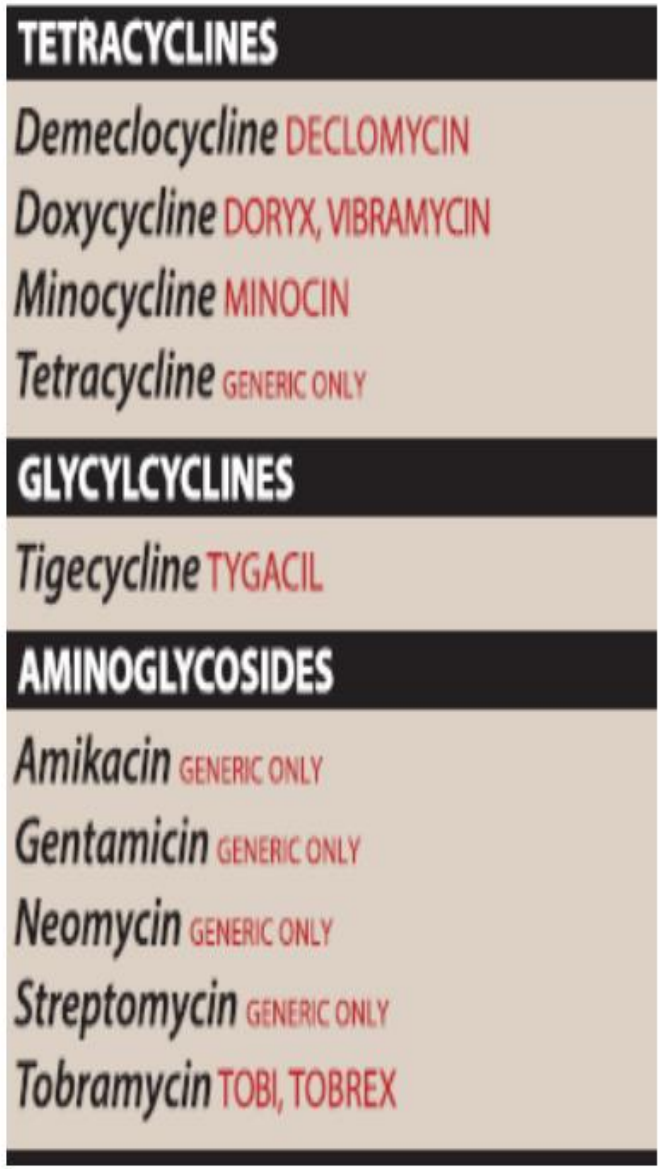
Protein Synthesis Inhibitors

Protein synthesis inhibitors

A number of antibiotics exert their antimicrobial effects by targeting bacterial ribosomes and inhibiting bacterial protein synthesis. Most of these agents exhibit bacteriostatic activity. Bacterial ribosomes differ structurally from mammalian cytoplasmic ribosomes and are composed of 30S and 50S subunits (mammalian ribosomes have 40S and 60S subunits).

In general, selectivity for bacterial ribosomes minimizes Potential adverse consequences encountered with the disruption of protein synthesis in mammalian host cells.

However, high concentrations of drugs such as *chloramphenicol* or the *tetracyclines* may cause toxic effects as a result of interaction with mitochondrial mammalian ribosomes, because the structure of mitochondrial ribosomes more closely resembles bacterial ribosomes.

