Pharmacology of Bacterial Protein Synthesis Inhibitors

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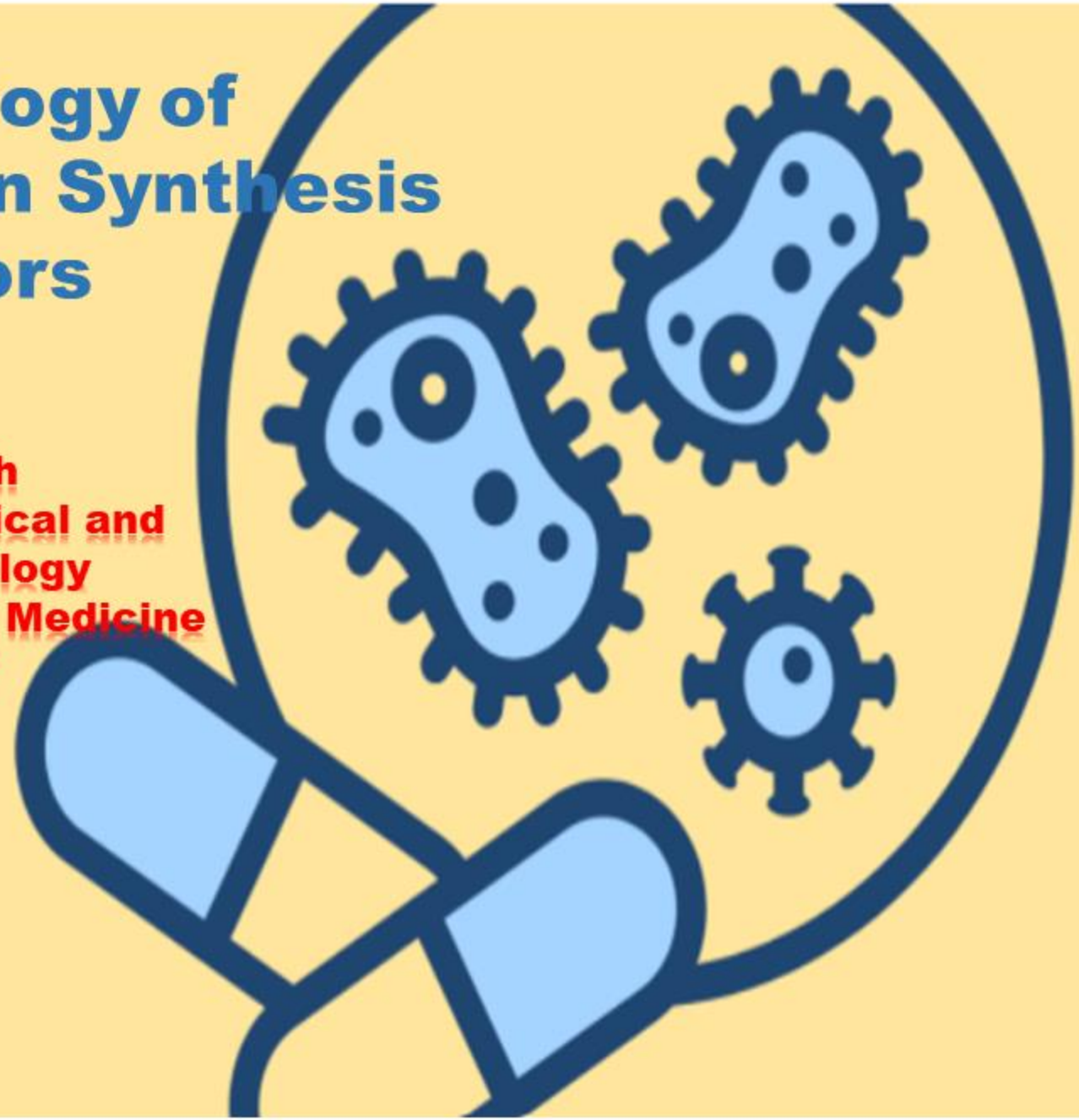
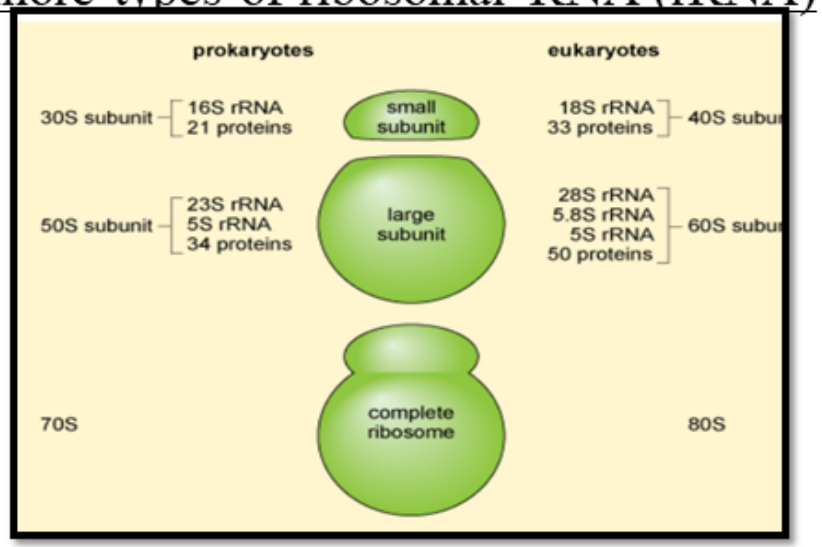


