Protein synthesis inhibitors

Pharmacology 3

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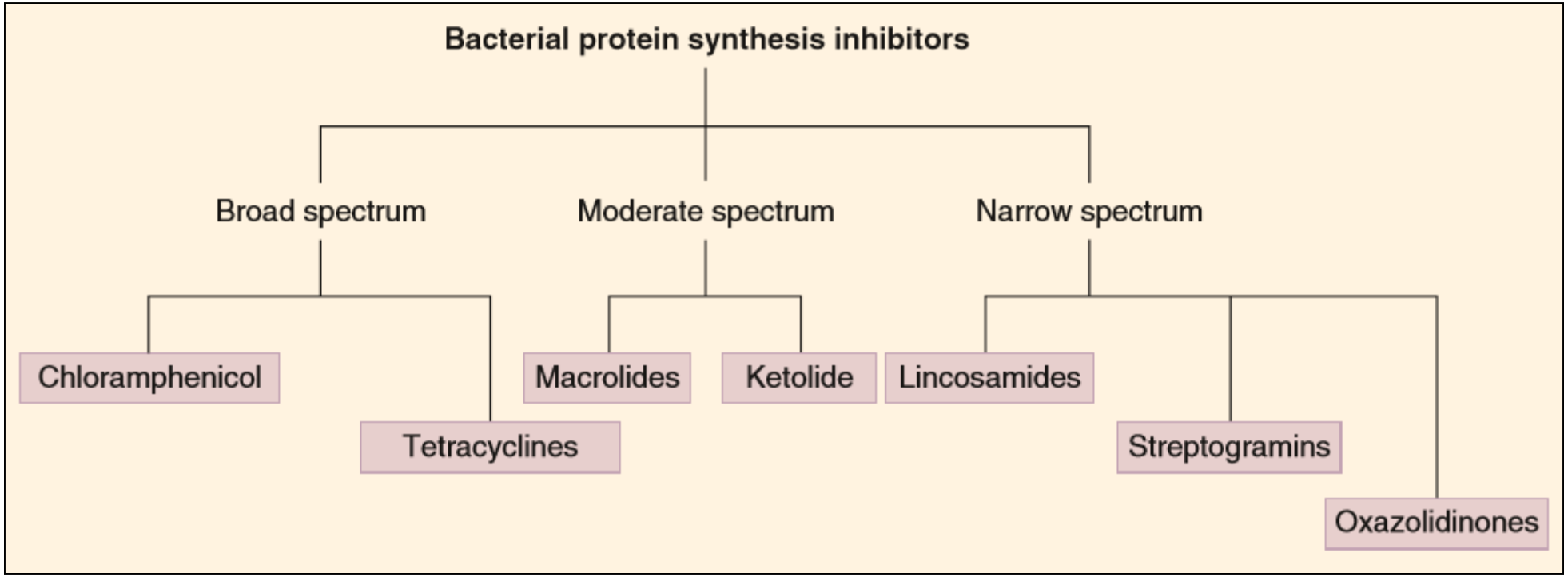
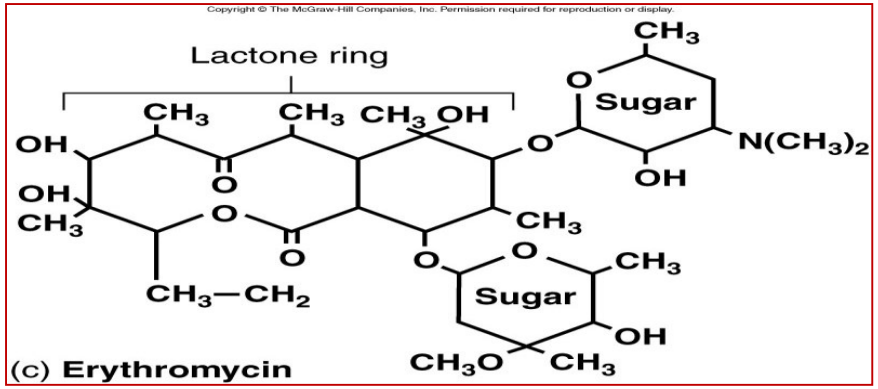
Protein Synthesis Inhibitors



I. Macrolides and ketolides

- The macrolides are a group of closely related compounds characterized by a macrocyclic lactone ring (usually containing 14 or 16 atoms) to which deoxy sugars are attached.

