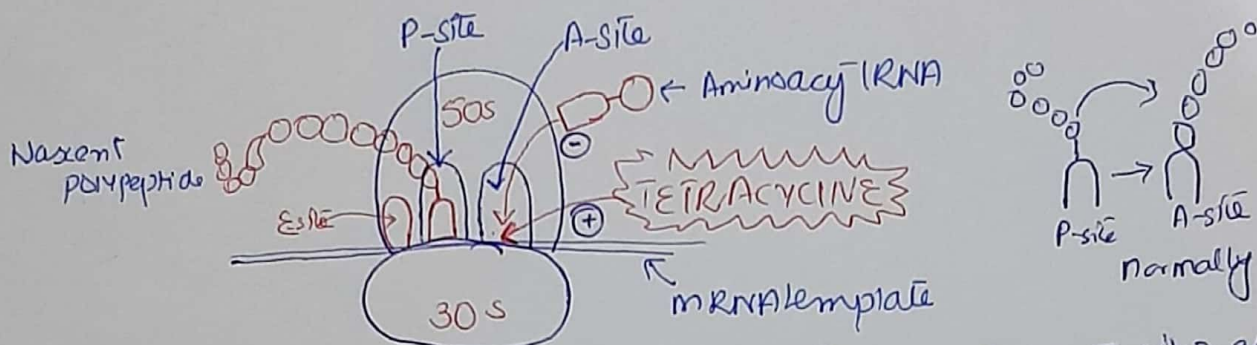
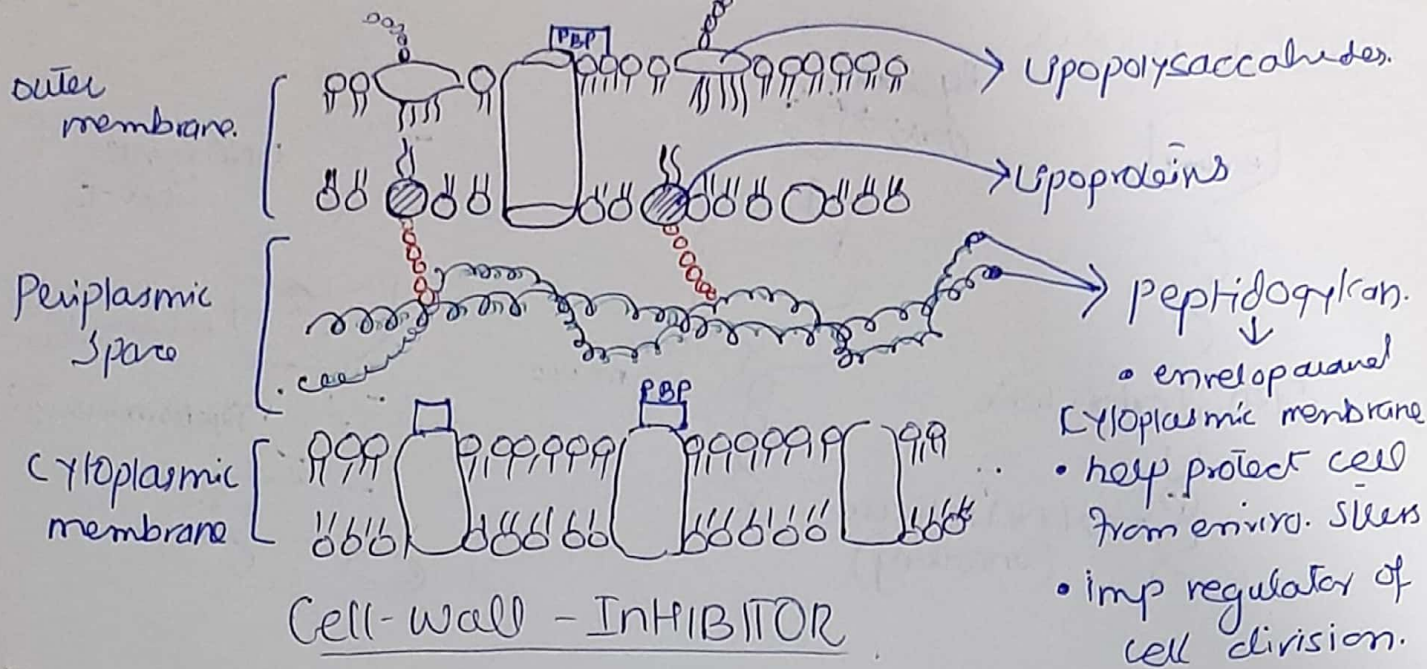




