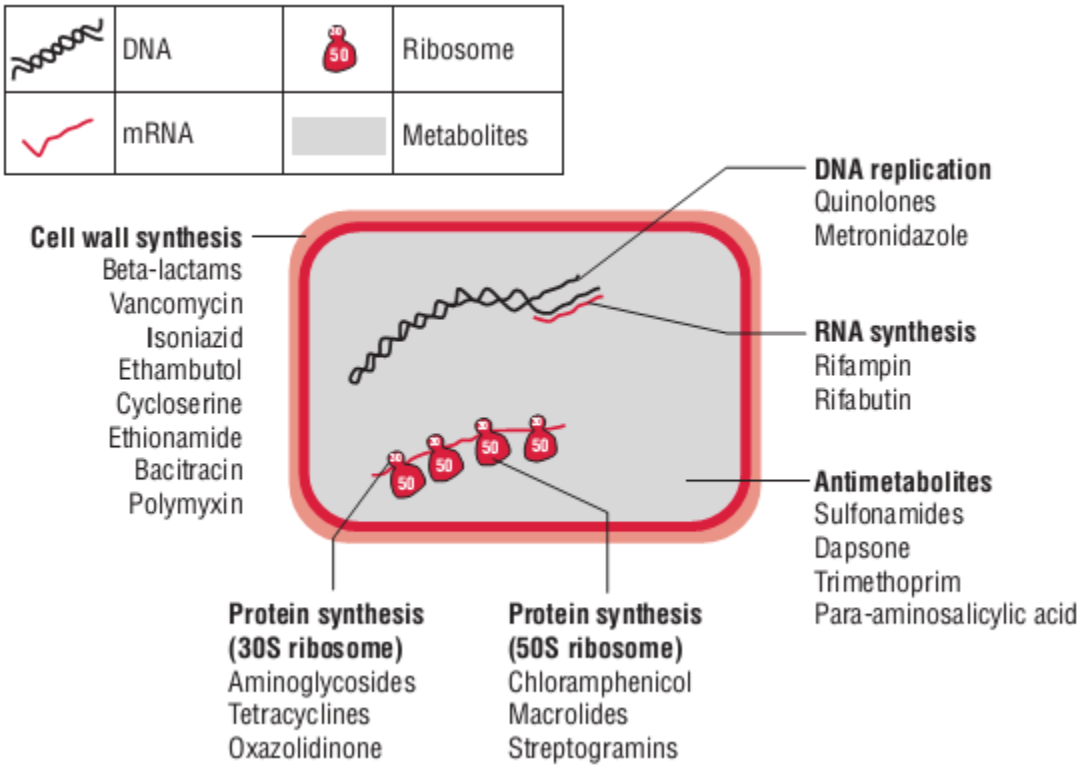
1.2 CLASSES OF ANTIMICROBIAL AGENTS AND THEIR MECHANISMS OF ACTION

Antibacterial drugs

Their mechanisms of action fall into four categories: inhibition of cell wall synthesis, damage to cell membrane function, inhibition of nucleic acid synthesis or function, and inhibition of protein synthesis.

Mechanism of action for antibacterial agents

There are five main target sites for antibacterial action, see the diagram below.

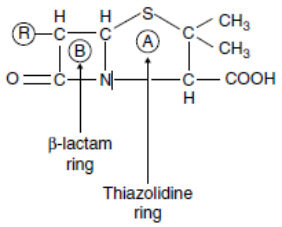


1.2.1 BETA-LACTAM ANTIBIOTICS

All β-lactam antibiotics contain a beta-lactam ring and include penicillins, cephalosporins, carbapenems, monobactams, and penems.

Penam penicillins

Penicillin was originally extracted from *Penicillium notatum* but now it is collected from a related mutant mould *P. chrysogenum*. **Penicillins** contain the active moiety, 6-aminopenicillanic acid (essential for antibacterial activity) which consists of a thiazolidine ring (A) attached to a beta-lactam ring (B) that carries a secondary amino group (R-NH-) (as illustrated).



Substitutions can be made on the beta-lactam ring to synthesize other molecules.

Mechanism of action of Beta-lactam antibiotics

Beta-lactam antibiotics prevent the bacterial cell wall from forming by interfering with the final stage of peptidoglycan synthesis. They inhibit the activity of the transpeptidases and other peptidoglycan-active enzymes called penicillin binding proteins (PBPs; transpeptidases, carboxypeptidases). PBPs are found on the outside of the cytoplasmic membrane and are involved in synthesizing and remodelling the cell wall, i.e., they catalyze cross-linkage of the glycopeptide polymer units that form the cell wall. The targets of all beta-lactam drugs are the PBPs, i.e., penicillins target 4-7 PBPs that are present in bacteria. The susceptibility of a bacterium to penicillin depends on a combination of affinity for the PBP, ability to penetrate the cell wall, and ability to resist beta-lactamase enzymes. Beta-lactam drugs are bactericidal, but cause lysis only of growing cells, i.e., those undergoing active cell-wall synthesis. In addition to interfering with transpeptidation, many of these drugs promote autolysin activity causing cell lysis. Tolerance to β-lactam antibiotics exhibited by some bacteria may relate to an inability of the antibiotic to induce autolysin activity.

Categorisation of 6-aminopenicillanic acid derivatives (Penam penicillins)

Group	Important Derivatives	Antimicrobial Advantage
1. Benzyl penicillins	Procaine (long-acting form)	Gram-positive bacteria
2. Orally absorbed benzyl penicillins	Phenoxymethyl penicillin	Gram-positive bacteria
3. Antistaphylococcal isoxazolyl penicillins	Cloxacillin, dicloxacillin, oxacillin, methicillin, nafcillin	Activity against penicillinase-producing (but not methicillin-resistant) *S. aureus* and *S. pseudintermedius*
4. Extended- (broad) spectrum penicillins	Aminobenzylpenicillins (ampicillin, hetacillin, pivampicillin, amoxicillin); amidopenicillins (mecillinam)	Broader spectrum than benzyl penicillins, but beta-lactamase sensitive
5. Antipseudomonal penicillins	Ureidopenicillins (azlocillin, mezlocillin, piperacillin); carboxypenicillins (carbenicillin, ticarcillin)	*P. aeruginosa* activity, reduced Gram-positive activity
6. Beta-lactamase-resistant penicillins	Temocillin	Beta-lactamase resistance (but not methicillin resistance)

Pharmacokinetic properties

The penicillins are organic acids that are generally available as the sodium or potassium salt of the free acid. The penicillins are predominantly ionized in plasma; they are generally distributed widely throughout the body, they are bound in varying degrees to plasma proteins and they cross the placenta. Most penicillins are rapidly excreted largely unchanged by the kidneys into the urine.

Drug interactions

Penicillins have synergistic activity against certain bacteria when used with aminoglycosides or cephalosporins or with beta-lactamase inhibitors. Aminobenzylpenicillins and ureidopenicillins are increasingly combined with betalactamase inhibitors (e.g., amoxicillin-potassium clavulanate). Use of bacteriostatic antibiotics (e.g., tetracyclines) with penicillins is generally not recommended.

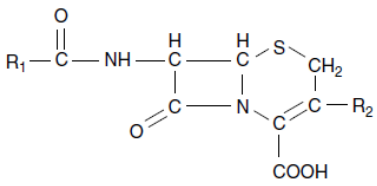
Toxicity and adverse effects

Beta-lactam antibiotics generally are remarkably free of toxic effects even at overdosage. The major adverse effects are acute anaphylaxis (less common when given per os rather than after injection) and collapse; milder hypersensitivity reactions (urticaria, fever, angioneurotic oedema) are more common. All penicillins are cross-sensitizing and cross-reacting. Less common adverse reactions include haemolytic anemia and thrombocytopenia.

