Pharmacology of Protein Synthesis inhibitors

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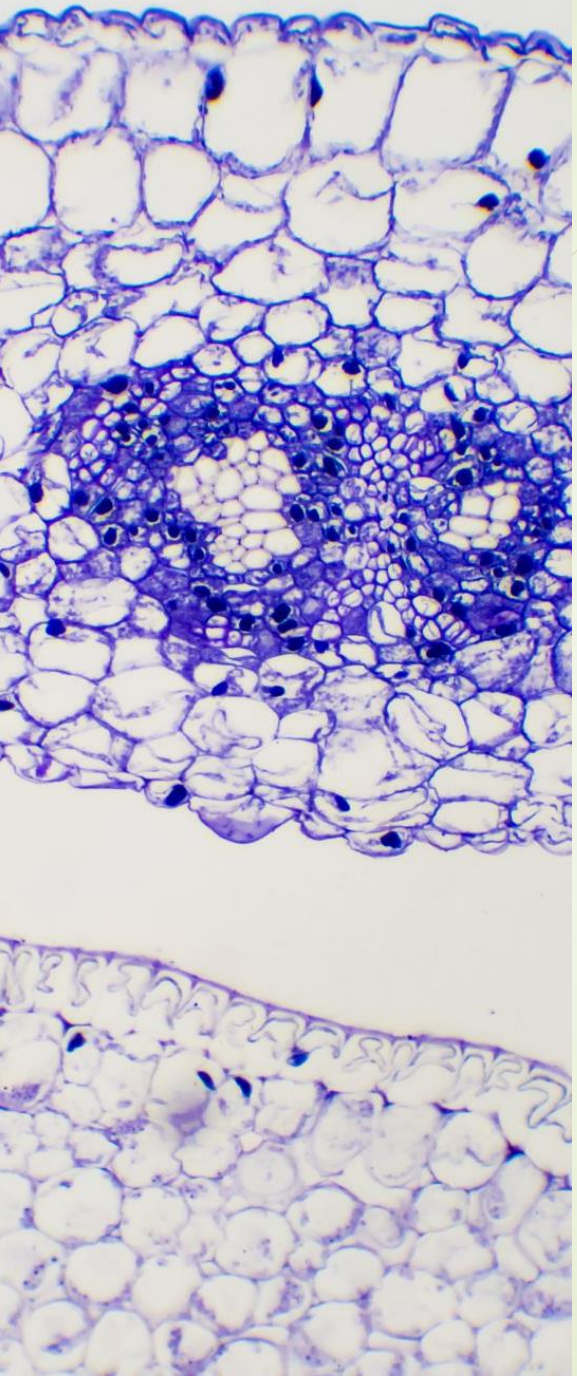
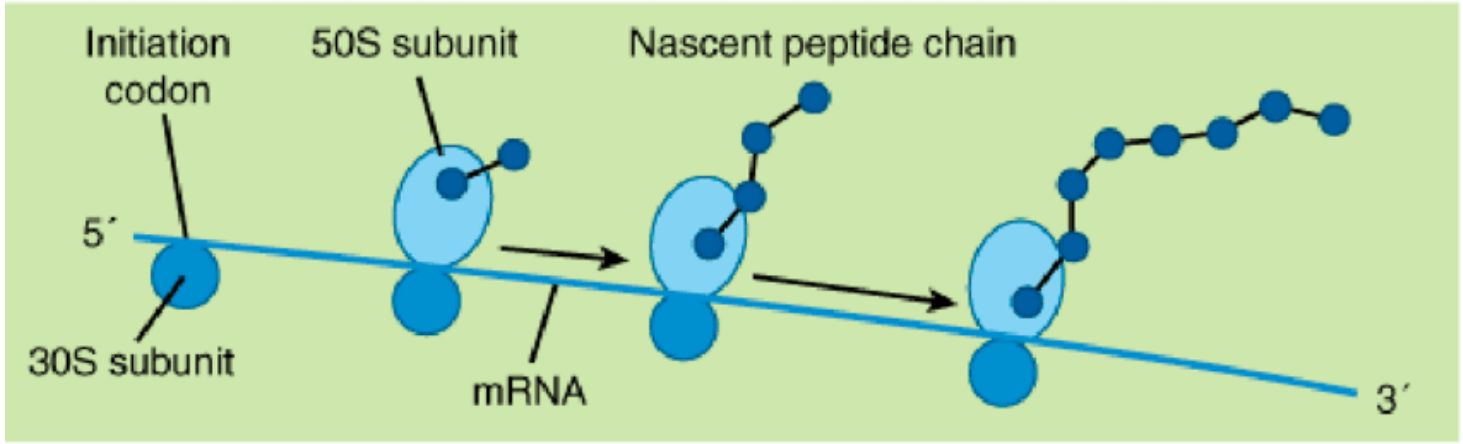
Objectives

