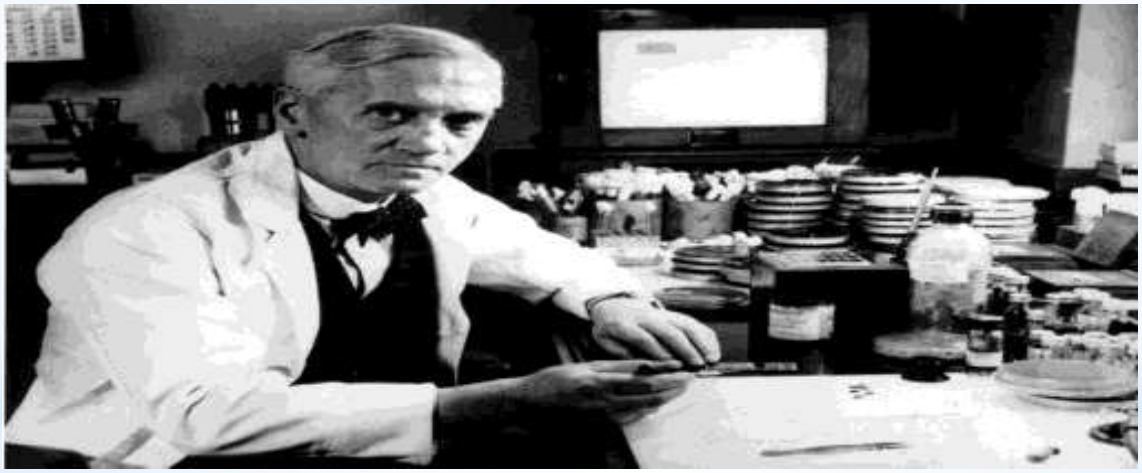
CHEMOTHERAPEUTIC AGENTS-II

BETA-LACTAM ANTIBIOTICS



The first antibiotic was discovered by Sir Alexander Fleming in 1928

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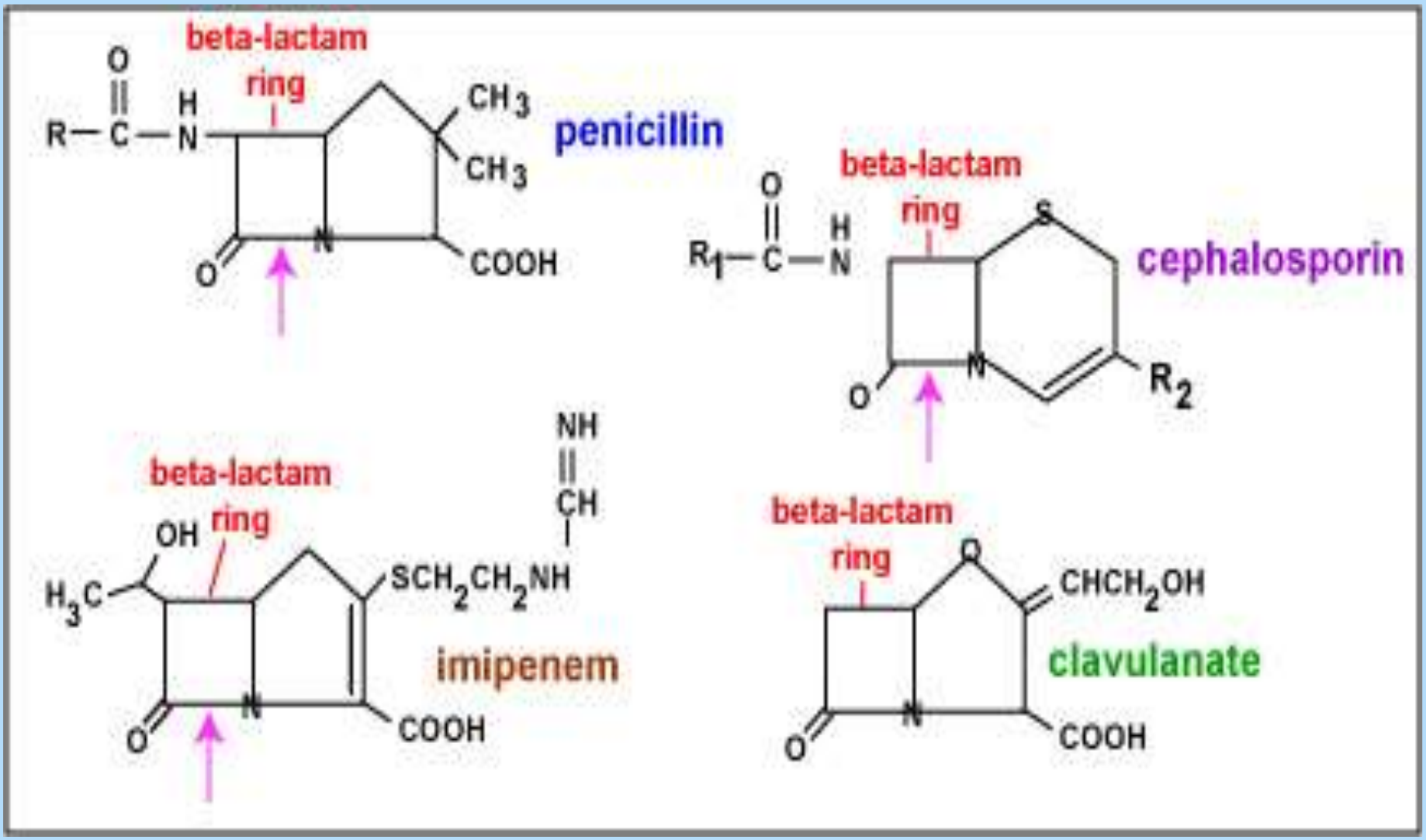
OBJECTIVES

