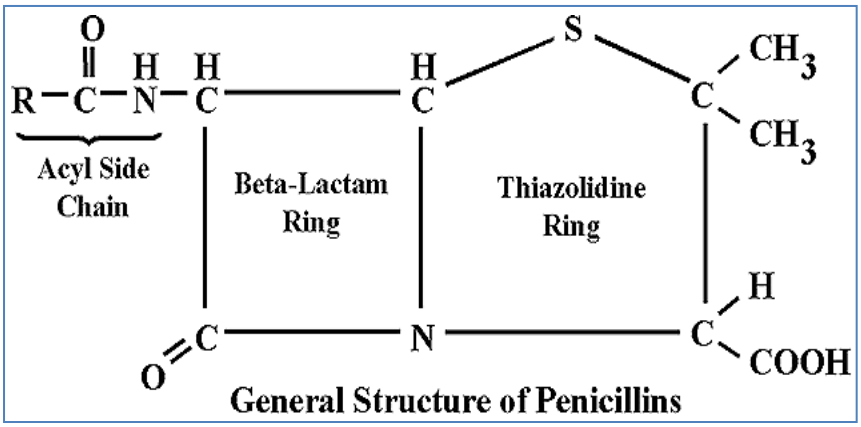
3- one or more substituted amino acid side chains

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

Different β-lactam 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 β-lactamases.

The Penicillin

The penicillin all share <u>a β-lactam ring attached to a thiazolidine ring</u>.

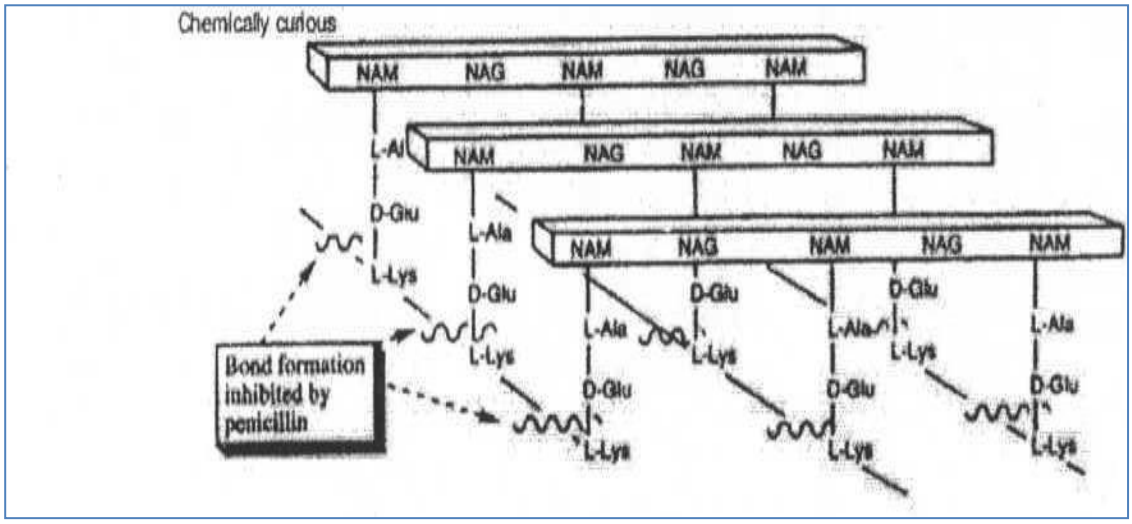


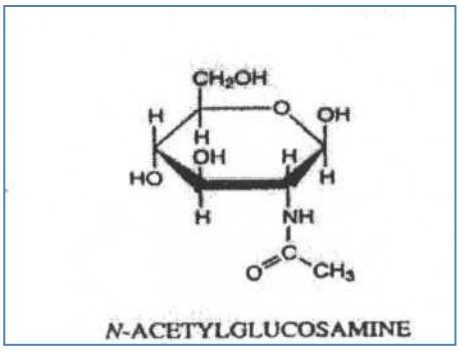
General Structure of Penicillins

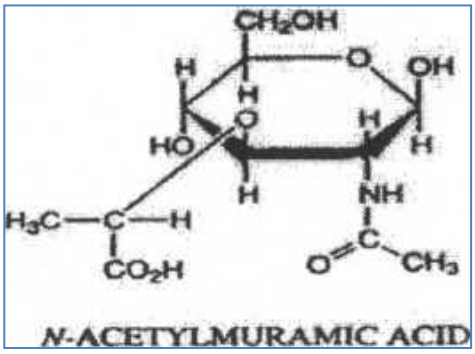
The ring is very strained and the bond between the carbonyl and the nitrogen in the β-lactam ring is very labile (site of cleavage by bacterial penicillinase or by acid) and responsible for the molecule reactivity. The penicillin nucleus (6- amino-penicillanic acid) itself is the chief structural requirement for biological activity; metabolic transformation or chemical alteration of this portion of the molecule causes loss of all significant antibacterial activity. The R-group of the penicillin nucleus can be changed to give the molecule different antibacterial properties, change its pharmacokinetic properties, ability to get through porins of gram negatives, stability to β-lactamases, …etc.

Mode of action

The targets of the penicillin are enzymes (transpeptidase) which called penicillin-binding proteins (PBPs), the transpeptidase is involved in the synthesis of the cell wall. Penicillin attacks bacterial cells by inactivating this enzyme which is essential for bacterial growth (peptidoglycan transpeptidase catalyzes 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 lysis 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.

