Doctor 2022

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Medicine – MU

Pharmacology Sheet

Protein Synthesis Inhibitors

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Pharmacology of Protein Synthesis Inhibitors

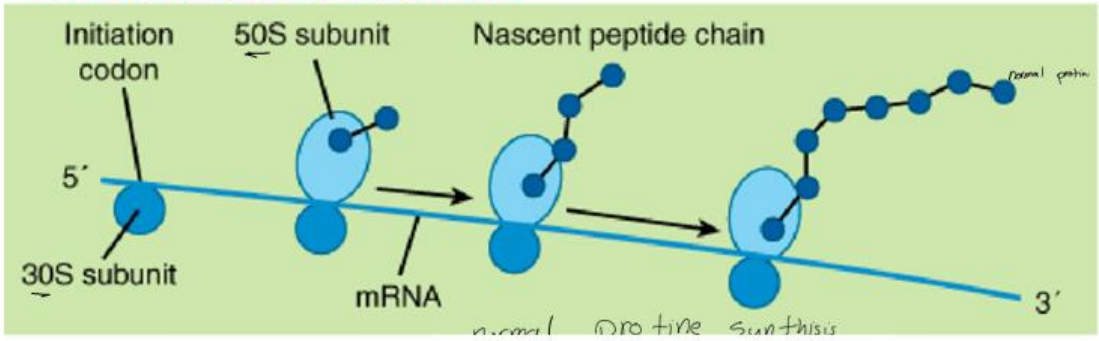
Objectives:

1. Protein synthesis in bacterial ribosomes
2. Mechanism of action of protein synthesis inhibitors antibiotics
3. Classification of protein synthesis inhibitors
4. Aminoglycosides
5. Macrolides
6. Tetracyclines
7. Chloramphenicol
8. Clindamycin

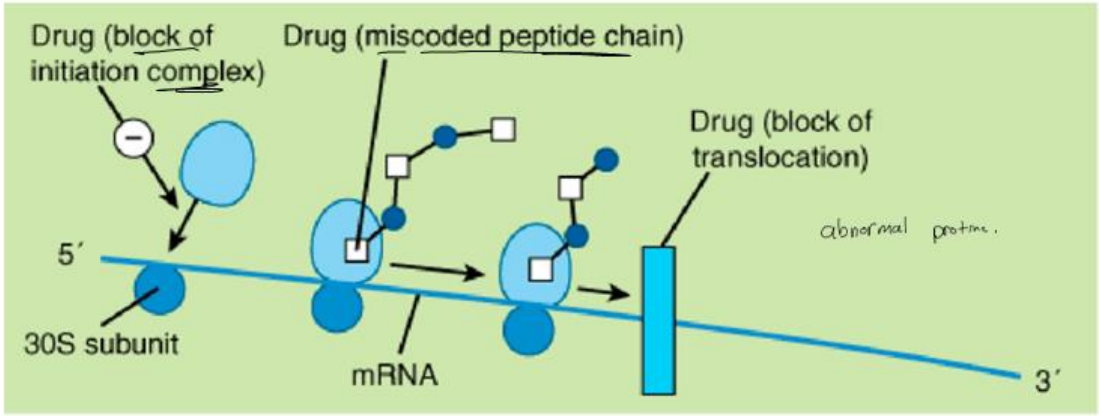
Ribosomes: Site of Protein Synthesis

- **Prokaryotic ribosomes are 70 S;**
  - **Large subunit: 50 S**
    - **33 polypeptides**
  - **Small subunit: 30 S**
    - **21 polypeptides**
- **Eukaryotic are 80 S**