After completion of this lecture you will be able to understand

* What are beta-lactam antimicrobials
* Types of Penicillin, MOA, Uses, ADRs
* Classification of Cephalosporin, MOA, Uses, ADRs
* Members of Carbapenem and Monobactam, Uses, ADRs

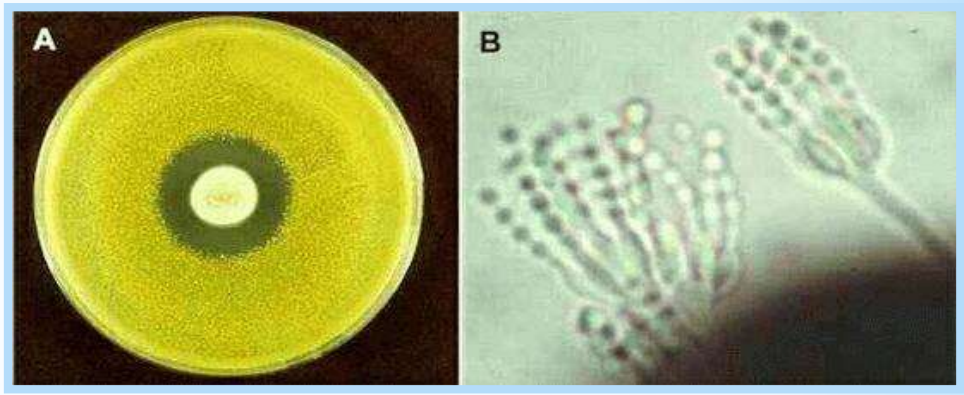
The Beta-Lactam Antibiotics

* Antibiotics having Beta-Lactam ring in their structure.



Penicillins

* *Penicillium notatum* is the only naturally occurring agent – penicillin G or benzyl-penicillin is being Produced from.
* Dosage and potency based on IU (1 IU = 0.6 micrograms pure penicillin G)
* *P. chrysogenum* produces 6-aminopenicillanic acid, raw material for semi-synthetics.
* Dosage and potency are based on weight of the patient.
* Spectrum of activity based on R groups added to 6-aminopenicillanic acid core
* All are bactericidal and inhibit transpeptidases
* Mechanisms of resistance
  * Alter affinity of transpeptidase
  * Enzymatically cleave the beta-lactam ring
  * Efflux pumps
  * Poor penetration into cell



