Pharmacology of Bacterial Protein Synthesis Inhibitors

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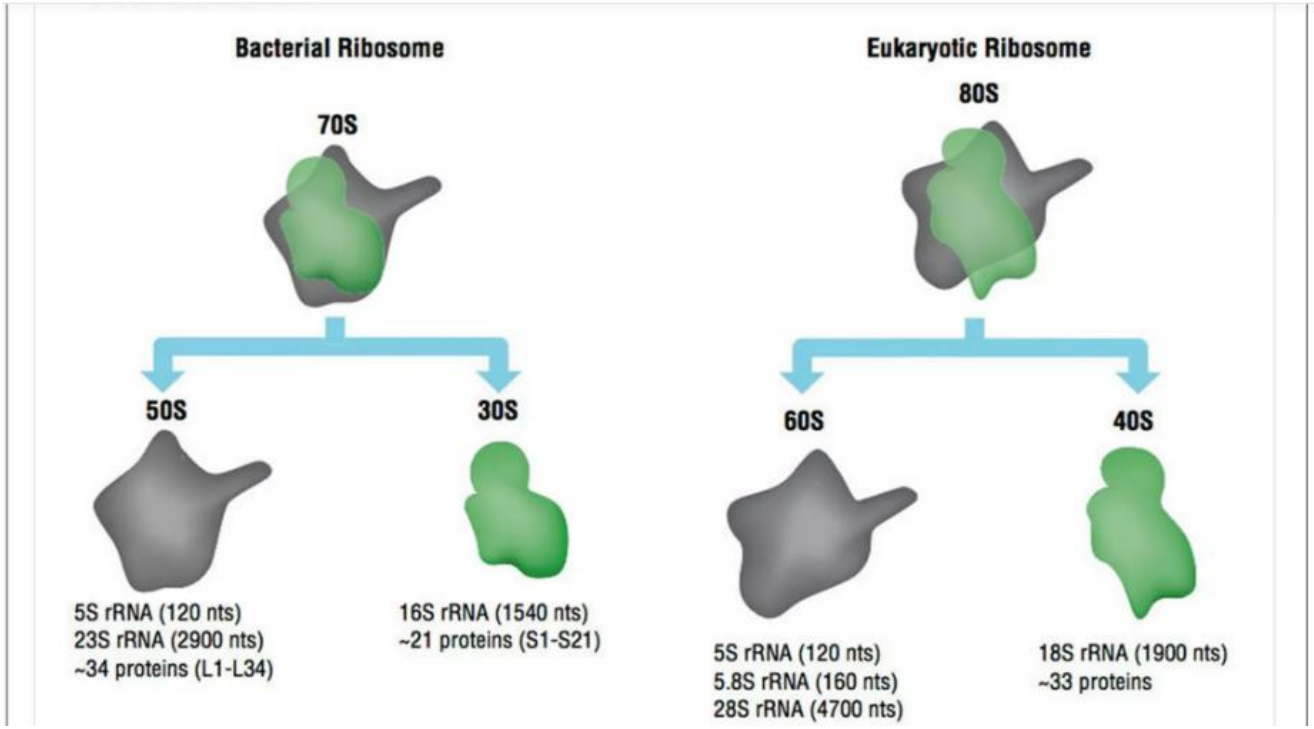
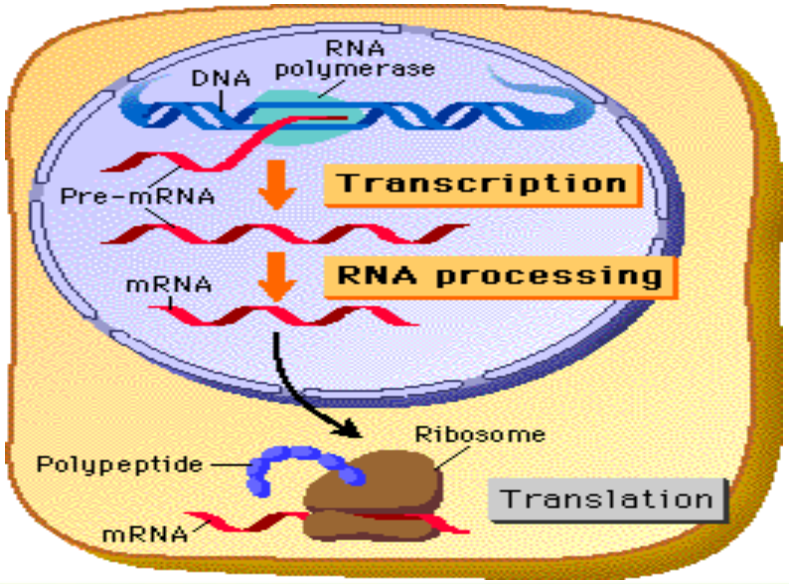
Objectives