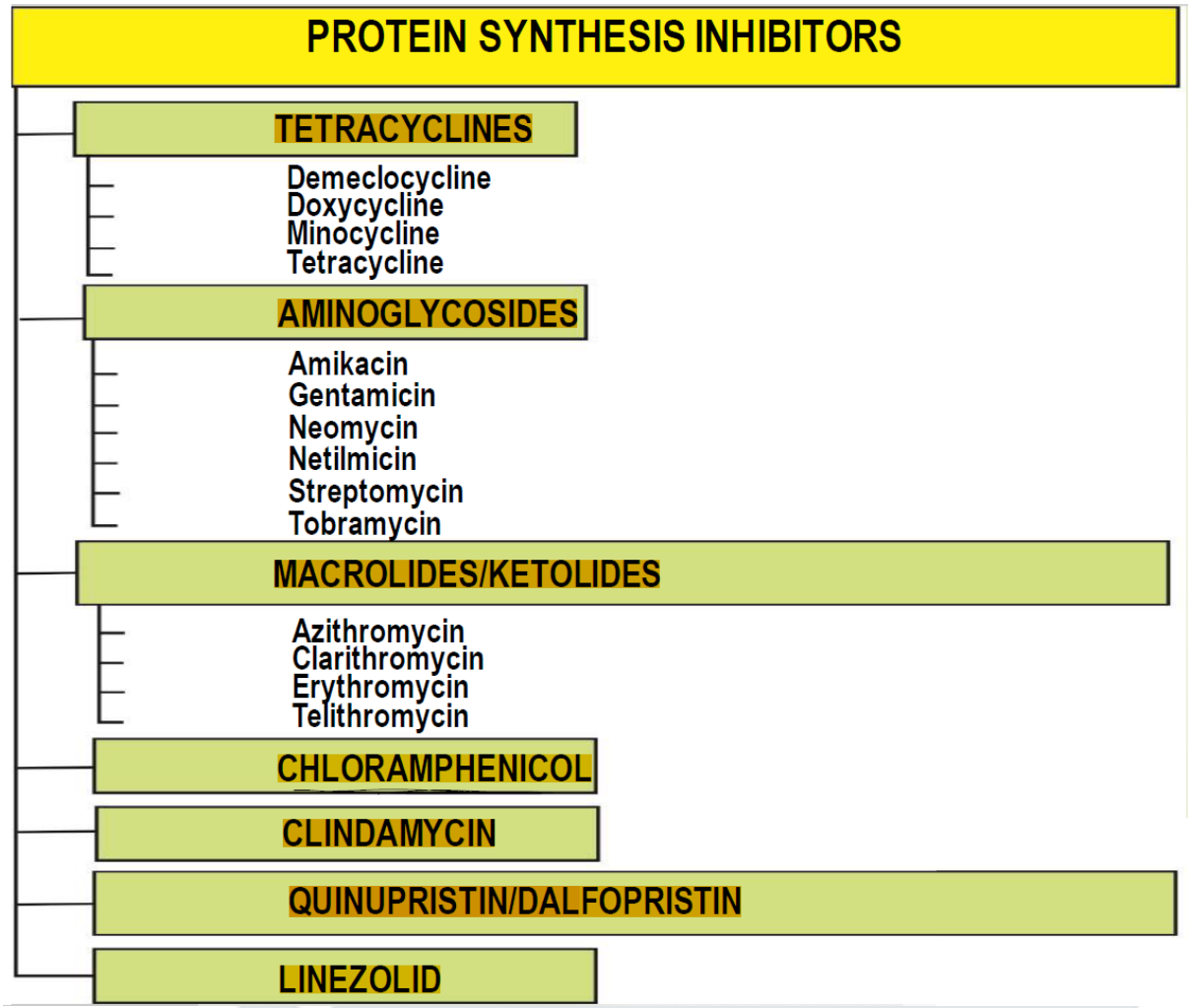
Normal Protein Synthesis in Bacterial Cell:



Aminoglycoside-treated bacterial cell (Abnormal Protein Synthesis)



Protein Synthesis Inhibitors (According to Lippincott's Pharmacology):



