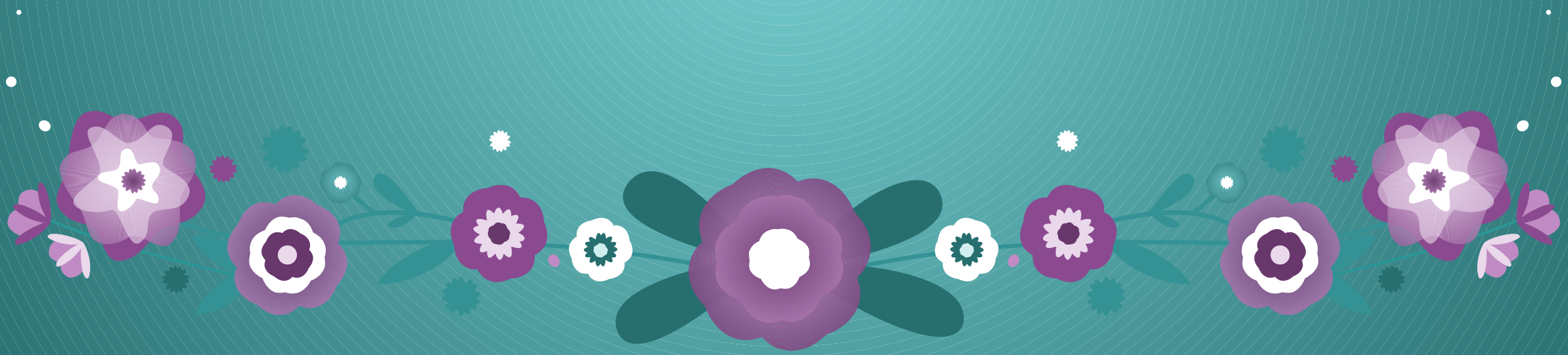
Macrolides & Chloramphenicol



Aims and objectives

Enlist Macrolides.

Describe anti-microbial spectrum of Macrolides

Describe pharmacokinetics of Macrolides

Describe the mechanism of action of Macrolides

Describe the principal mechanism of resistance to Macrolides

Describe clinical uses of Macrolides

Describe adverse effects of Macrolides.

Describe drug interactions of Macrolides

Differentiate the salient features of Erythromycin, Clarithromycin and Azithromycin in respect of dosing and clinical use.

Relate pharmacokinetics and pharmacodynamics of Macrolides with their clinical applications / uses.

Describe anti-microbial spectrum of Chloramphenicol

Describe mechanism of action of Chloramphenicol

Enlist clinical uses of Chloramphenicol

Describe the reason for obsoleting the systemic use of Chloramphenicol

Enlist adverse effects of Chloramphenicol

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached.

Erythromycin was the first of these drugs to find clinical application.

The newer members of this family,

- *clarithromycin (a methylated form of erythromycin)*
- *azithromycin (having a larger lactone ring),.*
- *Telithromycin, a semisynthetic*