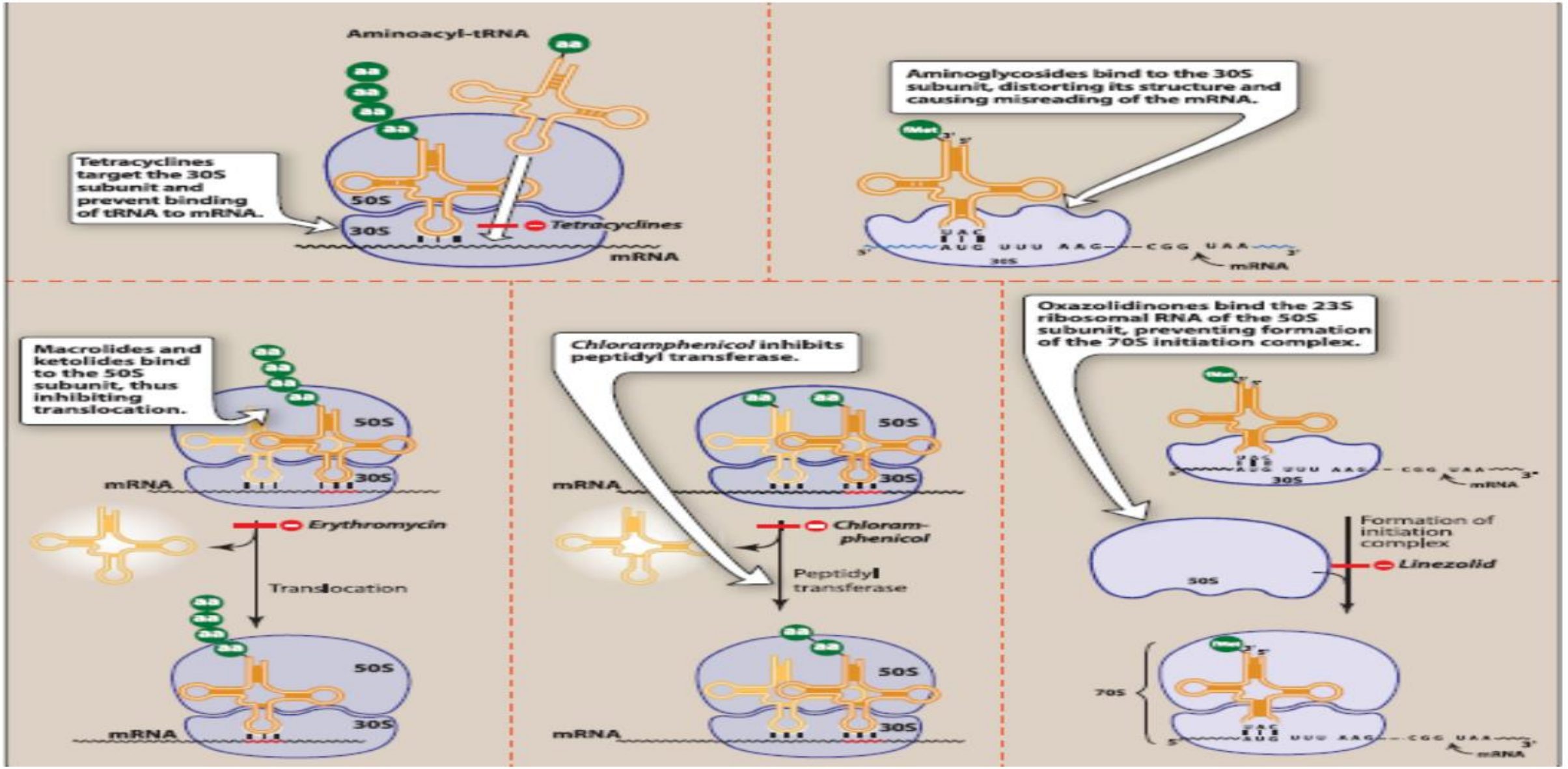


Summary of protein synthesis inhibitors.

Tetracyclines

A. Mechanism of action:

- Tetracyclines enter susceptible organisms via passive diffusion and by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane.
- Tetracyclines concentrate intracellularly in susceptible organisms.
- The drugs bind reversibly to the 30S subunit of the bacterial ribosome.
- This action prevents binding of tRNA to the mRNA-ribosome complex, thereby inhibiting bacterial protein synthesis.