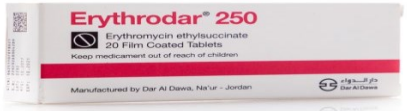


- Generally bacteriostatic they may be bactericidal at higher doses
- Their names end in “romycin” and mostly in “thromycin”

Macrolides

- **Erythromycin** – problems with acid liability, narrow spectrum, GI intolerance, short elimination half-life

- Structural derivatives include **clarithromycin** and **azithromycin:**
  - **Broader spectrum of activity**
  - **Improved PK properties** – better bioavailability, better tissue penetration, prolonged half-lives
  - **Improved tolerability**



Macrolides Spectrum of Activity

Anaerobes – activity against upper airway anaerobes

Atypical Bacteria – all macrolides have **excellent** activity against atypical bacteria including:

- *Legionella pneumophila*
- *Chlamydia sp.*
- *Mycoplasma sp.*

Gram-Positive Aerobes – erythromycin and clarithromycin display the best activity

(Clarithro>Erythro>Azithro)

Methicillin-susceptible *Staphylococcus aureus*

Streptococcus pneumoniae (only PSSP)

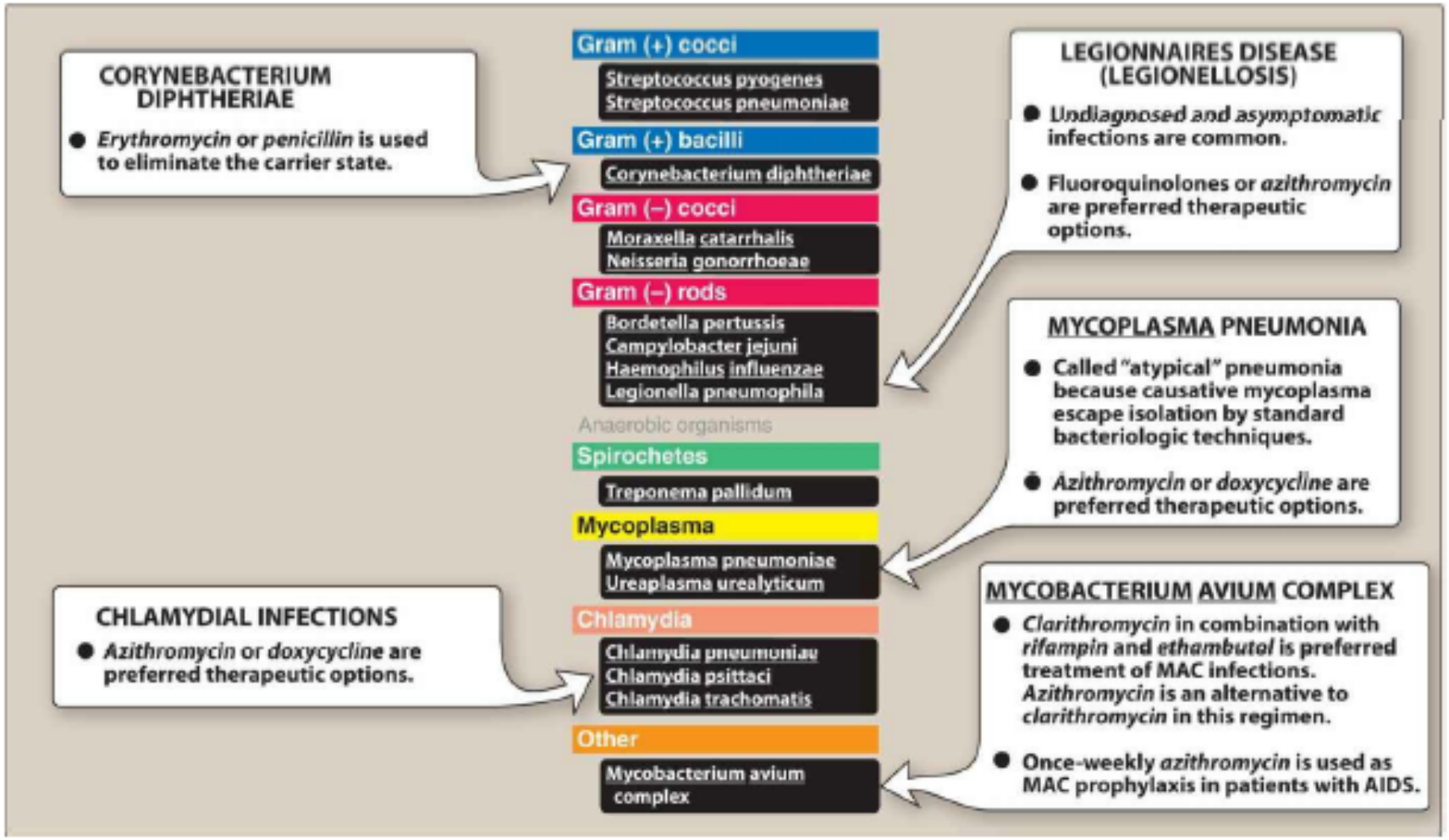
Mycobacterium avium complex. (Azithro and Clarithro)

Gram-Negative Aerobe

(Azithro>Clarithro>Erythro)

