# Pharmacology of Protein Synthesis inhibitors

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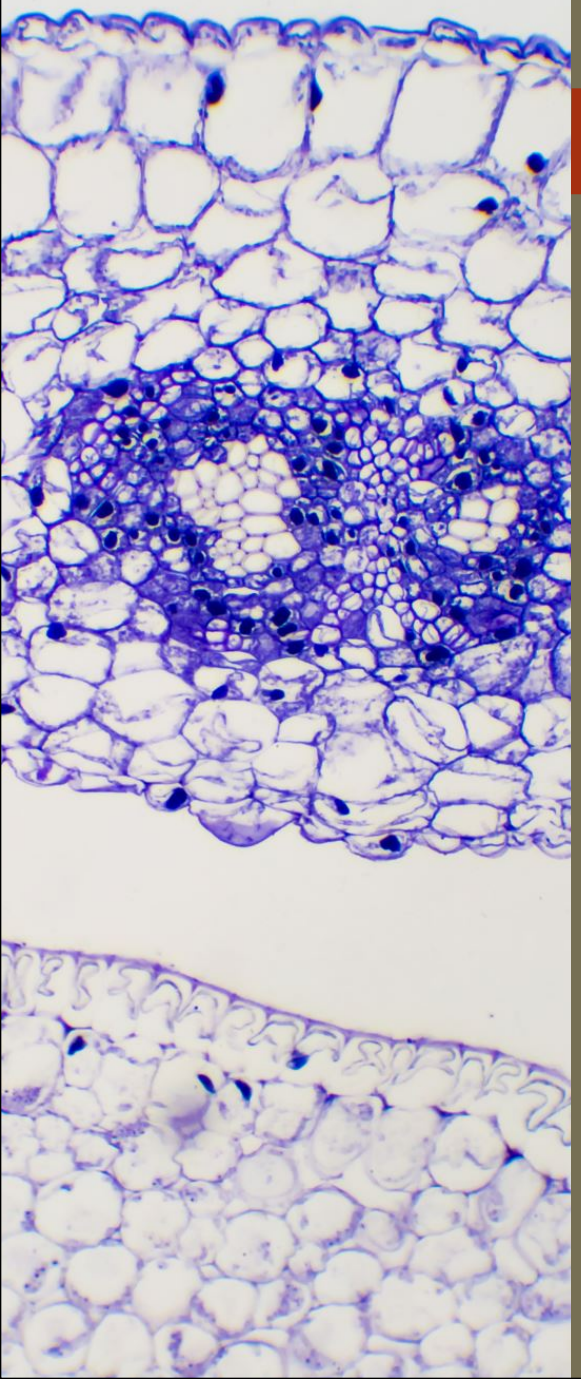
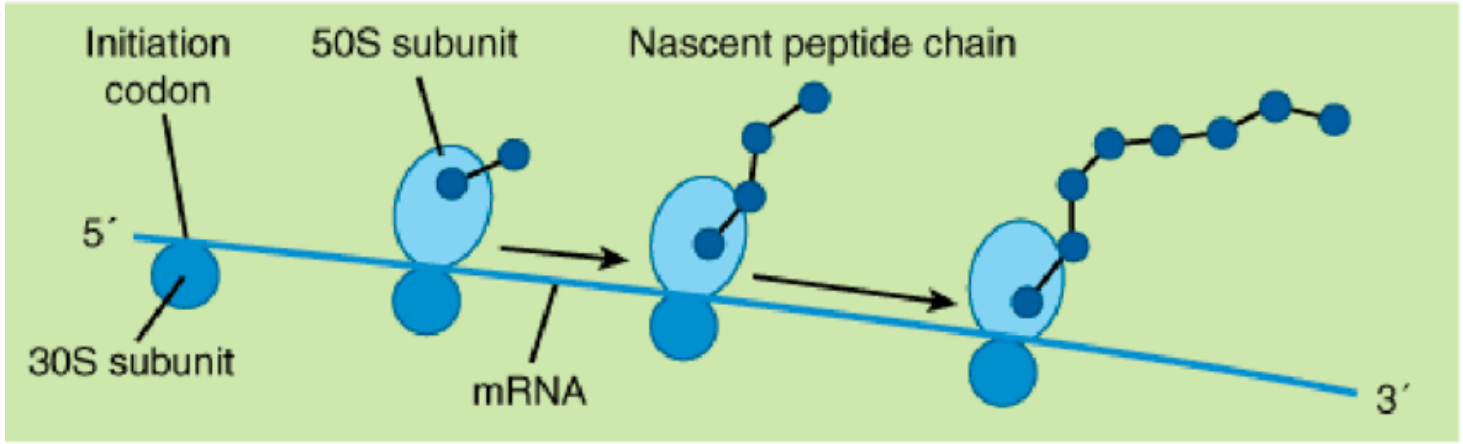
# Objectives

