PROTEIN SYNTHESIS INHIBITORS

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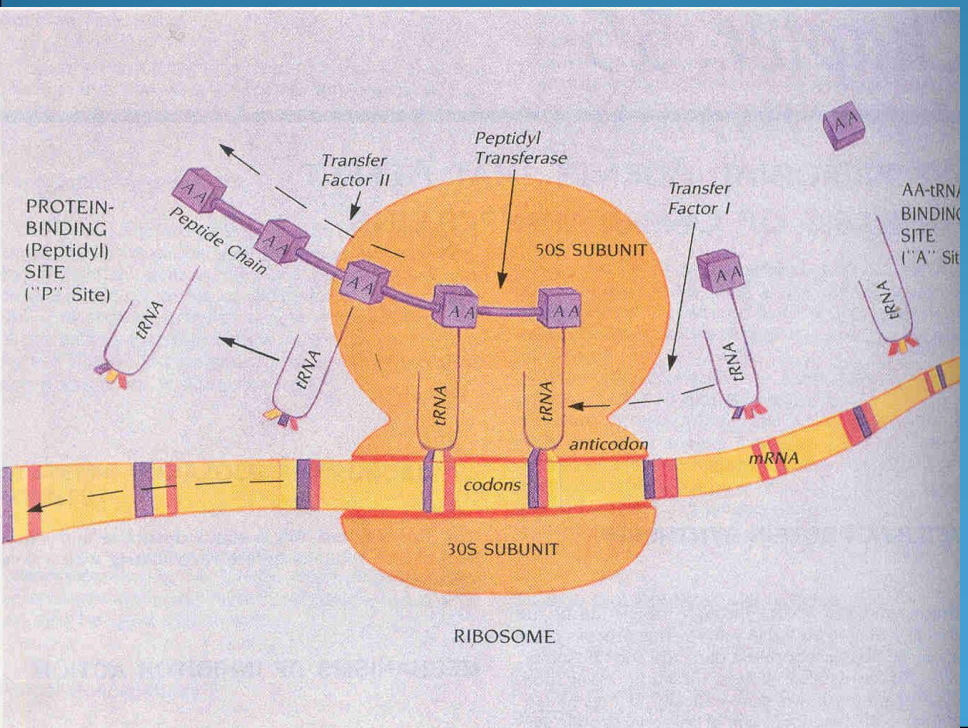


PROTEIN SYNTHESIS INHIBITORS

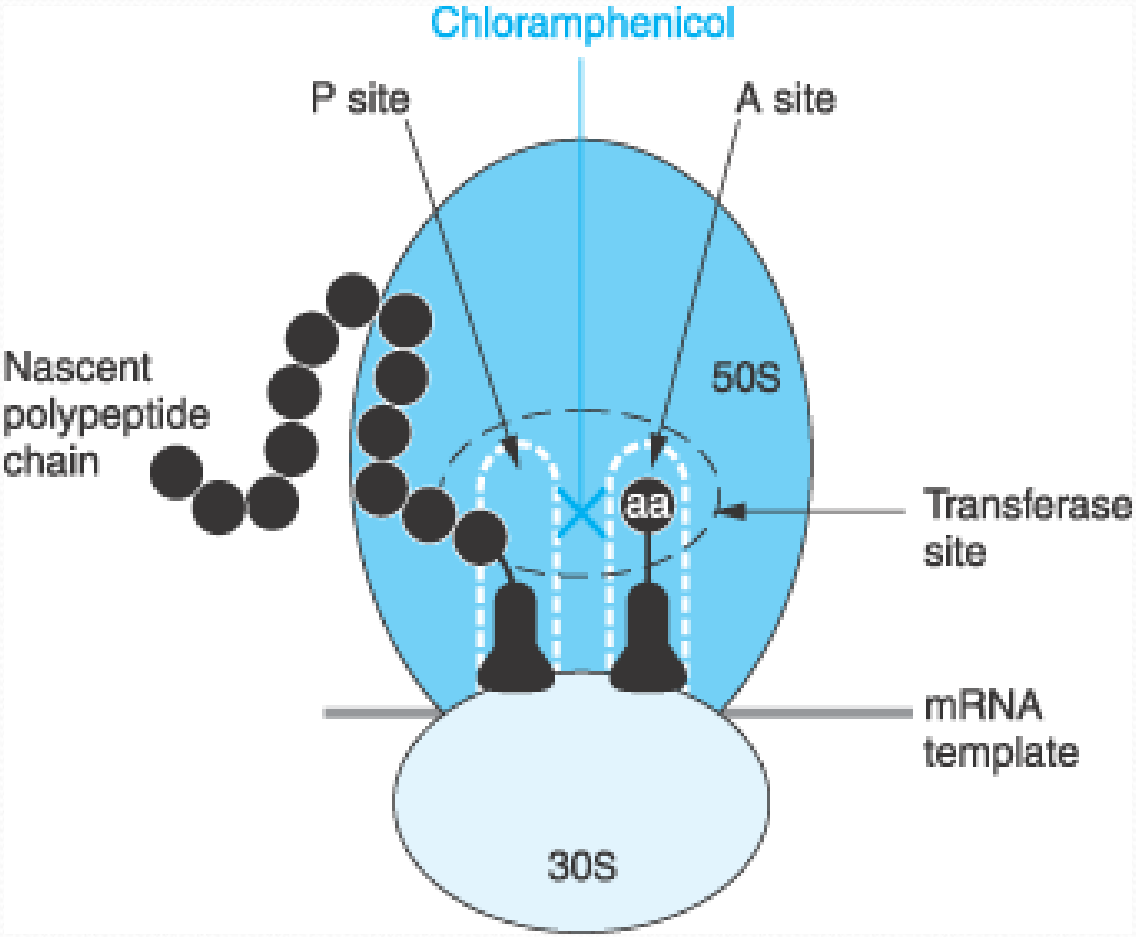
- **TETRACYCLINES**
  - *Demeclocycline*
  - *Doxycycline*
  - *Minocycline*
  - *Tetracycline*
- **GLYCYLCYCLINES**
  - *Tigecycline*
- **AMINOGLYCOSIDES**
  - *Amikacin*
  - *Gentamicin*
  - *Neomycin*
  - *Streptomycin*
  - *Tobramycin*
- **MACROLIDES/ KETOLIDES**
  - *Azithromycin*
  - *Clarithromycin*
  - *Erythromycin*
  - *Telithromycin*
- **CHLORAMPHENICOL**
- **CLINDAMYCIN**
- **QUINUPRISTIN/ DALFOPRISTIN**
- **LINEZOLID**