→ Aminoglycosides also binds to A-site

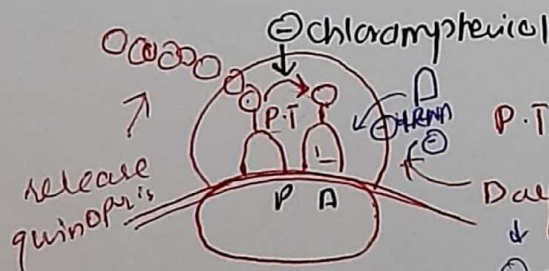
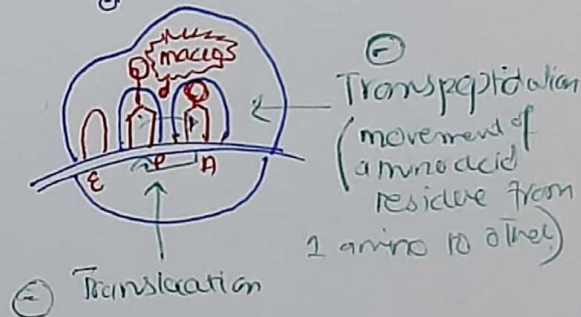
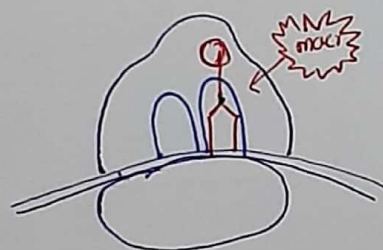
Ribosome (protein factory)

interferes w/ ribo. assembly by causing distortion

mistake mRNA

A-site → P-site translocation

Macrolides



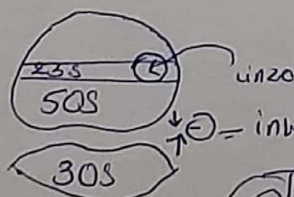
P.T = present in 50S subunit

Peptide transferase

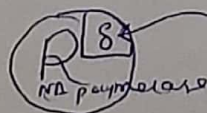
↓

add. of new A.A to growing peptide chain

Linezolid



Fidaxomicin = (macrolide)



clindamycin like Aminoglyc. but belong to lincosamide

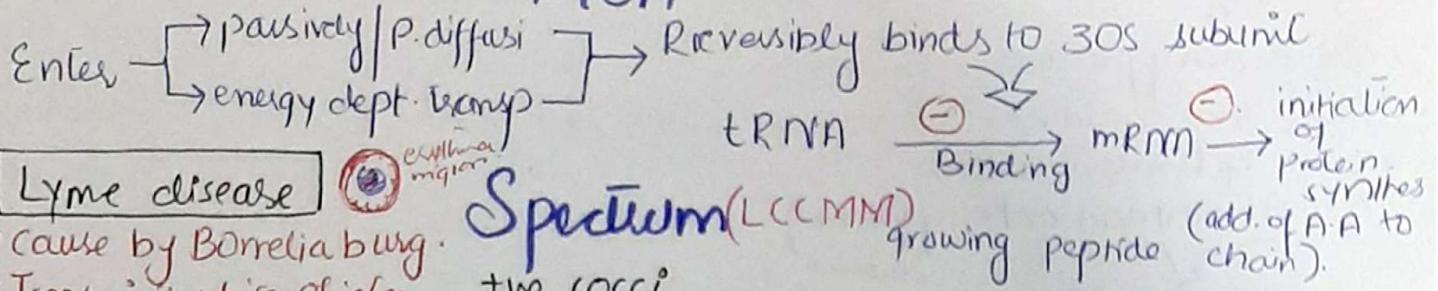
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TETRACYCLINES

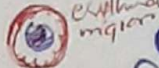
(Bacteriostatic)

- four fused rings & a system of conjugated double bonds.
- substit. on these rings alter → kinetics • spectrum

MOA



Lyme disease



Spectrum (LCCMM)

- cause by *Borrelia burg.*
- Transm. by bite of infect. ticks
- Result in skin lesions, St. pneumoniae headache, fever → Meningo +ve bacilli
- encephalitis → arthritis: *Bacillus anthracis*
- Bull's eye pattern rash -ve rods

Red outer ring, called "erythema migrans" is Hallmark of Lyme disease.

