Pharmacology

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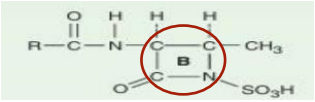
ARKAN ACADEMY

β-Lactam Antibiotics

- β-Lactam Antibiotics (sharing a 4-membered ring) are classified into:
  - *Penicillin*
    - ✓ Penicillin G is the first antibiotic to be discovered
  - *Cephalosporins*
  - *Carbapenams*
  - *Monobactams*



- β-Lactam ***inhibit the synthesis of peptidoglycans*** of the bacterial cell wall
  - Peptidoglycans are complexes of polysaccharides and polypeptides
  - Bacterial cell wall synthesized by 3 steps using 30 enzymes called **PBPs** (penicillin binding proteins)
  - The 3rd step involves a ***transpeptidation (TP)*** reaction which involves completing cross-linking in the cell wall which gives it ***rigidity*** and inhibited by β-Lactam
  - β-Lactams are ***bactericidal*** (kills the bacteria)
    - ✓ Loss of cross-links converts bacterial cell to a spheroblast that undergoes *rapid lyses and death*
    - ✓ Bacterial cell wall contains inhibitors for *autolysin*, when it is lost causes autolysis and death
    - ✓ β-Lactam antibiotics kill bacterial cells when they are *actively growing and synthesizing cell wall*

- Mechanisms of Bacterial Resistance to β-Lactam Antibiotics:
  - ***Generation of β-lactamases***
    - ✓ It destroys the β-lactam antibiotics, which differ in their susceptibility to β-lactamases
    - ✓ β-lactamases include β-Penicillinase, β-Cephalosporinase, β-Carbonase
    - ✓ Is the most common mechanism of resistance
    - ✓ Produced by ***Staphylococcus***, ***Haemophilus sp***, ***Escherichia coli*** where they prefer *penicillin*
    - ✓ ***AmpC β-lactamase*** (***gram negative bacteria*** such as ***Pseudomonas aeruginosa***) 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***
  - ***Inability*** of the β-Lactam antibiotic ***to penetrate*** to its site of action (PBPs)
    - ✓ In some ***gram-negative bacteria***
  - The presence of ***efflux pump***
    - ✓ In ***Salmonella typhimurium*** and other ***gram-negative organisms***
  - Development of ***high molecular weight PBPs*** with decreased affinity for the β-lactam antibiotic
    - ✓ In ***Penicillin-resistant Streptococci***, ***Penicillin-resistant Enterococci*** and ***Methicillin-resistant Staphylococcus aureus (MRSA)***

Penicillin

- **Penicillin G and Penicillin V**
  - Highly active against *gram positive cocci*
  - Active against some *gram-negative cocci* and non-βlactamase producing *anaerobe*
  - NOT *gram-negative rods*
  - Hydrolyzed by penicillinase, and thus, ineffective against *Staphylococcus aureus*
  - 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 of penicillin G and higher for penicillin V
    - ✓ ***Probenecid*** inhibits their active renal tubular secretion which **increases their half life**
      - Eliminated by the kidney, 10% by glomerular filtration and 90% by active tubular secretion
    - ✓ ***Repository preparations*** of penicillin G which release it slowly, there are 2 types:
      - Penicillin G ***procaine*** which lasts in the body for 4-5 days after IM injection
      - Penicillin G ***benzathine*** which lasts in the body for 26 days after IM injection
  - It can be used to treat ***dental infections***, ***rheumatic fever*** patients to prevent repeated ***tonsillitis***

- **Penicillinase-resistant penicillin** or **anti-staphylococcal penicillin**
  - ***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)*, *anaerobic bacteria* (enterococci, Listeria) and *gram-negative cocci and rods*

- **Extended-Spectrum Penicillin**
  - Antibacterial activity extended to cover some *gram-negative bacteria*

  1. ***Ampicillin & Amoxicillin***
     - ✓ They are active against *gram positive cocci*, *anaerobes* enterococci, Listeria monocytogenes and β-lactamase-negative strains of *gram negative cocci* and *bacilli* (Haemophilus influenzae, E.coli, Proteus mirabilis and Salmonella sp)
     - ✓ **Ampicillin**, but not amoxicillin, is effective against ***shigellosis***

  2. ***Antipseudomonal penicillins*** (***Mezlocillin***, ***Piperacillin, ticarcillin***)
     - ✓ They have antibacterial activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Indole- positive Proteus*, *Enterobacter* sp, in addition to the antibacterial spectrum of ampicillin except that on Enterococci
     - ✓ ***Rapidly hydrolyzed by penicillinase***

- Major Adverse Effect of penicillin
  - ***Hypersensitivity*** reactions, ***anaphylaxis***
  - Toxic nonallergic ***skin rash*** in patients with *infectious mononucleosus* given *Ampicillin* (100% of patients)

- ***Bone marrow depression***, granulocytopenia (recurrent infections), thrombocytopenia (bleeding) and ***hepatitis*** – *oxacillin, nafcillin*
- ***Superinfection:*** Due to inhibition of normal flora by *extended-spectrum penicillin*
  - ✓ ***Pseudomembranous colitis*** due to Clostridium difficile
  - ✓ ***Diarrhea*** and ***vaginal candidiasis***
- ***Heart failure*** with *antipseudomonal penicillins* due to **water retention** caused by Na^+ overload and hypokalemia (Piperacillin contains 2 mEq Na^+/ gram)