Penicillins

- Effective against aerobic G+ organisms except *Staphylococcus*, Pen G active against *Neisseria* and anaerobes
- 2/3 of oral Pen G destroyed by stomach acid, Pen V is more resistant so more is delivered to serum
- Rapid elimination through kidney so probenecid, procaine, of benzathine added to slow excretion
- Most drug is bound to serum albumin but significant amounts show up in liver, bile, kidney, semen, joint fluid, lymph, etc.
- Cautious use in neonates and infants because renal function is not fully established
- Patients with renal failure clear the drugs through liver although at a slow pace

Penicillin Members

- **Penicillins**
  - **Penicillin G (Benzylpenicillin)** -- Parenteral
    - Sodium Penicillin (Crystaline Penicillin)
    - Procaine Penicillin (most allergic)
    - Benzathine Penicillin (longest duration)
  - **Penicillin V (Phenoxymethylpenicillin)** -- Oral

- **Aminopenicillins**
  - Ampicillin
  - Amoxicillin
  - Hetacillin

- **Extended spectrum penicillins (Antipseudomonal penicillins)**
  - Carbenicillin
  - Mezlocillin
  - Piperacillin
  - Ticarcillin

- **Beta-lactamase resistant penicillins (Antistaphylococcal penicillins)**
  - Methicillin
  - Cloxacillin
  - Dicloxacillin
  - Nafcillin
  - Oxacillin

MOA

* **Mode of Action:**

* Penicillins, and other beta-lactam antibiotics, work by interfering with interpeptide linking of peptidoglycan, the a strong, structural molecule found specifically bacterial cell walls. Cell walls without intact peptidoglycan cross-links are structurally weak, prone to collapse and disintegrate when the bacteria attempts to divide. Since the eukaryotic cells of humans do not have cell walls, our cells are not damaged by penicillins.

Classification of Penicillins

- **Penicillin – G (Benzyl Penicillin)-** Acid labile, Narrow spectrum
  - Sod. Penicillin G (Crystalline Penicillin)-
  - Procaine Penicillin G
  - Benzathine Penicillin G
- **Semi-synthetic Penicillin**
  - **Acid Resistant alternative to Penicillin G**
    - Phenoxymethyl penicillin (Penicillin V)- Oral
  - **Penicillinase Resistant (Have side chains to protect beta lactam ring)**
    - Methicillin- Acid labile, Injection only, Inducer of penicillinase, Interstitial nephritis
    - Cloxacillin- Acid reistant, Oral also,
    - Oxacillin, Dicloxacillin, Flucloxacillin, Nafcillin

Classification of Penicillins

- **Extended spectrum Penicillin**
  - **Aminopenicillins**
    - Ampicillin
    - Amoxicillin
    - Bacampicillin (Prodrug of Ampicillin)
  - **Antipseudomonal Penicillins**
  - **Carboxypenicillins**
    - Carbencillin
    - Ticarcillin
  - **Ureidopenicillins**
    - Piperacillin
    - Mezlocillin

Pharmacological Aspects

- **Penicillin – G (PnG) or Benzyl Penicillin**
  - **Acid labile-** Destroyed in stomach,
  - Poor CSF penetration,
  - Rapid renal excretion by tubular secretion.
  - Susceptible to Penicillinase
  - **Narrow spectrum-** gram positive (Strepto, Staphylo, Bacillus anthracis, Corynebacterium)

    - **Sodium Penicillin G (Crystalline Penicillin)- IM or IV- Soluble**
    - **Procaine Penicillin G- Not by IV, Most allergic, Painless**
    - **Benzathine Penicillin- Longest acting penicillin (Once in month)**

- **Limitations**
  - **Poor oral efficacy**
  - **Narrow spectrum,**
  - **Susceptibility to Penicillinase**

Pharmacological Aspects

- **Extended Spectrum Penicillins -**
  - All are sensitive to Beta Lactamase

  - **Acid Stable (Aminopenicillins)**
    - Ampicillin, (incomplete oral absorption and high chance of diarrhea)
    - Amoxicillin
    - Bacampicillin (Prodrug)
    - Talampicillin, (Prodrug)