Treatment: Doxycycline

MYCOPLASMA PNEUMONIAE

or walking pneumonia, common cause of CAP - common in young adults & people who live in close confines such as in military camps.

Treatment: Macrolid or Doxycycline is effective.

RESISTANCE:-

- 1) impaired influx
- 2) efflux pumps
- 3) enzymatic inactivation
- 4) inhibition of binding to rib. by protein production

• Desferrioxamine, anti-diabetic hormone prepare SAID

+ve cocci

St. aureus (incl. MRSA)

Cholera

- caused by *Vibrio ch.*
- ingested in fecally contaminated food & water
- multiplies in GIT → secrete enterotoxins

Bacillus sp.

Vibrio cholerae

Yersinia pestis

Anaerob. organism

Clostridium perfringens

C. tetani - Tetanus

Spirochetes

Borrelia burgdorferi

Leptospira interrogans

Treponema pallidum (Syphilis)

Mycoplasma (don't possess cell wall)

Chlamydia (ch. sp.)

Other (Rickettsia rickettsii)

TREATMENT:

doxycycline → ↓ se no. of infect. vibrio.

fluid rep.

Chlamydial Infections

C. trachomatis major cause of STD in US

causes → Non-gonococcal urethritis → pelvic inflamm.

→ Lymphogranuloma venereum (LGV)

C. psittaci (Skin lesion + lymphadenopathy in groin or pelvis)

cause psittacosis which usually takes the form of pneumonia

other clinical form: Hepatitis, myocarditis & cancer

• Doxycycline or Azithromycin

Rocky Mountain Spotted fever

- caused by *Rickettsia Rickettsii*
- fever, chills & joint pain, bone ache
- Tetracycline response is prompt if drug started in early disease process.

PHARMACOKINETICS

Absorp.

- abs. orally.
- tabs & diary products or subs. that contains divalent & trivalent cations (mg & Al antacid or Fe supplement)

Distribution

- well distrib. in bile, liver, kid. gingival fluid, & skin
- Binds to tissues undergo calcification or tumors (high Ca^{2+} content)
- All of them cross placental barrier & concentrate in fetal bones & dentition.

Elimination

- Tetracycline & doxy NOT metabol. by liver
- Tetracycline $\xrightarrow{\text{unchanged}}$ urine
- mino $\xrightarrow{\text{hepatic}}$ less kidney excret. (use ceftriaxone)
- Doxy $\xrightarrow{\text{Bile excret.}}$ (useful in renal compromise)

Chelate formation $\rightarrow$ Doxy & Mino $\rightarrow$ oral & IV

- Mino & Doxy $\rightarrow$ CSF (meningococcal carrier state eradica)
- Mino $\rightarrow$ Tears & saliva



ADRS

Gastric Discomfort

- Epigastric discomfort
- Esophagitis (use $\bar{e}$ O-adm of food or fluids)
- take capsules rather than tab) - should be taken on empty stomach.

Effect on Calcified Tissue

- Discoloration & Hypoplasia of teeth
- Temp. summing of growth

Hepatotox.

- High dose
- pregnan.
- renal impair

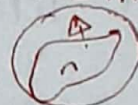
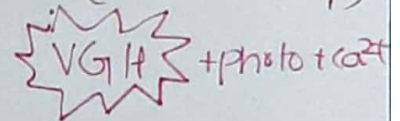


photo-toxic.

- more $\bar{e}$ Tetracycline & demedocyc.

vestibular dysfunction.

- Dizziness
- vertigo
- Tinnitus (mino & doxy.)



