Antibacterial Agents

β-Lactam Antibiotics

β-Lactam antibiotics, named after the active chemical component of the drug (the 4-membered β-lactam ring), include the 6-membered ring–structured penicillins, monobactams, and carbapenems; and the 7-membered ring–structured cephalosporins and cephamycins. In addition to their chemical structure, the major difference between these two subclasses of β-lactams is their susceptibility to β-lactamase destruction, with the cephalosporins, in general, being more resistant.

Antimicrobial Activity

Mode of Action:

β-Lactams impair the development of bacterial cell walls by interfering with transpeptidase enzymes responsible for the formation of the cross-links between peptidoglycan strands. These enzymes are associated with a group of proteins in both gram-positive and gram-negative bacteria called the penicillin-binding proteins (PBPs). At least nine different PBPs comprise the cell wall; different β-lactam antibiotics may target different PBPs, accounting for differences in spectrum and resistance. During bacterial cell growth, while the peptidoglycan structure is being formed, autolysins continually cleave cell wall lattices, in

anticipation of providing acceptor sites for new strands of bacterial cell synthesis. Normal bacterial growth depends on a balance between cell wall autolysis and synthesis. The β-lactam drug mimics the PBP substrate, thus inhibiting the PBP and thus cell wall synthesis. In the face of continued autolysin activity, the cell wall becomes deformed. The cell, which is generally hypertonic compared with its environment, is no longer impermeable to the flow of small molecules and is susceptible to osmotic lysis. The effect of the β-lactams when present in sufficient concentrations is generally bactericidal toward most bacteria (an exception is in listeriosis for which penicillins are bacteriostatic and cephalosporins are ineffective). However, at subinhibitory concentrations, β-lactam antibiotics do exert residual effects on bacterial structure and function that, in turn, promote host-mediated cell death.

Some bacterial isolates, when treated with inhibitors of cell-wall synthesis, undergo inhibition of growth but not lysis at usual concentrations. These "tolerant" organisms are defective in their production or use of autolytic enzymes and can survive exposure to β-lactam antibiotics. Clinically, relapses and failures in serious infections due to tolerant organisms may be prevented by the frequently synergistic effect of the aminoglycosides with β-lactam antibiotics. As with other bactericidal drugs, β-lactams are most effective during the log phase of growth. In any bacterial population, a few organisms will always be quiescent. Because the β-lactams are active against only growing bacteria, the static organisms are unaffected and may persist. These "persisters" may then develop normally after the antibiotic is removed.

β-Lactam antibiotics have little influence on formed bacterial cell walls, and even susceptible organisms must be actively multiplying or growing. β-Lactams are most active during the logarithmic phase of bacterial growth. They also tend to be somewhat more active in a slightly acidic environment (pH 5.5–6.5), perhaps because of enhanced membrane penetration. They also are likely to be less effective in the presence of hypertonic tissues.

Efficacy of the β-lactams is related to the time that plasma or tissue drug concentrations exceed the minimum inhibitory concentration (MIC) of the infecting organism (T >MIC). Generally, concentrations should remain above the MIC for approximately 25% (carbapenems) to100% (amoxicillin) of the dosing interval.

Bacterial Resistance:

Only microorganisms that have cell walls are susceptible to the action of β-lactam antibiotics. Within this range of bacteria, resistance to β-lactams is well recognized and takes a number of forms.

Permeability Barrier:

In gram-positive organisms, capsular materials may hinder access to the cytoplasmic membrane, but this rarely limits the diffusion of the cell-wall inhibitors. Gram-negative bacteria have a restricting sieving mechanism (porins) in their outer membranes (external cell wall), which reduces the penetration of several types of antibiotics. Different species of gram-negative bacteria exhibit varying permeability barriers to β-lactam antibiotics, and these impair access of the antibiotics to the membrane-associated binding proteins. For example, the permeability barrier of *Haemophilus influenzae* is readily crossed by β-lactam antibiotics, *Escherichia coli* presents a greater obstacle to these agents, and the outer membranes of *Pseudomonas aeruginosa* are penetrated with great difficulty by most β-lactam compounds. Penicillins, aminopenicillins, first- and second-generation cephalosporins, and selected other

β-lactams cannot penetrate the outer membrane of *P aeruginosa*. In addition, porins are frequently associated with efflux proteins that effectively remove drug that has successfully penetrated the lipopolysaccharide covering of gram-negative organisms.