  - **Acid Labile- (Antipseudomonal Penicillins)-**
    - **A**zlocillin
    - **C**arbencillin
    - **P**ipracillin **(A-CPTM)**
    - **T**icarcillin,
    - **M**ezlocillin

Pharmacological Aspects

*Semi-synthetic Penicillins Produced by combination of specific side chain in place of benzyl to over come limitations

➢ Acid Resistant

- Phenoxymethyl penicillin **(Penicillin V)-**
  - Acid stable rest is same as that of PnG

➢ Penicillinase resistant (Protects Beta lactam ring by side chain but bacteria also gets protected from beta lactam ring- **not good** in non- Penicillinase producing bacteria)

- **Cloxacillin** – Acid resistant, Has isoxazolyl side chain,
- **Oxacillin**
- **Dicloxacillin**
- **Flucloxacillin**
- **Nafcillin-** Eliminated only by biliary route and safe in renal failure

Pharmacological Aspects

* **Methicillin-**
  - Not in use due to Nephrotoxicity
  - Inducer of Penicillinase
  - Acid Labile
  - As tradition Staphylococcus aureus resistant to cloxacillin or nafcilllin are called as methicilliin resistant staphylococcus aureus (**MRSA**)

Pharmacological Aspects

Extended spectrum

- **Aminopenicillins**-
  - Have amino side chain,
  - Damaged by Penicillinase enzyme,
  - Also have gram negative action
    - Ampicillin, - Incomplete absorption, diarrhea is common
    - Amoxicillin – Better oral bioavailability, diarrhea is less
    - Bacampicillin,
    - Pivampicllin,
    - Talampicillin-

} **Prodrug of Ampicillin**

Pharmacological Aspects

* **Carboxypenicillins and Ureidopenicillins are Antipseudomonal Penicillins (A-CPMT)**
* **Carboxypenicillins-**
  - **Carbencillin-**
    * Antipseudomonal,
    * Neither Penicillinase nor acid resistant,
    * Interfere with platelets,
    * May cause overloading of Sodium (Beware in CHF)
  - **Ticarcillin** – More potent rest is same
* **Ureidopenicillins-**
  - **Pipracillin** – Antipseudomonal, Follows **zero order kinetics (Best Antipseudomonal penicillin)**
  - **Mezlocillin** – Hepatic metabolism

Pharmacological Aspects

* Azlocillin, Carbencillin, Pipracillin, Mezlocillin, Ticarcillin **(A-CPMT)** available as sodium salt –
  * Caution in CHF and renal failure.

* Mezlocillin has significant hepatic metabolism –
  * Caution in hepatic insufficiency.

* Inactivate Aminoglycosides-
  * Should not be used in same syringe or same infusion **(Pharmaceutical DDI)**

Pharmacological Aspects

* **Amidinopenicillin (Mecillinam and Pivmecillinam)**
* **Mecillinam**
  * Amidino group at position 6 of Penicillanic acid
  * Mainly gram negative bacteria
  * Also called **Reverse Spectrum Penicillin**
* **Pivmecillinam** (Prodrug of Mecillinam)

Pharmacological Aspects

*Beta Lactamase inhibitors

- Resemble beta Lactam antibiotics
- Don't have antimicrobial action.
- Bind irreversibly to beta-Lactamase
- Prevent hydrolysis of Penicillins

➢ **Clavulanic acid –**

- Pk matches with Amoxicillin,
- **Good oral absorption**,
- Excreted by glomerular filtration,
- Not affected by Probenecid