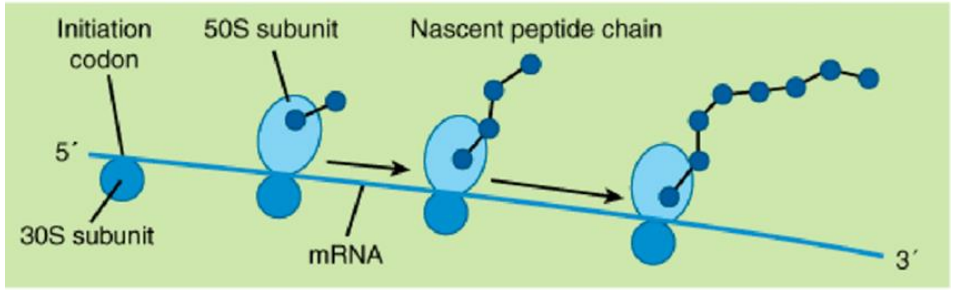
- 1- Protein synthesis in bacterial ribosomes
- 2- Mechanism of action of protein synthesis inhibitors antibiotics
- 3- Classification of protein synthesis inhibitors
- 4- Aminoglycosides
- 5- Macrolides
- 6- Tetracyclines
- 7- Chloramphenicol
- 8- Clindamycin

Ribosomes: site of protein synthesis

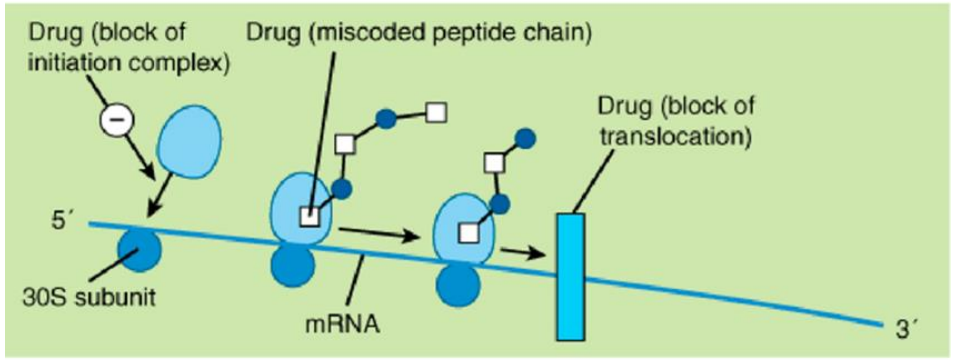
- **Prokaryotic ribosomes are 70S**:
- Large subunit: 50 S
    - 33 polypeptides
- Small subunit: 30 S
    - 21 polypeptides
- **Eukaryotic are 80S**
- **Selective toxicity:**
- **acting at the ribosomal level taking the advantage of major differences prokaryotic and eukaryotic ribosome structure**



