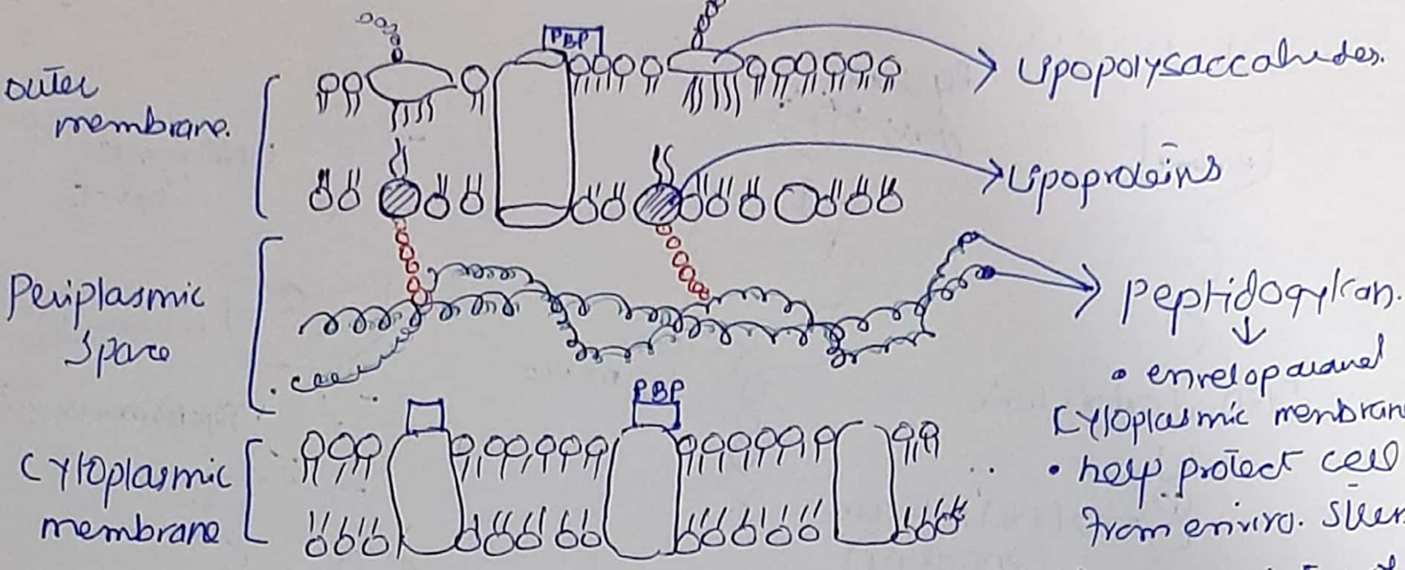
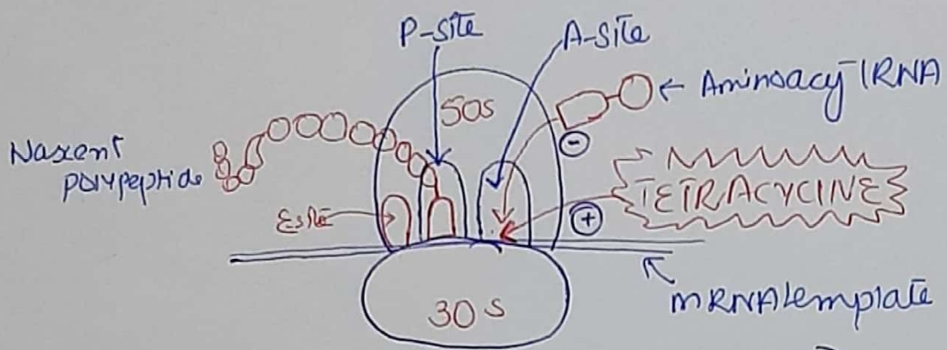
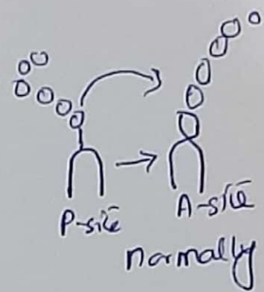


peptidoglycan.
↓
- envelop around cytoplasmic membrane
- help protect cell from enviro. stress
- imp regulator of cell division.