- The miscellaneous drugs under this heading discussed are:
  - Clindamycin
  - Chloramphenicol
  - Linezolid

Chloramphenicol

- It is a broad spectrum antibiotic
  - usually bacteriostatic
  - sometimes bactericidal against certain species of microorganisms.

MECHANISM OF ACTION



MOA

- Chloramphenicol binds to the 50S ribosomal subunit at the peptidyltransferase site and inhibits the transpeptidation reaction.
- Chloramphenicol binds to the 50S ribosomal subunit near the site of action of clindamycin and the macrolide antibiotics.
- These agents interfere with the binding of chloramphenicol and thus may interfere with each other's actions if given concurrently.

MOA

- The interaction between peptidyltransferase and its amino acid substrate cannot occur, and peptide bond formation is inhibited

- Chloramphenicol inhibits protein synthesis in bacteria, and to a lesser extent, in eukaryotic cells.

Pharmacokinetics

- oral -- **Chloramphenicol palmitate**
  - Absorbed rapidly from GIT
- Parenteral – **Chloramphenicol succinate**

- **Distribution**
  - Well distributed in body fluids, CSF etc.
  - May accumulate in brain tissue
  - Present in bile, milk and crosses placental barrier
  - Penetrates aqueous humor after sub-conjunctival injection

- **Elimination**
  - is primarily through the liver, it is converted to inactive glucuronide, with this metabolite as well as chloramphenicol itself is excreted in urine by filtration secretion.
  - Dose need not to be adjusted in renal patients BUT checked in patients with impaired liver functions

Spectrum Of activity

- Bacteriostatic wide spectrum antibiotic
- Bactericidal for certain sp. e.g.,
  - H. Influenzae,
  - N. meningitidis
  - S. pneumoniae
- More than 95% of the following Gram-ve bacteria are inhibited:
  - H. influenzae,
  - N. meningitidis,
  - N. gonorrhoeae,
  - Brucella,
  - Bordetella pertussis.
- Anaerobic bacteria including
  - Clostridium
  - G-ve rods including B. Fragilis.

