

# Pharmacology of Antibiotics: Protein Synthesis Inhibitors

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I am available to groups and individuals for pharmacology help and discussions by appointment.

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After completing the preparation materials, students should be able to:

1. Correlate the pharmacokinetic properties of each of the classes of protein synthesis inhibitors with their clinical relevance for optimizing patient care.
2. Identify and differentiate the mechanisms of action, resistance, and cross-resistance of each of the protein synthesis inhibitors.
3. Construct a chart or mind map of the spectrums of activity for each of the protein synthesis inhibitors correlated with their therapeutic applications.
4. Apply your knowledge of the mechanisms of drug-drug, drug-disease, and drug-food interactions, potential adverse drug reactions, and contraindications of each of the protein synthesis inhibitors when given a case vignette.

Mechanisms  
Mechanisms  
Mechanisms

Chunk  
concepts  
together

Apply  
your  
knowledge

## Preparation Materials (links are in the CPG and on the next slide)

### Required

- ScholarRx Bricks | Practice Questions and Clinical Vignettes

### Highly relevant optional materials:

- Video lecture | Dr. Goldstein's Word handout | Guided reading questions
- Textbooks and Examination Review Books (please see next slide)

### SUGGESTIONS:

- *Use the resources that work best for you.*
- *You do not need to study all of them. (ScholarRx Bricks & Practice Questions are required.)*
- *Work through the GUIDED READING QUESTIONS with pen/pencil and paper.*

*Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.*

- *Practice questions (not graded): Simple Recall and Case Vignettes*

## Links to Materials

Name of Discipline/ Organ System: General Microbiology > Antimicrobial Agents

Title of Brick(s): Antibacterial Drugs > Protein Synthesis Inhibitors

Link: <https://exchange.scholarrx.com/brick/protein-synthesis-inhibitors>

Access Medicine Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 44: Tetracyclines, Macrolides, Clindamycin, Chloramphenicol, Oxazolidones, & Pleuromutilins

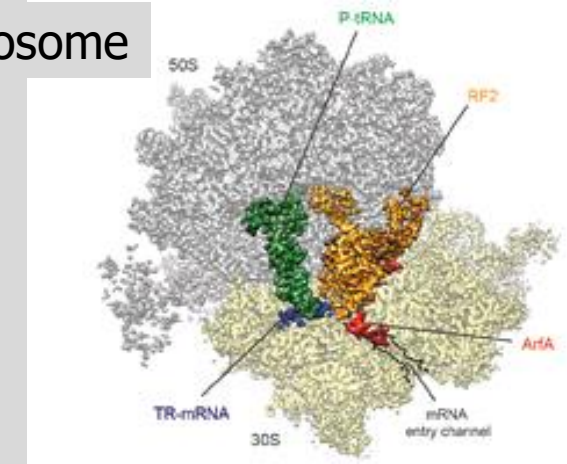
<https://accessmedicine.mhmedical.com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281754666>

Access Medicine Katzung's Basic & Clinical Pharmacology: Examination & Board Review, 13e, 2024; Chapter 44: Tetracyclines, Macrolides, Clindamycin, Chloramphenicol, & Oxazolidones

<https://accessmedicine.mhmedical.com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285597887>

LWW Health Libraries Medical Education: Lippincott's Illustrated Reviews, Pharmacology, 8e, 2023; Chapter 30: Protein Synthesis Inhibitors

<https://meded-lwwhealthlibrary-com.idm.oclc.org/content.aspx?sectionid=253328689&bookid=3222>



## Key points: What you need to know and understand

- Several antibiotics produce antimicrobial effects by targeting bacterial ribosomes and inhibiting bacterial protein synthesis.
- Bacterial ribosomes are composed of 30S and 50S ribosomal subunits. They differ structurally from mammalian cytoplasmic ribosomes, which are composed of 40S and 60S subunits. However, mitochondrial ribosomes are similar to bacterial ribosomes in structure and size.
- In general, the antibacterial protein synthesis inhibitors are selective for the bacterial ribosome, minimizing potential adverse effects that would occur with inhibition of host protein synthesis.
- Protein synthesis inhibitors are bacteriostatic for the most part. Some have bactericidal activity against some bacteria. Aminoglycosides are bactericidal.
- Some protein synthesis inhibitors, notably chloramphenicol and linezolid and possibly others, can cause dose-dependent toxic effects due to inhibition of mitochondrial protein synthesis in host cells.

### Definitions:

- The 30S and 50S ribosomes form the nucleosome complex that translates mRNA into protein.
- The 16S rRNA of the 30S ribosome is required for the initiation of protein synthesis and stabilization of correct codon-anticodon pairing in the A site of the ribosome during mRNA translation.
- The 23S rRNA of the 50S ribosome makes up the peptidyl transferase center, which catalyzes the polymerization of amino acids through peptide bonds.

**Tetracyclines** enter susceptible organisms by passive diffusion and by an energy-dependent transport protein mechanism unique to the bacterial inner membrane.

- Tetracyclines concentrate inside the bacterial cells and prevent protein synthesis by binding reversibly to the A site of the 30S ribosomal subunit, which prevents the binding of aminoacyl-tRNA to the mRNA-ribosome complex. This prevents addition of amino acids to the growing peptide chain.
- Tetracyclines are effective against a broad spectrum of microorganisms – aerobic gram-positive and gram-negative bacteria, some anaerobes, spirochetes, atypical bacteria, rickettsia and protozoa.

**Many strains of bacteria that cause common infections are now resistant.**

- Mechanisms of resistance to tetracyclines are: 1) increased efflux or impaired influx, 2) ribosome protection by production of proteins that interfere with drug binding to the ribosome, and 3) enzymatic inactivation (less important than the first two mechanisms).
- Tet(AE) efflux pump expressed by gram-negative species confers resistance to tetracycline, doxycycline, and minocycline, but not to tigecycline and the other newer agents, which remain effective.
- Tet(K) efflux pump confers staphylococcal resistance to tetracycline, but not to doxycycline, minocycline, tigecycline and the other newer agents.
- Tet(M) ribosomal protection protein expressed by gram-positives confers resistance to tetracycline, doxycycline, and minocycline but not to the newer agents.
- *Pseudomonas aeruginosa* and *Proteus* spp are intrinsically resistant to all tetracyclines due to chromosomally-encoded MDR efflux pumps.

## Key points

- Tetracyclines are absorbed adequately from the GI tract. Tetracycline's bioavailability is ~75-85% - some of the dose stays in the gut lumen and can alter the gut flora. Doxycycline and minocycline have nearly complete absorption. Administration with dairy products or other products containing divalent and trivalent cations form non-absorbable chelates, which decreases drug absorption, therefore, bioavailability. Doxycycline and minocycline are available in oral and intravenous forms. Tigecycline and eravacycline are IV only, omadacycline oral and IV, and sarecycline oral only.
- Tetracyclines bind plasma proteins to a moderate degree. They are widely distributed to body fluids and tissues, except CSF (concentrations 10-25% of plasma concentrations). They cross the placenta and are excreted in breast milk. Tetracyclines bind to calcium in growing long bones and teeth. Permanent tooth discoloration may occur, particularly with repeated or long-term exposure.
- Tetracyclines are excreted in urine and feces as unchanged drug and metabolites. Doxycycline and tigecycline are excreted mainly via the biliary system (nonrenal route) and do not accumulate in renal failure. Half-lives vary according to the individual drugs.

## Key points

- The tetracyclines have similar efficacy. Doxycycline is the most frequently used agent in the class. It can be administered twice daily, given orally and IV, and achieves reasonable concentrations when given with food (but not with di-, trivalent cations).
- Doxycycline is the drug of choice for the treatment of Lyme disease (*Borrelia*, a spirochete) and Rocky Mountain spotted fever (*Rickettsia rickettsii*) and other zoonotic infections. Tetracyclines have excellent activity against the atypicals, *Mycoplasma pneumoniae* and *Chlamydia* spp. Doxycycline is used in combination with other antibacterial agents against zoonoses and *Helicobacter pylori* (peptic ulcer disease).
- Minocycline is an alternative for eradication of meningococcal carrier state (resistance increasing). Demeclocycline is not used as an antibiotic. It has been used in the treatment of syndrome of inappropriate antidiuretic hormone, due to its side effect (nephrogenic diabetes insipidus).
- Tigecycline, eravacycline, and omadacycline (oral) have a broad spectrum of activity, including against tetracycline-resistant strains. Sarecycline (oral) has a narrow spectrum: *Cutibacterium acnes* and other acne-causing gram-positive bacteria with little to no activity against gram-negative bacteria. It was specifically designed to treat acne.

## Key points

- Most of the tetracyclines' adverse effects are due to direct toxicity or alteration of the microbiota. Hypersensitivity reactions (skin rashes, drug fever) are uncommon.
- GI discomfort due to direct local irritation – nausea, vomiting, diarrhea – are the most common adverse effects. Secondary infections, ie, *C. difficile* infection, due to alteration of the normal GI flora. Phototoxicity that can result in severe sunburn in sun-exposed skin. Impaired hepatic function is seen especially in pregnancy or patients with preexisting liver disease. Increased BUN/azotemia can occur in patients with renal impairment. Dizziness, vertigo, tinnitus, and benign increase intracranial pressure reported. Intravenous injection can cause venous thrombosis.

### Drug-specific adverse effects:

- Minocycline – vestibular toxicity (reversible) and blue-gray or brown discoloration of skin and mucous membranes with long-term use.
- Demeclocycline – renal insensitivity to ADH (nephrogenic diabetes insipidus)
- Tigecycline – increase in all-cause mortality and acute pancreatitis
- Sarecycline is well tolerated with a low potential for adverse effects (nausea, vulvovaginal candidiasis).

## Key points

**Macrolides** reversibly bind the 23S rRNA of the 50S subunit near the peptidyl transferase center, which blocks the polypeptide exit tunnel, and the unfinished peptide dissociates from the ribosome.

- Macrolides have excellent activity against streptococci and staphylococci (resistance is increasing), some gram-negative respiratory pathogens (resistance is increasing) and atypical bacteria, *Mycoplasma* (resistance is increasing), *Chlamydia* spp, and *Legionella*. They are generally bacteriostatic.
- Resistance mechanisms are: 1) ribosomal binding site modification by constitutive or inducible methylase production or chromosomal mutation expressing methylase (*erm* gene), 2) reduced permeability of the cell membrane or active efflux, 3) production of esterases by Enterobacterales that hydrolyze the drugs. Methylase production and efflux are the most important mechanisms of resistance. Cross-resistance occurs between the macrolides. Cross-resistance due to methylation of the ribosomal binding site occurs between the macrolides, clindamycin, and streptogramin B, which is called MLS<sub>B</sub> and is encoded by the *erm* gene.