The chemical nature of β-lactams (penicillins, cephalosporins, and the β-lactamase inhibitors), as well as their concentration gradients, also greatly influence their penetration of bacteria to their targets at the surface of the cytoplasmic membrane, giving rise to the differences between antibacterial spectra of the various classes of penicillin. β-Lactams are often used in combination with other antibiotics that disrupt the integrity of the membranes and thereby facilitate access by β-lactams. The genetic loci controlling permeability generally have been considered to be chromosomally located, but they also may be plasmid-specified genes.

β-Lactamase Resistance:

The most important mechanism of bacterial resistance to β-lactam antibiotics is enzymatic inactivation by β-lactamases by cleavage of the 4-member β-lactam ring. Cleavage results in the inability of the drugs to bind to the target PBPs. There currently are >800 different β-lactamases, representing six major classes, with the enzyme varying with the organism and drugs targeted varying with the enzyme. The increase in the number of enzymes reflects, in part, pressure brought with the increasingly widespread use of β-lactams and the continued manipulation of the drugs in an attempt to circumvent bacterial β-lactamase production. For example, the addition of larger R groups on the β-lactam structure rendered cephalosporins to be resistant to penicillinases. However, cephalosporinases emerged with continued use of first-generation cephalosporins. Second- and third-generation cephalosporins reflect modifications, including larger R groups that hindered β-lactamase access to the β-lactam ring. Inhibitors of β-lactamases (clavulanic acid, sulbactam) were added to minimize penicillin destruction. As a result, newer β-lactamases emerged. Approval and use of third-generation cephalosporins have been associated with emergence of extended-spectrum β-lactamases (ESBLs), particularly by *E coli*, *Klebsiella*, and *Proteus*, that target third-generation cephalosporins (but not cephamycins such as cefoxitin). In contrast, carbapenems (imipenem and meropenem) are not subject to ESBLs that target third-generation cephalosporins, but they are subjected to carbapenemases. β-Lactamases do not discriminate among the drugs within class, meaning both human and veterinary drugs will be targeted. Interestingly, clavulanic acid is not susceptible to ESBLs; susceptibility data indicating resistance to cephalosporins but susceptibility to amoxicillin-clavulanic acid indicates ESBL formation.

β-Lactamases are produced by both gram-positive (*Staphylococcus aureus, S epidermidis, S pseudintermedius* but generally not enterococci) and gram-negative organisms. Some of these enzymes are active exclusively against penicillins, others are principally active against cephalosporins, and several types hydrolyze both equally. The type and concentration of β-lactamases are also specific to bacterial species. Gram-positive β-lactamases generally are excreted into the external environment as exoenzymes, produced in large quantity, plasmid mediated (single determinant), usually inducible (rarely constitutive), unable to initiate self-transmission (rely principally on transduction), and are active primarily against penicillins. Staphylococcal strains are the main gram-positive bacteria in which β-lactamase resistance develops, often very quickly. Gram-negative β-lactamases generally are heterogeneous (wide range), retained within the periplasmic space, produced in small quantity, often constitutive (less often inducible), able to initiate self-transmission (conjugation mechanisms), and active against both penicillins and cephalosporins. The impact of β-lactamase protectors such as

clavulanic acid may not be as positive for treatment of gram-negative versus gram-positive organisms. Gram-negative bacteria capable of resistance as a result of β-lactamase production include *Escherichia*, *Haemophilus*, *Klebsiella*, *Pasteurella*, *Proteus*, *Pseudomonas*, and *Salmonella* spp; resistance may take longer to develop in some of these strains.

Specific Bacterial-binding Proteins:

Resistance to β-lactam antimicrobial agents can be acquired by alterations in the PBP targets of these drugs. A loss or decrease in affinity of crucial PBP can lead to a significant increase in resistance to β-lactams. For example, resistance of enterococci to cephalosporins appears to reflect the lack of affinity of a PBP to this subclass of drugs. Changes in PBP-2 of *Staphylococcus* spp render the organism resistant to all β-lactams. Methicillin resistance in *Staphylococcus* spp reflects acquisition of the *mec* gene, which results in a mutation in PBP-2. As such, no β-lactam can bind to this protein, resulting in resistance to all β-lactam drugs. Problematically, genes conferring methicillin resistance may be accompanied by genes conferring multidrug resistance.

Cell Wall–deficient Microbes:

Organisms that have no cell wall, such as *Mycoplasma*, are intrinsically resistant to β-lactams. A phenotypic form of resistance can occur when spheroplasts (incomplete cell wall) or protoplasts (absence of cell wall) are present. These so-called "L-forms" must be present in a hyperosmotic environment (eg, the renal medulla) to survive; otherwise, they will lyse. The clinical significance of this form of resistance is unclear.