- Active against
  - Mycoplasma, chlamydia and rickettsiae. E. Coli, Klebsiella pneumoniae (most strains)
  - Proteus mirabilis
  - V. Cholera
  - Shigella
  - Salmonella resistant to multiple drugs including Chloramphenicol are on the rise

Resistance:

- Resistance develops due to enzymatic deactivation of chloramphenicol by a plasmid-encoded acetyl-transferase

Therapeutic Uses:

- Therapy with chloramphenicol must be limited to infections for which the benefits of drug-use out weigh the risks of potential toxicity
- When other antibiotic are available which are less toxic and equally effective, then they should be preferred.
- Typhoid: (and other salmonella infections)
  - It is an important drug in the treatment of salmonella infections
    - but now there are many resistant organism
    - and moreover much safer drugs are available
  - 3rd generation Cephalosporins and quinolones are used

- Bacterial Meningitis:
  - Excellent activity in meningitis caused by

    H. Influenza, (it is bactericidal and better than ampicillin)

  - 3rd generation cephalosporins are now used due to less toxicity but chloramphenicol remains alternative for treatment of meningitis when Beta Lactams are contraindicated

- Anaerobic infections:
  - Used for the treatment of serious intraabdominal infections or brain abscesses.

    (alternative available)

- Rickettsial infections:
  - Tetracyclines are more preffered but chloramphenicol can be used as an alternative treatment in
    - Rocky mountain spotted fever,
    - epidemic typhus,
    - murine, scrub and recrudescent typhus
    - Q. fever
- Brucellosis:
  - Tetracyclines are more effective when tetracyclines are contraindicated chloramphenicol may be used.

Adverse Effects:

- Chloramphenicol inhibits the synthesis of proteins of the inner mitochondrial membrane that are synthesized in mitochondria, probably by inhibiting the ribosomal peptidyl transferase. (in eukaryotic cells)

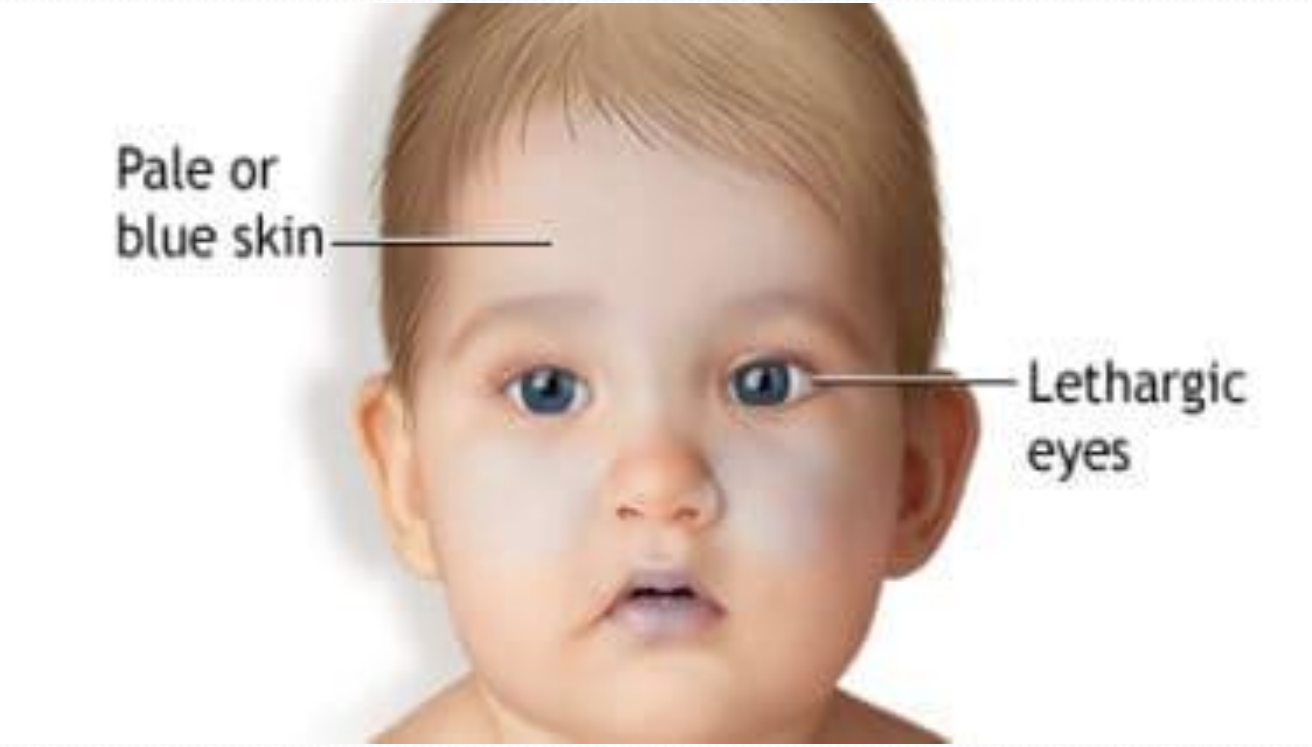
- Hematological Toxicity:
  - The most important adverse effect of chloramphenicol is on the bone marrow. It causes bone marrow depression, aplastic anemia which may lead to fatal pancytopenia.

