Linzolid, Streptogramins, Clindamycin

Describe mechanism of action of Linezolid

Describe clinical uses of Linezolid with special emphasis on methicillin-resistant staphylococci
and vancomycin-resistant enterococci

Enumerate Streptogramins.

Describe clinical use of Quinupristin-Dalfopristin in VRE (Vancomycinresistant enterococci).

Describe mechanism of action of Clindamycin.

Enumerate clinical uses of Clindamycin.

Describe antibiotic-associated (pseudomembranous) colitis.

Linezolid

Linezolid is a totally synthetic Oxazolidinone.

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 and penicillin - resistant streptococci.

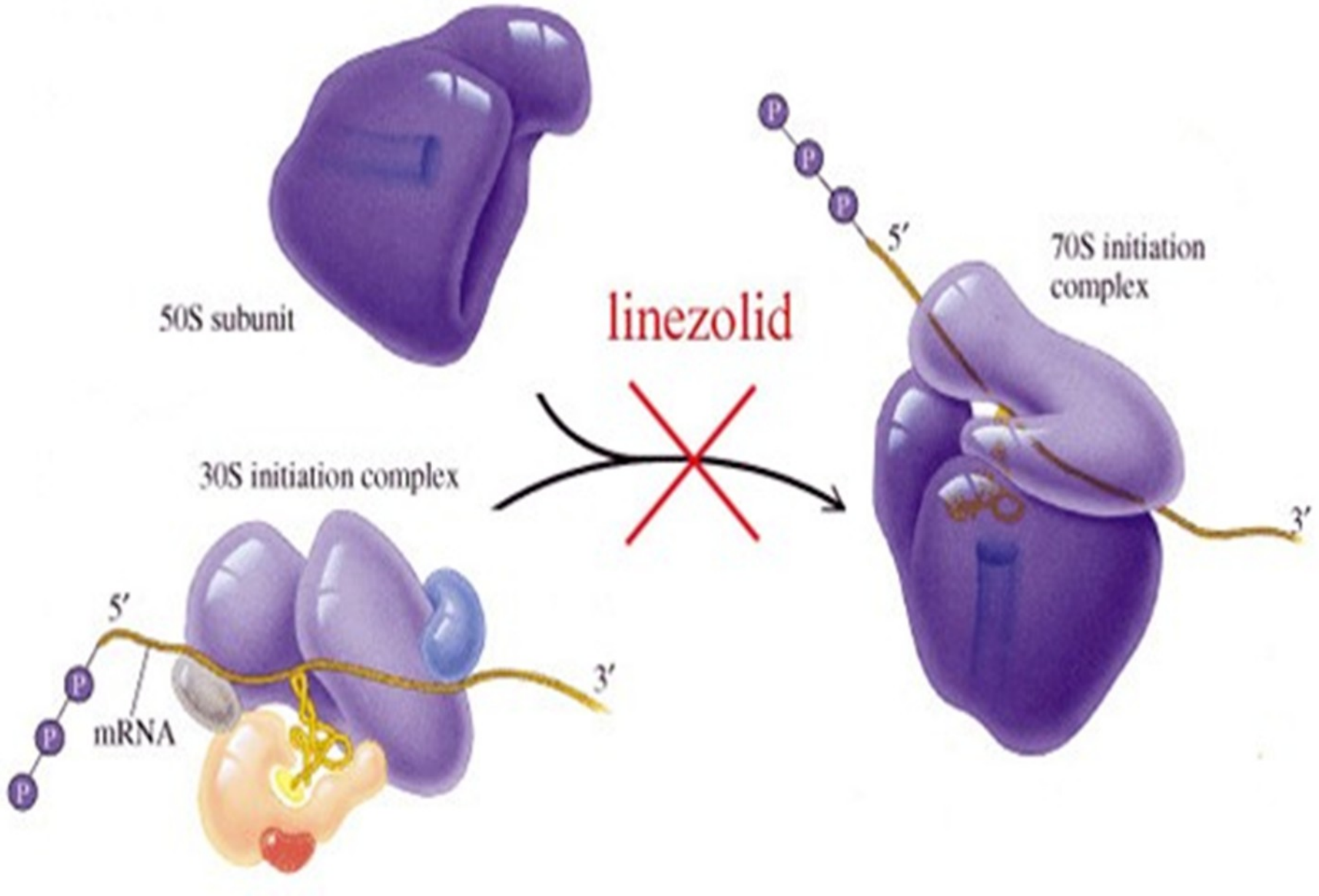
Mechanism of action

- inhibit protein synthesis (bacteriostatic)

bind to the 50S ribosome near the 30S ribosome interface

- prevents initiation of protein synthesis

Inhibits 70S initiation complex.


