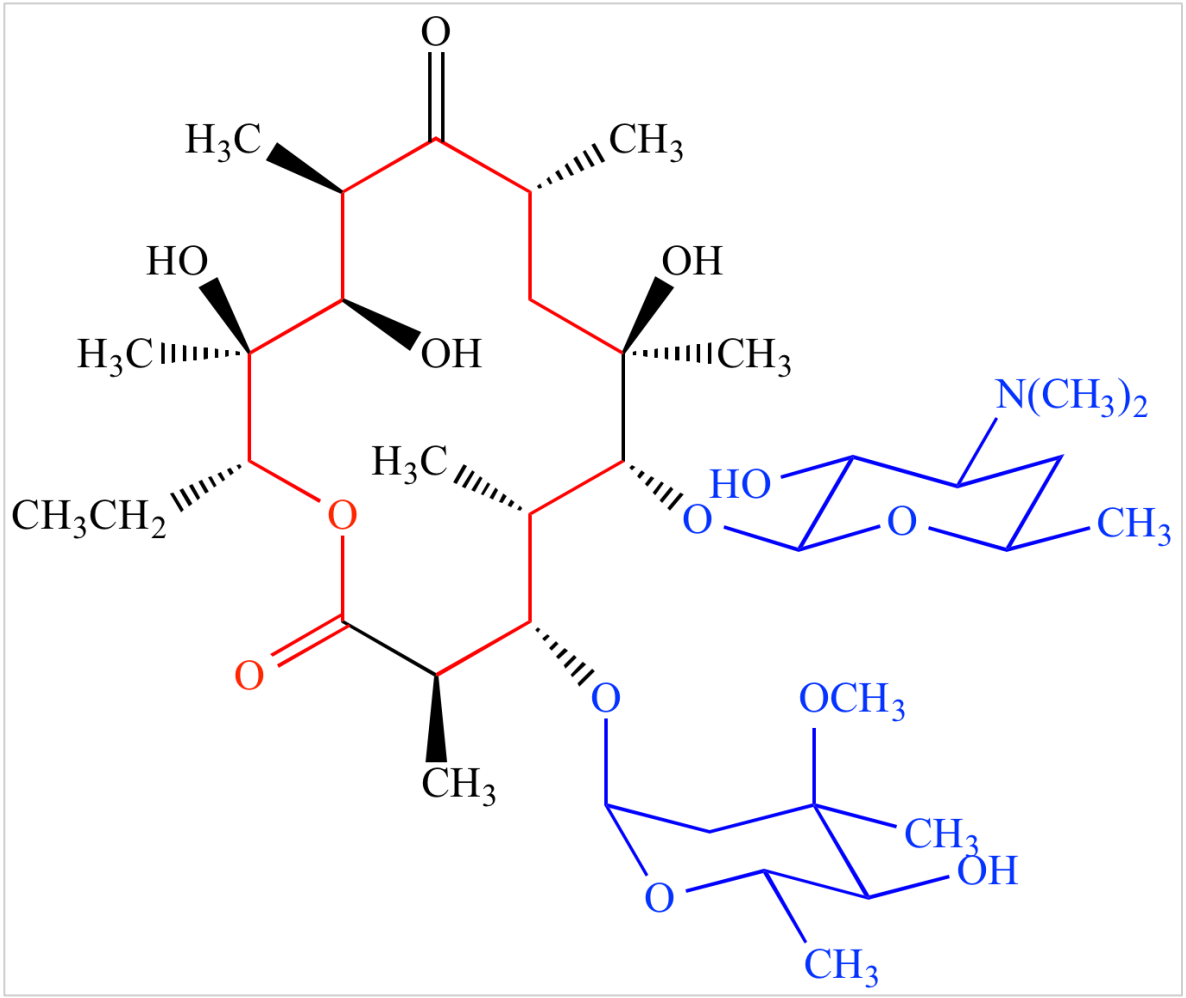
# Macrolides and Ketolides

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

| MACROLIDES/KETOLIDES |
| --- |
| *Azithromycin* ZITHROMAX |
| *Clarithromycin* BIAXIN |
| *Erythromycin* E.E.S., ERY-TAB |
| *Telithromycin* GENERIC ONLY |




Molecular structure of erythromycin, a widely used macrolide antibiotic. Atoms of the large-ring lactone is shown in red, and the deoxysugars in blue.

