BETA LACTAM ANTIBIOTICS

- PENICILLINS
- CEPHALOSPORINS
- MONOBACTAMS
- CARBAPENEMS
Alexander flemming
Inventor of penicillin
ORIGINALLY OBTAINED FROM FUNGUS *PENICILLIUM NOTATUM*.

DISCOVERED IN 1928.

AL. FLEMMING WAS WORKING IN HIS LAB TRYING TO KILL A DEADLY BACTERIA WHEN HE NOTICED A BLUE MOULD GROWING ON THE DISH (NOTATUM), AROUND THAT BACTERIA WERE GETTING KILLED.

PENICILLIN FOUND IN THIS MOULD

NOW FROM *P. CHRYSOGENUM* BECAUSE AMOUNT GOT FROM NOTATUM NOT SUFFICIENT.
Penicillin

The mould Penicillium notatum
A THIAZOLIDINE RING (A) ATTACHED TO β-LACTAM RING (B) THAT CARRIES A SECONDARY AMINO GROUP
STRUCTURE

- β LACTAM RING CARRIES A SECONDARY AMINO GROUP TO WHICH SIDE CHAINS ATTACHED THROUGH AN AMIDE LINKAGE.
- PEN.G (PROTOTYPE)
  - BENZYL SIDE CHAIN.
- SIDE CHAINS SPLIT OFF BY AN AMIDASE TO PRODUCE –
- 6-AMINOPENICILLANIC ACID.
PENCILLIN –G ( BENZYL PENICILLIN)

- A narrow spectrum antibiotic
- Mainly against gram positive bacteria
- Streptococci
- Pneumococci
- B.Anthracis
- Corynebacterium diphtheriae
- Clostridia
- Listeria
- Treponema pallidum
- Actinomyces israelii
- Gram negative cocci – N.gonorroeae and meningitidis
P/K (PEN. G)

- Pen.G is acid labile.
  Give 30 min before or 2 hrs after meals.
- Very rapid renal excretion
- 10% by glomerular filtration
- Rest by tubular secretion (ts)
- Ts can be blocked by probenecid
- To get higher and longer lasting plasma conc.
P/K (contd.)

- Insoluble salts of pen.G.
- Given deep i/m.

- **Procaine pen**: 0.5 – 1 mu, 12–24 hrly as aq. suspension.
- Plasma conc. Sustained for 1–2 days.
P/K

- BENZATHINE PEN.
  - Extremely slow release of pen.
  - 0.6–2.4 mu every 2–4 wks.
  - Effective for prophylactic purposes for up to 4 wks.
USES OF PEN.G

1. Streptococcal infections: Pharyngitis, otitis media, scarlet fever, rheumatic fever.
2. Pneumococcal infections
3. Meningococcal infections
4. Anthrax, gas gangrene, diphtheria, syphilis, tetanus.
5. Gonorrhoea
USES

6. Prophylactic use–

   A) Rheumatic fever: Benzathine pen. : 1.2 MU every 4 wks till 18 years of age.

   B) Gonorrhoea or syphilis : Procaine or Benzathine pen. 2.4 MU single dose within 12 hrs of contact.
USES contd.

9. Surgical infections – Procaine pen. 1 MU with an aminoglycoside injected i.m 1 hr before and 8–12 hrs after surgery can reduce wound infections.
MECHANISM OF ACTION

- Interferes with last step of synthesis of cell wall that is – transpeptidation or cross linkage
- Cell wall deficient forms of bact. Are formed which swell and burst – bacterial lysis.
- Bactericidal action
- Inhibits ENZYME, PENICILLIN BINDING PROTEINS, pbps, INVOLVED IN SYN. Of cell wall.
MECHANISM OF ACTION

- PBPS catalyse formation of cross linkages between peptidoglycan chains.

- Penicillins inhibit transpeptidase–catalysed reactions, thus hindering the formation of cross links essential for cell wall integrity and close knit structure of cell wall.

- Effective only against multiplying org. As resting org. are not making new cell wall
Polysaccharides in the cell wall contain alternating amino sugars ——
N-acetylglucosamine & N-acetylmuramic acid.
A five amino acid peptide is linked to N-acetylmuramic acid sugar.
This peptide terminates in D-alanyladalanyl-D-alanine.
PBP removes the terminal alanine in the process of forming a cross link with a nearby peptide.