Cephalosporins

They differ from penicillins in having 7-aminocephalosporanic acid instead of 6-aminopenicillanic acid in their structure. The 7-aminocephalosporanic acid molecule provides more sites than the aminopenicillanic acid molecule for manipulating the production of semisynthetic drugs.

Structural formula of the cephalosporin nucleus



Changes at position 7 (R1) alter beta-lactamase stability and antibacterial properties particularly whereas changes at position 3 (R2) tend to alter metabolic stability and pharmacokinetic properties. True cephalosporins contain the common 7-aminocephalosporanic acid of *Cephalosporium acremonium*, whereas cephamycins are derived from *Streptomyces* species or are synthetic derivatives produced by substituting oxygen for sulfur.

Antimicrobial activity and pharmacokinetic properties

The mechanism of action of the cephalosporins is that of beta-lactam antibiotics. Cephalosporins are bactericidal and are effective against both Gram-positive and Gram-negative bacteria and are stable to many bacterial β-lactamases. The basic pharmacokinetic and drug disposition characteristics of cephalosporins are typical of beta-lactams, with an elimination half-life of 1-2 hours. Some drugs, however (e.g., cefotetan and ceftriaxone) have significantly longer half-lives. Clearance is through the kidney in most cases although drugs with high molecular weight and protein binding, such as cefoperazone, are largely excreted in the bile.

Classification of cephalosporins into groups (and generations)

By convention, cephalosporins discovered before 1975 are spelled with a "ph" and after 1975 with a "f." Based on route of administration and antibacterial activity, cephalosporins are grouped as follows.

Group	Characteristics	Examples
1 (first generation)	Parenteral; resistant to staphylococcal beta-lactamase; sensitive to enterobacterial beta-lactamase; moderately active	Cephacetrile, cephaloridine, cephalothin, cephapirin, cephazolin
2 (first generation)	Oral; resistant to staphylococcal beta-lactamase; moderately resistant to some enterobacterial beta-lactamase; moderately active	Cefadroxil, cephadrine, cephalexin
3 (second generation)	Parenteral; resistant to many beta-lactamases; moderately active	Cefaclor, cefotetan, cefoxitin, cefuroxime, cefamandole
4 (third generation)	Parenteral; resistant to many beta-lactamases; highly active	Cefotaxime, ceftiofur, ceftriaxone, latamoxef
5 (third generation)	Oral; resistant to many beta-lactamases; highly active	Cefetamet, cefixime, cefpodoxime
6 (third generation)	Parenteral; resistant to many beta-lactamases; active against *Pseudomonas aeruginosa*	Cefoperazone, cefovecin, cefsulodin, ceftazidime
7 (fourth generation); included with group 6 in some classifications	Parenteral; resistant staphylococcal, enterobacterial, and pseudomonal beta-lactamases; highly active	Cefepime, cefquinome, cefpirome

Drug interactions

Cephalosporins are synergistic with aminoglycosides.

Toxicity and adverse effects

Cephalosporins are among the safest antimicrobial drugs, although individual drugs may have specific adverse effects. For example, hypoprothrombinamia and platelet abnormalities causing bleeding disorders have been noted with some newer cephalosporins. The broad spectrum of antibacterial activity of 2nd to 4th generation drugs may cause overgrowth of the patients by inherently resistant bacteria including *Clostridium difficile*, which no longer have to compete with susceptible members of the microbial flora.

The emergence of multiresistant enterococci as nosocomial infections in human hospital intensive care units is an example of this effect. Gastrointestinal disturbances are among adverse effects, particularly with drugs excreted through the bile. Human patients allergic to penicillin are sometimes (5–8%) also allergic to cephalosporins. Many 2nd and 3rd generation drugs are painful on injection and are usually administered IV or per os.

Beta-lactamase inhibitors, carbapenems, and monobactams

Carbapenem and monobactam class antibiotics have been introduced into human medicine but none have been approved for use in veterinary medicine; however, some beta-lactamase inhibitors (clavulanate, sulbactam, tazobactam) have been successfully introduced into veterinary medicine in combination with aminobenzylpenicillins, producing broad-spectrum antibacterial drugs that overcome the limitations some of the acquired resistance had placed on the older extended-spectrum penicillins.

Beta-lactamase inhibitors

They have little antibacterial activity in their own right but have a high affinity for beta-lactamases, and can be administered with a beta-lactam that would be highly active against the pathogen if it were not for its beta-lactamases. Their binding to these inhibitors is irreversible, thus allowing the active beta-lactam to kill the organism since beta-lactamase is effectively absent.

Pharmacokinetic properties

Clavulanate is well absorbed after oral administration and has pharmacokinetic properties similar to amoxicillin. Half-life is about 75 minutes. The drug is largely eliminated unchanged in the urine. Interesting, in dogs, higher doses than those recommended for treatment appear to show an inhibitory effect of amoxicillin on the absorption of the clavulanate component, but the significance of this observation is unclear.

Toxicity and side effects

The combination is well tolerated. Mild gastrointestinal upset has been reported in dogs and cats. Other side effects are those of penicillins generally. The drug should not be administered orally to herbivores or by injection to horses. It should also not be used in rabbits, guinea pigs, hamsters, or gerbils.

Administration

Clavulanate is highly moisture sensitive; precautions must be taken to ensure dryness during storage.

Other examples of non B-lactams antibiotics that inhibit cell wall synthesis include **isoniazid, ethionamide and ethambutol**; they are used to treat mycobacterial infections.

1.2.2 PEPTIDE ANTIBIOTICS: polymyxins, glycopeptides, bacitracin, and fosfomycin

Polymyxins

The polymyxins are isolated from *Bacillus polymyxa* subspecies *colistinus*; the only polymyxins used clinically are Polymyxin E (colistin) and polymyxin B (a mixture of two closely related compounds: polymyxin B1 and polymyxin B2). In horses, dogs and cats, there is interest in their systemic use at subantimicrobial doses for binding and inactivating endotoxin.

Chemistry

Polymyxins are basic cyclic decapeptides. Polymyxin E is chemically related to polymyxin B. Dosages are given in International Units or metric units depending on the source; 10 units of polymyxin B = 1 μg, 10 units of colistin sulphate or colistin methanesulphonate = 0.5 μg. They are stable, highly water-soluble drugs.

Mechanism of action

Polymyxins are cationic, surface-active agents that displace Mg_2^+ or Ca_2^+ and disrupt the structure of cell membrane phospholipids and increase cell permeability by a detergent-like action. Polymyxins disorganize the outer membrane of Gram-negative bacteria by binding lipopolysaccharides (LPS, a.k.a. endotoxin) through direct interaction with the anionic lipid A region; this action neutralizes the endotoxin capacity of LPS.

Antimicrobial Activity

Polymyxin B and colistin are similarly rapidly bactericidal and highly active against many species of Gram negative organisms. Polymyxin B is primarily used for resistant Gram-negative infections; it is effective against almost all Gram-negative bacilli except the *Proteus* group.

Pharmacokinetic properties

The polymyxins are not absorbed from the GI tract. Polymyxins bind moderately to plasma proteins but extensively to muscle tissue, diffuse poorly through biologic membranes, and attain low concentrations in transcellular fluids and in milk. The strong affinity of the polymyxins to the muscle tissue results in persistent drug residues. The polymyxins are slowly excreted unchanged by glomerular filtration into urine.

Drug interactions

Polymyxins are synergistic with a variety of antimicrobial drugs through their disorganizing effects on the outer and cytoplasmic membranes. To widen the range of antimicrobial activity, neomycin and bacitracin are combined with polymyxin B in topical preparations.