H. influenzae (not erythro), *Neisseria sp.*

Typical therapeutic applications of macrolides



Spectrum of Activity

- **Erythromycin:** This drug is effective against many of the same organisms as *penicillin G*, it may be used in patients with *penicillin* allergy.
- **Clarithromycin:** Its activity against intracellular pathogens, such as Chlamydia species and Helicobacter pylori, is higher than that of *erythromycin.*
- ***Azithromycin*** is more active against respiratory infections due to H. influenzae and Moraxella catarrhalis, it is the preferred therapy for urethritis caused by Chlamydia trachomatis.
- **Telithromycin-(KETOLIDES):** This drug has an antimicrobial spectrum similar to that of *azithromycin.* Moreover, the structural modification neutralizes the most common resistance mechanisms

Adverse effects

1. **Gastric distress and motility:** most common, may lead to poor patient compliance (especially with *erythromycin*). *Clarithromycin* and *azithromycin* seem to be better tolerated. Higher doses of erythromycin lead to smooth muscle contractions.

2. **Cholestatic jaundice:** This side effect occurs especially with the estolate form (not used in the United States) of erythromycin; however, it has been reported with other formulations.

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

Drug interactions

1. Erythromycin, telithromycin, and clarithromycin inhibit cytochrome P450 enzymes and, thus, increase the serum concentrations of numerous drugs, including theophylline, warfarin, cyclosporine, and methylprednisolone.

2. They increase serum concentrations of oral digoxin by increasing its bioavailability (the antibiotic eliminates a species of intestinal flora that ordinarily inactivates digoxin, thus leading to greater drug reabsorption from the enterohepatic circulation).

<u>Azithromycin does not inactivate cytochrome P450 enzymes</u> and, therefore, is free of the drug interactions that occur with erythromycin and clarithromycin.

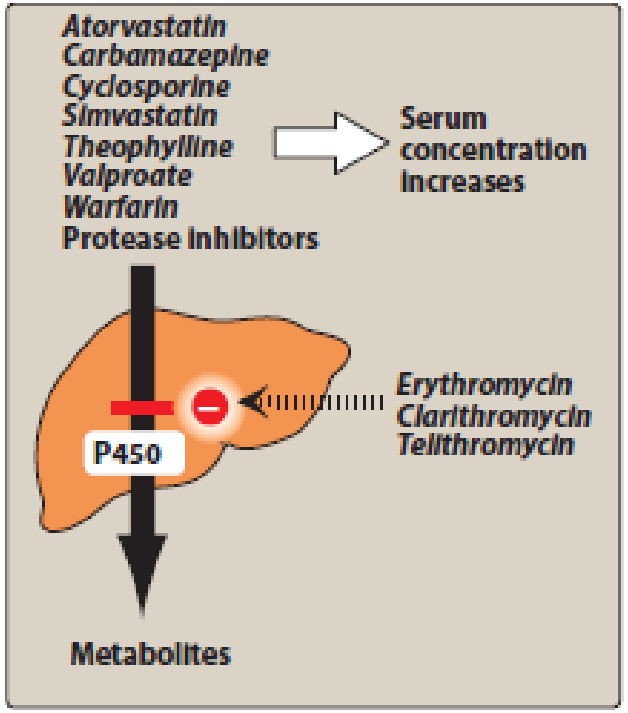
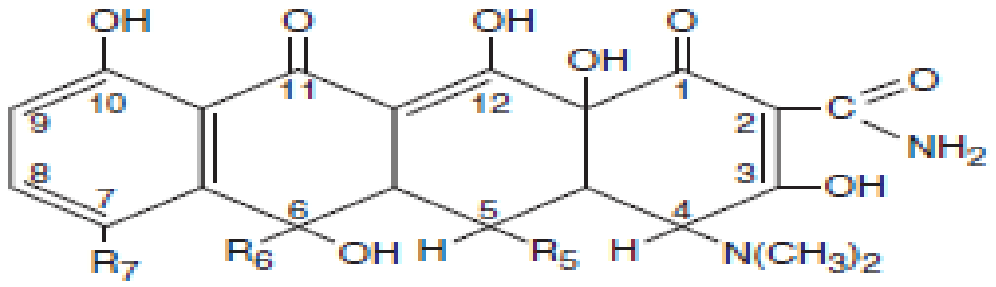


Figure 39.14
Inhibition of the cytochrome P450 system by *erythromycin*, *clarithromycin*, and *telithromycin*.

II. Tetracyclines



	R_7	R_6	R_5	Renal Clearance (mL/min)
Chlortetracycline	—Cl	—CH_3	—H	35
Oxytetracycline	—H	—CH_3	—OH	90
Tetracycline	—H	—CH3	—H	65
Demeclocycline	—Cl	—H	—H	35
Methacycline	—H	=CH_2*	—OH	31
Doxycycline	—H	—CH_3*	—OH	16
Minocycline	—$N(CH_3)_2$	—H	—H	10

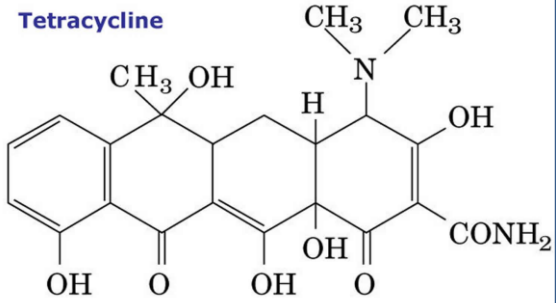
*There is no — OH at position 6 on methacycline and doxycycline.

