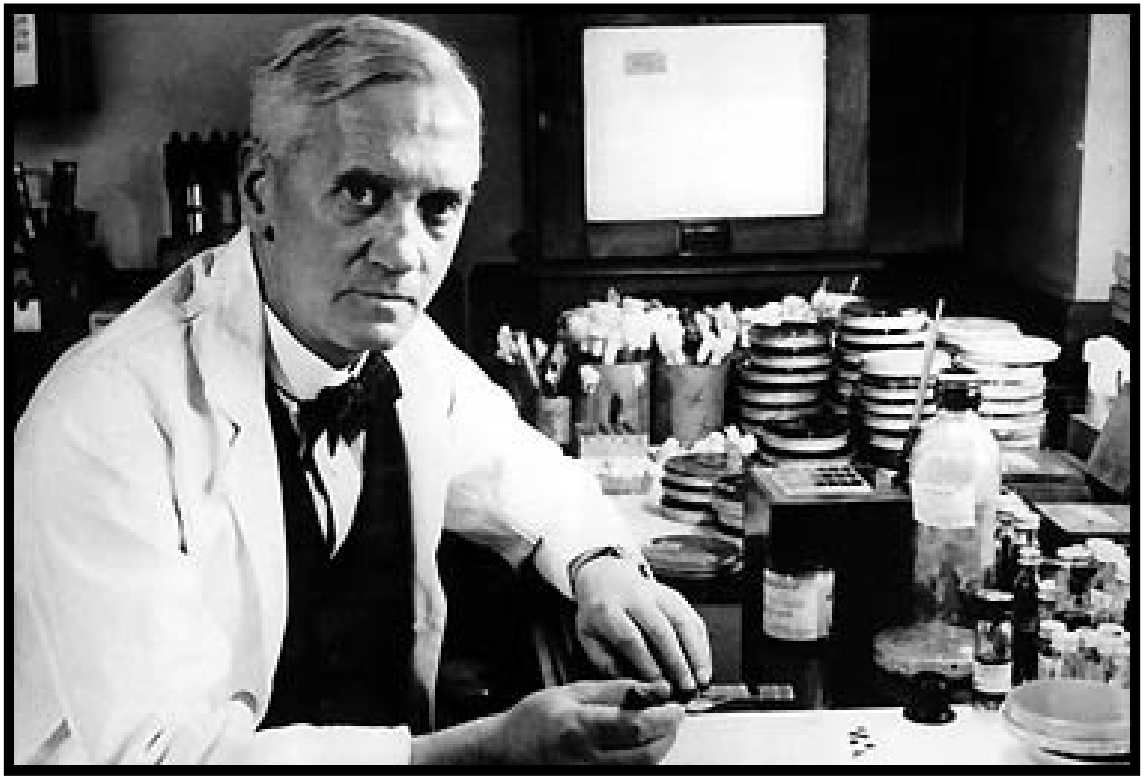
BETA LACTAM ANTIBIOTICS

- PENICILLINS
- CEPHALOSPORINS
- MONOBACTAMS
- CARBAPENEMS

Alexander flemming
Inventor of penicillin



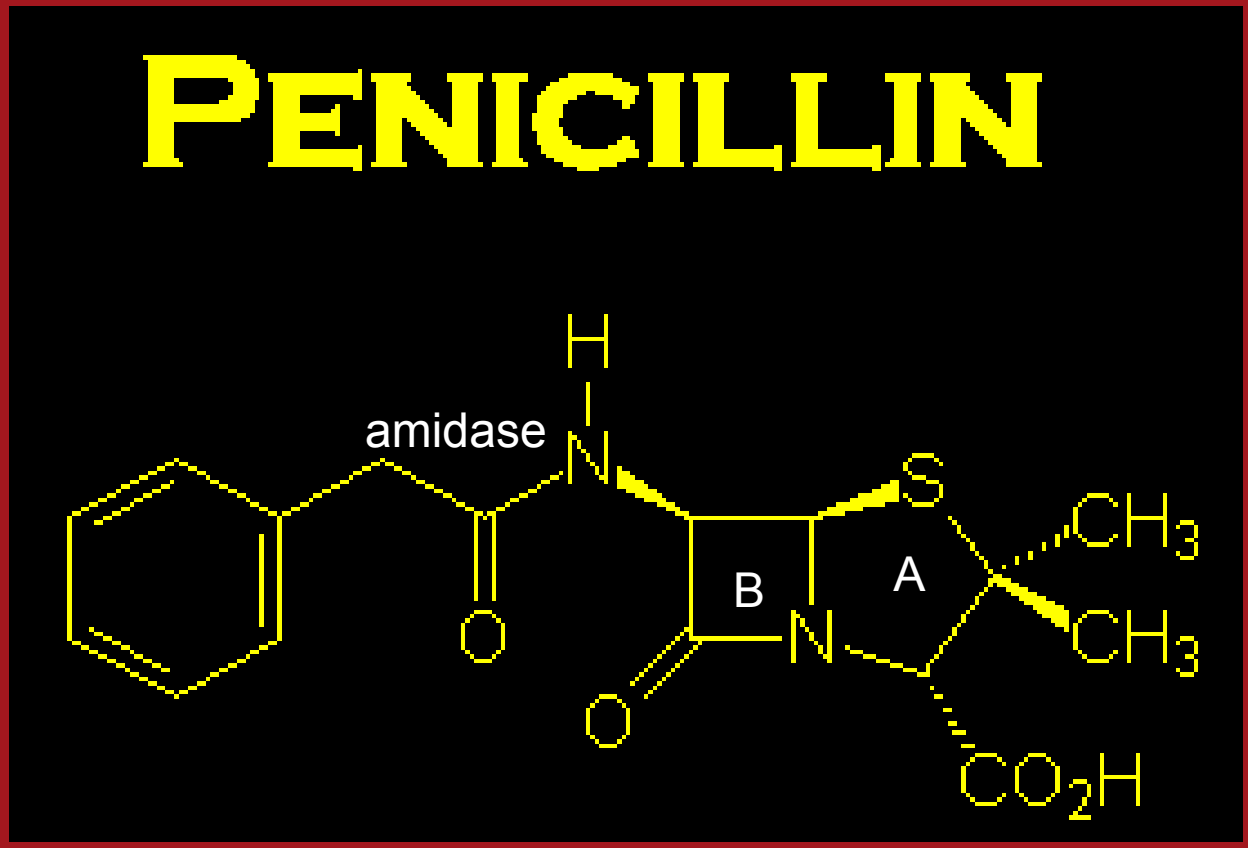
- ORIGINALLY OBTAINED FROM FUNGUS *PENICILLIUM NOTATUM.*
- DISCOVERED IN 1928.

- 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 Penicillum notatum

Structure



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-AMINOPENCILLANIC 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 filteration
- 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.
- **Repository prep** : release pen.G slowly.
- Given deep i/m.

- **Procaine pen.** 0.5 – 1mu,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 upto 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.

7. Bacterial endocarditis-
   extractions, endoscopies,catheterization, surgical procedures.
8. Agranulocytosis - alone or in combination.
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.