Pharmacological Aspects

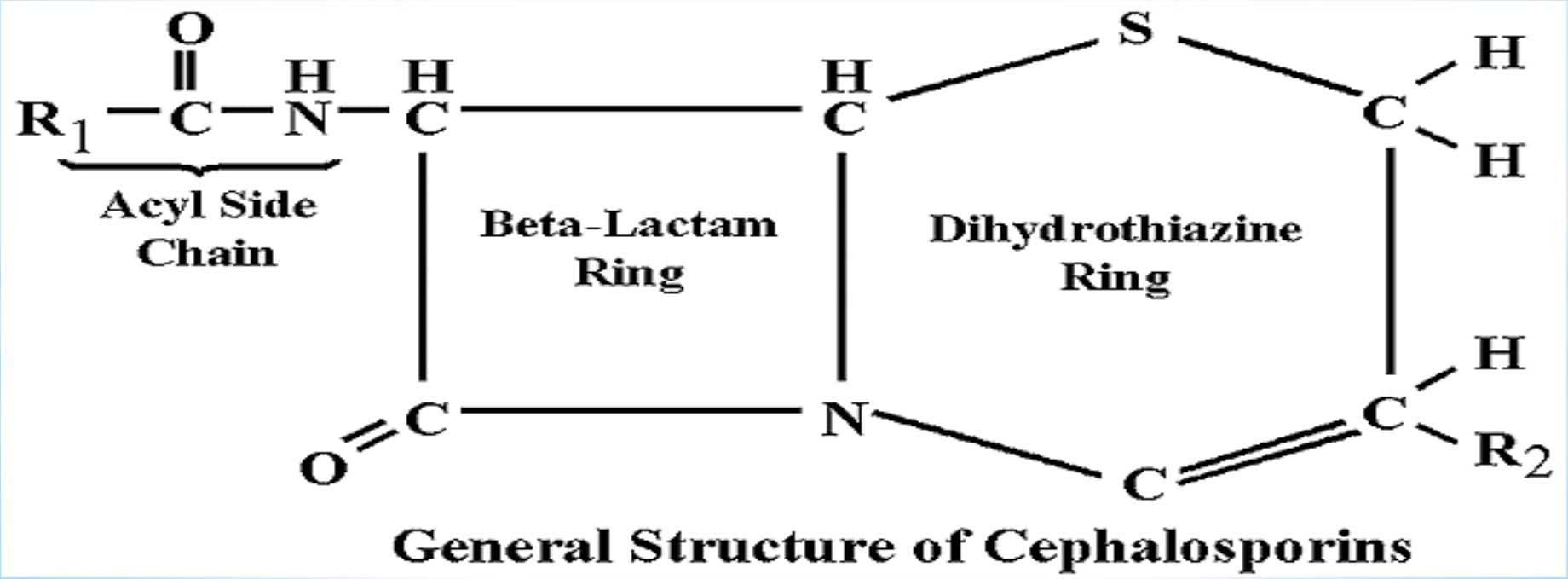
- **Sulbactam –**
  - Less potent than Clavulanic acid,
  - Poor oral absorption,
- **Tazobactam –**
  - Structural analogue of Sulbactam.
  - Pk matches with Pipracillin,
  - Poor oral absorption.

*According to their common pharmacokinetics

- **Clavulanic acid with Amoxicillin (Oral)**
- **Clavulanic acid with Ticarcillin (injection)**
- **Sulbactam with Ampicillin (Injection and oral)**
- **Tazobactam with Piperacillin (Injection)**

Cephalosporins

- **Natural and Semi-synthetic**
- **Natural is- Cephalosporin-C, obtained from Cephalosporium**
- **Chemistry-** Nucleus (7-aminocephalosporanic acid) contains- Beta-Lactam ring + ***Dihydrothiazine ring***



General Structure of Cephalosporins

Cephalosporins

- **Alterations**
  - At Betalactam ring position – Altered Pd
  - At Dihydrothiazine ring position – Altered Pk

- **All are bactericidal**
  - Inhibit cell wall synthesis (bind to different protein)

- **Cephalosporinase = Betalactamase = Penicillinase**

- **Probenecid** - Inhibits tubular secretion

- **Like Penicillin** –
  - Combination of Cephalosporins with Beta Lactamase inhibitors (Sulbactam and Clavulanic acid and Tazobactam) are used

Cephalosporin Members

First generation (Gram positive mainly)

- Oral
  - Cephalexin
  - Cephradine
  - Cefadroxil
- Parenteral
  - Cephalothin
  - Cefazolin

Third generation

(More active against gram negative (Pseudomonas), Resistant to beta Lactamase, Less active against gram positive and anaerobes