Classification:

The penicillin's can be classified according to their antibacterial activity:

Natural penicillin, Anti-staphylococcal penicillin, Amino-penicillins, Extended-spectrum penicillin : carboxy-penicillin and ureido-penicillin

1- Natural penicillin (Narrow spectrum - penicillinase (lactamase) sensitive)

Natural penicillin, including penicillin G and penicillin V, is produced by fermentation of *Penicillium chrysogenum.* They are active against non β-lactamase-producing gram-positive cocci (*Pneumococci, Staphylococci, and Streptococci),* few gram-negative cocci (*meningococci* and *gonococci),* gram-positive bacilli *(Bacillus anthracis* and *Corynebacterium diphtheriae),* anaerobes (*Clostridium perfringens, C. tetani),* and spirochetes (*Treponema pallidum* 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 β-lactamases.

a- Penicillin G (Benzyl-penicillin) is the prototype of the class and the most potent of all penicillin's against susceptible gram-positive bacteria. It is sensitive to stomach acids and requires intravenous or intramuscular administration. Penicillin G (intravenous use) is short acting duration, 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, duration of antimicrobial activity 12 hrs., used for 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 hydrolyzed 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 like Penicillin G and it is less active against gram (-) microbes, especially *Neisseria* and certain anaerobes, dose 4x a day.

Antibiotics

Lec 2

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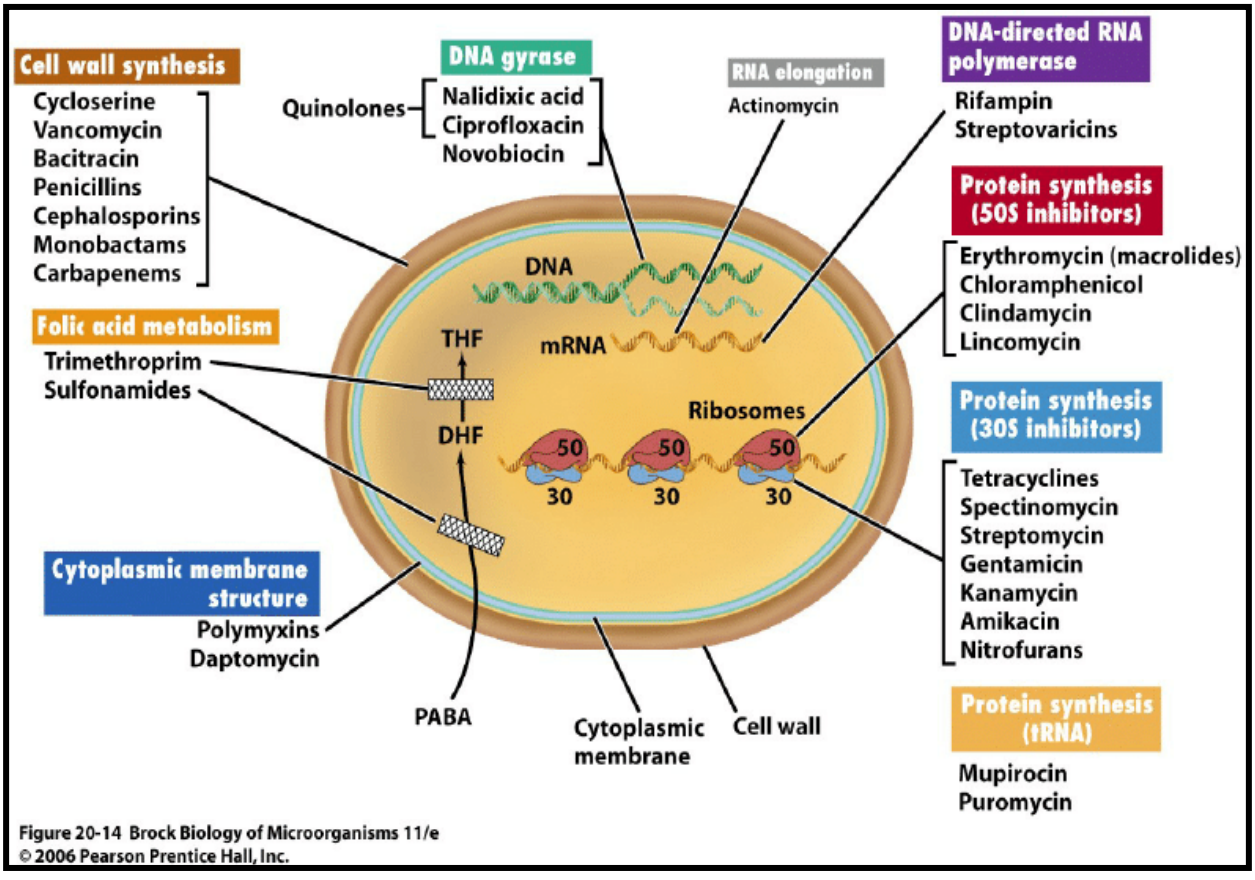

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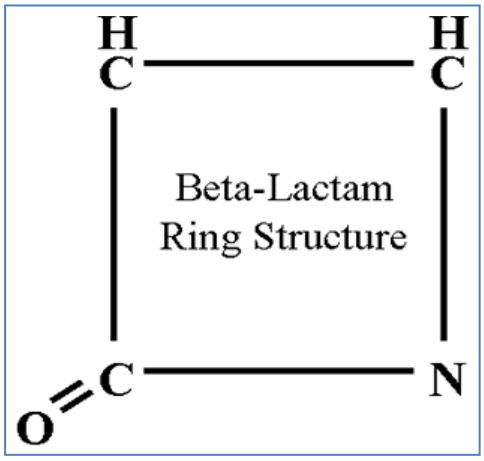