- Hypersensitivity reactions:
  - Relatively uncommon, macular or vesicular skin rashes occur
  - Fever may appear simultaneously or as a sole manifestation.
- Toxic & irritative effects:
  - Nausea, vomiting, unpleasant taste, diarrhea and perineal irritation may follow oral administration.
  - RARE: blurring of vision, digital paresthesia, optic neuritis in children.

Adverse effect

- Fatal toxicity in neonates specially premature babies exposed to high dose – Grey Baby Syndrome. Newborn infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol. Consequently, when infants are given dosages above 50 mg/kg/d, the drug may accumulate, resulting in the **gray baby syndrome**, with vomiting, flaccidity, hypothermia, gray color, shock, and collapse

Grey baby syndrome



Drug Interactions:

- Chloramphenicol inhibits micorsomal cytochrome P450 enzyme thus may prolong the half-lives of drugs metabolized by this enzyme.
  - Warfarin,
  - Dicumarol,
  - Phenytoin,
  - Chlorpropamide,
  - Tolbutamide.

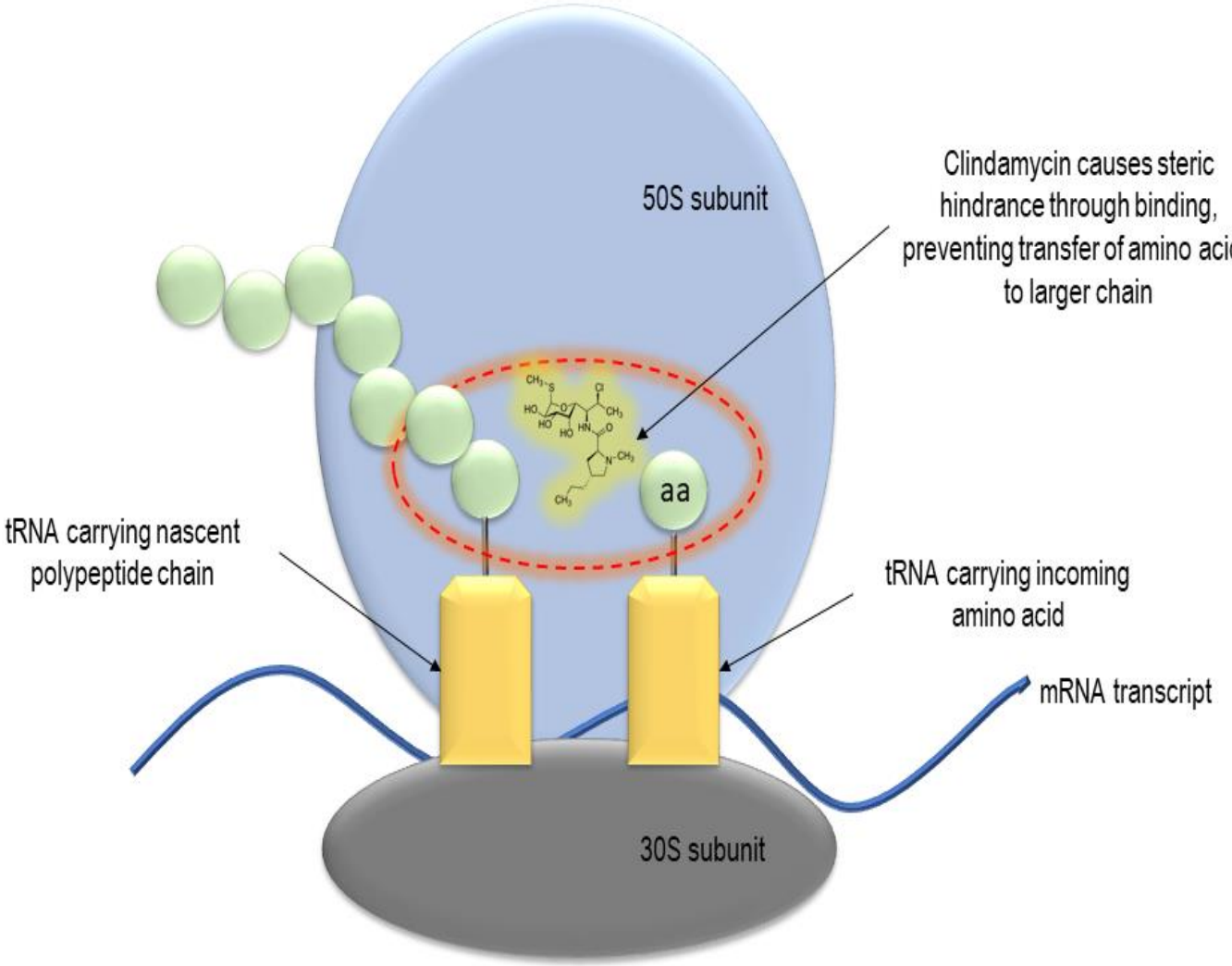
- Phenobarbital (chronic use) & Rifampin acute administration shorten the t½ of chloramphenicol may be due to enzyme induction and may result in sub therapeutic concentrations of the drug