- Tetracyclines are broad-spectrum bacteriostatic antibiotics that inhibit protein synthesis.
- Tetracyclines enter microorganisms in part by passive diffusion and in part by an energy-dependent process of active transport.

Tetracyclines

Their names end in “cycline”

Examples: *Demeclocycline*, *Doxycycline*, *Minocycline*, *Tetracycline*, Tigecycline

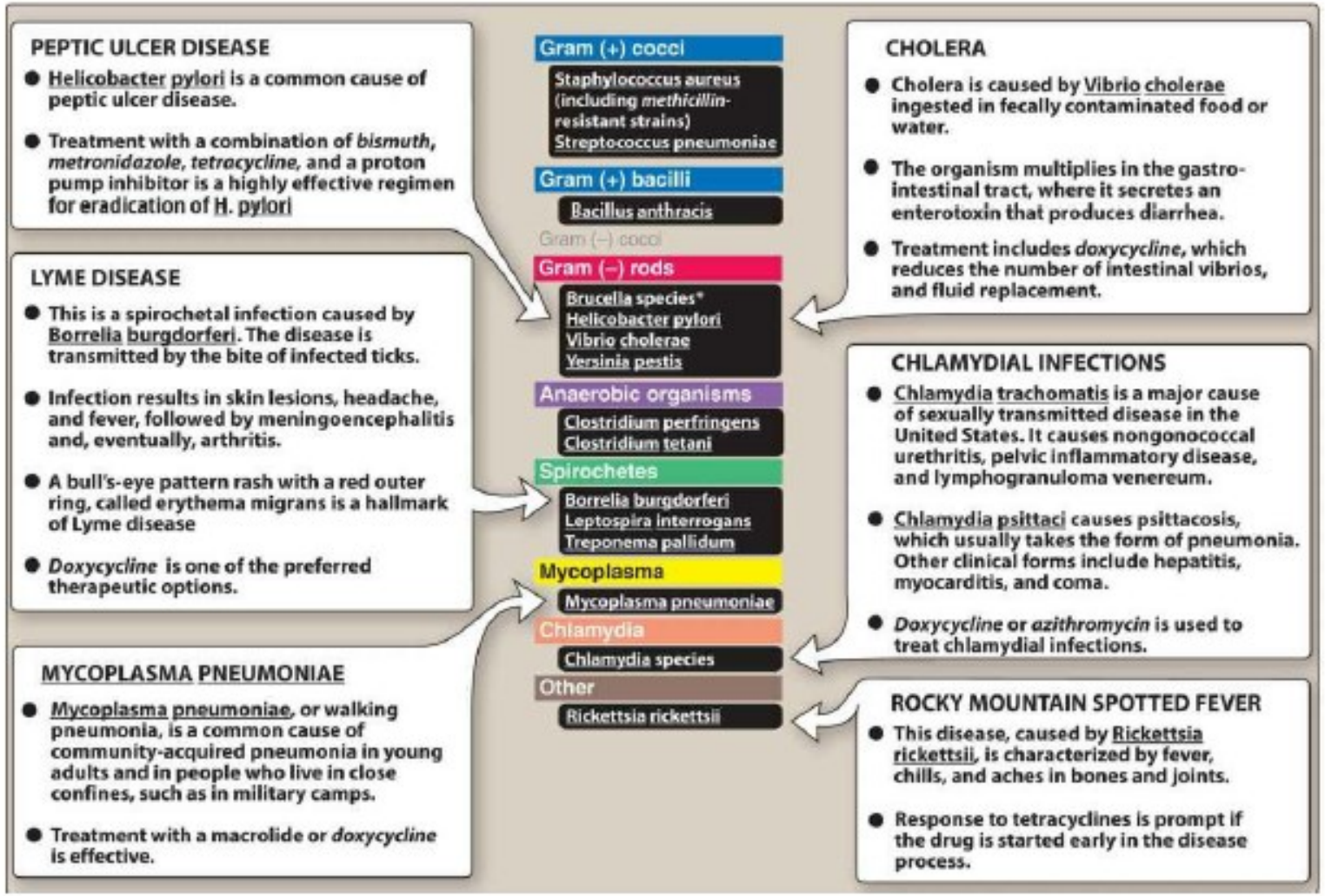


Are broad-spectrum bacteriostatic antibiotics that inhibit protein synthesis.

Tetracyclines are active against many gram-positive and gram-negative bacteria, including certain anaerobes, rickettsiae, chlamydiae, and mycoplasmas.