- 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
- 9- Quinupristin / dalfopristin
- 10- Linezolid

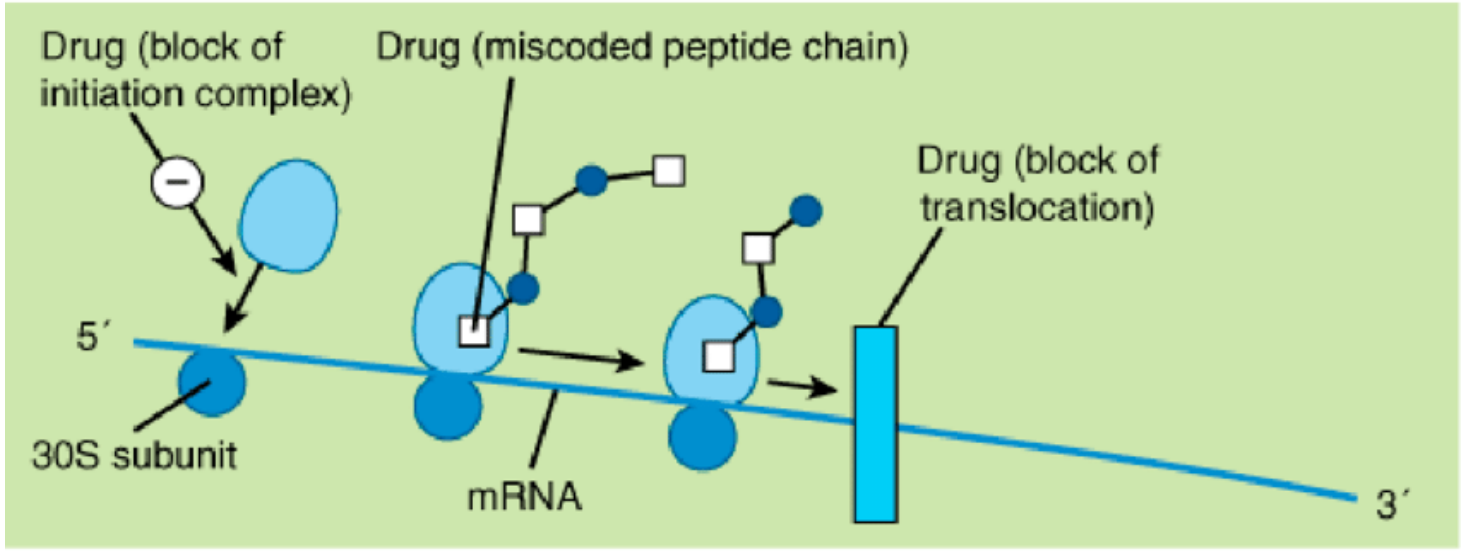


# Ribosomes: site of protein synthesis

- 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

A number of ATBs are targeting the bacterial ribosome, which has components that differ structurally from those of the mammalian cytoplasmic ribosome.

In general, the bacterial ribosome is smaller (70S) than the mammalian ribosome (80S), and is composed of 50S and 30S subunits (as compared to 60S and 40S subunits).

The mammalian mitochondrial ribosome, however, more closely resembles the bacterial ribosome $\Rightarrow$ high levels of drugs (e.g., chloramphenicol, tetracyclines) may cause toxic effects as a result of interaction with the mitochondrial ribosomes.

# 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 (bactericidal)

**streptomycin**, kanamycin, gentamicin, tobramycin, amikacin, neomycin (topical)

- **Mode of action** - The aminoglycosides irreversibly bind to the 30S ribosomal RNA and freeze the 30S initiation complex (30S-mRNA-tRNA)
- They also slow down protein synthesis that has already initiated and induce misreading of the mRNA.
- **Spectrum of Activity** -Many gram-negative and some gram-positive bacteria
- **Resistance** - Common
- **Synergy** - The aminoglycosides synergize with β-lactam antibiotics.
- The β-lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.