- Erythromycin base is destroyed by stomach acid. Clarithromycin, azithromycin, and the salt forms of erythromycin are stable in stomach acid and well absorbed. Erythromycin and azithromycin are in oral and IV formulations; clarithromycin is oral. They are widely distributed in body fluids and tissues. The drugs concentrate in neutrophils and macrophages. They cross the placenta.
- Erythromycin and clarithromycin are substrates and strong inhibitors of CYP3A4. Azithromycin metabolism by CYP3A4 is minimal and it does not inhibit the drug metabolizing enzymes.
- Azithromycin is concentrated and excreted in the bile as active drug. Erythromycin is excreted in the bile as active drug and metabolites. Clarithromycin and its metabolites are excreted mainly in urine (dose adjustment in renal impairment).
- Azithromycin is sequestered in tissues and has a very long half-life (~70 hours).
- Azithromycin and clarithromycin are the most frequently prescribed macrolides.
- They are used in the treatment of respiratory infections, sexually transmitted infections, and other common infections. Macrolide resistance is increasing. NOTE: The CDC no longer recommends ceftriaxone-azithromycin dual therapy for uncomplicated gonorrhea as a strategy for preventing ceftriaxone resistance and possible *Chlamydia* coinfection. Erythromycin is used as a prokinetic agent (increase GI motility) by acting on motilin receptors in the gut. Topical uses include ocular infections and acne.

## Key points

- All macrolides can increase the QT interval on EKG due to their effect on cardiac potassium channels, potentially resulting in ventricular fibrillation (torsades de pointes). Avoid in patients with proarrhythmic conditions, and with other drugs that cause QT prolongation or increase macrolide levels.
- Nausea, vomiting, and diarrhea are common with erythromycin. Azithromycin and clarithromycin are better tolerated.

**Clindamycin** binds the 23S rRNA on the 50S ribosome near the peptidyl transferase center and interferes with transfer of amino acids to the growing peptide chain, interrupting protein synthesis.

- Clindamycin is used primarily in the treatment of streptococcal, staphylococcal (including MRSA) and anaerobic infections. It is bacteriostatic.
- Resistance mechanisms are, 1) modification of the receptor site by constitutively expressed methylase (MLS<sub>B</sub> expressed by the *erm* gene) (see macrolides), 2) mutation of the ribosomal receptor site, and 3) enzymatic inactivation of clindamycin.
- Bacterial strains harboring inducible iMLS<sub>B</sub> methylase will appear susceptible to clindamycin. The D-zone test is recommended for infections caused by *Staphylococcus*, *S. pneumoniae*, and beta-hemolytic streptococci to determine if the iMLS<sub>B</sub> determinant is present. If present, constitutive production of methylase may be selected out, resulting in clindamycin therapy failure or recurrence of infection.

- Clindamycin is oral and IV, distributes well in body fluids but low concentrations in CSF. It penetrates well into abscesses, bones and joints, and is actively taken up into phagocytic cells. It is converted by CYP3A4 to inactive metabolites; it is not a CYP inhibitor or inducer. Small amounts of active drug and metabolites are excreted urine and feces. Dose adjustment for renal insufficiency is not necessary. It has a half-life of ~3 hours (2 to 4 divided doses per 24 hours).
- Clindamycin has been associated with severe *C. difficile* colitis (remember: all antibiotics can cause *C. difficile* infection). Diarrhea (non-*C. difficile*), nausea, and skin rashes are common. Impaired liver function and neutropenia sometimes occur. Pain / abscess with IM injection.

**Chloramphenicol** is a lipophilic broad-spectrum antibiotic restricted to treatment of life-threatening infections that have no alternatives because of its toxicities.

- It reversibly binds the 23S rRNA of the 50S ribosome in the peptidyl transferase, interferes with tRNA binding to peptidyl transferase, which prevents peptide bond formation between the incoming amino acid and the growing peptide chain. It is bacteriostatic.
- Resistance is due to plasmid-mediated acetyltransferase that covalently acetylates the drug. Efflux and ribosomal mutation have been described.
- The main uses are rickettsial infection (alternative to doxycycline), meningococcal meningitis (bacteriostatic), and typhoid fever
- Chloramphenicol also inhibits mitochondrial protein synthesis. Serious potential adverse effects include bone marrow toxicity, idiopathic aplastic anemia (low incidence, high fatality rate), gray syndrome affecting neonates and elderly, secondary infection, and GI adverse effects. It is a CYP2C9 inhibitor.

## Key points

### **Chloramphenicol pharmacokinetics knowledge is important for optimal clinical outcomes:**

- Chloramphenicol is administered IV. It is lipophilic and poorly soluble in water so is formulated as the succinate salt, which is rapidly hydrolyzed by esterases to active chloramphenicol. A portion of the salt form is rapidly cleared through the kidney before conversion to the active drug.
- It is moderately bound to plasma proteins. Free chloramphenicol is widely distributed in body fluids and tissues with high concentrations in CSF.
- Chloramphenicol is converted to inactive glucuronide metabolites.

### **Important – About babies:**

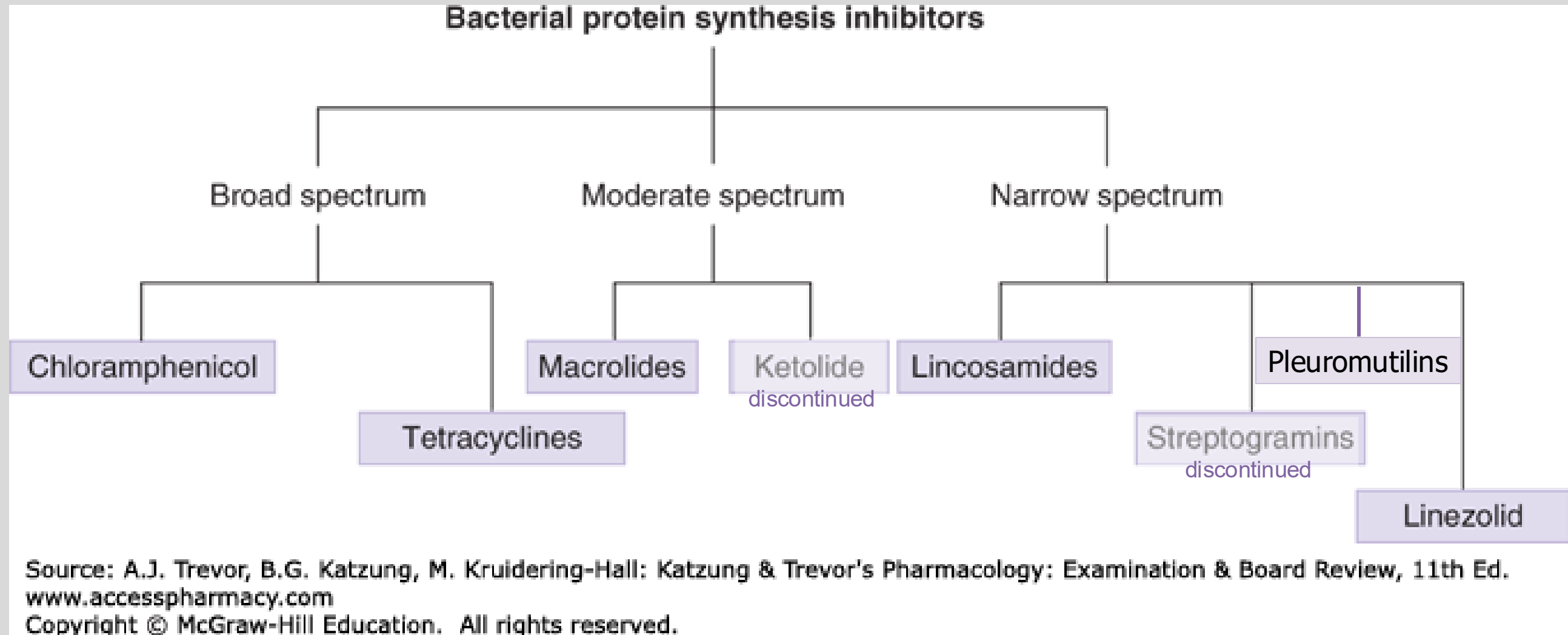
- Neonates have immature metabolizing capacity and renal function.
- Immature UDP-glucuronyltransferase → reduced ability to metabolize chloramphenicol → potential for drug accumulation
- Reduced levels of plasma proteins → higher fraction of free drug
- Immature kidney function → ↑ plasma concentrations of drug
- Increased drug concentration → increased risk of concentration-dependent toxicity:

**Gray (baby) syndrome** with lethargy, cyanosis, respiratory depression, cardiovascular collapse, and death.

**Linezolid** binds to a unique site on the 23S rRNA of the 50S subunit and perturbs the peptidyl transferase center, which affects tRNA positioning and binding to the A site, which inhibits the formation of the 70S initiation complex.

- Point mutations of the 23S rRNA genes encoding the binding site can lead to resistance (the most common resistance mechanism). Resistance among normally susceptible microorganisms remains relatively low. There is no cross-resistance with other drug classes.
- It is active against **gram-positive** MDR streptococci, staphylococci, enterococci, and gram-positive rods corynebacteria, *Listeria monocytogenes*, and *Nocardia*. Bactericidal against streptococci. Bacteriostatic against staphylococci and enterococci. Gram-negative and anaerobic organisms are intrinsically resistant.
- Linezolid is formulated for IV or oral administration, which has ~100% bioavailability. It is widely distributed in body fluids and tissues with high CSF concentrations. Metabolism is minimal (inactive metabolites). Excreted primarily in urine. Half-life is up to 3 hours; twice daily dosing.
- It is used in the treatment of MDR gram-positive infections.
- It is generally well tolerated. The main toxicities are thrombocytopenia, neutropenia, anemia, mitochondrial toxicities – peripheral neuropathies and lactic acidosis.
- Linezolid is a weak MAO inhibitor and is associated with serotonin syndrome in patients taking MAO inhibitors or serotonin reuptake inhibitors.