Objectives

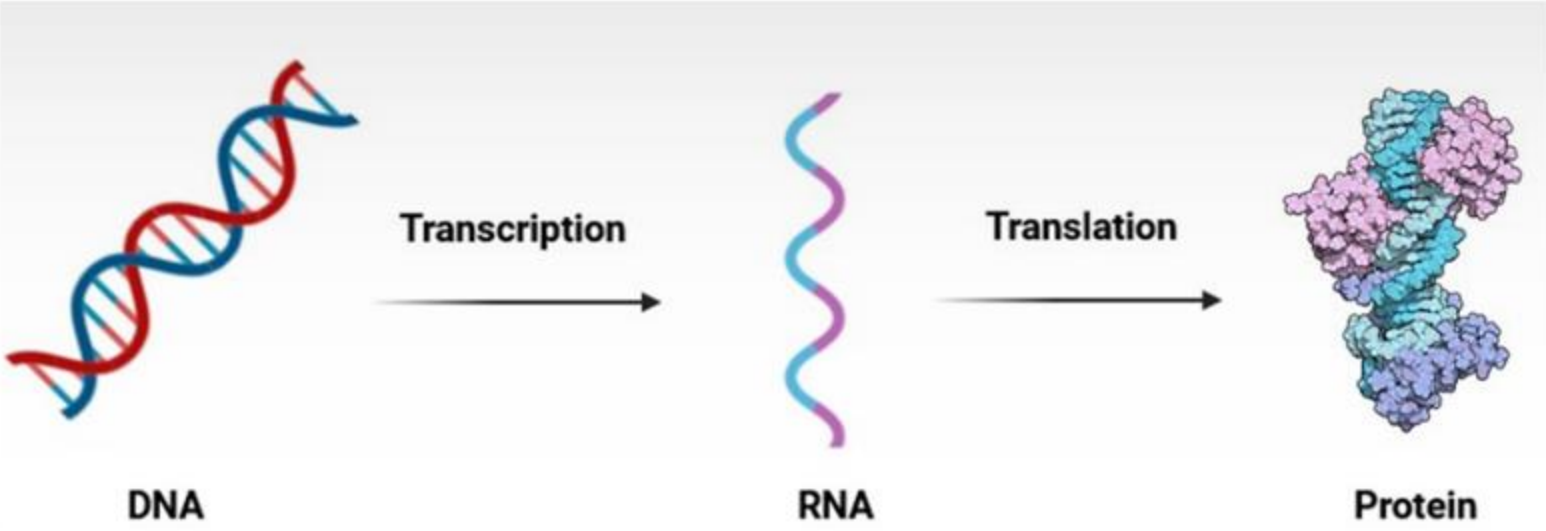
- 1- Protein synthesis in bacterial ribosomes
- 2- Mechanism of action of protein synthesis inhibitors antibiotics
- 3- Classification of protein synthesis inhibitors
- 4- Aminoglycosides
- 5- Macrolides
- 6- Tetracyclines
- 7- Chloramphenicol
- 8- Clindamycin

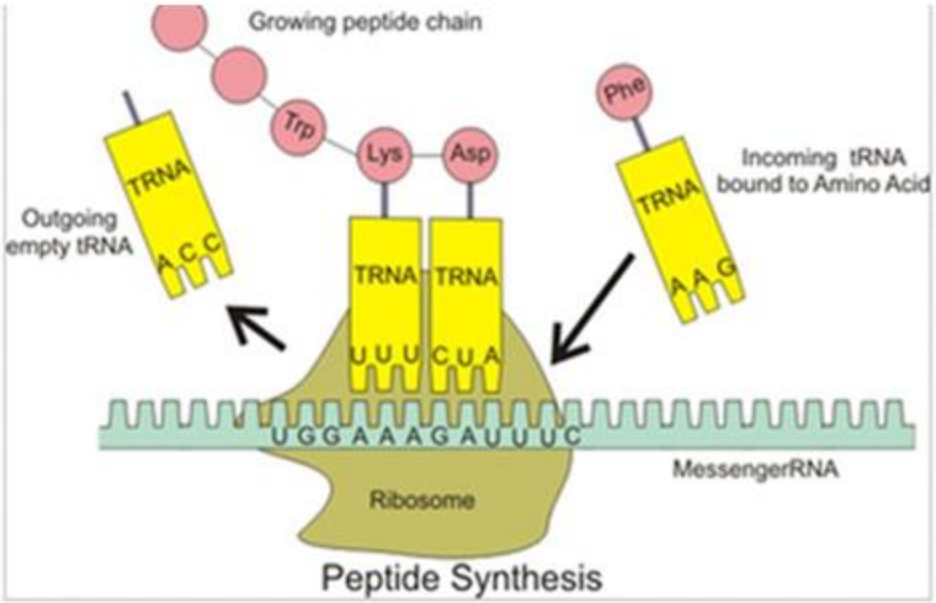
Ribosomes: site of protein synthesis

- Eukaryotic and prokaryotic ribosomes differ primarily in their **size and composition**:
- **prokaryotic ribosomes** are smaller (70S), with a (50S) large and (30S) small subunit, while **eukaryotic ribosomes** are larger (80S) with (60S) and (40S) subunits.
- **Eukaryotic ribosomes** are more complex, containing more types of ribosomal RNA (rRNA) and proteins than prokaryotic ribosomes.
- **Prokaryotic ribosomes are 70S:**
- Large subunit: 50 S
- Small subunit: 30 S
- **Eukaryotic are 80S**



- **Selective toxicity:**
- Acting at the ribosomal level taking the advantage of major differences between prokaryotic and eukaryotic ribosome structure





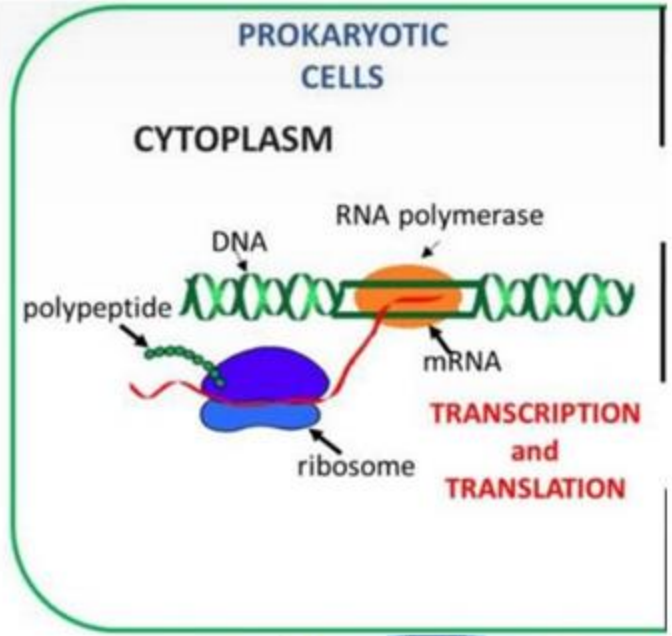
Steps of translation:

1- Initiation: mRNA attached to ribosome

2- Elongation: reading of mRNA by ribosome and extension by tRNA: codon(3 aa in mRNA): polypeptide