- 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

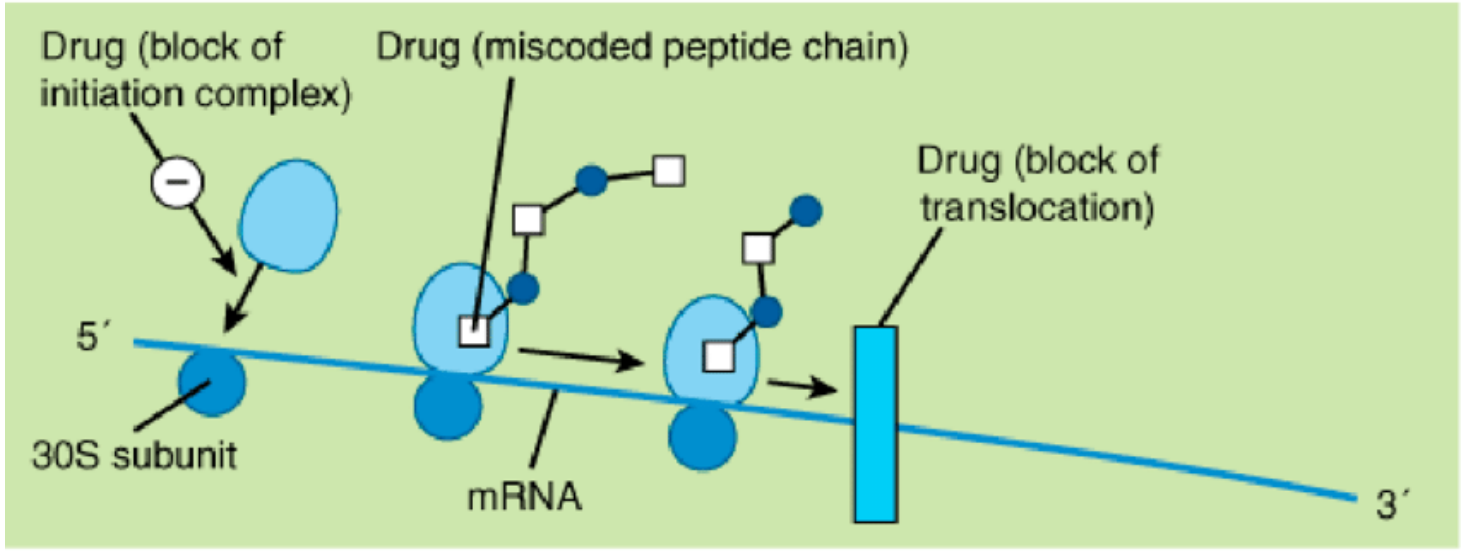


Ribosomes: site of protein synthesis

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



Aminoglycoside-treated bacterial cell