Cross-links give the cell wall its structural rigidity.

Beta lactam antibiotics, structural analogs of the D-ala-D-ala substrate, bind to active site of PBP.

This inhibits the trans-peptidation reaction preventing the peptidoglycan synthesis and cell dies.
Figure 43-1. Beta-lactams and bacterial cell wall synthesis. The outer membrane shown in this simplified diagram is present only in gram-negative organisms. It is penetrated by proteins (porins) that are permeable to hydrophilic substances such as beta-lactam antibiotics. The peptidoglycan chains (mureins) are cross-linked by transpeptidases located in the cytoplasmic membrane, closely associated with penicillin-binding proteins (PBPs). Beta-lactam antibiotics bind to PBPs and inhibit transpeptidation, the final step in cell wall synthesis. They also activate autolytic enzymes that cause lesions in the cell wall. Beta-lactamases, which inactivate beta-lactam antibiotics, may be present in the periplasmic space or on the outer surface of the cytoplasmic membrane. (Reproduced, with permission, from Katzung BG, editor: Basic & Clinical Pharmacology, 10th ed. McGraw-Hill, 2007.)
Figure 49.2 Schematic diagram of a single layer of peptidoglycan from a bacterial cell (e.g. Staphylococcus aureus), showing the site of action of the β-lactam antibiotics. In S. aureus, the peptide crosslinks consist of five glycine residues. Gram-positive bacteria have several layers of peptidoglycan. (NAG, N-acetylglucosamine; NAMA, N-acetylmuramic acid; more detail in Fig. 49.3.)
BACTERIAL RESISTANCE

- TARGET INSENSITIVE
  PBPs WITH LOW AFFINITY FOR BINDING BETA LACTAMS,
- LOCATED DEEPER UNDER LIPOPROTEIN BARRIER.

- IMPAIRED PENETRATION OF DRUG TO TARGET PBP.
  OCCURS IN GRAM NEGATIVE BACT DUE TO IMPERMEABLE OUTER CELLWALL MEMBRANE
BACTERIAL RESISTANCE

- PENICILLINASE PRODUCTION
- INACTIVATION OF ANTIBIOTIC BY $\beta$ LACTAMASES
- STAPH, GONOCCOCCI, B.SUBTILIS, E.COLI, H.INFLUENZAE PRODUCE PENICILLINASE.

- EFFLUX– GRAM NEGATIVE ORGANISMS MAY PRODUCE AN EFFLUX PUMP WHICH TRANSPORT $\beta$ LACTAM ANTIBIOTICS FROM THE PERIPLASM BACK ACROSS THE OUTER MEMBRANE.
Adverse drug reactions

- **Hypersensitivity**
- Most common drug implicated in drug allergy
- Rash, itching, urticaria, fever, wheezing, angioneurotic edema, serum sickness, exfoliative dermatitis and anaphylaxis, Rare but fatal.
- More common with parenteral administration.
- Highest with procaine penicillin.
Partial cross sensitivity b/w different types
A scratch test or intradermal test
TEST WITH BENZYL– PENICILLOYL POLYLYSINE, serves as a hapten to cause an immune reaction.
Topical use highly sensitising,
Contact dermatitis and other reactions, so banned.
- Pain at inj site
- Thrombophlebitis of injected vein
- Nausea on oral use
- Diarrhoea – with extended spectrum penicillin, caused by a disruption of the normal balance of intestinal organisms. Ampicillin has been associated with pseudo-membranous colitis.
- **Toxicity to brain:**
  - mental confusion, Muscle twitchings
  - Convulsions & coma
  - Epileptics are at risk particularly.
- **Nephritis** – all can cause but seen particularly with methicillin, so not used.

- **Hematologic toxicities** – decreased coagulation with antipseudomonal, to some extent with Pen.G. caution in pts who are predisposed to hemorrhage, or receiving anticoagulants.
JARISCH-HERXHEIMER REACTION –

PENICILLIN INJECTED IN A SYPHILITIC PATIENT – SHIVERING, FEVER, MYALGIA, EXACERBATION OF LESIONS & VASCULAR COLLAPSE.
DUE TO SUDDEN RELEASE OF SPIROCHAETAL LYTIC PRODUCTS AND LASTS FOR 12–24 HRS ASPIRIN AND SEDATION HELP.
SEMISYNTHETIC PENICILLINS