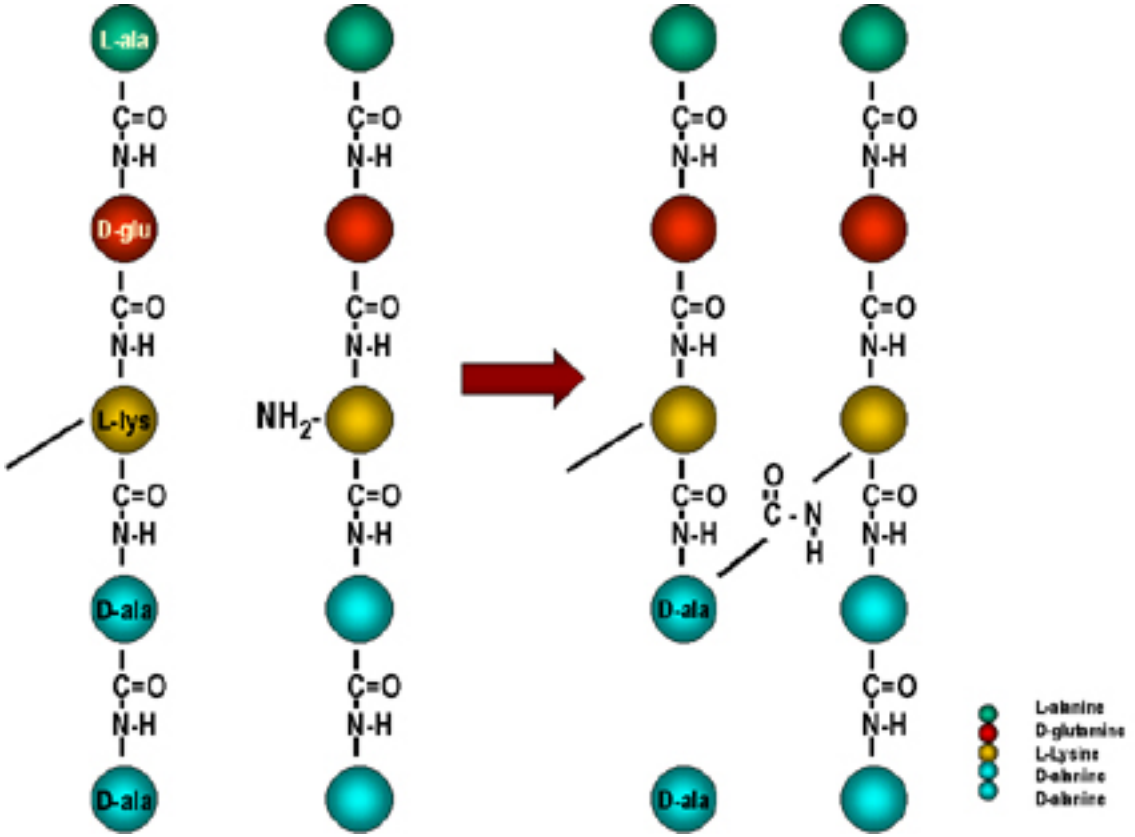
MECHANISM OF ACTION

- 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

MOA


L-ala
D-glu
L-lys
D-ala
D-ala
NH2-
D-ala
D-ala
L-alanine
D-glutamine
L-Lysine
D-alanine
D-alanine

MOA

- 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-alanyl-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.