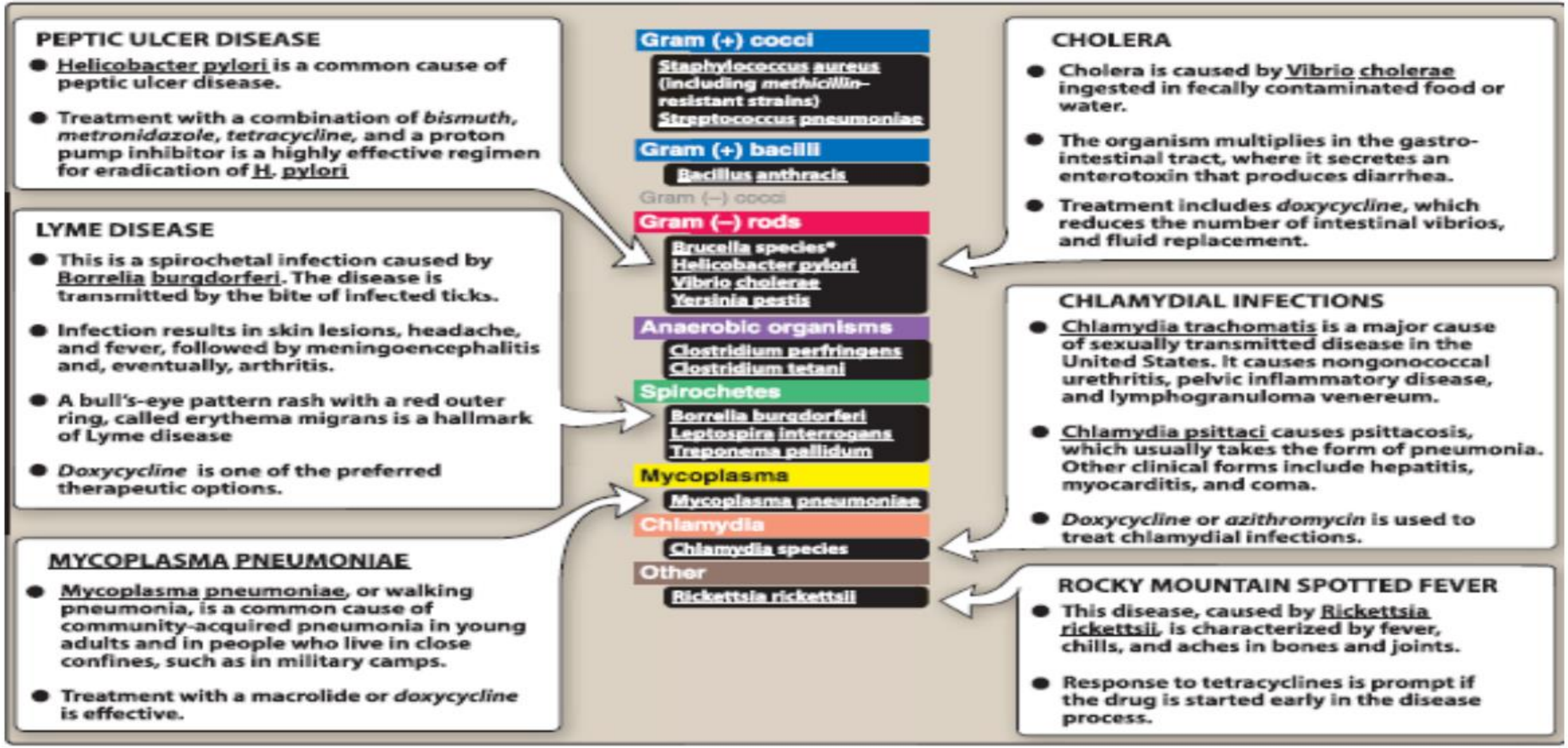


✓ **Mechanisms of action of the various protein synthesis inhibitors. aa = amino acid.**

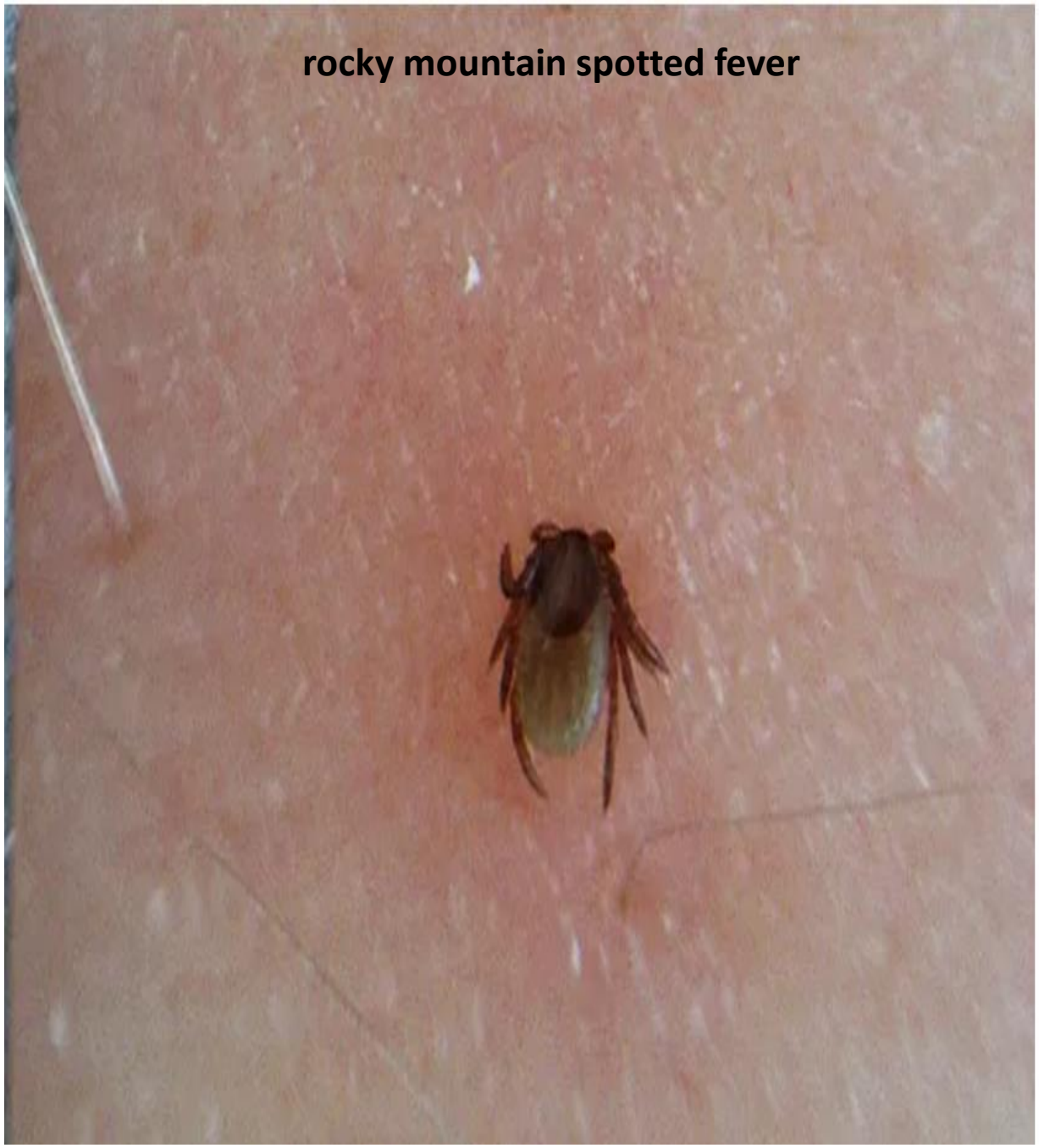
B. **Antibacterial spectrum of Tetracyclines:**