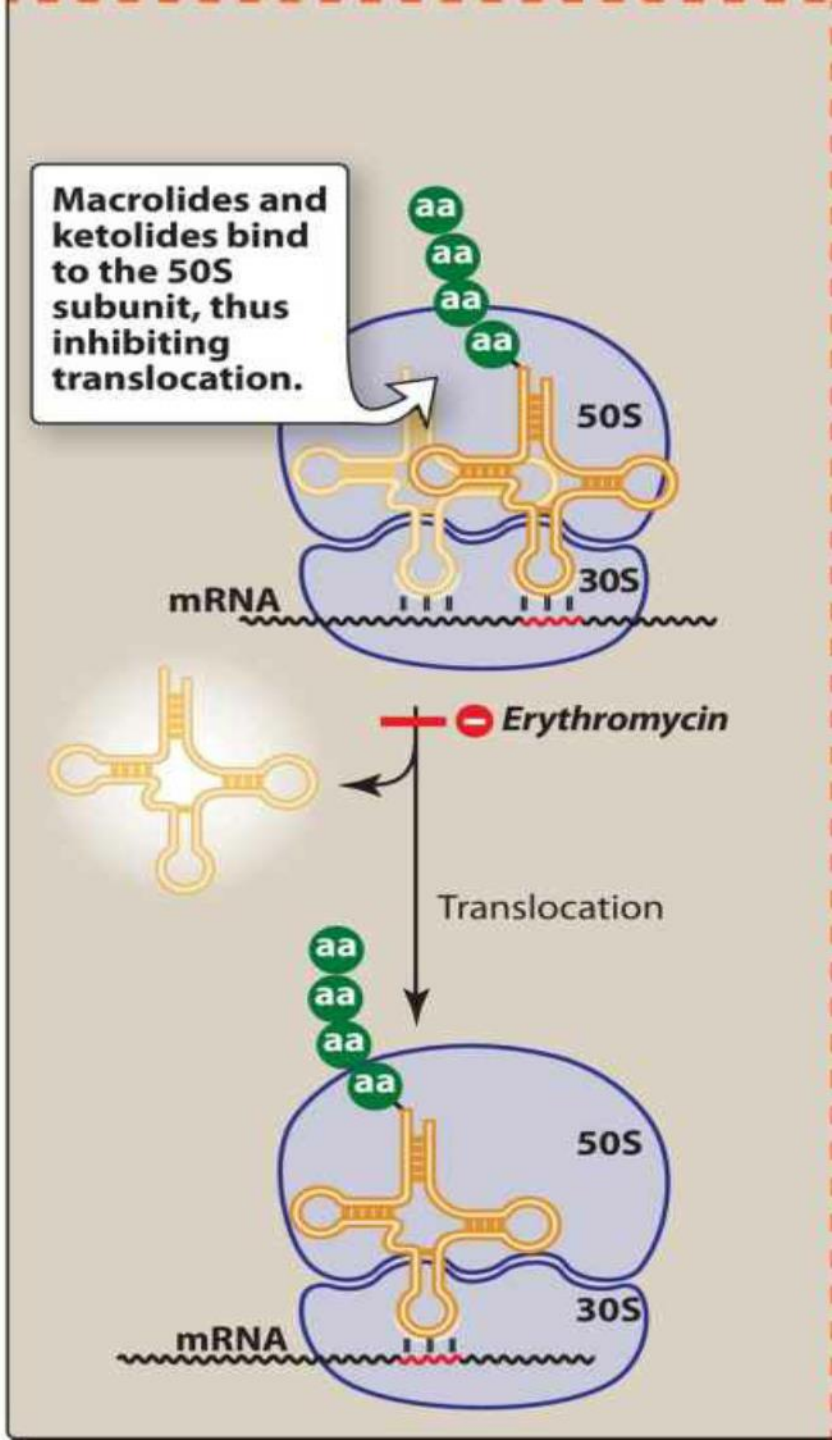
# Macrolides and Ketolides

- ***Erythromycin*** was the first of these drugs to have clinical application, both as a **drug of first choice and as an alternative** to *penicillin* in individuals with an **allergy** **to β-lactam antibiotics**.
- ***Clarithromycin*** (a methylated form of *erythromycin)* and
- ***Azithromycin*** (having a larger lactone ring) have some features in common with, and others that improve upon, *erythromycin*.
- ***Telithromycin*** a semisynthetic derivative of *erythromycin*, is a "ketolide" antimicrobial agent.

# Macrolides and Ketolides

## A. Mechanism of action

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



# Macrolides and Ketolides

## A. Mechanism of action

- Generally considered to be **bacteriostatic**, they may be **bactericidal** at **higher** doses.
- Their binding site is either identical to or in close proximity to that for ***clindamycin*** and ***chloramphenicol***.

**Protein synthesis (50S inhibitors)**

- Erythromycin (macrolides)
- Chloramphenicol
- Clindamycin
- Lincomycin

**Protein synthesis (30S inhibitors)**

- Tetracyclines
- Spectinomycin
- Streptomycin
- Gentamicin
- Kanamycin
- Amikacin
- Nitrofurans

# Macrolides and Ketolides

## B. Antibacterial spectrum

1. **Erythromycin:** This drug is **effective** against many of the same organisms as ***penicillin G*** ; therefore, it may be considered as an **alternative in patients with *penicillin* allergy**.


**Spectrum of penicillin G**

# Macrolides and Ketolides

## B. Antibacterial spectrum

2. **Clarithromycin:** *Clarithromycin* has activity similar to *erythromycin*, but

- It is also effective against ***Haemophilus influenzae*** and

- It has greater activity **against intracellular pathogens** such as

1. ***Chlamydia,***
2. ***Legionella,***
3. ***Moraxella,***
4. **Ureaplasma *species*, and**
5. ***Helicobacter pylori***

# Macrolides and Ketolides

## B. Antibacterial spectrum

### 3. Azithromycin:

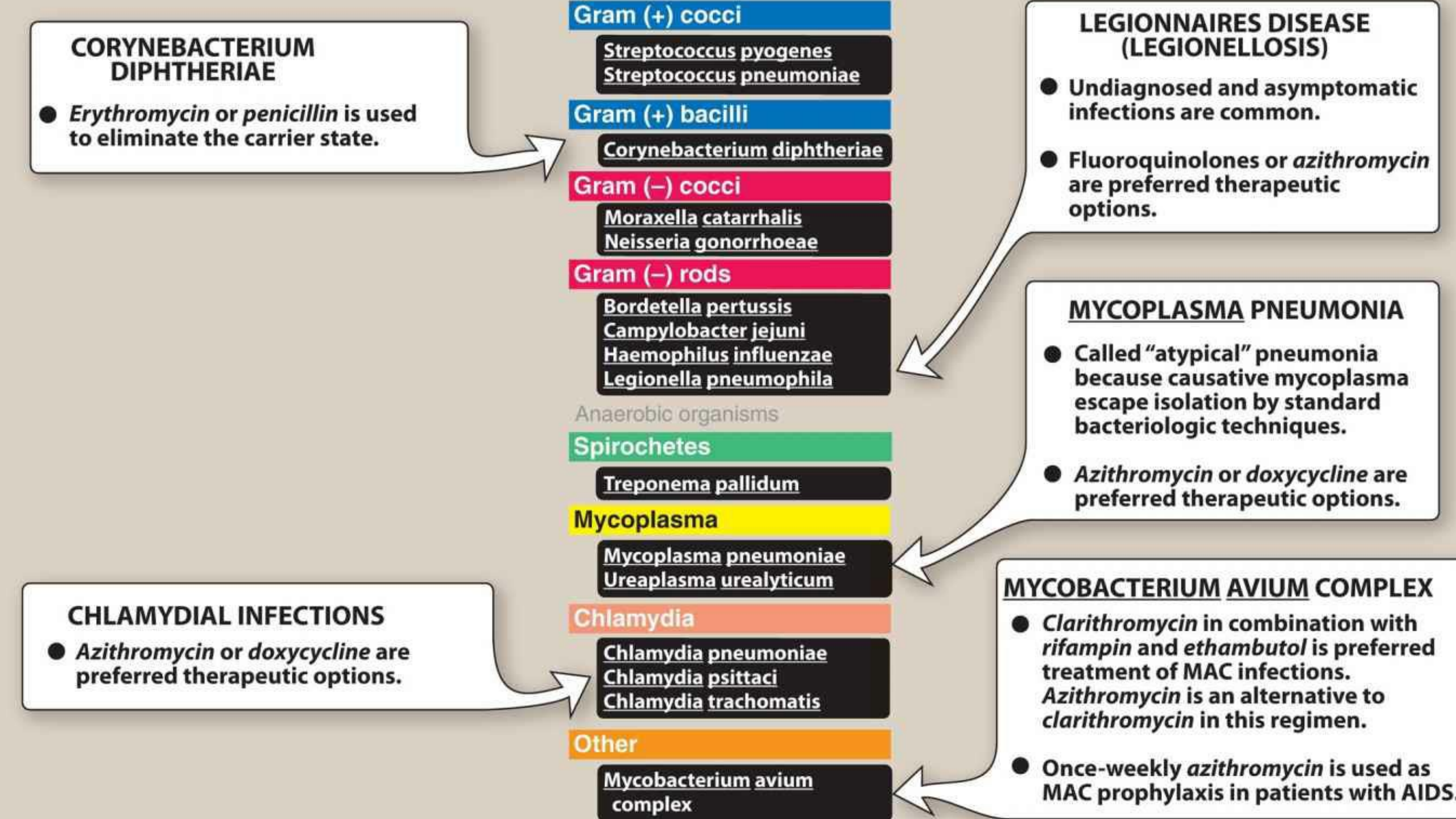
- Although less active than *erythromycin* against **streptococci** and **staphylococci**,
- *Azithromycin* is far **more active** against **respiratory** pathogens such as ***H. influenzae*** and ***Moraxella catarrhalis*.**

# Macrolides and Ketolides

## B. Antibacterial spectrum

### 4. Telithromycin:

- Telithromycin has an antimicrobial spectrum **similar** to that of **azithromycin**.
- Moreover, the structural **modification** within **ketolides neutralizes** the most common **resistance mechanisms** that render macrolides ineffective.