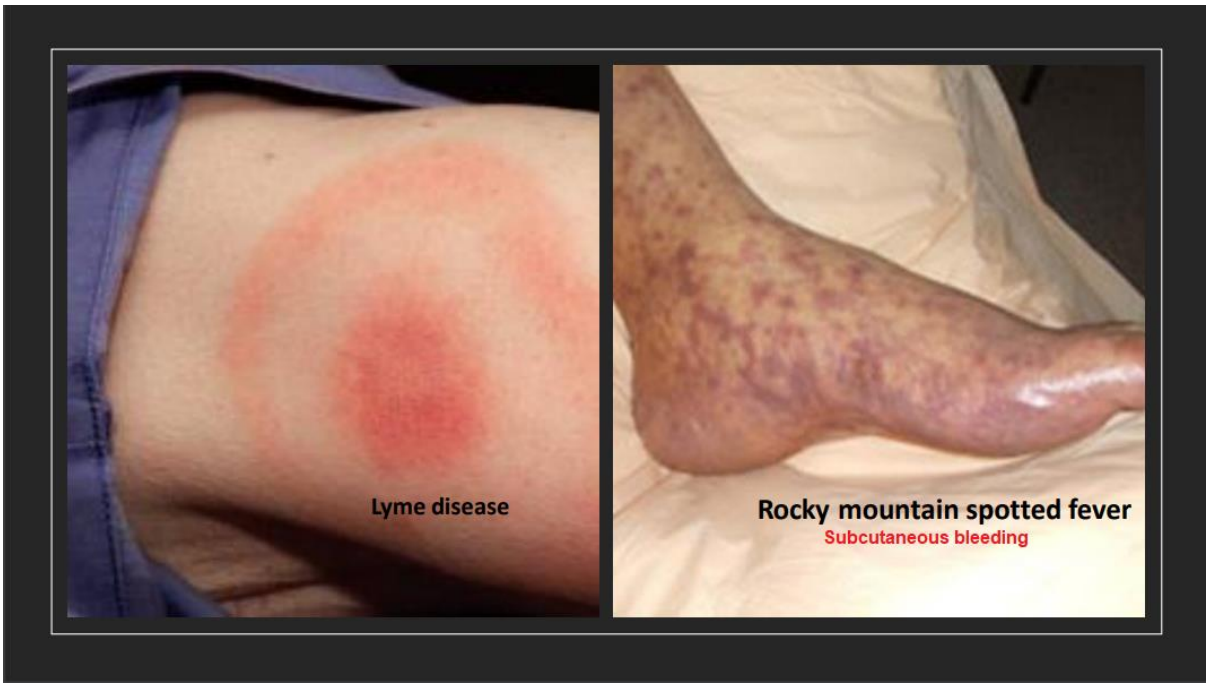
	Aminoglycosides (cidal)	Macrolides (static) Moderate spectrum	Chloramphenicol (Static- broad spectrum)	Clindamycin (static)	Tetracyclines (static-broad spectrum)
Notes Regarding Their Names & Structures:	- Amino-: has amine in its amide group. amin+ sugar. - Have high molecular weights (MWs). - Have an -OH group. Having -OH group(s) will: 1. Make it have positive (+) charges, so it is ionized. 2. Thus, it is water-soluble drug. - - 3 Ns adverse effects.	- Macro-: large and has a 16 membered macrolactone ring. - Can become (cidal) when given in high concentrations.	- Chlor-: has a chlorine group. - Has two arms: gram +ve aerobic and gram -ve anaerobic. Highly toxic and rarely used	- Similar action to macrolides.	- Tetra/cyclines: has 4 cycles in its structure. - The most commonly used protein synthesis inhibitors antibiotics. - Among them, Doxycycline is the most frequently used. - Full of exceptions (in its spectrum).
PDs (Pharmaco-dynamics)	- Irreversible binding (and thus strong) to 30S subunit: • misreading of mRNA	- Binding of 50S subunit: • (weak reversible binding) - Increasing concentration turns the drug into cidal - MW >500 (for any drug to be absorbed orally; MW should be < than 500)	- Binding (weak) to 50S subunit - MW<500, only 2 –OH groups (no full oral absorption), 2 Cl atoms (wide spectrum and high toxicity). - Not used nowadays except topical for eye infections	- Binding to 50 S subunit; (as erythromycin) at the same binding site - MW <500	- Reversible (weak) binding to 30S subunit - MW<500 except tigecycline (parentral) Containing –OH groups, least in minocycline