# Classes of Common Protein Synthesis Inhibitors

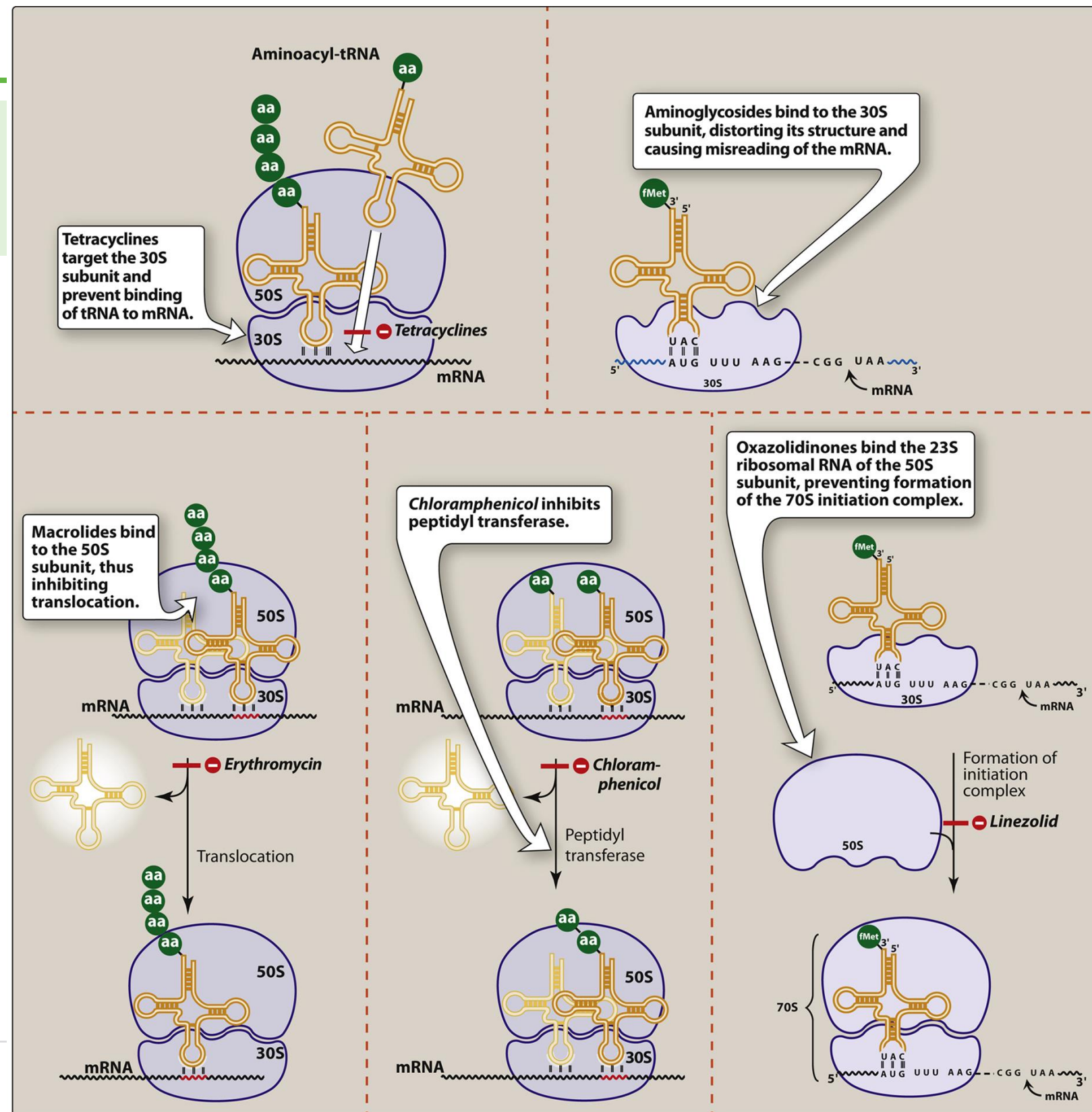


The following are not included in this lecture. If you are interested, the pharmacology of these drugs is described in the Notes Handout.

- The marketing of the streptogramins product, quinupristin/dalfopristin, has been discontinued.
- The pleuromutilin, lefamulin, binds the A- and P-sites of the peptidyl transferase, which prevents tRNA binding and peptide transfer for the treatment of community acquired pneumonia caused by *S. pneumoniae*, MSSA, *H. influenzae*, and *atypicals*.

From: **30 Protein  
Synthesis Inhibitors**

Lippincott® Illustrated Reviews:  
Pharmacology 8e, 2023



**Legend:**

Mechanisms of action of the  
various protein synthesis  
inhibitors.

Date of download: 8/22/2023


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## Antibiotic Resistance

**Intrinsic resistance:** The microorganism has features that make it inherently resistant

**Acquired resistance:** Normally responsive organism acquires spontaneous, random chromosomal mutations, or transfer of resistance genes from other bacteria.

1. Drug does not reach target
2. Drug inactivation
3. Target alteration
4. Organism expresses alternative metabolic pathways

 ***Frequent or long-term use of a particular drug increases the risk of microbial mutations that produce resistance to the drug.***

It is the responsibility of all health care professionals on a patient-to-patient basis to combat resistance by following stewardship guidelines and educating patients.

- Tetracyclines

Semisynthetic:

- \* Tetracycline

- Oxytetracycline

- \* Doxycycline

- \* Minocycline

- \* Demeclocycline

Synthetic:

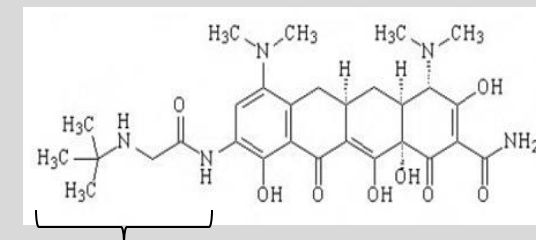
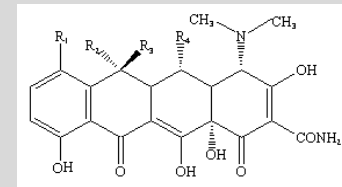
- \* Tigecycline (glycylcycline)

- Eravacycline (halogenated)

- Omadacycline

- Sarecycline

(The pharmacology of eravacycline, omadacycline, and sarecycline is described in the Pharmacology of the Protein Synthesis Inhibitors notes handout.)



glycylamido  
group

PK-PD Profile: Data is limited

Bacteriostatic

## Tetracyclines Class Pharmacokinetics Properties, in brief

<p>Oral, acid stable</p> <p>I.V.: Doxy- and Mino-Tigecycline (only I.V.)</p> <p>Bioavailability:</p> <p>Tetra- variable ~75-85%</p> <p>→ <b>Doxy- 95%   Mino- 100%</b></p> <p>Omadacycline ~35%</p>	<p>Protein binding 60-90%</p> <p>Widely distributed in body fluids</p> <p>Deposits in growing bones and tooth enamel.</p> <p>Doxycycline has low affinity for calcium.</p> <p>Avoid TCNs in pregnant women, children &lt;8 years</p> <p>→ <b>Exception:</b> Doxycycline ≤21 days of treatment</p>	<p><b>All:</b></p> <p>Chelation in GI tract by:</p> <p>Di- and trivalent cations</p> <p>Avoid antacids and mineral supplements</p> <p><b>Food:</b></p> <p>TCN, demeclo-, omadacycline: Empty stomach</p> <p>Doxy-, Mino-, Sarecycline</p> <p>May be taken with food, including dairy products</p>
<p>TCN, Doxy-: not metabolized</p> <p>Mino-, Tige-: hepatic</p> <p>Excreted in urine,</p> <p>→ except <b>Doxy in feces</b></p>	<p><b>Tetracyclines that remain in the gut lumen modify intestinal flora.</b></p>	
<p>t<sub>1/2</sub> 9-16h, drug-specific</p> <p>Tigecycline ~40 h</p>		

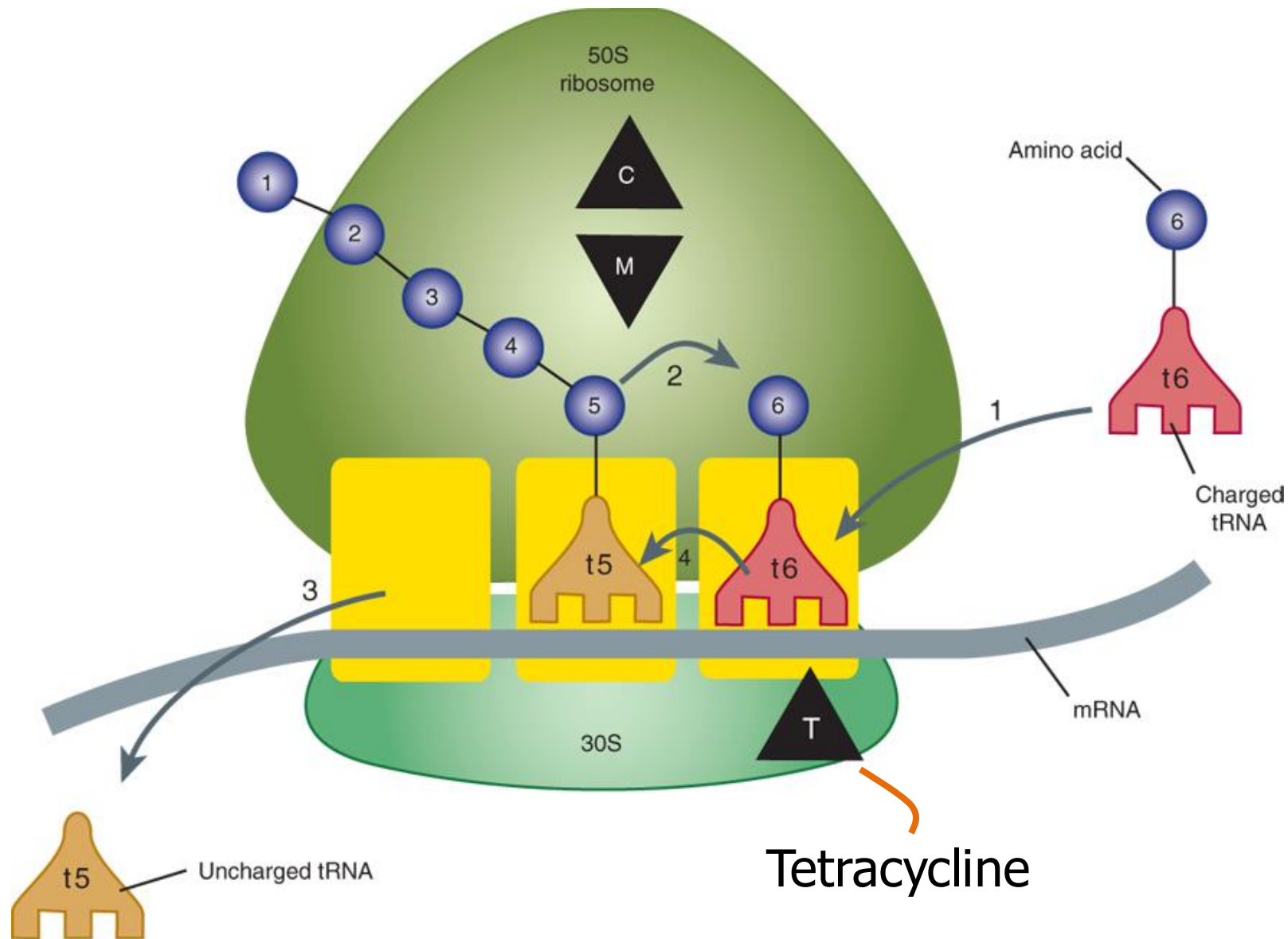


[http://id3442.securedata.net/cosmetic-dentistry/tetracycline\\_stained\\_teeth.htm](http://id3442.securedata.net/cosmetic-dentistry/tetracycline_stained_teeth.htm)

## Tetracycline-stained teeth

Doxycycline binds calcium less avidly and has not been shown to cause staining of permanent teeth.