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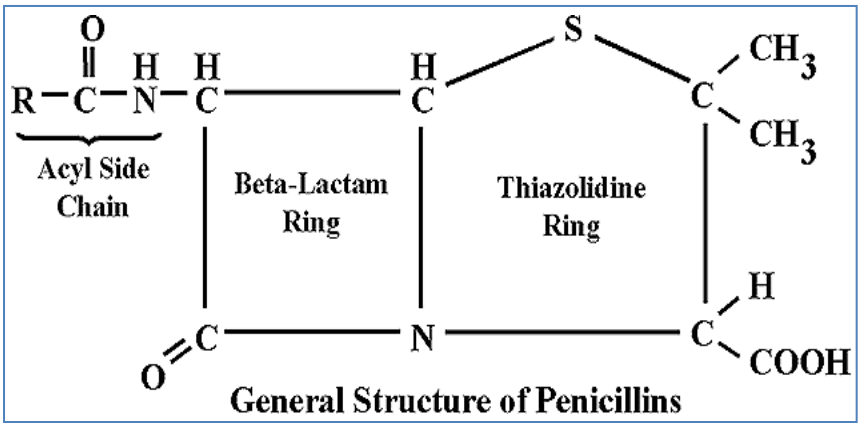

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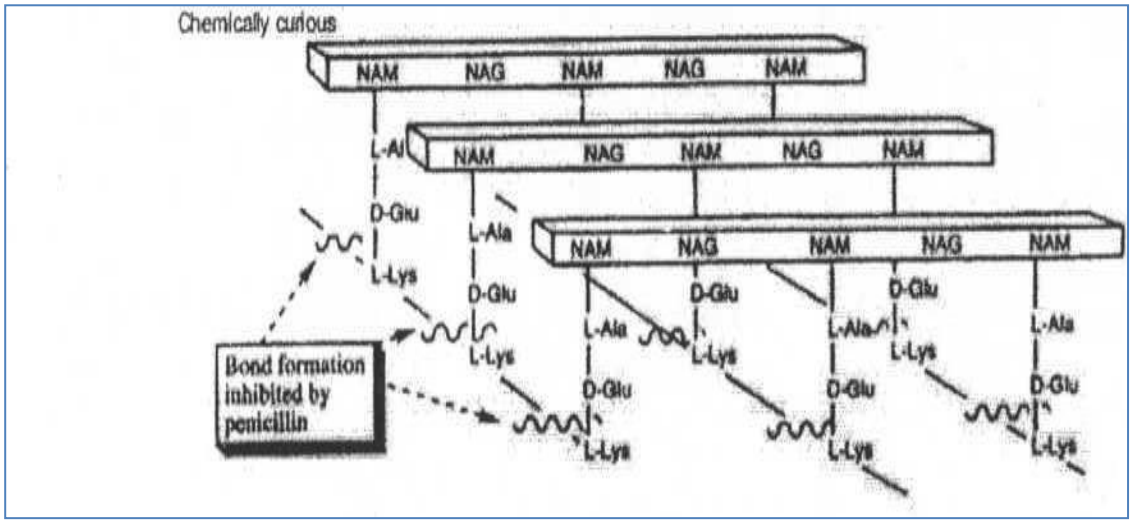

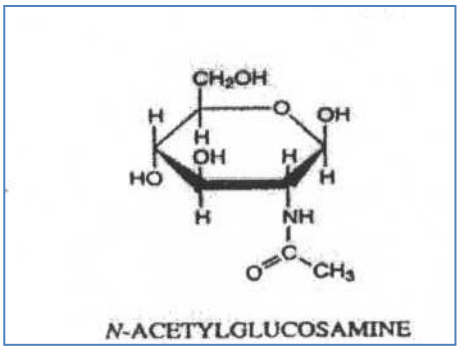

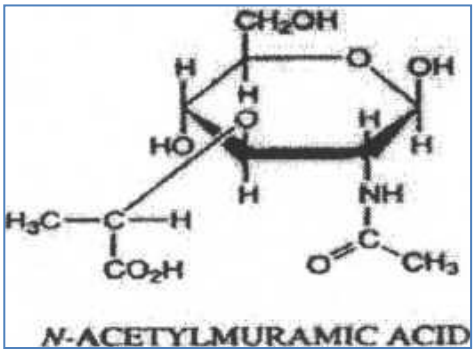

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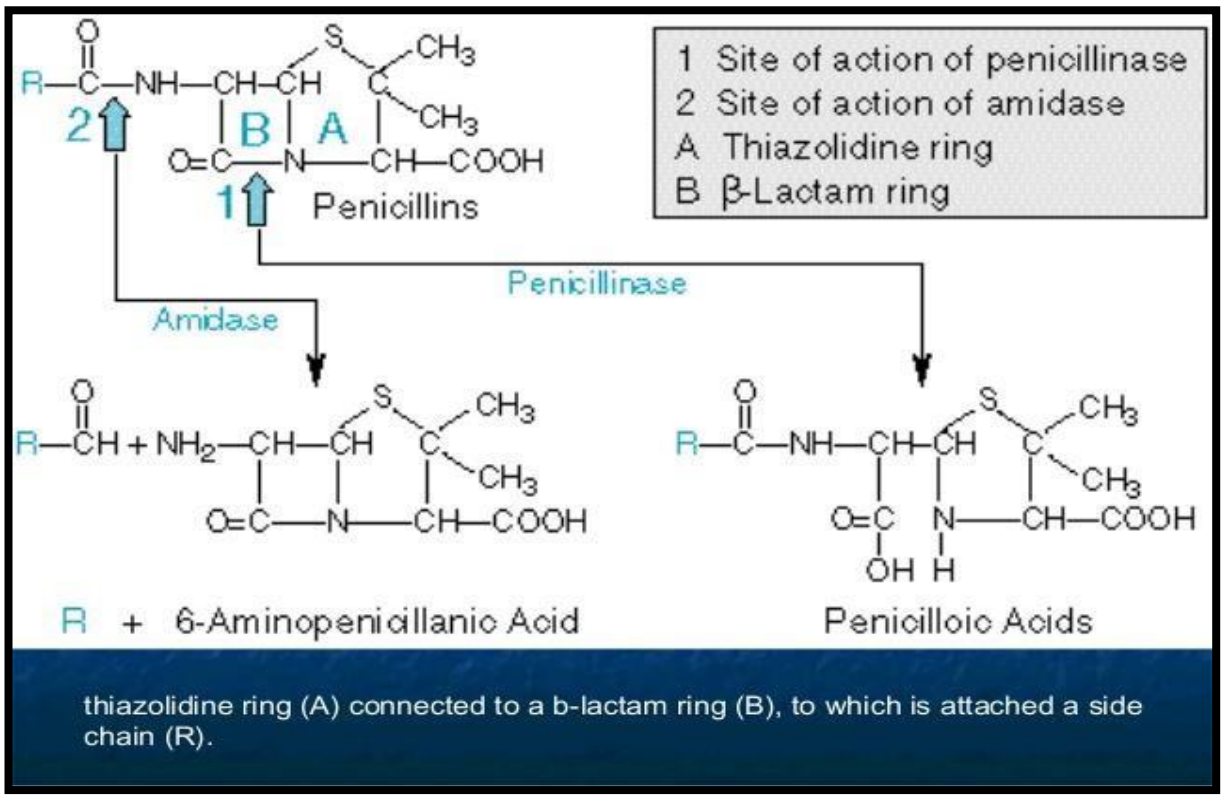
Antibiotics