Aminoglycosides
**Clinical pharmacokinetics**

These are poorly lipid soluble and, therefore, not absorbed orally

Parenteral administration is required for systemic effect.

They do not enter the CNS even when the meninges are inflamed.

They are not metabolized.

# Aminoglycosides **Resistance**

- Resistance results from bacterial enzymes which break down aminoglycosides
- or to their decreased transport into the cells.

# Aminoglycosides **Examples**

- *Gentamicin* is the most commonly used, covering Gram-negative aerobes, e.g. Enteric organisms *(E.coli, Klebsiella, S. faecalis, Pseudomonas and Proteus spp.)*
- It is also used in antibiotic combination against *Staphylococcus aureus*.
- It is not active against aerobic *Streptococci.*

# Aminoglycosides

## **Examples**

*Tobramycin:* used for pseudomonas and for some gentamicin-resistant organisms.

Some aminoglycosides,e.g. Gentamicin, may also be applied topically for local effect, e.g. In ear and eye ointments.

*Neomycin* is used orally for decontamination of GI tract.

# Aminoglycosides
## **Adverse effects**

The main adverse effects are:

Nephrotoxicity

Toxic to the 8th cranial nerve (ototoxic), especially the vestibular division.

Other adverse effects are not dose related, and are relatively rare, e.g. Allergies.

# Macrolides (bacteriostatic)

**erythromycin**, clarithromycin, azithromycin, spiramycin

- **Mode of action** - The macrolides inhibit translocation by binding to 50 S ribosomal subunit
- **Spectrum of activity** - Gram-positive bacteria, *Mycoplasma, Legionella (intracellular bacterias)*
- **Resistance - Common**

# Macrolides
## **Examples and clinical pharmacokinetics**

Macrolides are widely distributed in the body except to the brain and cerebrospinal fluid

The spectrum includes *Staphylococcus aureus, Streptococcuss pyogenes, S. pneumoniae, Mycoplasma pneumoniae and Chlamydia* infections.

# Macrolides – side effects

- Nauzea, vomiting
- Allergy
- Hepatitis, ototoxicity
- Interaction with cytochrome P450 3A4 (inhibition)

# Clindamycin (bacteriostatic)

- **Mode of action** - as erythromycin

- **Spectrum of activity** - clindamycin - Restricted range: g-ve and anaerobic bacteria
- **Resistance** - Common
- **Adverse effects –**
- skin rashes
- - the most serious - potentially fatal pseudomembranous colitis !! (caused by overgrowth of Clostridium difficile, which elaborates toxins).
- P.o. administration of vancomycin - usually effective in the treatment
- impaired liver function
- - inhibition of neuromuscular transmission ⇒ ↑ effect of neuromuscular blocking drugs

# Clindamycin

Clindamycin, although chemically distinct, is similar to erythromycin in mode of action and spectrum.

It is rapidly absorbed and penetrates most tissues well, except CNS.

It is particularly useful systematically for *S. aureus* (e.g.osteomyelitis as it penetrates bone well) and anaerobic infections.

# Chloramphenicol

- This inhibits bacterial protein synthesis.
- **It binds to the bacterial 50S ribosomal subunit ⇒ inhibition of protein synthesis at the peptidyl transferase reaction.**
- It is well absorbed and widely distributed , including to the CNS.
- It is metabolized by glucoronidation in the liver.
- Although an effective broad-spectrum antibiotics, its uses are limited by its serious toxicity.
- **Resistance**
- **- Presence of an R factor that inactivates chloramphenicol.**
- **- Inability to penetrate the organism.**

# Chloramphenicol

- The major indication is to treat bacterial meningitis caused by *Haemophilus influenzae,* or to *Neisseria menigitidis* or if organism is unknown.
- It is also specially used for *Rikettsia* (typhus).
- **Serious life-threatening infections (H.influenzae, Bacteroides fragilis**
- **-In typhoid fever: amoxycillin and cotrimoxazole less toxic.**
- **-safe and effective in bacterial conjunctivitis (given topically).**

**Pharmacology**

-Administered i.v. or orally.

-Completely absorbed after oral route (its lipophilic nature).

-Widely distributed including the CSF !!! It readily enters the normal CSF.