Toxicity and side effects

Polymyxins are well tolerated after oral or local administration, but systemic use causes nephrotoxic (acute renal tubular necrosis), neurotoxic, and neuromuscular blocking effects. Colistin is less toxic than polymyxin B. Anaphylactic reactions occurred in cats after applying ophthalmic formulations containing polymyxins B, whereas pemphigus vulgaris developed in dog after instilling ear drops of polymyxin B.

Glycopeptides: vancomycin, teicoplanin, and avoparcin

Vancomycin, teicoplanin, and avoparcin are glycopeptides antibiotics with activity against Gram-positive bacteria and particularly against Gram-positive cocci. Vancomycin and teicoplanin are currently available as formulations for human use in various parts of the world, whereas avoparcin is only available for veterinary use in some countries. Vancomycin and teicoplanin have often been considered the drugs of "last resort" for serious staphylococcal and enterococcal infections.

Mechanism of action

The glycopeptides are large, rigid molecules that inhibit bacterial cell wall peptidoglycan synthesis. Their three-dimensional structure contains a cleft into which peptides of only a highly specific configuration can fit (D-alanyl-D-alanine: this configuration is found only in Gram positive bacteria cell walls).

Avoparcin

Avoparcin was used extensively as an antibiotic growth promoter in poultry and swine in Europe. The recognition that it selected for vancomycin-resistant enterococci (VRE) in animals, and VRE contaminated a high proportion of meat products derived from these animals, led to its withdrawal from use in Europe.

BACITRACIN

Bacitracin is a polypeptide product of *Bacillus subtilis*; it inhibits the formation of bacterial cell-wall peptidoglycan by complexing directly with the pyrophosphate carrier and inhibiting the dephosphorylation reaction required for its regeneration. It is bactericidal to Gram-positive bacteria but has little activity against Gram-negative bacteria. Bacitracin is not absorbed from the GI tract, i.e., no residues are found in meat when the product is given per os. Bacitracin is often combined with neomycin and polymyxin B for broad-spectrum activity in treating minor skin wounds or bacterial keratitis. Bacitracin is considered a first line treatment in horses and in some countries; it is given per os in poultry and swine for growth promotion and for prevention and treatment of enteritis.

FOSFOMYCIN

Fosfomycin is a phosphoenolpyruvate analogue that irreversibly inhibits pyruvyl transferase, the enzyme catalysing the first step of peptidoglycan biosynthesis. It is produced by various *Streptomyces spp*. It has a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria. It is highly active against Gram-positive pathogens such as *Staphylococcus aureus* and *Enterococcus*, and against Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Klebsiella pneumonia.* It may provide a synergistic effect to other classes of antibiotics including beta-lactams, aminoglycosides, and fluoroquinolones. Fosfomycin is considered a time-dependent antimicrobial. Activity is reduced by alkaline pH and the presence of glucose, sodium chloride or phosphates in culture media.

Resistance, which can be chromosomal or plasmid-mediated, is uncommon. There is no cross resistance with other antibacterial drugs; there is increasing interest in the use of fosfomycin in treating multidrug-resistant Gram-negative infections in veterinary species.

1.2.3 LINCOSAMIDES, PLEUROMUTILINS, AND STREPTOGRAMINS

These drugs are structurally distinct but share many common properties; they are basic compounds characterized by high lipid solubility, wide distribution in the body, and capacity to penetrate cellular barriers.

Lincosamides: lincomycin, clindamycin, and pirlimycin

Chemistry

Clindamycin is a chlorine substitute derivative of lincomycin (the parent compound); the latter one was originally isolated from *Streptomyces lincolnensis*. Pirlimycin, a clindamycin analog, is approved as an intramammary infusion for treating mastitis in cattle. Clindamycin binds to the ribosomal 50S unit and thereby blocks protein elongation. Clindamycin and lincomycin are more effective antibacterial agents for anaerobes.

Mechanism of action

The lincosamides inhibit protein synthesis by binding to the 50S ribosomal subunit and inhibiting peptidyl transferases. The ribosomal binding sites are the same as or closely related to those that bind macrolides, streptogramins, and chloramphenicol. Lincosamides can be bactericidal or bacteriostatic, depending on the drug concentration, bacterial species, and inoculum of bacteria.

Antimicrobial activity

Lincosamides are moderate-spectrum antimicrobial drugs; they are active against Gram-positive bacteria [*Bacillus spp*., *Corynebacterium spp., Erysipelothrix rhusiopathiae*, staphylococci, streptococci (but not enterococci)], anaerobic bacteria (*Actinomyces spp*., *Fusobacterium spp*., *Bacteroides spp*., and *C. perfringens)* and some mycoplasma. They lack activity against most Gram-negative bacteria, but are effective against *Campylobacter jejuni*. The lincosamides may be useful in treating *Pneumocystis jiroveci* infection and *Toxoplasma gondii.*

Pharmacokinetic properties

Lincosamides are basic compounds with pKa values of about 7.6. They have high lipid solubility and consequently large apparent volumes of distribution. They are well absorbed from the intestine of non-herbivores and eliminated mainly by hepatic metabolism, although about 20% is eliminated in active form in the urine.

Because of the lincosamide's basic character, ion trapping also occurs in tissues, such as the udder and prostate where pH is lower than blood.

Drug interactions

Combination with spectinomycin appears to give marginally enhanced activity against mycoplasmas *in vitro*. Clindamycin is commonly combined with an aminoglycoside or a fluoroquinolone in human medicine to treat or prevent mixed aerobic-anaerobic bacterial infections, particularly those associated with intestinal spillage into the peritoneum. Clindamycin has synergistic effects with metronidazole against *Bacteroides fragilis* but only additive effects with trimethoprim-sulfamethoxazole combination against common Gram-negative or Gram-positive aerobes. Combination with macrolides Combination with macrolides or chloramphenicol is antagonistic *in vitro*.

Toxicity and adverse effects

The major toxic effect of the lincosamides is their ability to cause serious and fatal diarrhea in humans, horses, rabbits, and other herbivores.

Pleuromutilins: tiamulin and valnemulin

Tiamulin and valnemulin are semisynthetic derivatives of the naturally occurring diterpene antibiotic pleuromutilin. Pleuromutilins have outstanding activity against anaerobic bacteria and mycoplasma and are used almost exclusively in animals, largely in swine.

Mechanism of action

Pleuromutilin antibiotic derivatives inhibit protein synthesis by binding to the 50S subunit of the bacteria. Tiamulin and valnemulin are strong inhibitors of peptidyl transferase.

Drug interactions

There is little information on drug interactions of pleuromutilins with other drugs, are likely to be similar to those described for lincosamides and macrolides. Tiamulin and valnemulin have been shown to interact with ionophores. Animals should not receive these products during at least 5 days before or after treatment with pleuromutilins. Tiamulin is preferred over macrolides for many infections.

Toxicity and side effects

Tiamulin should not be fed at therapeutic concentrations with ionophores such as monensin, narasin, and salinomycin to animals (pigs, poultry) because of the dose-dependent fatal effects of such combinations, i.e., tiamulin's potent inducer-inhibiting activity against cytochrome P-450 in the liver.

Streptogramins

Streptogramins are a group of natural (virginiamycin, pristinamycin) or semisynthetic (quinupristin /dalfopristin) cyclic peptides. The natural streptogramines are produced as secondary metabolites by *Streptomyces spp.* Streptogramins are unique among antibiotics since each member of the class consists of at least two structurally unrelated molecules: group A streptogramins (macrolactones) and group B streptogramins (cyclic hexadepsipeptides). Virginiamycin has been developed largely as a growth promoter and has been studied in veterinary species.