Cell-wall - INHIBITOR





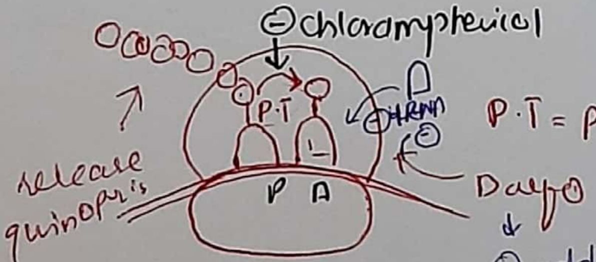
Ribosome (protein factory).

→ Aminoglycosides (gr-ve cff) also binds to A-site → interfere c̄ ribo. assembly by causing distortion
→ misread mRNA
→ ⊖ A-site → p-site translocation

Macro-lides ⇒

⊖ Transpeptidation (movement of amino acid residue from 1 amino to other)

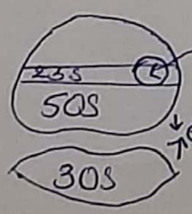
⊖ Translocation



P.T = present in 50S subunit
Peptidyl transferase

Dalfo
↓
⊖ add. of new A.A to growing peptide chain

- Linezolid



linzo
⊖ = inhibit formation of initiation complex.

- Fidaxomicin = (macrocyclic).

R — S — binds to sigma subunit
RNA polymerase

- clindomycin like Aminogl. but belong to Lincosamide.

CELL-WALL INHIBITOR — PENECILLINS

- To be max. effective — cell 'be in actively proliferating (dividing microorg)
- Member of this family differ from one another in R_1-subs.
  (of 6-AMINO PENICILLANIC ACID RESIDUE
  ↳ This side chain affect — (1) spectrum (2) stability to stomach acid (3) cross-hypersen. (4) susceptibility to β-lactamases.
- These're bactericidal & work in Time-dep. fashion.

Penecillin = 1928.

MECHANISM

⊖ PBPs (⊖ → peptidoglycan biosynthesis)
- ↓se maintaince of morphol. features
- ↓ cross-link.
- PBP're in periplasmic space

⊖ Transpeptidase
- inhibit cross-links b/w peptidoglycan chain
- ↓se cell wall integrity

⊕ Autolysins
- ↑se degradation & cut synthesis of new wall.

ANT-BACTERIAL SPECTRUM

- Penecillin easily transversed gram +ve org.
- Gram -ve bac.; have outer lipo-polysacc. membrane — barrier to water-soluble penecillin.
  - However have protein — act as porins or water filled channel → allow permeability

Natural penecillins
1) Pen-G (BENZYL-PENECI.) is cornerstone of therapy for a number of gram +ve, -ve (cocci) gr. +ve (bacilli) spirochete
2) Gas gangrene (DOC) — clostridium perfringens.
3) syphilis (STD) (Treponema pallidum)
⇒ Pen-V (more acid stable — given orally — spectrum same/similar to G)
(minim. inhibi. conc. = PenV)

Anti-staphylococcal
- β-lactamase resistant
- use for treatment of MSSA
- minimal — No activity against (gram -ve)

Extended-spectrum
- Spec. similar to Pen-G BUT more effective against Gr. -ve Bacilli
- Listeria monocytogenes (gram +ve bacillus) (food poisoning)
- Enterococcal species
- Respir. infec.
- Prevention of endocarditis
- When combined ē sulbactum or clavulinic acid → effective against MSSA, otherwise MSSA is resistant to them

Antipseudomonal
- Avail as parenteral prep only
- piperacillin is most eff. in this class.
- Combination ē clarinic acid or Tazobactum ↑se the spectrum
- Ticarcillin
- carbenicillin

(HHNN-D)
DH²N²

ADRs

Hypersensitivity
- 5% patients
- Rashes → Angioedema (Lip swelling, tongue, periorbital area)
- cross-allergic rex.

Diarrhea
- mostly due to extended spec. antibio.

Nephritis
- Particularly ē methicillin

Neurotoxicity
- Intrathecal injec. can cause seizures
- cause Gabaergic inhibition.

Hemo. toxicity
- ↓se coagulat. (Piperac, Ticar- and Nafcillin)
- cytopenias (MT 2 week therapy)

Resistance

[mycobacterium has cell wall (mycolic acid)]

- absence of peptidoglycan wall (e.g Mycoplasma pneumonia) — doesn't contain cell wall.
- cell wall impermeable to drugs.