Lec 3

Semi-synthetic Penicillins

Semisynthetic penicillins first appeared in 1959. A mold produces the main part of the molecule (6-amino penicillanic 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 the 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 1950s, staphylococcal infections in hospitals were resistant to penicillin due to the production of β-lactamase.

Anti-Staphylococcal Penicillins are semi-synthetic and have big bulky side chains that provide a hindrance to protect the β-lactam from cleavage by the β-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 penicillin developed through rational drug modification. Since then all bacteria which are resistant to methicillin are designated as methicillin-resistant (i.e. **MRSA - Methicillin-Resistant *S.aureus***).

3- Broad spectrum - penicillinase (lactamase) sensitive (Amino-penicillins) Ampicillin, amoxicillin, bacampicillin, Pivampicillin, Talampicillin.

The amino-penicillins have a wider range of activity than natural or anti-staphylococcal penicillins. However, they lack the bulky side groups and are susceptible to inactivation by β-lactamase. Amino-penicillins have additional hydrophilic groups, allowing the drug to penetrate into Gram-negative bacteria via the porins.

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

Spectrum: Amino-penicillins are more active against ***enterococci*** and ***Listeria monocytogenes*** compared to penicillin G.

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

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

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

In general, the anti-pseudomonal 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 carboxy-penicillins is their activity against ***Pseudomonas aeruginosa*** and ***Proteus***

Ureido-penicillins 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 anti-pseudomonas 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 amino-penicillins are more potent against these organisms.

Adverse effects

The penicillins have minimal toxicity and the most serious side effect of penicillins is an allergy.

Penicillin Hypersensitivity

Penicillins are the most common cause of drug allergy. Allergic reactions occur in 0.7% - 8.0% of treatments, 10% of allergic reactions may be fatal. Manifestations of allergy to penicillins include rash, fever, bronchospasm, serum sickness, exfoliative dermatitis.

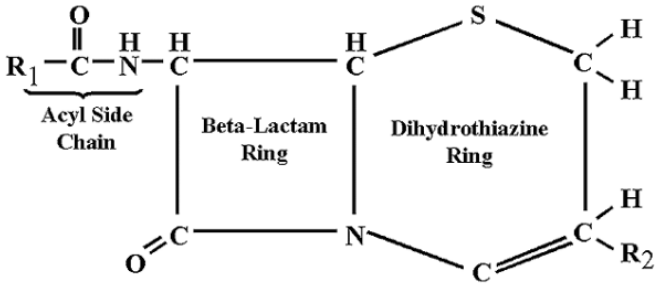
- Common side effects: Many persons who take penicillins experience diarrhea, nausea, and vomiting.

- Hepatotoxicity 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

are structurally and pharmacologically related to the penicillins. Cephalosporins are β-lactam compounds in which the β-lactam ring is fused to a 6-membered dihydrothiazine ring, thus forming the cephem nucleus. **Side chain modifications to the cephem nucleus confer 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 low toxicity and a somewhat broader spectrum than natural penicillins. They are often used as penicillin substitutes against gram-negative bacteria β-lactamases and they tend to be resistant to β-lactamases from *S. aureus.* This 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 grouped into "**generations**" based on their spectrum of antimicrobial activity. **Major differences between generations**: increased activity against bacteria and increased resistance to class C β-lactamases "cephalosporins". The first cephalosporins were designated the 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 a decrease of dosing frequency.

Classification

1- First Generation

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 methicillin-resistant *Staphylococcus)*. They are more active against Gram-negative organisms *(E. coli, Klebsiella pneumoniae,* and the **indole negative** *Proteus mirabilis)* than natural penicillins. They are effective against some anaerobic cocci *(Peptococcus* and *Peptostreptococcus,* 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, upper respiratory infections, and otitis media.

2- 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 β-lactamase. They are useful agents for treating upper and lower respiratory tract infections, sinusitis, and otitis media. These agents are also active against ***E coil, 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 influenzae*
* **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.

3- Third Generation

Third generation **cephalosporins** have a broad spectrum of activity and

further increased activity against gram-negative organisms.

The parenteral third-generation cephalosporins (ceftriaxone and cefotaxime) have excellent activity against most strains of ***Streptococcus pneumoniae***

- **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.

3- 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 β-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*.

Adverse effects

- **Hypersensitivity** reactions are very similar to those that occur with penicillins.
- **Nephrotoxicity** has been reported, (cefamandole, moxalactam).
- **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, the resistant organisms can proliferate and may induce **superinfection.**
- **Hypoprothrombinemia**, **Thrombocytopenia**, **Platelet dysfunction**.

Administration of vitamin K(10mg) twice a week can prevent this case.