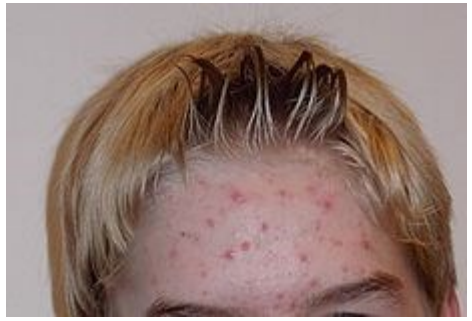
They are used in combination regimens to treat gastric and duodenal ulcer disease caused by *Helicobacter pylori*.

Typical therapeutic applications of tetracyclines

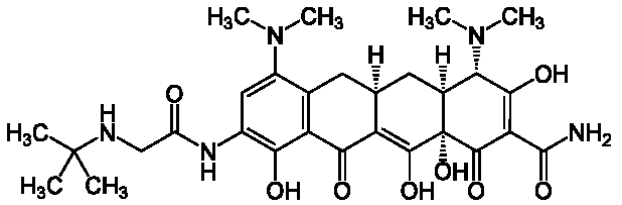


Secondary uses of Tetracyclines

- Alternative drug for syphilis
- Prophylaxis against chronic bronchitis
- Treatment of moderately severe acne



Tigecycline



- A newer tetracycline analog, **tigecycline**, is a glycylcycline and a semisynthetic derivative of minocycline.
- It is specifically designed to overcome tetracycline resistance, that utilize efflux pumps and/or ribosomal protection.
- It is indicated for the treatment of complicated skin and soft tissue infections, as well as complicated intra-abdominal infections (active against **MRSA**, vancomycin-resistance enterococci (**VRE**)).
- Following IV infusion, tigecycline exhibits a large volume of distribution.
- It penetrates tissues well but has low plasma concentrations. Consequently, tigecycline is a poor option for bloodstream infections.

Pharmacokinetics

Absorption:

- Most tetracyclines are adequately absorbed after oral ingestion (Doxycycline, minocycline)
- Tigecycline is poorly absorbed orally and must be administered intravenously.
- Administration with dairy products or other substances that contain divalent and trivalent cations (for example, magnesium and aluminum antacids or iron supplements) decreases absorption due to the formation of nonabsorbable chelates.
- Tetracycline and demeclocycline should be administered on an empty stomach, while doxycycline and minocycline absorption is not impaired by food.

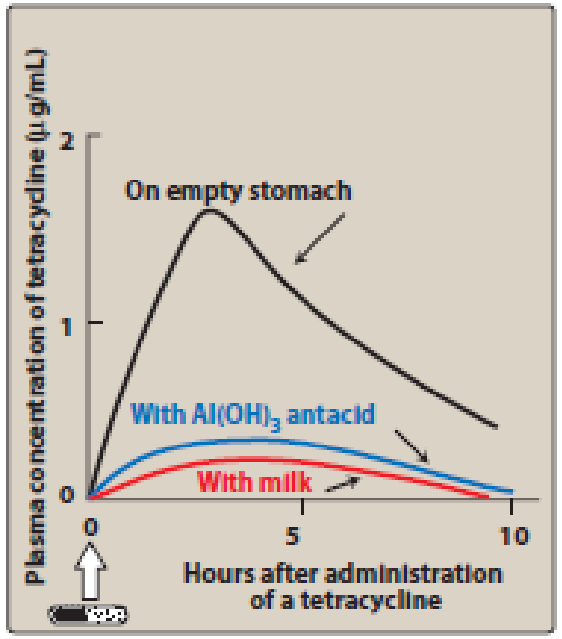
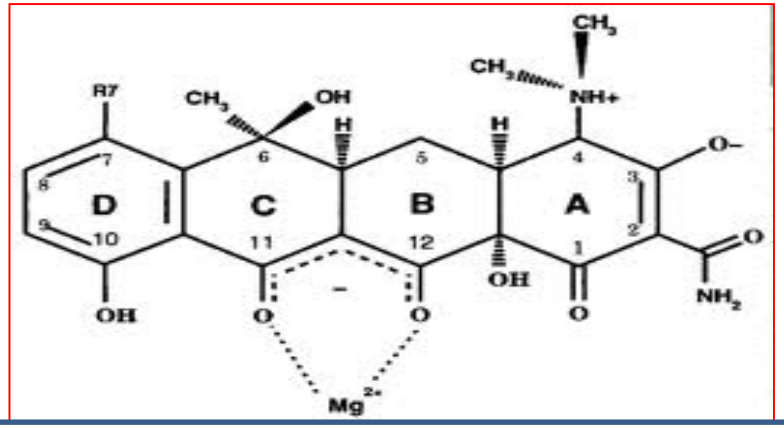


Figure 39.5
Effect of antacids and milk on the absorption of tetracyclines.