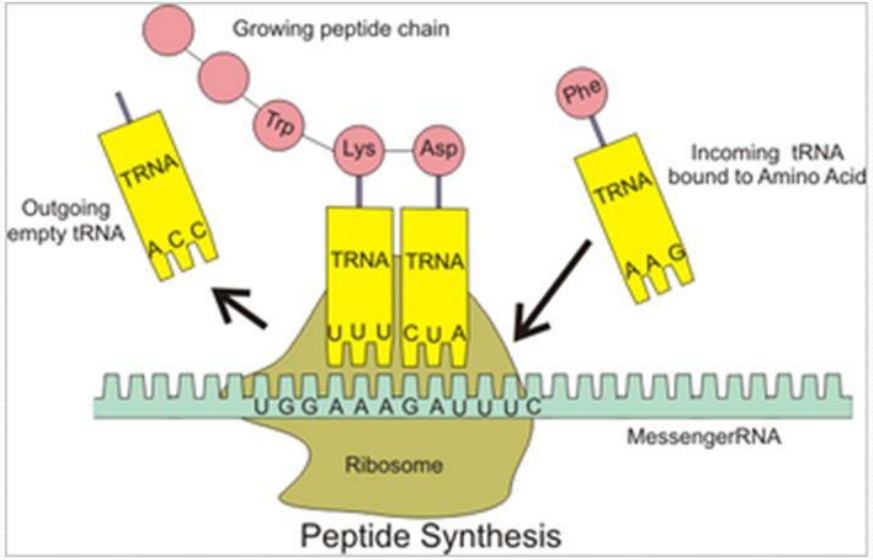




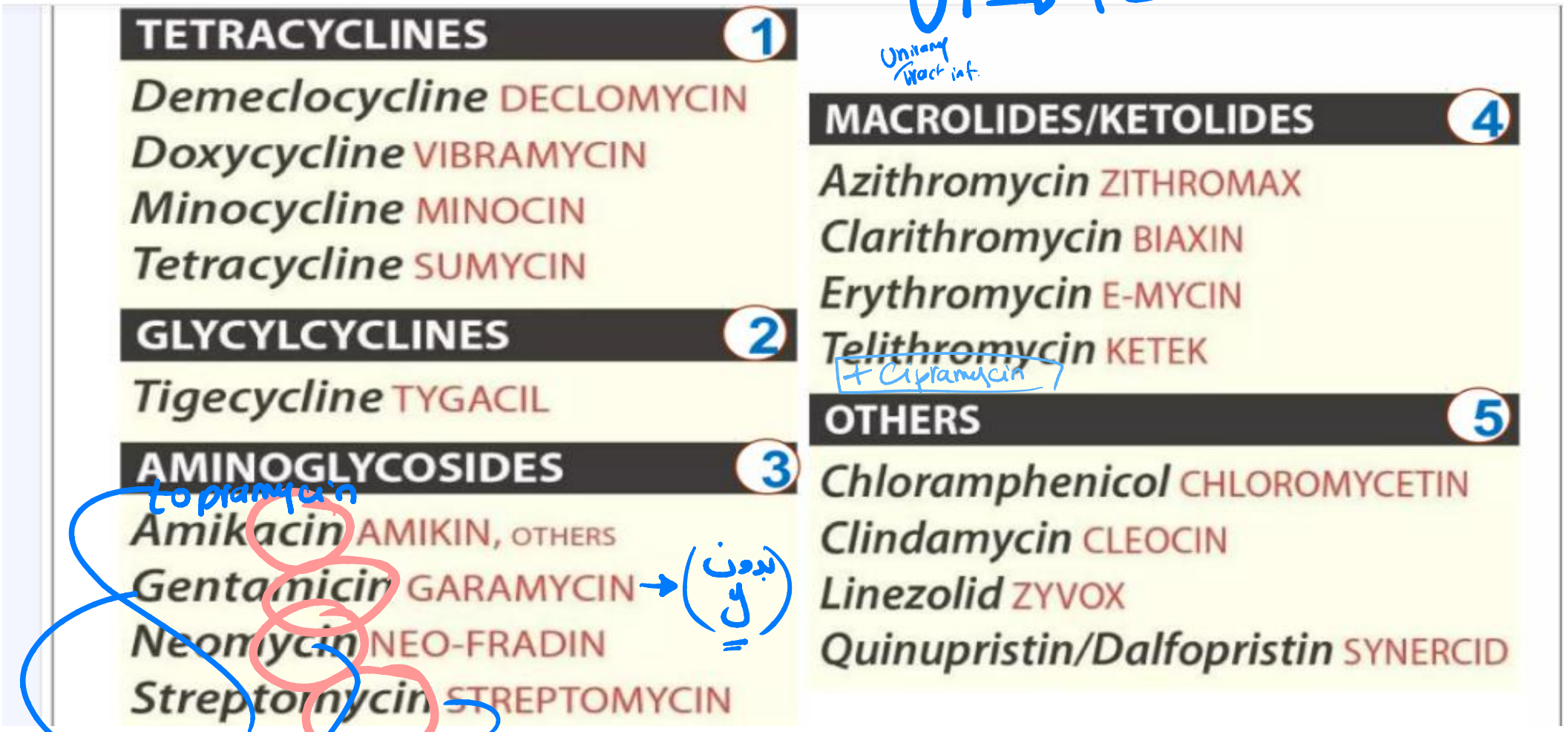
Aminoglycoside-treated bacterial cell



Bacteria protein synthesis

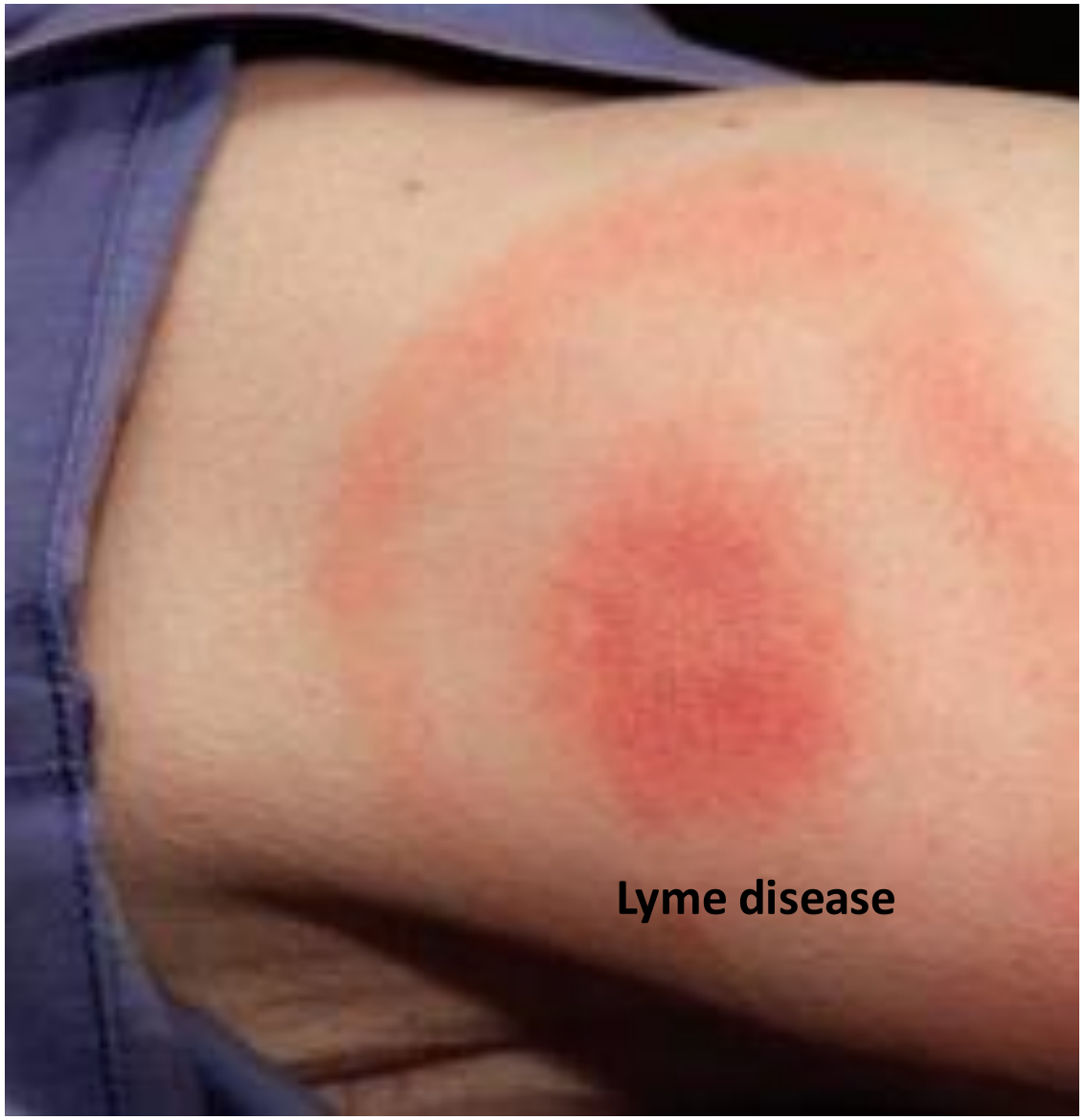


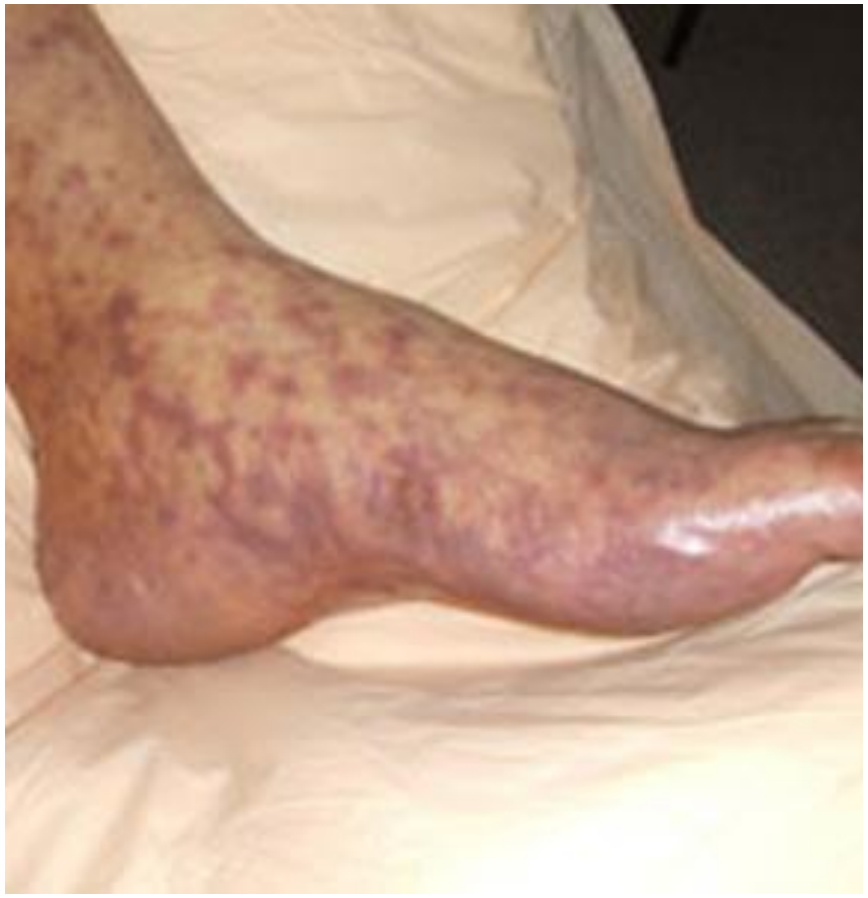
Classification



	Aminoglycosides (cidal)	Macrolides (static) Moderate spectrum	Chloramenipheol (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 NOT pass placenta and breast milk • Not metabolized • Excreted unchanged in urine: active in alkaline urine • 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) G(-) aerobic only	Macrolides (static)	Chloramphenicol (Static)	Clindamycin (static)	Tetracyclines (static) atypical
Indications	**1- UTIs: their use is not common due to a fear of nephrotoxicity** **2- Septicemia , meningococcal meningitis: gentamicin** **3- T.B. streptomycin among 1st line drugs of T.B.