CORYNEBACTERIUM DIPHTHERIAE
Erythromycin or penicillin is used to eliminate the carrier state.
Gram (+) cocci
Streptococcus pyogenes
Streptococcus pneumoniae
Gram (+) bacilli
Corynebacterium diphtheriae
Gram (–) cocci
Moraxella catarrhalis
Neisseria gonorrhoeae
Gram (–) rods
Bordetella pertussis
Campylobacter jejuni
Haemophilus influenzae
Legionella pneumophila
Anaerobic organisms
Spirochetes
Treponema pallidum
Mycoplasma
Mycoplasma pneumoniae
Ureaplasma urealyticum
Chlamydia
Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia trachomatis
Other
Mycobacterium avium complex
LEGIONNAIRES DISEASE (LEGIONELLOSIS)
Undiagnosed and asymptomatic infections are common.
Fluoroquinolones or azithromycin are preferred therapeutic options.
MYCOPLASMA PNEUMONIA
Called "atypical" pneumonia because causative mycoplasma escape isolation by standard bacteriologic techniques.
Azithromycin or doxycycline are preferred therapeutic options.
CHLAMYDIAL INFECTIONS
Azithromycin or doxycycline are preferred therapeutic options.
MYCOBACTERIUM AVIUM COMPLEX
Clarithromycin in combination with rifampin and ethambutol is preferred treatment of MAC infections. Azithromycin is an alternative to clarithromycin in this regimen.
Once-weekly azithromycin is used as MAC prophylaxis in patients with AIDS.

# Macrolides and Ketolides

## C. Resistance

- **Resistance to macrolides is associated with**:

1) The inability of the organism to **take up the antibiotic**,
2) The presence of **efflux pumps**,
3) A **decreased** affinity of the **50S ribosomal subunit for the antibiotic** due to **methylation of an adenine in the 23S bacterial ribosomal RNA in gram-positive organisms**,
4) The presence of **plasmid associated *erythromycin* esterases** in gram-negative organisms such as the Enterobacteriaceae.

# Macrolides and Ketolides

## C. Resistance

- *Erythromycin* has limited clinical use due to increasing resistance.
- Both *clarithromycin* and *azithromycin* share some cross-resistance with *erythromycin*.
- ***Telithromycin*** may be effective against **macrolide-resistant organisms**.

# Macrolides and Ketolides

## D. Pharmacokinetics

### 1. Absorption:

- The **Erythromycin** base is **destroyed** by gastric acid;

A. Thus, either **enteric coated tablets** or

**B. Esterified forms** of the antibiotic are administered and

- All have **adequate** oral absorption .

# Macrolides and Ketolides

## D. Pharmacokinetics

### 1. Absorption:

- **Clarithromycin**, **azithromycin**, and **telithromycin** are **stable in stomach acid** and are readily absorbed.
- Food interferes with the absorption of **erythromycin** and ***azithromycin*** but can **increase** that of **clarithromycin**.
- ***Telithromycin*** is administered orally without regard to meals.
- *Erythromycin* and *azithromycin* are available in **IV formulations**.

# Macrolides and Ketolides

## D. Pharmacokinetics

### 2. Distribution:

- *Erythromycin* distributes well to all body fluids **except the CSF**.
- It is one of the few antibiotics that diffuse into **prostatic fluid**, and it also accumulates in **macrophage**s.
- All four drugs **concentrate** in the **liver**.
- ***Clarithromycin, azithromycin,*** and ***telithromycin*** are widely distributed in the tissues.
- *Azithromycin* has the **largest volume of distribution** of the four drugs.

# Macrolides and Ketolides

## D. Pharmacokinetics

### 3. Elimination:

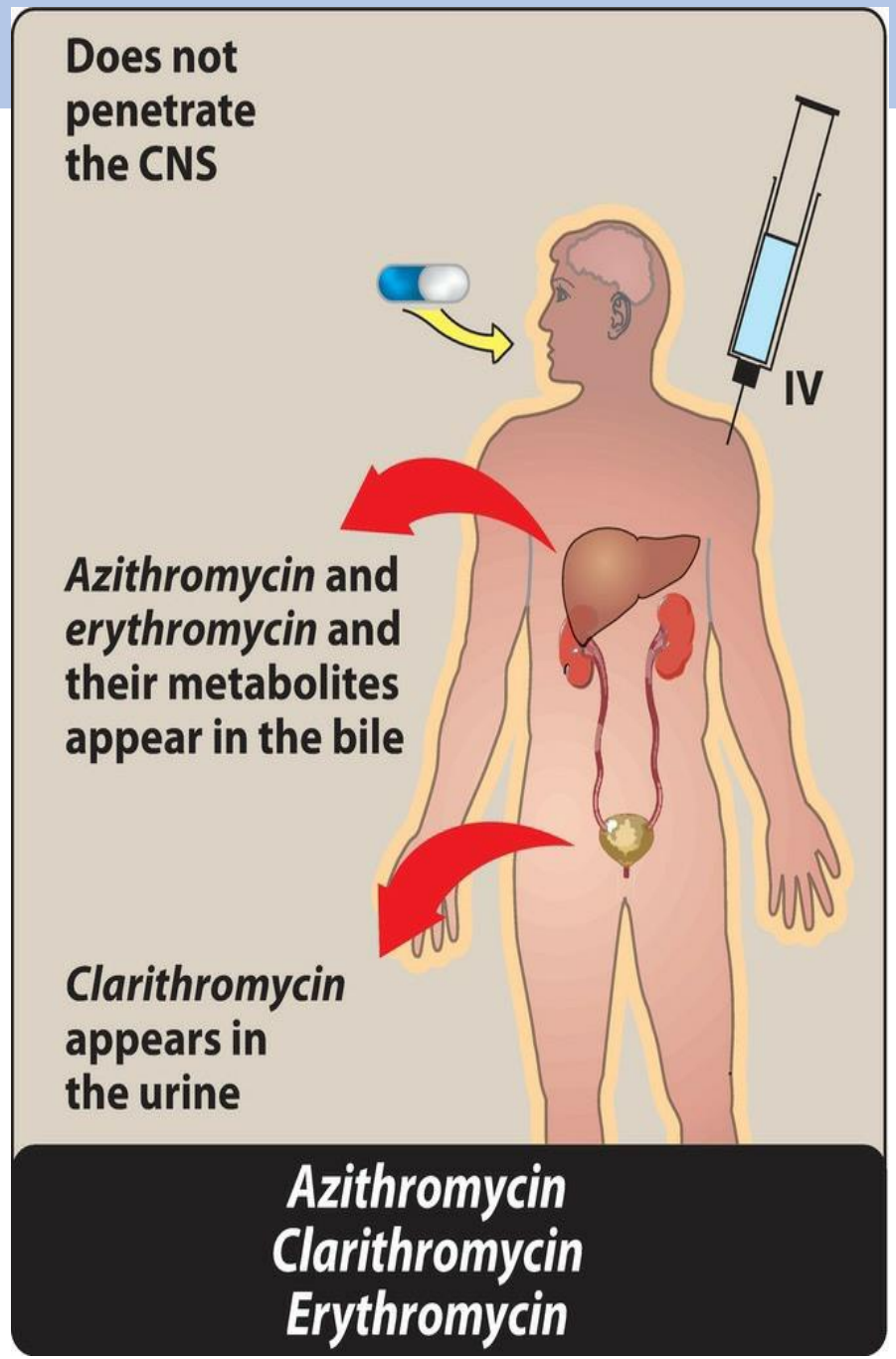
- **Erythromycin** and **telithromycin** undergo **hepatic metabolism**.
- They **inhibit** the oxidation of a number of drugs through their interaction with the cytochrome P450 system.
- Interference with the metabolism of drugs such as **theophylline**, **statins**, and numerous **antiepileptics** has been reported for **clarithromycin**.