Distribution

- The tetracyclines concentrate in the liver, kidney, spleen, and skin (used for acne).
- Tetracyclines cross the placenta to reach the fetus. As a result of chelation with calcium, tetracyclines are bound to—and damage—growing bones and teeth and are also excreted in breast milk.
- Tetracyclines are distributed widely to tissues and body fluids except for cerebrospinal fluid (only doxycycline and minocycline enters the CSF in sufficient concentrations).

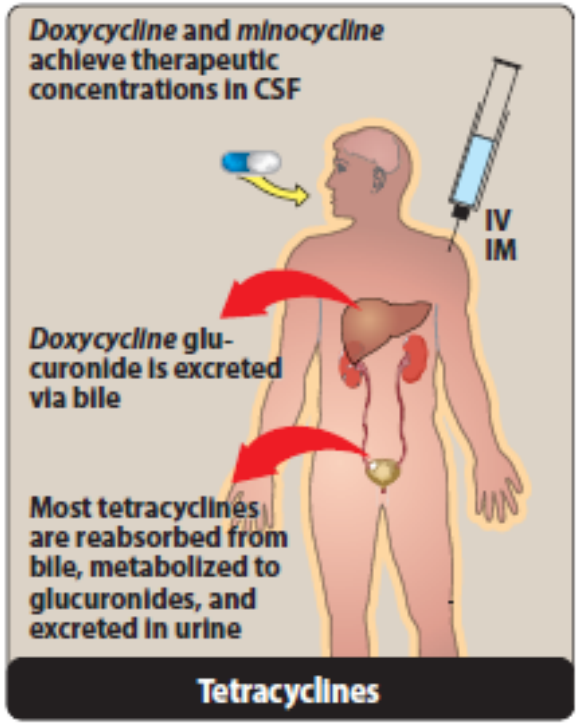
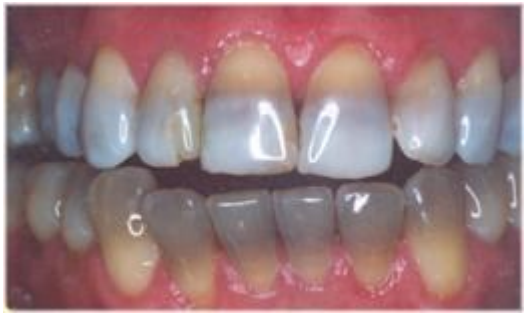


Figure 39.4
Administration and fate of tetracyclines. CSF = cerebrospinal fluid.



Elimination

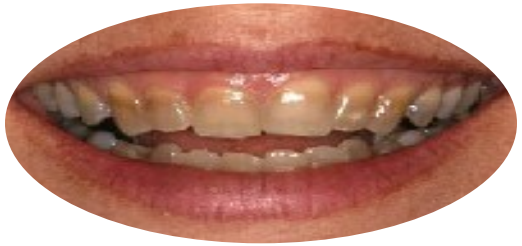
- Metabolized and conjugated in the liver to form soluble glucuronides.
- Carbamazepine, phenytoin, barbiturates, and chronic alcohol ingestion may shorten the half-life of doxycycline by 50% due to induction of hepatic enzymes that metabolize the drug.
- The parent drug and/or its metabolites are secreted into the bile
- Most tetracyclines are reabsorbed via enterohepatic circulation and enter the urine by glomerular filtration
- Obstruction of the bile duct and hepatic or renal dysfunction can increase their half-lives.

- **Doxycycline and tigecycline**, in contrast to other tetracyclines, are eliminated by **nonrenal mechanisms**, do not accumulate significantly, and require no dosage adjustment in renal failure.

Tetracyclines-Adverse effects

- **Gastric discomfort**: it results from irritation of the gastric mucosa and is often responsible for noncompliance in patients treated with these drugs. This discomfort can be controlled if the drug is taken with foods other than dairy products.

- **Deposition in the bone and primary dentition:** occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth resulting in brownish or yellowish discoloration.



- **Phototoxicity.** Systemically administered tetracyclines, especially demeclocycline and tetracycline, can induce **sensitivity to sunlight or ultraviolet light**, particularly in fair-skinned persons. Patients should be advised to wear adequate sun protection.

- **Vestibular problems**: These side effects (for example, dizziness, nausea, and vomiting) occur particularly with **minocycline.**

- **Superinfections**: Overgrowths of Candida and overgrowth of Clostridium difficile

Contraindications: The tetracyclines should not be used in pregnant or breast-feeding women or in children less than 8 years of age.

III. Clindamycin

- It has a similar spectrum as erythromycin+ B.fragilis

- Clindamycin is used primarily to treat infections caused by **gram-positive** organisms, including MRSA, streptococcus, and anaerobic bacteria.

As well it is also used to treat:

1. Bone and joint infections
2. Intra-abdominal sepsis
3. Topical clindamycin is used for treatment of acne vulgaris (topical gel, topical lotion, topical solution) And Treatment of bacterial vaginosis (vaginal cream, vaginal suppository)

Adverse reaction: **Diarrhea** - Pseudomembranous colitis due to C.difficile **[US Boxed Warning].**

TT: metronidazole or vancomycin.