- PRODUCED BY CHEMICALLY COMBINING SPECIFIC SIDE CHAINS
- AIM IS TO OVERCOME SHORTCOMINGS OF PnG –
  - POOR ORAL EFFICACY
  - SUSCEPTIBILITY TO PENCILLINASE
  - NARROW SPECTRUM OF ACTIVITY
  - HYPERSENSITIVITY
CLASSIFICATION

- ACID RESISTANT ALTERNATIVE TO PnG
  - Penicillin V

- PENICILLINASE RESISTANCE PENICILLINS
  - Methicillin, oxacillin, cloxacillin, dicloxacillin

- EXTENDED SPECTRUM PENICILLINS
  - a) AMINOPENICILLINS: Ampicillin, Bacampicillin, Amoxicillin
  - b) CARBOXYPENICILLINS: Carbenicillin, carbenicillin indanyl & phenyl, Ticarcillin
  - c) UREIDOPENICILLINS: Piperacillin, Mezlocillin
Penicillin V (Phenoxy Methyl Pen.V)

- ACID STABLE
- 1/5th AS ACTIVE AG. NEISSERIA, OTHER GRAM NEGATIVE BACTERIA AND ANEROBES.
- USED ONLY FOR-
  - STREP. PHARYNGITIS, SINUSITIS & OTITIS MEDIA
  - PROPHYLAXIS OF RHEUMATIC FEVER
  - PNEUMOCOCCAL INFECTIONS
PENICILLINASE RESISTANT PENICILLINS

- ANTI – STAPHYLOCOCCAL PEN.
  Have side chains that protect beta lactam ring from attack by staphylococcal penicillinase.

- Indication – Penicillinase producing staph

- METHICILLIN –
  - HIGHLY PENICILLINASE RESISTANT
  - NOT ACID RESISTANT – MUST BE INJECTED
  - MRSA (Methicillin resistant staph aureus)
MRSA

- INSENSITIVE TO ALL PENCILLINASE RESISTANT PEN.
- HAVE ALTERED PBPs WHICH DO NOT BIND PENICILLINS
- DRUG OF CHOICE—
  - VANCOMYCIN / LINEZOLID
  - CIPROFLOXACIN
S/Es(methicilllin)

- HAEMATURIA
- ALBUMINURIA
- REVERSIBLE INTERSTITIAL NEPHRITIS
- LARGELY REPLACED BY CLOXACILLIN
ISOXAZOLYL PENICILLINS

- OXA, CLOxacillin, DICLOxacillin
- All relatively stable in acidic medium
- Adequately absorbed after oral administration
- DICLOxacillin most active
- All less active against organisms sensitive to penicillin G
CLOXACILLIN

- ISOXAZOLYL SIDE CHAIN
  - Highly penicillinase resistant
  - More active than methicillin against penicillinase resistant staph
  - Relatively acid resistant.
  - However, food interferes with absorption so give one hour before or after meals.
  - 0.25–0.5 g orally every 6 hourly
  - For serious infections 0.25–1 g injected i.m. or i.v.
RAPIDLY ABSORBED FROM GIT
RAPIDLY EXCRETED BY KIDNEY
HALF LIFE – 30–60 MIN
DAILY DOSE OF OXACILLIN– 2–4 g in 4 DIVIDED DOSES
DICLOXA – 250 mg EVERY 6 HOURS
USED TO TREAT INFECTIONS SUCH AS OSTEOMYELITIS, SEPTICAEMIA, ENDOCARDITIS AND CELLULITIS CAUSED BY SUSCEPTIBLE STRAINS OF STAPH.

CLOxacillin can also be used to treat mild staphylococcal skin infections such as impetigo.
AMINOPENICILLINS