- Oral
  - Cefixime
  - Cefopodoxime proxetil (Prodrug)
  - Cefdinir-
  - Cefditoren-
  - Ceftibuten-
  - Ceftamet pivoxil –
- Parenteral
  - Cefotaxime -
  - Ceftrizoxime-
  - Ceftriaxone-
  - Ceftazidime -
  - Cefoperazone-

Second generation (Positive, Negative, Anaerobes, Not active agaist Pseudomonas, Least commonly used)

- Oral
  - Cefaclor
  - Cefuroxime axetil (Prodrug)
  - Cefprozil
- Parenteral
  - Cefuroxime - Crosses BBB
  - Cefoxitin (Cephamycin)-
  - Cefotetan (Cephamycin) -
  - Cefamendol

Fourth generation (Resistant to Beta lactamase, Parenteral)

- Cefipime-
- Cefpirome –
- Cefozopran-

Fifth generation (Increase in activity against gram positive than fourth generation, Parenteral)

- Ceftobiprole-
- Ceftaroline-

Classified into generations (Positive to Negative)

* **First generation-** (Gram positive mainly)

- **Oral**
  - Cephalexin
  - Cephradine
  - Cefadroxil

- **Parenteral**
  - Cephalothin
  - Cefazolin (Better penetration in tissues, used in surgical prophylaxis)

Classified into generations (Positive to Negative)

*Second generation- (Positive, Negative, Anaerobes, Not active against Pseudomonas, Least commonly used)

- **Oral**
  - Cefaclor
  - Cefuroxime axetil (Prodrug)
  - Cefprozil

- **Parenteral**
  - Cefuroxime – Crosses BBB
  - Cefoxitin (Cephamycin)- Good anaerobic activity
  - Cefotetan (Cephamycin) - Good anaerobic activity
  - Cefamandole

Classified into generations (Positive to Negative)

*Third generation- (More active against gram negative (Pseudomonas), Resistant to beta Lactamase, Less active against gram positive and anaerobes)

- **Oral**
  - Cefixime
  - Cefpodoxime proxetil- Prodrug of Cefpodoxime
  - Cefdinir-
  - Ceftibuten-
  - Cefetamet pivoxil –Prodrug

- **Parenteral**
  - Cefotaxime - Prototype
  - Ceftizoxime-
  - Ceftriaxone- Long half life, Good CSF penetration,
  - Ceftazidime – High activity against Pseudomonas,
  - Cefoperazone- High activity against Pseudomonas, Primarily excreted in bile, produces Disulfiram like reaction

Cefoperazone and Ceftriaxone are excreted through bile and no dosage adjustment is needed in renal impairment.

Classified into generations (Positive to Negative)

* **Fourth generation** (All are Parenteral and Resistant to Beta Lactamase)
  - Cefepime- Highly resistant to beta Lactamase,
  - Cefpirome – Has zwitterions which permits better penetration through porin.
  - Cefozopran-

* **Fifth generation** (All are Parenteral and Increase in activity against gram positive than fourth generation)
  - Ceftobiprole-
  - Ceftaroline-

MOA

* **Cephalosporin Mode of Action:**
* Cephalosporins are a type of ß-lactam antibiotic closely related to the penicillins. They are bactericidal, with the same MOA as other beta-lactams.

* Cephalosporins disrupt synthesis of the peptidoglycan layer of bacterial cell walls. Peptidoglycan is a strong structural molecule specific to the cells walls of bacteria. With the cell wall structure compromised, the bactericidal result is lysis and death of the cell.

* Our cells do not have cells walls or peptidoglycan, therefore, B-lactam antibiotics are able to target bacterial cells without harming human cells.