# Macrolides and Ketolides

## D. Pharmacokinetics

### 4. Excretion:

- ***Azithromycin*** is primarily concentrated and excreted in the **bile** as active drug.
- ***Erythromycin*** and its metabolites are also excreted in the **bile**.
- In contrast, ***clarithromycin*** is **hepatically** metabolized, and the active drug and its metabolites are mainly excreted in the **urine**.
- The dosage of this drug should be **adjusted in patients with renal impairment.**



# Macrolides and Ketolides

- **E. Adverse effects**

**1. Gastric distress and motility**:

- Gastrointestinal upset is the most common adverse effect of the macrolides and may lead to poor patient compliance (especially with *erythromycin).*
- Higher doses of *erythromycin* lead to smooth muscle contractions that result in the movement of gastric contents to the duodenum, an adverse effect sometimes employed **for the treatment of gastroparesis or postoperative ileus**.

# Macrolides and Ketolides

- **E. Adverse effects**

2. **Cholestatic jaundice**:

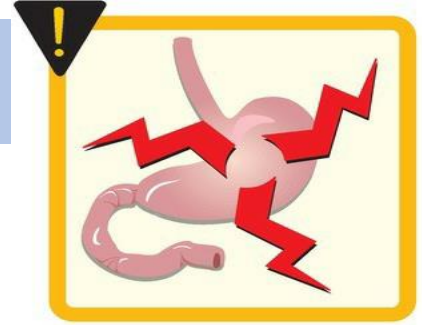
- This adverse effect occurs most commonly with the **estolate** form of *erythromycin* (not used in the United States);
- However, it has been reported with other formulations and other agents in this class.

# Macrolides and Ketolides

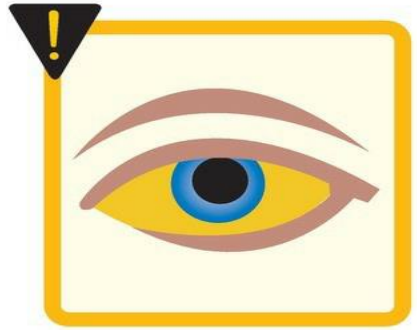
## E. Adverse effects

3. **Ototoxicity**:

- Transient **deafness** has been associated with *erythromycin*, especially at high dosages. *Azithromycin* has also been associated with **irreversible sensorineural hearing loss**.



GI disturbance



Jaundice

Ototoxicity

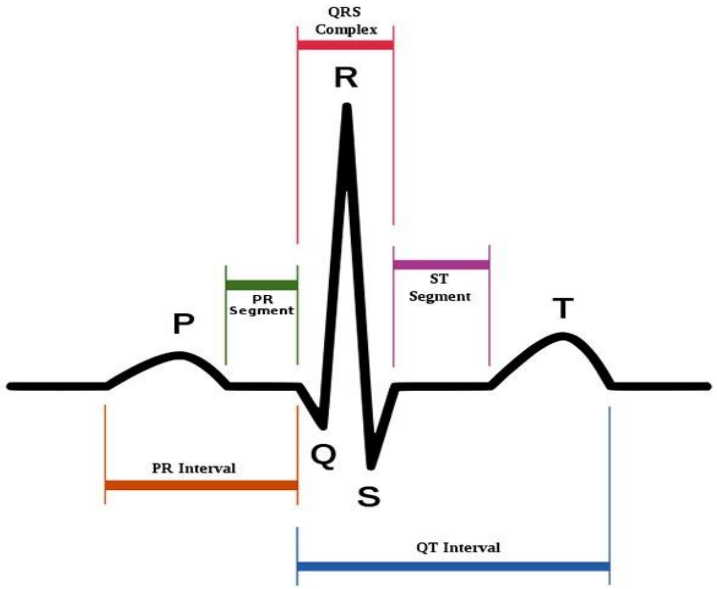
QTc prolongation

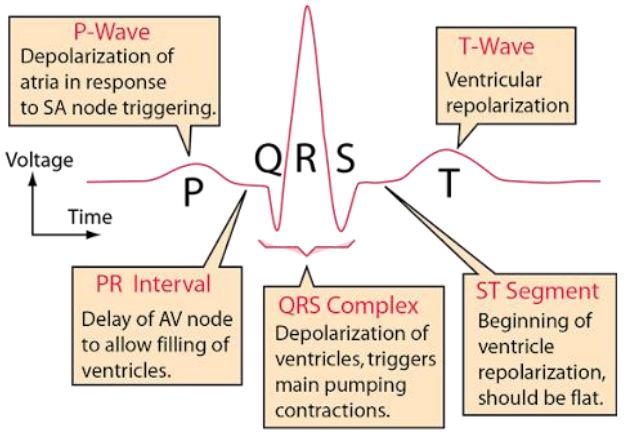
# Macrolides and Ketolides

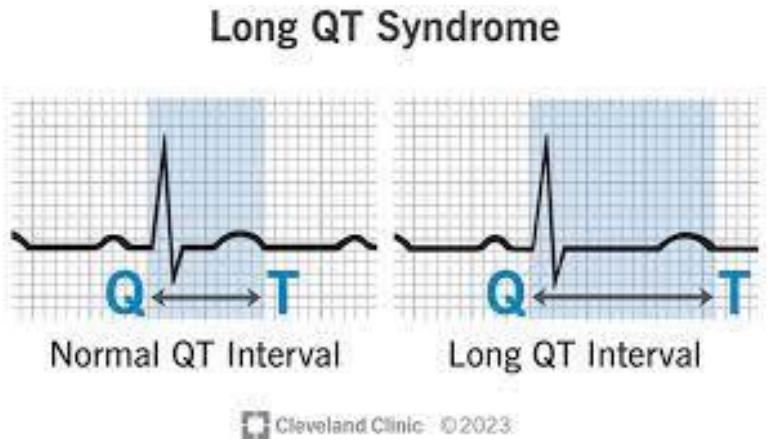
## E. Adverse effects

### 4. **QTc prolongation**:

- Macrolides and ketolides may prolong the OTc interval and should be used with caution in those patients with **proarrhythmic** conditions or **concomitant** use of **proarrhythmic agents**.



# Macrolides and Ketolides

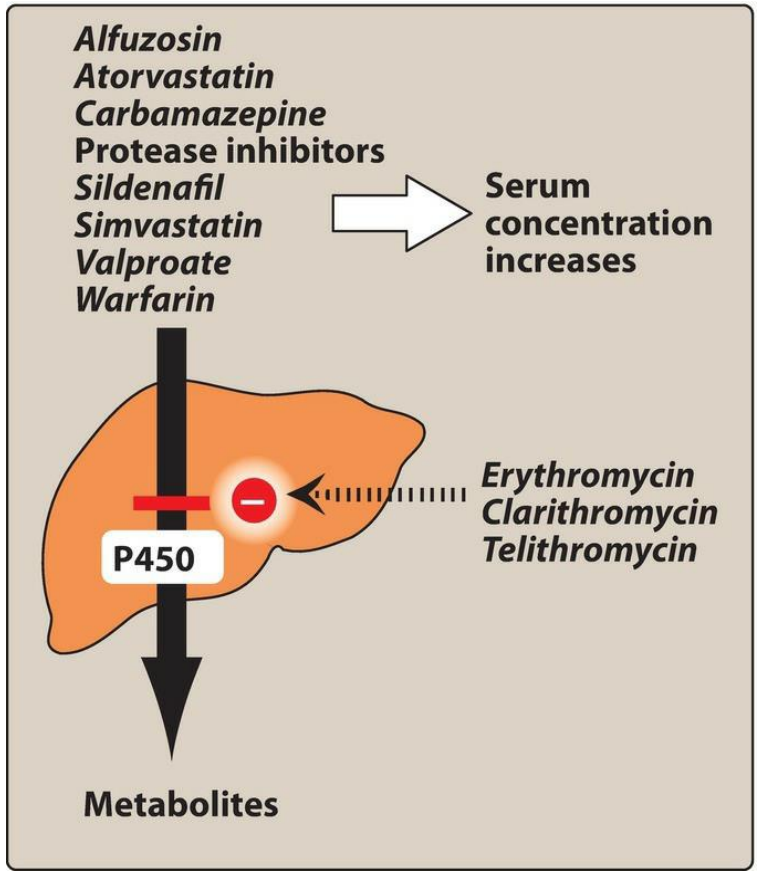
**Contraindication**:

- Patients with **hepatic dysfunction** should be treated cautiously with *erythromycin*, *telithromycin*, or *azithromycin*, because these drugs accumulate in the liver.
- **Severe hepatotoxicity** with *telithromycin* has limited its use.

# Macrolides and Ketolides

## Drug Interactions:

- ***Erythromycin, telithromycin,* and *clarithromycin* inhibit the hepatic metabolism** of a number of drugs, which can lead to **toxic accumulation** of these compounds.
- An interaction with *digoxin* may occur.
- One theory to explain this interaction is that the antibiotic **eliminates a species of intestinal flora that ordinarily inactivates *digoxin***, leading to greater reabsorption of *digoxin* from the enterohepatic circulation.



# Fidaxomicin

- *Fidaxomicin* is a macrocyclic antibiotic with a structure similar to the macrolides; however, it has a unique mechanism of action.
- *Fidaxomicin* acts on the **sigma subunit of RNA polymerase**, thereby **disrupting bacterial transcription**, **terminating** protein synthesis and resulting in **cell death** in susceptible organisms.

# Fidaxomicin

- *Fidaxomicin* has a **very narrow spectrum** of activity limited to **gram-positive aerobes and anaerobes**.
- While it possesses activity against **staphylococci and enterococci**,
- it is used primarily for its **bactericidal** activity against ***Clostridium difficile***.

# Fidaxomicin

- Because of the unique target site, **cross-resistance** with other antibiotic classes **has not been documented**.
- Following **oral administration**, *fidaxomicin* has **minimal systemic absorption** and **primarily remains within the gastrointestinal tract**.
- This is ideal for the treatment of ***C. difficile* infection**, which occurs in the gut.

# Fidaxomicin

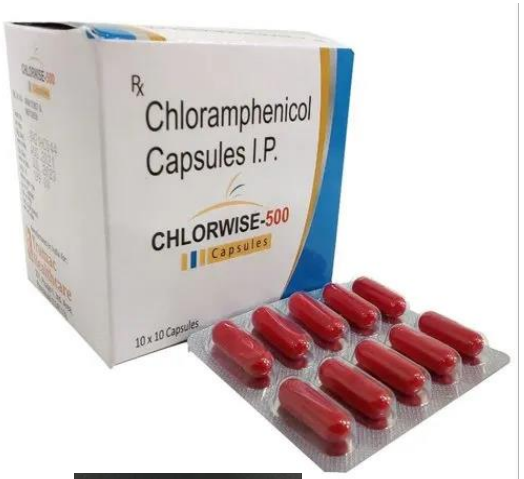
- The most common **adverse effects** include

1. Nausea, vomiting, and abdominal pain.
2. Anemia and neutropenia have been observed infrequently.
3. Hypersensitivity reactions including **angioedema**, dyspnea, and pruritus have occurred.


- *Fidaxomicin* should be used with caution in patients with a **macrolide allergy**, as they **may be at increased risk** for **hypersensitivity**.

# Chloramphenicol

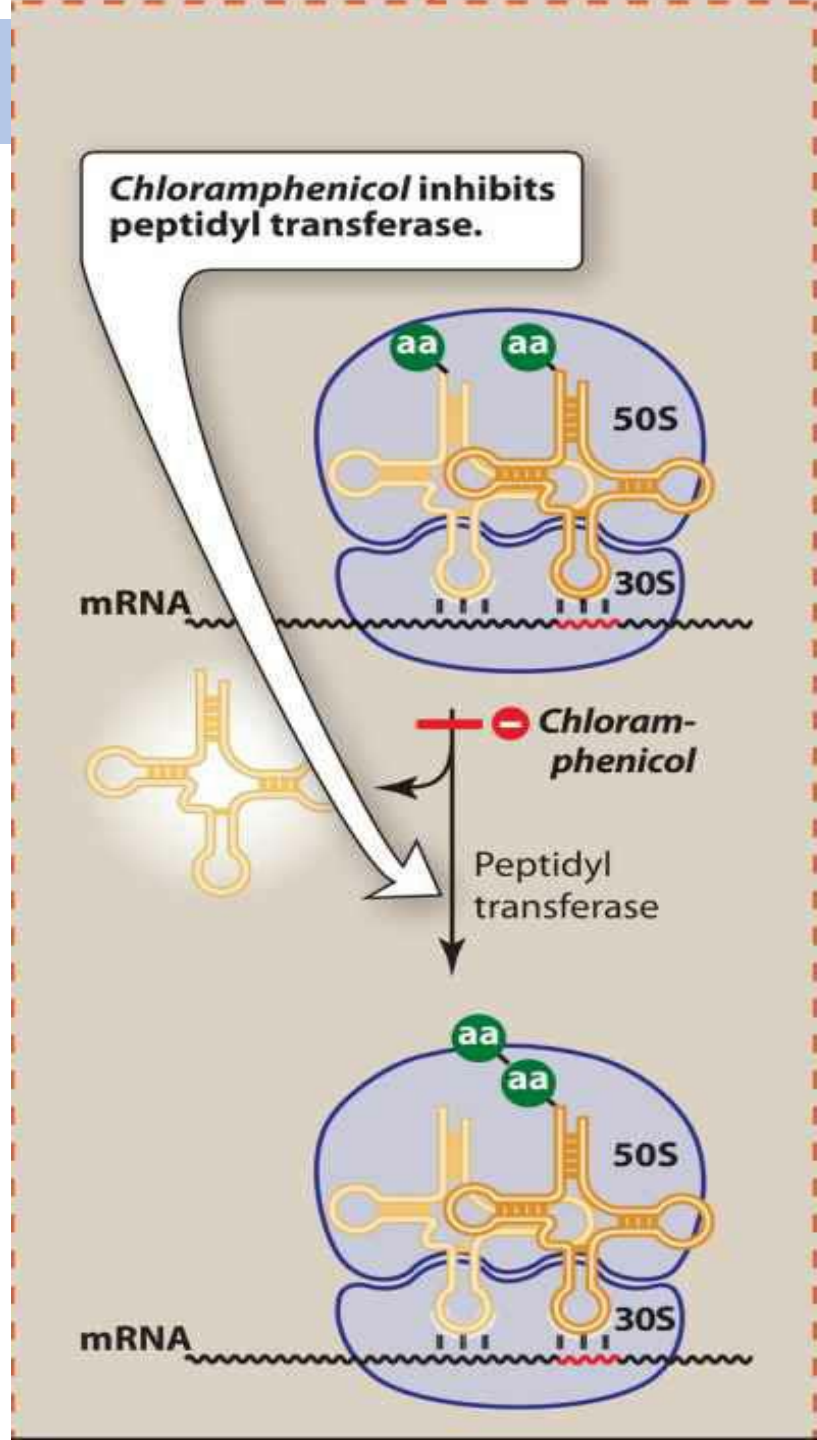
- The use of chloramphenicol, **a broad-spectrum antibiotic**, is restricted to **life-threatening infections** for which no alternatives exist.



