The β- Lactam Antibiotics

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The β- Lactam Antibiotics

- Penicillins.
- Cephalosporins.
- Carbapenems.
- Monobactams.
How β- Lactams work?

1. β-lactams bind to Penicillin Binding Protein (PBP).
2. PBP will be unable to crosslink peptidoglycan chains, responsible for the integrity of the cell wall.
3. Multiplying bacteria will not be able to synthesize a stable cell wall.
4. The bacteria will be lyzed by osmotic forces and will die.
Bacterium

Inhibition of cell wall synthesis

Cross-linked by transpeptidase

Amino acid chain
Sugar

Cell wall building block
Peptidoglycan Synthesis

“Penicillin binding protein”
The Penicillins

– **Natural Penicillins:**
  • Penicillin G,
  • Penicillin V
  • Procaine Penicillin
  • Benzathine Penicillin

– **Aminopenicillins:**
  • Ampicillin,
  • Amoxicillin

– **Anti-Staph Penicillins:**
  • Oxacillin
  • Dicloxacillin

– **Anti-Pseudomonal Penicillins:**
  • Ticarcillin
  • Piperacillin
Penicillins

- **Penicillin G**
- First natural antibiotic, 1941.
- Used IM, IV. Short acting, rapidly excreted.
- **Probencid**: was used when penicillin was very expensive to increase the half life and serum concentration of penicillin.

- **Uses**:
  - Endocarditis ( *S. viridans* or *Streptococcus bovis*)
  - Pharyngitis ( group A β-hemolytic streptococci)
  - Cat bite cellulitis ( *Pasteurella multocida*)
  - Syphillis ( *Treponema pallidum*)
  - Streptococcal meningitis
Penicillins

• Penicillin G.

• Long-acting forms:
  – Procaine Pen G, combined with procaine (a local anesthetic), painless and longer acting (12-24 hours).
  – Benzathine Pen (4 weeks), suitable for prophylaxis

• Phenoxyethyl penicillin G:
  – Acid-stable, so can be given orally.
  – Uses: Streptococcal infections when oral therapy is preferred, usually in children.
Adverse Reactions of Penicillins

– **Allergic reactions:** skin rash, serum sickness, drug fever, anaphylaxis (1 in 40,000).

– Very common.

– Cross allergenicity with all beta lactams.

– Hemolytic anemia, pancytopenia, neutropenia. Are rare reactions
Aminopenicillins

• Ampicillin (IV, PO), QID: replaced by:
• Amoxicillin (PO), BID

• Broad spectrum activity, same as Penicillin G, plus *H. influenzae*, some *E. coli*, and are integral drugs in *H. pylori* regimens.

• The most useful antibiotics for treating children

• Adverse effects:
  – Non-allergic rashes (9%) – especially when associated with a viral illness (infectious mononucleosis - EBV)
  – Amoxicillin is better tolerated orally and better absorbed (Ampicillin is partially absorbed and can cause diarrhea and can alter the normal intestinal flora and should be taken on empty stomach).
Anti-Staph Penicillins

- Methicillin
- Oxacillin
- Dicloxicillin

- However, there are Methicillin-resistant *Staphylococcus aureus*(MRSA).
Anti-Pseudomonal Penicillins

- **Piperacillin**
- **Ticarcillin**
  - Most active penicillin against *Pseudomonas*.
  - Cover *Pseudomonas*, most *Enterobacteriaceae* (*E. coli, Proteus, Klebsiella, Enterobacter, Serratia, Citrobacter, Salmonella and Shigella*)
  - Often used in combination with an Aminoglycoside or a Quinolone.
**Forms of Resistance to Penicillins**

A. **Production of β-lactamases** (penicillinases) which hydrolyse the lactam ring:

β-lactamase production is particularly important in staphylococci, but they are not made by streptococci.

At least 90% of staphylococcus species in the West now produce β-lactamases.

One strategy to overcome the problem is the use of β-lactamase inhibitors.

B. **Reduction in the permeability of the outer membrane** in Gram-negative bacteria.

C. **Mutations in the penicillin-binding proteins**.
**β-Lactamase Inhibitors**

- These are the drugs which can inhibit β-lactamases, and so usually combined (in a fixed combination) with few β-lactam antibiotics to prevent resistance.
- Structure resembles the β-lactam antibiotic.
- Some have minor antimicrobial activity by themselves.
- They increase the activity, and may be the spectrum of activity of the β-lactam antibiotic.
Types of β- lactamases

• **Penicillinases**, inhibited by clavulanic acid.

• **Penicillinases**, *not* inhibited by clavulanic acid.

• **Cephalosporinases**, not inhibited by clavulanic acid.