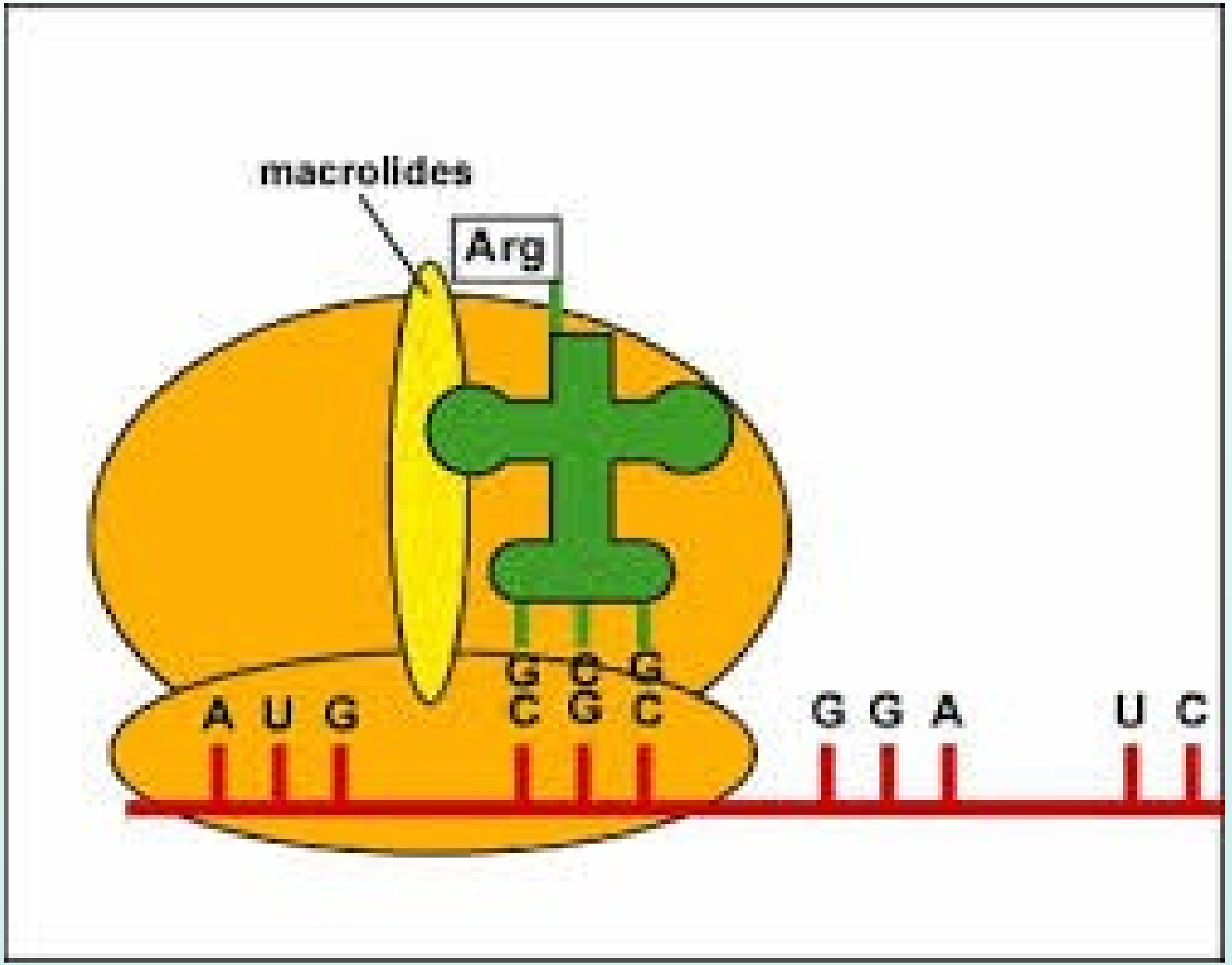
derivative of *erythromycin ,.*

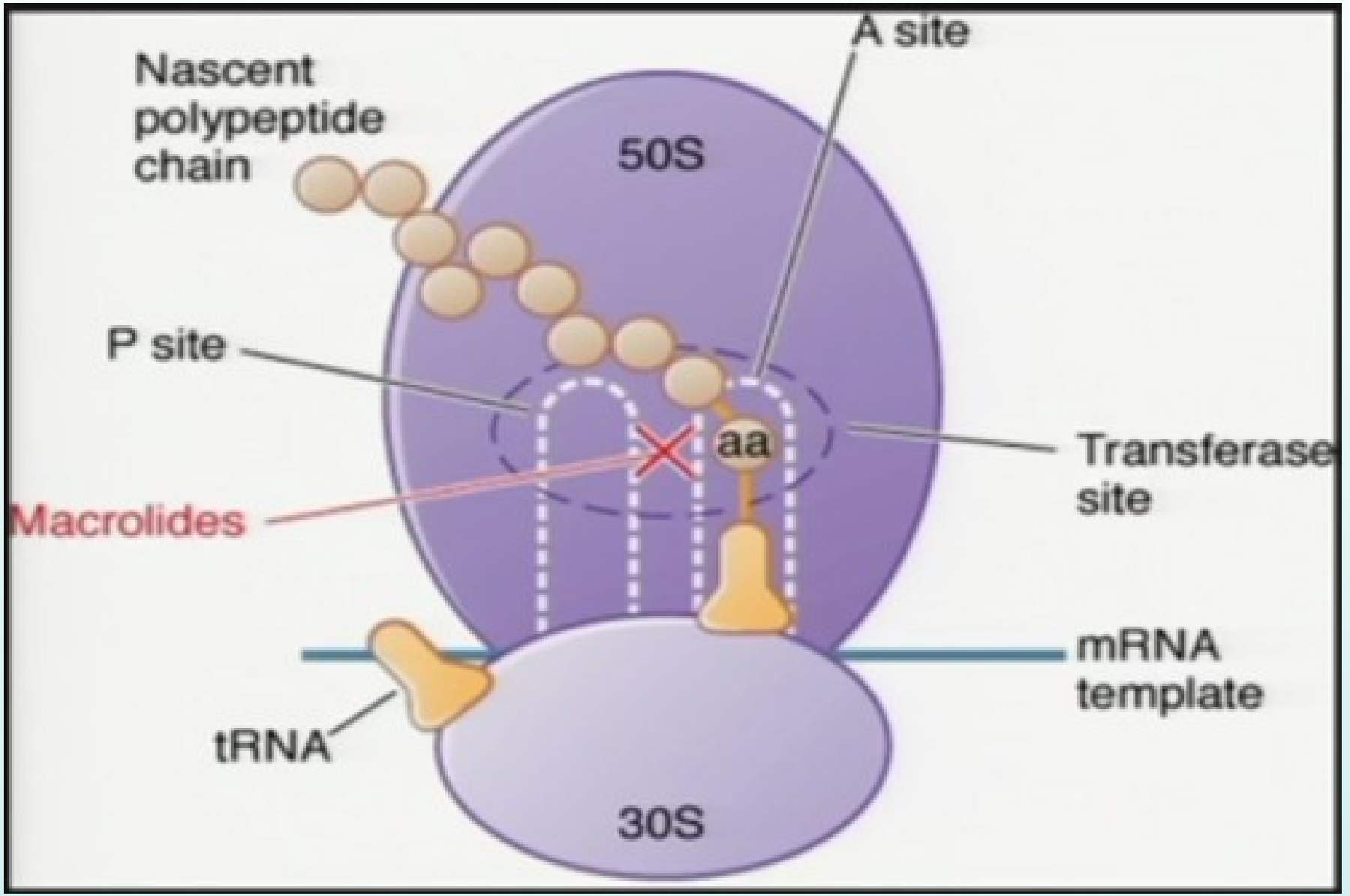
Mechanism Of Action

The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis. They may also interfere at other steps, such as transpeptidation

Ketolides

- Ketolides are antibiotics belonging to the macrolides group.
- Ketolides are derived from erythromycin by substituting the cladinose sugar with a keto-group and attaching a cyclic carbamate group in the lactone ring.
- These modifications give ketolides much broader spectrum than other macrolides.


macrolides
Arg
A U G
G G C
G G C
G G A
U C


A site
Nascent polypeptide chain
50S
P site
aa
Transferase site
Macrolides
mRNA template
tRNA
30S

Antibacterial Spectrum And Therapeutic Uses

As first choice

***M. pneumoniae** infections: erythromycin accelerates the rate of recovery*

***Diphtheria**: erythromycin is the drug of choice for carrier stage as well as for the acute stage*

***Liegionnaires pneumonia**;*

Azithromycin is the drug of choice.

***Pertussis**: erythromycin is the drug of choice for treatment and for prophylactic use in closed contacts.*

***Chlamydial infections**: erythromycin is the drug of choice in pregnancy and in children.*

Antibacterial Spectrum And Therapeutic Uses

. as an alternative drug in patients who are allergic to penicillin's

Tetanus;

streptococcal infections: tonsillitis, pharingitis, cellulitis, pneumonia. They respond to erythromycin.