** **4- Plague (Y. pestis): 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 respiratory and ENT infections**: 2nd choice after penicillins and cephalosporins **2- Clarithromycin:** eradication of H.pylori in peptic ulcer: 10 days **3- Syphilis**: 2nd choice after penicillin and cephalosporins **4- Atypical infections: eye and genital infections of chlamydia, atypical pneumonia, Legionnaires' disease** **5- Toxoplasmosis**	**2nd , EVEN 3rd CHOICE DUE TO TOXICITY** **1- Atypical microorganisms: after macrolides and doxycycline: 3rd choice** **2- Meningitis: after penicillins, cephalosporins 3rd choice** **3- Cholera: ampicillin, 3rd generation cephalosporins, floroquinolones 4th choice** **4- Eye infections: eye drops**	1- **Dental infections** 2- **Bone, joint infection:** osteomyelitis 3- **Toxic shock syndrome (Nafcillin, oxacillin, vancomycin or gentamicin** + Clindamycin) 4- **Topical :** acne 5- **Toxoplasmosis, malaria (off-label)** استخدام غير رسمي	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 3N	• **Nephrotoxicity** (old age, cephalosporins) • **Nerve toxicity**: 8th cranial nerve: ototoxicity: reversible if early • **Neuromuscular blocking**: ≠myasthenia graves , muscle weakness treated by Ca gluconate direct causing of ms. weakness	• **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: **Gray baby syndrome** late in pregnancy **Contraindications:** blood diseases, pregnancy, lactation, children less than 2 y.	**pseudomembranous colitis:** • 2-20% • most serious may be fatal • by **Clostridium difficile** • **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) **2- Renal impairment** (should be also avoided in renal disease) **2- GIT upset**: ≠peptic ulcer **4- liver: liver cell failure, cholestatic jaundice** **5- kidney: nephrogenic DI, Fanconi syndrome (outdated tetracyclines)** **6- Photosensitivity**