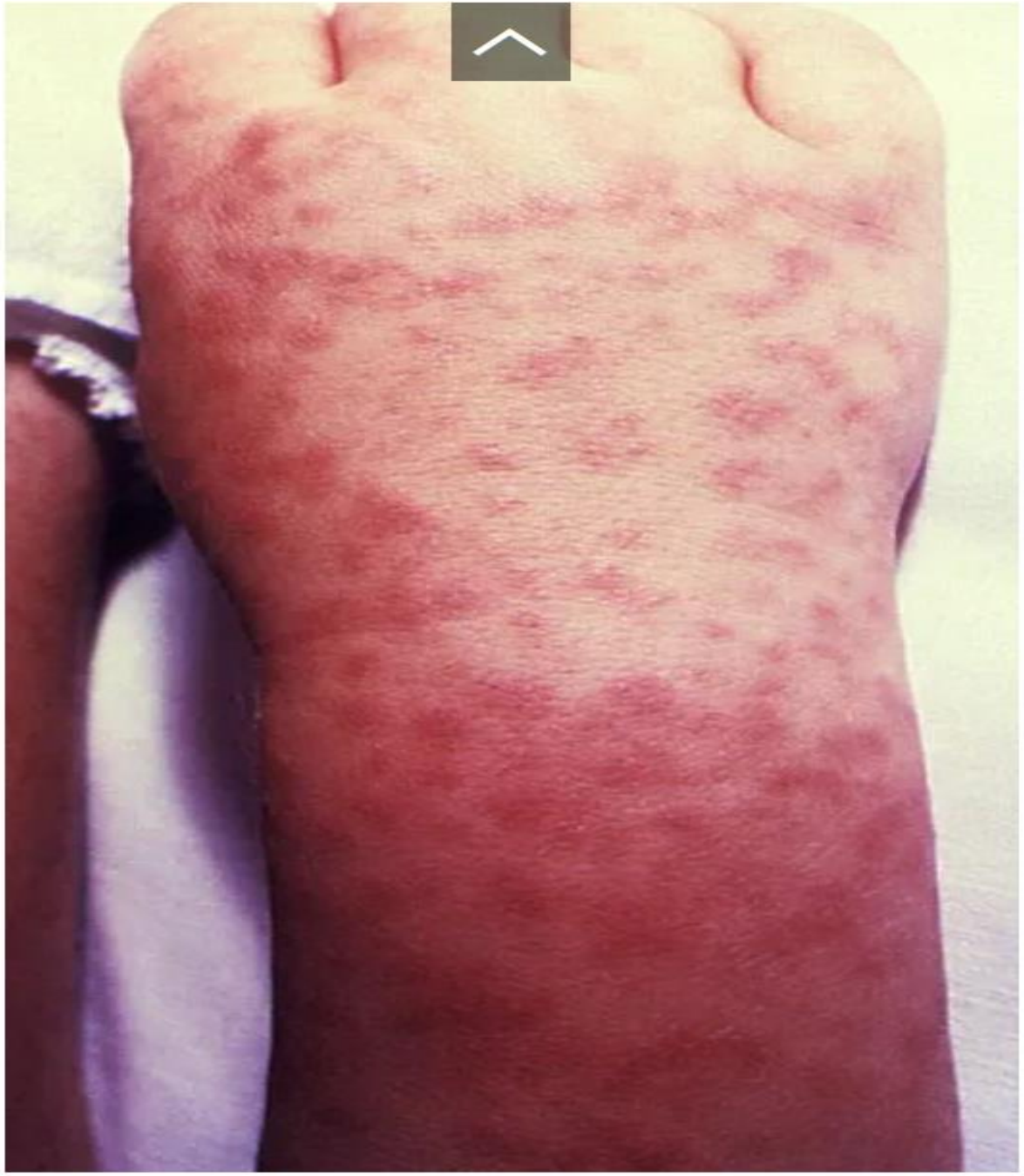
- The tetracyclines are bacteriostatic antibiotics effective against a wide variety of organisms, including **gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species**.

- They are commonly used in the treatment of acne and Chlamydia infections



Typical therapeutic applications of tetracyclines. *A *tetracycline+ gentamicin.*


rocky mountain spotted fever



C. Resistance

The most commonly encountered naturally occurring resistance to tetracyclines is an efflux pump that expels drug out of the cell, thus preventing intracellular accumulation. Other mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome. Resistance to one tetracycline does not confer universal resistance to all tetracyclines, and the development of cross-resistance may be dependent on the mechanism of resistance.