Staphlococcal infections

Prophylactically for the recurrence of rheumatic fever & before surgery to prevent bacterial endocarditis in those with valvular disease

Mechanism of resistance

1) the inability of the organism to take up the antibiotic or the presence of an efflux pump, both of which limit the amount of intracellular drug;

2) a decreased affinity of the 50S ribosomal subunit for the antibiotic, resulting from the methylation of an adenine in the 23S bacterial ribosomal RNA; and

3) the presence of a plasmid-associated ***erythromycin esterase.***

Pharmacokinetics
“Administration”

erythromycin is not acid stable.
Therefore given as enteric coated form or esterified form

clarithro., arithro and telithromycin (CAT) can withstand the acidic pH.

Presence of food decreases the absorption of erythro and azithromycin.
Food however increases the absorption of clarithromycin.
i/v erythromycin causes thrombophlebitis.

Distribution

:Erythromycin distributes well to all body fluids except the CSF.

It diffuses into prostatic fluid, and it has the unique characteristic of accumulating in macrophages.

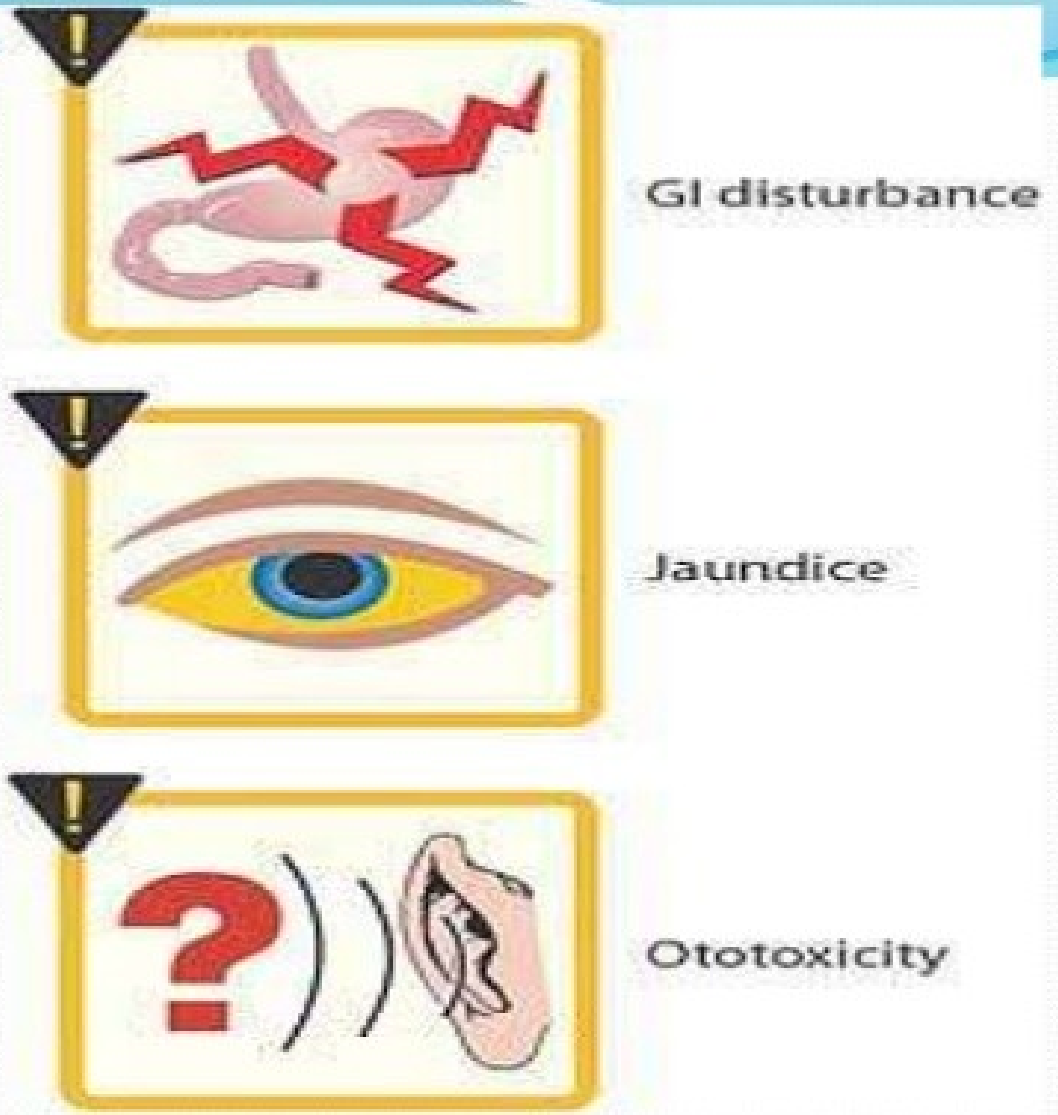
*clarithromycin, azithromycin , and telithromycin (*CAT) are widely distributed in the tissues.

