Mechanism of Action, In Details

- All β-lactam antibiotics, including penicillins, kill susceptible bacteria by specifically inhibiting the transpeptidase that catalyzes the final step in cell wall biosynthesis, the cross-linking of peptidoglycan.

- The cell wall is a rigid outer layer that is not found in animal cells.
  - It completely surrounds the cytoplasmic membrane, maintaining the shape of the cell and preventing cell lysis from high osmotic pressure
  - It is composed of a complex cross-linked polymer, peptidoglycan, consisting of polysaccharides and polypeptides.
  - The polysaccharide contains alternating amino sugars, N-acetylglucosamine and N-acetylmuramic acid
  - A five-amino-acid peptide is linked to the N-acetylmuramic acid sugar. This peptide terminates in D-alanyl-D-alanine.
  - Penicillin-binding proteins (PBP) catalyze the transpeptidase reaction that removes the terminal alanine to form a crosslink with a nearby peptide, which gives cell wall its structural rigidity.
  - β-Lactam antibiotics are structural analogs of the natural D-Ala-D-Ala substrate and they are covalently bound by PBPs at the active site.
Mechanism of Action, so what!!

After a β–lactam antibiotic attaches to the PBP, the transpeptidation reaction is inhibited, peptidoglycan synthesis is blocked, and the cell dies.

The final bactericidal event is the inactivation of an inhibitor of the autolytic enzymes in the cell wall → this leads to lysis of the bacterium.

In addition, because of the cell wall defects, the bacteria swell and burst.

- NB: β-Lactams exert a bactericidal action on growing or multiplying germs.

Mechanism of Action, In motion
Resistance to Penicillins

I. Production of β-lactamases
- This family of enzymes can inactivate penicillins by hydrolyzing the β-lactam ring
- The production of β-lactamases is considered the principal cause of bacterial resistance to b-lactam antibiotics
- Examples of bacteria that produce β-lactamases are *Staphylococcus aureus* and many strains of *H. influenzae*, *Neisseria*, and *Pseudomonas*

II. The occurrence of modified penicillin-binding sites
- Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect its bactericidal activity
- Example: penicillin resistance in *Streptococcus pneumoniae* (pneumococcus) is caused by altered PBPs

III. Decreased permeability to the drug
- Decreased penetration through the outer membrane prevents the drug from reaching the target PBP
- This occurs with G-ve organisms, which have an outer membrane that limits penetration of hydrophilic antibiotics. This is of particular relevance in determining the extraordinary resistance of *Pseudomonas aeruginosa* to most antibiotics

Classification of Penicillins, On the Basis of Antibacterial Spectrum

I. Narrow-spectrum:
1. Natural Penicillins
   - Examples: benzylpenicillin (penicillin G), phenoxymethylpenicillin (penicillin V)
   - Active against:
     - most gram-positive bacteria with the exception of penicillinase-producing S. aureus
     - most *Neisseria* species and some gram-negative anaerobes
   - Not active against: most gram-negative aerobic organisms
   - Penicillin G is the drug of choice for infections due to *Neisseria meningitidis*, *Bacillus anthracis*, *Clostridium perfringens* and *tetani*, *Corynebacterium diphtheriae* and *Treponema pallidum*…..
   - Penicillin V is less active than penicillin G against *Neisseria species*. It is satisfactory substitute for penicillin G against *Streptococcus pneumonia* and *S. pyogenes*. It is the first choice in the treatment of odontogenic infections
   - Adverse effects are generally uncommon. Only in patients with bacterial endocarditic, where the requirement for high doses can co-exist with reduced clearance due to immune complex glomerulonephritis, does a risk of dose related toxicity (convulsions) arise
   - The most important adverse effects are due to hypersensitivity with manifestations ranging from skin eruptions to anaphylactic shock
Classification of Penicillins, On the Basis of Antibacterial Spectrum

I. Narrow-spectrum Penicillins:
   1. Natural Penicillins, contd.
      - Pharmacokinetics:
        - Penicillin G diffuses widely, attaining therapeutic concentrations in most body tissues
        - The t₁/₂ of penicillin G is less than 1 hour and it is eliminated primarily by renal tubular secretion. This secretion can be inhibited by probenecid
        - Because renal dysfunction will compromise the elimination of penicillin, dosages may need to be reduced in patients with renal insufficiency (esp. in severe cases)
        - Procaine penicillin is best suited to the single-dose outpatient treatment of very sensitive organisms (e.g., penicillin-sensitive N. gonorrhea and group A streptococci)
        - Benzathine penicillin is another long-acting preparation given IM. It is used for prophylaxis of rheumatic fever and for treatment of syphilis
        - Penicillin V is a much more resistant to gastric acid than is penicillin G and therefore better absorbed from the GIT. It is the orally-active form of penicillin
        - All oral penicillins are best given on an empty stomach to avoid the absorption delay caused by food

II. Broad Spectrum Penicillins
   - Examples: aminopenicillins such as ampicillin and amoxicillin
   - These drugs retain the antibacterial spectrum of penicillin and have improved activity against gram-negative organisms
   - They are destroyed by β-lactamases
   - Ampicillin and amoxicillin are among the most useful antibiotics for treating children suffering from infections caused by sensitive gram-negative aerobic bacteria, enterococci, and β-lactamase-negative H. influenzae
   - Amoxicillin is the favored drug for the treatment of acute otitis media
   - Concentrations of amoxicillin are usually twice those of ampicillin after an equivalent oral dose. The distribution, t₁/₂, and excretion characteristics of these penicillins are similar to those of penicillin
Classification of Penicillins, On the Basis of Antibacterial Spectrum