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

Antibacterial spectrum

linezolid is directed primarily against gram-positive organisms, such as

staphylococci *streptococci*, *enterococci*,

Corynebacterium *Listeria monocytogenes*.

methicillin - and vancomycin - resistant Staphylococcus aureus

vancomycin -resistant E. faecium and E. faecalis

It is also moderately active against Mycobacterium tuberculosis.

Like other agents that interfere with bacterial protein synthesis, *linezolid is bacteriostatic. However, it is* ***cidal*** *against the* ***streptococci*** *and* ***Clostridium perfringens*** *.*

LINZOLID INDICATIONS

Community-acquired pneumonia

Skin and soft-tissue infections

MRSA infections

Hospital-acquired pneumonia

(with aztreonam or an

aminoglycoside)

VRE infections

Streptogramins

They is a mixture of two streptogramins in a ratio of thirty to seventy, respectively.

derived from a streptomycete and then chemically modified.

The drug is normally reserved for the treatment of *vancomycin -resistant Enterococcus faecium (VRE).*

Mechanism of action

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome, forming a stable ternary complex. Thus, they synergistically interrupt protein synthesis

Dalfopristin inhibits the early phase of protein synthesis in the bacterial ribosome it interferes with **peptidyl transferase.**

Dalfopristin binds to 23 S of ribosome , brings conformational change in the 50S , thereby increasing the binding affinity of quinupristin .

Quinupristin inhibits the late phase of protein synthesis it inhibits peptide chain elongation

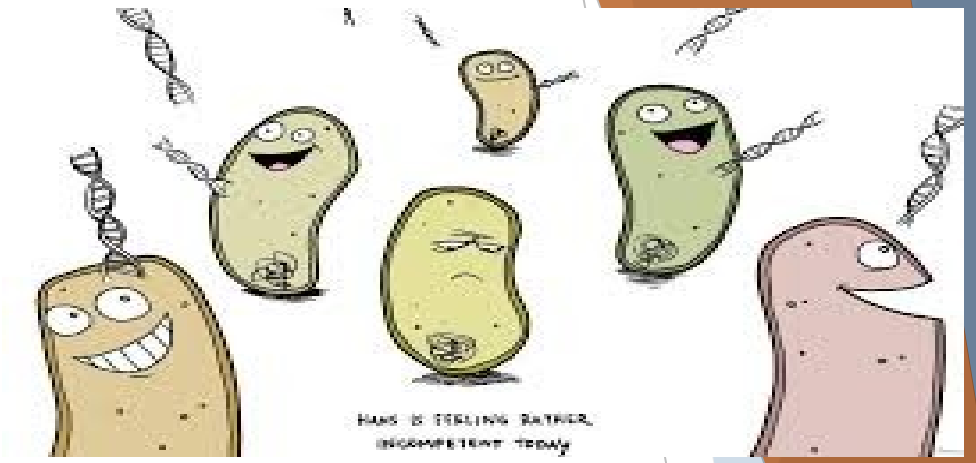
Mechanism Of Action

The combination of the two components acts synergistically.

More effective in vitro than each component alone.

The drug combination is bactericidal and has a long post antibiotic effect.

Antibacterial spectrum



gm+ive cocci.

Resistant strains of gm+ive cocci (methicillin resistant staph)MRSA.

Enterococcal feacium(VREfeacium)

Vancomycin resistant strains of bacteria

Streptogramins

- **Quinupristin-dalfopristin (Synercid®)**
  - Quinupristin = Streptogramin B 30%
  - Dalfopristin = Streptogramin A 70%
  - **Macrolide like mechanism of action ... bind at 50s subunit**
  - Spectrum
    - **Gram positive bacteria****
    - Multidrug resistant streptococci
    - Penicillin resistant pneumococci **(PRSP)****
    - **MRSA****
    - *Enterococcus faecium* (not *E. faecalis*)
    - ***Not to gram negative****

Mechanism of resistance

Resistance develops due to the action of enzymes.
the presence of a ribosomal enzyme that methylates the target bacterial 23S ribosomal RNA site can interfere in *quinupristin* binding.