Serum levels of *azithromycin* are low; the drug is concentrated in neutrophils, macrophages, and fibroblasts.

Azithromycin has the longest half-life and largest volume of distribution of the four drugs

Excretion: Erythromycin and azithromycin are primarily concentrated and excreted in an active form in the bile. Partial reabsorption occurs through the enterohepatic circulation.

clarithromycin and its metabolites are eliminated by the kidney as well as the liver, and it is recommended that the dosage of this drug be adjusted in patients with compromised renal function.



Some adverse effects of macrolide antibiotics.

Contraindications

EAT; should be used cautiously in hepatic dysfunction as they accumalates in liver. Hepatic failure has been reported with telithromycin.

Telithromycin also causes QT prolongation—so in pro-arrythmogenic patient it should be avoided. It is also contra-indicated In Mysthenia Gravis.

Telithromycin should be cautiously given in renally compromised.

Drug interactions

Erythromycin, telithromycin , and clarithromycin inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulations of these compounds

An interaction with digoxin may occur in some patients. In this case, the antibiotic eliminates a species of intestinal flora that ordinarily inactivates digoxin , thus leading to greater reabsorption of the drug from the enterohepatic circulation

Macrolides

- Coverage of:
  - Atypicals, Strep pneumo, & Hi.M. (Hflu & Mcat)
    - So, good for *respiratory* infections!
  - **N.B.** But doesn't cover PEcKSS or SPACE bugs
- **Erythromycin**
  - Efficacy: Poorer coverage of H.flu, MSSA
  - Toxicity:
    - Prokinetic – diarrhea!
    - Worse for QTc prolongation
  - Convenience: QID dosing

- **Clarithromycin**
  - Better Hflu &MSSA coverage
  - Less QTc prolongation vs E
  - Shorter half-life vs Azithro
    - BID dosing x 7-10days
    - New daily 'XL' formulation
- **Azithromycin**
  - An azalide, (not a macrolide)
    - Same spectrum of activity
    - Less QTc prolongation vs E & C!
  - Long t1/2 – QD dosing x 5d
    - **BUT** can breed resistant S.pneumo (since below [MIC] for long periods of time)

chloramphenicol

Chloramphenicol is active against a wide range of gram-positive and gram-negative organisms.