D. Pharmacokinetics

1. Absorption: Tetracyclines are adequately absorbed after oral ingestion. Administration with dairy products or other substances that contain divalent and trivalent cations {for example, magnesium, calcium and aluminum antacids, or iron supplements} decreases absorption, particularly for *tetracycline*, due to the formation of non-absorbable chelates. Both *doxycycline* and *minocycline* are available as oral and intravenous {IV} preparations.

2. Distribution: The tetracyclines concentrate well in the bile, liver, kidney, gingival fluid, and skin. Moreover, they bind to tissues undergoing calcification {for example, teeth and bones} or to tumors that have high calcium content. Penetration into most body fluids is adequate. Only *minocycline* and *doxycycline* achieve therapeutic levels in the cerebrospinal fluid {CSF}. *Minocycline* also achieves high concentrations in saliva and tears, rendering it useful in eradicating the meningococcal carrier state. All *tetracyclines* cross the placental barrier and concentrate in fetal bones and dentition.

3. Elimination: *Tetracycline* is primarily eliminated unchanged in the urine, whereas *minocycline* undergoes hepatic metabolism and is eliminated to a lesser extent via the kidney. *Doxycycline* is preferred in patients with renal dysfunction, as it is primarily eliminated via the bile into the feces.

E. Adverse effects

1. Gastric discomfort: Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance with tetracyclines. Esophagitis may be minimized through coadministration with food {other than dairy products) or fluids and the use of capsules rather than tablets. [Note: *Tetracycline* should be taken on an empty stomach.]

2. Effects on calcified tissues: Deposition in the bone and primary dentition occurs during the calcification process in growing children. This may cause discoloration and hypoplasia of teeth and a temporary stunting of growth. For this reason, the use of tetracyclines is limited in pediatrics.

3. Hepatotoxicity: Rarely hepatotoxicity may occur with high doses, particularly in pregnant women and those with preexisting hepatic dysfunction or renal impairment.

4. Phototoxicity: Severe sunburn may occur in patients receiving a tetracycline who are exposed to sun or ultraviolet rays. This toxicity is encountered with any tetracycline, but more frequently with *tetracycline* and *demeclocycline*. Patients should be advised to wear adequate sun protection.

5. Vestibular dysfunction: Dizziness, vertigo, and tinnitus may occur particularly with *minocycline,* which concentrates in the endolymph of the ear and affects function.

6. Pseudotumor cerebri: Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

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

GLYCYLCYCLINES

Tigecycline, a derivative of *minocycline,* is the first member of the glycylcycline antimicrobial class. It is indicated for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, and community-acquired pneumonia.

A. Mechanism of action

Tigecycline exhibits bacteriostatic action by reversibly binding to the 305 ribosomal subunit and inhibiting bacterial protein synthesis.

B. Antibacterial spectrum

Tigecycline exhibits broad-spectrum activity that includes *methicillin- resistant* staphylococci (MRSA), multidrug-resistant streptococci, vancomycin-resistant enterococci (VRE), extended-spectrum P-lactamase--producing gram-negative bacteria, Acinetobacter baumannii, and many anaerobic organisms.

Tigecycline is not active against Morganella, Proteus, Providencia. or Pseudomonas species.

C. Resistance

Tigecycline was developed to overcome the emergence of tetracycline class-resistant organisms that utilize efflux pumps and ribosomal protection to confer resistance. Resistance to *tigecycline* has been observed and is primarily attributed to overexpression of efflux pumps.

D. Pharmacokinetics

Following IV infusion, *tigecycline* exhibits a large volume of distribution. It penetrates tissues well but achieves low plasma concentrations. Consequently, *tigecycline* is a poor option for bloodstream infections. The primary route of elimination is biliary/fecal. No dosage adjustments are necessary for patients with renal impairment; however, a dose reduction is recommended in severe hepatic dysfunction.

E. Adverse effects

Tigecycline is associated with significant nausea and vomiting. Acute pancreatitis, including fatality, has been reported with therapy. Elevations in liver enzymes and serum creatinine may also occur. All-cause mortality in patients treated with *tigecycline* is higher than with other agents. A boxed warning states that *tigecycline* should be reserved for use in situations when alternative treatments are not suitable. Other adverse effects are similar to those of the tetracyclines and include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered in pregnancy. *Tigecycline* may decrease the clearance of *warfarin*. Therefore, the international normalized ratio should be monitored closely when *tigecycline* is coadministered with *warfarin*.

AMINOGLYCOSIDES:

A. Mechanism of action

Aminoglycosides diffuse through porin channels in the outer membrane of susceptible organisms. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. Inside the cell, they bind the 30S ribosomal subunit, where they interfere with assembly of the functional ribosomal apparatus and/or cause the 30S subunit of the completed ribosome to misread the genetic code.