	Aminoglycosides	Macrolides	Chloramphenicol	Clindamycin	Tetracyclines
PKs (Pharmaco-kinetics)	- Not absorbed orally; that is why it is given parenterally. - Not pass BBB, however, it is used in treating meningitis (the integrity of BBB is usually disrupted) + it is used due to its high efficacy against the causative agents (gram -ve bacteria mostly). - Can pass placenta and breast milk, causing congenital hearing defects. - Not metabolized, excreted unchanged in urine (normal urine pH is 5.6): active in alkaline urine (urine is alkaline during infection), it will be active -> used in treating urinary tract infections. - N.B.: Synergy - The aminoglycosides	- Poor oral absorption, affected by food (best to be given on empty stomach) as the presence of food will decrease its absorption. - Not pass BBB, not given in meningitis because of its lower efficacy against causative organisms. - Pass placenta but not teratogenic: safe in pregnancy: erythromycin, azithromycin (a common exam question) - Distribution: pass to most body fluids in good concentration (prostate) used in treating prostatic infections. - Concentrated in macrophages and polymorphs (they work as carriers to drive the drug to the site of infection): 1. (long biological half- life) 2. Single daily dose is needed. - Metabolism: liver - Excretion: bile, entero/([redacted])hepatic circulation: 1. Can go back to blood and have longer duration of action. 2. Can	- Well-absorbed, not affected by food - Pass BBB: ~~2nd~~ 3rd choice in meningitis (last resort). - Widely distributed: high Vd - Pass placenta, in breast milk - Metabolized by glucuronidation in liver: glucuronyl transferase enzyme. Metabolized in Phase II-> if given to a child it won't be metabolized -> higher toxicity. - Excreted in urine: inactive metabolites -> Not used in UTI	- Rapid complete oral absorption - pass BBB in small amounts enough to treat meningitis - Penetrat-es bone (used to treat osteomyelitis), tissue fluids including prostate - Pass placenta: not terato- genic - Metabolim: liver - Excretion: bile	- Partially absorbed-> the unabsorbed part causes problem. - Absorption decreased with: food, milk, antacid, iron (binds to heavy metals to form a complex that is not absorbed) - Incomplete passage to BBB - Concentrated in bone, teeth - Pass placenta (teratogenic) and breast milk (high affinity to Ca) ≠ pregnancy, lactation, children<8 y - Metabolism: extensive in liver - Excreted in urine 80% (inactive) more than in bile (enterohepatic circulation) - N.B. doxycycline and minocycline nearly complete oral absorption, 50% renal excretion, 50% in bile: can be used in renal impairment

	synergize with β-lactam antibiotics. - The β-lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.	go back to liver (load liver). - Members: erythromycin, clarithromycin, azithromycin, spiramycin			(especially minocycline).
	Aminoglycosides	**Macrolides**	**Chloramphenicol**	**Clindamycin**	**Tetracyclines**
Spectrum	- G-ve - Some G+ve (When given with another drugs). - Mycobacterium tuberculosis (TB).	- G+ve: pneumonia: staph aureus, strep. Peumoneae, strep. Pyogenes - IC (intracellular) organisms atypical: CALM MY LEG: Chlamydia (causes: 1. eye infections and 2. Genital infections manifested in females as urethral discharges), *Mycoplasma* (typical pneumonia) and *Legionella* (causes pneumonia and lives in humid spaces such as air conditioning (AC) systems). So, legionnaires' disease: a pneumonia caused by legionella. - *Toxoplasma* (not bacteria).	- broad-spectrum - Limited use because of toxicity	- Restricted: - G+ve aerobic: staph, strep, pneumococci (as macrolides, specifically erythromycin). - G-ve anerobic Bacteria	- Broad- spectrum - G +VE, -VE except 2 Ps (Pseudomonas aeruginosa and Proteus species.) - Anerobic: except clostridium difficilli - Atypical bacteria - BRC: borrelia, rickettsia, Coxiella - Protozoa: ameba, malaria, toxoplasma