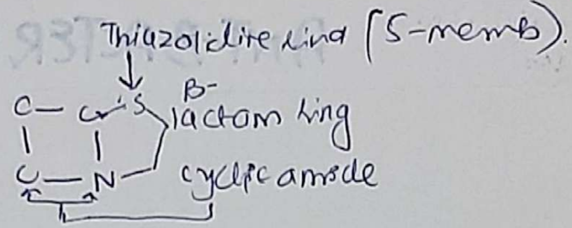
Mechanisms

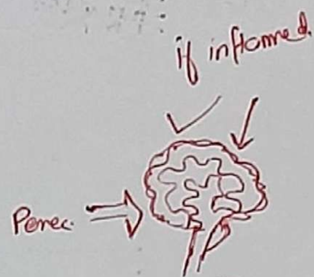
β-lactamase Activity
- β-lactamase hydrolyze [Break] the cyclic amide bond of β-lactam ring
- produce by chromosomes or acquired by transfer of plasmids
- Gram +ve → secrete extracellular β-lac.
  Gram -ve → periplasmic spaces.

↓se permeability to drug
presence of efflux pumps e.g in Klebsiella pneumoniae

Altered PBPs
modified PBPs ⇒ lowers affinity for β-lactam.

Do watch lecture on Pharmaco-study youtube





KINECTICS

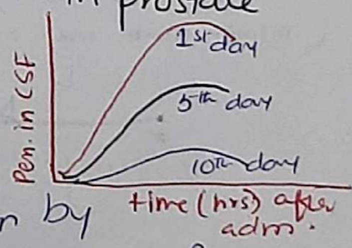
Routes of adm
[ampicilli + sulbac.]
[ticarci + clavini]
[piper + Tazobac] — must be IV / IM — Tonzo (Brand)
[nafcilli, oxacillin]

- pen V, amoxi, & dicloxacillin avail as oral, ampicillin
- amoxic ē clavin — oral.
- procain PenG & Benzathine PenG — IM — depot form } V — empty stomach preffered.

Absorp.
- incomp. abs. after oral adm.
- food ↓ abs. of penc.-resis-penicllin as ↓se gastric emptying = ↑se time in stomach = destroy by stomach acid

Distribu
- Distribute well
- cross-placenta → teratogenic
- penetrate in bones or CSF (in inflamed condition of meningies)
- NOT much penetrate/enter in prostate

PG



Excre:- Through Kidney.
PROBENECID inhibit secretion of penicillin by competing for active tubular secre. via organic acid transporter

- Also excreted in Breast milk — BF avoi

CEPHALOSPORINS

Most of them are produced semi-syn by chemical attachment of side chain to 7-aminocephalosporanic acid. Have sam MOA & same MOR. However, they tends to more resistant than penci to certain β-lactamases

GENERATIONS

First

* Cefazolin
- Parenteral
- Long DOA
- Spectrum similar to other
- penetrate in bones
* cephalexin
- Prototype of 1st oral gene
- BID PO effective → Pharyngitis
* -cefadroxil - PO ← cephradine
⇨ 1st gen. act as pen-G substitutes
⇨ Effective against
- MSSA
- P. mirabilis } -ve rods
- E.coli
- K-pneumoniae
- S. aureus
- S. epidermidis } +ve cocci
- St. pneumoniae
- St. pyogenes
- Anaer. strep

second

* -Cefuroxime -Na
• prototype of paren.
• long DOA
• cross-BBB
• CAP
* Cefux. axetil (PO ← cefuroxime)
• BID effec. against β-lactamase-Producing org
⇨ SPECTRUM
• more active against g.-ve
- H. influenza } -ve rods
- Enterobacter aerogenes
- Neisseria (-ve cocci)
Same.
weakly effective against
S. aureus } +ve cocci?
St. pneumoniae
St. pyogenes
Anaero. strep
* -Anaerobic org. (cefoxitin, cefotetan)

3rd (Cefoperazone less potent than 1st gene against MSSA)

* ceftriaxone cefotaxime
Penetrate CSF → DOC → Meningitis
* -ceftazidime, active against P. aeruginosa
* -cefdinir, cefixime OD PO.
* -ceftriaxone
• longest t½ of any cepho. (6-8 hr)
• so OD
• Against genital, anal & pharyneal Pen-resis N. gonorrhea
• excreted in bile
• can be use in renal insuff.
• penetrate into bones.