- AMINO SUBSTITUTION IN SIDE CHAIN
  AMPICILLIN

- SAME ORGANISMS AG. WHICH PEN.G IS EFFECTIVE

- GRAM -VE: E.COLI, SALMONELLA,
  PROTEUS, SHIGELLA

- MORE ACTIVE THAN PEN.G AGAINST:
  STREPT.VIRIDANS & ENTEROCOCCI

- P/K – NOT DEGRADED BY GASTRIC ACID

- ADEQUATE ORAL ABSORPTION BUT INCOMPLETE

- FOOD INTERFERS WITH ABSORPTION

- PLASMA HALF LIFE – ONE HOUR
AMPICILLIN

USES – UTI – RESISTANCE, FLUOROQUINOLONES/COTRIMOXAZOLE
  ▶ RTI – SINUSITIS, OTITIS MEDIA, BRONCHITIS
  ▶ DOSE – 0.5–2 g ORAL /I.M. /I.V. 6 HOURLY
  ▶ MENINGITIS – ALONG WITH THIRD GEN.CEPH.
  ▶ GONORRHEA – NPPG
  ▶ TYPHOID FEVER – RESISTANCE
  ▶ BACILLARY DYSENTRY – SHIGELLA (QUINOLONES PREFERRED)
  ▶ CHOLECYSTITIS – HIGH CONC. IN BILE
AMPICILLIN

- **S/Es** – diarrhoea, rashes resembling measles or rubella

**BACAMPICILLIN**

- PRODRUG, largely hydrolysed during absorption. Nearly completely absorbed from GIT.
- Tissue penetration better.
- Diarrhoea less (does not disturb intestinal ecology much)
AMOXICILLIN

- Oral absorption is better. Food does not interfere. Higher blood levels for longer time.
- Differences from Ampicillin:
  - Diarrhea is less.
  - Less active against Shigella and H. influenzae.
  - Preferred for – typhoid, UTI, gonorrhea, bronchitis, SABE.
  - Employed prophylactically by dentists for patients with heart valve DS, who have to undergo oral surgery.
- Dose – 250 mg – 1g tds oral
CARBOXY PENICILLINS

CARBENICILLIN

- ACTIVITY Ag. – PSEUDOMONAS AERUGINOSA
- – INDOLE POSITIVE PROTEUS
- USED IN SERIOUS INFECTIONS CAUSED BY THE TWO e.g. Burns, UTI, Septicemia.
- NEITHER PENICILLINASE RESISTANT NOR ACID RESISTANT.
- Inactive orally, excreted rapidly in urine.
- Used as sodium salt
- Not preffered. Piperacillin preffered.
- As sodium salt, can cause fluid retention, CHF in patients with borderline renal or cardiac function.
- Bleeding problems.
A DERIVATIVE CARBENICILLIN INDANYL SODIUM GIVEN ORALLY FOR UTI AND OTHER LESS SERIOUS INFECTIONS.

ACID STABLE ESTER OF CARBENICILLIN.

TICARCILLIN

MORE POTENT AG. PSEUDOMONAS

LESS ACTIVE THAN AMPICILLIN AGAINST ENTEROCOCCI.
PIPERACILLIN

8 times more active than carbenicillin
Good activity ag. Klebsiella
Used mainly in immuno-compromised patients, having gram negative infections and in burns.
Because of resistance problem antipseudomonal penicillin is combined with an aminoglycoside or fluoroquinolone.
MEZLOCILLIN

- INHIBITS KLEBSIELLA
- GIVEN PARENTERALLY FOR INFECTIONS CAUSED BY ENTERIC BACILLI.
- ACTIVITY SIMILAR TO TICARCILLIN AG. PSEUDOMONAS
BETA LACTAMASES: Enzymes produced by gram positive and gram negative bacteria that inactivate beta lactam antibiotics by opening beta lactam ring.

BETA LACTAMASE INHIBITORS
- CLAVULANIC ACID
- SULBACTAM
- TAZOBACTAM
CLAVULANIC ACID

- FROM *streptomyces clavuligerus*
- Has beta lactam ring
- No antibacterial activity of its own
- Inhibits many beta lactamases
- Inhibition increases with time, initially reversible becomes covalent with time—**Progressive inhibitor**
- Irreversible binder
- **Suicide inhibitor**, gets inactivated after binding to the enzyme.
- Well absorbed by mouth, also given parenterally
COMBINED WITH AMOXICILLIN AS AN ORAL PREP.

WITH TICAR CILLIN AS A PARENTERAL.

AMOXICILLIN + CLAVULANATE EFFECTIVE FOR BETA LACTAMASE PRODUCING STRAINS OF STAPH (NOT MRSA), H. INFLU, GONOCOCCI, E.COLI.
EFFECTIVE IN TREATMENT OF:

- Skin & soft tissue infections
- Gynae infections
- Urinary & biliary infections
- Acute otitis media in children
- Sinusitis
- Bite wounds, cellulitis, diabetic foot infections.