Mechanism of action

Streptogramins inhibit bacterial protein synthesis by undergoing strong irreversible binding to the 50S ribosomal subunit. The group A and B streptogramins bind to separate sites on the 50S subunit of the bacterial ribosome. Binding of group A streptogramins to the ribosome induces a conformational change that increases affinity of the ribosome for group B compounds. Group A streptogramins prevent peptide bond formation during the chain elongation step, while group B components cause the release of the incomplete peptide chains from the 50S ribosomal subunit. The group B streptogramins share an overlapping binding site with macrolides and lincosamides on the ribosome even though these antimicrobials are structurally unrelated to each other. Individually, the A and B compounds are bacteriostatic, whereas in combination they are bactericidal. Their synergistic activity tends to reduce the emergence of bacteria resistance to either drug.

Virginiamycin

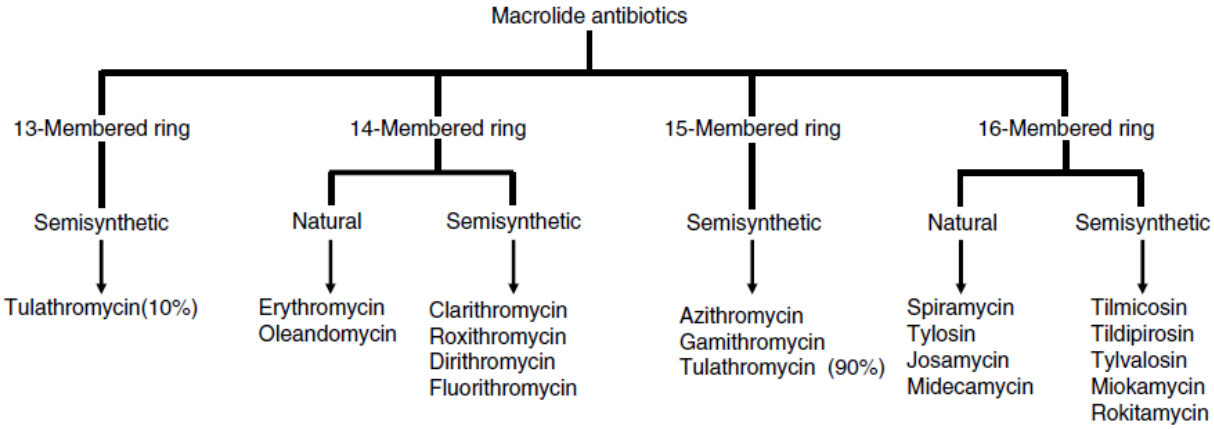
Virginiamycin is an antibiotic mixture of virginiamycin S (group B) and virginiamycin M (group A), produced as a fermentation product of *Streptomyces virginiae*. The drug is mainly active against Gram-positive aerobic and anaerobic bacteria (such as *Clostridium perfringens*). Most Gram-negative bacteria are resistant: *Histophilus*, *Lawsonia intracellularis*, *Leptospira* spp., and *B. hyodysenteriae* are exceptions. *Mycoplasma spp*. are often susceptible.

1.2.4 MACROLIDES, AZALIDES, AND KETOLIDES

The macrolide antibiotics contain 12- to 22-carbon lactone rings linked to one or more sugars.

The macrolides are classified according to the number of atoms comprising the lactone ring.

Classification of macrolide antimicrobials according to the size of the macrocyclic lactone ring



Tulathromycin, a semisynthetic macrolide approved for use in swine and cattle, consists of an equilibrated regioisomeric mixture of a 13-membered ring (10%) and a 15-membered ring (90%). The unique structural feature of this antimicrobial places it in a novel category of macrolides termed **triamilides**. The 15-membered ring macrolides are termed **azalides** as they have a nitrogen atom in the lactone ring. **Ketolides** are members of a new semisynthetic 14-membered ring macrolide, with a 3-keto group instead of an α-L-cladinose on the erythronolide A ring.

The two most widely studied ketolides are telithromycin and cethromycin. Their spectrum of activity is similar to that of the newer generation macrolides. The macrolides exhibit broad distribution in tissues and, in the case of some of the newer drugs, prolonged half-lives. They also have excellent activity against many important bacterial pathogens of animals. The macrolides are also known for their intracellular accumulation within phagocytes.

Mechanism of action

Macrolides inhibit protein synthesis by reversibly binding to 50S subunits of the ribosome. They inhibit the transpeptidation and translocation process, causing premature detachment of incomplete polypeptide chains. Their binding sites on the 23S rRNA of the 50S ribosomal subunit overlap with that of lincosamides, streptogramins, ketolides and oxazolidinones but are different from those of chloramphenicol. Macrolides are generally bacteriostatic agents but they may be bactericidal at high concentrations and against a low inoculum of some highly susceptible bacteria.

Drug interactions

There are few studies of the interactions of macrolide antibiotics with other antimicrobial drugs, combination of a macrolide and a fluoroquinolone or aminoglycoside may be synergistic, antagonistic, or indifferent depending on the microorganism studied.

Anti-inflammatory property of macrolides

Macrolides have immunomodulatory effects that are beneficial for humans suffering from many inflammatory pulmonary diseases such as cystic fibrosis, idiopatic bronchiectasis, and chronic obstructive pulmonary disease. The mechanisms of action for the anti-inflammatory properties of the macrolides are multifactorial and still under investigation. Macrolides inhibit the production of many pro-inflammatory cytokines including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-α by suppressing the transcription factor nuclear factor-kappa B or activator protein-1. Macrolides also inhibit formation of leukotriene B4, which attracts neutrophils and inhibit superoxide anion release by neutrophils that may be present in the airway.

In addition, macrolides block formation of adhesion molecules necessary for neutrophil migration. These anti-inflammatory and immunomodulatory effects have been described in animals such as foals, cattle and pigs. Macrolides approved for veterinary use include erythromycin, tylosin, spiramycin, tilmicosin, tulathromycin, gamithromycin, tildipirosin, and tylvalosin.

Erythromycin

Erythromycins are produced as a complex of six components (A to F) by *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*). Only erythromycin A has been developed for clinical use. Erythromycin has a macrocyclic lactone nucleus to which ketones and amino sugars are attached. Its base has a pKa of 8.8, is poorly soluble in water, and is unstable in gastric acid.

Antimicrobial Activity

Good susceptibility is generally seen in the following Gram-positive aerobes: *Bacillus* spp., *Corynebacterium spp., Erysipelothrix rhusiopathiae, Listeria spp*., *Rhodococcus equi*, staphylococci, and streptococci. Among Gram-negative aerobes: *Actinobacillus spp*., *Brucella spp*.; *Campylobacter spp*., *Leptospira spp*. Anaerobic bacteria: *Actinomyces spp., Bacteroides spp*. (except *B. fragilis*), *Clostridium spp*., some *Fusobacterium spp*., and anaerobic cocci. Erythromycin is also active against some *Chlamydia*/*Chlamydophila spp*. and *Mycoplasma* spp.

Pharmacokinetic properties

The erythromycin base is highly susceptible to degradation from gastric acids. Like all macrolides, erythromycin is well distributed in the body, being concentrated in tissues, although penetration into CSF is low. The drug is metabolized and excreted largely in the bile and, although some intestinal reabsorption occurs, most is lost in faeces. Urinary excretion is only 3–5% of the total applied dose.

Toxicity and side effects

One problem shared with all macrolides is their irritating nature, which leads to severe pain on IM injection, thrombophlebitis and periphlebitis after IV injection and an inflammatory reaction after intramammary administration. Dose-related gastrointestinal disturbances (nausea, vomiting, diarrhea, intestinal pain) occur in most animals species treated with erythromycin, either as a result of disruption of the normal intestinal microflora or as a result of stimulatory effects on smooth muscle because erythromycin binds motilin receptors. These adverse effects are not life threatening except in adult horses, where macrolides, because they are largely excreted in the bile, can lead to serious diarrheic illness.