STOP IT IF ANY DIARRHEA OCCURS

IV. Aminoglycosides

Ex. Amikacin, Tobramycin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Streptomycin

- Aminoglycosides are derived from either Streptomyces sp. (have –**mycin** suffixes) or Micromonospora sp. (end in –**micin**).

- They are bactericidal.
- Reach inside bacterial cells by
  - Diffusion through porins of G- (polycationic) to periplasmic membrane
  - Oxygen-dependent transport system across the cell membrane (therefore AGs are used only for aerobic G-)

Therapeutic Uses

1. Gram –ve bacillary infections specially septicemia and pelvic abdominal sepsis

   Caused by PEcK & P. aeroginosa

   Gentamicin + Beta lactam and or metronidazole

2. Bacterial endocarditis: Gentamicin+ benzyl penicillin – Strept.& enterococci

   and Gentamicin + cloxacillin – Staph

3. Other infections as TB and brucellosis-Streptomycin

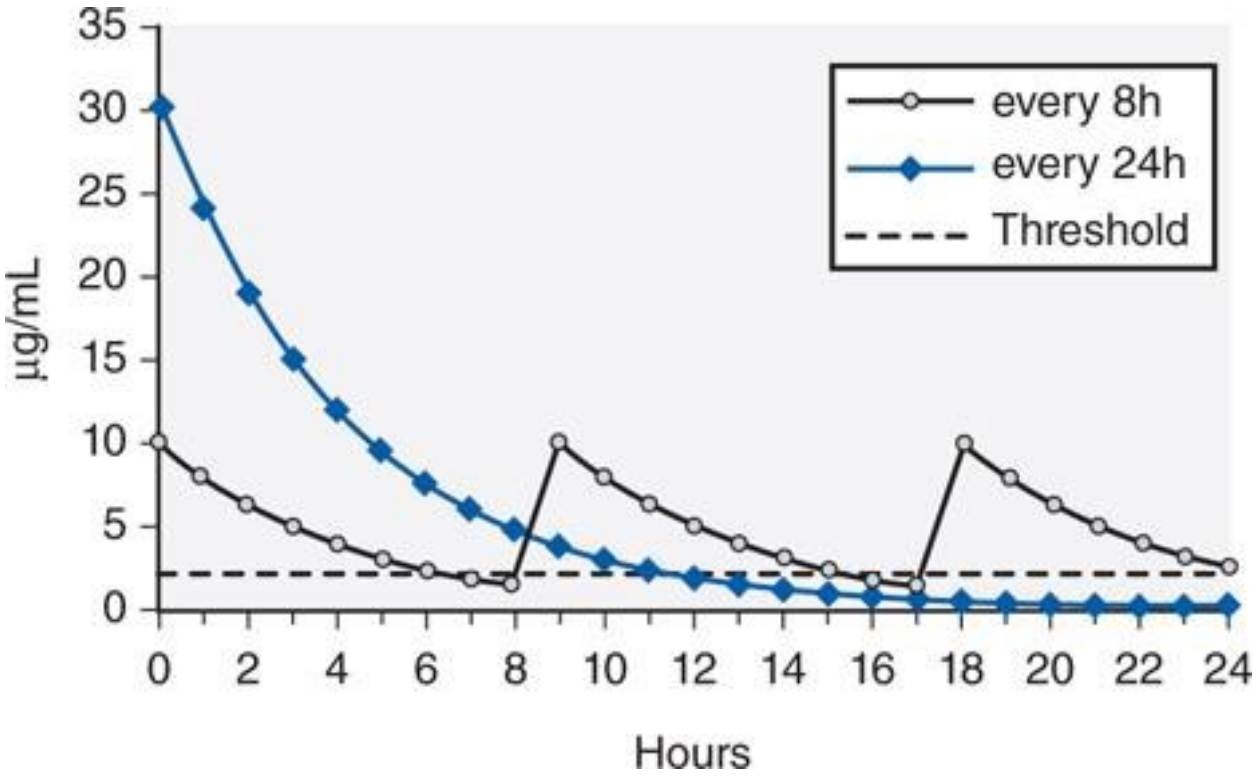
4. Topical use – Neomycin, too toxic for systemic use, as eye & ear drops or orally to sterilize bowel

Pharmacokinetics of AGs

Administration:

- Highly polar….No absorption after oral administration….All AGs must be given IV or IM
- *Neomycin* is limited to topical application for skin infections because of its nephrotoxicity
- The bactericidal effect of AGs is **concentration -dependent**; that is, the greater the concentration of drug, the greater the rate at which the organisms die (For AGs, the target Cmax is eight to ten times the MIC).
- AGs have a **postantibiotic effect**
  - No or very little drug level detectable in blood, but there still seems to be inhibition of bacterial re-growth
  - This is due to strong, irreversible binding to the ribosome, and remains intracellular long after blood levels drop
- Because of these properties, extended interval dosing (a single large dose given once daily) is now more commonly utilized than divided daily doses. This reduces the risk of nephrotoxicity and increases convenience with comparable efficacy with traditional, intermittent dosing.