Penicillins

The penicillins are among the earliest classes of antibacterial drugs. Penicillins are divided into subclasses based on chemical structure (eg, penicillins, monobactams, and carbapenems), spectrum (narrow, broad, or extended), source (natural, semisynthetic, or synthetic), and susceptibility to β-lactamase destruction. Manipulation of some drugs has improved the spectrum, resistance to β-lactamase destruction, or clinical pharmacologic characteristics that enhance efficacy.

Classes by Spectrum

All penicillins are ineffective toward cell wall–deficient microorganisms such as *Mycoplasma* or *Chlamydia* spp.

Narrow-spectrum β-Lactamase–sensitive Penicillins:

This group includes naturally occurring penicillin G (benzylpenicillin) in its various pharmaceutical forms and a few biosynthetic acid-stable penicillins intended for oral use (penicillin V [phenoxymethyl-penicillin] and phenethicillin). Penicillins in this class are active against many gram-positive but only a limited number of gram-negative bacteria. These

drugs are also effective against anaerobic organisms. They are, however, susceptible to β-lactamase (penicillinase) hydrolysis.

Penicillin G and its oral congeners (eg, penicillin V) are active against both aerobic and anaerobic gram-positive bacteria and, with a few exceptions (*Haemophilus* and *Neisseria* spp and strains of *Bacteroides* other than *B fragilis*), are inactive against gram-negative organisms at usual concentrations. Organisms usually sensitive in vitro to penicillin G include streptococci, penicillin-sensitive staphylococci, *Trueperella (Arcanobacterium) pyogenes*, *Clostridium* spp, *Erysipelothrix rhusiopathiae*, *Actinomyces bovis*, *Leptospira* Canicola, *Bacillus anthracis*, *Fusiformis nodosus*, and *Nocardia* spp.

Broad-spectrum β-Lactamase–sensitive Penicillins:

Penicillins in this class are derived semisynthetically and are active against many gram-positive and gram-negative bacteria. However, they are readily destroyed by the β-lactamases (produced by many bacteria). Many members of the group are acid stable and are administered either PO or parenterally. Of those used in veterinary medicine, aminopenicillins, eg, ampicillin and amoxicillin (which may also be produced naturally), are the best known. Several ampicillin precursors more completely absorbed from the GI tract also belong to this class (eg, hetacillin, pivampicillin, talampicillin).

A large number of gram-positive and gram-negative bacteria (but not β-lactamase–producing strains) are sensitive to the semisynthetic broad-spectrum penicillins (ampicillin and amoxicillin). Susceptible genera include *Staphylococcus*, *Streptococcus*, *Trueperella*, *Clostridium*, *Escherichia*, *Klebsiella*, *Shigella*, *Salmonella*, *Proteus*, and *Pasteurella*. Although bacterial resistance is widespread, the combination of β-lactamase inhibitors and broad-spectrum penicillins markedly enhances the spectrum and efficacy against both gram-positive and gram-negative pathogens. Clavulanate-potentiated amoxicillin is an excellent example of such a synergistic association.

Mecillinam is less active than ampicillin against gram-positive bacteria but is highly active against many intestinal organisms (except *Proteus* spp) that do not produce β-lactamases.

Broad-spectrum β-Lactamase–sensitive Penicillins with Extended Spectra:

Several semisynthetic broad-spectrum penicillins are also active against *Pseudomonas aeruginosa*, certain *Proteus* spp, and even strains of *Klebsiella*, *Shigella*, and *Enterobacter* spp in certain cases. Examples of this class include carboxypenicillins (carbenicillin, its acid-stable indanyl ester, and ticarcillin), ureido-penicillins (azlocillin and mezlocillin), and piperazine penicillins (piperacillin).

The anti-*Pseudomonas* and other extended-spectrum penicillins are active against most of the usual penicillin-sensitive bacteria. They often have a degree of β-lactamase resistance and are usually active against one or more characteristic penicillin-resistant organisms. Yet, as a class, they remain susceptible to destruction by β-lactamases. Examples include the use of carbenicillin, ticarcillin, and piperacillin against *P aeruginosa* and several *Proteus* strains, and the use of piperacillin against *P aeruginosa*, several *Shigella* and *Proteus* strains, and some *Citrobacter* and *Enterobacter* spp. *Streptococcus faecalis* is often resistant to these new extended-spectrum penicillins. Imipenem and meropenem are relatively resistant to β-lactamase destruction. Their spectrum includes a wide variety of aerobic and anaerobic

microorganisms, including most strains of *Pseudomonas*, streptococci, enterococci, staphylococci, and *Listeria*. Anaerobes, including *Bacteroides fragilis*, are highly susceptible.