Tylosin

Tylosin is a macrolide antibiotic isolated from *Streptomyces fradiae*. Its chemical structure and its mechanism of action is similar to other macrolide antibiotics.

Pharmacokinetic properties

The pharmacokinetic properties of tylosin are characteristic of the macrolides in general.

Toxicity and adverse effects

Tylosin is a relatively safe drug. Its toxic effects are usually similar to those reported for erythromycin.

Advanced-generation macrolide antibiotics: roxithromycin, clarithromycin, and azithromycin are effective against traditional and emerging human pathogens, including *Campylobacter spp*., *Helicobacter spp*., *Legionella spp*., as well as against intracellular organisms that have emerged through the AIDS epidemic, such as *Bartonella spp*. and *Mycobacterium spp.*

1.2.5 AMINOGLYCOSIDES

The aminoglycosides are also referred to as aminocyclitols or aminoglycosidic aminocyclitols. are bactericidal antibiotics primarily used to treat serious infections caused by aerobic Gram-negative bacteria and staphylococci. Renal accumulation of aminoglycosides results in detectable drug residues for prolonged periods, so their extra-label use in food animals is strongly discouraged.

Chemistry

Chemically, they consist of a hexose nucleus, to which amino sugars are attached by glycosidic linkages. Based on the type and substitution pattern of their aminocyclitol molecule, they can be divided into 4 groups: derivatives containing the aminocyclitol streptidine (e.g., **streptomycin** and dihydrostreptomycin), derivatives containing the aminocyclitol streptamine (e.g., spectinomycin), derivatives containing a 4, 5- disubstituted deoxystreptamine moiety (e.g., **neomycin**), and derivatives containing a 4, 6-disubstituted deoxystreptamine moiety (e.g., **gentamicin**, kanamycin, amikacin, tobramycin).

Mechanism of action of aminoglycosides

Aminoglycosides must penetrate bacteria to assert their effect. Penetration can be enhanced by the presence of a drug that interferes with cell wall synthesis, such as a beta-lactam antibiotic. Susceptible, aerobic Gram negative bacteria actively pump the aminoglycoside into the cell. This is initiated by an oxygen-dependent interaction between the antibiotic cations and the negatively charged ions of the bacterial membrane lipopolysaccharides. This interaction displaces divalent cations (Ca++, Mg++), which effects membrane permeability.

Once inside the bacterial cell, aminoglycosides bind to the 30S ribosomal sub-unit and cause a misreading of the genetic code, interrupting normal bacterial protein synthesis. This leads to changes in the cell membrane permeability, resulting in additional antibiotic uptake, further cell disruption, and ultimately, cell death.

Other effects of aminoglycosides include interference with the cellular electron transport system, induction of RNA breakdown, inhibition of translation, effects on DNA metabolism, and damage to cell membranes. Aminoglycoside action is bactericidal, and dose (concentration) dependent; the bactericidal effect is through the formation of abnormal cell membrane channels by misread proteins. The aminoglycosides have a significant post-antibiotic effect (PAE); the period of time where antimicrobial concentrations are below the bacterial MIC, but the antimicrobial-damaged bacteria are more susceptible to host defenses.

Antimicrobial activity

They are active against some Gram-positive bacteria, such as *Staphylococcus* spp. They are often effective against enterococci, but therapy against streptococci is more effective when combined with a beta-lactam antibiotic. *Salmonella* and *Brucella spp*. are intracellular pathogens and are often resistant. Some mycobacteria, spirochetes (*Leptospira spp*, etc) and mycoplasma are susceptible. The bactericidal action of the aminoglycosides on aerobic Gram-negative bacteria is markedly influenced by pH, being most active in an alkaline environment. Increased local acidity secondary to tissue damage or bacterial destruction may explain the failure of aminoglycosides to kill usually susceptible pathogens. Another factor affecting activity is the presence of purulent debris, which ionically binds to aminoglycosides and inactivates them. When using an aminoglycoside to treat purulent infections (e.g., abscesses), surgical debridement and/or drainage increases efficacy.

Pharmacokinetic properties

Following parenteral administration, effective concentrations are obtained in synovial, perilymph, pleural, peritoneal, and pericardial fluid. Aminoglycosides bind to a low extent to plasma proteins (less than 25%). As they are large molecules and highly ionized at physiological pHs, they are poorly lipid soluble and have limited capacity to enter cells and penetrate cellular barriers. These drugs do not readily attain therapeutic concentrations in transcellular fluids, particularly CSF and ocular fluid.

Elimination is entirely by renal excretion (glomerular filtration), and unchanged drug is rapidly excreted in the urine.

Drug interactions

Aminoglycosides are commonly additive and sometimes synergistic with beta-lactam drugs. Synergism does not usually occur in the presence of high-level plasmid-mediated or chromosomal resistance.

Aminoglycosides are physically incompatible with a number of drugs including many beta-lactams, so they should never be mixed in the same syringe. If administered sequentially through an infusion set, care should be taken to flush well between drugs.

Toxicity and adverse effects

All aminoglycosides can cause varying degrees of ototoxicity (vestibular damage, cochlear damage) and nephrotoxicity (acute tubular necrosis). The risk factors for aminoglycoside toxicity include prolonged therapy (> 7–10 days), multiple doses per day, acidosis and electrolyte disturbances (hypokalaemia, hyponatremia), volume depletion (shock, endotoxaemia), concurrent nephrotoxic drug therapy, age (neonates, geriatrics), pre-existing renal disease, and elevated trough concentrations.

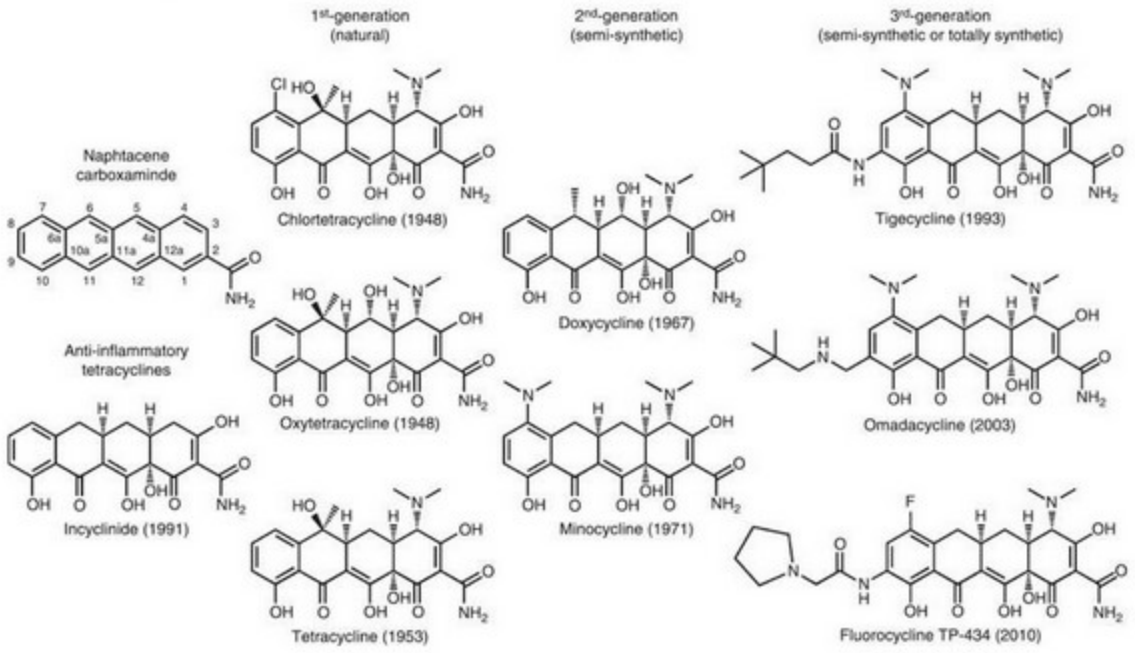
Drug	Vestibular Toxicity	Cochlear Toxicity	Renal Toxicity
Streptomycin	+++	++	(+)
Dihydrostreptomycin	++	+++	(+)
Neomycin	+	+++	+++
Kanamycin	+	++	++
Amikacin	(+)	+	++
Gentamicin	++	+	++
Tobramycin	(+)	(+)	(+)

1.2.6 TETRACYCLINES

Tetracyclines consist of a group of broad spectrum antibiotics. They are first-line drugs in food animals, including aquaculture species, exotic animals, and honeybees, but their use is much lower in companion animals, horses, and humans.