PGI & Bi-Feed. < 8yr child

ceftazidime = comp. skin infec

GLYCOCYCCLINES

"Tigecycline"

- Derivative of minocycline
- indicated for treatment of

- (1) complic. skin & soft tissue infec.
- (2) comp. intra-abdominal infec.

MOA

- Bac. static
- reversible binds to 30S. ribo.

Spectrum (Broad-spec.)

- MRSA
- multidrug resis. streptoc.
- VRE
- Exten. spec. β -lactam. produ. gram -ve bac (ESBLs)
- Acinetobacter baumannii
- many anaerobic

Resistan.

- Tigecycline is used for resistant bac (Tetracycline).
- However res. develop due to over expression of efflux pump.

KINETICS

- IV = large vol
- penetrates in tissue
- $\downarrow$ Cp (so NOT use for broad infections)
- excre via bile/feces

ADRS

- N/V
- photosem
- Discolor. of teeth
- Tetal naum
- Use cleare
- $\uparrow$ Liver enzyme
- $\uparrow$ serum creatinin

NOT Active against Morganella, Proteus, Providencia or pseudomonas sp.

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2 amino sugar joined by a glycosidic linkage to a central hexose nucleus. **AMINOGLYCOSIDES** Derived either from *Streptomyces* sp. (Bactericidal) (mycin) or *Micromonospora* sp. (mycin).

MOA

Difuses $\left\{ \begin{array}{l} \text{aqueous pores} \\ \text{O}_2\text{-dep. sys.} \end{array} \right\}$ $\rightarrow$ **Binds to 30S** $\rightarrow$ $\left\{ \begin{array}{l} \text{interfere ribo. assem. by causing distortion of binding at A-site} \\ \text{and/or} \\ \text{cause 30S rib. to misread genetic code} \\ \text{inhibit translocation of peptidyl-tRNA from A-site to P-site} \end{array} \right.$

- More Active @ yre org. $\rightarrow$ to the cytoplasm

- Bactericidal in nature & conc. • efficacy & (max) above MIC

- Cmax > (8-10 times) MIC - Exhibit post-antibiotic effect conc. (PAE) - continue bac. suppression after

The drug level falls below MIC. * $\uparrow$ dose = $\uparrow$ PAE so OD is preferred.

[mycin, micin, cin $\rightarrow$ aminoglycosi]
[Affect skin, eye & lymph nodes]

Spectrum And Therapeutic App. TB.

acquired during (rabbit fever or rabbit-hunting deer fly fever) season by hunters skinning infec. animals

Gram the cocci

- 1) Enterococcus sp.
- 2) strep. agalactiae

Gram-re. (DGC-Amino).

- 1) Acinetobacter Baumannii
- 2) Brucella sp. (gentam + Doxy)
- 3) Klebsiella sp
- 4) P. aerogenosa
- 5) Yersinia pestis (streptomycin)
- 6) Francisella Tularensis (genta)

Amnoglyc. may be added to β -lactam (ampi + genta) for synergy for serious gram neg infec.

P. aerogenosa mostly cause infec. in pts & sp. risk factor (recent antibiotic expos prolong hospitalization).

branchiectasis (permanent enlargement) of parais of airways

• **gentam. is effective** in treating this rare lymphoid disease. (Turn-page)

Resistance

- 1) Efflux pump
- 2) $\downarrow$ uptake
- 3) modif or inac. of enzym.
- 4) NO cross-resistance
- 5) Amikacin less vulnerable to enzy. than any other in this group.

Soframycin $\rightarrow$ Framycetin (Sofra = dressing Tulle)

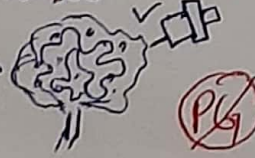
IV (Topical)

KINETICS

Ads.

Highly polar, polycationic steric. Prevent oral abs. $\Rightarrow$ Parenteral except

Neomycin (if it's given paren. it is highly nephro. or ORALLY for bowel preparation prior to colorectal surgery)

enter $\rightarrow$  (PG)

Distribut.

