College of Dentist Medicine 3rd year – pharmacology lecture.

Cell Wall Inhibitors

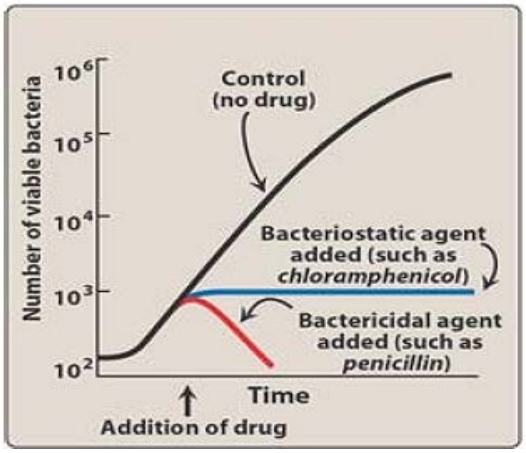
- Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall-a structure that mammalian cells do not possess.
- The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links.
- To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms; they have little or no effect on bacteria that are not growing and dividing.

Penicillins

The penicillins are among the most widely effective antibiotics and also the least toxic drugs known, but increased resistance has limited their use.

Mechanism of action

- The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane.
- Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins.
- These drugs are thus bactericidal.
- Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall.
- They are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi, and viruses.



Penicillin-binding proteins: Penicillins inactivate numerous proteins on the bacterial cell membrane. These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium.

Antibacterial spectrum

1- **Natural penicillins**:
These penicillins, are obtained from fermentations of the mold

Penicillium chrysogenum.
Other penicillins, such as **ampicillin**, are called semisynthetic.

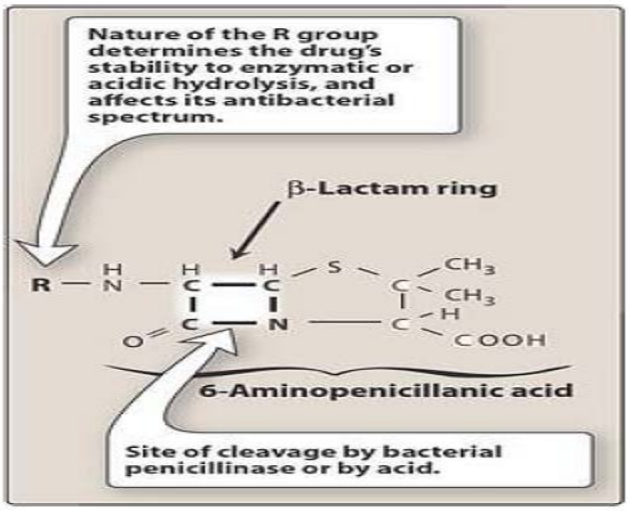
- **Penicillin G** (benzylpenicillin) is the cornerstone of therapy for infections caused by a number of gram-positive and gram-negative cocci, gram-positive bacilli, and spirochetes.
- Penicillin G is susceptible to inactivation by β-lactamases (penicillinases).

- **Penicillin V** has a spectrum similar to that of penicillin G, but it is not used for treatment of bacteremia because of its higher minimum bactericidal concentration (the minimum amount of the drug needed to eliminate the infection.
- Penicillin V is more acid-stable than penicillin G. It is often employed orally in the treatment of infections, where it is effective against some anaerobic organisms.

2-Antistaphylococcal penicillins: Methicillin ,nafcillin,oxacillin, and dicloxacillin are penicillinase-resistant penicillins.

Extended-spectrum penicillins: Ampicillin and amoxicillin have an antibacterial spectrum similar to that of penicillin G but are more effective against **gram-negative bacilli.** They are therefore referred to as extended-spectrum penicillins.