β-Lactamase–protected Penicillins:

Several naturally occurring and semisynthetic compounds can inhibit many of the β-lactamase enzymes produced by penicillin-resistant bacteria. When used in combination with broad- or extended-spectrum penicillins, there is a notable synergistic effect because the active penicillin is protected from enzymatic hydrolysis—and thus is fully active against a wide variety of previously resistant bacteria. Examples of this chemotherapeutic approach include clavulanate-potentiated amoxicillin and ticarcillin as well as sulbactam-potentiated ampicillin and tazobactam-potentiated piperacillin.

Narrow-spectrum β-Lactamase–resistant Penicillins:

This group, through substitution on the penicillin nucleus (6-aminopenicillanic acid), is refractory to a greater or lesser degree to the effects of various β-lactamase enzymes produced by resistant gram-positive organisms, particularly *Staphylococcus aureus*. However, penicillins in this class are not as active against many gram-positive bacteria as penicillin G and are inactive against almost all gram-negative bacteria. Acid-stable members of this group may be given orally and include isoxazolyl penicillins, such as oxacillin, cloxacillin, dicloxacillin, and flucloxacillin. Methicillin and nafcillin are available as parenteral preparations. Temocillin is a semisynthetic penicillin that is β-lactamase stable but also active against nearly all isolates of gram-negative bacteria except *Pseudomonas* spp.

The semisynthetic β-lactamase–resistant penicillins, such as oxacillin, cloxacillin, floxacillin, and nafcillin, have spectra similar to those noted above (although often at higher MIC) but also include many of the β-lactamase–producing strains of staphylococci (especially *S aureus* and *S epidermidis*).

Carbapenems:

Imipenem and meropenem are among the most active drugs against a wide variety of bacteria. Imipenem is derived from a compound produced by *Streptomyces cattleya*. Aztreonam is a related (monobactam) compound but differs from other β-lactams in that it has a second ring that is not fused to the β-lactam ring.

General Properties

Structure-activity Relationships:

The penicillins, particularly the β-lactam ring, are somewhat unstable, being sensitive to heat, light, extremes in pH, heavy metals, and oxidizing and reducing agents. Also, they often deteriorate in aqueous solution and require reconstitution with a diluent just before injection. Penicillins are poorly soluble, weak organic acids administered parenterally either as suspensions in water or oil or as water-soluble salts. For example, sodium or potassium salts of penicillin G are highly water soluble and are absorbed rapidly from injection sites, whereas organic esters in microsuspension such as procaine penicillin G or benzathine penicillin G are gradually absorbed over 1–3 (or even more) days, respectively. The trihydrate forms of the

semisynthetic penicillins have greater aqueous solubility than the parent compounds and are usually preferred for both parenteral and oral use.

The β-lactam nucleus that characterizes penicillins, when cleaved by a β-lactamase enzyme (penicillinase), produces penicilloic acid derivatives that are inactive but may act as the antigenic determinants for penicillin hypersensitivity. Modification of the 6-aminopenicillanic acid nucleus, either by biosynthetic or semisynthetic means, has produced the array of penicillins used clinically. These differ in their antibacterial spectra, pharmacokinetic characteristics, and susceptibility to microbial enzymatic degradation.

Pharmacokinetic Features

The pharmacokinetics of the many penicillins differ substantially. The general guidelines below emphasize singularly significant aspects.

Absorption:

Most penicillins in aqueous solution are rapidly absorbed from parenteral sites. Absorption is delayed when the inorganic penicillin salts are suspended in vegetable oil vehicles or when the sparingly soluble repository organic salts (eg, procaine penicillin G and benzathine penicillin G) are administered parenterally. Although prolonged absorption results in longer persistence of plasma and tissue drug concentrations, peak concentrations may not be sufficiently high to be effective against organisms unless MICs are low. The penicillin G repositol salts should never be injected IV. Only selected penicillins are acid stable and can be administered PO at standard doses. Absorption from the upper GI tract differs markedly in amount and rate among the various penicillins. Penicillin V must be given at high oral doses. The aminopenicillins are orally bioavailable, although food impairs the absorption of ampicillin. Paracellular (as opposed to transcellular) transport may play a major role in oral absorption. The indanyl form of carbenicillin is orally bioavailable, but effective concentrations are likely to be achieved only in the urine. Serum concentrations of penicillins generally peak within 2 hr of PO administration. Penicillins may also be absorbed after intrauterine infusion. There is no information regarding bioavailability of human generic products when used off-label in veterinary patients.