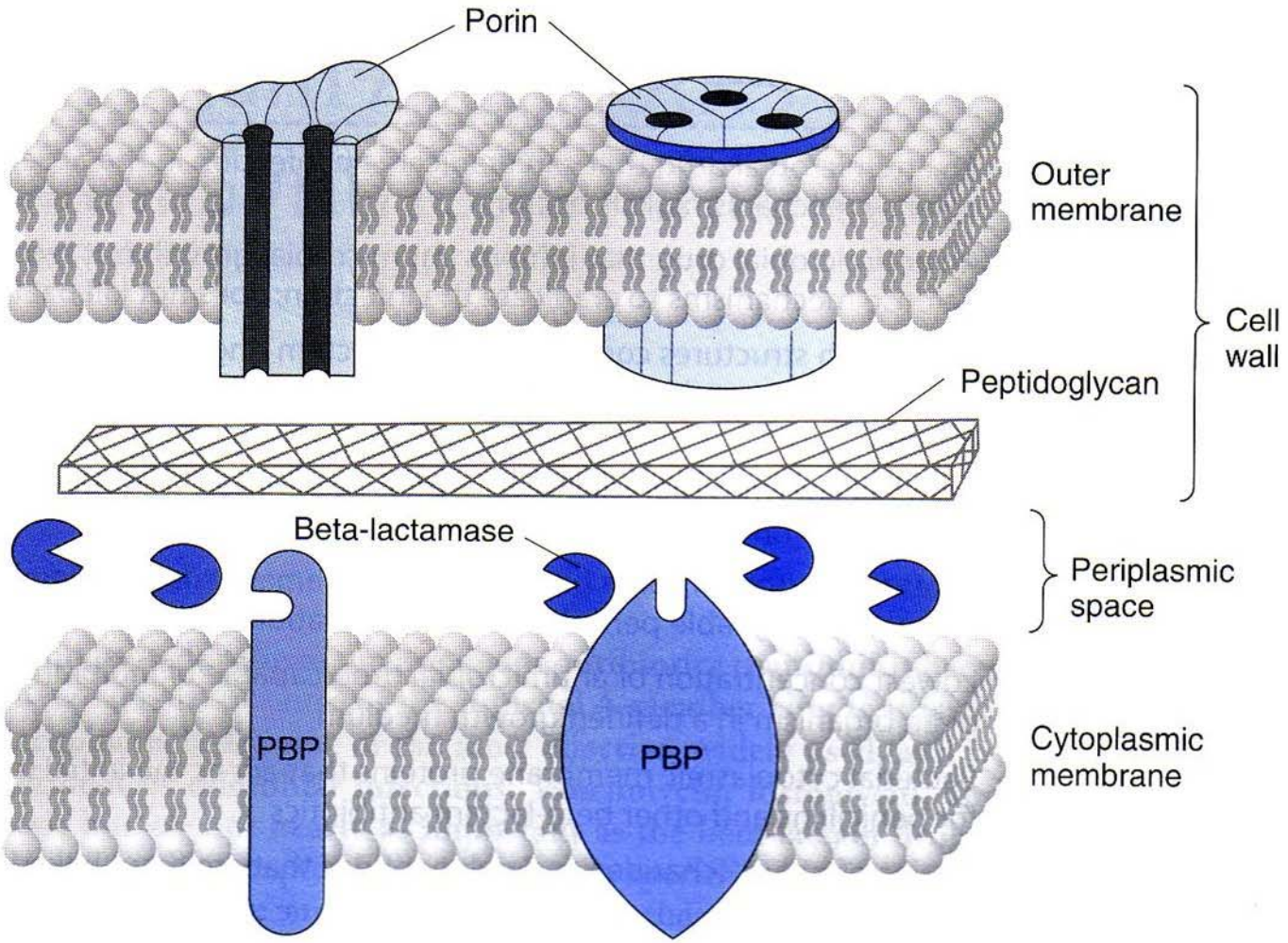


Figure 43–1. Beta-lactams and bacterial cell wall synthesis. The outer membrane shown in this simplified diagram is present only in gram-negative organisms. It is penetrated by proteins (porins) that are permeable to hydrophilic substances such as beta-lactam antibiotics. The peptidoglycan chains (mureins) 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.)