Chemistry

The tetracyclines are substituted 2-naphtacene carboxamides.



All first-generation congeners are produced by *Streptomyces* strains that possess aromatic polyketide synthases. The tetracyclines are amphoteric drugs that are ionized at all pH values. In solution, they form a mixture of zwitterions, cations, and anions, respective proportions of which depend on the pH of the medium. This class of drug molecules is fairly stable at physiological pH values with the exception of chlortetracycline, which degrades in basic mediums at a rate that increases with pH. 1st generation (natural) tetracyclines include chlortetracycline, oxytetracycline, and tetracycline. 2nd generation (semi-synthetic) include doxycycline, minocycline, while 3rd generation (semisynthetic or totally synthetic) include drugs like tigecycline, omadacycline and fluorocycline.

Mechanism of action

The tetracyclines are pleiotropic drugs that classically are used as protein synthesis inhibitors. To reach the ribosome, tetracyclines must first complex with Mg2+ to cross the Gram-negative outer cell wall via a porin. Upon binding to the 16S RNA (rRNA) and S7 protein of the 30S bacterial ribosome, they allosterically inhibit the binding of aminoacylated transfer RNA (AA-tRNA) to their docking site (A-site) on the ribosome. Overall, they exert a bacteriostatic effect on susceptible bacterial pathogens, with time dependent bactericidal activity that has been proven at least for tigecycline and doxycycline. They exert antiparasitic activity by inhibiting protein synthesis in endosymbionts or organelles that possess a genome and prokaryote-like ribosomal components; they alter the apicoplasts of *Plasmodium falciparum*, and likely of coccidia and *Babesia*.

In filaria, they kill the endosymbiont *Wolbachia pipientis* (Gram negative bacterium – it is a *Rickettsia)* that is essential to the growth and fertility of the nematode, and plays key role in its evasion from the host immune mechanisms. The tetracyclines possess an adjunct anti-inflammatory activity that is valuable in controlling infectious disease. They inactivate the matrix metalloproteinases by interacting with the structural (not catalytic) Zn2+ and/or Ca2+ of these proteins, and they scavenge the reactive oxygen species.

Antimicrobial activity

Tetracyclines are a broad-spectrum antibiotics family active against a wide range of microorganisms including gram-positive and gram-negative bacteria, Chlamydiae, mycoplasmas, rickettsiae, and protozoan parasites such as such as *Entamoeba histolytica*, *Giardia lamblia*, *Leishmania major*, *Plasmodium falciparum*, *Trichomonas spp*., and *Toxoplasma gondii*, *Wolbachia spp*. The antibacterial potency of the tetracyclines positively correlates with lipid solubility: the semisynthetic derivatives are most active, followed by the chlorinated tetracyclines, and lastly by oxytetracycline and tetracycline.

Pharmacokinetic properties

The absorption, distribution and elimination of the tetracyclines all depend on factors such as their molecular size, lipid/buffer partition behaviour, plasma protein binding, the acidity of biological mediums, their exposure to multivalent cations (Ca^{2+}, Mg^{2+}, Zn^{2+}, Cu^{2+}, Fe^{2+},Fe^{3+}, Al^{3+}), and the expression level of P-glycoprotein (P-gp) in the cell membranes they face. To be absorbed, the tetracyclines administered as solid oral dosage or long-acting injectable formulations must undergo the process of drug release.

Some excipients of the injectable products retain the tetracyclines at the injection site via different mechanisms that delay their absorption; for example, tissue irritation. The type of tetracycline salt influences its solubility and release, and therefore its extent of absorption (i.e., bioavailability). The tetracyclines are among a limited number of osteotropic drugs. Their multivalent cation-chelating properties cause their deposition in teeth and at sites of new bone formation. The drugs cross the placenta. The tetracyclines are excreted primarily by glomerular filtration, by biliary secretion at an extent that depends on their lipid solubility and by intestinal excretion. Tetracyclines undergo enterohepatic circulation, with much of the drug excreted in bile being reabsorbed from the intestine. This process contributes to the half-life of 6-10 hours. All tetracyclines are subject to reversible epimerization of carbon-4 at pH values between 2 and 6, especially when exposed to substances such as phosphate, urea, and multivalent cations.

Drug interactions

The absorption of tetracyclines is impaired by antacids containing Al^{3+} or other multivalent cations, by iron containing preparations, and by bismuth subsalicylate. Tetracyclines can be combined with macrolides (such as tylosin or tiamulin) to treat respiratory pathogens including *Mycoplasma* and *Pasteurella.* Combination with polymyxins may also give synergistic effects by enhancing bacterial uptake of the drugs. Doxycycline is synergistic with rifampin or streptomycin in treating brucellosis.

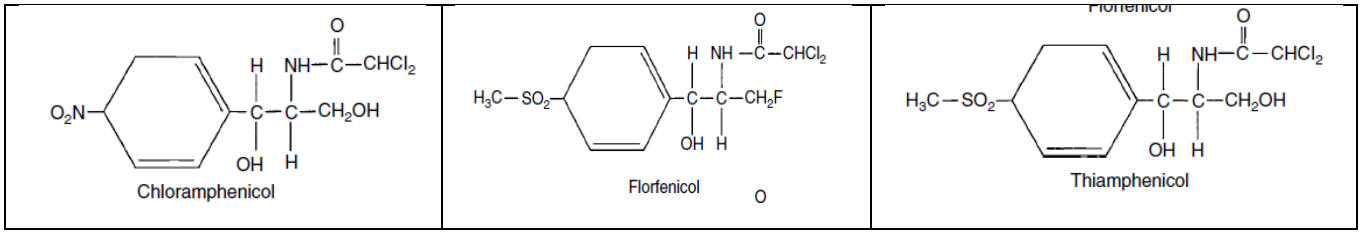
Toxicity and adverse effects

The tetracyclines are relatively safe. Their most serious adverse effects are attributed to anhydrotetracyclines that damage the plasma membranes and bind to serum albumin. These tetracycline degradation products that are found in expired or poorly preserved drug products have been associated with renal toxicity, and likely in hepatic and cardiovascular toxicity. The tetracyclines are irritants that may cause vomiting after oral dosing, and tissue damage at injection site. Their ability to bind calcium is associated with acute cardiac toxicity (IV should be given slowly). They also induce apoptosis in osteoclasts, i.e., risk of chronic bone toxicity. Oxytetracycline irritates tissues, i.e., risk of drug persistence at the injection site. Tetracyclines have antianabolic effects that may produce azotaemia; such effects can be exacerbated by corticosteroids. The drugs may also cause metabolic acidosis and electrolyte imbalance. Administration to growing puppies or pregnant bitches results in yellow discoloration of primary and, to a lesser extent, permanent teeth.