3- Termination: polypeptide detached from ribosome and released into cytoplasm

- **Translocation:** movement of ribosome along mRNA in the right direction



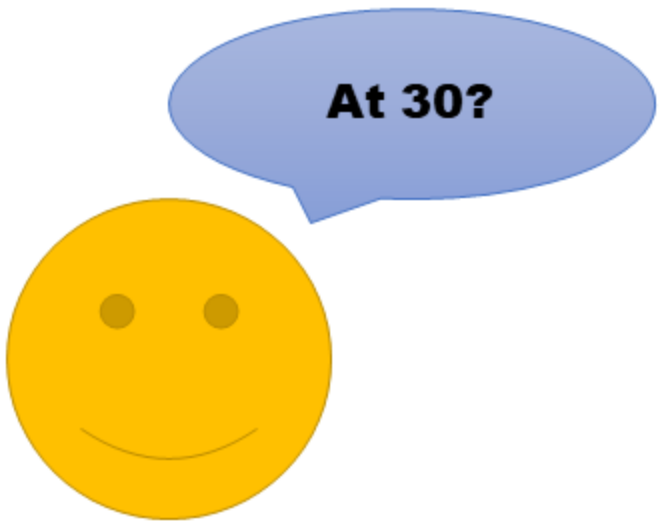
Translation on ribosome: decoding of mRNA

Classification

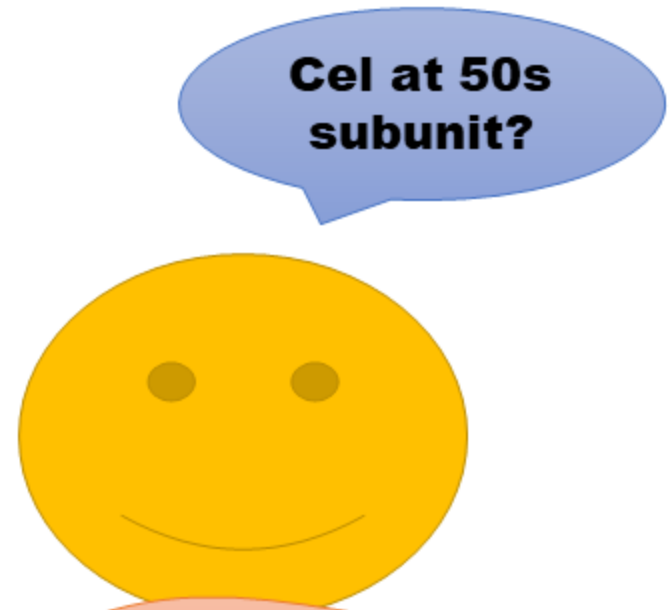
- They are classified based on their **ribosomal subunit target (binds to)**

Agent	Target	Bactericidal or static	Mechanism
Aminoglycosides **Narrow spectrum: mainly G-ve**	30 s subunit	**Cidal**	**irreversibly** binds to **the A-site (aminoacyl-tRNA acceptor site)** of ribosome
Tetracyclines **Broad spectrum**	30 s subunit	Static	Blocking the attachment of **aminoacyl-tRNA to the A-site of the ribosome.**
Macrolides **Moderate spectrum: G+ve & atypical microorganisms**	50 s subunit	Static **Increasing concentration turns the drug into cidal**	**block translocation** -.
(Lincosamides) Clindamycin **Restricted spectrum: Aerobic Gram-Positive Cocci, Anaerobic Bacteria, protozoa** **(similar to macrolides)**	50 s subunit	Static	**block translocation**.
Chloramphenicol **Broad spectrum**	50 s subunit	Static	**Inhibits the enzyme peptidyl transferase**, which is responsible for creating peptide bonds between amino acids.
Linezolid: **Narrow spectrum: G+ve: MRSA, VRE**	50 s subunit	Static: staphylococci and enterococci **Cidal**: streptococci, pneumococci, Bacteroides.	**Prevent the formation of the initiation complex**.

