**Aminoglycosides.**

are used for the treatment of serious infections due to aerobic gram-negative bacilli. However, their clinical utility is limited by serious toxicities. The term "aminoglycoside" stems from their structure—two amino sugars joined by a glycosidic linkage to a central hexose nucleus. Aminoglycosides are derived from either Streptomyces sp. (have *–mycin* suffixes) or Micromonospora sp.

**Mechanism of action** Aminoglycosides diffuse through porin channels in the outer membrane of susceptible organisms. Antibiotics that disrupt protein synthesis are generally bacteriostatic, however aminoglycosides may be bactericidal against some microorganisms. 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.

**Absorption:** The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. It is administered topically for skin infections or orally for bowel preparation. More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine.

**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 (vestibular and auditory) 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 *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:** 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.*

**Spectinomycin**

Spectinomycin is an aminocyclitol antibiotic that is structurally related to aminoglycosides. It lacks amino sugars and glycosidic bonds. spectinomycin is used almost solely as an alternative treatment for gonorrohea in patients who are allergic to penicillin or whose gonococci are resistant to other drugs. Strains of gonococci may be resistant to spectinomycin, but there is no cross-resistance with other drugs used in gonorrhea. Spectinomycin is rapidly absorbed after intramuscular injection. Side effects ( pain at the injection site , fever , nausea, nephrotoxicity and anemia ).

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**TETRACYCLINES**

Tetracyclines consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings alter the individual pharmacokinetics and spectrum of antimicrobial activity.

**A. Mechanism of action**

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

**B. Antibacterial spectrum**

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 (*doxycycline*).

**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 and aluminum antacids or iron supplements) decreases absorption, particularly for *tetracycline* due to the

formation of nonabsorbable 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 a 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 levels 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* and *doxycycline* are not hepatically metabolized. *Tetracycline* is primarily eliminated unchanged in th urine, whereas *minocycline* undergoes hepatic metabolism and is eliminated to a lesser extent via the kidney. In renally compromised patients, *doxycycline* is preferred, 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. 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. *Doxycycline* may also cause vestibular dysfunction.

**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.

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**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 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* (having a larger lactone ring) 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 the bacterial ribosome, thus inhibiting protein synthesis. Generally considered to be bacteriostatic, they may be bactericidal at higher doses.

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 against streptococci and staphylococci than *erythromycin, azithromycin* is far more active against respiratory infections due to H. influenzae and Moraxella catarrhalis.
4. **Telithromycin**: This drug has an antimicrobial spectrum similar to that of *azithromycin.*

Pharmacokinetics

1. Administration: The *erythromycin* base is destroyed by gastric acid. Thus, either enteric-coated tablets or esterified forms of the antibiotic are administered. All are adequately absorbed upon oral administration . *Clarithromycin, azithromycin,* and *telithromycin* are stable in stomach acid and are readily absorbed. *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 diffuses 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* concentrates in neutrophils, macrophages, and fibroblasts, and serum levels are low. It has the longest half-life and the largest volume of distribution of the four drugs .

3. Excretion: *Erythromycin* and *azithromycin* are primarily concentrated and excreted in the bile as active drugs . Partial reabsorption occurs through the enterohepatic circulation. In contrast, *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: This side effect occurs especially with the estolate form (not used in the United States) of *erythromycin*.
3. Ototoxicity: Transient deafness has been associated with *erythromycin*, especially at high dosages. *Azithromycin* has also been associated with irreversible sensorineural hearing loss.
4. Contraindications: Patients with hepatic dysfunction should be treated cautiously with *erythromycin*, *telithromycin*, or *azithromycin*, because these drugs accumulate in the liver.

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**CHLORAMPHENICOL**

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

Mechanism of action

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

Antibacterial spectrum

*Chloramphenicol* 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.

Pharmacokinetics

*Chloramphenicol* is administered intravenously and is widely distributed throughout the body. It reaches therapeutic concentrations in the CSF. *Chloramphenicol* primarily undergoes hepatic metabolism (glucuronidation) and secreted by the renal tubule and eliminated in the urine. Dose reductions are necessary in patients with liver dysfunction or cirrhosis. It is also secreted into breast milk and should be avoided in breast feeding 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: *Chloramphenicol* 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 (methislin res. Staph.) and streptococcus, and anaerobic bacteria. Resistance mechanisms are the same as those for *erythromycin*, and cross-resistance has been described. C. difficile is always 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 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.

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## Antifolate

**Drugs Sulfonamides** **(** Sulfacytine, Sulfisoxazole, Sulfamethizole, Sulfadiazine, Sulfamethoxazole, Sulfapyridine, Sulfadoxine, Pyrimidines, Trimethoprim).

Susceptible microorganisms require extracellular PABA(*p*-aminobenzoic acid) in order to form dihydrofolic acid an essential step in the production of purines and the synthesis of nucleic acids. Sulfonamides are structural analogs of PABA that competitively inhibit dihydropteroate synthase.

Sulfonamides inhibit both gram- positive and gram-negative bacteria, nocardia, *Chlamydia trachomatis*, and some protozoa. Some enteric bacteria, such as *E coli*, klebsiella, salmonella, shigella, and enterobacter, are inhibited.

Sulfonamides can be divided into three major groups: (1) oral, absorbable; (2) oral, nonabsorbable; and (3) topical. Sodium salts of sulfonamides in 5% dextrose in water can be given intravenously. They are absorbed from the stomach and small intestine and distributed widely to tissues and body fluids (including the central nervous system and cerebrospinal fluid), placenta, and fetus. Sulfonamides are excreted into the urine.

Clinical Uses
Oral Absorbable Agents
1.**urinary tract infections**, sulfisoxazole or sulfamethoxazole.
**2.acute toxoplasmosis**: Sulfadiazine with pyrimethamine .Folinic acid, should also be administered to minimize bone marrow suppression.