PROTEIN SYNTHESIS INHIBITORS

TETRACYCLINES

- Demeclocycline
- Doxycycline
- Minocycline
- Tetracycline

AMINOGLYCOSIDES

- Amikacin
- Gentamicin
- Neomycin
- Netilmicin
- Streptomycin
- Tobramycin

MACROLIDES/KETOLIDES

- Azithromycin
- Clarithromycin
- Erythromycin
- Telithromycin

CHLORAMPHENICOL

CLINDAMYCIN

QUINUPRISTIN/DALFOPRISTIN

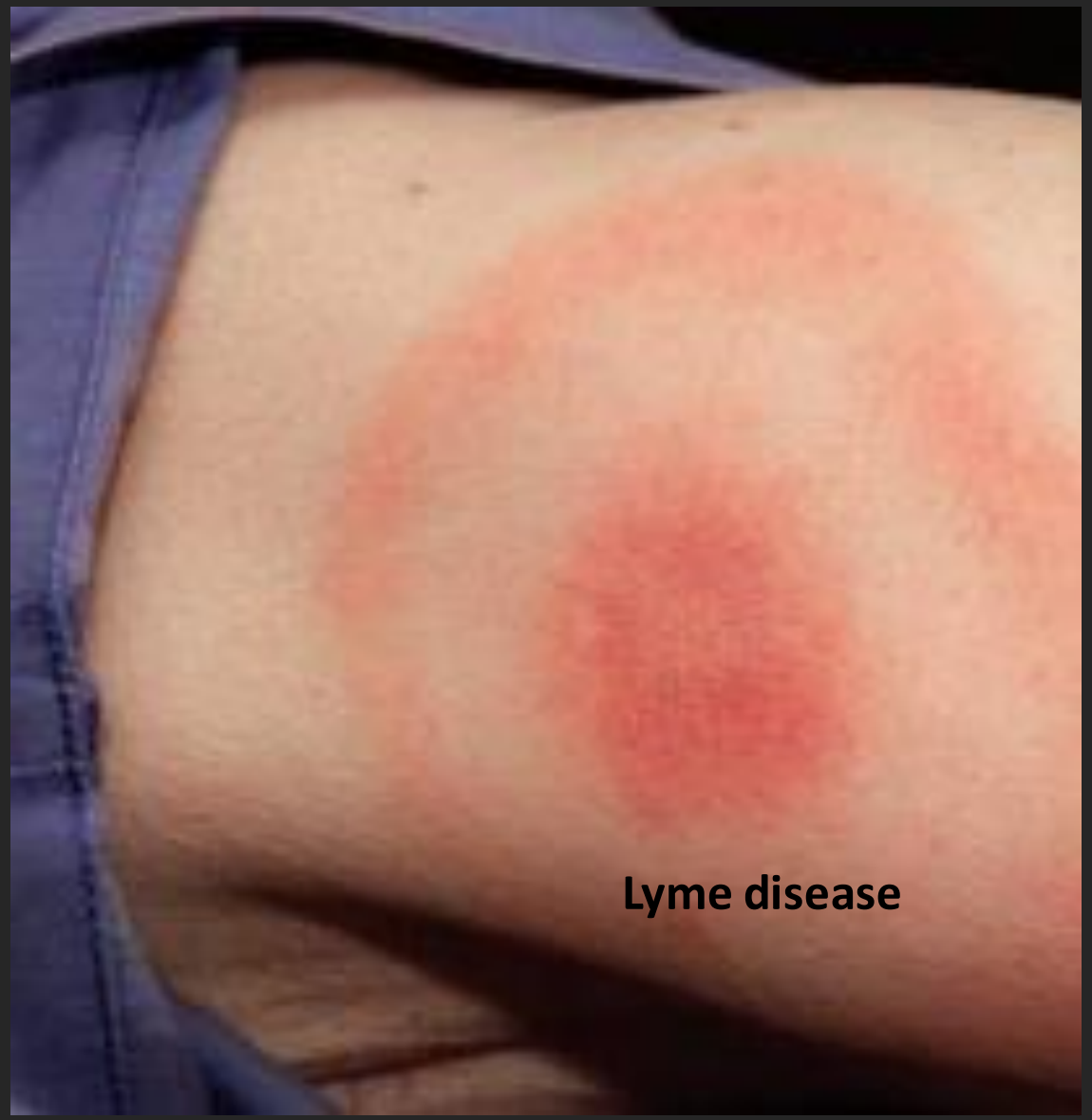
LINEZOLID

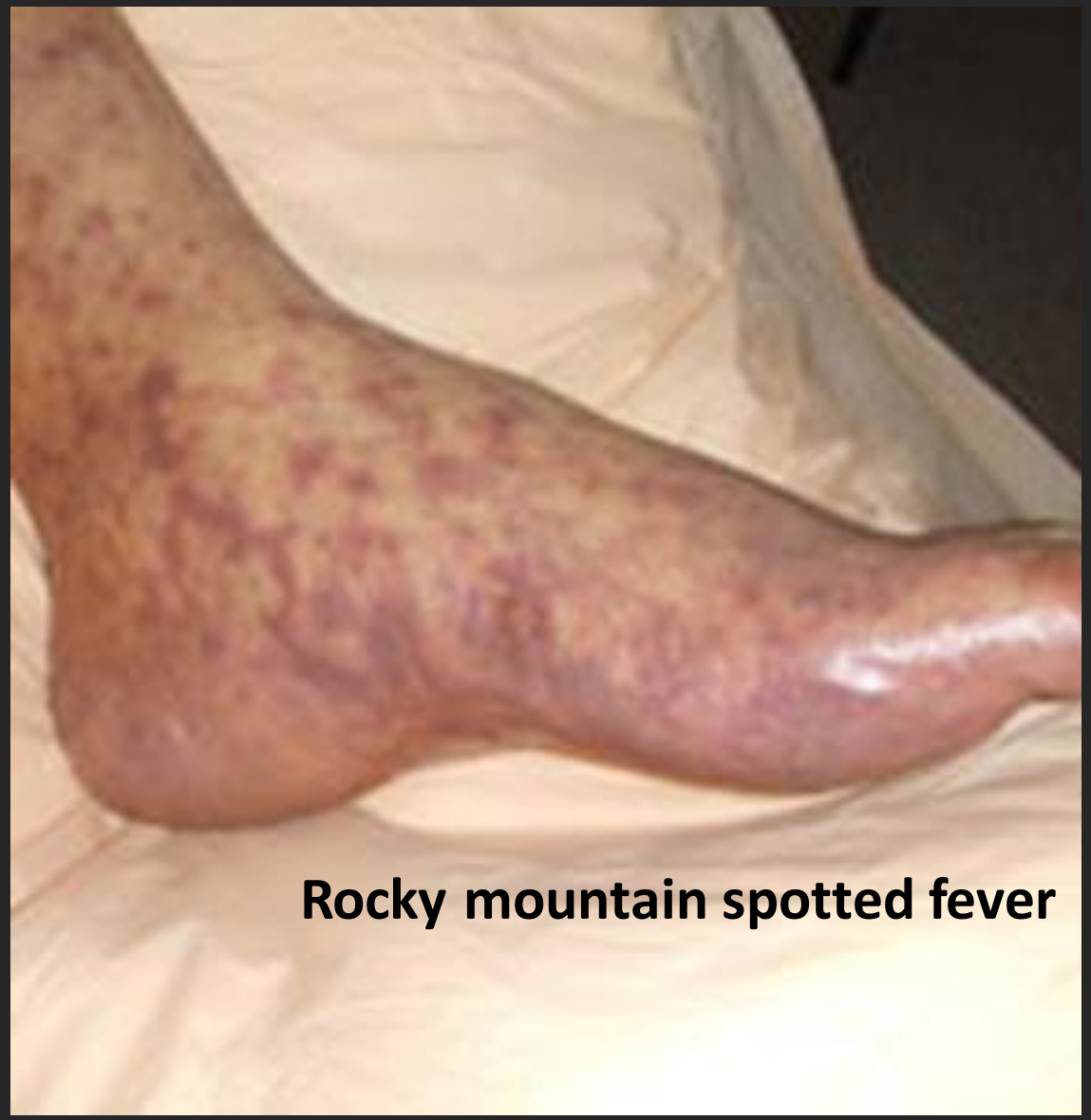
(according to Lippincott´s Pharmacology)