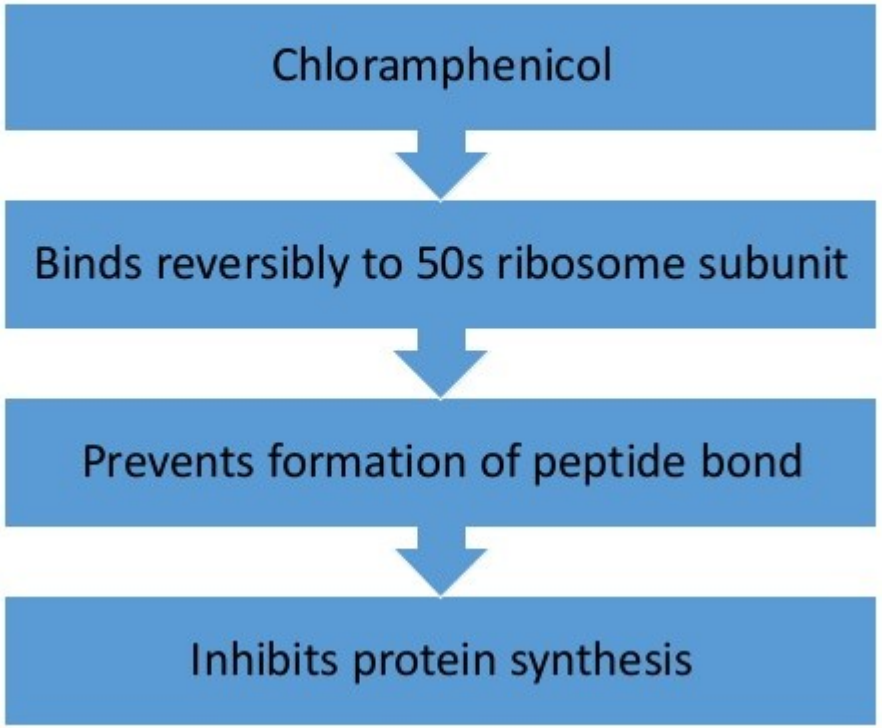
However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

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

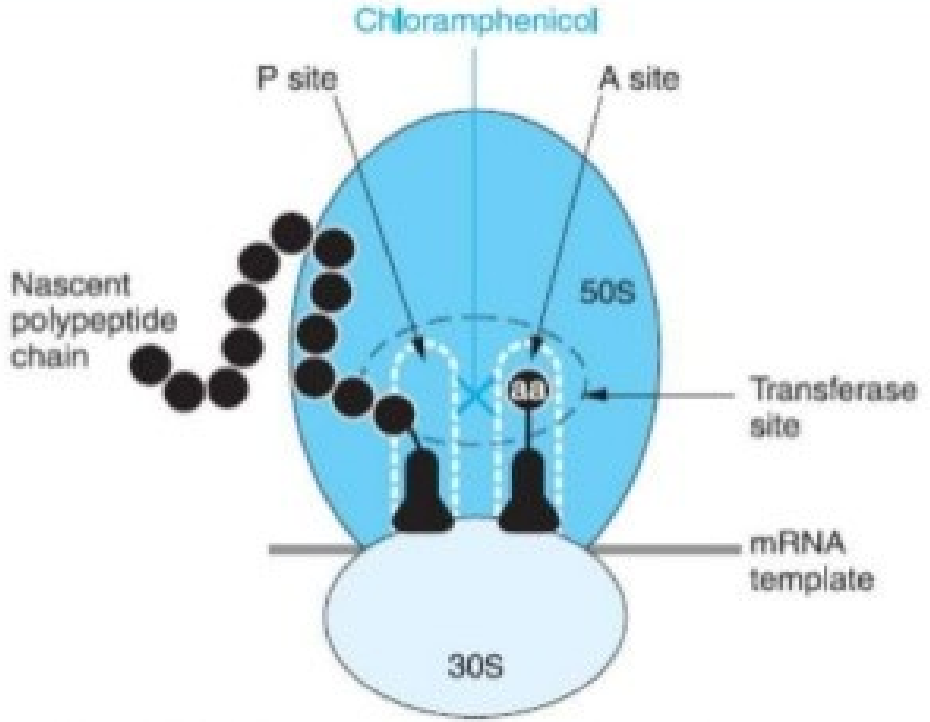


FIGURE 46–2 ***Inhibition of bacterial protein synthesis by chloramphenicol.*** Chloramphenicol binds to the 50S ribosomal subunit at the peptidyltransferase site and inhibits the transpeptidation reaction. Chloramphenicol binds to the 50S ribosomal subunit near the site of action of clindamycin and 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

Other reversible anemias may also appear that are dose related.

Aplastic anemia, which although rare is idiosyncratic and usually fatal. [Aplastic anemia is independent of dose and

may occur after therapy has ceased.]

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.

Dear students

Hope you will revise it