-About 10% of chloramphenicol are excreted by glomerular filtration. It is also secreted into breast milk.

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# Chloramphenicol
## **Adverse effects**

A rare anemia, probably immunological in origin but often fatal

Reversible bone marrow depression caused by its effect on protein synthesis in humans

Liver enzyme inhibition

## Adverse effects

-Anemia: Hemolytic anemia in patients with low levels of glucose 6-phosphate dehydrogenase.

- Other types of anemia - include reversible anemia (apparently dose-related, occurs concomitantly with therapy).
- Aplastic anemia (is idiosyncratic and usually fatal !!!) - Aplastic anemia is independent of dose and may occur after therapy has ceased !!!
- Pancytopenia
- Potential teratogenic effects.
- GIT disturbances, diarrhea, hypovitaminosis B and K
- Overgrowth of Candida albicans.

- **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.**

**Interactions:**

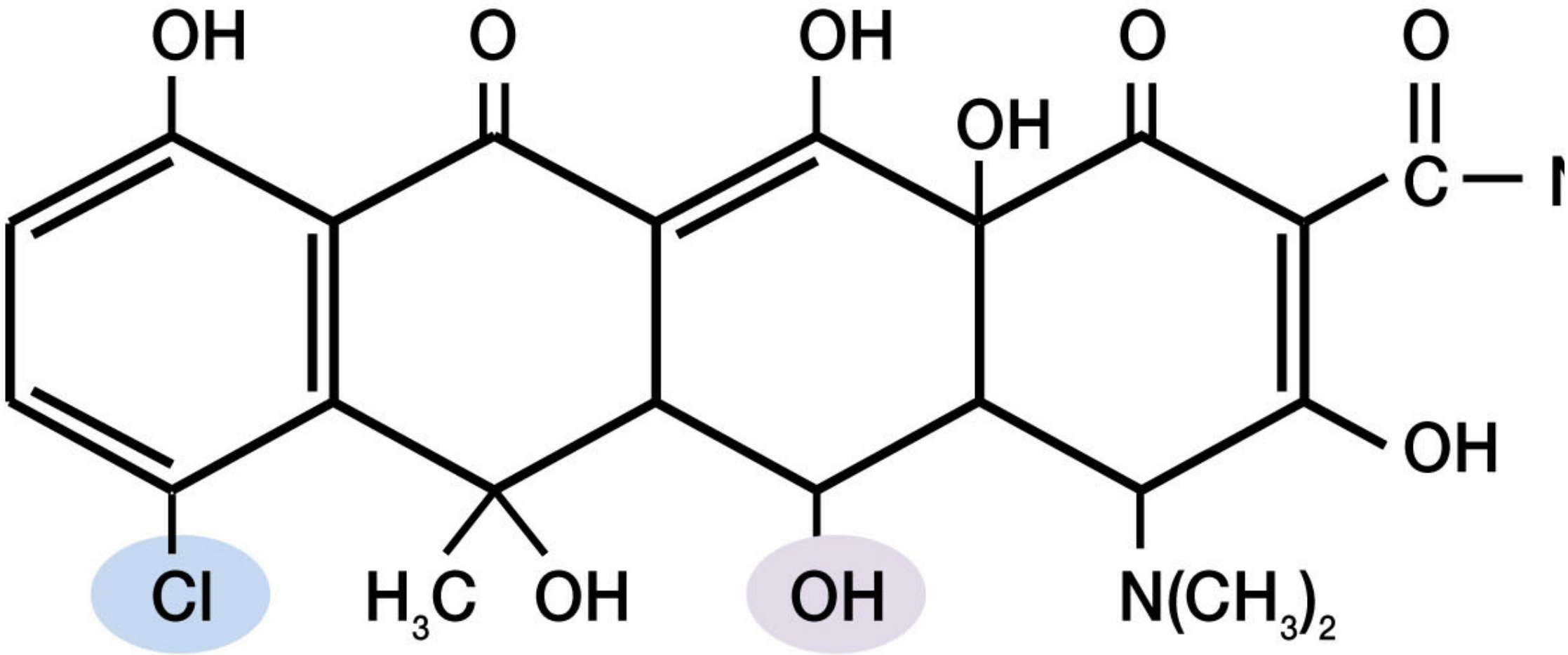
**It inhibits some hepatic mixed-function oxidases and blocks the metabolism of drugs (warfarin, phenytoin, tolbutamide, chlorpropamide) - ↑ of their concentrations and potentiating their effects.**