Gram +ve cocci
• strep [pneumonea / pyog
• Anaero. strep
-ve cocci (N. gonor)
-ve rods (same as previous including Serratia marcescens)

fourth

cefepime
- against P. aeruginosa
- parentral.
⇨ only methicilin-SENSITIVE (staphy & strep)
• Aerobic gr. -ve
- Enterobactor
- E. coli
- K-pneumoniae
- P. mirabilis
- P. aeruginosa
[opportunistic gr-ve: Respir infec. wound infec meningitis, UTI

ADVANCED GENER.

- ceftaroline (broad spec.) (IV as prodrug) (ceftaurine fosamil)
- Indicated for MRSA (Penicillin binding protein), CAP, Complicated skin infec.
- Binds to PBP2a (found in MRSA) and PBP 2x (strep. pneum)
- gram -ve coverag similar to ceftriaxone
* -Cephalosp'rs susceptible to ESBLs (E. coli, k. pneum), NOT succeptible to hydrolysis by S. Penicillares
Extended-spectrum β-lactamases

KINETICS

ADMINIS

- must be given IV/Im except those as previously told.

Distribution

- Distribute well
- penetrate CSF, regardless of inflamm. (cefotaxime, ceftriax)
- cefazolin ($t_{\frac{1}{2}}$ 1.8hr) use as single prophylactic ~~agent~~ (dose) prior to surgery (S. aureus).
  - esp. orthopedic surgery due to ability to penetrate bones.
- All of them cross → placenta

Elimination

Kidney. (GFR + secretion)

exception ceftriaxone → (Bile)

ADRs

- allergic rxn (Pt ē penecillin induced disease SJ-syndrome or toxic epidermal necrosis)
- Diarrhea

Do watch lecture on Pharmaco-study youtube

CARBAPENEMS — β-lactam antibiotics

- In its structure sulfur atom has been externalized from Thiazolidine ring and has been replaced by C atom.
- compounded ē cilastatin to protect it from metabo. by renal dehydropeptidase (This enzy produce Nephro toxic inactive metab. in proximal brush border)

Spectrum

Resist β-lactamases except Metallo-β-lactamases

Imipenems/Mero/Dori

- +ve cocci
  - S. aureus
  - S. epidermidis
  - Strep. A, B, C
  - Strep. pneumoniae
  - Enterococcus faecalis
- +ve bacilli – Listeria. mo.
- -ve cocci – Neiss. gonorr. Neiss. meningitis
- -ve rods
  - Acinetobacter, citrobacter, Enterobacter (species).
  - E. coli
  - H. influenza
  - Klebsiella sp.
  - proteus sp.
  - Gardnerella vaginalis
  - Providencia sp.
  - P. aeruginosa
  - Salmonella
  - serratia.
- Anaerobic org.
  - Clostridium
  - Peptococcus
  - Peptostreptococcus
  - Bacteroides
  - Fusobacterium

  (species)
- Other
  - Actinomyces
  - Nocardia sp.

Kinectics

- Imip/cilastatin & meroperem are adm — IV
- penetrate CSF (when inflamed)
- Meroperem reaches therap. level even without inflam
- Ertaperem — IV/IM OD (This drug lack coverage against P. aero, Enterocc, Acineto.
- Doses must be adj in renal insufficiency → Ar. or Adj

ADRs.

- N/V/D.
- eosinophilia } less common than other
- Neutropenia }
- High level = seizures

MONOBACTAMS

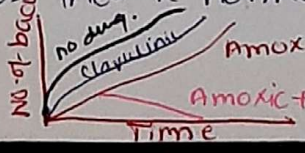
Aztreonam

- β-lactam antibio, but rings are not fused to each other
- Directed primarily against (gr.-ve) [enterobacteriaceae & P. aerog.]
- lack activity against gr +ve. (like 2nd gene. ceph)
- Resist β-lactamase except ESBLs.
- IV/IVM
- Accumulate in renal insuff. → Ar. Adj
- ⇨ Relatively Non-toxic., may cause Phlebitis, skin rash, abnor. LFT
- ⇨ Safer for pt. allergic to pencill, cepha or carbapenems.