Aminoglycosides have concentration-dependent bactericidal activity; They also exhibit a postantibiotic effect (PAE), which is continued bacterial suppression after drug concentrations fall below the MIC. Because of these properties, high-dose extended-interval dosing is commonly utilized. This dosing strategy also reduces the risk of nephrotoxicity and increases convenience.

B. Antibacterial spectrum

The aminoglycosides are effective for the majority of aerobic gram-negative bacilli, including those that may be multidrug resistant, such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterobacter sp. Additionally, aminoglycosides are often combined with a β-lactam antibiotic to employ a synergistic effect, particularly in the treatment of Enterococcus faecalis and Enterococcus faecium infective endocarditis.

C. Resistance

Resistance to aminoglycosides occurs via: 1) efflux pumps, 2) decreased uptake, and/or 3) modification and inactivation by plasmid- associated synthesis of enzymes. Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance cannot be presumed. [Note: *Amikacin* is less vulnerable to these enzymes than other antibiotics in this group.]

D. Pharmacokinetics

1. Absorption: 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 concentrations [Note: *Neomycin* is not given parenterally due to severe nephrotoxicity. It is administered topically for skin infections or orally to decontaminate the gastrointestinal tract prior to colorectal surgery.]

2. Distribution: Because of their hydrophilicity, aminoglycoside tissue concentrations may be subtherapeutic, and penetration into most body fluids is variable. Concentrations achieved in CSF are inadequate, even in the presence of inflamed meninges.

For central nervous system infections, the intrathecal or intraventricular routes may be utilized. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

3. Elimination: More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine . Accumulation occurs in patients with renal dysfunction; thus, dose adjustments are required. *Neomycin* is primarily excreted unchanged in the feces.

E. Adverse effects

The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. Ototoxicity: Ototoxicity (vestibular and auditory) is directly related to high peak plasma concentrations and the duration of treatment. Deafness may be irreversible and has been known to affect developing fetuses. Patients simultaneously receiving concomitant ototoxic drugs, such as *cisplatin* or loop diuretics, are particularly at risk. Vertigo (especially in patients receiving *streptomycin)* may also occur.

2. Nephrotoxicity: Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes. This results in kidney damage ranging from mild, reversible renal impairment to severe, potentially irreversible acute tubular necrosis.

3. Neuromuscular paralysis:high doses infused over a short period or concurrent administration with neuromuscular blockers. Patients with myasthenia gravis are particularly at risk. Prompt administration of *calcium gluconate* or *neostigmine* can reverse the block that causes neuromuscular paralysis.

4. Allergic reactions: Contact dermatitis is a common reaction to topically applied *neomycin*.

MACROLIDES AND KETOLIDES:

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. *Erythromycin* was the first of these drugs to have clinical application, both as a drug of first choice and as an alternative to *penicillin* in individuals with an allergy to β-lactam antibiotics. *Clarithromycin* (a methylated form of *erythromycin)* and *azithromycin* (having a larger lactone ring) have some features in common with, and others that improve upon, *erythromycin. Telithromycin* a semisynthetic derivative of *erythromycin,* is a "ketolide" antimicrobial agent.

A. Mechanism of action

The macrolides and ketolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting translocation steps of protein synthesis. They

may also interfere with other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be bactericidal at higher doses. Their binding site is either identical to or in close proximity to that for *clindamycin* and *chloramphenicol*.