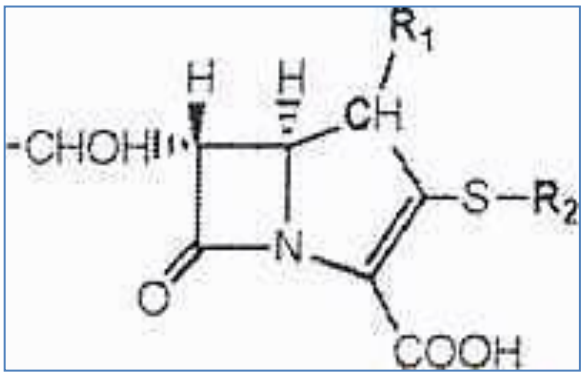
Antibiotics

Lec 3

Lec 3

Other β-lactams

Carbapenems: are new classes of antibiotics which are structurally similar to the penicillin. These drugs are derived from *Streptomyces* species and developed to deal with β-lactamase producing Gram-negative organisms, which were resistant to a broad spectrum and extended spectrum penicillin.



carbapenems

* The semi-synthetic Carbapenems are **imipenem, meropenem, ertapenem** which act in the same way as the other β-lactams. Wide spectrum but may be inactivated by class β-lactamase (carbapenems).

- **Imipenem:**

* Imipenem, like other β-lactams, binds to penicillin-binding proteins, it is **bactericidal**. Imipenem differs from the penicillin 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 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 dihydropeptidase.

***Side effects:** Individuals who are allergic to the penicillin may demonstrate cross-reactivity with imipenem.

Imipenem may produce nausea and vomiting.

- **Meropenem**

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

2- Monobactam (Aztreonam):

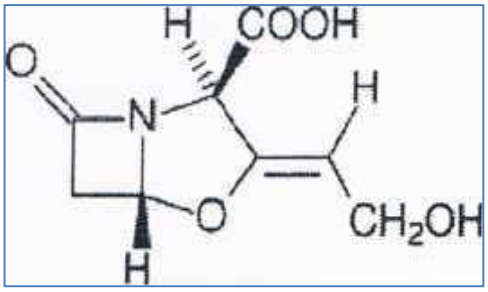
***Aztreonam:** This drug is a synthetic monocyclic β-lactam (a monobactam), originally isolated from the bacterium *Chromobacterium violaceum*. It's given IV, IM. Aztreonam interacts with penicillin binding proteins and induces the formation of long filamentous bacteria; **monobactams** are useful for 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 β-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 β- lactamase produced by gram-negative organisms.

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

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



The structure of clavulanic acid.

Beta-Lactamase

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 beta-lactamase, showing specificity for penicillin.
*Cephalosporinases that can also hydrolyze cephalosporins.
*Broad-spectrum {beta}-lactamases, meaning that they are capable of inactivating penicillin and cephalosporins at the same rate.
*Extended spectrum of activity, represents the ESBLs, which are capable of inactivating third-generation cephalosporins (cefotaxime, cefpodoxime) as well as monobactams (aztreonam)
*Carbenicillinase, these enzymes inactivate carbenicillin more than benzylpenicillin, with some effect on cloxacillin.
*Carbapenemases can hydrolyze 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 penicillin from inactivating by these enzymes.
-they are beta-lactam structures, beta-lactamases inhibitor because they are beta-lactam analog

They are available only in fixed combinations with specific penicillin:

Ampicillin + sulbactam= Unasyn

Amoxicillin + clavulanic acid= Augmentin

Ticarcillin + clavulanate potassium=Timentin

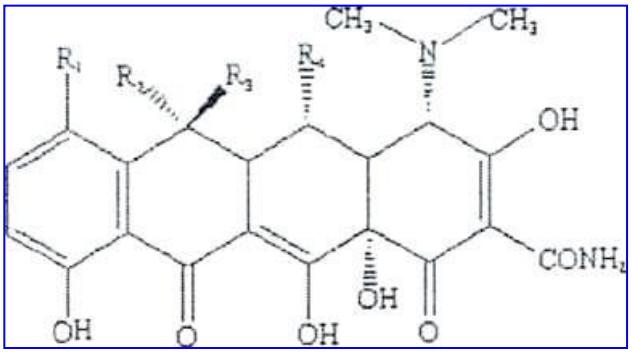
Piperacillin + tazobactam sodium= Tazocin (Zosyn)

Antibiotics

Lec 4

Tetracycline's

The **tetracyclines consist** of eight related antibiotics which are all natural products of *Streptomyces,* although some can now be produced semi-synthetically or synthetically. The basic tetracycline structure consists of four benzene rings with various constituents on each ring. The crystalline bases are faintly yellow, odorless and slightly bitter.



The tetracycline core structure

The tetracyclines are broad-spectrum antibiotics with a wide range of activity against both Gram (+) and Gram (-) bacteria. *Pseudomonas aeruginosa* is less sensitive. The tetracyclines are **bacteriostatic** compounds. They inhibit protein synthesis (act on 3OS ribosomal subunit).

The tetracyclines have 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 commonly used to treat acne today.

Chlorotetracycline, the first tetracyclines, was developed in 1948 as a Product of *Streptomyces aureofaciens,* followed by oxytetracycline and tetracyclines in 1950, 1952 respectively.

Despite the success of the early tetracyclines, analogs were developed to improve water solubility either to allow parenteral administration or to enhance oral absorption.

Resistance:

Although tetracyclines antibiotics have some roles in human and veterinary medicine, the widespread emergence of microbial resistance due to efflux and ribosomal protection mechanisms has 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.

The tetracyclines may be divided according to source into:

- **Naturally occurring:** tetracycline, chlorotetracycline, oxytetracycline.

- **Semi-synthetic:** doxycycline, lymecycline, meclocycline, methacycline.

The tetracyclines may be divided into three groups based on their pharmacokinetic traits.