β-LACTAMASE INHIBITORS

★ – contain β-lactam ring — NOT significant antibacterial activity or adrs.

★ – They bind & inactivate β-lactamases thus protecting Antibiotics that r/e normal substrate for these enzym.



POLYMYXINS

* - are cation polypeptides — binds to phospholipids on bac cell membrane of gr-ve bac.
* - Detergent like effect — disrupt cell mem. integrity → cellular compon. leaks ↓ death.
* - conc. dep. bactericidal agent.

Spectrum

P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter sp, Enterobacter sp.

Resistance: - alteration in cell mem of lipid polysaccharide (Proteus & serratia)

Forms < B – avail in parenteral, enteral (oral or tube feeding), opth, otic & topical preps.
E (colistin) – avail only as pro-drug (colistimethate Na+)
↓
IV, inhaler via nebulizer

Systemic Adminis. ↑se risk of Nephro & Neurotox ↓ sunken speech, muscle weakness

* - Now-a-days commonly used as Salvage Therapy ē MDI (infections)

[careful dosing & monitoring of adr = maximize safety & efficacy.

FOSFOMYCIN

* - Bactericidal syn. derivative of phosphonic acid
* - Inhibitor of enzy UDP-N-acetylglucosamine enolpyruvyl transferase (UDP-NAGET)
Fosfo ⊖ ↓
catalyze 1st step in peptidoglycan synthesis

Therap. use:- UTI (caused by E. coli or E. faecalis) OD ↓ as it maintain high conc. in urine.

- NO cross resis ē other antimicro.
- rapidly abs. after oral adm.
- Distrib. well to kidneys, bladder & prostate
- excreted well in active form in urine & feces.

(1g 1 day 1 time)

ADRs: Diarrhea, vaginitis, Nauseas & headache.

Characteri.	VANCOMYCIN	DAPTOMYCIN	TELAVACIN
MOA	Inhibit cell wall phospho-lipid as well as peptidoglycan polymeri.	Cause rapid depolarization of cell mem., inhibit intracellular syn. of DNA, RNA & protein	Inhibit cell wall synthesis, disrupt cell memb.
DYNAMICS	Time-dependent bactericidal	conc. dep. Bactericidal	conc. dep. -cidal
common Spectrum	+ve (S. aureus [including MRSA], Strep pyogenes, S. agalactiae, Penicillin resis S. pneumoniae, Corynebacterium jeikeium, vanco.-susceptible Enterococcus faecalis & E. faecium.		
Unique Spectrum	Clostridium difficile (oral only) g+ve	vanco. resis. E. faecalis and E. faecium (VRE)	vanco-resis. entero cocci (VRE)
Route	IV/PO	IV	IV
Typical adm. Time	60-90 min IV infusion	2 min IV push 30 min IV infus.	60min IV infus.
Kinectics	- Renal elimination - $t_{1/2}$: 6-10hr - Dose adj based on renal func. & serum trough level	- Renal elimi - $t_{1/2}$: 7-8hr - Dose adjustment on renal func.	- Renal elim (T) - $t_{1/2}$ 7-9hr - " " (↑QTc) (PG)
Unique ADRs	Infusion related rex due to histamin release: fever, chills, Phlebitis, Flushing (Red-man syndome) - Dose-related oto-Nephrotoxicity	• Myalgias, • ↑ hepatic transaminases & creatinine phospholcinases (check weekly) • Rhabdomyolysis (consider holding HMG-CoA red. inhib. statin, while on therapy)	• Taste disturbance • foamy urine, QTc prolon • Interfer ē coag. labs (PT/INR, aPTT, ACT) NOT recommended in Pregnancy. (Taste distw also in AECI)
Key learning points:	• DOC — Sever MRSA • Oral form used only for C. difficile Resistance: • Plasmid-medi changes in drug permeab. • ↓ Vanco binding to receptor mol. • monitor serum trough conc. for safety & effc	• Dapto. inactivated by pulmanory surfactants • Never used in Pneumonia Reduce surface tension at air-liquid interface L.P.S = Complex of lipid & protein found in lipid lining alveolar surface of lungs	• Caution in pt ē renal dysfunction (CrCl<50ml/min) • Necessary coag. lab. should be drawn just prior to Telavancin dose to avoid interaction