# Chloramphenicol

- **A. Mechanism of action**
- *Chloramphenicol* binds **reversibly** to the bacterial **50S ribosomal** subunit and inhibits protein synthesis at the **peptidyl transferase reaction** .
- Because of some **similarity of mammalian mitochondrial ribosomes** to those of bacteria, **protein and ATP synthesis** in these organelles may be **inhibited** at high circulating *chloramphenicol* concentrations, producing **bone marrow toxicity.**
- [Note: The **oral formulation** of *chloramphenicol* was removed from the US market due to this toxicity.]



# Chloramphenicol

- **B. Antibacterial spectrum**
- *Chloramphenicol* is active against many types of microorganisms including

1. **Chlamydiae,**
2. **Rickettsiae,**
3. **Spirochetes**, and
4. **Anaerobes**.

| Bacterial | Species | Disease(s) Caused |
|---|---|---|
| Chlamydiae | Chlamydia trachomatis | Chlamydia (STI), Trachoma, Neonatal Pneumonia, Neonatal Conjunctivitis |
| | Chlamydophila pneumoniae | Atypical Pneumonia, Bronchitis |
| | Chlamydophila psittaci | Psittacosis (Parrot Fever) |
| Rickettsiae | Rickettsia rickettsii | Rocky Mountain Spotted Fever |
| | Rickettsia prowazekii | Epidemic Typhus |
| | Rickettsia typhi | Endemic (Murine) Typhus |
| Spirochetes | Treponema pallidum | Syphilis |
| | Borrelia burgdorferi | Lyme Disease |
| | Leptospira interrogans | Leptospirosis |

- The drug is primarily **bacteriostatic**, but it may exert **bactericidal** activity depending on the dose and organism.

# Chloramphenicol

## C. Resistance

- Resistance is conferred by the presence of **enzymes** **that inactivate *chloramphenicol.***
- Other mechanisms include **decreased ability to penetrate** the organism and **ribosomal binding site alterations**.

# Chloramphenicol

## D. Pharmacokinetics

- *Chloramphenicol* is administered **intravenously** and is widely distributed throughout the body.
- It reaches therapeutic concentrations in the **CSF**.
- *Chloramphenicol* primarily undergoes **hepatic metabolism** to an inactive **glucuronide**, which is secreted by the renal tubule and **eliminated in the urine**.
- Dose reductions are necessary in patients with **liver dysfunction or cirrhosis**.
- *Chloramphenicol* is also **secreted into breast milk** and should be avoided in breastfeeding mothers.

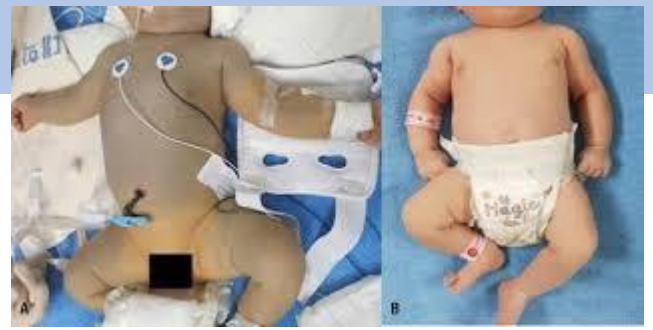
# Chloramphenicol

## E. Adverse effects

### 1. Anaemias:

- Patients may experience dose-related anemia, **hemolytic anemia** (observed in patients with **glucose-6-phosphate dehydrogenase deficiency**), and **aplastic anemia**.
- [Note: **Aplastic anemia** is independent of dose and may occur after therapy has ceased] its called **idiosyncratic reactions**

# Chloramphenicol



## E. Adverse effects

### 2. Gray baby syndrome:

- Neonates have a low capacity to **glucuronidate** the antibiotic, and they have underdeveloped renal function, which decreases their ability to excrete the drug.
- This leads to drug accumulation to concentrations that interfere with the **function of mitochondrial ribosomes**, causing **poor feeding**, **depressed breathing**, **cardiovascular collapse**, **cyanosis** (hence the term "gray baby"), and **death**.
- ***Adults*** *who have received* ***very high doses of chloramphenicol*** *may also exhibit this toxicity*.

# Chloramphenicol

## 3. Drug Interactions:

- *Chloramphenicol* **inhibits** some of the hepatic mixed-function **oxidases**, **preventing** the metabolism of drugs such as ***warfarin*** and ***phenytoin***, which may potentiate their effects.

# Clindamycin

- *Clindamycin* has a mechanism of action that is **similar** to that of the **macrolides**.
- *Clindamycin* is used primarily in the treatment of infections caused by

1. **Gram-positive organisms**, including **MRSA and streptococcus**, and **anaerobic** bacteria.


- Resistance mechanisms are the same as those for *erythromycin*, and cross resistance has been described.
- ***C. difficile* is resistant to clindamycin**, and
- The utility of *clindamycin* for **gram-negative anaerobes** (for example, Bacteroides sp.) is **decreasing** due to **increasing resistance**.

# Clindamycin

- *Clindamycin* is available in both **IV** and **oral** formulations, **but** use of oral *clindamycin* **is limited by gastrointestinal intolerance**.
- It distributes well into all body fluids but **exhibits poor entry into the CSF**.
- *Clindamycin* **undergoes extensive oxidative metabolism** to active and inactive products and is excreted **into bile and urine**.
- **Low urinary excretion** of active drug limits its clinical utility for **urinary tract infections.**
- **Accumulation** has been reported in patients with either **severe renal impairment** or **hepatic failure**.

# Clindamycin

- In addition to **skin rash**, the most common adverse effect is **diarrhea**, which may represent a serious **pseudomembranous colitis** caused by overgrowth of **C. difficile**.
- Oral administration of either ***metronidazole*** **or** ***vancomycin*** is usually effective in the treatment of C. difficile infection.

# Quinupristin/Dalfopristin

- *Quinupristin/dalfopristin* is a **mixture of two streptogramins** in a ratio of 30 to 70, respectively.
- Due to **significant adverse effects**, this combination drug is normally **reserved** for the treatment of **severe infections** caused by ***vancomycin-resistant Enterococcus faecium (VRE)*** in the absence of other therapeutic options.

# Quinupristin/Dalfopristin

## A. Mechanism of action

- Each component of this combination drug **binds to a separate site on the 50S bacterial ribosome**.
- *Dalfopristin* **disrupts** elongation by interfering with the addition of new amino acids to the peptide chain.
- *Quinupristin* **prevents** elongation similar to the macrolides and causes release of incomplete peptide chains.
- Thus, they **synergistically** interrupt **protein synthesis**.
- The combination drug has **bactericidal** activity against most susceptible organisms and has a **long PAE**.

