β-Lactam Antibiotics

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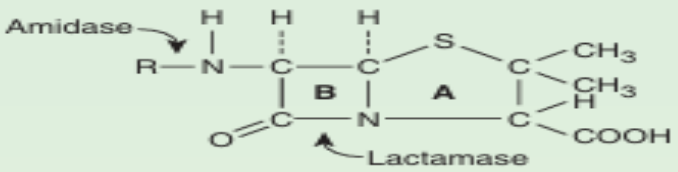
β-Lactam Antibiotics

Classification:

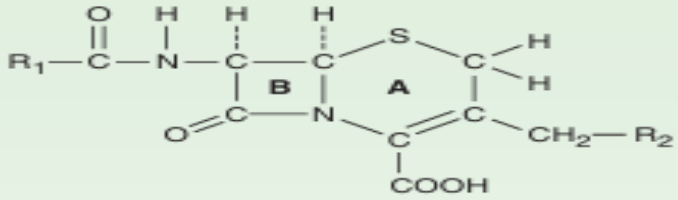
1. **Penicillins**
2. **Cephalosporins**
3. **Carbapenams**
4. **Monobactams**

- **All of them share a four-membered β-lactam ring.**



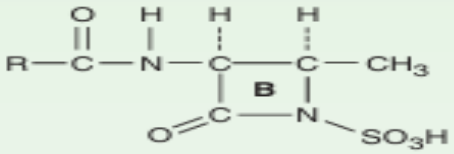
Penicillin

Substituted 6-aminopenicillanic acid



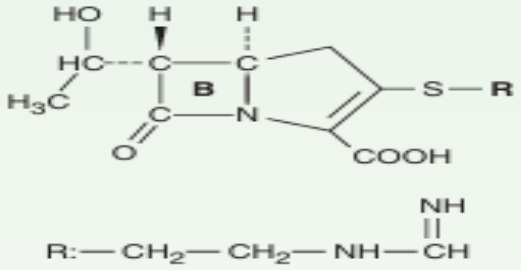
Cephalosporin

Substituted 7-aminocephalosporanic acid



Monobactam

Substituted 3-amino-4-methylmonobactamic acid (aztreonam)



Carbapenem

Substituted 3-hydroxyethylcarbapenemic acid (imipenem)

β-Lactam Antibiotics

Mechanism of Action:

- **Inhibition of the formation of peptidoglycans (a complex cross-linked polymer of polysaccharides and polypeptides) of bacterial cell wall.**
- **Cell wall synthesis occurs in 3 steps and requires the action of around 30 bacterial enzymes [penicillin-binding proteins (PBPs)].**

β-Lactam Antibiotics

- **The third step, the formation of the peptidoglycan, involves a transpeptidation (TP) reaction.**
- **TP completes cross links in bacterial cell wall which gives the cell its rigid mechanical stability. This step is inhibited by β-Lactam antibiotics.**

β-Lactam Antibiotics

- **Loss of cross-links converts the bacterial cell to a spheroblast that undergoes rapid lyses and death (bactericidal).**
- **Some of the action may be explained by loss of inhibitors of autolysins leading to autolysis and bacterial cell death.**
- **β-Lactam antibiotics kill bacterial cells when they are actively growing and synthesizing cell wall.**

β-Lactam Antibiotics

Mechanisms of Bacterial Resistance to β-Lactam Antibiotics:

1. **Generation of β-lactamases which destroy the β-lactam antibiotics, which differ in their susceptibility to β-lactamases.**

- **Is the most common mechanism of resistance.**
- **Produced by *Staphylococcus, Haemophilus sp, Escherichia coli* & others. They prefer penicillins**

β-Lactam Antibiotics

- **AmpC β-lactamase produced by gram negative bacteria (*Pseudomonas aeruginosa,* & others); and Extended spectrum β-lactamases (ESBLs) hydrolyze both penicillins and cephalosporins.**
- **Carbapenems are highly resistant to hydrolysis by the above β-lactamases but are hydrolyzed by metallo- β-lactamase and carbapenemases.**

β-Lactam Antibiotics

2. **Inability of the β-Lactam antibiotic to penetrate to its site of action (PBPs), (In some gram negative bacteria).**
3. **The presence of efflux pump (in *Salmonella typhimurium* and other gram negative organisms).**

β-Lactam Antibiotics

4. **Development of high molecular weight PBPs with decreased affinity for the β-lactam antibiotic. (in Penicillin-resistant *Streptococci and Enterococci;* and Methicillin-resistent *Staphylococcus aureus.***

Penicillins

Classification (According to Antibacterial Spectrum):