The American Academy of Pediatrics now supports the use of doxycycline in young children if it is administered for  $\leq 21$  days since the risk is low when short courses are used.



Source: Bertram G. Katzung, Todd W. Vanderah:  
Basic & Clinical Pharmacology, Fifteenth Edition  
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**Tetracycline Mechanism of Action**  
(T) Tetracyclines bind to the acceptor site on the 30S ribosome and prevent the aminoacyl-tRNA from accessing the acceptor site on the mRNA-ribosome complex



Tetracyclines prevent addition of amino acids to the growing peptide chain.

Figure adapted by LG

# Tetracyclines Mechanisms of Resistance

<b>Active transport protein pump</b> Impaired influx or Increased efflux	<b>Ribosomal protection proteins (RPPs)</b> Production of proteins that interfere with tetracycline binding to the ribosome	Enzymatic inactivation
<ul style="list-style-type: none"><li>– Tet(K) efflux pump: Staphylococcus confers <b>resistance to tetracycline</b> but not to the others</li><li>– Tet(AE) efflux pump: Gram-negative bacteria confers <b>resistance to TCN, doxy- and mino-</b> but not to tigecycline, eravacycline, or omadacycline</li></ul>	<p>Tet-type RPPs</p> <p>Several classes expressed by gram-positive and gram-negative bacteria confer resistance</p> <p>Tet(M): Streptococci, staphylococci, and enterococci resistance to tetracycline, doxycycline, and minocycline but not the newer agents.</p>	Minor importance

**Intrinsic resistance** to all tetracyclines:

*Proteus, P. aeruginosa* intrinsic resistance by chromosomally encoded MDR efflux pumps

Mnemonics	<b>TetK:</b> K almost looks like X – efflux K sounds like C – Cocci ( <i>S. aureus</i> is a G+ coccus)	<b>Tet(AE):</b> E=Efflux A=aerobic; E=enteric = Enterobacterales	<b>TetM:</b> M is in ribosoMe
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Broad spectrum, Bacteriostatic; Activity against susceptible gram-positive and gram-negative aerobic and anaerobic bacteria.

*Widespread resistance of bacteria causing common infections limits tetracyclines' clinical use.*

**Know the bugs and diseases in bold.**

**Doxycycline** is the most frequently used drug in the class.

Infection	Disease examples	Pathogen
<b>Zoonotic infections</b> Doxycycline is a first-line agent. Frequently combined with fluoroquinolone or aminoglycoside.	Anthrax Ehrlichiosis Leptospirosis <b>Lyme disease</b> , Relapsing fever <b>Plague</b> Psittacosis Q fever <b>Rocky Mountain spotted fever</b> <b>Tularemia</b> “rabbit fever”	<i>Bacillus anthracis</i> <i>Ehrlichia spp</i> <i>Leptospira interrogans</i> <b><i>Borrelia spp</i></b> (spirochete) <b><i>Yersinia pestis</i></b> <i>Chlamydia psittaci</i> <i>Coxiella burnetti</i> <b><i>Rickettsia ricketsii</i></b> <b><i>Fransicella tularensis</i></b>
<b>Respiratory infections</b> Doxycycline has good activity against respiratory pathogens	Community-acquired pneumonia Acute bacterial rhinosinusitis	<b><i>H. influenzae</i></b> <b><i>M. catarrhalis</i></b> <b><i>Mycoplasma pneumoniae</i></b> <b><i>C. pneumoniae</i></b>

Infection	Disease examples	Pathogen
<b>Skin and skin structure infections</b> <b>Mild, localized infection</b>	Acne vulgaris, severe (low dose)	<i>Propionibacterium</i>
	Various uncomplicated, community-acquired infections	<b>MSSA</b> <b>MRSA</b>
<b>GI infections</b>	Cholera	<i>Vibrio cholerae</i>
	Peptic ulcer disease 4-drug regimen	<i>Helicobacter pylori</i>
<b>Sexually transmitted diseases, serious</b> Doxy- may be an choice for monotherapy or used in combination with other active drugs for severe infections	Pelvic inflammatory disease, Salpingitis Endometritis Peritonitis Lymphogranuloma venereum Nonspecific urethritis	<b><i>Chlamydia trachomatis</i></b> (obligate intracellular)
	Syphilis, primary or secondary alternative to penicillin (x14-28 d)	<b><i>Treponema pallidum</i></b> (spirochete)
<b>Malaria</b>	Prophylaxis alternative (1x daily) Treatment with quinine	<i>Plasmodium</i> spp

Therapeutic uses	Contraindicated uses
<p>Complicated skin and skin structure infections:</p> <p>MRSA</p> <p>vancomycin-sensitive <i>E. faecalis</i></p>	<p>Do not use for the following infections:</p> <p>Hospital-acquired pneumonia (HAP)</p> <p>Healthcare-acquired pneumonia (HCAP)</p> <p>Ventilator-associated pneumonia (VAP)</p>
<p>Complicated intra-abdominal infections:</p> <p>Enterobacterales</p> <p>Gram-negative anaerobes (excellent activity)</p>	<p>Tigecycline v. comparator antibiotic in clinical trials demonstrated:</p> <ul style="list-style-type: none"> <li>➤ Lower efficacy,</li> <li>➤ Lower cure rates, and</li> <li>➤ Increased mortality.</li> </ul>
<p>Community-acquired bacterial pneumonia:</p> <p>Monotherapy <i>alternative</i> to both beta-lactams and fluoroquinolones due to association with increased mortality</p>	<p>Diabetic foot ulcers: Other agents are more effective.</p> <p><b>DEMECLOCYCLINE</b></p> <p>Not used for antibiotic properties.</p> <p>Causes nephrogenic diabetes insipidus.</p> <p>Historically used for SIADH treatment.</p>

## Tetracyclines / Tigecycline Adverse Effects

<p><b>Secondary infections <i>C. difficile</i>; <i>Candida</i></b> Modification of microbiota</p>	<p><b>GI</b> Nausea / vomiting / non-C. diff. diarrhea</p>
<p><b>Kidney</b> Increased blood urea nitrogen (BUN) / Azotemia (caution in patients with ↓ renal function) Fanconi syndrome with outdated TCN</p>	<p><b>Bones / Teeth</b> (TCNs chelate calcium) Deposit in bones/teeth of fetus, growing children TCNs are <b><i>contraindicated</i></b> in pregnancy, nursing infants, and children &lt;8 years old. Exception: Doxy now recommended ≤ 21 days</p>
<p><b>Hepatotoxicity</b> Rare but can be fatal</p>	<p><b>Skin</b> Photosensitivity, mild to severe</p>
<p><b>Rare but serious</b> Increased intracranial pressure (young/old) Thrombophlebitis (IV) Neutropenia, Thrombocytopenia</p>	<p><b>Hypersensitivity reactions</b> Reported (not common) Rash, fever, hepatitis, pneumonitis, angioedema, and anaphylaxis</p>

# Drug-specific Toxicities and Drug Interactions

## Drug-specific Toxicities

## Drug Interactions

### Minocycline

vestibular toxicity  
blue-gray or brownish discolorations of skin and mucous membranes with long-term use

### Decreased absorption

Antacids  
Di-/trivalent cations in food and supplements  
Bile acid binding resins

### Demeclocycline

nephrogenic diabetes insipidus  
–insensitivity of the kidneys to vasopressin, also known as antidiuretic hormone–

**Warfarin:** ↑ risk of bleeding due to injury to vitamin K producing bacteria in the gut  
**Oral contraceptives:** ↓ enterohepatic circulation of estrogen → ↓ blood levels of the hormone → may reduce the efficacy of the hormone

### Tigecycline

Increase in all-cause mortality when treating serious infections.  
Acute pancreatitis

### Combined toxicity

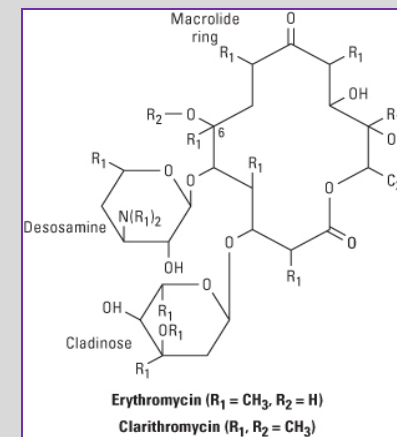
Oral retinoids (acne medicine) and tetracyclines both can cause increased intracranial pressure. The combination should be avoided.

## Macrolides

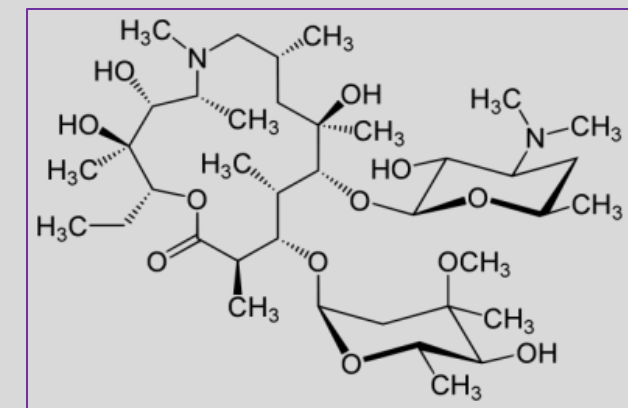
\*Erythromycin

\*Clarithromycin

\*Azithromycin



E, C: 14-membered  
ring structure  
Lactone, 2 deoxy sugars



Azithromycin: 15-membered  
ring structure  
Lactone, 2 deoxy sugars

PK-PD Profile:

Erythromycin  $T > \text{MIC}$

Clarithromycin and Azithromycin:

Clinical efficacy appears to be associated with  $\text{AUC/MIC}$

Bacteriostatic

# Macrolides Pharmacokinetics Key Points

<p>Erythromycin: Oral variable absorption; I.V.          Azithromycin: Oral, I.V. } bioavailability: ~50%          Clarithromycin: Oral</p>		<p>Widely distributed in tissues          Accumulate in pulmonary tissue, middle ear fluid,          and in phagocytic cells (PMNs and macrophages)</p>	
Hepatic metabolism		Excretion   t <sub>1/2</sub>	
<p>Erythromycin,          Clarithromycin:</p> <ul style="list-style-type: none"> <li>■ CYP3A4, P-gp substrates</li> <li>■ And strong CYP3A4, P-gp inhibitors</li> </ul> <p><b>High potential for drug interactions</b></p>	<p>Azithromycin:</p> <ul style="list-style-type: none"> <li>■ Minimal CYP3A4 metabolism</li> <li>■ Not a CYP3A4 inhibitor</li> <li>■ Does inhibit P-gp</li> </ul>	<p>Clarithromycin feces and urine, including active drug and active metabolite</p> <ul style="list-style-type: none"> <li>■ dose adjustment for renal impairment</li> </ul>	<p>Erythromycin, feces          Azithromycin, biliary</p> <ul style="list-style-type: none"> <li>■ No dose adjustment necessary for renal impairment</li> </ul>
		<p>t<sub>1/2</sub> Erythromycin ~2 h          t<sub>1/2</sub> Clarithromycin 3-9 h</p>	<p>t<sub>1/2</sub> Azithromycin ~70 h          1x daily dose          Tissue sequestration, prolonged antimicrobial effect</p>