B. Antibacterial spectrum

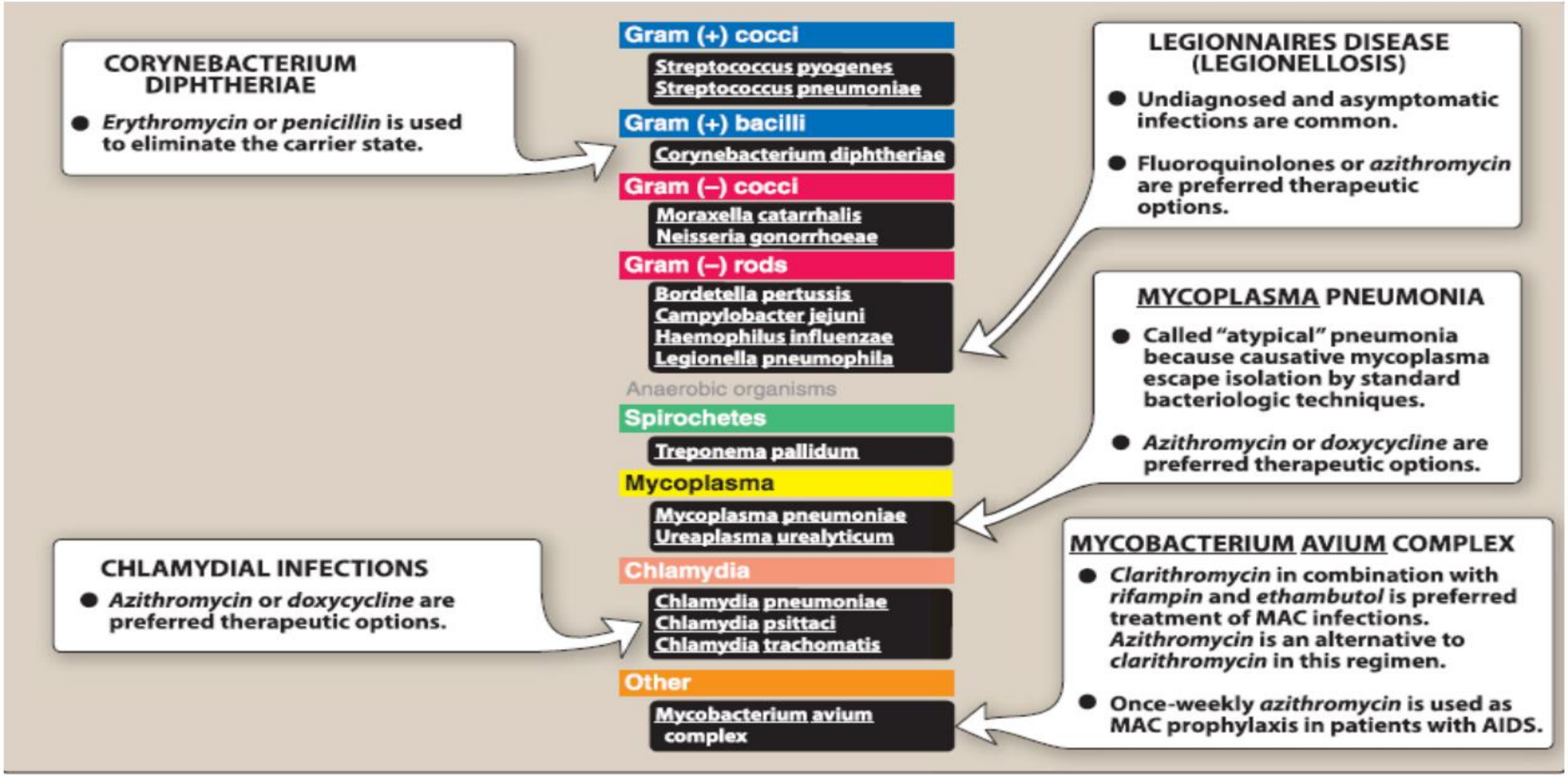
1. Erythromycin: This drug is effective against many of the same organisms as *penicillin G* ; therefore, it may be considered as an alternative in patients with *penicillin* allergy.

2. Clarithromycin: *Clarithromycin* has activity similar to *erythromycin,* but it is also effective against *Haemophilus influenzae* and has greater activity against intracellular pathogens such as *Chlamydia, Legionella, Moraxella, Ureaplasma species*, and *Helicobacter pylori*

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

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

Typical therapeutic applications of macrolides



C. Resistance

Resistance to macrolides is associated with: 1) the inability of the organism to take up the antibiotic, 2) the presence of efflux pumps, 3) a decreased affinity of the 50S ribosomal subunit for the antibiotic due to methylation of an adenine in the 23S bacterial ribosomal RNA in gram-positive organisms, and 4) the presence of plasmid-associated *erythromycin* esterases in gram-negative organisms such as the Enterobacteriaceae. *Erythromycin* has limited clinical use due to increasing resistance. Both *clarithromycin* and *azithromycin* share some cross-resistance with *erythromycin*. *Telithromycin* may be effective against macrolide-resistant organisms.

D. Pharmacokinetics

1. Absorption: The *erythromycin* base is destroyed by gastric acid; thus, either enteric-coated tablets or esterified forms of the antibiotic are administered and all have adequate oral absorption . *Clarithromycin, azithromycin,* and *telithromycin* are stable in stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin* and *azithromycin* but can increase that of *clarithromycin. Telithromycin* is administered orally without regard to meals. *Erythromycin* and *azithromycin* are available in IV formulations.

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

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

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

E. Adverse effects

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

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

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

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

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

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

FIDAXOMICIN

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

Fidaxomicin has a very narrow spectrum of activity limited to gram-positive aerobes and anaerobes. While it possesses activity against staphylococci and enterococci, it is used primarily for its bactericidal activity against Clostridium difficile. Because of the unique target site, cross-resistance with other antibiotic classes has not been documented.

Following oral administration, *fidaxomicin* has minimal systemic absorption and primarily remains within the gastrointestinal tract. This is ideal for the treatment of C. difficile infection, which occurs in the gut.

The most common adverse effects include nausea, vomiting, and abdominal pain. Anemia and neutropenia have been observed infrequently. Hypersensitivity reactions including angioedema, dyspnea, and pruritus have occurred. *Fidaxomicin* should be used with caution in patients with a macrolide allergy, as they may be at increased risk for hypersensitivity.