These groups are:

- **Short-Acting Tetracyclines** (half-life is 6-8 hrs.):

Include **oxytetracycline** and **tetracycline,**. Frequent dosing is needed because of the very short half-life of these agents. Tetracycline has a broad spectrum of activity with coverage of much aerobic gram (-) bacilli, atypical bacteria *(Chlamydia* and *Mycoplasma*), and spirochetes. Also used against *Treponema pallidum*, Rickettsial infections, typhus, trachoma, non-gonococcal urethritis, and acne.

- **Intermediate-Acting Tetracyclines (half-life ~ 12 hrs):**

The only intermediate-acting agent available is **meclocycline** and its no longer used as an antibiotic.

- **Long-Acting Tetracyclines (half-life 16 hrs. or more):**

Allowing being used one or twice daily only, **doxycycline** and **minocycline** are the most recently developed drugs. The main difference between these and the short-acting agents is that these may be dosed less frequently.

Doxycyclines 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 Tyme disease and Rocky fountain

spotted fever.

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.

Glycylcycline antibiotics long-acting tetracycline, inhibit bacterial reproduction by blocking bacterial protein synthesis. They have a broad spectrum of activity against gram (-) and gram (+) bacteria but are more potent against bacteria that is resistance to tetracyclines. Glycylcycline antibiotics are active against resistant organisms such as methicillin-resistant staphylococci, penicillin-resistant *Streptococcus pneumoniae* and vancomycin resistant enterococci. The drug is licensed 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, liver failure, kidney failure.

-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. Although bone and tooth defects are associated with the total dose of tetracycline given and occur more often after repeated courses, it must avoid giving to pregnant women and children under the age of 8.

- Allergic reactions and skin toxicity. Because skin photosensitivity, so exposure to the Sun or intense light is not recommended as it causes **"phototoxicity"** darkening of & sunburn when patient exposed to sunlight.

- It can be inactivated by Ca++ 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 the patient with severe liver disease.

Aminoglycosides Lec.5

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.

-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.

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.

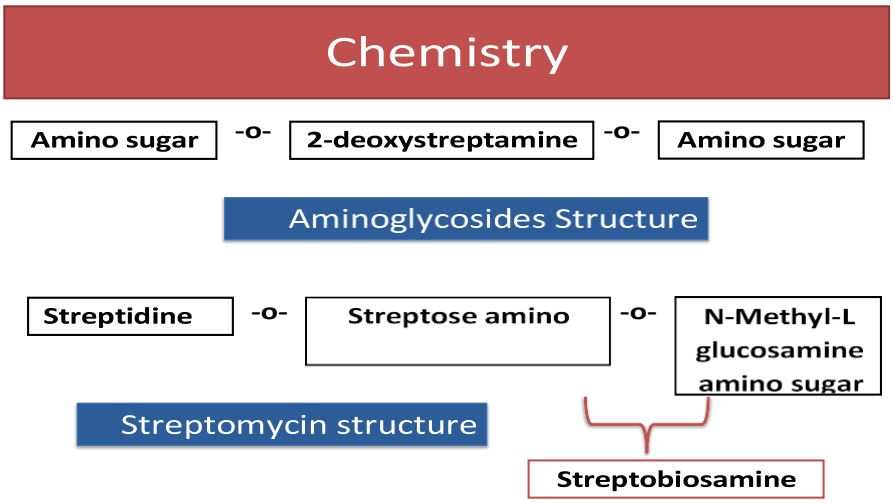
Routes of administration

Since they are not absorbed from the gut (broken down easily in the stomach), they are administered intravenously and intramuscularly. Some are used in topical preparations for wounds

<u>Structure</u> 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.

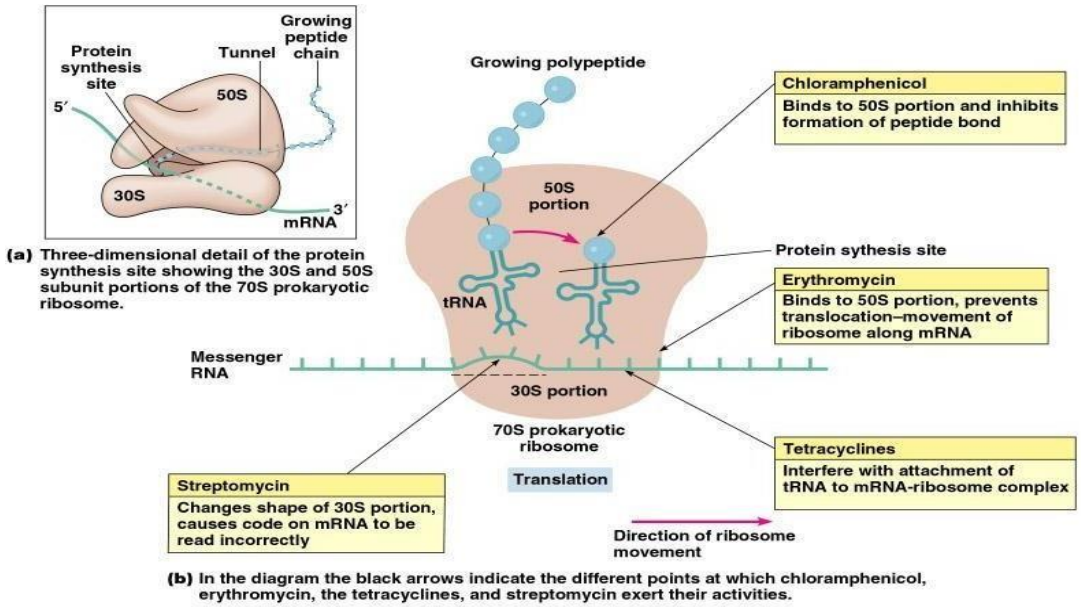


Mechanism of Action

The aminoglycosides act directly on the bacterial ribosome to inhibit the initiation of protein synthesis. 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).

They can also disrupt the integrity of the bacterial cell membrane



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.