Oral Nonabsorbable Agents

Sulfasalazine is widely used in ulcerative colitis, enteritis, and other **inflammatory bowel disease**.

Topical Agents
**1.Bacterial conjunctivitis** and **:** Sodium sulfacetamide.
**2.Burn wounds** : Silver sulfadiazine is a much less toxic topical sulfonamide and is used for prevention of infection of burn wounds.

Adverse Reactions:
fever, skin rashes, exfoliative dermatitis, photosensitivity, urticaria, nausea, vomiting, diarrhea, and difficulties referable to the urinary tract. Stevens-Johnson syndrome, potentially fatal type (eruption of skin & mucous membrean)in 1%.

## Trimethoprim & Trimethoprim-Sulfamethoxazole Mixtures

Trimethoprim, inhibits bacterial dihydrofolic acid reductase leading to inhibition of the synthesis of purines and ultimately to DNA. Trimethoprim & pyrimethamine, given together with sulfonamides, resulting in marked enhancement (synergism) of the activity of both drugs. The combination often is bactericidal, compared to the bacteriostatic activity of a sulfonamide alone.

Pharmacokinetics
Trimethoprim is usually given **orally**, alone or in combination with sulfamethoxazole, the latter chosen because it has a similar half-life. Trimethoprim-sulfamethoxazole can also be given **intravenously**. Trimethoprim is absorbed efficiently from the gut and distributed widely in body fluids and tissues, including cerebrospinal fluid, sulfonamide and of the trimethoprim (or their respective metabolites) are excreted in the urine within 24 hours.Trimethoprim concentrates in prostatic fluid and in vaginal fluid, which are more

acidic than plasma. Therefore, it has more antibacterial activity in prostatic and vaginal fluids than many other antimicrobial drugs.

Clinical Uses
a.Oral Trimethoprim
Trimethoprim can be given alone in **acute urinary tract infections**.

b.Oral Trimethoprim-Sulfamethoxazole
combination of trimethoprim-sulfamethoxazole (cotrimoxazole)is effective treatment for **pneumonia**, **shigellosis**, **systemic salmonella infections** (caused by ampicillin- or chloramphenicol-resistant organisms), **complicated urinary tract infections**, **prostatitis**, some **nontuberculous mycobacterial infections**, , **upper respiratory tract infections** and **community-acquired bacterial pneumonia**.

c.Intravenous Trimethoprim-Sulfamethoxazole
A solution of the mixture containing trimethoprim plus sulfamethoxazole diluted in 5% dextrose in water can be administered by intravenous infusion s. It is the agent of choice for moderately severe to severe **pneumocystis pneumonia**, **gram-negative bacterial sepsis**; **shigellosis**; **typhoid fever**; or **urinary tract infection** caused by a susceptible organism when the patient is unable to take the drug by mouth.

Adverse Effects
megaloblastic anemia, leukopenia, and granulocytopenia. This can be prevented by the simultaneous administration of folinic acid. In addition, the combination trimethoprim-sulfamethoxazole may cause all of the untoward reactions associated with sulfonamides. Nausea and vomiting, drug fever, vasculitis, renal damage, and central nervous system disturbances occasionally occur also.
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## DNA Gyrase Inhibitors

**Fluoroquinolones** (Ciprofloxacin, Clinafloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin, Sparfloxacin, Trovafloxacin).They are active against a variety of gram-positive and gram-negative bacteria. Quinolones block bacterial DNA synthesis by inhibiting bacterial DNA gyrase. Inhibition of DNA gyrase prevents the normal transcription and replication.

Pharmacokinetics
After oral administration, the fluoroquinolones are well absorbed and distributed widely in body fluids and tissues. Serum half-lives range from 3 hours up to 10. The relatively long half-lives of levofloxacin, moxifloxacin, sparfloxacin, and trovafloxacin permit once-daily dosing.
. Most fluoroquinolones are eliminated by renal mechanisms, either tubular secretion or glomerular filtration. Nonrenally cleared fluoroquinolones are contraindicated in patients with hepatic failure.

Clinical Uses

1-**urinary tract infections** Norfloxacin, ciprofloxacin, and ofloxacin given orally twice daily are all effective.

2-**bacterial diarrhea (** shigella, salmonella, toxigenic *E coli,* or campylobacter)

3- **infections of soft tissues**, **bones, and joints and in intra-abdominal and respiratory tract infections** Fluoroquinolones (except norfloxacin, which does not achieve adequate systemic concentrations) have been employed in**,** including those caused by multidrug-resistant organisms such as pseudomonas and enterobacter.

**4-gonococcal infection**: Ciprofloxacin and ofloxacin

**5-chlamydial urethritis or cervicitis** ofloxacin is effective for.

Owing to their marginal activity against the pneumococcus, fluoroquinolones have not been routinely recommended for empirical treatment of pneumonia and other upper respiratory tract infections.

Adverse Effect

Fluoroquinolones are extremely well tolerated. The most common effects are nausea, vomiting, and diarrhea. Occasionally, headache, dizziness, insomnia, skin rash, or abnormal liver function tests develop. Fluoroquinolones may damage growing cartilage and cause an arthropathy. Thus, they are not routinely recommended for use in patients under 18 years of age. However, the arthropathy is reversible, and there is a growing consensus that fluoroquinolones may be used in children in some cases (eg, for treatment of pseudomonal infections in patients with cystic fibrosis).

**Nalidixic Acid & Cinoxacin**

Nalidixic acid, the first antibacterial quinolone. It is excreted too rapidly to be useful for systemic infections. Their mechanism of action is the same as that of the fluoroquinolones. These agents were useful only for the treatment of urinary tract infections and are rarely used now.