## Proteins Synthesis Inhibitors:

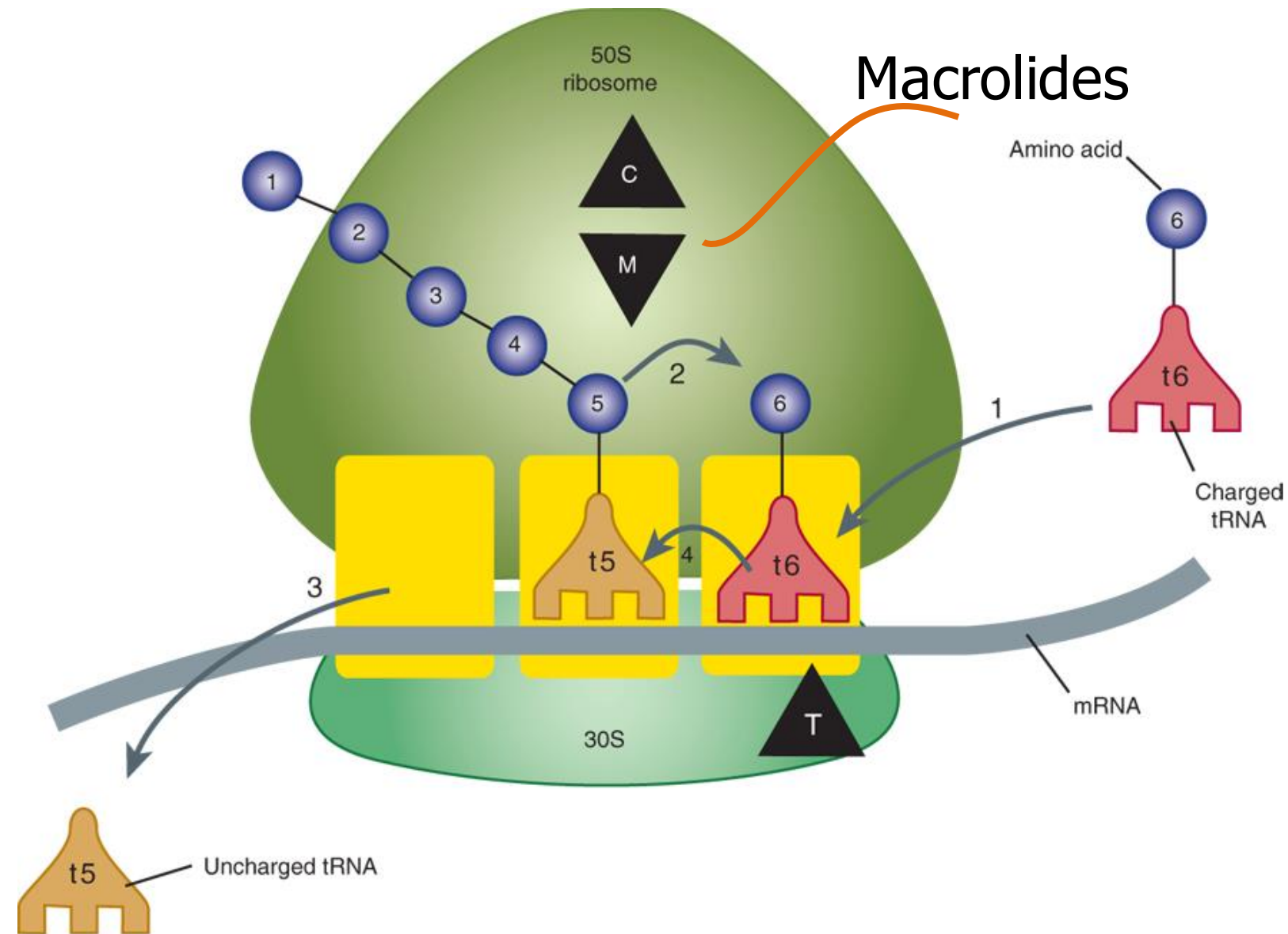
### Macrolides Mechanisms of Action

(M) Macrolides bind the 50S ribosome at a site near the peptidyl transferase center.

Chain elongation (transpeptidation) is prevented by blocking the polypeptide exit tunnel within the enzyme.

(Some refer to macrolides as “tunnel plugs”.)

As a result, the unfinished peptide dissociates from the ribosome, interrupting protein synthesis.



Source: Bertram G. Katzung, Todd W. Vanderah:  
Basic & Clinical Pharmacology, Fifteenth Edition  
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Format of figure adapted by LG

# Resistance Mechanisms

<b>Intrinsic</b>	Enterococci; Enterobacterales; <i>Pseudomonas</i> ; <i>C. difficile</i> ; <i>B. fragilis</i> Reduced permeability to drug or production of drug modifying enzymes
<b>Acquired:</b> (main mechanisms)	
<b>Efflux</b>	<i>mrsA</i> gene: staphylococci   <i>mefA</i> gene: GAS   <i>mefE</i> gene: <i>S. pneumoniae</i> Plasmid encoded
<b>Ribosomal modification</b>	<b>Methylase</b> modifies the macrolide binding site → decreases drug binding Constitutive, inducible or chromosomal mutation → <i>erm</i> genes (erm: erythromycin ribosomal methylase) • Expressed by <i>S. pneumoniae</i> , <i>S. aureus</i> , <i>S. pyogenes</i>
<b>CROSS-RESISTANCE</b> Ribosomal modification → resistance to all macrolides	
<b>MLS<sub>B</sub>:</b> Macrolide-Lincosamide-Streptogramin B phenotype conferred by the <i>erm</i> gene Resistance to macrolides, clindamycin, and streptogramin B, which all bind the same 23S target.	

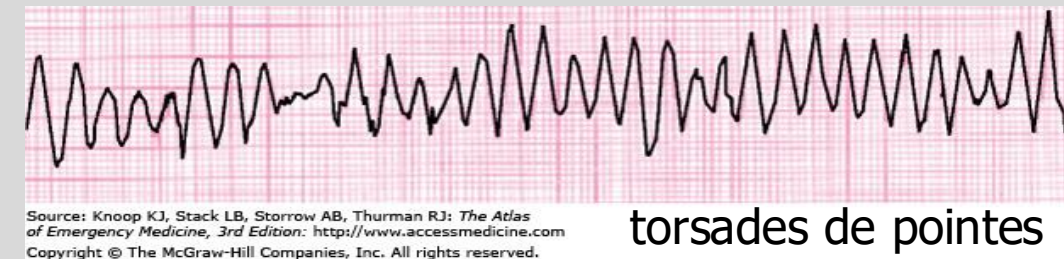
# Azithromycin & Clarithromycin

are the most frequently used macrolide antibiotics.

Empiric treatment of respiratory infections	Upper respiratory infections, including in patients with COPD	<i>M. catarrhalis, H. influenzae, S. pneumoniae</i>
	Community-acquired pneumonia	<i>M. pneumoniae, C. pneumoniae, L. pneumophila</i>
	Whooping cough	<i>Bordetella pertussis</i>
	Nontuberculosis mycobacterial	<i>Mycobacterium avium-intracellulare</i> (MAC)
STD	<ul style="list-style-type: none"> <li>• Lymphogranuloma venereum</li> <li>• Chancroid</li> <li>• Gonorrhea</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Chlamydia trachomatis</i>, alternative to doxy</li> <li>• <i>H. ducreyi</i>, Azithromycin (or ceftriaxone)</li> <li>• <b>Azithromycin is NO LONGER recommended for Gonorrhea / Chlamydia infection (with ceftriaxone)</b></li> </ul>
Skin / skin structure	Widespread resistance <b><i>Macrolides should only be used if in vitro susceptibility has been documented.</i></b>	
GI	<ul style="list-style-type: none"> <li>• Peptic ulcer disease</li> <li>• Gastroenteritis</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Helicobacter pylori</i>, Clarithromycin</li> <li>• <i>Campylobacter jejuni</i>) Azithromycin</li> </ul>
Zoonotic	Relapsing fever	<i>Borrelia louse-</i> or tick-borne, alternative to doxy

## Macrolides Adverse Effects

- **GI:** Abdominal cramps, nausea, vomiting, and diarrhea
  - Erythromycin acts on motilin receptors | Azithro, Clarithro better tolerated
- **Cardiac:** QTc prolongation → ventricular arrhythmias
  - torsades de pointes (“twisting of the points”)
- **Hepatotoxicity:** esp. erythromycin estolate
  - Azithromycin-induced liver injury: Hepatitis; most patients recover but deaths have occurred
  - Hepatitis also reported with clarithromycin use.
- **Hypersensitivity:** immediate reactions reported; angioedema, urticaria, anaphylaxis
- **Pregnancy:** Azithromycin may be given.