- Hydrophilic
- less disl. to fatty tissue
- Dose give acc to lean body mass instead of actual body wt.
- CSF conc. = Inadeq.
- CROSS PLACENTA $\rightarrow$ Accum in fetal plasma
- Body wt - Body fat

Excretion.

- Unchanged in urine
- Dose adj. in renal dysfn.

↓
Otoxicity

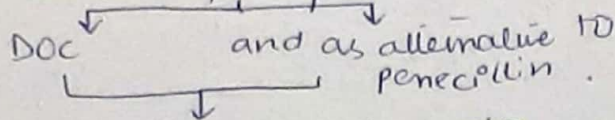
- vertigo (esp. e. sleep) (m. c.)

A $\left\{ \begin{array}{l} \text{Amalgam} \rightarrow \text{TB} \\ \text{A-site} \\ \text{Amalgam} \rightarrow \text{resistance} \\ \text{Amalgam} \rightarrow \text{reproductive disease} \end{array} \right.$



MACROLIDES

- have macrocyclic lactone struc. to e one or more deoxy sugar 're attach
- **Erythromycin** - first of these drugs



- clarithromycin (methylated erythromycin)
- Azithromycin (large lactone ring)

some due to efflux pump in penicillin allergy features're common

KETOLIDES

- Telithromycin (semi-syn. derivative of erythromycin) - first ketolide.

- * - Keto and macrolid have similar antimicrobial coverage. However ketolides are active against many macrolide-resistant gram +ve strains.

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Mechanism

Binds to 50S subunit - inhibit translocation step (movement of newly elongated peptidyl chain from aminoacyl site to peptidyl site of ribosome) → interfere e transpeptidation (amino acid residue transferred from one amino compound to other)

- Generally **Bacteriostatic** - **cidal at high doses**
- Binding site - identical or in close proximity to that for **clindamycin** & **chloramphenicol** - sometimes antagonism at action

C. Diphtheriae

Spectrum And Uses

Erythromycin or penicillin is used to eliminate the carrier state

Chlamydial infec.

Azithro OR DOXYCYCLE are preferred.

Erythromycin

- Spec. same as pen. G
- may be use in Pt e penicillin allergy.

Clarithromycin - ketoacid

Similar activity like erythro

But more effective for (resp.)

- H. influenza
- Chlamydia
- Ureaplasma
- H. pylori (ulcer)

Azithromycin

- less active again steep or stop than erythromycin (Gram -ve)
- More active against resp. infection (H. influenza & Moraxella)
- preferred for **Melthoff's** caused by chlamydia trachomatis

Corynebacterium diphtheriae

- (+) cocci
- Step. pyogenes
- Step. pneumoniae
- (+) bacilli
- Moraxella catarrhalis
- N. gonorrhoeae
- (-) rod
- Bordetella pertussis
- Campylobacter jejuni
- H. influenza
- Legionella pneumophila

Spirochetes

Treponema pallidum

Mycoplasma

M. pneumoniae

Ureaplasma urealyticum

Chlamydia

- C. pneumoniae
- C. psittaci
- C. trachomatis

Other

Mycobac. avium complex

Legionellosis

Undiagnosed & asymptomatic all common.

- * - Fluoroquinolone OR Azithromycin are preferred.

M. pneumoniae

- Also called "atypical pneum"

- * Azithro or Doxycycline are preferred.

M. Avium complex

Azithro in comb. e rifampin & ethambutol is preferred.

- * Once-weekly azithro is use as prophylaxis in AIDS pts.

Telithromycin

Spec. similar to azithro

- use for macrolid resis spec. as it neutralises the most common resis. mechanism (methylase-mediated)

(efflux mediated)

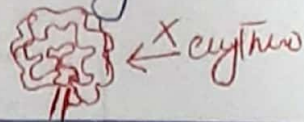
RESISTANCE

30S rSOS = 10S bac. rib.

- Inability of organism to take-up the antibiotic
- Efflux pumps
- Plasmid-associated eryth esterases in g-ve such as in enterobacteriaceae
- Use of affinity for 50S sub-unit - due to methylation of adenine in 23S bac. ribo. RNA

clarith & azithro share some cross-resis. e erythromycin.
BUT TELITHROMYCIN may be effective against macro-resis. org.