Clindamycin

- Clindamycin is a semisynthetic derivative of lincomycin which was isolated from Streptomyces lincolnesis in 1962

Mechanism Of Action Of Clindamycin

- Inhibits protein synthesis by binding exclusively to the 50S ribosomal subunit
- Binds in close proximity to macrolides – competitive inhibition
- Clindamycin typically displays bacteriostatic activity, but may be bactericidal when present at high concentrations against very susceptible organisms


50S subunit
Clindamycin causes steric hindrance through binding, preventing transfer of amino acids to larger chain
aa
tRNA carrying nascent polypeptide chain
tRNA carrying incoming amino acid
mRNA transcript
30S subunit

Mechanism of resistance

- Altered target sites – encoded by the erm gene which alters the clindamycin binding site on the ribosome; confers high level resistance to all macrolides, clindamycin.

- Active efflux –efflux pump which pumps the macrolides out of the cell but NOT clindamycin; confers low level resistance to macrolides, but clindamycin still active

Spectrum of clindamycin

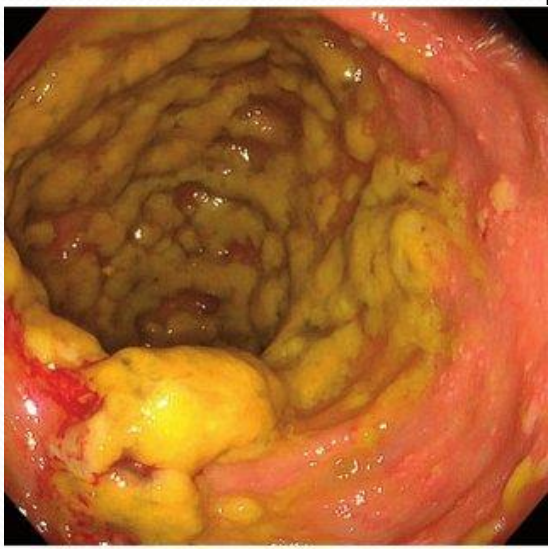
- Similar to Erythromycin for:
  - Pneumococci, S.pyogenes and viridans streptococcus including macrolides-resistant. And MSSA
- More active against:
  - Anaerobic bacteria esp. B.fragilis
  - Bacteroides melaninogenicus, Fusobacterium
  - Peptostreptococcus, peptococcus
  - C. perfringens
  - Actinomyces israelli, Nocardia asteroides.
- Atypical organisms and parasites:
  - Pneumocystis carinii
  - T. gondii
  - Babesiosis (treatment)
  - ***[Note: Clostridium difficile is always resistant to clindamycin.]***

Pharmacokinetics

- **Absorption** – available IV and PO
  - Rapidly and completely absorbed (F = 90%); food with minimal effect on absorption
- **Distribution**
  - Good serum concentrations with PO or IV
  - Good tissue penetration including bone; minimal CSF penetration
- **Elimination**
  - Clindamycin primarily metabolized by the liver; half-life is 2.5 to 3 hours
  - Clindamycin is NOT removed during hemodialysis

Adverse effects Clindamycin

- Gastrointestinal – 3 to 4 %
  - Nausea, vomiting, diarrhea, dyspepsia
  - C. difficile colitis – one of worst offenders(pseudomembranous colitis)
  - Mild to severe diarrhea
  - Requires treatment with metronidazole
- Hepatotoxicity - rare
  - Elevated transaminases
- Allergy – rare