Miscellaneous About Cephalosporins

- Cephalothin used by I.V (only)
- Cefuroxime axetil, Cefpodoxime proxetil, and Cefditoren pivoxil are Prodrug
- Cephalosporin absorption reduced if given with meals
- Cefoperazone, Ceftriaxone and Cefpiramide, secreted in bile
- Cefuroxime, Cefotaxime, Ceftriaxone, Ceftizoxime and Cefepime attain high concentration in CSF.
- Cephalexin, Cefadroxil, Ceftriaxone, safe in pregnancy

Miscellaneous About Cephalosporins

* Cefotetan, Cefoxitin are against anaerobes like bacteroides fragilis
* **Cefazolin is DOC of surgical prophylaxis**
* Ceftazidime and Cefoperazone are active against Pseudomonas
* Ceftizoxime has maximum activity against bacteroides
* **Ceftriaxone** is first choice for Gonorrhoea, Salmonella, E.Coli sepsis, proteus, Haemophilus

Miscellaneous About Cephalosporins

- Resistance to Cephalosporins is same as Penicillins
  - Altered Cephalosporin binding sites
  - Decrease in permeability of outer membrane
  - Beta Lactamase or Cephalosporinase

- **No Cephalosporins active against MRSA, Enterococcus fecalis**

- **Nephrotoxicity- Cephaloridine and Cephalothin**

- Loop diuretics enhance Nephrotoxicity of Cephalosporins **EXCEPT** Cefoperazone and Cefpiramide (Excreted through Bile)

- Cross allergy between Cephalosporins and penicillin 20%

- There is no reliable skin test for cephalosporin

Miscellaneous About Cephalosporins

- ✓ Diarrhea more with Cefoperazone and Cefpiramide
- ✓ Betalactam having Methyl Tetrazole Thiomethyl **(MTT)** group at position 3 of Dihydrothiazine ring may cause
  - ✓ Thrombocytopenia and hypothrombinemia, inhibition of vitamin K activation and platelet dysfunction.
  - ✓ Disulfiram like reaction
- ✓ Bleeding and Disulfiram like reaction by
  - ✓ **Moxalactam**
  - ✓ **Cefotetan**
  - ✓ **Cefamandole**
  - ✓ **Cefoperazone**
- ✓ Treatment of bleeding in these cases is injection of Vitamin K.

Miscellaneous About Cephalosporins

- Disulfiram like reaction is noticed with agents having MTT group (inhibition of Aldehyde dehydrogenase)

- Disulfiram like reaction by
  - Cefamandole,
  - Cefotetan,
  - Moxalactam,
  - Cefoperazone

- Commonly used Cephalosporin by oral route are Cephalexin, Cefadroxil, Cefaclor, Cefuroxime axetil, Cefixime, Cefdinir, Cefditoren pivoxil, Cefetamet pivoxil and Cefpodoxime proxetil.

Miscellaneous About Cephalosporins

- Ceftriaxone is curable as single dose treatment in Chancroid and Gonorrhea

- Ceftriaxone may cause Biliary Pseudolithiasis

- Ceftriaxone for typhoid fever 4g iv for 2 days followed
* by 2g daily continued 2 days after the fever subsides
- Ceftazidime is the most effective 3rd generation cephalosporin against Pseudomonas

- Ceftazidime may produce Neutropenia

Miscellaneous About Cephalosporins

* Renal tubular secretion of Cephalosporins is reduced by Probenecid **EXCEPT** Cefoperazone and Cefpiramide
- Ceftizoxime is preferred for Bacteriod fragilis
- Ceftobiprole and Ceftaroline are fifth gerneration Cephalosporins for MRSA
- Cefotaxime (Ceftriaxone) best for meningitis.
- Hypoprothrombinemia –
  - More with Cefoperazone and Ceftriaxone
- Neutropenia with Ceftazidime
- Nephrotoxicity- Cephaloridine and Cephalothin
* (Don't give with Aminoglycosides and loop diuretics)
- Aminoglycosides- not in same syringe. (Pharmaceutical)
- Ceftazidime plus aminoglycoside is the treatment of choice for pseudomonas infection

Monobactams

- Beta-Lactam antibiotic – other ring = only one ring = (Lack Thiazolidine ring)
- Bind to PBP
- Usually not destroyed by Beta Lactamase
- Does not show cross allergy with penicillin and Cephalosporins (Only Beta lactam that can be used in penicillin allergic patients)
- Excreted unchanged in urine and dose reduction required in renal dysfunction
- Used as alternatives to Aminoglycosides
  - **Aztreonam (Currently used)**
  - Tigemonam
  - Carumonam
- Active against gram negative
- **Inhalational formulation of Aztreonam for treatment of cystic fibrosis.**