1. **Penicillin G and Penicillin V:**

- **Highly active against gram positive cocci.**
- **Active against some gram negative cocci and non-β-lactamase producing anaerobes but NOT gram negative rods.**
- **The are hydrolyzed by penicillinase, and thus, ineffective against *Staphylococcus aureus.***

Penicillins

- **Penicillin G is destroyed by gastric acid. It should be given by injection.**
- **Penicillin V is stable in gastric acid and can be given orally.**
- **t½ ~ 30 min**
- **Probenecid inhibits their renal tubular secretion**

Penicillins

Repository preparations of penicillin G which release it slowly:

a. **Penicillin G procaine which lasts in the body for 4-5 days after IM injection.**

b. **Penicillin G benzathine which lasts in the body for 26 days after IM injection.**

- **Eliminated by the kidney, 10% by glomerular filtration and 90% by active tubular secretion.**

Penicillins

2. Penicillinase-resistant penicillins or anti-staphylococcal penicillins (oxacillin, cloxacillin, dicloxacillin, nafcillin, methicillin).

- **Active against penicillinase producing *Staphylococcus aureus,* but not other gram positive bacteria.**
- **Not active against methicillin-resistant *Staphylococcus aureus* (MRSA), enterococci, Listeria, anaerobic bacteria and gram negative cocci and rods.**

Penicillins

3. Extended-Spectrum Penicillins:

- **Antibacterial activity extended to cover some gram negative bacteria.**

A. Ampicillin and Amoxicillin:

- **They are active against gram positive cocci, anaerobes, enterococci, *Listeria monocytogenes* and β-lactamase-negative strains of gram negative cocci and bacilli such as:**

Penicillins

Haemophilus influenzae, E. coli, proteus mirabilis **and** ***Salmonella sp*****.**

- **Ampicillin, but not amoxicillin, is effective against shigellosis.**

Penicillins

B. Antipseudomonal penicillins”

- **Mezlocillin, Piperacillin.**
- **Have antibacterial activity against *Pseudomonas, Klebsiella pneumoniae*, Indole-positive *Proteus, Enterobacter* sp, in addition to the antibacterial spectrum of ampicillin except that on Enterococci.**
- **Rapidly hydrolyzed by penicillinase.**

Penicillins

Major Adverse Effect:

1. **Hypersensitivity reactions, anaphylaxis.**
2. **Toxic nonallergic skin rash in patients with infectious mononucleosus given ampicillin (100% of patients).**
3. **Bone marrow depression, granulocytopenia and hepatitis – oxacillin, nafcillin.**

Penicillins

4. **Superinfection: pseudomembranous colitis due to *Clostridium difficile* and diarrhea, vaginal candidiasis with extended-spectrum penicillins.**
5. **Heart failure with antipseudomonal penicillins due to Na^+ overload → hypokalemia. Piperacillin contains 2 mEq Na^+ / gram.**

Cephalosporins

Classification:

1. **First-generation cephalosporins:**

   Cefazolin, Cephalexin, Cefadroxil.

- **Have good activity against gram positive bacteria (Pneumococci, Streptococci, Staphylococci), with modest activity against gram negative bacteria (*Moraxella catarrhalis, E. coli, Klebsiella pneumoniae* and *Proteus mirabilis*).**

Cephalosporins

- **Active against oral cavity anaerobes (*Peptococcus* and *Peptostreptococcus*), but not active against *Bacteroides fragilis*.**
- **Not active against *Enterococci*, Methicillin-resistant *Staphylococcus aureus*, Penicillin-resistant *Streptococcus*, *Listeria monocytogenes, Pseudomonas aeruginosa*, Indole positive *Proteus, Serratia marcescens*, *Citrobacter, Enterobacter* and *Acinetobacter*.**

Cephalosporins

2. **Second-generation Cephalosporins:**

- **Have somewhat increased activity against gram negative bacteria.**

A. Cefuroxime:

- **It is active against gram positive bacteria as the first generation, but have extended gram negative coverage.**
- **Active against *E. coli, Klebsiella, Proteus, Haemophilus influenzae, Moraxella catarrhalis*.**

Cephalosporins

- **Not active against *Serratia, Bacteroides fragilis, Enterobacter, Pseudomonas*, Enterococci and penicillin-resistant pneumococci.**

Cephalosporins

B. Cefoxitin, Cefotetan:

- **Similar in spectrum of activity to cefuroxime but less active against *Haemophilus influenzae.***
- **Active against *Bacteroides fragilis* (anaerobe).**

Cephalosporins

3. **Third-generation cephalosporins:**

- **Have extended gram negative coverage.**
- **Able to cross blood-brain-barrier → useful in meningitis.**
- **Active against *Citrobacter, Providentia* and *Serratia marcescens,* but these organisms can produce cephalosporinase which renders them unsusceptible.**
- **Hydrolyzed by AmpC β-lactamase**
- **Not active against *Enterobacter*.**

