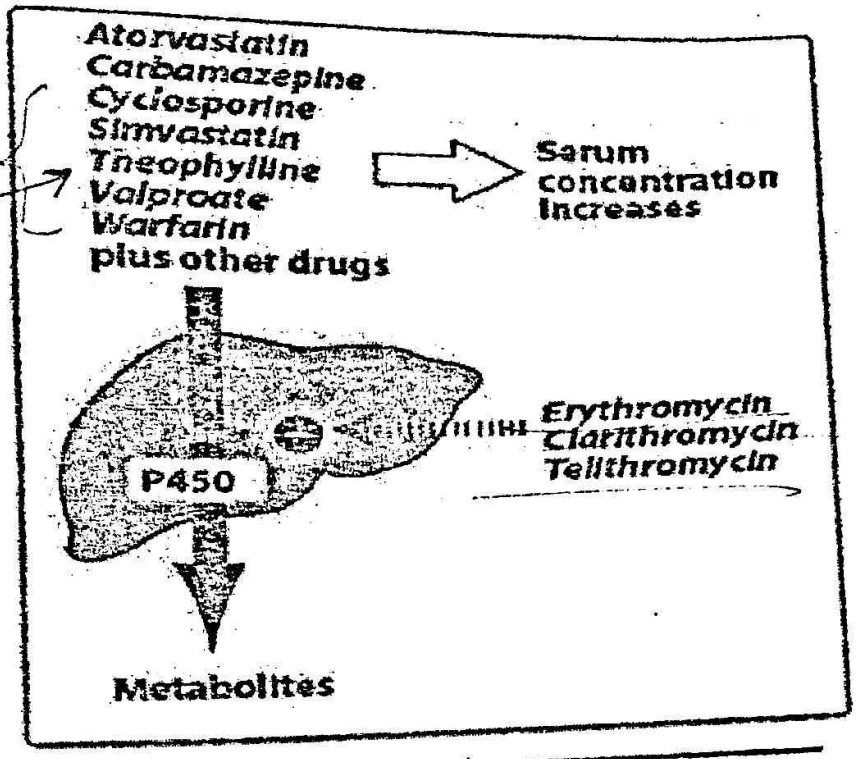


Figure 32.16
Inhibition of the cytochrome P450 system by *erythromycin, clarithromycin,* and *telithromycin.*

4. Excretion: *Erythromycin* and *azithromycin* are primarily concentrated and excreted in an active form in the bile. Partial reabsorption occurs through the enterohepatic circulation. Inactive metabolites are excreted into the urine. *Clarithromycin* and its metabolites are eliminated by the kidney as well as the liver .

E. Adverse effects

1. Epigastric distress: This side effect is common and can lead to poor patient compliance for *erythromycin*. *Clarithromycin* and *azithromycin* seem to be better tolerated by the patient.

2. Cholestatic jaundice: occurs especially with the estolate form of *erythromycin*, as the result of a hypersensitivity reaction to the estolate form.

3. Ototoxicity: Transient deafness has been associated with *erythromycin*, especially at high dosages.

4. Contraindications: Patients with hepatic dysfunction should be treated cautiously with *erythromycin*, *telithromycin*, or *azithromycin*.

Severe hepatotoxicity with telithromycin use have been reported. Telithromycin has the potential to prolongate the QTc interval in some patients. Patients who are renally compromised should be given *telithromycin* with caution. *Telithromycin* is contraindicated in patients with myasthenia gravis.

5. Intravenous administration of *erythromycin* is associated with a high incidence of **thrombophlebitis.**

6. 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.

No interactions have been reported for *azithromycin*.

3. Azithromycin: Although less active against streptococci and staphylococci than *erythromycin*, *azithromycin* is far more active against infections due to H. influenzae and Moraxella catarrhalis. *Azithromycin* is the preferred therapy for urethritis caused by Chlamydia trachomatis. It also has activity against Mycobacterium avium-intracellulare complex

4. Telithromycin: This ketolide drug has an antibacterial spectrum similar to that of *azithromycin. It is active against many macrolide-resistant gram positive strains.*

C. Resistance

1) The inability of the organism to take up the antibiotic or the presence of an efflux pump, (decreased intracellular drug)

2) A decreased affinity of the 50S ribosomal subunit for the antibiotic ;

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

Both *clarithromycin* and *azithromycin* show cross-resistance with *erythromycin*, but *telithromycin* can be effective against macrolide-resistant organisms, *The structural modification within ketolides neutralizes the most common macrolide resistance mechanisms (methylase-mediated and efflux-mediated.*

D. Pharmacokinetics

1. Administration: The *erythromycin* base is destroyed by gastric acid. Thus, either enteric-coated tablets or esterified forms of the antibiotic are administered. All are adequately absorbed upon oral administration.

Clarithromycin, azithromycin, and *telithromycin* are stable to stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin* and *azithromycin,* but can increase that of *clarithromycin*

2. Distribution: *Erythromycin* distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuses into prostatic fluid, and it has the unique characteristic of accumulating in macrophages.

All four drugs concentrate in the liver. *Clarithromycin, azithromycin,* and *telithromycin* are widely distributed in the tissues. Serum levels of *azithromycin* are low. *Azithromycin* has the longest half-life and largest volume of distribution of the four drugs.

3. Elimination: *Erythromycin* and *telithromycin* are extensively metabolized and are known to inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system. *Clarithromycin* is oxidized to the 14-hydroxy derivative, which retains antibiotic activity.

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

B. Antibacterial spectrum

1. Erythromycin: This drug is effective against many of the same organisms as *penicillin G*; therefore, it may be used in patients who are allergic to the penicillins.