Therapeutic indications of clindamycin

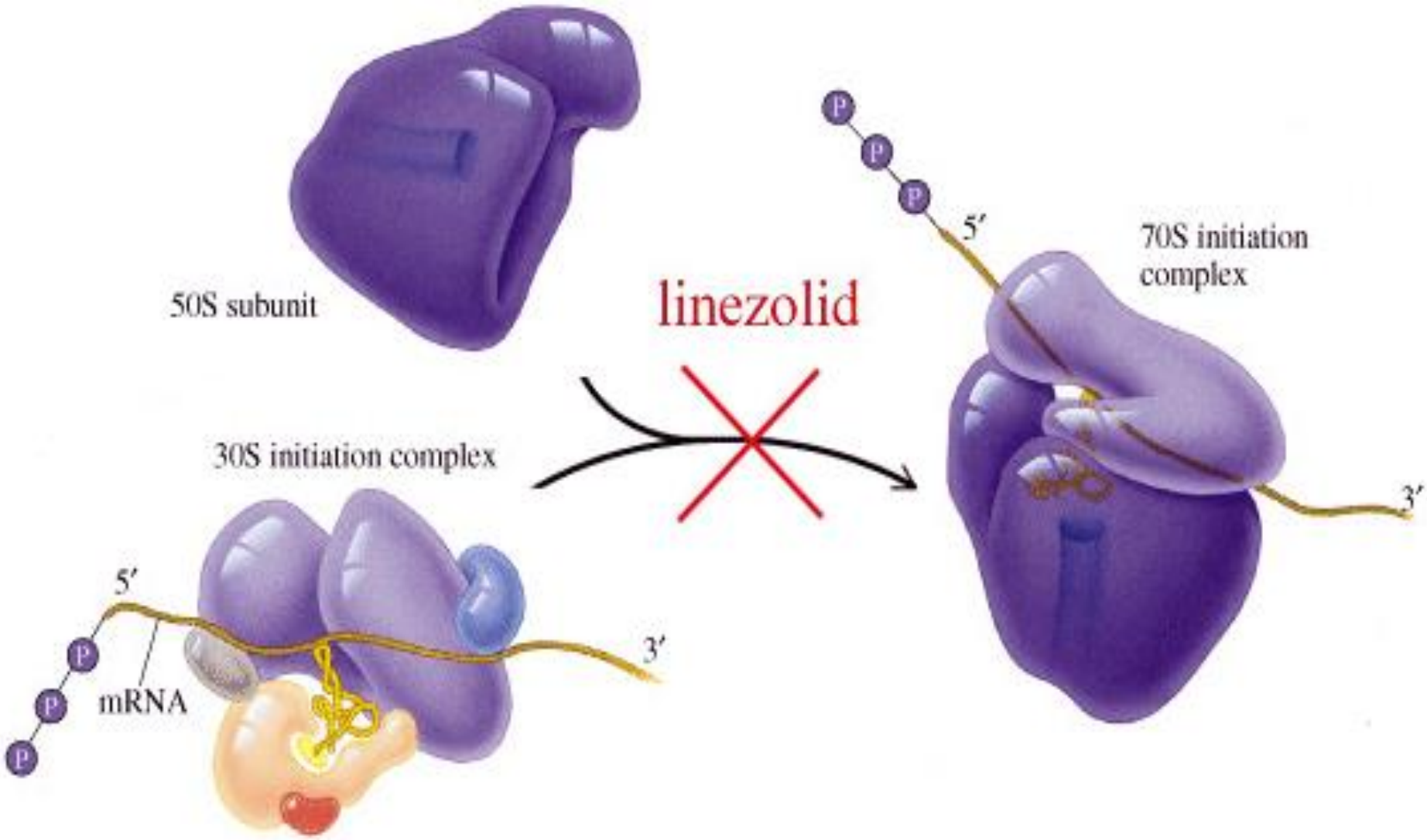
- Severe anaerobic infections caused by bacteroides and other anaerobes
- Penetrating wounds of gut (in combination with aminoglycosides or Cephalosporins
- Female genital tract infections: septic abortion, pelvic abscess
- Aspiration pneumonia
- Endocarditis (prophylactically)
- Topical applications:
  - Solutions, gels, lotions and vaginal creams for acne vulgaris and bacterial vaginosis

