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College of Osteopathic Medicine

# 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)

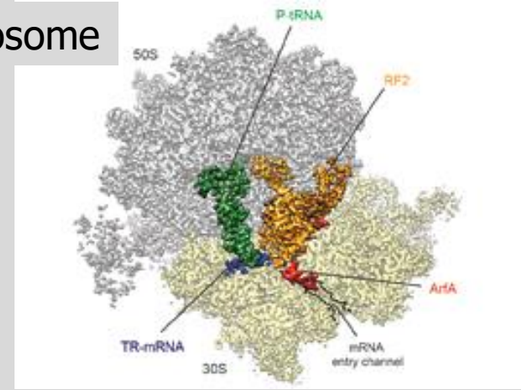
**SUGGESTIONS:**

- ***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***

bacterial ribosome




## 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.

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

**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-encodes MDR efflux pumps.

## 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 $MLS_B$ and is encoded by the *erm* gene.

## Key points

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- 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 proarrythmic 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 ($MLS_B$ expressed by the *erm* gene) (see macrolides), 2) mutation of the ribosomal receptor site, and 3) enzymatic inactivation of clindamycin.
- Bacterial strains harboring inducible $iMLS_B$ 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 $iMLS_B$ determinant is present. If present, constitutive production of methylase may be selected out, resulting in clindamycin therapy failure or recurrence of infection.

## Key points

- 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 insufficient 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.

## Key points

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**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.

# Tetracyclines Class Pharmacokinetics Properties, in brief

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| | | |
|---|---|---|
| Oral, acid stable<br>I.V.: Doxy- and Mino- Tigecycline (only I.V.)<br>Bioavailability:<br>Tetra- variable ~75-85%<br>→ **Doxy- 95% \| Mino- 100%**<br>Omadacycline ~35% | Protein binding 60-90%<br>Widely distributed in body fluids<br>Deposits in growing bones and tooth enamel.<br>Doxycycline has low affinity for calcium.<br>Avoid TCNs in pregnant women, children <8 years<br>→ **Exception:** Doxycycline ≤21 days of treatment | **All:**<br>Chelation in GI tract by:<br>Di- and trivalent cations<br>Avoid antacids and mineral supplements<br>**Food:**<br>TCN, demeclo-, omadacycline: Empty stomach<br>Doxy-, Mino-, Sarecycline<br>May be taken with food, including dairy products |
| TCN, Doxy-: not metabolized<br>Mino-, Tige-: hepatic<br>Excreted in urine,<br>→ except **Doxy in feces** | **Tetracyclines that remain in the gut lumen modify intestinal flora.** | |
| t½ 9-16h, drug-specific<br>Tigecycline ~40 h | | |

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.***

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

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

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

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

# Clindamycin Resistance: $MLS_B$ ribosomal methylation

- *Staphylococci* and *Streptococcus pneumoniae*:

Inducible **$iMLS_B$ → may lead to $cMLS_B$ during therapy:** Bacterial strains will appear to be sensitive to clindamycin but clindamycin treatment in patients infected with organisms harboring $cMLS_B$ (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**.

$iMLS_B$ is prevalent in MRSA and *S. pneumoniae*.

The D test is recommended *to determine if the $iMLS_B$ 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.

Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing, 29th ed, CLSI supplement M100, Wayne, Pennsylvania 2019

# 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 continue.

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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

# Bacterial protein synthesis inhibitors

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