Cephalosporins

- **First-generation cephalosporins (FGC): *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*)
  - Active against ***oral cavity anaerobes*** (*Peptococcus* and *Peptostreptococcus*) but not active against another *anaerobe Bacteroides fragilis*, not active against *Enterococci*, *MRSA*, *Penicillin- resistant Streptococcus*, *Listeria* monocytogenes, *Pseudomonas aeruginosa*, *Indole positive Proteus*, *Serratia marcescens*, *Citrobacter*, *Enterobacter* and *Acinetobacter*

- **Second-generation Cephalosporins (SGC)**
  - Have somewhat increased activity against *gram negative bacteria*
  - ***Cefuroxime***
    - ✓ Active against *gram positive bacteria* as first generation, but ***extended gram-negative coverage***
    - ✓ Active against ***E. coli***, *Klebsiella*, *Moraxella catarrhalis*, *Proteus*, ***Haemophilus influenzae***
    - ✓ Not active against *Serratia*, *Bacteroides fragilis*, *Enterobacter*, *Pseudomonas*, *Enterococci* and *penicillin-resistant pneumococci*
  - ***Cefoxitin, Cefotetan***
    - ✓ Similar in spectrum of activity to *cefuroxime* but ***less active against Haemophilus influenzae***
    - ✓ Active against *Bacteroides fragilis* (anaerobe)

- **Third-generation Cephalosporins (TGC)**
  - 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 which is also a cephalosporinase
  - Not active against *Enterobacter*
  - It includes Cefotaxime, Ceftriaxone, Ceftazidime, Ceftizoxime, Moxalactam

- ***Cefotaxime***, ***Ceftriaxone***: Active against *Serratia*, *Haemophilus influenzae*, *Neisseria gonorrheae*
  - ✓ Active against *Enterobacteriaceae* but resistance develops readily during therapy because of induction of βlactamases
  - ✓ Activity against *Staphylococcus aureus*, *Streptococcus pyogens* is comparable to first generation
- ***Ceftazidime:*** Active against *Pseudomonas aeruginosa* (anti-pseudomonas)
  - ✓ Less active against *gram positive cocci*
- ***Ceftizoxime, Moxalactam:*** Are active against *Bacteroides fragilis anaerobe*

- **Fourth-generation Cephalosporins (TGC)**
  - ***Cefepime:*** Have **extended spectrum** of activity compared to third generation
    - ✓ **More resistant** to hydrolysis by β-lactamases
    - ✓ Good activity against *Psuedomonas*, *Enterobacteriaceae*, *Staphylococcus aureus*, *Streptococcus pneumoniae* (including penicillin resistant), *Haemophilus influenzae*

- Major Adverse Reactions for cephalosporins
  - ***Hypersensitivity*** reactions, anaphylaxis as penicillin
  - ***Bone marrow depression*** causing granulocytopenia, hypoprothrombinemia, thrombocytopenia and platelet dysfunction causing serious bleeding
    - ✓ May increase severity of anemia
  - ***Nephrotoxicity***
  - ***Diarrhea*** (more with *cefoperazone* which is excreted in bile) and related to super-infection

Carbapenems

- **Imipenem:** Has a ***wide spectrum of activity***
  - Combined with ***cilastatin*** to inhibit imipenem degradation by 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: *Streptococci*, *penicillin-resistant pneumococci*, *Enterococci* (excluding *E. faecium* and *penicillin-resistant Enterococci*), *Staphylococci* but not *MRSA*, *Listeria*, *Enterobacteriaceae*, ***Pseudomonas*** in combination with **aminoglycosides**, *acinetobacter*, *anaerobes* including Bacteroides fragili and not active against *Stenotrophomonas maltophilia*, *Burkholderia capacia*, & *Clostridium difficile*

- **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
- Major Adverse Reactions for Carbapenems
  - *Hypersensitivity* reactions
  - *Nausea*, *vomiting* and diarrhea (super infection)
  - *Seizure*

Monobactams

- Major Adverse Reactions: *GIT upset*, *thrombocytopenia* and *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
  - Inactivate *class A β-lactamases* produced by *staphylococci*, *H. influenzae*, *N. gonorrhea*, *Salmonella*, *Shigella*, *E. coli*, *Klebsiella* pneumoniae
  - Have no activity against inducible β- lactamases (class C) produced by *some gram negative bacilli* such as *Enterobacter*, *Citrobacter*, *Serratia*, *Pseudomonas*, during treatment with SGCs and TGCs
  - **Clavulanic acid**
    - ✓ Clavulanic acid with ***amoxicillin*** = **Augmentin** which is active against staphylococci, H. influenzae, gonococci, & E.coli
    - ✓ Clavulanic acid with ***ticarcillin*** = **Timentin** spectrum resembles ***imipenem*** (but no increased activity against Pseudomonas)
  - **Sulbactam**
    - ✓ Sulbactam with ***ampicillin*** = **Unasyn**: active against Staph. aureus and H. influenzae
  - **Tazobactam**
    - ✓ Tazobactam with ***piperacillin*** = **Zosyn**: active against ***Pseudomonas***.

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