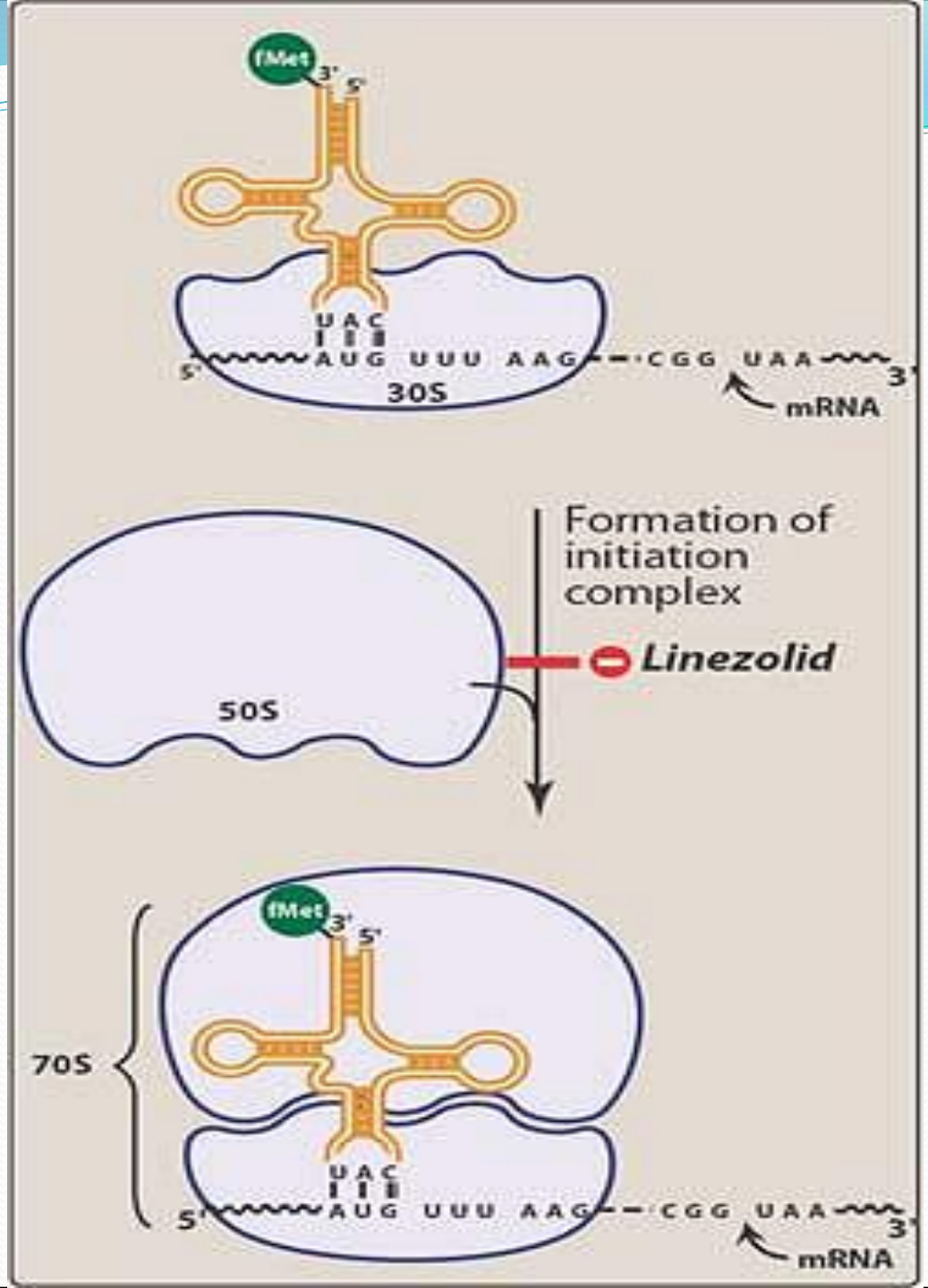
LINEZOLID

- Linezolid was introduced recently to combat resistant gram-positive organisms, such as
- methicillin- and vancomycin-resistant Staphylococcus aureus,
- vancomycin-resistant E. faecium and E. faecalis,
- penicillin-resistant streptococci.