- Ampicillin is the drug of choice for the gram-positive bacillus Listeria monocytogenes. These agents are also widely used in the treatment of respiratory infections,
- **amoxicillin is employed prophylactically by dentists for patients with abnormal heart valves who are to undergo extensive oral surgery**.
- Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated penicillinase.
- [Note: ***Escherichia coli and Haemophilus influenzae*** are frequently resistant.]
- Formulation with a β-lactamase inhibitor, such as clavulanic acid or sulbactam, protects amoxicillin or ampicillin, respectively, from enzymatic hydrolysis and extends their antimicrobial spectrum.



3-Antipseudomonal penicillins:

- Carbenicillin,ticarcillin, and piperacillin are called antipseudomonalpenicillins because of their activity against P. aeruginosa.
- Piperacillin is the most potent of these antibiotics.
- They are effective against many gram-negative bacilli.
- Formulation of ticarcillin or piperacillin with clavulanic acid or tazobactam, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms.

Penicillins and aminoglycosides:

- The antibacterial effects of all the β-lactam antibiotics are synergistic with the aminoglycosides.
- Because cell wall synthesis inhibitors alter the permeability of bacterial cells, these drugs can facilitate the entry of other antibiotics (such as aminoglycosides) that might not ordinarily gain access to intracellular target sites.
- This can result in enhanced antimicrobial activity.

Resistance

1-Natural resistance to the penicillins occurs in organisms that either lack a peptidoglycan cell wall (for example, mycoplasma).

2- Acquired resistance to the penicillins by plasmid transfer has become a significant clinical problem, because an organism may become resistant to several antibiotics at the sametime .

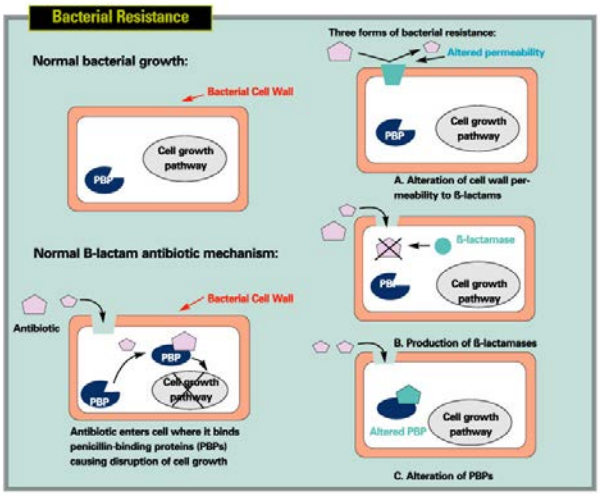
β-Lactamase activity: This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity .

Decreased permeability to the drug:

the

the
the
binding

- The efflux reduce



- Decreased penetration of the antibiotic through outer cell membrane prevents drug from reaching target penicillin protein PBPs.

presence of an pump can also the amount of

intracellular drug.

Pharmacokinetics

- Absorption: Most of the penicillins are incompletely absorbed after oral administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora.
- However, amoxicillin is almost completely absorbed.
- Absorption of all the penicillinase-resistant penicillins is decreased by food in the stomach, because gastric emptying time is lengthened, and the drugs are destroyed in the acidic environment. Therefore, they must be administered 30 to 60 minutes before meals or 2 to 3 hours after meals.

- Distribution: The β-lactam antibiotics distribute well throughout the body. **All the penicillins cross the placental barrier, but none has been shown to be teratogenic.**
- The penicillins are also excreted into breast milk.

Adverse reactions

Penicillins are among the safest drugs, However, the following adverse reactions may occur .

1-Hypersensitivity: This is the most important adverse effect of the penicillins.

2-Diarrhea: This effect, which is caused by a disruption of the normal balance of intestinal microorganisms, is a common problem. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum.

Cephalosporins

The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins. Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms.

Antibacterial spectrum

- Cephalosporins have been classified as **first, second, third, or fourth** generation, based largely on 1- their bacterial susceptibility patterns
  And 2- resistance to β-lactamases .