• **Metallo-β-lactamases**
β-Lactamase Inhibitors

- **Clavulanic Acid** usually combined with Amoxicillin.
- **Sulbactam** usually combined with Ampicillin.
- **Tazobactam** usually combined with Piperacillin.
The Cephalosporins

• Came one decade after the penicillins.
• Rarely the drugs of first choice for any infection.
• Mainly used for surgical prophylaxis.
• Expensive, especially the newer generations.
• Same toxicity as penicillins.
• Cross allergic with the penicillins.
• Activity and method of administration differ among the generations.
Cephalosporins

- **1st Generation:**
  - Cephalexin
  - Cefazolin

- **2nd Generation:**
  - Cefoxitin
  - Cefuroxime

- **3rd Generation:**
  - Cefotaxime
  - Ceftriaxone

- **4th Generation:**
  - Cefepime

- **5th Generation:**
  - Ceftaroline
Cephalosporins

• **First generation**: streptococci, methicillin-sensitive *S. aureus*, and a few gram-negative bacilli.

• **Second generation**: greater stability against -lactamase inactivation and possess a broader spectrum of activity to include gram-positive cocci, gram-negative organisms, and anaerobes.
Cephalosporins

• **Third generation**, have high potency and lactamase stability and a broader spectrum of action against many common gram-negative bacteria and anaerobes, while retaining good activity against streptococci.

• Third-generation cephalosporins are less active against staphylococci than the earlier generations.

• **Fourth generation** Cefepime has broad spectrum activity, used in the empirical treatment of meningitis.
The Cephalosporins

*Not effective against Enterococcus or Listeria

1\textsuperscript{st} Generation
Gram (+)

2\textsuperscript{nd} Generation
Decreasing Gram (+)
and Increasing Gram (-)

3\textsuperscript{rd} Generation
Gram (-), but also some
Gram (+)

4\textsuperscript{th} Generation
Gram (+) and Gram (-)
Ceftaroline

• Ceftaroline is a broad-spectrum cephalosporin that has bactericidal activity against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and *S. pneumoniae*, as well as many gram-negative bacteria. It lacks activity against *Pseudomonas aeruginosa*.
Ceftaroline

• Ceftaroline is a fifth-generation cephalosporin administered as a prodrug whose active metabolite has bactericidal activity against MRSA and vancomycin-intermediate S. aureus (VISA) as well as some gram-negative pathogens.

• Ceftaroline has in vitro activity against staphylococci with reduced susceptibility to Vancomycin, Daptomycin, or Linezolid.
Ceftaroline

• The FDA has approved Ceftaroline for the treatment of:
  1. Complicated skin and skin tissue infection.
  2. Community acquired pneumonia.

• For treatment of complicated skin and skin structure infection, Ceftaroline has been found to be non-inferior to Vancomycin plus Aztreonam.
Distribution of Cephalosporins

- Only few (cefepime, cefuroxime, cefotaxime, ceftriaxone, and ceftazidime) achieve therapeutic concentrations in cerebrospinal fluid.

- Cefotaxime and ceftriaxone are antibiotics of first choice for the empirical treatment of brain abscess and meningitis.
Adverse Reactions of Cephalosporins

Hypersensitivity reactions including anaphylaxis, bronchospasm, urticaria, skin rash.
Nephrotoxicity.
Thrombophlebitis after i.v administration.
Superinfection.
Diarrhea with oral cephalosporins.
Carbapenems

- Imipenem
- Doripenem,
- Ertapenem,
- Meropenem

- The treatment of choice for infections caused by extended-spectrum beta-lactamase–producing gram-negative bacteria.

- Imipenem has a wide spectrum of activity against many gram-negative rods, including *P. aeruginosa*, gram-positive organisms, and anaerobes.

- Imipenem is inactivated by dehydropeptidases in renal tubules, so, usually administered together with an inhibitor of renal dehydropeptidase, Cilastatin.
Monobactams

- **Aztreonam:**
  - Spectrum: ONLY for Gram negative aerobic bacteria
    - Some *P. aeruginosa* are resistant,
  - Well distributed into tissues, especially inflamed tissues, with renal clearance.
  - Resistant to most β-lactamases.
  - Adverse reactions include skin rash.
  - No cross-reactivity with other β-lactam drugs.
  - Used in serious infections such as pneumonia, meningitis, and sepsis caused by susceptible gram-negative pathogens.
Cross reactivity of β-Lactam Antibiotics

• Cephalosporin /Penicillin: 1 – 10%.

• Aztreonam/Penicillin or Cephalosporin: 0%.

• Carbapenems/Penicillins: 10%.