Mechanism of action

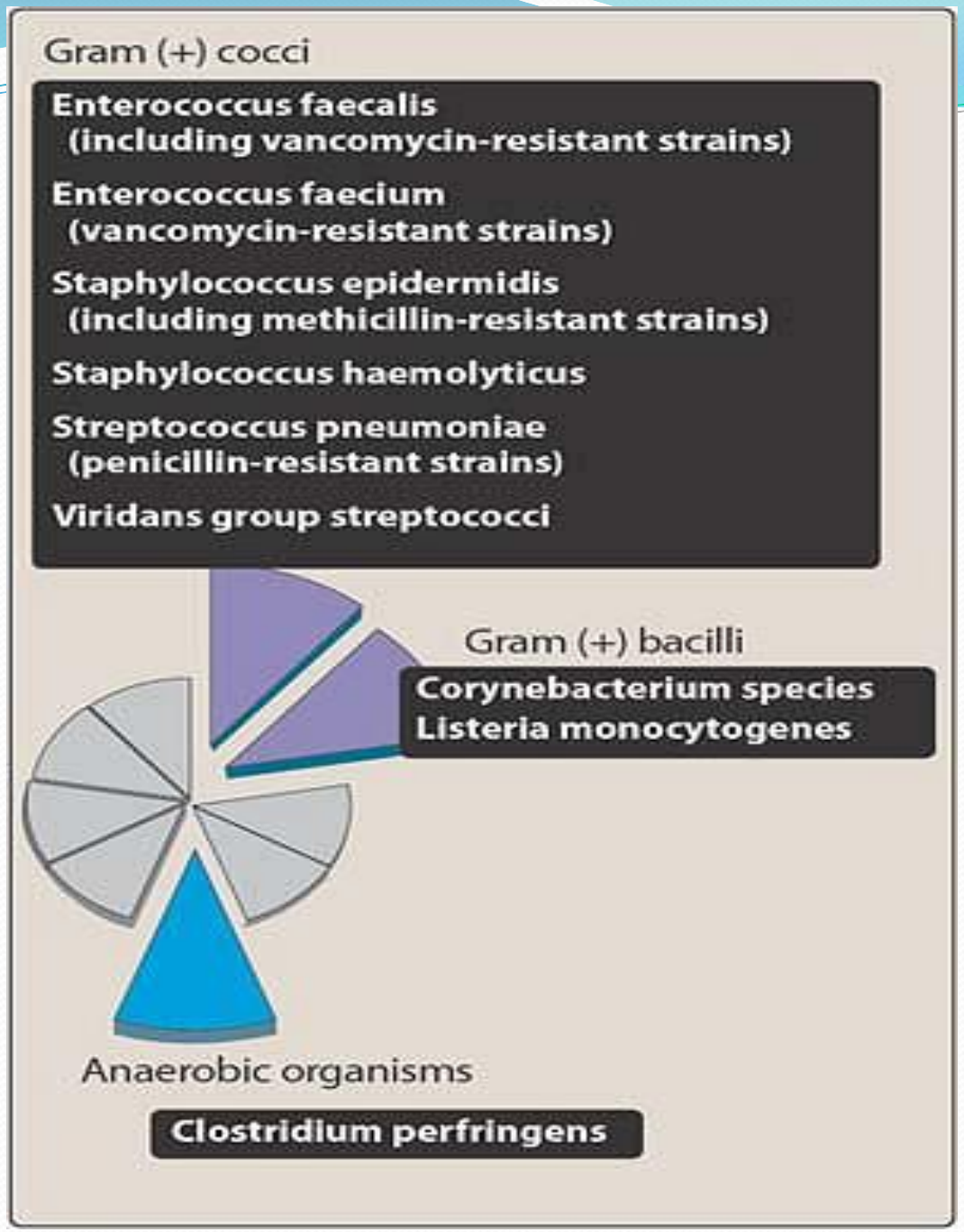
- The drug inhibits bacterial protein synthesis by ***inhibiting the formation of the 70S initiation complex***. Linezolid binds to a site on the 50S subunit near the interface with the 30S subunit.


50S subunit
linezolid
70S initiation complex
5′
3′
30S initiation complex
5′
3′
mRNA
P
P
P


fMet
3'
5'
UAC
AUG UUU AAG
CGG UAA
5'
3'
30S
mRNA
Formation of initiation complex
Linezolid
50S
70S
fMet
3'
5'
UAC
AUG UUU AAG
CGG UAA
5'
3'
mRNA

Resistance

- Decreased binding to the target site confers resistance on the organism.
- ***Antibacterial spectrum***
- The antibacterial action of linezolid is directed primarily against gram-positive organisms, such as ***staphylococci, streptococci, and enterococci***, as well as ***Corynebacterium species and Listeria monocytogenes*** . It is also moderately active against Mycobacterium tuberculosis Like other agents that interfere with bacterial protein synthesis, linezolid is ***bacteriostatic.***


Gram (+) cocci
Enterococcus faecalis (including vancomycin-resistant strains)
Enterococcus faecium (vancomycin-resistant strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus
Streptococcus pneumoniae (penicillin-resistant strains)
Viridans group streptococci
Gram (+) bacilli
Corynebacterium species
Listeria monocytogenes
Anaerobic organisms
Clostridium perfringens

Pharmacokinetics

- Linezolid is completely absorbed on oral administration. An intravenous preparation is also available. The drug is widely distributed. The drug is excreted both by renal and nonrenal routes. The metabolites rely on the kidney for elimination.

Adverse effects

- GIT related
- Headache, rash
- MAO Inhibition

Thank you