CHLORAMPHENICOL

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

A. Mechanism of action

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

B. Antibacterial spectrum

Chloramphenicol is active against many types of microorganisms including chlamydiae, rickettsiae, spirochetes, and anaerobes. The drug is primarily bacteriostatic, but it may exert bactericidal activity depending on the dose and organism.

C. Resistance

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

D. Pharmacokinetics

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

E. Adverse effects

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

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

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

CLINDAMYCIN

Clindamycin has a mechanism of action that is similar to that of the macrolides. *Clindamycin* is used primarily in the treatment of infections caused by gram-positive organisms, including MRSA and streptococcus, and anaerobic bacteria.

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

Clindamycin is available in both IV and oral formulations, but use of oral *clindamycin* is limited by gastrointestinal intolerance. It distributes well into all body fluids but exhibits poor entry into the CSF. *Clindamycin* undergoes extensive oxidative metabolism to active and inactive products and is excreted into bile and urine. Low urinary excretion of active drug limits its clinical utility for urinary tract infections. Accumulation has been reported in patients with either severe renal impairment or hepatic failure. In addition to skin rash, the most common adverse effect is diarrhea, which may represent a serious pseudomembranous colitis caused by overgrowth of C. difficile. Oral administration of either *metronidazole* or *vancomycin* is usually effective in the treatment of C. difficile infection.

QUINUPRISTIN/DALFOPRISTIN

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

A. Mechanism of action

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome. *Dalfopristin* disrupts elongation by interfering with the addition of new amino acids to the peptide chain. *Quinupristin* prevents elongation similar to the macrolides and causes release of incomplete peptide chains. Thus, they synergistically interrupt

protein synthesis. The combination drug has bactericidal activity against most susceptible organisms and has a long PAE.

B. Antibacterial spectrum

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

C. Resistance

Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 238 ribosomal RNA site can interfere in *quinupristin* binding. In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic. Plasmid associated acetyltransferase inactivates *dalfopristin.* An active efflux pump can also decrease levels of the antibiotics in bacteria.

D. Pharmacokinetics

Quinupristinldalfopristin is available intravenously. It does not achieve therapeutic concentrations in CSF. Both compounds undergo hepatic metabolism, with excretion mainly in the feces.

E. Adverse effects

Venous irritation commonly occurs when *quinupristin/dalfopristin* is administered through a peripheral rather than a central line.

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

OXAZOLIDINONES

Linezolid and *tedizolid* are synthetic oxazolidinones developed to combat gram-positive organisms, including resistant isolates such as *methicillin-resistant* Staphylococcus aureus, VRE, and *penicillin-resistant* streptococci.

A. Mechanism of action

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

B. Antibacterial spectrum

The antibacterial action of the oxazolidinones is directed primarily against gram-positive organisms such as staphylococci, streptococci, and enterococci, Corynebacterium species and Listeria monocytegenes. It is also moderately active against Mycobacterium tuberculosis. The main clinical use of *linezolid* and *tedizolid* is to treat infections caused by drug-resistant gram-positive organisms.

Like other agents that interfere with bacterial protein synthesis, *linezolid* and *tedizolid* are bacteriostatic; however, *linezolid* has bactericidal activity against streptococci. *Linezolid* is an alternative to *daptomycin* for infections caused by VRE. Because they are bacteriostatic, the oxazolidinones are not recommended as first-line treatment for MRSA bacteremia.

C. Resistance

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

D. Pharmacokinetics

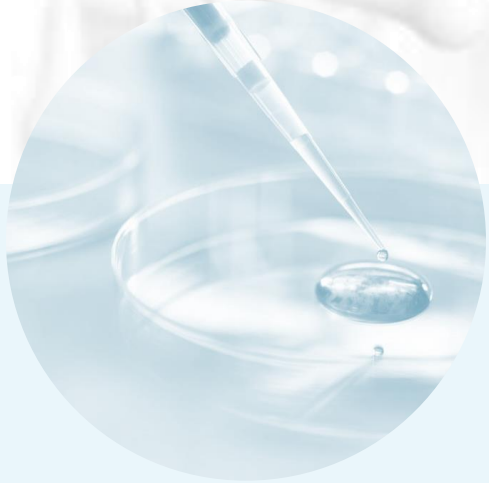
Linezolid and *tedizolid* are well absorbed after oral administration. IV formulations are also available. These drugs distribute widely throughout the body. Although the metabolic pathway of *linezolid* has not been fully determined, it is known that it is metabolized via oxidation to two inactive metabolites.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

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

E. Adverse effects

The most common adverse effects are gastrointestinal upset, nausea, diarrhea, headache, and rash. Thrombocytopenia has been reported, usually in patients taking the drug for longer than 10 days.

Linezolid and *tedizolid* possess nonselective monoamine oxidase activity and may lead to serotonin syndrome if given concomitantly with large quantities of tyramine-containing foods, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors. The condition is reversible when the drug is discontinued. Irreversible peripheral neuropathies and optic neuritis causing blindness have been associated with greater than 28 days of use, limiting utility for extended-duration treatments.



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