Avoid clarithromycin and erythromycin estolate

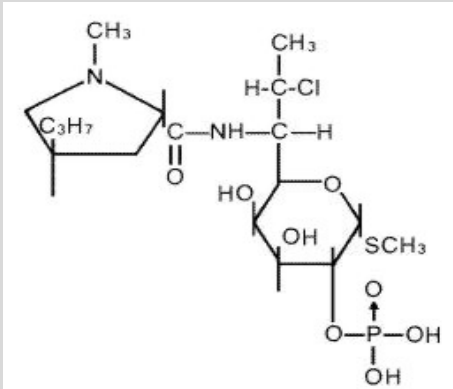
## Macrolides Drug Interactions

### Pharmacodynamics

- Drugs that act at/near 50S ribosomal subunit
- Drugs that prolong QT interval
- Warfarin (elimination of microbiome → ↓ vit K synthesis)

### Pharmacokinetics: Erythromycin, Clarithromycin

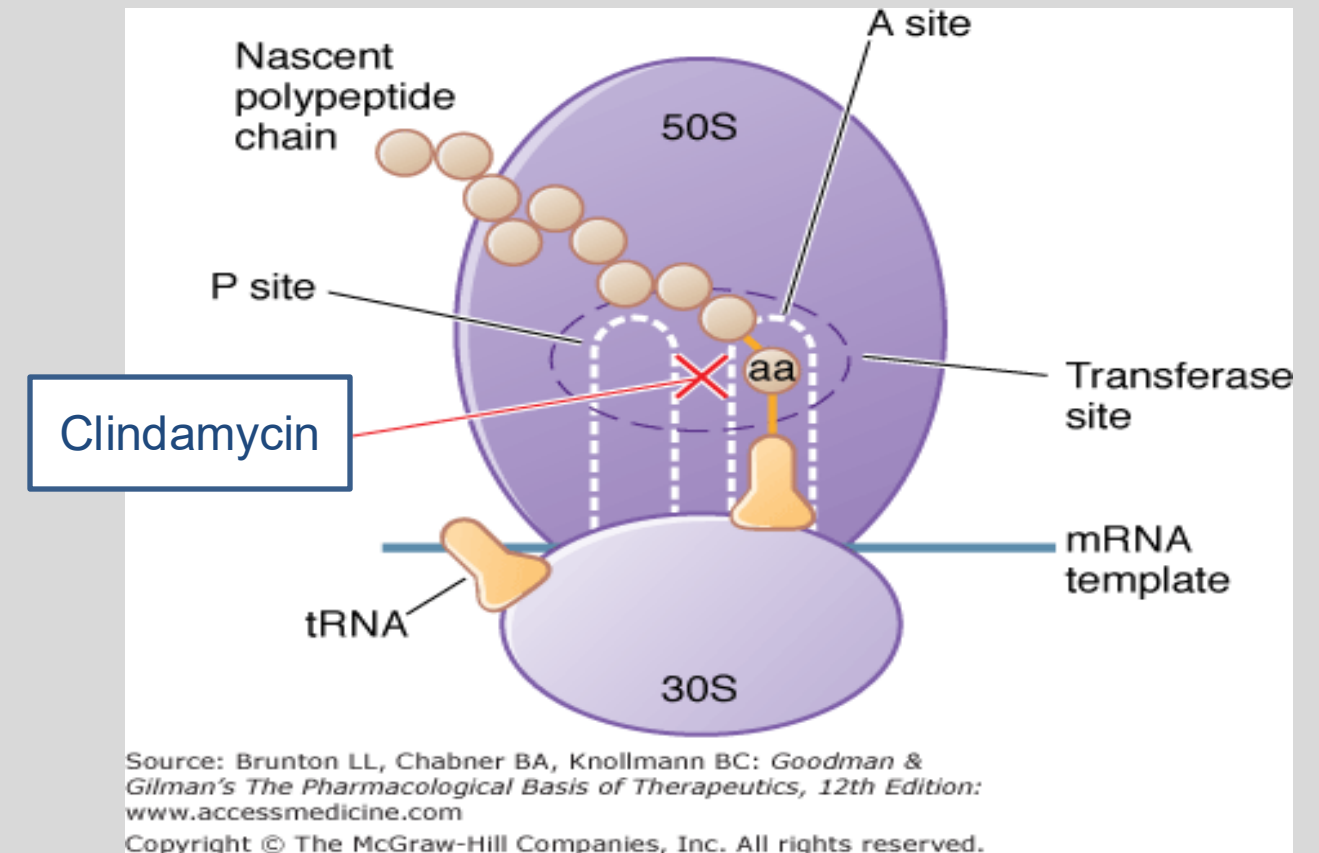
- **Inhibition of CYP3A and P-glycoprotein** → ↑ concentrations of many drugs, such as:
  - glucocorticoids; cyclosporine; lovastatin, simvastatin, atorvastatin; theophylline; triazolam; carbamazepine; valproate; ergot alkaloids
  - digoxin (probably by inhibition of P-gp)
- CYP3A4/P-gp inhibitors → ↑ risk of QT prolongation by azithromycin



# \*Clindamycin (a lincosamide)

# PK-PD Profile: T>MIC

## Bacteriostatic



Blocks transpeptidation by binding to the 23S of the 50S subunit near the peptidyl transferase center – the macrolides site

# Clindamycin Properties

<b>PK</b>	Oral, IM, IV, topical; distributes to bone, abscesses, phagocytes, but low amounts in CSF even with inflamed meninges; CYP3A4 metabolism; active drug and metabolites excreted in urine/feces; $t_{1/2}$ 2-3 h
<b>Activity</b>	Gram-positive aerobes, caMRSA; G-positive and G-negative anaerobes Parasites: <i>Plasmodium</i> spp, <i>Toxoplasma gondii</i> , <i>Pneumocystis jiroveci</i>
<b>Resistance</b>	See next slide
<b>Uses</b>	Lung abscess, pelvic inflammatory disease, skin/skin structure infections, orofacial infections (dental use), acne (topical), bacterial vaginosis (vaginal), malaria, toxoplasmosis, <i>Pneumocystis</i> pneumonia
<b>Adverse effects</b>	<i>C. difficile</i> infection (dose-, time-related) → mild to severe (colitis, toxic megacolon), skin rashes (mild to severe), hepatic impairment reported
<b>Pregnancy</b>	Considered safe in pregnant patients.
<b>Drug interactions</b>	Other drugs that target 23S ribosome interfere with each other's actions, CYP3A4-mediated, oily base in vaginal cream may weaken condoms and contraceptive diaphragms

## Clindamycin Resistance: MLS<sub>B</sub> ribosomal methylation

- *Staphylococci* and *Streptococcus pneumoniae*:

Inducible **iMLS<sub>B</sub>** → **may lead to cMLS<sub>B</sub> during therapy**: Bacterial strains will appear to be sensitive to clindamycin but clindamycin treatment in patients infected with organisms harboring cMLS<sub>B</sub> (activated mRNA encoding methylase) may cause these mutants with constitutive production of methylase to be selected out and emerge **during therapy → therapy failure or disease recurrence**.

iMLS<sub>B</sub> is prevalent in MRSA and *S. pneumoniae*.

The D test is recommended *to determine if the iMLS<sub>B</sub> determinant is present*.

A positive D test suggests that a subpopulation of microbes resistant to clindamycin may emerge and lead to clinical failure or recrudescence.

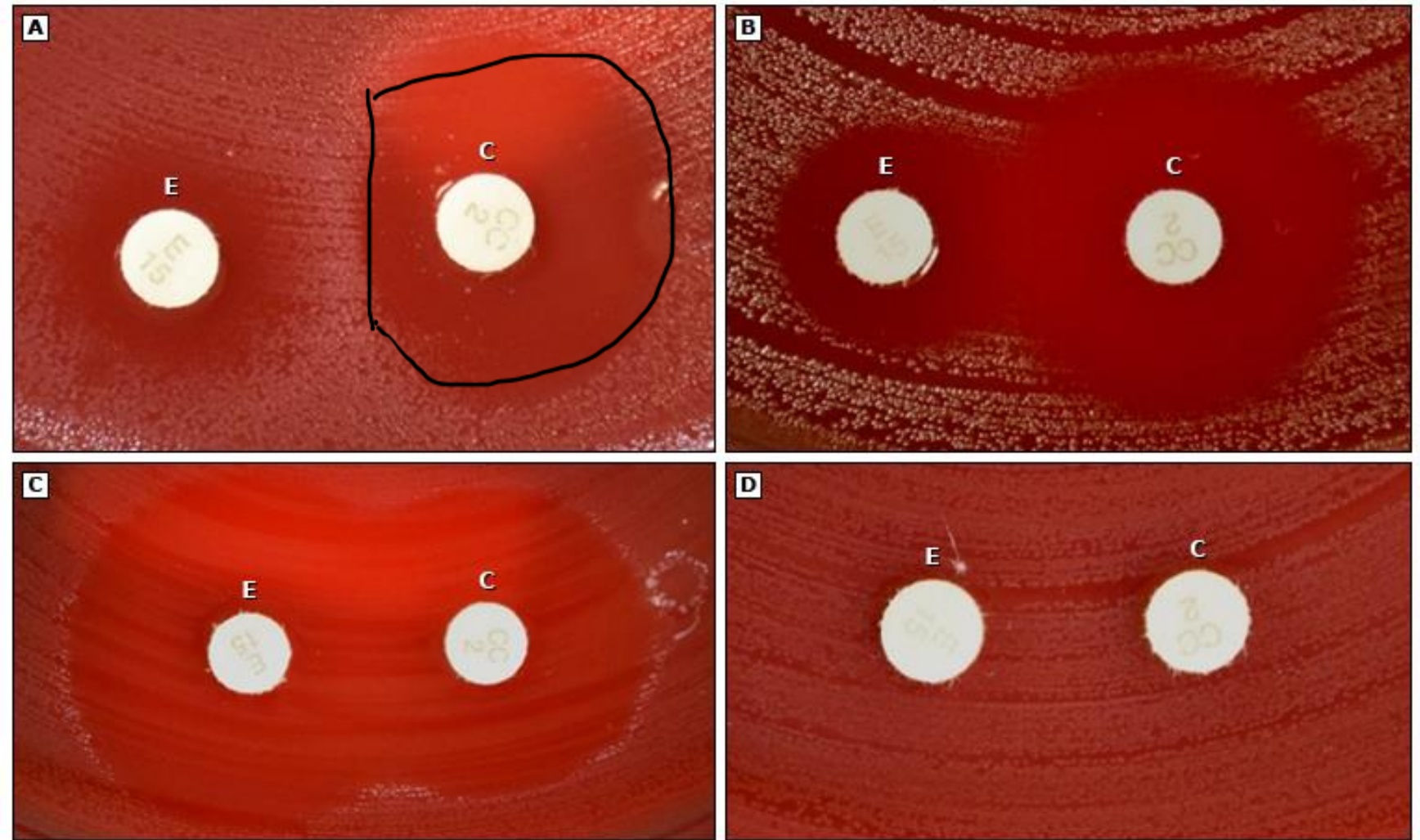
A positive D test should be reported as resistant.

## D Test

**Panel A** shows the isolate is resistant to erythromycin but has blunting of the zone of inhibition around the clindamycin disk adjacent to the erythromycin disk (D zone), which is the hallmark of the inducible  $MLS_B$  resistance phenotype.

(Tracing around the D zone by LG)

Panels B,C, and D are described under the figure.



Commercially available erythromycin and clindamycin disks are placed in a standardized fashion on an agar plate inoculated with a standardized inoculum of the test organism. The plates are incubated for 16 to 24 hours and then visually inspected.

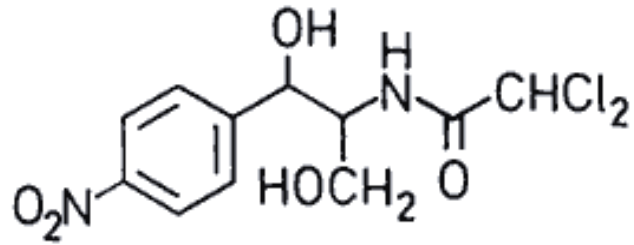
(A) Flattening of the clindamycin zone of inhibition (D-zone) adjacent to the erythromycin disk, indicating inducible clindamycin resistance.