Cephalosporins

A. Cefotaxime, Ceftriaxone:

- **Active against *Serratia, Haemophilus influenzae, Neisseria gonorrheae*.**
- **Active against Enterobacteriaceae but resistance develops readily during therapy because of induction of β-lactamases.**
- **Activity against *Staphylococcus aureus, Streptococcus pyogens* is comparable to first generation agents**

Cephalosporins

B. Ceftazidime:

- **Also active against Pseudomonas aeruginosa.**
- **Less active against gram positive cocci.**

C. Ceftizoxime, Moxalactam:

- **Are active against *Bacteroides fragilis* (anaerobes)**

Cephalosporins

4. Fourth-generation cephalosporins:

Cefepime

- **Have extended spectrum of activity compared to third generation.**
- **More resistant to hydrolysis by β-lactamases.**

Cephalosporins

- **Has good activity against *Psuedomonas, Enterobacteriaceae, Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant), *Haemophilus influenzae*.**

Cephalosporins

Major Adverse Reactions:

1. **Hypersensitivity reactions, anaphylaxis**
2. **Bone marrow depression, granulocytopenia.**
3. **Nephrotoxicity**
4. **Diarrhea (more with cefoperazone which is excreted in bile).**
5. **Serious bleeding: hypoprothrombinemia, thrombocytopenia and platelet dysfunction**

Carbapenams

Imipenem:

- **Has a wide spectrum of activity.**
- **Given in combination with “cilastatin” to inhibit imipenem degradation by the renal tubular cell dehydropeptidase.**
- **It is resistant to hydrolysis by most β-lactamases but not metallo- β-lactamase.**
- **Antibacterial spectrum: Active against a wide variety of gram positive organisms and gram negative bacilli, both aerobes and anaerobes, including:**

Carbapenams

Streptococci, penicillin-resistant strains of pneumococci, Enterococci (excluding *E. faecium* and penicillin-resistant strains), Staphylococci but not MRSA, *Listeria*, Enterobacteriaceae, *Pseudomonas* in combination with aminoglycosides, *Acinetobacter*, anaerobes including *Bacteroides fragilis*.

Carbapenams

- **Not active against *Stenotrophomonas maltophilia, Burkholderia capacia, & Clostridium difficile*.**

Carbapenams

Meropenem:

- **Similar to imipenem, but with more activity against gram negative aerobes and less activity against gram positive organisms.**
- **Not significantly degraded by renal dehydropeptidase and does not require an inhibitor.**

Carbapenams

Major Adverse Effects:

1. **Hypersensitivity reactions**
2. **Nausea, vomiting and diarrhea**
3. **Seizures**

Monobactams

Aztreonam:

- **Resistant to many β-lactamases elaborated by most gram negative bacilli.**
- **Antibacterial activity differs from other β-lactam agents and resemble that of aminoglycosides (gram negative bacteria).**
- **Gram positive bacteria and anaerobes are resistant to aztreonam.**

Monobactams

- **Active against the Enterobactriaceae (*Serratia*) and *Pseudomonas aeruginosa* in addition to *H. influenzae* and gonococci.**
- **Can be used in place of an aminoglycoside.**

Monobactams

Major Adverse Reactions:

1. **GIT upset**
2. **Thrombocytopenia**
3. **Neutropenia**

β-Lactamase Inhibitors

- **They do not have any intrinsic antimicrobial activity.**
- **Bind β-lactamases (but not all of them), destroy them, and prevent their action on β-lactam antibiotics.**

  1. Inactivate class A β-lactamases produced by staphylococci, *H. influenzae, N. gonorrhea, Salmonella, Shigella, E. coli, Klebsiella pneumoniae.*

β-Lactamase Inhibitors

2. Have no activity against inducible β-lactamases (class C) produced by some gram negative bacilli such as *Enterobacter, Citrobacter, Serratia, Pseudomonas*, during treatment with some SGCs and TGCs.

- **Examples:**

1. **Clavulanic acid:**

- **+ amoxicillin = augmentin: active against staphylococci, *H. influenzae*, gonococci, & *E.coli*.**

β-Lactamase Inhibitors

- **+ ticarcillin = timentin: spectrum resembles imipenem (aerobic gram negative bacilli, *Staph*., *Bacteroides* sp, but no increased activity against *Pseudomonas*).**

2. **Sulbactam:**

   + ampicillin = Unasyn: active against *Staph. aureus* and *H. influenzae*.

3. **Tazobactam:**

   + piperacillin = Zosyn: active against *Pseudomonas*.