First generation:

- The first-generation cephalosporins act as penicillin G substitutes.
- They are resistant to the staphylococcal penicillinase and also have activity against Proteus mirabilis, E. coli, and Klebsiella pneumoniae.

Second generation:

- The second-generation cephalosporins display greater activity against three additional gram-negative organisms: H. influenzae, Enterobacteraerogenes, and some Neisseria species, whereas activity against gram-positive organisms is weaker .

Third generation:

- These cephalosporins have assumed an important role in the treatment of infectious disease.
- Although inferior to first-generation cephalosporins in regard to their activity against gram-positive cocci, the third-generation cephalosporins have enhanced activity against gram-negative bacilli.
- **Ceftriaxone or cefotaxime have become agents of choice in the treatment of meningitis**.
- **Ceftazidime has activity against P. aeruginosa.**

Fourth generation:

- Cefepime is classified as a fourth-generation cephalosporin and must be administered parenterally.
- Cefepime has a wide antibacterial spectrum, being active against streptococci and staphylococci .
- Cefepime is also effective against aerobic gram-negative organisms, such as enterobacter, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa.

Pharmacokinetics

Administration: Many of the cephalosporins must be administered IV or IM because of their poor oral absorption.

Distribution: All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, are achieved only with the third-generation cephalosporins. For example, ceftriaxone or cefotaxime are effective in the treatment of neonatal and childhood meningitis caused by H. influenzae.

Cefazolin is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone. **All cephalosporins cross the placenta**.

Adverse effects

Allergic manifestations: Patients who have had an anaphylactic response to penicillins should not receive cephalosporins. The cephalosporins should be avoided or used with caution in individuals who are allergic to penicillins.

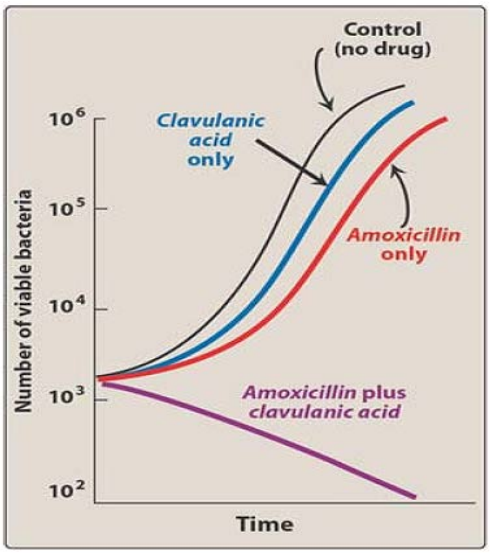
Other β-Lactam Antibiotics

Carbapenems

Are synthetic β-lactam antibiotics that differ in structure from the penicillins.**Imipenem**, **meropenem** and **ertapenem** are the only drugs of this group currently available.

β-Lactamase Inhibitors

- Hydrolysis of the β-lactam ring, either by enzymatic cleavage with a β-lactamase or by acid, destroys the antimicrobial activity of a β-lactam antibiotic.
- β-Lactamase inhibitors, such as clavulanic acid, sulbactam and tazobactam, contain a β-lactam ring but, by themselves, do not have significant antibacterial activity.
- Instead, they bind to and inactivate β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes.
- The β-lactamase inhibitors are therefore formulated in combination with β-lactamase sensitive antibiotics.



1st generation cephalosporines(cefadroxil, cefazolin, cephalexin)

2ndgeneration cephalosporines(cefador, cefprozil, cefuroxime, cefoxitin)

3rd generationcephalosporines (cefdinir, cefixime, cefotaxime, ceftazidime, Ceftriaxone
4th generation cephalosporines (cefepime).

Monobactams
* Aztreonam
- resistant to most β-lactamase
- given parenterally
- unusual spectrum of activity:-
* effective only G-ve aerobic organism.
* no action on G+ve organism or anaerobes .
Clinical uses
- septicemia,complicated UTI,
side effects:- rash ,GI upset, hepatitis.