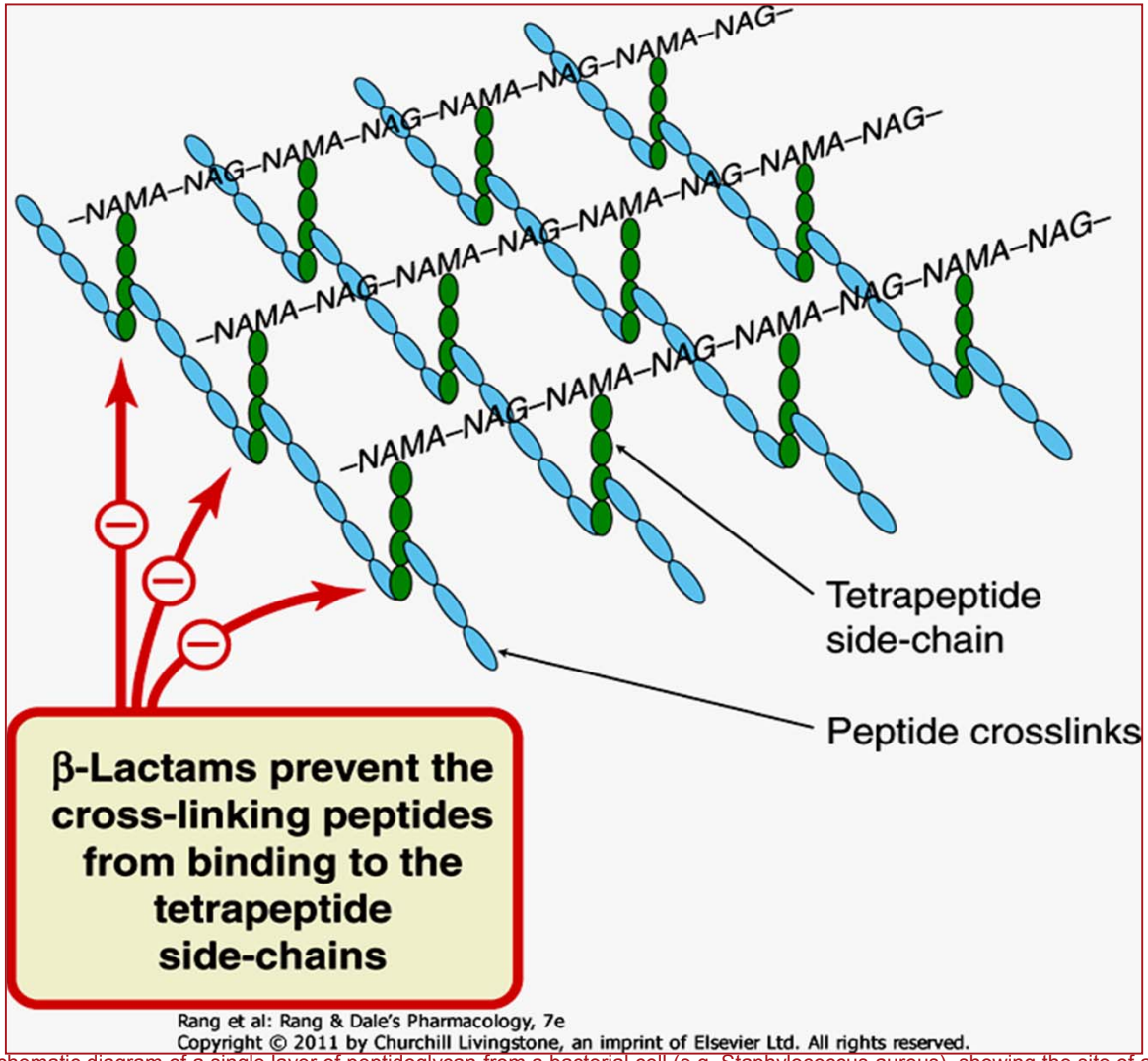


Figure 49.2 Schematic diagram of a single layer of peptidoglycan from a bacterial cell (e.g. Staphylococcus aureus), showing the site of action of the β-lactam antibiotics. In S. aureus, the peptide crosslinks consist of five glycine residues. Gram-positive bacteria have several layers of peptidoglycan. (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 β LACTAMASES
- STAPH, GONOCOCCI, B.SUBTILIS, E.COLI, H.INFLUENZAE PRODUCE PENCILLINASE.

- EFFLUX– GRAM NEGATIVE ORGANISMS MAY PRODUCE AN EFFLUX PUMP WHICH TRANSPORT β 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 penicllin, 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
- Methicilin, 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
- PNEMOCOCCAL 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(methicillin)

- 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 AG. 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.

PENICILLINASE RESISTANT PEN.contd

- 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 OSTEOMYLITIS, 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 AG. SHIGELLA AND H.INFLUENZAE.
- PREFFERED 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.

UREIDOPENICILLIN

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 LACTAMASE INHIBITORS

- **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 TICARCILLIN 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 imepenem 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 syst 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 DEHDROPEPTIDASE, CILASTATIN . A PREPRATION 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 EMPERICAL 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 DE USED ALONE - RESISTANCE RISK

Imipenem

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

MONOBACTAMS

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.

ANTIBACT.ACTIVITY

- 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.

P/K

- 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-aminocephalosporanic 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. MONOCYTOGENES , C. DIFFICLE , ENTEROCOCCI*

C/F

FIRST GENERATION

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

SECOND GENERATION

- PARENTERAL
- CEFUROXIME
- CEFOXITIN

- ORAL
- CEFACLOR
- CEFUROXIME AXETIL

THIRD GENERATION

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

- ORAL
- CEFIXIME
- CEFDINIR
- CEFPODOXIME
- CEFTIBUTEN

FOURTH GENERATION

- PARENTERAL
- CEFEPIME
- CEFPIROME

Table 7–2. Clinical uses of cephalosporins.

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

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 Penicilln 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 AG. KLEBSIELLA & E.COLI
- SUSCEPTIBLE TO STAPH BETA-LACTAMASE
- PREFFERED 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.
- ANEROBIC & 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 TS. INFECTIONS, MENINGITIS, SEPTICAEMIAS .
- EXCRETED MAINLY IN BILE
- **DISULFIRAM LIKE REACTION WITH ALCOHOL.**

CEFIXIME

- ORALLY ACTIVE WITH HIGH ACTIVITY ag. Entero-bacteriaceae, H.Influenzae, strep. Pyogenes , strep. Pneumoniae
- 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 AG. 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

S/Es of Cephalosporins

- 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 cephaloridine (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.