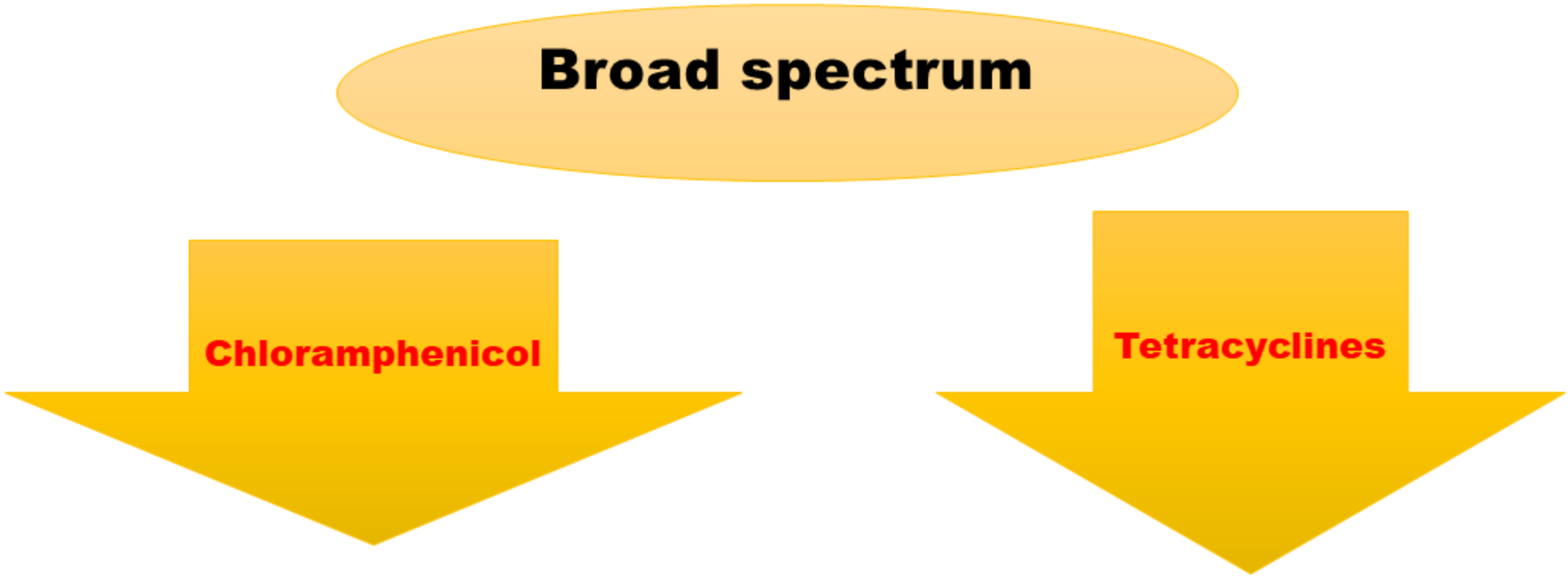
Mechanism of action



- **A**minoglycosides
- **T**etracyclines

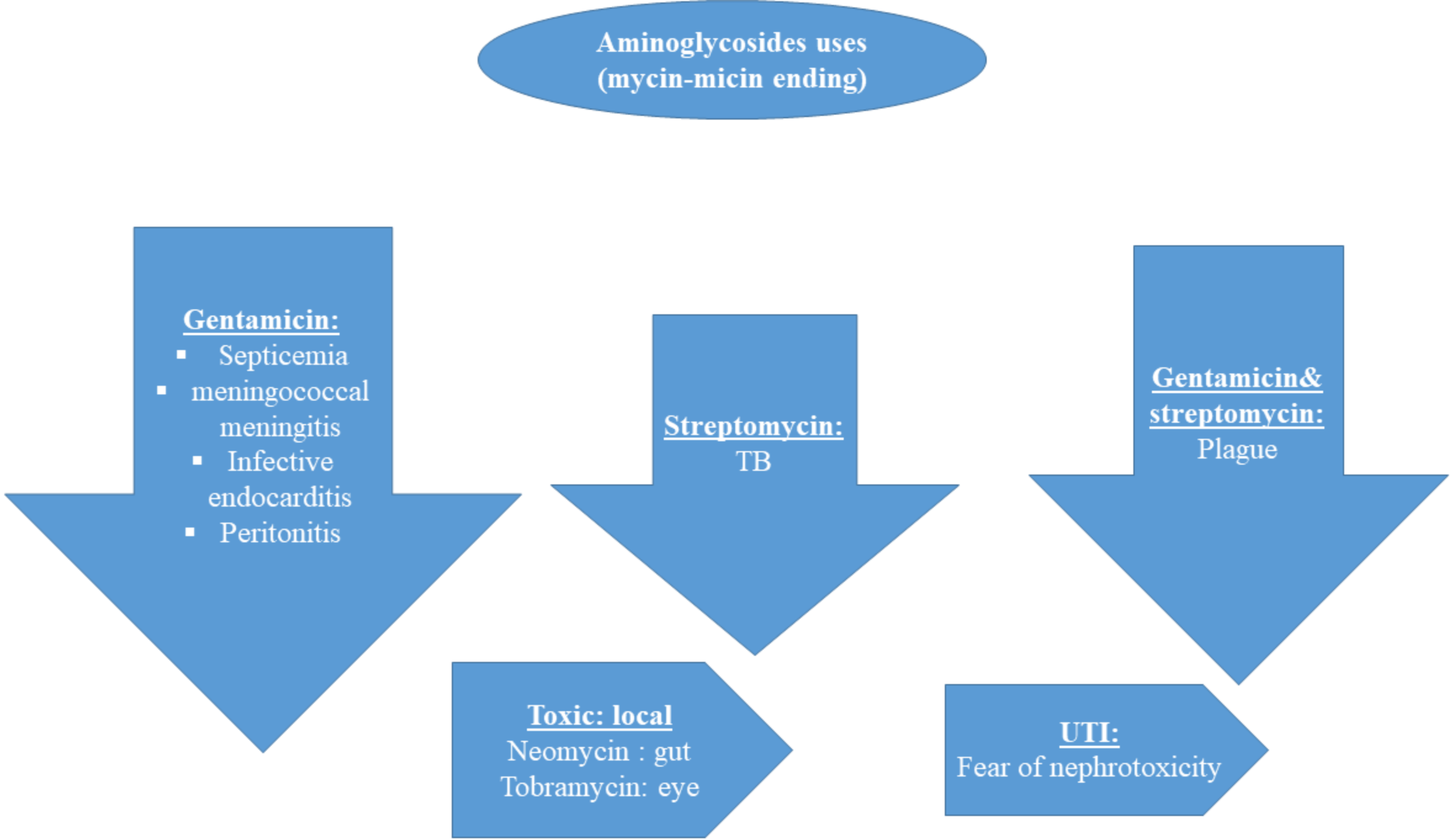


- **C**hloramphenicol, **C**lindamycin
- **E**rythromycin: Macrolides
- **L**inezolid


Broad spectrum
Chloramphenicol
Tetracyclines

	Aminoglycosides (cidal) Narrow spectrum	Macrolides (static) Moderate spectrum	Chloramenipheol (Static- broad spectrum)	Clindamycin (static)	Tetracyclines (static-broad spectrum)
PDs	**Irreversible** binding to 30S subunit **highly water-soluble, polar molecules** **Synergism:** The aminoglycosides synergize with β-lactam antibiotics. The β-lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.	▪ Binding of 50S subunit: **(weak reversible binding)** ▪ Increasing concentration turns the drug into cidal MW>500 (**macro**)	Binding **(weak)** to 50S subunit MW<500, only 2 –OH groups, 2 Cl atoms (antibacterial activity) Not used nowadays except topical for eye infections	Binding to 50 S subunit **(strong)** (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 • Parenteral • **Not** pass BBB • Can **PASS** placenta (specific transport mechanisms) and breast milk (small amounts) • **Not** metabolized • **Excreted unchanged** in urine: active in alkaline urine (non-ionized form easily penetrates into bacteria)	• **Poor oral absorption**, **affected by food (on empty stomach)** • **Not** pass BBB • **Pass placenta** but **NOT teratogenic:** safe in pregnancy: erythromycin, azithromycin • **Pass to most body fluids** in good concentration (prostate) • **Concentrated in macrophages and polymorphs** (long biological half life) • Metabolism: liver • Excretion: bile, enterohepatic circulation • Members: ACE Azithromycin Clarithromycin Erythromycin Spiramycin (Toxoplasmosis during pregnancy)	• **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 (enterohepatic circulation)**	• **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**