Rocky mountain spotted fever

Q FEVER

symptoms

HEADACHE

FEVER

COUGH

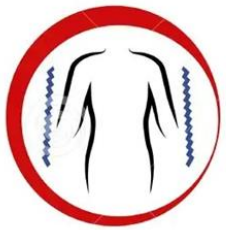
DIARRHEA

STOMACH PAIN

VOMITING

WEIGHT LOSS

FATIGUE



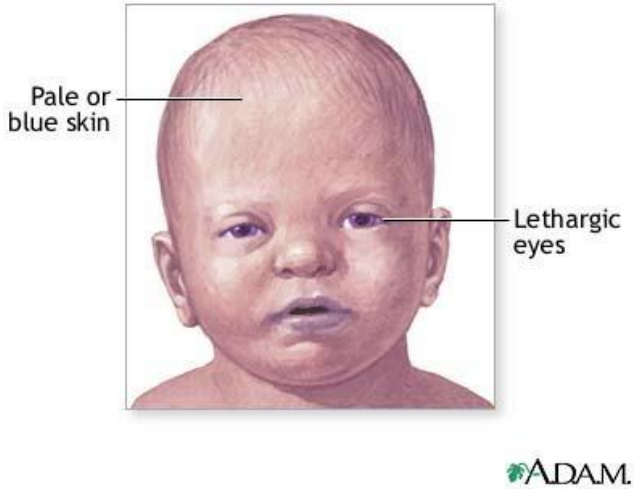
CHILLS

CHEST PAINT

SWEATS

Teratogenicity of Chloramphenicol

- There are no literature reports linking the use of this drug in pregnancy to birth defects
- **Its administration** late in pregnancy has been associated with adverse effects in the neonate **(grey baby syndrome).**
- **Low capacity to glucoronyl transferase enzyme and underdeveloped renal function ⇒ a decreased ability to excrete the drug ⇒ drug accumulates to levels that interfere with the function of mitochondrial ribosomes »»»» poor feeding, depressed breathing, cardiovascular collapse, cyanosis (⇒ "grey baby") and death.**



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Thank you