PROTEIN SYNTHESIS INHIBITORS
TETRACYCLINES (Tets)

Mechanism of action

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

Antibacterial spectrum

The Tets 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 (doxycycline).

Resistance

The most commonly encountered naturally occurring resistance to Tets is an efflux pump that expels drug out of the cell, thus preventing intracellular accumulation. Other mechanisms of bacterial resistance to Tets include enzymatic inactivation of the drug and production of bacterial proteins that prevent Tets from binding to the ribosome. Resistance to one Tet does not confer universal resistance to all Tets.

Pharmacokinetic:

1- Tets are adequately absorbed after oral ingestion.
2- They should not be administered with dairy products, magnesium and aluminium antacids or iron supplements as these materials can decrease absorption, particularly for Tet, due to the formation of nonabsorbable chelates.
3- The Tets concentrate well in the bile, liver, kidney, gingival fluid, and skin. Moreover, they bind to tissues undergoing calcification (for example, teeth and bones). Penetration into most body fluids is adequate. All Tets cross the placental barrier and concentrate in fetal bones and dentition.

Adverse effects

- **Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance with Tets. Esophagitis may be minimized through coadministration with food (other than dairy products) or [Note: Tet should be taken on an empty stomach.]
- **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. The use of Tets is limited in pediatrics.
- **Phototoxicity:** Severe sunburn may occur in patients receiving a Tet who are exposed to sun or ultraviolet rays. This toxicity is encountered with any Tet, but

more frequently with Tet. Patients should be advised to wear adequate sun protection.

- Dizziness, vertigo, and tinnitus may occur particularly with minocycline, which concentrates in the endolymph of the ear and affects function.
- **Contraindications:** The Tets should not be used in pregnant or breast-feeding women or in children less than 8 years of age.

Note: Tigecycline is a protein synthesis inhibitor, which is indicated for the treatment of complicated skin and soft tissue infections, as well as complicated intra-abdominal infections. Its adverse effects are similar to those of the Tets and include photosensitivity, discoloration of permanent teeth when used during tooth development, and fetal harm when administered in pregnancy. Acute pancreatitis, including fatality, has been reported with therapy.

Aminoglycosides (AGs)

AGs are used for the treatment of serious infections due to aerobic gram-negative bacilli. However, their clinical utility is limited by serious toxicities. AGs are derived from either Streptomyces sp. (have -mycin suffixes) or Micromonospora sp. (end in -micin).

Mechanism of action

AGs 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 resulting in protein synthesis disruption.

Antibiotics that disrupt protein synthesis are generally bacteriostatic; however, AGs are unique in that they are bactericidal. The bactericidal effect of AGs is concentration dependent; that is, efficacy is dependent on the maximum concentration (Cmax) of drug above the minimum inhibitory concentration (MIC) of the organism. For AGs, the target Cmax is eight to ten times the MIC. They also exhibit a postantibiotic effect (PAE), which is continued bacterial suppression after drug levels fall below the MIC.

Resistance

Resistance to AGs 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 AGs specificity; therefore, cross-resistance cannot be presumed.

Pharmacokinetics

- The highly polar, polycationic structure of the AGs prevents adequate absorption after oral administration. Therefore, all AGs (except neomycin) must be given parenterally to achieve adequate serum levels.
- More than 90% of the parenteral AGs are excreted unchanged in the urine. Accumulation occurs in patients with renal dysfunction, and dose adjustments are required.

Adverse effects

Therapeutic drug monitoring of gentamicin, tobramycin, and amikacin plasma levels is imperative to ensure adequacy of dosing and to minimize dose-related toxicities. The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1- **Ototoxicity:** Ototoxicity is directly related to high peak plasma levels and the duration of treatment. The antibiotic accumulates in the endolymph and perilymph of the inner ear. Deafness may be irreversible and has been known to affect developing fetuses. Patients simultaneously receiving concomitant ototoxic drugs, such as loop diuretics, are particularly at risk. Vertigo (especially in patients receiving streptomycin) may also occur.
2- **Nephrotoxicity:** Retention of the AGs 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:** This adverse effect is associated with a rapid increase in concentrations (for example, 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 (MCDs)

- Erythromycin was the first of these drugs to find 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 have some features in common with, and others that improve upon, erythromycin.
- Telithromycin, a semisynthetic derivative of erythromycin, is the first "ketolide" antimicrobial agent. Ketolides and macrolides have similar antimicrobial coverage. However, the ketolides are active against many macrolide-resistant gram-positive strains.