1.2.7 CHLORAMPHENICOL, THIAMPHENICOL, AND FLORFENICOL

Chloramphenicol was first produced from cultures of *Streptomyces venezuelae* but it is now synthesized chemically. Chloramphenicol is a stable, lipid-soluble, neutral compound; it is a derivative of dichloracetic acid and contains a nitrobenzene moiety. This *p*-nitro group is associated with idiosyncratic (non-dose-dependent) aplastic anemia in humans. Thiamphenicol has a similar antibacterial spectrum to chloramphenicol but differs from the parent compound in that the *p*-nitro group attached to the benzene ring is replaced by a sulfomethyl group. Florfenicol is a structural analogue of thiamphenicol that also lacks the *p*-nitro group, and it is more active than thiamphenicol. Neither thiamphenicol nor florfenicol are associated with dose independent aplastic anemia in humans or any other species, but both are associated with dose-dependent bone marrow suppression.

Chemical structure of chloramphenicol, florfenicol, and thiamphenicol



Chloramphenicol - mechanism of action

Chloramphenicol is a potent inhibitor of microbial protein synthesis. It binds irreversibly to a receptor site on the 50S subunit of the bacterial ribosome, inhibiting peptidyl transferase and preventing the amino acid transfer to growing peptide chains and subsequently inhibiting protein formation. Chloramphenicol also inhibits mitochondrial protein synthesis in mammalian bone marrow cells in a dose-dependent manner.

Antimicrobial activity

Chloramphenicol is active against a wide range of Gram-positive and many Gram-negative bacteria against which it is usually bacteriostatic. Anaerobic bacteria are inhibited at usual therapeutic Concentrations (5–15 μg/ml). Resistance to chloramphenicol is seen in bacteria producing plasmid-encoded chloramphenicol acetyl transferase.

Drug interactions

Chloramphenicol should not be used concurrently with bactericidal antimicrobials in treating infections where host defenses are poor. Chloramphenicol acts on the same ribosomal site as macrolides antibiotics. Chloramphenicol is antagonistic to the fluoroquinolones. Because chloramphenicol inhibits microsomal enzyme activity, hepatic metabolism (oxidative reactions and glucuronide conjugation) of drugs given concurrently is slowed, resulting in prolonged pharmacologic effect. Thus chloramphenicol markedly prolongs the effect of barbiturates.

Toxicity and adverse effects

A few cases of aplastic anemia in humans have occurred following contact exposure (ophthalmic use, medicated sprays, handling), so that veterinarians and owners should wear protective gloves and face masks when handling chloramphenicol products. In animals, chloramphenicol toxicity is related to both the dose and duration of treatment, and cats are more likely than dogs to develop toxicity. Chloramphenicol causes changes in the peripheral blood and bone marrow due to reversible, dose-related disturbances in red cell maturation.

Clinical Applications

The potential for idiosyncratic fatal aplastic anemia in humans has led to prohibition of chloramphenicol use in food animals in many parts of the world. Chloramphenicol is used only in life-threatening situations when no other drug is adequate; it is used less frequently nowadays. For example, it can be used in some anaerobic infections, serious ocular infections, prostatitis, otitis media/interna and salmonellosis in horses, dogs and cats. The treatment should not exceed 10 days. Human toxicity from handling chloramphenicol should be discussed with the owner and appropriate precautions taken when prescribing chloramphenicol for use in dogs and cats.

Thiamphenicol

Thiamphenicol does not induce irreversible bone marrow aplasia in humans, although it may cause dose-dependent bone marrow suppression more frequently than chloramphenicol. There is little information on pharmacokinetic and clinical studies in animals; suitable dosage in animals would appear to be similar to that of chloramphenicol.

Florfenicol

Like thiamphenicol, florfenicol does not cause idiosyncratic aplastic anemia in humans but can cause dose-dependent bone marrow suppression in animals. Florfenicol is slightly more active than chloramphenicol in its range of antimicrobial activity. Florfenicol is the appropriate analogue to use in food animals.

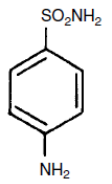
1.2.8 SULFONAMIDES, DIAMINOPYRIMIDINES

Sulfonamides or sulfa drugs

The first **antimetabolites** to be used successfully as chemotherapeutic agents were the sulphonamides. Sulphonamides are structurally related to sulfanilamide, an analog of p-aminobenzoic acid, or PABA. They include sulphaguanidine, sulfadiazine, sulfathiazole, sulfamethoxazole, and sulfadoxine, etc.

Chemistry

The sulfonamides are derivatives of sulfanilamide, which contains the structural prerequisites for antibacterial activity. The sulfonamides differ in the radical (R) attached to the amido (–SO2NHR) group or occasionally in the substituent on the amino (–NH2) group.



Sulfanilamide

The sulfonamides are quite insoluble; they are more soluble at an alkaline pH than at an acid pH. In a mixture of sulfonamides, each component drug exhibits its own solubility.

Mechanism of action

Sulfonamides interfere with the biosynthesis of folic acid in bacterial cells by competitively preventing para-aminobenzoic acid (PABA) from incorporation into the folic (pteroylglutamic) acid molecule. Specifically, sulfonamides compete with PABA for the enzyme dihydropteroate synthetase. Their selective bacteriostatic action depends on the difference between bacterial and mammalian cells in the source of folic acid. Susceptible microorganisms must synthesize folic acid, whereas mammalian cells use preformed folic acid. The bacteriostatic action can be reversed by an excess of PABA, so that any tissue exudates and necrotic tissue should be removed if animals are to be treated with sulfonamides. **Dapsone** and **p-aminosalicylic acid** (PAS) are also antifolates, and are used in treating leprosy and tuberculosis, respectively.

Antimicrobial activity

Sulfonamides are effective against a broad range of Gram-positive and Gram-negative organisms which include *Nocardia*, Chlamydia, and some protozoa (coccidiosis nd toxoplasmosis), but their antibacterial activity is significantly limited by the extensive resistance that has developed over years.

Drug interactions

Sulfonamides interact with antibacterial diaminopyrimidines, such as trimethoprim and baquiloprim. Sulfonamides appear not to antagonize the bactericidal effect of penicillins, but the procaine of procaine penicillin is an analog of PABA that will antagonize sulfonamides. Combination with pyrimethamine is the treatment of choice for toxoplasmosis and some other protozoal infections.

Toxicity and adverse effects

The sulfonamides can produce a wide variety of usually reversible side effects, some of which may have an allergic basis and others are the result of direct toxicity. The more common adverse effects are urinary tract disturbances (crystalluria, hematuria, or even obstruction), hematopoietic disorders (thrombocytopenia, anemia, leukopenia), and dermatologic reactions.

Significant reactions, however, are generally uncommon in animals treated with conventional doses of common sulfonamides (other than sulfaquinoxaline) for less than 2 weeks. Rarely, 0.25% of humans or animals treated with sulphonamide can produce idiosyncratic drug reactions, i.e., unpredictable and occurring 10 days to 3 weeks after first exposure. These reactions are sometimes described as hypersensitivity reactions (drug fever, urticaria) since they seem to involve immune reactions such as a T-cell-mediated response to proteins haptenated by sulphonamide metabolites but may involve a limited capacity to detoxify metabolites of sulfonamides.

Clinical applications

Widespread resistance greatly limits the effectiveness of sulfonamides in treating bacterial diseases of animals, so that indications for primary use are few.