Addition of clavulanic acid to ticarcillin extends its spectrum such that it resembles imipenem to include aerobic gram negative bacilli, S. Aureus, bacteriodes.
Dosage should be adjusted for patients with renal insufficiency.

Combination is especially useful for mixed nosocomial infections, often used with aminoglycosides.

Activity ag. Pseudomonas is not increased.

Git tolerance is poorer.

Super-infections are more.

Amoxicillin 250 + clavulanate 125 mg
SULBACTAM

- Semisynthetic Beta–lactamase inhibitor.
  - given orally/parenterally along with beta lactam antibiotic.
    Combined with ampicillin.
  - Dosage adjusted in patients with impaired renal fxn.
  - Good activity ag.Gram positive cocci, including beta–lactamase producing strains of staph aureus, gram negative aerobes and anaerobes.
  - Used effectively for mixed intra–abdominal and pelvic infections.
TAZOBACTAM

- Beta lactamase inhibitor
- Has been combined with Piperacillin as a parenteral prep.
- 3 g Piperacillin, 375 mg Tazobactam every 4–8 hourly.
- Equal to Ticarcillin plus clavulanate.
CARBAPENEMS

- BETA LACTAMS THAT CONTAIN A FUSED β-lactam ring and a 5-membered ring system that differs from pen. In being unsaturated and containing a carbon atom instead of sulphur atom.

- Have a broader spectrum of activity than do most other β-lactam antibiotics have.
CARBAPENEMS

- IMIPENEM
- MEROPENEM
- ERTAPENEM
IMIPENEM

- DERIVED FROM A COMPOUND PRODUCED BY *STREPTOMYCES CATTLEYA*
- BINDS TO PBPs, DISRUPTS BACTERIAL CELL WALL SYNTHESIS.
- VERY RESISTANT TO HYDROLYSIS BY MOST BETA LACTAMASES.
P/K

- NOT ABSORBED ORALLY
- IS RAPIDLY HYDROLYSED BY A DEHYDRO-PEPTIDASE FOUND IN THE BRUSH BORDER OF PROXIMAL RENAL TUBULES.
- GIVEN WITH AN INHIBITOR OF DEHYDROPEPTIDASE, CILASTATIN. A PREPARATION WITH EQUAL AMOUNTS OF BOTH.
- BOTH HAVE A HALF LIFE OF ONE HOUR.
- DOSE – 0.5 g i.v. 6 hourly.
- DOSAGE SHOULD BE MODIFIED FOR PATIENTS WITH RENAL INSUFFICIENCY.
ANTIMICROBIAL SPECTRUM

- IMIPENEM / CILASTATIN AND MEROPENEM ARE THE **BROADEST** SPECTRUM BETA LACTAM ANTIBIOTICS.
- PLAYS A ROLE IN EMPIRICAL THERAPY BECAUSE IT IS ACTIVE AGAINST PENICILLINASE PRODUCING GRAM– POSITIVE AND GRAM NEGATIVE ORGANISMS, ANAEROBES, AND *P. AERUGINOSA*.
- **STREPTOCOCCI** (INCL. PENICILLIN RESISTANT *S. PNEUMONIAE*), *ENTEROCOCCI, STAPH, LISTERIA, SOME STRAINS OF MRSA, ACINETOBACTER, B. FRAGILIS.*
ADVERSE EFFECTS

- NAUSEA & VOMITING
- SEIZURES, WHEN HIGH DOSES GIVEN IN PATIENTS WITH CNS LESIONS AND THOSE WITH RENAL INSUFFICIENCY.
- ALLERGIC TO PEN. MAY SHOW HYPERSENSITIVITY.
- LESSER EOSINOPHILIA AND NEUTROPENIA
THERAPEUTIC USES

- **IMIPENEM / CILASTATIN FOR**
  - UTI, LOWER RESPIRATORY TRACT INFECTIONS, INTRAABDOMINAL AND GYNAECOLOGICAL INFECTIONS.
  - SKIN AND SOFT TISSUE, BONE AND JOINT INFECTIONS.
  - DRUG COMBINATION ESP. USEFUL FOR INFECTIONS CAUSED BY CEPHALOSPORIN-RESISTANT NOSOCOMIAL BACT, SUCH AS CITROBACTER AND ENTEROBACTER.
  - FOR EMPERICAL TREATMENT OF SERIOUS INF. IN HOSPITALISED PT.
  - SHOULD NOT BE USED ALONE – RESISTANCE RISK.
Figure 31.14
Antimicrobial spectrum of imipenem.
MEROPENEM