Mechanism of action

The macrolides 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.

Antibacterial spectrum

1. **Erythromycin:** This drug is effective against many of the same organisms as penicillin G. Therefore, it may be used in patients with penicillin allergy.
2. **Clarithromycin:** Clarithromycin has activity similar to erythromycin, but it is also effective against Haemophilus influenzae. Its activity against intracellular

pathogens, such as Chlamydia, Legionella, Moraxella, Ureaplasma species and Helicobacter pylori, is higher than that of erythromycin.

3. **Azithromycin:** Although less active than Ery against streptococci and staphylococci, *azithromycin* is far more active against respiratory pathogens such as H. influenzae and Moraxella catarrhalis. Extensive use of *azithromycin* has resulted in growing Streptococcus pneumoniae resistance.

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, resulting in gram-positive organisms, and 4) the presence of plasmid associated erythromycin esterases in gram-negative organisms such as Enterobacteriaceae.
- Resistance to erythromycin has been increasing, thereby limiting its clinical use (particularly for Streptococcus pneumoniae).
- Both clarithromycin and azithromycin share some cross-resistance with erythromycin, but telithromycin may be effective against macrolide resistant organisms.

Pharmacokinetics

- The Ery base is destroyed by gastric acid. Thus, enteric-coated tablets of antibiotic are administered, which is adequately absorbed upon oral administration.
- Clarithromycin, azithromycin, and telithromycin are stable in stomach acid and are readily absorbed.
- Food interferes with the absorption of Ery and azithromycin but can increase that of clarithromycin. Ery and azithromycin are available in IV formulations.
- Ery is one of the few antibiotics that diffuses into prostatic fluid, and it also accumulates in macrophages. Clarithromycin, azithromycin, and telithromycin are widely distributed in the tissues. Azithromycin has the longest half-life and the largest volume of distribution of the four drugs.
- Ery and telithromycin are extensively metabolized hepatically. 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.
- Clarithromycin and its metabolites are eliminated by the kidney as well as the liver. The dosage of this drug should be adjusted in patients with renal impairment.

Adverse effects

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

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

Contraindications: Patients with hepatic dysfunction should be treated cautiously with *erythromycin, telithromycin,* or *azithromycin,* because these drugs accumulate in the liver. Additionally, macrolides and ketolides may prolong the QTc interval and should be used with caution in those patients with proarrhythmic conditions or concomitant use of proarrhythmic agents.

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. In this case, the antibiotic eliminates a species of intestinal flora that ordinarily inactivates *digoxin*, thus leading to greater reabsorption of the drug from the enterohepatic circulation.

CHLORAMPHENICOL (CHL.)

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

Mechanism of action : CHL binds reversibly to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction. Due to some similarity of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating CHL levels, producing bone marrow toxicity.

Antibacterial spectrum

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

Resistance

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

Pharmacokinetics

CHL is administered intravenously and is widely distributed throughout the body. CHL primarily undergoes hepatic metabolism. So, dose reductions are necessary in patients with liver dysfunction or cirrhosis. It is also secreted into breast milk and should be avoided in breastfeeding mothers.

Adverse effects

1. **Anemias:** Patients may experience dose-related anemia, hemolytic anemia (seen 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. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes. This leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term "gray baby"), and death. Adults who have received very high doses of the drug can also exhibit this toxicity.
3. **Drug interactions:** *CHL* inhibits some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of drugs such as *warfarin* and *phenytoin*, thereby elevating their concentrations and potentiating their effects.

CLINDAMYCIN

- ✓ Clindamycin has a mechanism of action that is the same as that of erythromycin.
- ✓ 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.
- ✓ Clostridium difficile is always resistant to clindamycin, and the utility of clindamycin for G -ve anaerobes is decreasing due to increasing resistance.
- ✓ Clindamycin is available in both IV and oral formulations but use of the oral form is limited by gastrointestinal intolerance. It distributes well into all body fluids including bone but exhibits poor entry into the CSF.
- ✓ Clindamycin undergoes extensive oxidative metabolism to inactive products and is primarily excreted into the bile. Low urinary elimination 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 rashes, 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.