Comparison of single-dosee and divided dose regimens for gentamicin



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Pharmacokinetics of AGs

Distribution:

- Levels achieved in most tissues are low (because of AGs polarity).
- High concentrations accumulate in the renal cortex and in the endolymph and perilymph of the inner ear (nephrotoxic and ototoxic)

Excretion:

- Rapidly excreted into the urine, predominantly by glomerular filtration
- Accumulation occurs in patients with renal failure and requires dose modification

Side Effects of AG

- **There is a significant variability in the relationship between the dose administered and the resultant plasma level in blood. Therefore, it is important to monitor plasma levels of *AGs to avoid concentrations that cause dose-related toxicities.***

- **Ototoxicity:** related to high peak plasma levels and the duration of treatment
- **Nephrotoxicity**
- **Neuromuscular paralysis:** Prompt administration of *calcium gluconate* or *neostigmine can reverse the block that causes neuromuscular* paralysis
- **Allergic reactions:** Contact dermatitis is a common reaction to topically applied *neomycin*

- Because ototoxicity has been reported after fetal exposure, the aminoglycosides should not be given in pregnancy unless their potential benefits are judged to outweigh risk.

V. Cloramphenicol

- Active against a wide range of G+ & G – (including most anaerobic organisms) and Ricketssia.
- Because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist except for topical **treatment of bacterial conjunctivitis** (because of its broad spectrum and its penetration of ocular tissues and the aqueous humor).
- It is <u>not</u> effective for chlamydial infections.

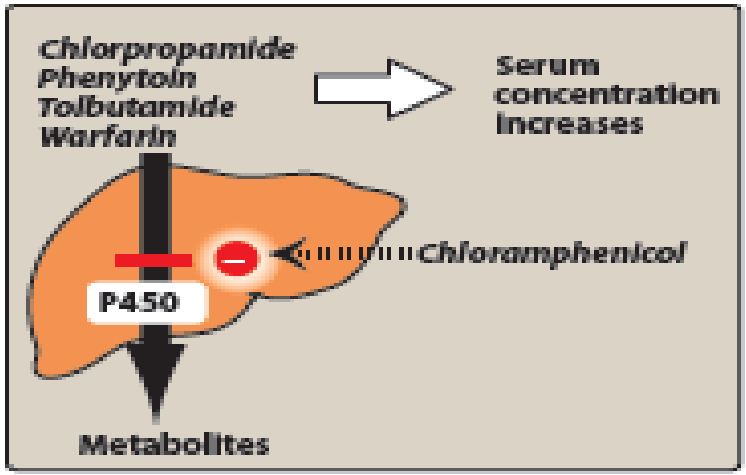
Chloramphenicol

Pharmacokinetics:

- Administered IV, widely distributed throughout the body including CSF
- **Metabolized to glucuronide derivative in liver and secreted in urine**

Interactions:

- Chloramphenicol inhibits cytochrome P450
- Blocks the metabolism of warfarin, phenytoin, tolbutamide, and chlorpropamide.



Adverse effects of Chloramphenicol

✓ Bone marrow suppression and idiosyncratic aplastic anemias **[US Boxed Warning]**

Due to some similarity of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating chloramphenicol levels producing bone marrow toxicity.

✓ Gray baby syndrome (Occurs in neonates if the dose of chloramphenicol is not properly adjusted)

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 vascular collapse.

VI. Oxazolidinones

Linezolid : Used for serious infections caused by resistant G+ organisms, such as MRSA, VRSA , VRE , and penicillin resistant streptococci.

- Its primary clinical use is against drug-resistant gram-positive organisms.
- Is completely absorbed after oral administration. An IV preparation is also available.

- Adverse effects
  - N/V/D.
  - Thrombocytopenia-monitor full blood count weekly.
  - Avoid tyramine-containing food
  - Severe optic neuropathy (rare)

VII. Streptogramins

- Derived from a streptomycete then chemically modified
- **Quinupristin-dalfopristin** is a combination of two streptogramins in a 30:70 ratio.
- Used for vancomycin-resistant Enterococcus faecium (G+) **(VRE)**
- Bactericidal

MOA:

- Each component of this combination binds to a separate site on the 50S bacterial ribosome, forming a stable ternary complex
- Synergistically interrupt protein synthesis

Streptogramins

Pharmacokinetics

- IV
- Penetrates macrophages and polymorpho nucleocytes (important because VRE are intracellular)

Adverse effects

1. Infusion-related events, such as pain at the infusion site
2. arthralgia-myalgia syndrome.
3. Hyperbilirubinemia

Questions??