- DOES NOT REQUIRE CO-ADMINISTRATION WITH CILASTATIN, NOT SENSITIVE TO RENAL DIPEPTIDASE.
- LESS LIKELY TO CAUSE SEIZURES.
- ACTIVITY AG. P. AERUGINOSA.
- LESS ACTIVITY AG GRAM + VE COCCI.
- THERAPEUTICALLY EQ.TO IMIPENEM
AZTREONAM

- MONOCYCLIC BETA LACTAM COMP.
- BETA LACTAM RING IS NOT FUSED TO ANOTHER RING.
- ISOLATED FROM *CHROMOBACTERIUM VIOLACEUM*
- INTERACTS WITH PBPs OF SUSCEPTIBLE BACT, INDUCES THE FORMATION OF LONG FILAMENTOUS BACT. STRUCTURES.
DIFFERS FROM BETA LACTAM, RESEMBLES AMINOGLYCOSIDES
GRAM +VE AND ANAEROBES ARE RESISTANT.
EXCELLENT ACT. AG. – ENTEROBACTERIACEAE, PSEUDOMONAS, H. INFLU (At very low conc.), GONOCOCCI.
RES. TO ACTION OF MANY BETA LACTAMASES.
ADM. I/M OR I/V
ELIMINATION HALF LIFE 1.7 HOURS
CAN ACCUMULATE IN PTs. WITH RENAL FAILURE.
USUAL DOSE FOR SERIOUS INFECTIONS – 2 g 6–8 HOURLY, BUT DECREASED IN RENAL DS PTs.
S/Es

- WELL TOLERATED
- LOW IMMUNOGENIC POT.
- MAIN ADVANTAGE – **PATIENTS WHO ARE ALLERGIC TO PENICILLINS OR CEPHALOSPORINS DO NOT REACT TO AZTREONAM.**
- QUITE USEFUL FOR TREATING GRAM NEGATIVE INFECTIONS, THAT COULD BE TREATED WITH ABOVE DRUGS, BUT H/O ALLERGY WAS THERE.
CEPHALOSPORINS

- Produced semisynthetically by chemical attachment of side chains to 7-aminoccephalosporanic acid.
  - Same mode of action, same resistance mech.
  - But tend to be more resistant than penicillins to certain beta-lactamases.
ANTIBACTERIAL SPECTRUM

- CLASSIFIED AS FIRST, SECOND, THIRD OR FOURTH GENERATION BASED ON:
  - BACTERIAL SUSCEPTIBILITY PATTERNS
  - RESISTANCE TO BETA-LACTAMASES

- NOT EFFECTIVE AGAINST –
  - MRSA, L. MONOCYTTOGENES, C. DIFFICILE, ENTEROCOCCI
FIRST GENERATION

- PARENTERAL –
- CEPHALOTHIN
- CEFAZOLIN
- ORAL –
- CEPHALEXIN
- CEPHRADINE
- CEFADROXIL
SECOND GENERATION

- PARENTERAL
- CEFUROXIME
- CEFOXITIN
- ORAL
- CEFACLOR
- CEFUROXIME AXETIL
THIRD GENERATION

- PARENTERAL
  - CEFOTAXIME
  - CEFTIZOXIME
  - CEFTRIAXONE
  - CEFTAZIDIME
  - CEFOPERAZONE

- ORAL
  - CEFIXIME
  - CEFPODOXIME
  - CEFDINIR
  - CEFTIBUTEN
FOURTH GENERATION

- PARENTERAL
- CEFEPIME
- CEFPIROME
Table 7–2. Clinical uses of cephalosporins.