# Quinupristin/Dalfopristin

## B. Antibacterial spectrum

- *Quinupristin l dalfopristin* is active primarily against **gram-positive cocci**, including those resistant to other antibiotics.
- Its primary use is for the treatment of ***E. faecium*** infections, including VRE strains, against which it is ***bacteriostatic***.
- *Quinupristin l dalfopristin* **is not effective** against **E. faecalis**.

# Quinupristin/Dalfopristin

## C. Resistance

- **Enzymatic processes** commonly account for resistance to these agents.
- For example, the presence of a **ribosomal enzyme that methylate's** the target bacterial 23s ribosomal RNA site can interfere in *quinupristin* binding.
- In some cases, 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.

# Quinupristin/Dalfopristin

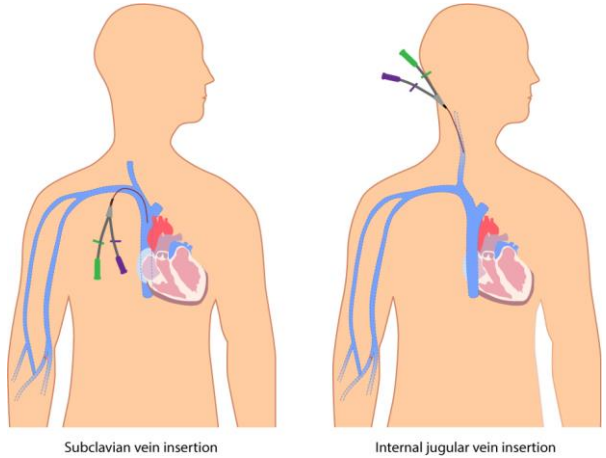
## D. Pharmacokinetics

- *Quinupristin l dalfopristin* is available **intravenously**.
- It **does not achieve** therapeutic concentrations in **CSF**.
- Both compounds undergo **hepatic metabolism**, with **excretion** mainly in the **feces**.

# Quinupristin/Dalfopristin

## E. Adverse effects

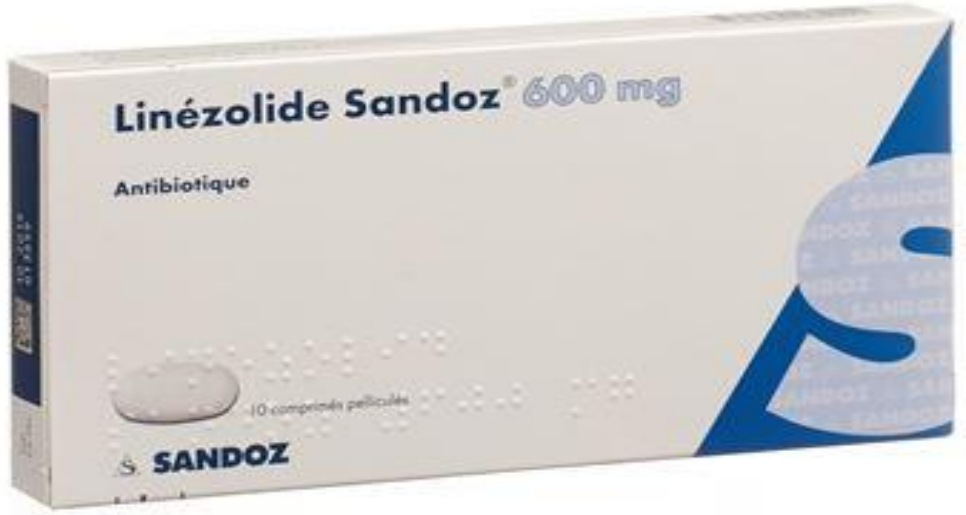
- **Venous irritation** commonly occurs when *Quinupristin / dalfopristin* is administered through a **peripheral** rather than **a central line**.
- **Hyperbilirubinemia** occurs in about 25% of patients, resulting from a competition with the antibiotic for excretion.
- **Arthralgia** and **myalgia** have been reported when higher doses are administered.
- *Quinupristin/dalfopristin* **inhibits the cytochrome P450 CYP3A4** isoenzyme, and concomitant administration with drugs that are **metabolized** by this pathway **may lead to toxicities**.



# Oxazolidinones

- ***Linezolid*** **and** ***tedizolid*** are synthetic oxazolidinones developed to combat **gram positive organisms**, including resistant isolates such as

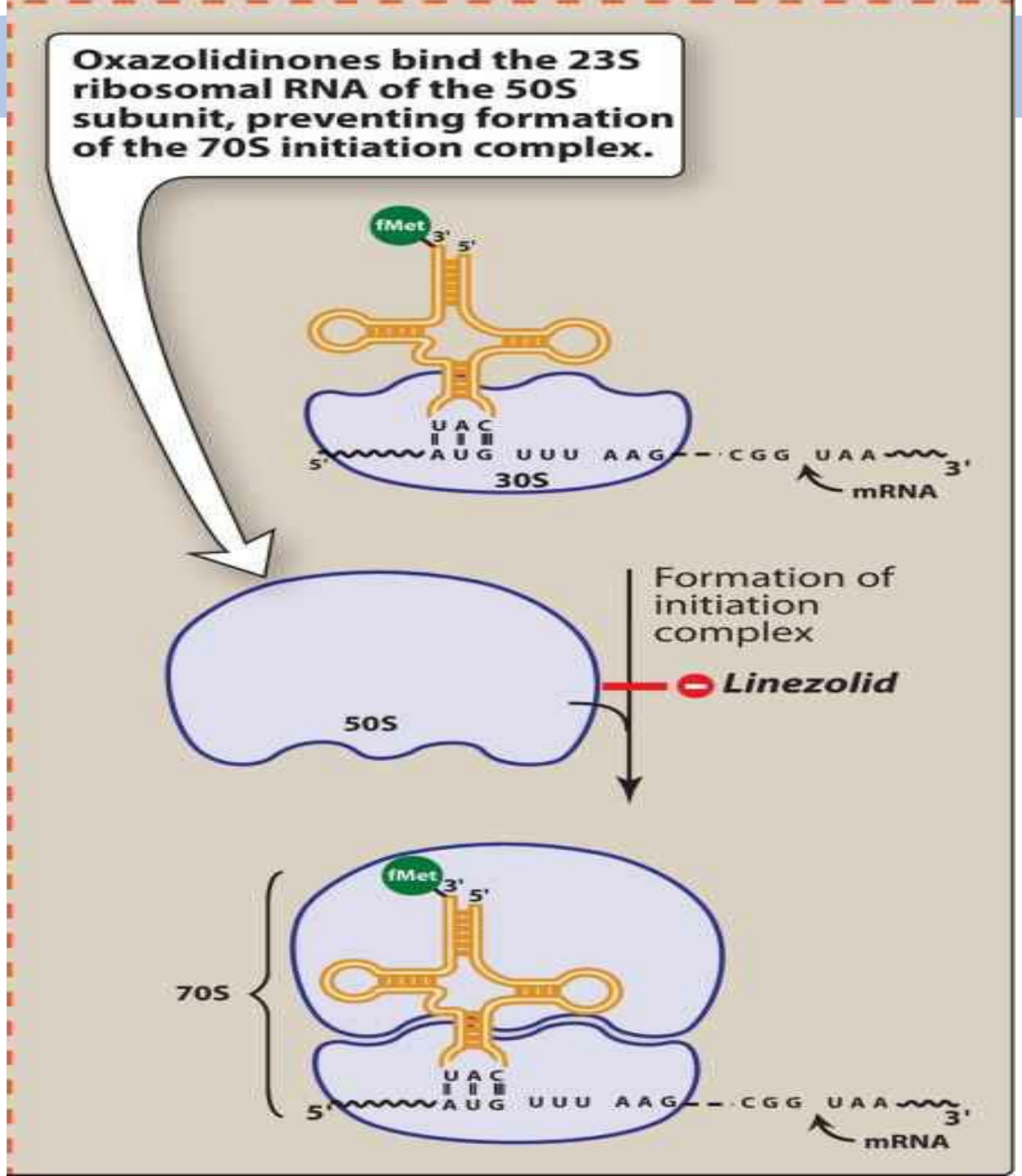
1. *methicillin-resistant* Staphylococcus aureus,
2. VRE, and
3. *penicillin-resistant* streptococci.