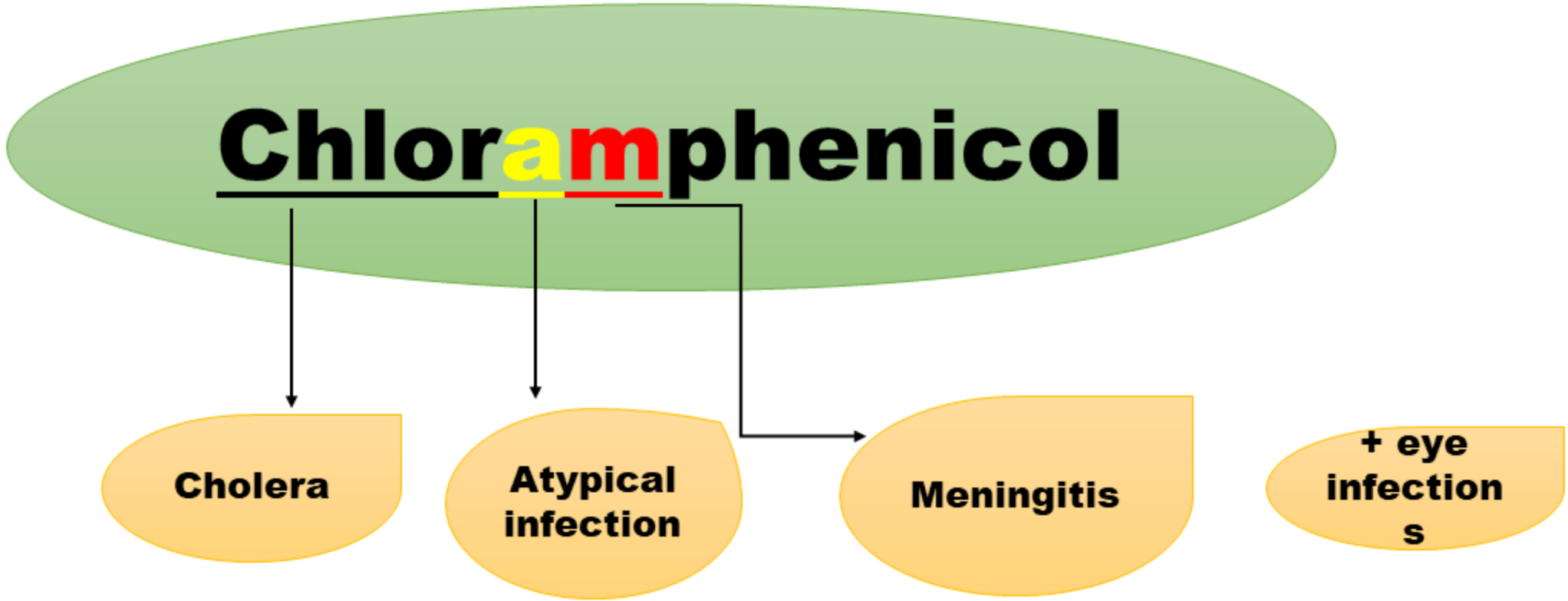
	Aminoglycosides (cidal)	Macrolides (static)	Chloramphenicol (Static)	Clindamycin (static)	Tetracyclines (static)
Indications	**1- Septicemia , meningococcal meningitis: gentamicin** **2- Gentamicin: combined with other antibiotics:** **Infective endocarditis with vancomycin** **Peritonitis with penicillin and metronidazole** **3- T.B. streptomycin** **4- Plague (Y. pestis): 1st line (streptomycin, gentamicin)** **5- Neomycin (toxic): local: oral for gut decontamination, hepatic coma** **6- Tobramycin (toxic)**: eye drops 7- **UTIs**: their use is **not common** due to a fear of nephrotoxicity	**1- G+ve infections respiratory and ENT infections**: 2nd choice after penicillins and cephalosporins 2- skin and soft tissue infections 3- Other bacterial infections: Diphtheria, whooping cough (pertussis), and cat scratch fever. 4- Atypical infections: eye and genital infections of chlamydia, atypical pneumonia, Legionnaires' disease, toxoplasmosis 5- Penicillin allergy: A common alternative for patients who are allergic to penicillin. **6- GIT: Clarithromycin:** eradication of **H.pylori** in peptic ulcer: 10 days, **C. difficile**	**2nd , 3rd even 4th 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, fluoroquinolones (4th choice)** **4- Eye infections: eye drops, ointment**	**1- Dental infections** **2- Bone, joint infection:** osteomyelitis **3- Toxic shock syndrome :Nafcillin, oxacillin, vancomycin or gentamicin** **4- Topical**: acne **5- Toxoplasmosis, malaria (off-label)**	**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 • **3 Ns**	• **GIT upset**: common • **Cholestatic Hepatitis** • **Enzyme inhibitor**: hepatic cytochrome enzyme: aggravates myopathy induced by statins • **Prolongation of QT interval**: sudden cardiac death • **GIT, QT, Enzyme inhibitor**	**TOXIC: Bone marrow, gray baby, enzyme inhibitor)** 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** **Contraindications:** blood diseases, pregnancy, lactation, children less than 2 y	**pseudomembranous colitis:** • 2-20% • most serious may be fatal • by **Clostridium difficile** • **Treatment: IV 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) 3- kidney: nephrogenic DI, Fanconi syndrome (outdated tetracyclines) **4- GIT upset**: ≠peptic ulcer **5- liver: liver cell failure, cholestatic jaundice** **6- Photosensitivity**