# **Tetracyclines** (bacteriostatic)

**tetracycline**, minocycline and doxycycline

- **Mode of action** - The tetracyclines reversibly bind to the 30S ribosome
- **Spectrum of activity** - Broad spectrum; Useful against intracellular bacteria
- **Resistance** - Common

# etracycline (chlortetracycline, doxycycline)



Tetracyclines

**Examples and clinical pharmacokinetics**

*Tetracycline, oxytetracycline* have short half-lives.

*Doxycycline* has a longer half-life and can be given once per day.

These drugs are only partly absorbed.

They bind to heavy metal ions and so absorption is greatly reduced if taken with food, milk, antacids or iron tablets.

# Tetracyclines

## Examples and clinical pharmacokinetics

- They should be taken at least half an hour before food.
- Tetracyclines concentrate in bones and teeth.
- They are excreted mostly in urine, partly in bile.
- They are broad spectrum antibiotics, active against most bacteria except *Proteus or Pseudomonas.*

# Tetracyclines
## **Adverse effects**

- Gastrointestinal upsets
- Superinfection
- Discolouration and deformity in growing teeth and bones (contraindicated in pregnancy and in children < 12 years)
- Renal impairment (should be also avoided in renal disease)

# Doxycycline is DOC for..

www.medinaz.com

**M**ycoplasma hominis (urogenital)

**P**lague prophylaxis

**R**ickettsia

**B**orrelia, **B**rucella

**C**hlamydia, **C**holera

- QUINUPRISTIN / DALFOPRISTIN

- Mixture of 2 antibiotics (in a ratio of 30 to 70).
- Reserved for the treatment of vancomycin-resistant Enterococcus faecium (VRE).
- <u>Mechanism of action</u>

- Each component binds to a separate site on the 50S bacterial ribosome ⇒ they synergistically interrupt protein synthesis.

- The combination is bactericidal.

- **Resistance**
- Enzymatic processes modify the target bacterial ribosomal RNA site which interfere in quinupristin binding).
- Active efflux pump.

- **Antibacterial spectrum**

- The combination drug is active primarily against G+ cocci, incl. those resistant to other ATBs (e.g., MRS).
- Primary use - treatment of Enterococcus faecium infections, (incl. VRE /vancomycin/ strains).
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- Administration: I.v. in 5 % dextrose solution
- Distribution: They penetrate macrophages and polymorphonucleocytes – important (because VRE are intracellular).
- Levels in the CSF are low.
- Excretion: Most of drugs and metabolites - cleared through the liver and eliminated via the bile into the feces.
- Urinary excretion is secondary.

- Adverse effects
- - Venous irritation
- - Hyperbilirubinemia: Total bilirubin is elevated in about 25 % of patients, (resulting from a competition with ATB for excretion).
- Interactions
- Inhibition of CYP3A4 ⇒ ↑ toxicity of concomitantly administered drugs metabolized by this pathway (e.g. macrolide ATB, fluoroquinolones, antidepressants, antihistamines)

# LINEZOLID

**Spectrum**: Treatment of resistant G+ organisms (e.g., methicillin- and vancomycin-resistant S. aureus, vancomycin-resistant Enterococcus faecium and Enterococcus faecalis, and PNC-resistant streptococci).

**Mechanism of action**

Inhibition of bacterial protein synthesis by binding to 50s subunit

Cidal for streptococci

Static for staph and enterococci

**Resistance**

Decreased binding to the target site.

**Pharmacokinetics**

Ccompletely absorbed on oral administration

## Adverse effects

**Well-tolerated.**

**- thrombocytopenia in ≈ 2 % (when used > 2 weeks) - reversible when drug suspended.**

**- not to consume large quantities of tyramine-containing foods (weak nonspecific inhibition of MAO).**

**Phototoxicity**

- Tetracyclines
- Sulfonamides
- Quinolones

# Antimicrobial drugs contraindicated in Pregnancy

**S**ulfonamides
**A**minoglycosides
**F**luoroquinolones
**E**rythromycin
**M**etronidazole
**T**etracyclines
**R**ibavirin
**G**riseofulvin
**C**hloramphenicol

# Thank you