Streptomycin

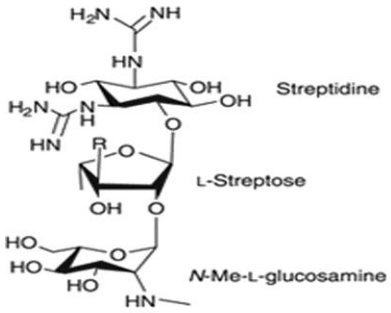
Streptomycin was the first aminoglycoside—it was discovered in the 1940s as a product of *Streptomyces griseus*. It was studied in great detail and became the prototype of this class of drugs.

After intramuscular injection, streptomycin is rapidly absorbed and widely distributed in tissues except the central nervous system.

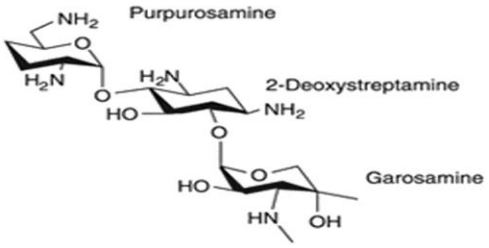
Only 5% of the extracellular concentration of streptomycin reaches the interior of the cell.

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

Gentamicin
gentamicin is bactericidal for many gram- positive and gram-negative bacteria, including many strains of proteus, serratia, and pseudomonas.

Tobramycin
This aminoglycoside closely resembles gentamicin, and there is some cross-resistance between them.

Sisomicin
Identical to gentamicin , more potent on pseudomonas and β-hemolytic streptococci

Netilmicin
Semisynthetic derivative of sisomicin , relatively resistant to aminoglycoside inactivating enzymes .

Neomycin
wide spectrum active against Gm-ve bacilli and some gm+ve cocci
limited to topical use **.**

Kanamycin
is a close relative of neomycin,

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.

- **Advantages and disadvantiges of aminoglycosides**

Advantages of aminoglycosides

Rapid bactericidal action

Relatively low cost

Chemical stability

Broad spectrum activity

No allergic reaction

Synergistic action with other antibiotics

Post antibiotic effect

Dis advantages of aminoglycosides

Inactivity against anaerobes

Toxicities: ototoxicity, nephro toxicity

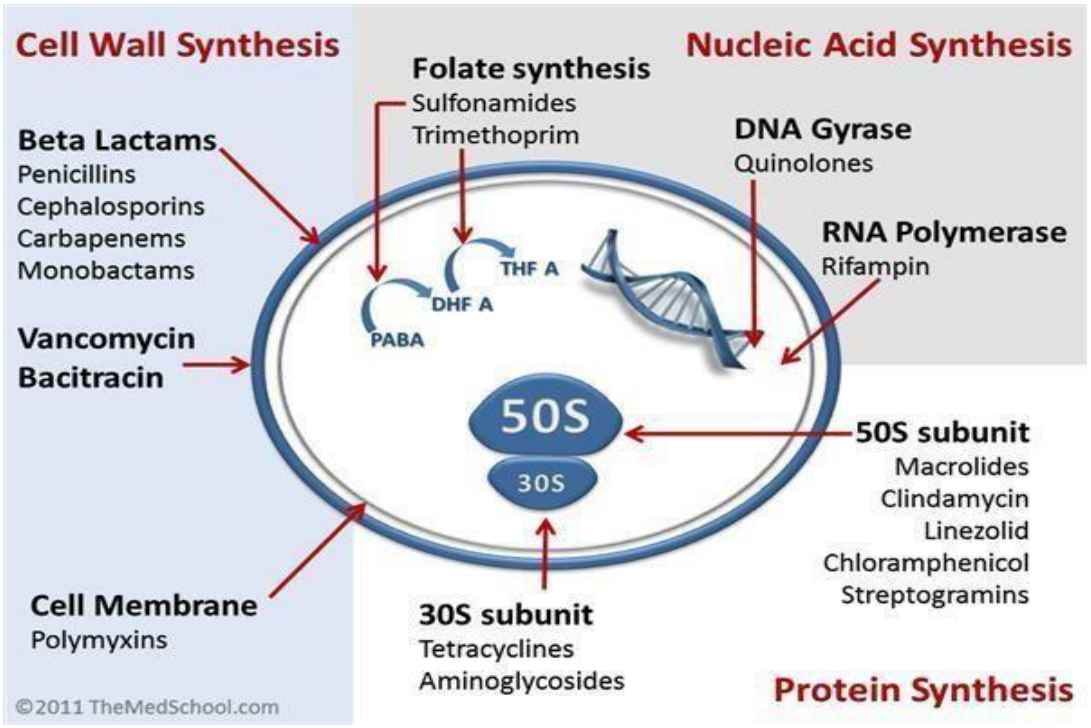
Lack of oral absorption

Lec6: **Antibiotics**

Antibiotics and their mechanisms of action:

Different **mechanisms of action** include:

1) Inhibition of cell wall synthesis
2) Inhibition of protein synthesis
3)Inhibition of nucleic acid synthesis
4) Inhibition of folate metabolism