(B) An isolate that is erythromycin-resistant but clindamycin-susceptible.

(C) An isolate that is susceptible to both clindamycin and erythromycin.

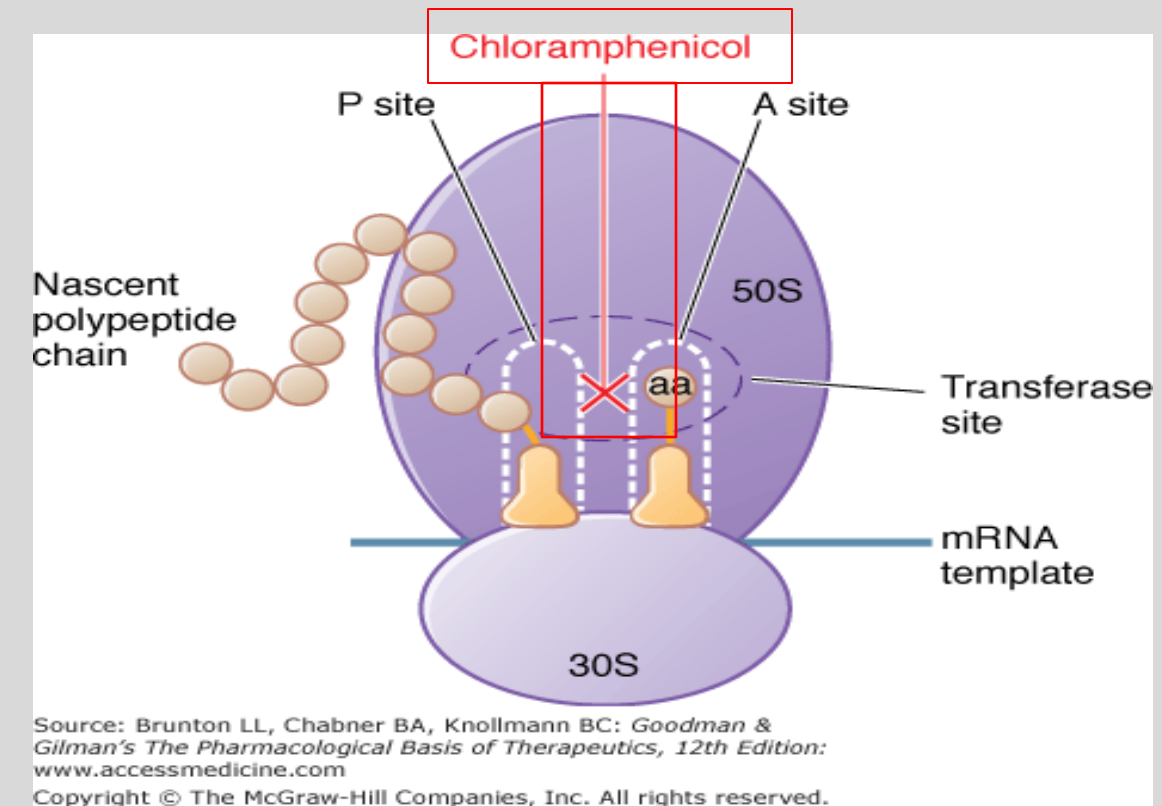
(D) An isolate with constitutive resistance to both clindamycin and erythromycin.

C: clindamycin disk; E: erythromycin disk.



## \*Chloramphenicol

Binds reversibly to 23S rRNA in 50S ribosome within peptidyl transferase center.  
Interferes with tRNA binding to the A site →  
Prevents the interaction between peptidyl transferase and the amino acid substrate →  
Prevents peptide bond formation



Chloramphenicol is highly lipophilic and poorly soluble in water.  
It is formulated as water soluble inactive succinate sodium salt for I.V. administration.

# Chloramphenicol Properties

<b>PK</b>	IV, succinate salt is rapidly converted by esterases to active chloramphenicol protein binding ~60% widely distributed with good penetration of CSF, ocular tissues, prostate glucuronide conjugation, inactive metabolites; urine, $t_{1/2}$ ~4 h
<b>Activity</b>	Broad-spectrum, bacteriostatic ( <i>P. aeruginosa</i> is intrinsically resistant.)
<b>Resistance</b>	Drug inactivation by covalent acetylation by bacterial acetyltransferase
<b>Uses</b>	Limited: <b><i>restricted to life-threatening infections</i></b> when no alternative can be used Rocky Mountain spotted fever ( <i>R. rickettsii</i> ), enteric (typhoid) fever meningococcal meningitis (bacteriostatic)
<b>Adverse effects</b>	Mitochondrial toxicity – due to inhibition of mitochondrial protein synthesis Bone marrow toxicity, idiopathic aplastic anemia, Gray syndrome (next slide) GI: nausea, vomiting, diarrhea, stomatitis, glossitis optic neuritis, peripheral neuritis, headache, confusion
<b>Pregnancy</b>	Recommended <i>alternative</i> for treatment of Rocky Mountain spotted fever and plague ( <i>Y. pestis</i> ) Caution in 3 <sup>rd</sup> trimester (concern about gray baby syndrome)
<b>DDIs</b>	CYP2C9 inhibitor; other drugs with same adverse effects

Chloramphenicol is a high-risk medication in pediatric patients.

Neonates (premature and full-term newborns and infants) have immature hepatic and renal functions.

1. Immature UDP-glucuronyltransferase (UGT) → reduced ability to metabolize chloramphenicol → potential for drug accumulation
  2. Reduced levels of plasma proteins → higher fraction of free drug
  3. Immature kidney function → ↑plasma concentrations of drug
- Increased drug concentration → increased risk of concentration-dependent toxicity.

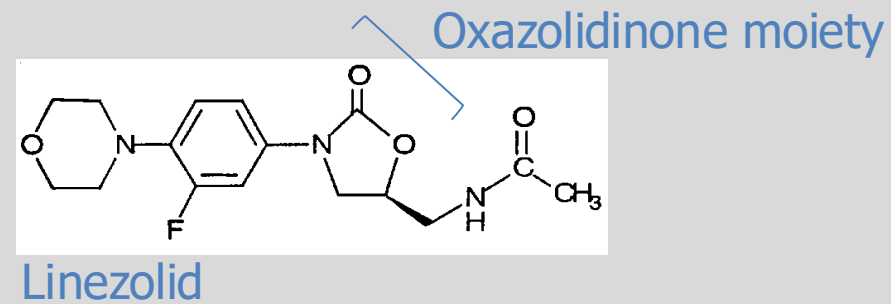
### **Gray (baby) syndrome**

- Drug accumulation in neonate → toxic levels
- Vomiting, flaccid muscles, abdominal distension, hypothermia, gray color (cyanosis)
- Vasomotor collapse, irregular respirations, death

Onset: 2-9 days after starting therapy

**Progression of symptoms is rapid. Prompt termination of therapy is required.**

🔑 Monitor serum chloramphenicol concentrations in neonates, infants, children, and patients with impaired hepatic function.

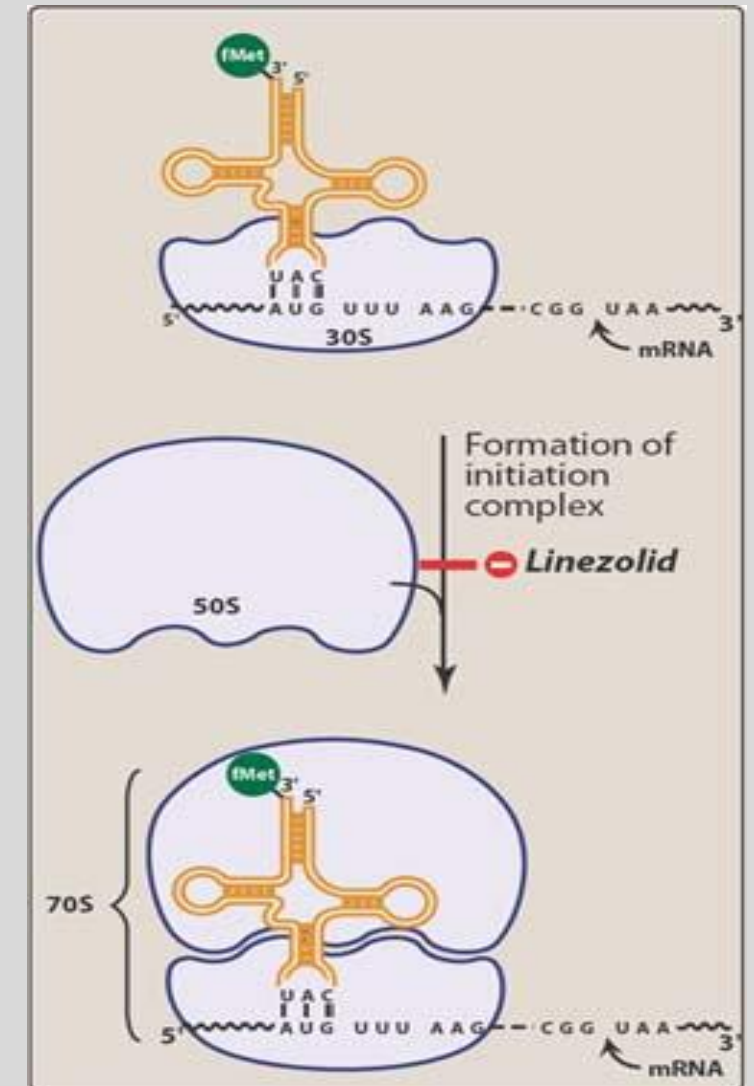


# Oxazolidinones

## \*Linezolid

### ■ Tedizolid

1. Bind the 23S rRNA in the 50S subunit in the A site pocket near the interface with the 30S subunit
2. Prevent the formation of the ribosomal-fMet-tRNA complex that initiates protein synthesis
3. Inhibit formation of the first peptide bond of the nascent peptide



# Linezolid Properties

**PK** IV and oral, 100% bioavailability; widely distributed including lung tissue, bone, and CSF (high concentrations); hepatic but minimal metabolism, inactive metabolites; nonrenal and renal excretion;  $t_{1/2}$  ~5 h adults, 1.5-3 h children

**Activity** Bactericidal against streptococci  
gram- Bacteriostatic against staphylococci, including MRSA, and enterococci, including VRE  
positive *Mycobacterium tuberculosis* (MDR and XDR strains)

MDR: multidrug resistance  
XDR: extensive drug resistance

**Resistance** Low level resistance, no cross-resistance  
Mechanism: Point mutations in the binding site on the 23S ribosomal rRNA gene confer resistance in staphylococci and enterococci

Intrinsic Resistance: Aerobic gram-negative bacteria and anaerobic bacteria

**Uses** Skin/skin structure; nosocomial and ca-pneumonia, CNS infections, bone and joint infections, drug-resistant tuberculosis, and more

**Adverse effects** Thrombocytopenia (Tx duration >2 weeks); Mitochondrial toxicities – peripheral neuropathy, optic neuritis, lactic acidosis (reported with Tx duration  $\geq 28$  days)

**DDIs** Next slide

# Linezolid Adverse Effects

Linezolid is a weak  
monoamine oxidase (MAO) inhibitor



increases levels of serotonin and norepinephrine  
in the brain and periphery



increases the risk of serotonin syndrome in  
patients taking serotonergic drugs

Serotonin syndrome typically is reversible and ranges  
from mild to a potentially life-threatening event  
resulting from drug combinations that increase  
serotonin levels in the brain:

headache, confusion, palpitations, hyperreflexia,  
hyperthermia, hypertensive crisis

Pregnancy: Limited data

## Drugs-disease interactions:

- Uncontrolled hypertension
- Pheochromocytoma
- Thyrotoxicosis

## Drug-drug interactions

**Avoid** concomitant use with:

- Serotonin reuptake inhibitors
- Tricyclic antidepressants
- Meperidine
- Sympathomimetic agents
- Vasopressive agents

## Drugs-food interactions:

- Dietary tyramine

Tyramine is deactivated by intestinal and  
hepatic MAO.