2. Clarithromycin: This antibiotic has a spectrum of antibacterial activity similar to that of *erythromycin*, but it is also effective against Haemophilus influenzae. It has activity against intracellular pathogens, such as Chlamydia, Legionella, Moraxella, and Ureaplasma species and also on Helicobacter pylori that is higher than activity of *erythromycin*.

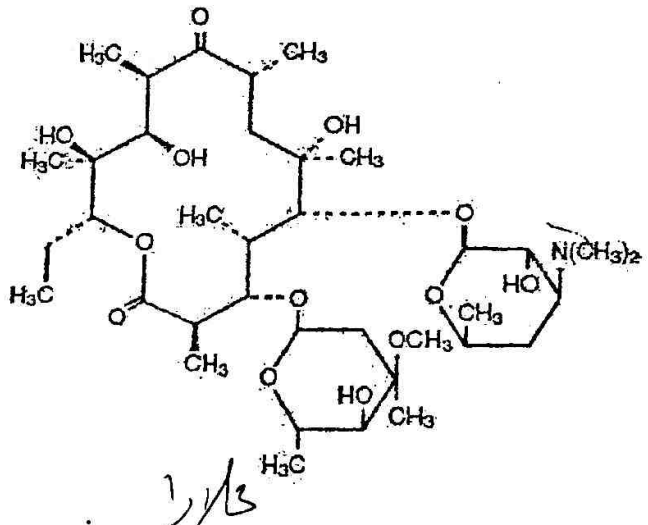
patients simultaneously receiving another ototoxic drug, such as *cisplatin* or the loop diuretics, *furosemide*, *bumetanide*, or *ethacrynic acid*, are particularly at risk. Vertigo and loss of balance (especially in patients receiving ***streptomycin***) may also occur

2. Nephrotoxicity: Retention of the aminoglycosides by the proximal tubular cells, and this results in kidney damage ranging from mild, reversible impairment to severe, acute tubular necrosis, which can be irreversible.

3. Neuromuscular paralysis: The mechanism responsible is a decrease in both the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site. Patients with myasthenia gravis are particularly at risk.

MACROLIDES

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



The newer members of this family, *clarithromycin* (a methylated form of *erythromycin*) and *azithromycin* (having a larger lactone ring), have some features in common with, and others that improve on, *erythromycin*. *Telithromycin*, a semisynthetic derivative of *erythromycin*, is the first "ketolide" antimicrobial agent that has been approved. Ketolides and macrolides have very similar antimicrobial coverage. However, the ketolides are active against many macrolide-resistant gram positive strains.

A. 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.

1) decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides is absent

2) plasmid-associated synthesis of enzymes (for example, acetyl transferases, nucleotidyltransferases, and phosphotransferases) that modify and inactivate aminoglycoside antibiotics. Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance is variable.

Amikacin is less vulnerable to these enzymes than are the other antibiotics of this group.

Pharmacokinetics

1. Administration: The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. Therefore, all aminoglycosides (except *neomycin*) must be given parenterally to achieve adequate serum levels.

The severe nephrotoxicity associated with *neomycin* precludes parenteral administration, and its current use is limited to topical application for skin infections or oral administration to prepare the bowel prior to surgery. The bactericidal effect of aminoglycosides is concentration dependent. They also have a postantibiotic effect. Because of these properties, once-daily dosing with the aminoglycosides can be employed.

The exceptions are neonatal infections, and bacterial endocarditis, in which these agents are administered in divided doses every 8 hours.

2. Distribution: Levels achieved in most tissues are low, and penetration into most body fluids is variable. Concentrations in CSF are inadequate. Except for *neomycin*, the aminoglycosides may be administered intrathecally (for CNS infections).

High concentrations accumulate in the renal cortex and in the endolymph and perilymph of the inner ear, which may account for their nephrotoxic and ototoxic potential. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma.

Adverse effects

It is important to monitor plasma levels of *gentamicin*, *tobramycin*, and *amikacin* to avoid concentrations that cause dose-related toxicities. When the drugs are administered two to three times daily, both peak and trough levels are measured. When once-daily dosing is employed, only the trough concentrations are monitored for toxicity.

1. Ototoxicity: Ototoxicity (vestibular and cochlear) is directly related to high peak plasma levels and the duration of treatment. Deafness may be irreversible and has been known to affect fetuses in utero.

B

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دورة / تشريحيا

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AMINOGLYCOSIDES

Aminoglycoside antibiotics had been the mainstays for treatment of serious infections due to aerobic gram-negative bacilli. Their polycationic nature precludes their easy passage across tissue membranes. (include gentamicin, amikacin, neomycin, Streptomycin & tobramycin)

Mechanism of action

Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. The antibiotic then binds to the 30S ribosomal subunit prior to ribosome formation.

- It interferes with assembly of the functional ribosomal apparatus and/or can cause the 30S subunit of the completed ribosome to misread the genetic code.

- **Antibacterial spectrum**

The aminoglycosides are effective in combination for infections due to aerobic gram-negative bacilli, including Pseudomonas aeruginosa. To achieve synergistic effect, aminoglycosides are often combined with a β-lactam antibiotic, vancomycin, or a drug active against anaerobic bacteria. Aminoglycosides are bactericidal. The aminoglycosides are effective only against aerobic organisms because strict anaerobes lack the oxygen-requiring drug transport system.

Spectrum includes :

a)**Gram positive cocci :**

Enterococcus species (Streptococcus (gentamicin with ampicillin),

b) **Gram negative rods :**

Brucella (Gentamicin with doxycycline),

Francisella tularensis, Klebsiella (Gentamicin with antipseudomonal penicillin),

P.aureginosa (Gentamicin with antipseudomonal penicillin),

Yersinia pestis (with doxycycline)

Resistance

Resistance can be caused by :