The enzymatic modification can change the action from bactericidal to bacteriostatic

Plasmid-associated acetyltransferase inactivates *dalfopristin*

An active efflux pump can also decrease levels of the antibiotics in bacteria.

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Pharmacokinetics

Quinupristin/dalfopristin is injected intravenously in a 5 percent dextrose solution (the drug is incompatible with a saline medium). The combination drug penetrates macrophages and polymorphonucleocytes, a property that is important, because VRE are intracellular. Levels in the CSF are low. Both compounds undergo metabolism

Pharmacokinetics

The products are less active than the parent in the case of ***quinupristin*** *and are equally active in* the case of ***dalfopristin*** . Most of the parent drugs and metabolites are cleared through the liver and eliminated via the bile into the feces . Urinary excretion is secondary

SYNERCID (TRADE NAM

Drug interactions

- Cyclosporin
- Antihistamines
- NNRTIs
- Benzodiazepines
- calcium channel blockers
- HMG-CoA reductase inhibitors
- Cisapride
- methylprednisolone, carbamazepine
- digoxin (in the same manner as with erythromycin)

ADVERSE EFFECTS

Venous irritation

Arthralgia and myalgia

Hyperbilirubinemia

Clindamycin

Clindamycin has a mechanism of action that is the same as that of erythromycin .

Clindamycin is employed primarily in the treatment of infections caused by anaerobic bacteria, such as **Bacteroides fragilis** , which often causes abdominal infections associated with trauma.

However, it is also significantly active against nonenterococcal, gram-positive cocci.

MRSA.

Clostredium defficile is resistant to clindamycin.

Clostridium difficile is always resistant to *clindamycin*

Clindamycin is well absorbed by the oral route.

It distributes well into all body fluids except the CSF. Adequate

levels of *clindamycin are not achieved in the brain, even when meninges are*

inflamed.

Penetration into bone occurs even in the absence of inflammation.

Accumulation has been reported in patients with either severely compromised

renal function or hepatic failure

skin rashes

pseudomembranous colitis caused by overgrowth of C. difficile

chloramphenicol

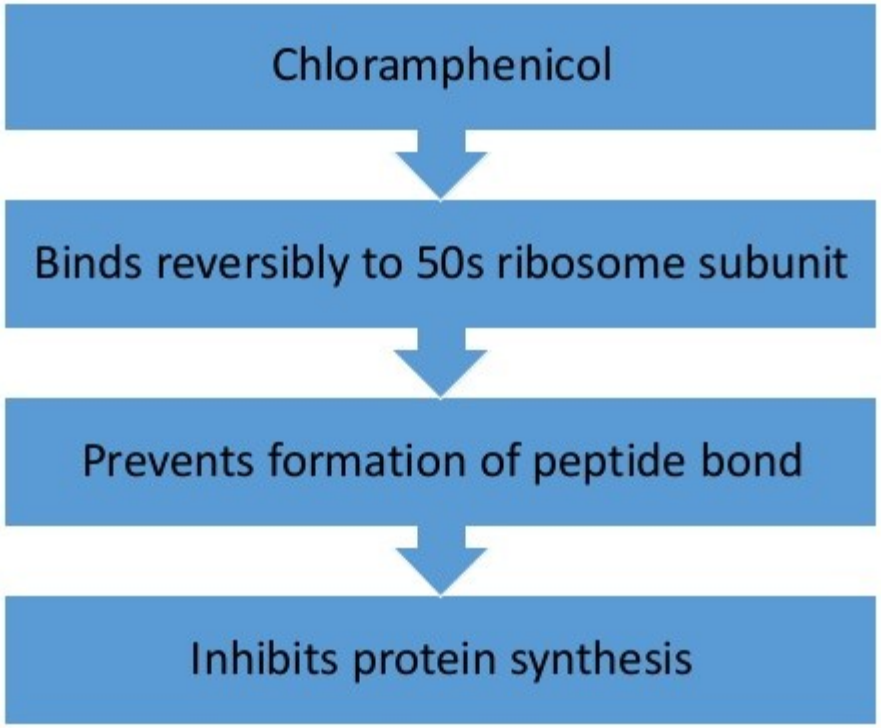
Chloramphenicol is active against a wide range of gram-positive and gram-negative organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

Mechanism of action

The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction.

Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating *chloramphenicol levels*, *producing* bone marrow toxicity.

Mechanism of action



Mechanism action of chloramphenicol

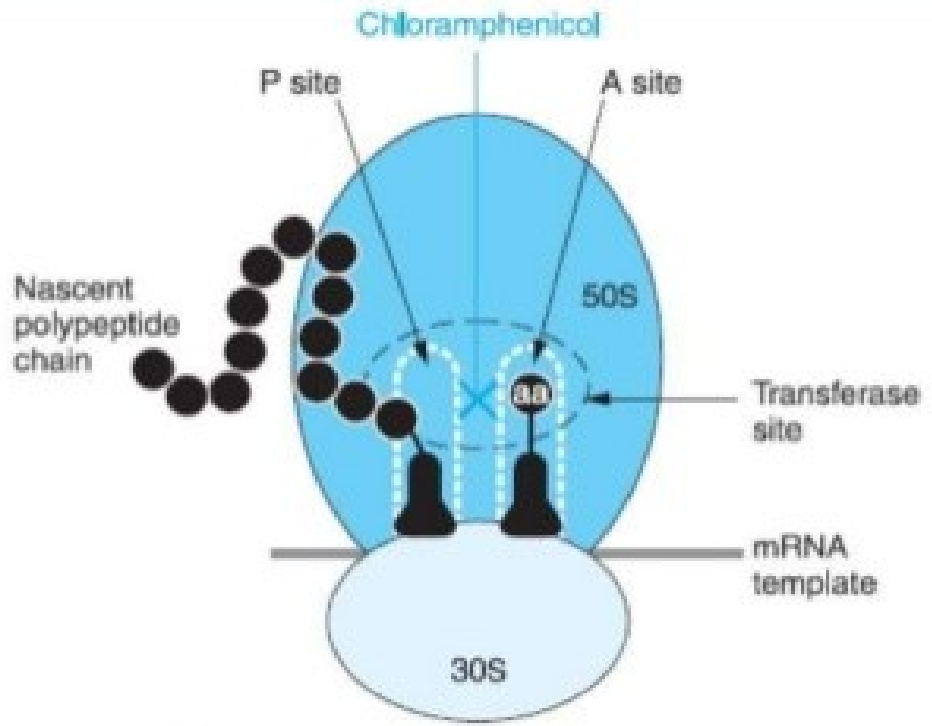


FIGURE 46–2 ***Inhibition of bacterial protein synthesis by chloramphenicol.*** Chloramphenicol binds to the 50S ribosomal subunit at the peptidyltransferase site and inhibits the transpeptidation reaction. Chloramphenicol binds to the 50S ribosomal subunit near the site of action of clindamycin and the macrolide antibiotics. These agents interfere with the binding of chloramphenicol and thus may interfere with each other's actions if given concurrently. *See* Figure 46–1 and its legend for additional information.

Mechanism of resistance

- Resistance is conferred by the presence of an R factor that codes for an acetyl coenzyme A transferase. This enzyme inactivates *chloramphenicol.*

- *Another mechanism for resistance is associated with an inability of the* antibiotic to penetrate the organism

Adverse effects

The clinical use of *chloramphenicol is limited to life-threatening infections because of the serious adverse* effects associated with its administration.

In addition to gastrointestinal upsets, overgrowth of Candida albicans may appear on mucous membranes

Anemias:

Hemolytic anemia in G6PD deficient patients

Adverse effects

Gray baby syndrome:

This adverse effect occurs in neonates if the dosage regimen of *chloramphenicol is not properly adjusted. Neonates have a low capacity to glucuronylate the* antibiotic, and they have underdeveloped renal function. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes. This leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence called grey baby syndrome), and death.

Interactions

Chloramphenicol is able to inhibit some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of such drugs as warfarin, phenytoin, tolbutamide, and chlorpropamide , thereby elevating their concentrations and potentiating their effects.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