	Aminoglycosides (cidal)	Macrolides (static) Moderate spectrum	Chloramenihecol (Static- broad spectrum)	Clindamycin (static)	Tetracyclines (static-broad spectrum)
PDs	Irreversible binding to 30S subunit: misreading of mRNA	Binding of 50S subunit: (weak reversible binding) Increasing concentration turns the drug into cidal MW>500	Binding (weak) to 50S subunit MW<500, only 2 –OH groups, 2 Cl atoms 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
PKs	• Not absorbed orally • Parentral • Not pass BBB • Can pass placenta and breast milk • Not metabolized • Excreted unchanged in urine: active in alkaline urine (urine is alkaline during infection) • N.B. **Synergy** - The aminoglycosides synergize with β-lactam antibiotics. The β-lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.	• Poor oral absorption, affected by food (on empty stomach) • Not pass BBB • Pass placenta but not teratogenic: safe in pregnancy: erythromycin, zithromycin • Pass to most body fluids in good concentration (prostate) • Concentrated in macrophages and polymorphs (long biological half life) • Metabolism: liver • Excretion: bile, enterohepatic circulation • **Membres:** **erythromycin**, clarithromycin, azithromycin, spiramycin	• Well-absorbed, not affected by food • Pass BBB: 2nd choice in meningitis • Widely distributed: high Vd • Pass placenta, in breast milk • Metabolized by glucorunidation in liver: glucoronyl transferase phase II • Excreted in urine: inactive metabolites	• Rapid complete oral absorption • pass BBB in small amounts enough to treat meningitis • Penetrates bone, tissue fluids including prostate • Pass placenta: not teratogenic • Metabolism: liver • Excretion: bile	• Partially absorbed • Absorption decreased with: food, milk, antacid, iron (binds to heavy metals) • 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

	Aminoglycosides (cidal)	Macrolides (static)	Chloramenihecol (Static)	Clindamycin (static)	Tetracyclines (static)
Spectrum	• G-ve • Some G+ve • Mycobacterium tuberculosis	• **G+ve**: pneumonia: staph aureus, strep. Peumoneae, strep. pyogenes • **IC organisms atypical**: chlamydia, *Mycoplasma, Legionella,* • ***Toxoplasma***	• **broad-spectrum** • Limited use because of toxicity	• **restricted**: • **G+ve aerobic**: staph, strep, pneumococci (as macrolides) • **G-ve anerobic** bacteria	• **broad- spectrum** • **G +VE, -VE except 2 Ps** • **Anerobic**: except clostridium difficilli • **Atypical bacteria** • **BRC:** borrelia , rickettsia, Coxiella • **Protozoa**: ameba, malaria, toxoplasma
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**

	Aminoglycosides (cidal)	Macrolides (static)	Chloramenihecol (Static)	Clindamycin (static)	Tetracyclines (static)
Indications	**1- UTIs** **2- G-ve: septicemia , meningococcal meningitis? gentamicin** **3- T.B. streptomycin among 1st line drugs of T.B.** **4- Plague: 1st line** **5- neomycin (toxic): local: oral for gut decontamination, hepatic coma** **6- gentamicin**: combined with other antibiotics: Infective endocarditis with vancomycin Peritonitis with penicillin and metronidazole **7- tobramycin**: eye drops	**1- G+ve infections**: 2nd choice after penicillins and cephalosporins **2- 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, gonorrhea**: 2nd choice after penicillin and cephalosporins	2ND, EVEN 3RD CHOICE DUE TO TOXICITY **1- atypical microorganisms: after macrolides and doxycycline** **2- meningitis: after penicillins, cephalosporins** **3- cholera: ampicillin, 3rd generation cephalosporins, floroquinolones** **4- eye infections: eye drpos**	1- **dental infections** 2- **bone, joint infection:** osteomyelitis 3- **toxic shock syndrome** : or gentamicin (penicillin?) 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: 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** : DEMECLOCYCLINE
Adverse effects	• **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: aggrevates 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 y.	**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**


Lyme disease


Rocky mountain spotted fever

- 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.**

Thank you