3. Anti-Pseudomonal Penicillins

- Examples: ticarcillin, pipracillin, azlocillin, and mezlocillin
- These antibiotics have a broader spectrum of gram-negative activity than do the aminopenicillins, and include activity against most strains of *P. aeruginosa*
- These antibiotics are used in the treatment of urinary tract, lung, and bloodstream infections caused by ampicillin-resistant enteric gram-negative pathogens

- **Beta-lactamase Inhibitors**
  - β-Lactamase inhibitors competitively inhibit β-lactamase enzymes, restoring the original spectrum of activity to enzyme-susceptible antibiotics
  - Some infections are polymicrobial and may involve anaerobes; for these the addition of a β-lactamase inhibitor might be of value
    - These infections include infected animal and human bites, odontogenic infections, chronic sinusitis, and intra-abdominal infections
  - β-lactamase inhibitors in clinical use include clavulanic acid (usually combined with amoxicillin → Augmentin®), sulbactam (usually combined with ampicillin → Unasyn®)

Examples of Penicillins
Cephalosporins, Overview

- Cephalosporins were first obtained from a filamentous fungus “Cephalosporium”
- Cephalosporins are similar to penicillins chemically, in mechanism of action, and in toxicity
- Cephalosporins are affected by the same resistance mechanisms as penicillins. However, they tend to be more resistant than the penicillins to β-lactamases
- Cephalosporins are more stable than penicillins to many bacterial β-lactamases and therefore usually have a broader spectrum of activity
- Methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered resistant to all cephalosporins
- The intrinsic antimicrobial activity of natural cephalosporins is low, but the attachment of various R₁ and R₂ groups (see next slide) has yielded drugs of good therapeutic activity and low toxicity

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Cephalosporins

- Cephalosporins are divided into four generations with original agents being referred to as first-generation cephalosporins, and the most recent agents as fourth-generation cephalosporins
- In general, the spectrum of activity of cephalosporins increases with each generation because of decreasing susceptibility to bacterial β-lactamases

First-Generation Cephalosporins

- They are active against most staphylococci, *pneumococci*, and all *streptococci*, with the important exception of *enterococci*
- Their activity against aerobic G-ve bacteria and against anaerobes is limited
- They act as penicillin G substitutes. They are resistant to β-lactamase
- These antibiotics distribute widely throughout the body, but do not penetrate well into the CSF (not used for meningitis)
- Their $t_{1/2}$ ranges from 30 minutes to 1.5 hours, and they are eliminated unchanged in the urine.
- They should not be administered to patients with a history of immediate-type hypersensitivity reactions to penicillins
Cephalosporins

- **Second-Generation Cephalosporins**
  - They have a broader bacteriologic spectrum than do the first-generation agents.
  - They are more resistant to β-lactamase than the first-generation drugs.
  - For example, cefamandole, cefuroxime, and cefaclor not only are more active against G-negative enteric bacteria but are active against both β-lactamase-negative and -positive strains of *H. influenzae*.
  - Their half-lives are similar to those of the first-generation agents. There are "long-acting" agents currently being marketed (e.g., cefadroxil).
  - Excretion is primarily renal, and they distribute widely. However, they do not attain sufficient concentrations in the CSF to warrant their use in the treatment of bacterial meningitis.

- **Third-Generation Cephalosporins**
  - These agents retain much of the G-positive activity of the first two generations, although their anti-staphylococcal activity is reduced. They are remarkably active against most G-negative enteric isolates.
  - Some third-generation cephalosporins (e.g., ceftaxime and cefoperazone) also are active against most isolates of *P. aeruginosa*.
  - In healthy subjects, their half-lives range from 1 hour (ceftaxime) to between 6 and 8 hours (ceftriaxone).
  - These antibiotics diffuse well into most tissues (e.g., cefotaxime and ceftriaxone).
  - Excretion is primarily renal (exception cefoperazone, which is excreted primarily in the bile).
  - Indications include suspected bacterial meningitis and treatment of hospital-acquired multiple-resistant G-negative aerobic infections and suspected infections in certain compromised hosts.
  - Ceftriaxone is the drug of choice in treating infections caused by *N. gonorrhoeae* in geographic areas with a high incidence of penicillin-resistant isolates.
Cephalosporins

- **Fourth-Generation Cephalosporins**
  - This newest generation of cephalosporins (e.g., cefapime) combines the anti-staphylococcal activity of first-generation agents with the G-ve spectrum (including Pseudomonas) of third-generation cephalosporins
  - Possible indications for use include the therapy of infections suspected or proved to be caused by multiple-resistant pathogens.

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Cephalosporins, Side Effects

- Serious, adverse reactions to the cephalosporins are uncommon. As with most antibiotics, the full spectrum of hypersensitivity reactions may occur, including rashes, fever, eosinophilia, serum sickness, and anaphylaxis
  - The incidence of immediate-type allergic reactions to the cephalosporins is increased among patients known to be allergic to penicillins

- Adverse reactions attributable to irritation at the site of administration are common. These reactions include local pain after i.m. injection, phlebitis after i.v. administration, and minor gastrointestinal complaints after oral administration

- Some of the cephalosporins are associated with dose-related nephrotoxicity, probably due to tubular damage (e.g., cephaloridine), whereas others are associated with an interstitial nephritis (e.g., cephalothin)

- The third-generation drugs may cause transient elevations of liver function test results and blood urea nitrogen concentrations. They also have a profound inhibitory effect on the vitamin K-synthesizing bacterial flora of the GIT. In addition, agents that possess an N-methylthiotetrazole side chain (e.g., cefoperazone) can cause hypoprothrombinemia and bleeding