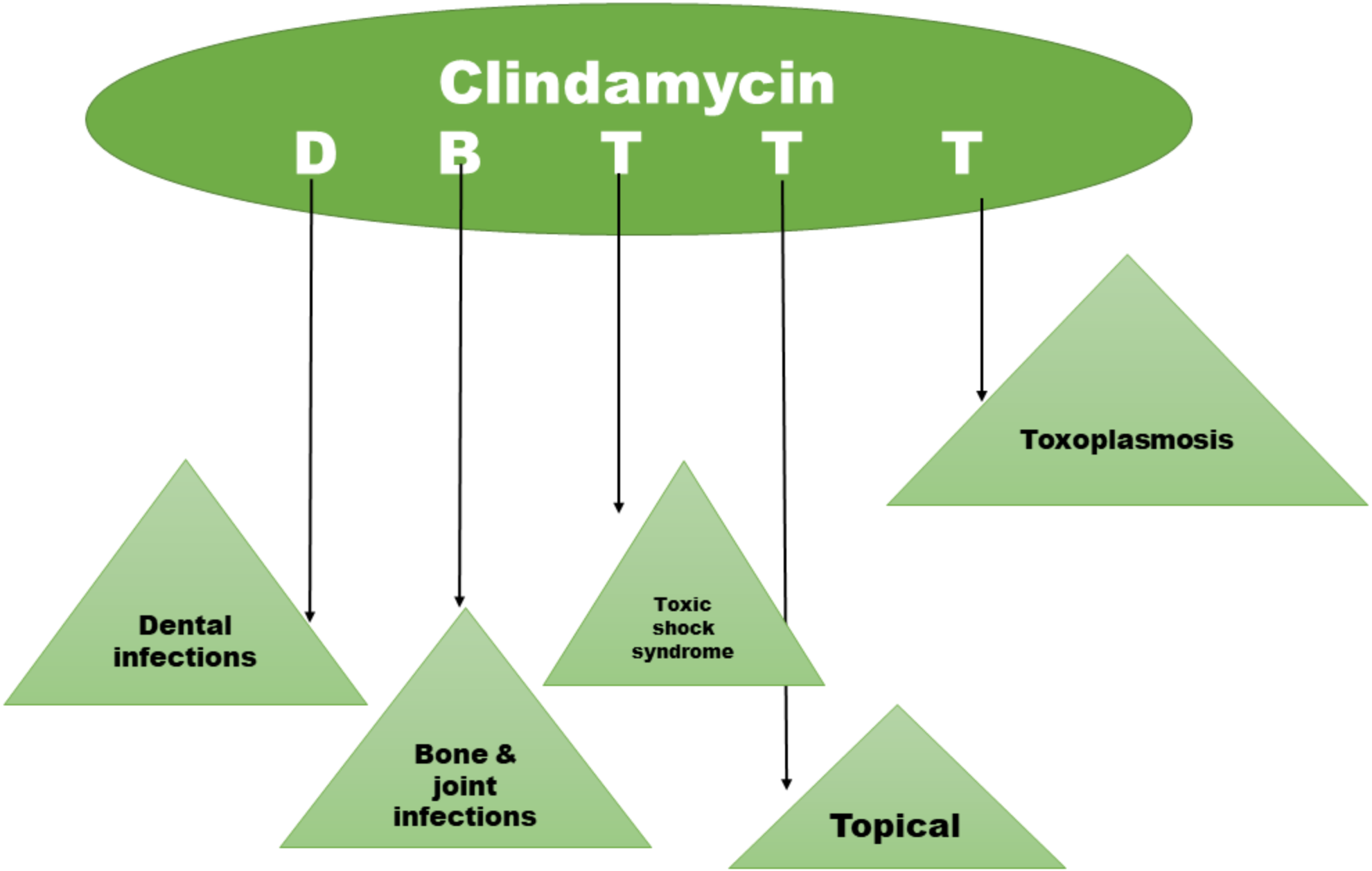

Aminoglycosides uses
(mycin-micin ending)
Gentamicin:
Septicemia
meningococcal meningitis
Infective endocarditis
Peritonitis
Streptomycin:
TB
Gentamicin& streptomycin:
Plague
Toxic: local
Neomycin : gut
Tobramycin: eye
UTI:
Fear of nephrotoxicity

Macrolides (thromycin-ending)

Uses:
Resk of atypical allergy in GIT

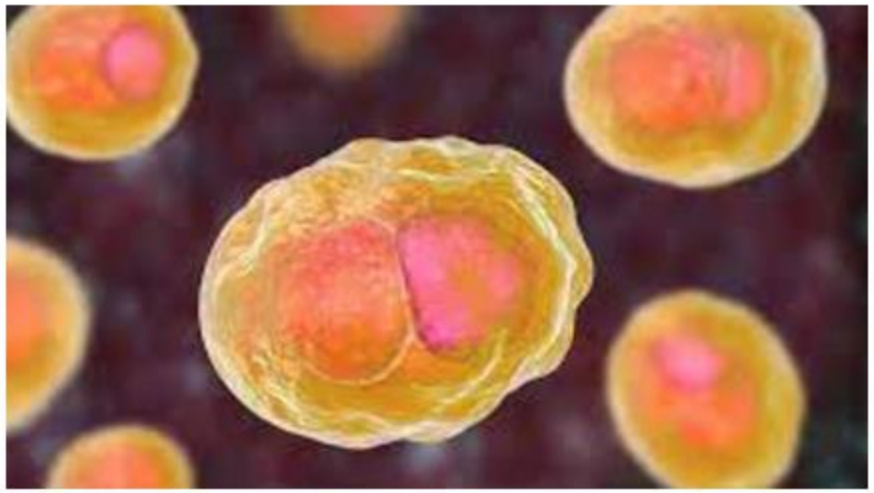
1- Re : respiratory infections
2- Sk: skin and soft tissue infections
3- O: other infections
4- Atypical infections
5- Penicillin allergy
6- GIT infections


Chloramphenicol
Cholera
Atypical infection
Meningitis
+ eye infections


Clindamycin
D
B
T
T
T
Dental infections
Bone & joint infections
Toxic shock syndrome
Topical
Toxoplasmosis

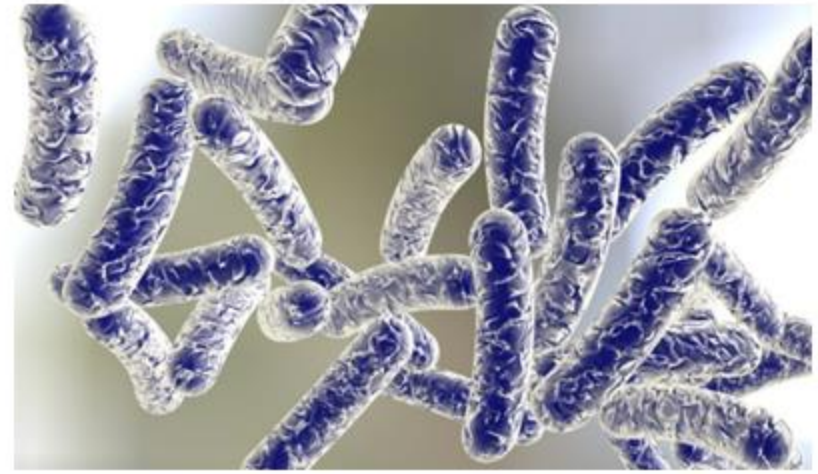
calm my leg:

- Chlamydia
- Mycoplasma
- Legionella



Chlamydia

Mycoplasma



Legionella

BRC:

- Borrelia
- Rickettsia
- Coxiella

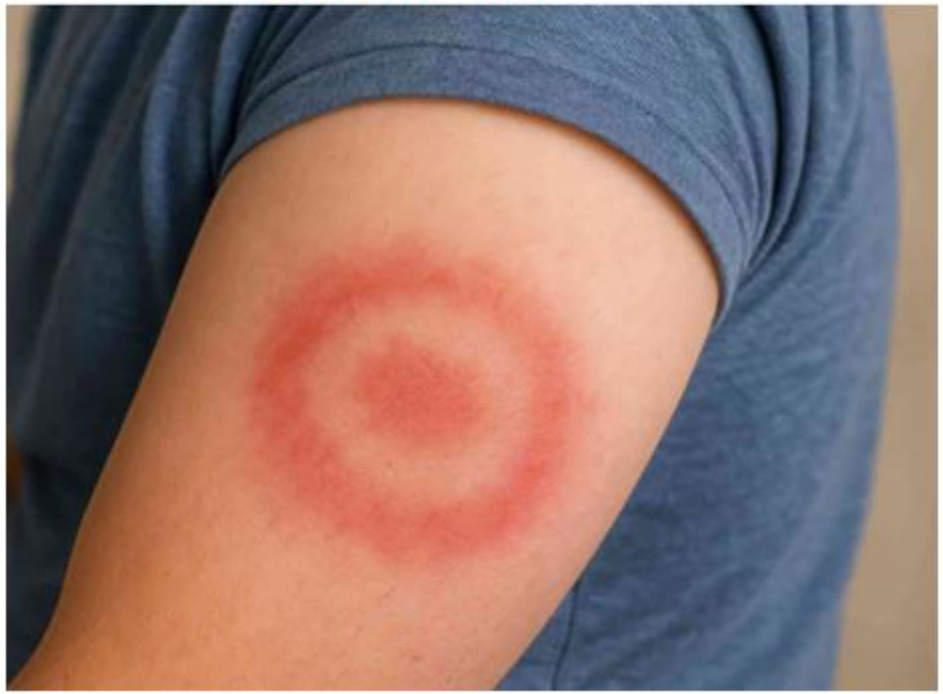
SIADH:

Syndrome of inappropriate ADH secretion

Tetracyclines uses:

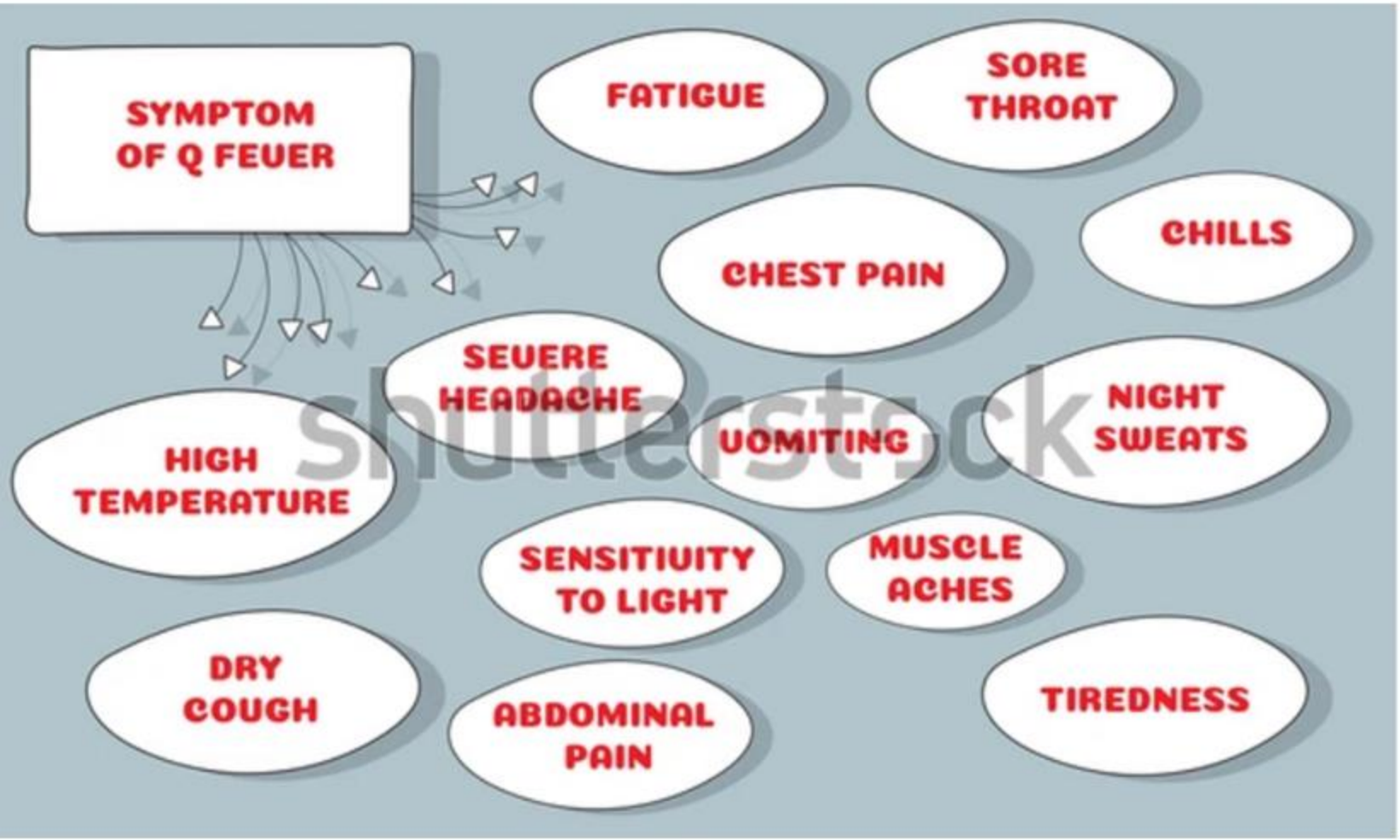
- Calm my leg
- BRC
- SIADH has cholera and acne