# Oxazolidinones

- **A. Mechanism of action**

- *Linezolid* and *tedizolid* bind to the *bacterial 23S ribosomal RNA of the 50S subunit*, thereby inhibiting the formation of the 70S initiation complex and translation of bacterial proteins.



# Oxazolidinones

## B. Antibacterial spectrum

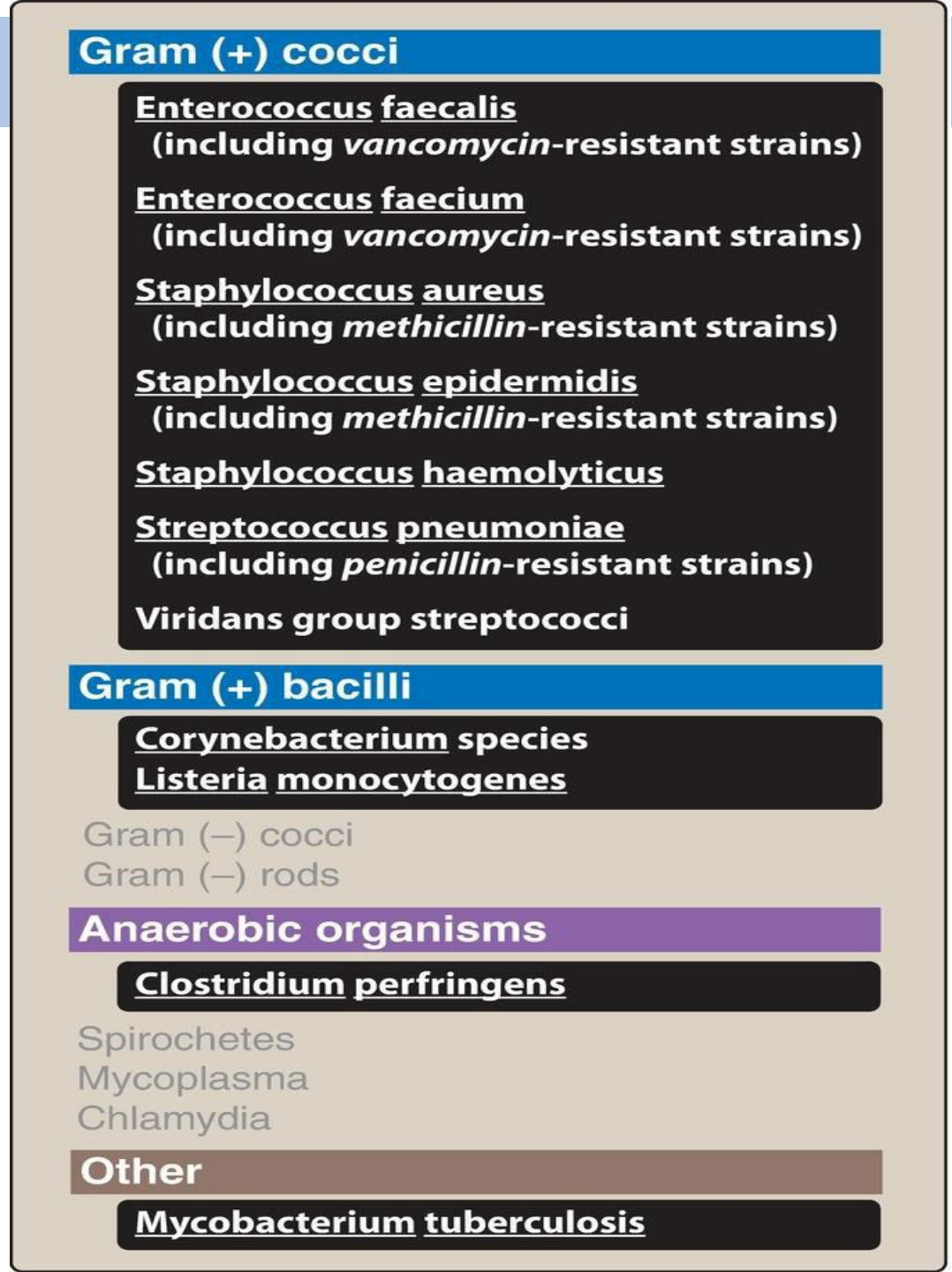
- The antibacterial action of the oxazolidinones is directed primarily against

1. **gram-positive organisms** such as staphylococci, streptococci, and enterococci, Corynebacterium species and Listeria monocytegenes.
2. It is also **moderately** active against **Mycobacterium tuberculosis**.
3. The **main clinical use** of *linezolid* and *tedizolid* is to **treat infections caused by drug-resistant gram-positive organisms**.
4. *Linezolid* is an alternative to **daptomycin** for infections caused by **VRE**.

# Oxazolidinones

## B. Antibacterial spectrum

- Like other agents that interfere with bacterial protein synthesis, linezolid and tedizolid are **bacteriostatic**; however, linezolid **has bactericidal** activity against **streptococci**.
- Because they are **bacteriostatic**, the oxazolidinones are ***not recommended*** as first-line treatment for **MRSA bacteremia**.



# Oxazolidinones

## C. Resistance

- Resistance **primarily** occurs via ***reduced binding at the target site***.
- Reduced susceptibility and resistance have been reported in **S. aureus and Enterococcus sp**.
- **Cross-resistance with other protein synthesis inhibitors does not occur**.

# Oxazolidinones

## D. Pharmacokinetics

- *Linezolid* and *tedizolid* are well absorbed after **oral administration**.
- **IV formulations** are also available.
- These drugs **distribute widely** throughout the body.
- Although the metabolic pathway of *linezolid* has not been fully determined, it is known that it is **metabolized via oxidation** to two **inactive metabolites**.

# Oxazolidinones

## D. Pharmacokinetics

- The drug is excreted both by **renal and non-renal routes**.
- Tedizolid is **metabolized** by **sulfation**, and the majority of **elimination** occurs via the **liver**, and drug is mainly excreted in the **feces**.
- **No dose adjustments** are required for either agent for **renal or hepatic dysfunction**.

# Oxazolidinones

## E. Adverse effects

- The most common adverse effects are **gastrointestinal upset**, **nausea, diarrhea, headache, and rash**.
- **Thrombocytopenia** has been reported, usually in patients taking the drug for longer than 10 days.
- *Linezolid* and *tedizolid* possess nonselective monoamine oxidase activity and may lead to **serotonin syndrome** if given concomitantly with large quantities of **tyramine-containing foods**, *selective serotonin reuptake inhibitors*, or *monoamine oxidase inhibitors*. The condition is reversible when the drug is discontinued.
- **Irreversible peripheral neuropathies** and **optic neuritis** causing **blindness** have been associated with greater than 28 days of use, limiting utility for extended-duration treatments.