	Aminoglycosides	Macrolides	Chloramphenicol	Clindamycin	Tetracyclines
Resistance:	- Common	- Common: rapidly developing within 10 days - Duration of administration not more than 10 days	- Common, easy developed 1. R factor: inactivation of drug: acetyltransferase: CAT 2. Inability to penetrate bacterial cells	- Common: if developed to macrolides?	- Common
Adverse Effects:	- 3 Ns (N N N): - Nephrotoxicity (old age, cephalosporins) - Nerve toxicity: 8th cranial nerve: ototoxicity: reversible if early - Neuromuscular blocking: ≠myasthenia graves, muscle weakness treated by Ca gluconate	- GIT upset: common - Cholestatic Hepatitis - Enzyme inhibitor: hepatic cytochrome enzyme: aggravates myopathy induced by statins - Prolongation of QT interval: sudden cardiac death	- Toxic: 1. fatal anemia: rare (immunological): not dose-dependent, irreversible, after stopping the drug 2. bone marrow depression?: reversible, mild, dose-dependent, during treatment 3. hepatic enzyme inhibitor 4. teratogenic 5. Gray baby syndrome - Contraindications: blood diseases, pregnancy, lactation, children less than 2 years.	- pseudomembranous colitis: 2-20%, most serious, may be fatal by clostridium, Treatment: oral metronidazole for 7-10 days or oral vancomycin	1. teeth, bone: Discoloration and deformity in growing teeth and bones (contraindicated in pregnancy, lactation and in children < 8 years) Renal impairment (should be also avoided in renal disease) 2. GIT upset: ≠peptic ulcer 3. Superinfection with clostridium and candida 4. liver: liver cell failure, cholestatic jaundice 5. kidney: nephrogenic DI, Fanconi syndrome (outdated tetracyclines) 6. photosensitivity

	Aminoglycosides	Macrolides	Chloramphenicol	Clindamycin	Tetracyclines
Indications:	1. UTIs: in the past. 2. G-ve: septicemia , meningococcal meningitis? Gentamicin (according to the source of bacetria). 3. T.B. streptomycin (prototype) among 1st line drugs of T.B. 4. Plague: 1st line 5. neomycin (toxic): local: oral for gut decontamination (the poor oral absorption makes it work locally in stomach) and hepatic coma (ammonia produced by bacteria causes coma). 6. gentamicin: combined with other antibiotics: Infective endocarditis with vancomycin, Peritonitis with penicillin an metronidazole (mixed infusion) 7. tobramycin: eye drops	1. G+ve infections: 2nd choice after penicillins and cephalosporins 2. 1st line for atypical infections: eye and genital infections of chlamydia, atypical pneumonia, legionnaire's disease 3. clarithromycin: eradication of H.pylori in peptic ulcer: 10 days 4. toxoplasmosis 5. ENT infections 6. Syphilis (+ve) gonorrhea (+ve): 2nd choice after penicillin and cephalosporins End by thromycin except spiramycin	- 2nd , EVEN 3rd CHOICE DUE TO TOXICITY 1. atypical microorganisms: after macrolides and doxycycline 2. meningitis: after penicillins 1st , cephalosporins 2nd 3. cholera: ampicillin (extended spectrum), 3rd generation cephalosporins, floroquinolones 4. eye infections: eye drpos	1. dental infections 2. bone, joint infection: osteomyelitis 3. Important: toxic shock syndrome: Severe staphylococcus infections (exo-toxins): these toxins come inside the blood and cause severe damages (multi- organ failure), manifested in fever and hypotension. We use clindamycin or gentamicin (penicillin? It breaks the cell wall causing the toxin to leak out) 4. Anerobic infection: ~~e.g. clostridium~~ 5. topical : acne	1. CALM MY LEG: 2nd choice after macrolides 2. BRC: 1st choice, 2nd choice: macrolides: • borrelia: tick-born spirochetes causes Lyme disease: doxycycline 100mg twice daily for 14 days • Rickettsia: rocky mountain fever: 100mg doxycycline twice daily for 7-10 days • Coxiella: Q fever : 100mg doxycycline twice daily for 14 days 3. cholera: 300 mg doxycycline single oral dose 4. acne: doxycycline oral with topical clindamycin 5. SIADH: Syndrome of inappropriate antidiuretic hormone secretion (ADH is produced from posterior pituitary gland and reduces the volume of urine). To treat SIADH we use DEMECLOCYCLINE



Chloramphenicol:

- **Adverse Effects:**
  - **Gray baby syndrome: in neonates if the dosage is not adjusted.**
  - **Low capacity to glucuronylate chloramphenicol and underdeveloped renal function -> a decreased ability to excrete the drug -> ATB accumulates to levels that interfere with the function of mitochondrial ribosomes »»» poor feeding, depressed breathing, cardiovascular collapse, cyanosis (-> "gray baby") and death.**