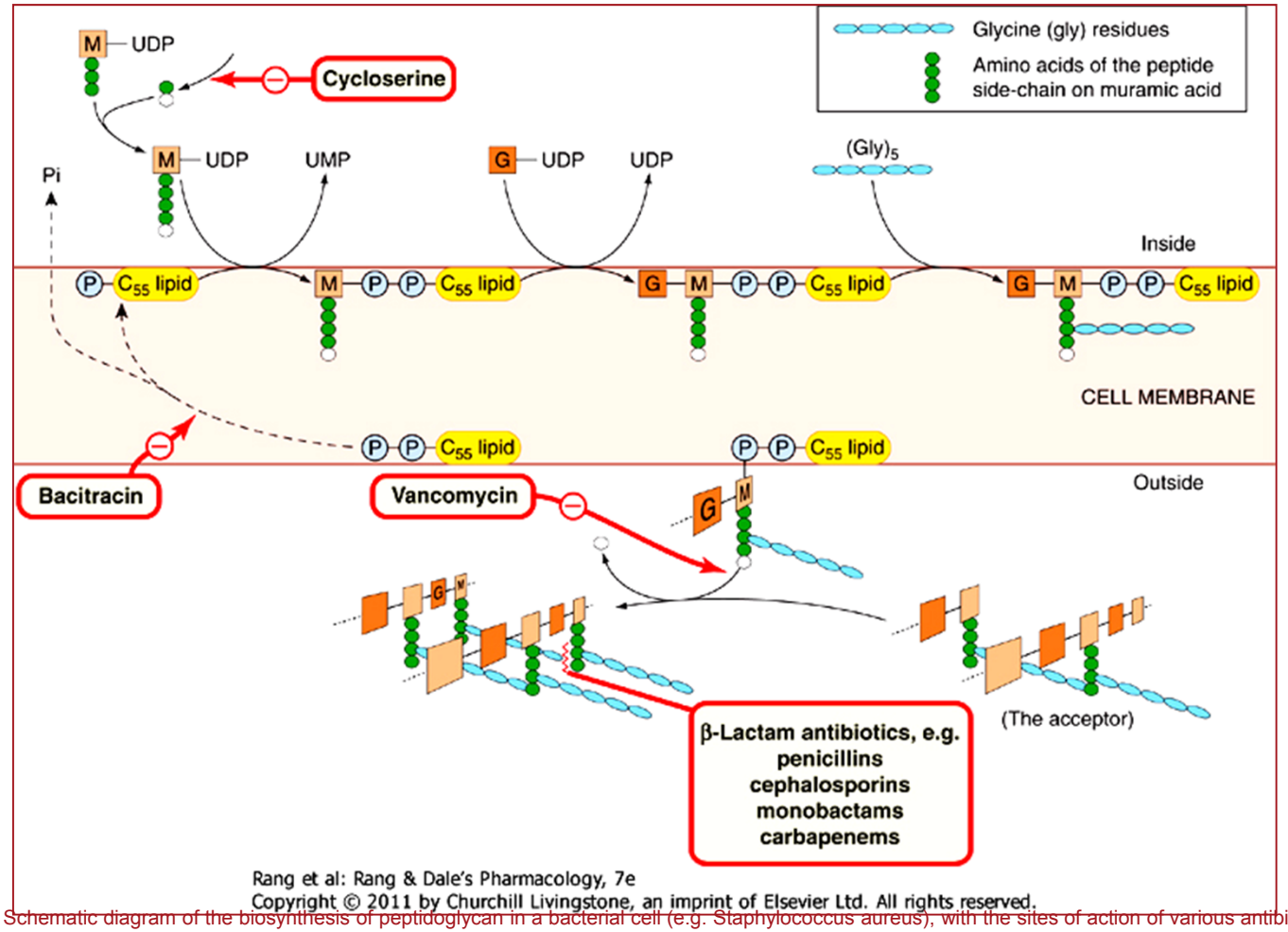


Figure 49.3 Schematic diagram of the biosynthesis of peptidoglycan in a bacterial cell (e.g. Staphylococcus aureus), with the sites of action of various antibiotics. The hydrophilic disaccharide-pentapeptide is transferred across the lipid cell membrane attached to a large lipid (C55 lipid) by a pyrophosphate 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.