Carbapenems

- A Beta lactam ring and five member ring system
- Broader spectrum than other beta lactam
- Significant PAE against gram negative
- Eliminated unchanged in urine
- Bind to PBP and inhibit cell wall
- Penetration in CSF and other body fluid is good
- Reserved antimicrobials
- Only Beta lactam reliable against Extended Spectrum Beta-lactamase producing bacteria

* **Carbapenem members**
  - **Imipenem- (+Cilastatin)**
  - **Meropenem**
  - Ertapenem
  - Doripenem
  - Faropenem

Summary

* Betalactam have Beta-lactam ring and members are Penicillins, Cephalosporins, Carbapenems, Monobactams
* Contains Beta-lactam ring joined by side chain
* Beta lactam ring broken by Betalactamase (Product is Penicillanic acid- allergen without antimicrobial activity)
* Side chain broken by Amidase
* Pharmacokinetic properties governed by side chain
* Antimicrobial activity is governed by Beta lactam ring
* Natural penicillin is Penicillin G (Benzyl Penicillin), Thermo and acid labile
* Penicillin salts are sodium, potassium, procaine (most allergen) and Benzathine
* 6-Aminopenicllaninc acid is active moiety (Raw material)

* One unit of penicillin = 0.6micrograms
* Cross bridging is transpeptidation (blocked by penicillin by attaching with PBP)
* Aminoglycosides – synergistic
* Tetracyclines, chloramphenicol, erythromycin- antagonist
* Methicillin is nephrotoxicity
* Jarisch Herxheimer reaction in syphilis
* Penicillin members- Benzyl penicillin (Penicillin G), Methicillin, Ampicillin, Amoxicillin, Bacampicillin, Talampicillin, Carbencillin, Ticarcillin, Pipracillin, Mezlocillin, Azlocillin, Phenoxymethyl penicillin (Penicillin V),
* Penicillinase resistant members- Cloxacillin, Oxacillin, Dicloxacillin, Flucloxacillin
* Betalactamase inhibitors- Clavulanic acid, Sulbactam, Tazobactam

Cephalosporin Members

First generation (Gram positive mainly)

- **Oral**
  - **Cephalexin**
  - **Cephradine**
  - **Cefadroxil**
- **Parenteral**
  - **Cephalothin**
  - **Cefazolin**

Third generation

(More active against gram negative (Pseudomonas), Resistant to beta Lactamase, Less active against gram positive and anaerobes

- **Oral**
  - **Cefixime**
  - **Cefpodoxime proxetil-**
  - **Cefdinir-**
  - **Cefditoren-**
  - **Ceftibuten-**
  - **Cefetamet pivoxil –**
- **Parenteral**
  - **Cefotaxime -**
  - **Ceftizoxime-**
  - **Ceftriaxone-**
  - **Ceftazidime –**
  - **Cefoperazone-**

Second generation (Positive, Negative, Anaerobes, Not active against Pseudomonas, Least commonly used)

- **Oral**
  - **Cefaclor**
  - **Cefuroxime axetil (Prodrug)**
  - **Cefprozil**
- **Parenteral**
  - **Cefuroxime – Crosses BBB**
  - **Cefoxitin (Cephamycin)-**
  - **Cefotetan (Cephamycin) -**
  - **Cefamandole**

Fourth generation (Resistant to Beta Lactamase, Parenteral)

- Cefepime-
- Cefpirome –
- Cefozopran-

Fifth generation (Increase in activity against gram positive than fourth generation, Parenteral)

- **Ceftobiprole-**
- **Ceftaroline-**

Monobactams

- **Aztreonam (Currently used)**
- Tigemonam
- Carumonam

Carbapenems

- **Imipenem**-
  - **Cilastatin** (reversible inhibitor of dipeptidase I) with Imipenem
- **Meropenem-**
  - Not hydrolyzed by renal dipeptidase,
- **Faropenem-**
  - Orally active Carbapenem
- Doripenem
- Razupenem
- Ertapenem

THANKS FOR THINKING AND LEARNING