Questions: You might want to pause the video to think about them.

1. Which drug classes fit the following mechanisms of action?
  - A. Bind the 30S subunit of the bacterial ribosome, preventing binding of tRNA to the mRNA–ribosome complex.
  - B. Bind the 30S ribosomal subunit, interfering with assembly of the functional ribosomal apparatus and cause misreading of the code.
  - C. Bind the bacterial 23S ribosomal RNA of the 50S subunit, inhibiting the formation of the 70S initiation complex.
  - D. Bind to a site on the 50S subunit of the bacterial ribosome, inhibiting translocation steps of protein synthesis (“tunnel plug”).
  - E. Bind to a site on the 50S subunit of the bacterial ribosome, inhibiting the interaction between the amino acid and peptidyl transferase
2. Why does the American Academy of Pediatrics support the use of doxycycline for up to 21 days in young children?
3. What is the mechanism by which chloramphenicol may cause vomiting, flaccid muscles, hypothermia, cyanosis, vasomotor collapse, irregular respirations, and death in the newborn?

## Questions continue.

4. Which drug is the preferred treatment for many zoonotic infections, including Rocky Mountain spotted fever?
5. What are the three toxicities associated with the class of drugs that utilize the microbe's oxygen transport system to gain access to the protein synthesis apparatus?
6. What is the current CDC recommendation regarding treatment of gonorrhea and potential chlamydia coinfection with azithromycin?
7. What drug is safe and effective in all trimesters for the outpatient treatment of community acquired pneumonia (CAP) for a generally healthy pregnant patient?
8. A patient with a diabetic foot infection caused by methicillin-resistant *S. aureus* identified by culture and sensitivity testing requires treatment. The patient is taking citalopram for depression (a selective serotonin reuptake inhibitor). What drug would be effective but contraindicated?
9. A 70-year-old patient is diagnosed with community acquired pneumonia. The patient takes sotalol (antiarrhythmic) for management of atrial flutter. What class of drugs may increase the risk of torsades de pointes in this patient?
10. What protein synthesis inhibitors do not require dose adjustments for renal insufficiency because they are not excreted as active drug in urine? mnemonic **D**ear **A**unt **C**atherine's **Q**uilt

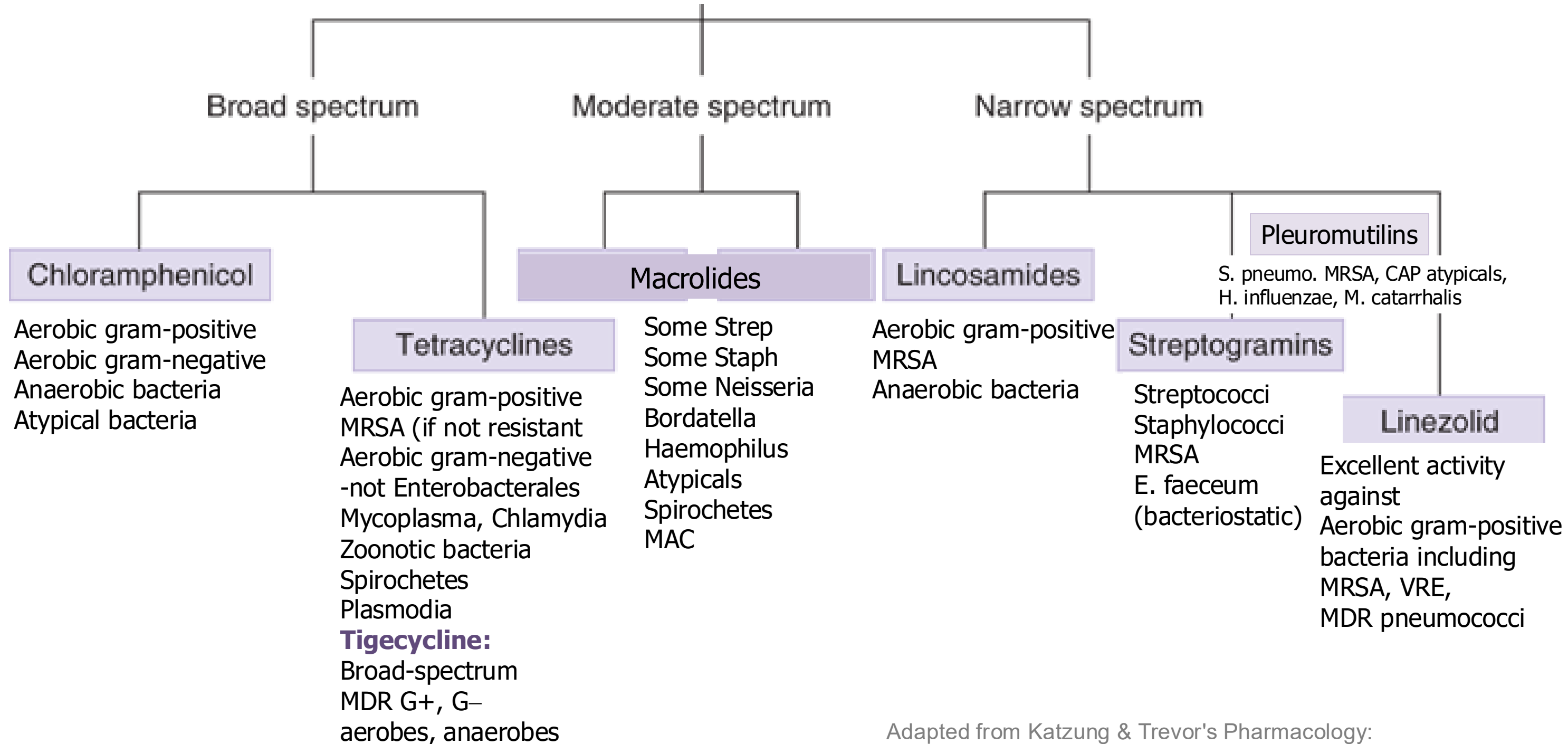
# Summary of Protein Synthesis Inhibitors

## Synopsis

- Protein synthesis inhibitors have diverse chemical structures, pharmacokinetic properties, actions, and antibacterial spectrums.
- The protein synthesis inhibitors subclasses vary in their sites of action on the bacterial ribosome to inhibit addition of amino acids to the growing peptide chain.
- Protein synthesis inhibitors, as a group, are predominantly bacteriostatic against a wide array of bacteria, including intracellular organisms and those lacking a cell wall. Most have activity against susceptible ca-MRSA. The macrolides are not.
- Resistance is increasing. Efflux or reduced influx and alteration of the ribosomal target are common mechanisms. Drug inactivation is less common but important for chloramphenicol resistance.
- Toxicity potential ranges from negligible to severe.

# Bacterial protein synthesis inhibitors

## Summary of Spectrums of Activity, if bacterial resistance is absent



1. A. tetracyclines B. aminoglycosides C. linezolid (oxazolinones) D. macrolides E. chloramphenicol
2. Doxycycline does not bind calcium as avidly as tetracycline does and the risk of tooth discoloration is low when used for  $\leq 21$  days.
3. Elevated serum chloramphenicol levels due to immature UGT and renal function and lower albumin levels (greater free drug fraction) significantly prolongs half-life and increases risk of mitochondrial toxicity → cyanosis and Gray Syndrome.
4. Doxycycline and for several other zoonoses. (Tularemia is treated with an AG, streptomycin or gentamicin.)
5. Aminoglycosides' toxicities are nephrotoxicity, ototoxicity, and neuromuscular blockade / respiratory failure.
6. Azithromycin is not recommended because of increasing gonococcal resistance. If there is a high suspicion of chlamydia coinfection, doxycycline is recommended.
7. Azithromycin may be given in pregnancy. AVOID clarithromycin, erythromycin estolate, tetracyclines, fluoroquinolones, chloramphenicol, lefamulin. (Linezolid and clindamycin would not be effective against all potential pneumonia-causing bacteria.)
8. Linezolid is a weak MAO inhibitor and should be avoided in patients taking drugs that increase synaptic serotonin levels. Serotonin syndrome. Linezolid is an alternative for patients who do not respond to other agents (cost/toxicity).
9. Macrolides and antiarrhythmics that block cardiac potassium channels both cause prolongation of the QT interval. The risk of ventricular arrhythmia is increased when used together.
10. **D**ear **A**unt **C**atherine's **Q**uilt – **D**oxycycline, **A**zithromycin, **C**lindamycin, and **Q**uinupristin-dalfopristin do not require dose adjustment in patients with renal insufficiency.

## References

- Access Medicine Goodman & Gilman's The Pharmacological Basis of Therapeutics 14e, 2023; Chapter 60: Protein Synthesis Inhibitors
- Access Medicine Harrison's Principles of Internal Medicine, 20e, 2018; Chapter 163: Cholera and Other Vibrioses
- Access Medicine Jawetz, Melnick, & Adelberg's Medical Microbiology, 27e, 2016; Chapter 14: The Streptococci, Enterococci, and Related Genera; Chapter 15: Enteric Gram-Negative Rods (enterobacteriaceae)
- Access Medicine Katzung's Basic & Clinical Pharmacology 16e, 2024; Chapter 44: Tetracyclines, Macrolides, Clindamycin, Chloramphenicol, Streptogramins, Oxazolidinones & Pleuromutilins
- Lexidrugs monographs
- The Sanford Guide to Antimicrobial Therapy, 55e, 2025

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<https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R>