Antibiotics and their mechanisms of action

Inhibition of bacterial protein synthesis

Macrolides

Macrolide were first discovered in the

1950 from the *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

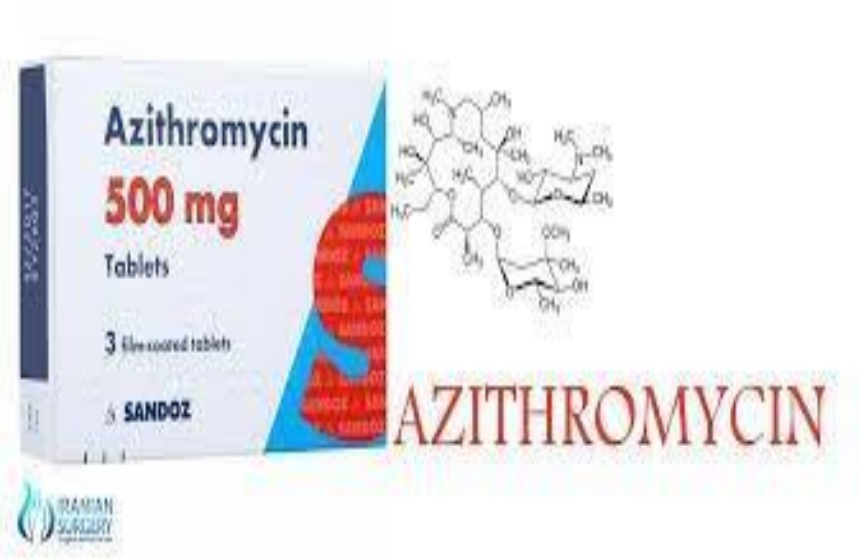
Macrolides act as antibiotics by binding to bacterial 50S ribosomal subunit and interfering with protein synthesis, they have growth- inhibiting (bacteriostatic) effects on bacteria (broad-spectrum activity).

- 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, including *Chlamydia* ,*Mycoplasma* and *Legionella*.

*For urinary tract infections including bronchitis, pneumonia.

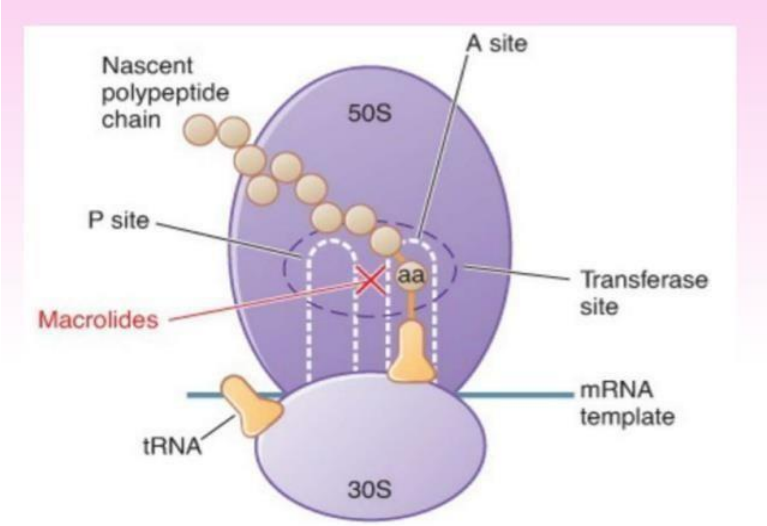
*For skin and soft tissue infections.

*For urinary tract infections.

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

.**Mechanism 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)

-

Lec 7:

Lincosamides:

*Lincosamides constitute a relatively small group of antibiotics with a chemical structure consisting of amino acid and sugar moieties.

***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.

*Clindamycin 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.

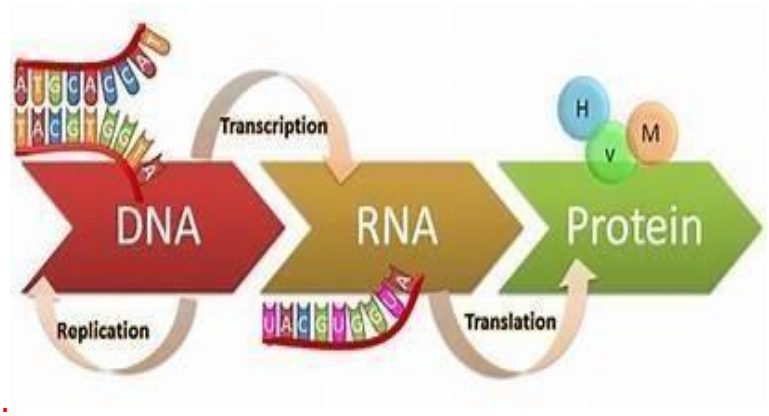
* Has good activity against those anaerobic bacteria that cause bacterial vaginosis, including *Bacteroides fragilis*.

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.

Inhibition of Bacterial Nucleic Acid Synthesis



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),

The fluoroquinolones, second-generation quinolones that include **levofloxacin, norfloxacin**, and ciprofloxacin, are active against both Gram-negative and Gram-positive bacteria.

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 , moxifloxacin, Nalidixic acid.

Therapeutic Uses of Quinolones

1- **Gnetourinary infections:**

2- **Prostatitis**

3- **Respirtory diseases**

4- **Sexually transmited diseases**

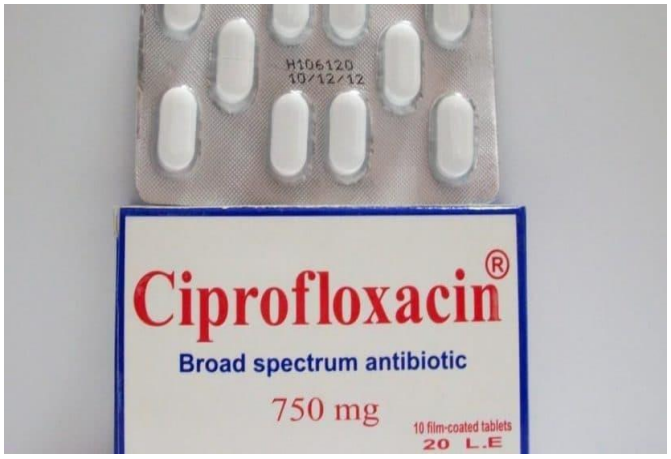
5- **Gastroenteritis:**

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

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.

*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.

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.

Adverse effects

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

Lec 8

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,

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,.

Examples of polyene mycotics

Amphotericin B

Nystatin

Flucytosine:

The acquisition and spread of antibiotic resistance in bacteria:

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.

Vertical gene transfer

*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 .

Horizontal gene transfer

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.

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 Nalidixic acid, are taken orally only. Antibiotics may also sometimes be administered topically, as with eye drops or ointments.