<table>
<thead>
<tr>
<th>Cephalosporins</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation: <strong>cefazolin, cephalexin</strong></td>
<td>Gram-positive cocci (not MRSA), <em>Escherichia coli</em>, <em>Klebsiella pneumoniae</em>, and some <em>Proteus</em> species</td>
</tr>
<tr>
<td>Second generation: <strong>cefotetan, cefaclor</strong></td>
<td>Gram-negative bacilli including <em>Bacteroides fragilis</em> (cefotetan); <em>Hemophilus influenzae</em> and <em>Moraxella catarrhalis</em> (cefaclor)</td>
</tr>
<tr>
<td>Third generation</td>
<td>Many gram-positive and gram-negative cocci and gram-negative bacilli including β-lactamase-forming strains; individual drugs have activity against specific organisms including <em>Pseudomonas</em> (<strong>ceftazidime</strong>), anaerobes (<strong>ceftizoxime</strong>), and gonococci (<strong>ceftiraxone, cefixime</strong>)</td>
</tr>
<tr>
<td>Fourth generation</td>
<td><strong>Cefipime</strong> combines the gram-positive activity of the first-generation drugs with the gram-negative activity of the third-generation drugs</td>
</tr>
</tbody>
</table>

B. Clinical Uses

1. Clinical uses of cephalosporins vary depending on the generation of the drug.
2. Table 7–2 lists the clinical uses of cephalosporins.
FIRST GENERATION

CEPHALOTHIN

- ACTIVE AGAINST MOST Penicillin G SENSITIVE ORG. i.e.
- Streptococci (pyogenes & viridans), staphylococcus (including those producing penicillinase), not MRSA
- Gonococci, meningococci, C. diphtheriae Clostridia, actinomyces
- Main indication – penicillinase producing staph
- i.v. 1–2 g 6 hrly (i/m Painful)
CEFAZOLIN

- MORE ACTIVE AGAINST KLEBSIELLA & E.COLI
- SUSCEPTIBLE TO STAPH BETA-LACTAMASE
- PREFERRED PARENTERAL FIRST GEN
  SPECIALLY FOR SURGICAL PROPHYLAXIS
- Can be given i.m. also, less painful
- 0.25 g 8 hourly, 1 g 6 hrly i.m, i.v.
CEPHALEXIN

- Orally effective
- Similar to cephalothin in spectrum, but less active ag. Penicillinase producing staph and ag. H. influenzae.
- Little bound to plasma proteins, attains high conc. In bile.
- Excreted unchanged in urine
- 0.25 – 1 g 6–8 hrly
CEPHRADINE
- ORALLY ACTIVE, SIMILAR TO CEPHALEXIN
- DIARRHOEA
- PARENTERAL ALSO

CEFADROXIL
- A CLOSE CONGENER OF CEPHALEXIN
- GOOD TS. PENETRATION
- MORE SUSTAINED ACTION AT THE SITE OF INFECTION
- CAN BE GIVEN 12 HRLY, EXCRETED UNCHANGED IN URINE
SECOND GENERATION CEPHALOSPORINS

CEFOXITIN

- More active against Serratia, Indole positive Proteus, B. Fragilis
- Highly resistant to B-lactamases produced by Gram -ve bact.
- Anaerobic & mixed obs/surgical inf.
- Lung abscess
- Dose – 1–2 g I.M / I.V every 6–8 hrs
CEFUROXIME

- Resistant to beta-lactamases produced by gram-ve bacteria.
- High activity ag. org. producing these enzymes incl. PPNG and ampicillin resistant H.influenzae.
- Have significant activity on gram positive cocci.
- Attains high CSF levels.
- Most imp. use is meningitis caused by H.influenzae, meningococci, pneumococci.
CEFACLOR

- HIGHLY SIGNIFICANT ACTIVITY BY ORAL ROUTE
- MORE ACTIVE THAN FIRST GEN. COMP. AGAINST *H. INFLUENZAE*, *E. COLI*, *P. MIRABILIS*
THIRD GENERATION CEPHALOSPORINS

- HIGH ACTIVITY AGAINST GRAM NEGATIVE ENTEROBACTERIACEAE
- PSEUDOMONAS
- RESISTANT TO BETA–LACTAMASES FROM GRAM NEGATIVE BACT.
- LESS ACTIVE ON GRAM POSITIVE COCCI
CEFOTAXIME

- PROTOTYPE
- AEROBIC GRAM NEGATIVE & GRAM POSITIVE BACT.
- NOT VERY ACTIVE ON ANEROBES, STAPH, Ps. AERUGINOSA
- INDICATIONS – MENINGITIS BY GRAM –VE
- LIFE THREATENING HOSPITAL ACQUIRED INFECTION, SEPTICEMIAS
- INFECTION IN IMMUNOCOMPROMISED PATIENTS
- 1–2 g i.m. or i.v. 6–12 hrly
- Single dose therapy (1g i.m. and 1g probenecid) for PPNG urethritis.
- De-acetylated in the body
- Metabolite exerts weaker but synergistic action with the parent drug.
CEFTRIAXONE