KINETICS



ADMINI

Erythro - destroyed by gastric acid

Thus (enteric coated or esterified form used)

• CAT → stable in stomach

Food

↓ use abs of A-E ↑ use - abs clar

A-E - avail in IV

Distribu.

- Eryth - everywhere except CSF macroph

(even in prostatic fluid and in)

Metabo.

- By liver
- Inhibit meta (oxid) of drug by interacting e

CYP450 e.g

STAP-W

All 4 - concn in liver

Azithro - larg Vd & t_{1/2} among the rest of 3

conc. in
✓ neutrophils
✓ macro.
✓ fibroblasts

• wafain • Theophylline
• protease inhibitor • statins
• anti-epilept

→ serum level low

• Drogxin interact (as they kill the normal flora that inactivate drogon)

Excretion:-

A-E - via bile as active drug

C - Kid + Liver

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ADRS

Gastric distress

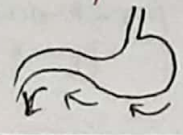
gastric upset (esp e erythro)

• ↑ dose of ery = muscle contraction

↓ good movem from stomach to duodenum

(This effect sometime use therapeutically for gastroparesis or post-opera ileus)

• Diarrhea due to activation of motilin rep in gut



cholestatic

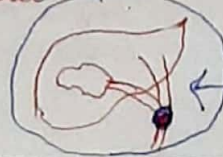
jaundice

(occur esp e)

estolate

Na-lauryl soap salt of erythromycin

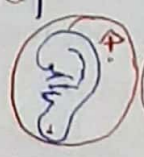
Bile produced by liver is either blocked or else retained in blood. Also known as obstructive jaundice



Otoxicity

Transient deafness e erythro

• irrens. sensorineural hearing loss

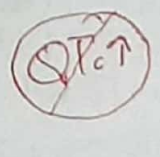
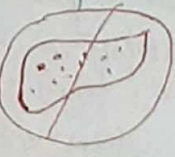


caution/contraindication

- Hepatic dysfun
- prolong QTc interval

- in proerythm condition

- or in concomitant use of proerythm agents



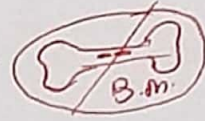
CHLORAMPHENICOL

- Broad-spectrum
- Its use is restricted to life-threatening infections to which no alternative exist becoz it is potentially toxic

Mechanism

Binds reversibly to 50S ribosomal sub-unit and inhibit protein at peptidyl-transferase rxn.

- at high level = Bone-marrow toxicity



Spectrum And Uses

Similar to Tetracycline

- Chlamydiae
- Rickettsiae (rickettsial infec. such as typhus & rocky mountain spotted fever)
- Spirochetes (Lyme disease, Borrelia burgdorferi)
- anaerobes
- Primarily bacteriostatic = Dep. upon dose & org may be bactericidal in ocular tissue

- Alternative to β -lactam for bac. meningitis

- Applied Topically for eye infec becoz of its broad spectrum & penetration in ocular tissue

RESISTANCE

enzymes inactivate chloramphenicol

↓ penetration ability

Ribosomal binding site alterations

KINETICS

adm = IV

wide distri including CSF

Hepatic metabo

inactive glucuronide

Eliminated in urine (secretion by renal tubules)

secreted in Breast milk and should be avoided.

ADVERSE EFFECTS

Anemias

dose-related hemolytic anemias seen in (G-6 PD deficiency) and aplastic anemia
↓
in which bone marrow & hematopoietic cell damage
↓
WBCs, RBCs, Plate.
∴ Aplastic anemia is indep. of dose.

Gray-baby syndrome

Neonates have low capacity to glucuronidate
The antibiotic & underdevelop. renal func.
↓
accumulate drug → interfere w/ mitochond. function.
poor feeding, depressed breathing, CVS collapse, cyanosis
⇒ Adults also exhibit this toxicity if high dose is given

Drug interactions

Chloramphenicol inhibits MFOs. And thus blocks meta. of drugs such as
• warfarin
• phenytoin

~~PM & Chl~~

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