Trimethoprim or other antibacterial diaminopyrimidine-sulfonamide combinations have largely replaced sulfonamides as therapeutic agents used in companion animals, although resistance also increasingly limits their use. Purulent material must always be removed, since free purines neutralize the effect of sulfonamides.

Antibacterial diaminopyrimidines

Diaminopyrimidines interfere with folic acid production by inhibition of dihydrofolate reductase.

Some diaminopyrimidines have marked specificity for bacterial dihydrofloate reductases (aditoprim, baquiloprim, ormetoprim, trimethoprim), others for protozoal enzymes (pyrimethamine), and others for mammalian enzymes (methyltrexate). The earliest antibacterial diaminopyrimidine introduced for clinical use was trimethoprim, a synthetic drug that is widely used in combination with sulfonamides. It is a weak base with a pKa of about 7.6 and is poorly soluble in water.

Mechanism of action

Diaminopyrimidines interfere with the synthesis of tetrahydrofolic acid from dihydrofolate by combining with the enzyme dihydrofolate reductase. Selective antibacterial activity occurs because of greater affinity for the bacterial rather than the mammalian enzyme. Diaminopyrimidines thus inhibit the same metabolic sequence as the sulfonamides, preventing bacterial synthesis of purines and thus of DNA. A synergistic and bactericidal effect occurs when the diaminopyrimidines are combined with sulfonamides (sulphonamide-diaminopyrimidine combinations), and for this reason these drugs are invariably used with a sulphonamide in veterinary medicine.

Antimicrobial Activity

Antibacterial diaminopyrimidines are generally bacteriostatic, broad-spectrum drugs active against Gram positive and Gram-negative aerobic bacteria, but not usually against anaerobes.

Toxicity and adverse effects

The antibacterial diaminopyrimidines are relatively nontoxic drugs. Their main, though clinically unimportant, potential toxic effect is to induce folic acid deficiency at high doses, so care should be used in pregnant animals.

Antibacterial diaminopyrimidine-sulfonamide combinations

Antibacterial diaminopyrimidines are combined with a variety of sulfonamides in a fixed (1:5) ratio, which in people produces a 1:20 ratio of drug concentrations in the plasma after oral or parenteral administration.

Antimicrobial Activity

Diaminopyrimidine-sulfonamide combinations have a generally broad and usually bactericidal action against many Gram-positive and Gram-negative aerobic bacteria, and protozoa such as *Toxoplasma*. They are not active against anaerobic bacteria *in vivo* because thymidine and PABA in the necrotic tissue antagonizes their antibacterial effect. Such an antagonistic effect is not limited to anaerobes so that this combination may not be fully effective in closed, non-draining, infections where there is significant tissue debris.

Clinical applications

Diaminopyrimidine-sulfonamide combinations have the advantage of good distribution into tissues, safety, a relatively broad-spectrum bactericidal activity, and oral administration. A disadvantage is antagonism of action by infected tissue debris.

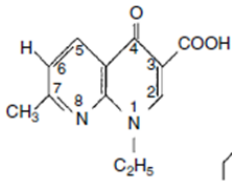
Trimethoprim

Trimethoprim is structurally similar to dihydrofolic acid. Trimethoprim binds to dihydrofolate reductase (DHFR), the enzyme responsible for converting dihydrofolic acid to tetrahydrofolic acid, competing against the dihydrofolic acid substrate. Sulfonamides and trimethoprim, each can be used alone to inhibit bacterial growth. If used together (**potentiated sulphonamide)**, e.g., sulphadoxine + trimethoprim they produce sequential blocking, resulting in a marked synergism of activity. Co-trimoxazole is a combination containing sulphamethoxazole and trimethoprim.

1.2.8 FLUOROQUINOLONES

The fluoroquinolones are synthetic compounds, also known as quinolones, 4- quinolones, pyridine-β-carboxylic acids, and quinolone carboxylic acids. At appropriate drug concentration: MIC ratios, the fluoroquinolones are rapidly bactericidal, exhibit concentration-dependent killing, and may exhibit a prolonged *in vivo* post-antibiotic effect (PAE) on certain bacteria. The fluoroquinolones are classified into different groups based on their chemical structure or their biological activities. Classification by chemical structure is dependent on the number of rings associated with the pyridine- β -carboxylic acid nucleus. Group I is composed of monocyclic derivatives. Group II, which is the majority of fluoroquinolones on the market today, is composed of bicyclic derivatives.

This group is divided into two subgroups based on substitutions at position 8 of the quinolone nucleus. Group III is composed of tricyclic derivatives and includes marbofloxacin. Group IV is comprised of those molecules that are quadricyclic, of which only a few have been synthesized and none are marketed for use in veterinary medicine. The biological classification places the 4-quinolones in three groups or generations. First-generation quinolones are those with antibacterial activity restricted to the Enterobacteriaceae (e.g., nalidixic acid and flumequine).



Nalidixic Acid

Second-generation quinolones have an extended spectrum of antibacterial activity. Most quinolones approved for use in people (including ciprofloxacin, norfloxacin, and ofloxacin) and all but one of the fluoroquinolones approved for use in veterinary medicine are second-generation fluoroquinolones.

Third-generation fluoroquinolones have considerably improved activity against streptococci and obligate anaerobes. Examples of third-generation fluoroquinolones approved for use in people include trovafloxacin, gatifloxacin, and moxifloxacin. Pradofloxacin is the only third-generation quinolone approved for use in animals. Fluoroquinolones used in veterinary medicine include **enrofloxacin**, ciprofloxacin, danofloxacin, difloxacin, ibafloxacin, marbofloxacin, pradofloxacin, orbifloxacin.

Mechanism of Action

Quinolones are bactericidal and act by inhibiting bacterial DNA synthesis by blocking DNA gyrase. DNA gyrase is the enzyme that unwinds DNA strands, so they can be replicated.

Inhibition of DNA gyrase disrupts DNA replication and repair, bacterial chromosome separation during division, and other cell processes involving DNA.

Antimicrobial Activity

The fluoroquinolones have excellent activity *in vitro* against a wide range of aerobic Gram-negative bacteria, including the Enterobacteriaceae, *Actinobacillus pleuropneumoniae*, *Histophilus somni*, *Mannheimia haemolytica*, and *Pasteurella spp*. They are also active against *Bordetella bronchiseptica, Brucella* spp., *Chlamydia/Chlamydophila spp*., *Mycoplasma spp.,* and *Ureaplasma spp*. Fluoroquinolones are active against rapidly growing mycobacteria isolated from dogs and cats.

Drug interactions

The fluoroquinolones are synergistic when used with beta-lactams, aminoglycosides, and vancomycin against some bacterial pathogens.

Toxicity and adverse effects

Fluoroquinolones are relatively safe antimicrobial drugs. Administered at therapeutic doses, toxic effects are mild and generally limited to gastrointestinal disturbances such as nausea, vomiting, and diarrhea.

Chronic, high-dose fluoroquinolone therapy causes articular cartilage lesions in juvenile dogs, particularly in weight bearing joints. Retinal degeneration has been reported in cats treated with high doses (20 mg/kg every 24 hours) of enrofloxacin. Vision may or may not return after enrofloxacin therapy is discontinued.

1.2.9 MISCELLANEOUS ANTIMICROBIALS

They include ionophore antibiotics, nitrofurans, nitroimidazoles, rifamycins, oxazolidinones, quinoxalines, fusidic acid, isoniazid, mupirocin, methenamine, and novobiocin.

ALTERNATIVES TO ANTIMCROBIAL DRUGS

Alternatives to antimicrobial drug use include vaccines, probiotics, etc. A vaccine is a substance used to stimulate the production of antibodies and provide immunity against one or more diseases. It is prepared from causative agent of disease, its products, treated to act as antigen without causing disease.