- Longer duration of action (half life 8 hrs)
- Once or twice daily dosing
- Good CSF penetration
- High efficacy in bacterial meningitis
- Multi-resistant typhoid fever
- Complicated UTI
- Abdominal sepsis, Septicemias
- A single dose of 250 mg. i.m. – curative in gonorrhea including PPNG and chancroid.
CEFTAZIDIME

- High activity ag. Pseudomonas
- Sp. useful in febrile neutropenic pts. with hematological malignancy, burn.
- Enterobacteriaceae
- Less active on staph. aureus and gram positive cocci.
- Half life 1.5–1.8 hr.
- Neutropenia, thrombocytopenia, rise in plasma trans-aminases and blood urea has been reported.
CEFOPERAZONE

- Stronger activity on Pseudomonas
- Good for S. Typhi & B. Fragilis
- More susceptible to β-lactamases
- Indications --
  - Severe urinary, biliary, respiratory, skin-soft tissue infections, meningitis, septicaemias
- Excreted mainly in bile
- Disulfiram like reaction with alcohol.
CEFIXIME

- Resistant to many beta lactamases.
- Longer acting.
- 200–400 mg b.d. For respiratory, urinary & biliary infections.
- Diarrhea common side effect.
CEFPODOXIME

- ORALLY ACTIVE, PRODRUG
- ENTEROBACT, STREP, STAPH
- RESPIRATORY, URINARY, BILIARY INF.
CEFDINIR

- GOOD ACTIVITY Ag. BETA LACTAMASE PRODUCING ORG.
- PNEUMONIA, ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS, ENT, SKIN INFECTIONS.
CEFTIBUTEN

- ACTIVE AG. BOTH GRAM POSITIVE AND NEGATIVE
- STABLE TO BETA LACTAMASES
- INDICATED IN RESPIRATORY, URINARY, GI INFECTIONS
FOURTH GENERATION CEPH.

**CEFEPIME**

- Highly resistant to beta-lactamases
- Spectrum similar to third gen
- Additional activity against bacteria resistant to other drugs.
- *P. aeruginosa, Staph* also inhibited
- Effective in many serious infections like nosocomial, febrile neutropenia, bacteremia, septicaemia

1–2 g i.v. 8–12 hrly
CEFPIROME

- SERIOUS AND RESISTANT HOSPITAL ACQUIRED INFECTIONS
- SEPTICEMIAS
- LOWER RESP. TRACT INFECTIONS
- BETTER PENETRATION THROUGH PORIN CHANNELS OF GRAM NEGATIVE BACTERIA
- RESISTANT TO MANY BETA-LACTAMASES
Local irritation can produce severe pain after i.M. Injection, thrombophlebitis after i.v.
Diarrhoea due to disturbed gut ecology
Hypersensitivity reactions similar to Penicillins including anaphylaxis, fever, skin rashes, nephritis, granulocytopenia and hemolytic anemia. Cross allergenicity around 5–10 %.
Nephrotoxicity including interstitial nephritis and even tubular necrosis, highest with cephaloridin (withdrawn) cephalothin also causes.
S/Es

- Hypoprothrombinemia and bleeding disorders by cefamandole, cefmetazole, cefotetan, cefoperazone. Vit. K 10 mg twice weekly can prevent it.

- A disulfiram-like interaction with alcohol with cefoperazone.

- Neutropenia and thrombocytopenia rarely, with ceftazidime.
Figure 49.3 Schematic diagram of the biosynthesis of peptidoglycan in a bacterial cell (e.g., Staphylococcus aureus), with the sites of action of various antibiotics. The hydrophilic disaccharide-pentapeptide is transferred across the lipid cell membrane attached to a large lipid (C55 lipid) by a pyrophosphate bridge (\(-P-P-\)). On the outside, it is enzymically attached to the "acceptor" (the growing peptidoglycan layer). The final reaction is a transpeptidation, in which the loose end of the (Gly)\(_5\) chain is attached to a peptide side-chain of an M in the acceptor and during which the terminal amino acid (alanine) is lost. The lipid is regenerated by loss of a phosphate group (Pi) before functioning again as a carrier. G, N-acetylglucosamine; M, N-acetylmuramic acid; UDP, uridine diphosphate; UMP, uridine monophosphate.