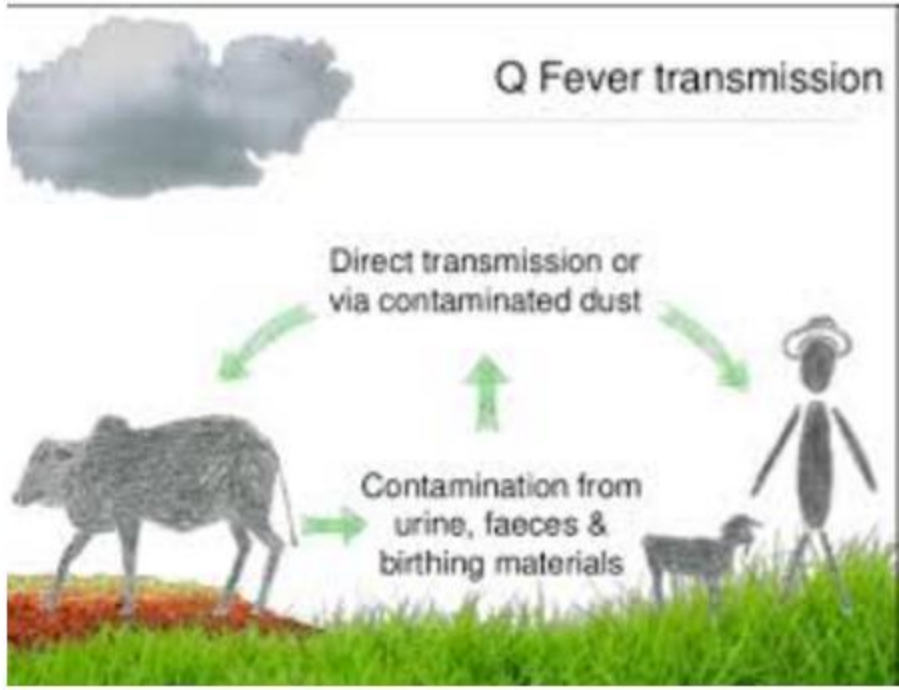
Lyme disease



Rocky mountain spotted fever

Q fever


SYMPTOM OF Q FEUER
FATIGUE
SORE THROAT
CHILLS
CHEST PAIN
SEUERE HEADACHE
HIGH TEMPERATURE
UOMITING
NIGHT SWEATS
SENSITIUITY TO LIGHT
MUSCLE ACHES
DRY COUGH
ABDOMINAL PAIN
TIREDNESS
shutterstock

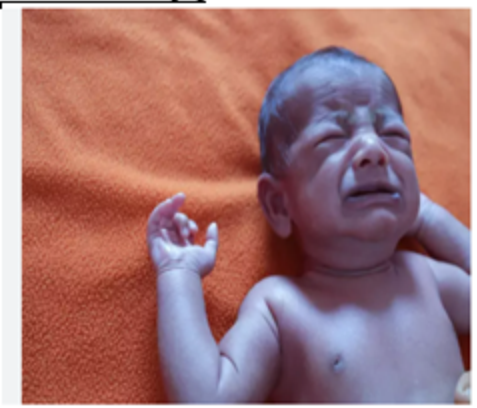

Q Fever transmission
Direct transmission or via contaminated dust
Contamination from urine, faeces & birthing materials

Is Chloramphenicol teratogenic?

- **Studies on humans** have largely found that **chloramphenicol has little, if any, teratogenic risk** (meaning it does not cause physical birth defects) when used during early pregnancy.
- However, its use, especially **in late pregnancy or at high doses**, is severely restricted due to the risk of a different, potentially fatal condition in newborns called **"Gray Baby Syndrome".**

Gray Baby Syndrome

- **Chloramphenicol readily crosses the placenta**, and fetal blood concentrations can approach maternal levels.
- Newborns, particularly **premature infants**, have immature livers that cannot produce sufficient amounts of the **enzyme (UDP-glucuronyltransferase)** needed to metabolize and excrete the drug effectively.
- This accumulation leads to **"Gray Baby Syndrome," a life-threatening condition** characterized by **vomiting, abdominal distension, progressive gray skin discoloration, irregular respiration, hypothermia, flaccidity**, and **cardiovascular collapse**.
- **Topical chloramphenicol** (eye drops and ointments) is generally considered safe during pregnancy because only tiny amounts are absorbed into the bloodstream, but caution is still recommended.

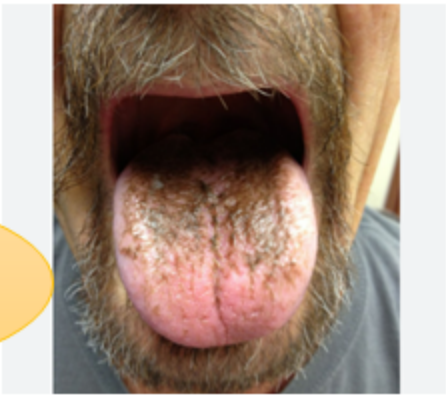


Linezolid

- Primarily used to treat **serious infections** caused by **multidrug-resistant Gram-positive bacteria**, such as methicillin-resistant Staphylococcus aureus **(MRSA)** and vancomycin-resistant enterococci **(VRE).**
- **It is not effective against Gram-negative bacteria.**
- **Indications:**
- Hospital-acquired pneumonia
- Community-acquired pneumonia
- Complicated and uncomplicated skin and skin structure infections
- VRE infections

Linezolid

- **Dose**: 600 mg/12 hours oral or IV
- **Duration of administration**:
- It is generally **safe for short courses** (less than 14 days).
- **Prolonged use** (over 28 days) increases the risk of serious side effects
- **ADR:** diarrhea, headache, nausea, vomiting, **bone marrow depression (serious)**
- **Black hairy tongue**: abnormal hypertrophy and elongation of filiform papillae
- **Management**: **stop** the drug for 2-3 weeks and re-introduction(If needed) with **oral hygiene**



Linezolid contraindications

- **1- Pregnancy/Breastfeeding:**
- Linezolid is generally in **pregnancy category C**, meaning it should be used only if the potential benefit outweighs the risk.
- It passes into **breast milk**, so caution is advised for breastfeeding mothers.
- **2- Concurrent administration with:**
- **Antidepressants (SSRIs, TCAs):** potentially life-threatening **Serotonin Syndrome**
- **Large amounts of high-tyramine foods** and beverages (e.g., aged cheeses, cured meats, red wine, soy sauce, and tap beer): **hypertensive crisis**
- **Mechanism**: Linezolid is a weak, reversible monoamine oxidase (MAO) inhibitor.

Tap beer

References

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Thank you