Distribution:

After absorption, penicillins are widely distributed in body fluids and tissues. The volume of distribution tends to reflect extracellular compartmentalization, although some penicillins (including carbapenems) penetrate tissues quite well. Potentially therapeutic concentrations of the various penicillins are generally found in the liver, bile, kidneys, intestines, muscle, and lungs, but only very low concentrations are found in poorly perfused areas such as the cornea, bronchial secretions, cartilage, and bone. The diethylamino salt of penicillin G produces particularly high concentrations in pulmonary tissue. The penicillins usually do not readily cross the normal blood-brain, placental, mammary, or prostatic barriers unless massive doses are given or inflammation is present. Penicillins may be substrates for P-glycoprotein efflux from the CNS. Selected penicillins are able to penetrate nonchronic abscesses and pleural, peritoneal, or synovial fluids. Penicillins are reversibly and loosely bound to plasma proteins. The extent of this binding varies with particular penicillins and their concentration, eg, ampicillin is usually ~20% bound, and cloxacillin may be ~80% bound. Pregnancy increases

the volume of distribution, which has the effect of lowering the concentration of drug produced by a given dose.

Biotransformation:

Penicillins are generally excreted unchanged, but fractions of a given dose may undergo metabolic transformations by unknown mechanisms (usually <20% metabolized). Penicilloic acid derivatives that are formed tend to be allergenic.

Excretion:

Most (60%–90%) of a parenterally administered penicillin is eliminated in the urine within a short time (eg, up to 90% of penicillin G within 6 hr), which results in high concentrations in urine. Approximately 20% of renal excretion occurs by glomerular filtration and ~80% by active tubular secretion—a process that may be deliberately inhibited (to prolong effective concentrations in the body) by probenecid and other weak organic acids. Anuria may increase the half-life of penicillin G (normally ~30 min) to 10 hr. The biliary route also may be a major excretory pathway for the broad-spectrum semisynthetic penicillins. Clearance is considerably lower in neonates than in adults. Penicillins are also eliminated in milk, although often only in trace amounts in the normal udder, and may persist for up to 90 hr. Penicillin residues in milk also have been found after intrauterine infusion.

Pharmacokinetic Values:

Selected pharmacokinetic values for some penicillins in a few species are listed in Elimination, Distribution, and Clearance of Penicillins. Penicillins, in general, have very short elimination half-lives, which is problematic for time-dependent drugs. For example, ~90% of amoxicillin will be eliminated within 4 hr in dogs, suggesting that an 8-hr dosing interval is appropriate. Formulations that prolong absorption after IM administration are appropriate for time-dependent drugs, assuming peak concentrations surpass the MIC of the infecting microbes. Dosage modifications may be necessary because of age or disease. However, the general safety of β-lactams may negate the need for dose adjustment in all but profound renal disease.

Table. Elimination, Distribution, and Clearance of Penicillins

Penicillin	Species	Elimination Half-life (min)	Volume of Distribution (mL/kg)	Clearance (mL/kg/min)
Penicillin G	Dogs	30	156	3.6
	Horses	38	301	5.5
Ampicillin	Dogs	48	270	3.9
Amoxicillin	Cattle	84	493	4.0
Ticarcillin	Dogs	48	347	4.9

Therapeutic Indications and Dose Rates

The penicillins are commonly used to treat or prevent local and systemic infections caused by susceptible bacteria. Several acute infectious disease syndromes are specifically responsive. Because of their synergistic interaction with other antimicrobials, they are often used as part

of combination therapy. Penicillins also are used topically in the eye and ear as well as on the skin; intramammary administration is common for treatment or prevention of bovine mastitis. Amoxicillin with or without clavulanic acid is among the first-choice antimicrobials for treatment of canine or feline urinary tract infections.

A selection of general dosages for some penicillins is listed in Dosages of Penicillins. The dose rate and frequency should be adjusted as indicated by changes in MICs in target antimicrobial populations, and as necessary to achieve and maintain an appropriate T>MIC for circumstances presented in the individual animal.

Table. Dosages of Penicillins

Penicillin	Dosage, Route, and Frequency
Sodium penicillin G	10,000–20,000 IU/kg, IV or IM, qid
Potassium penicillin G	25,000 IU/kg, PO, qid
Procaine penicillin G	10,000–30,000 IU/kg, IM or SC, once to twice daily
Benzathine penicillin G	10,000–40,000 IU/kg, IM (horses) or SC (cattle), every 48–72 hr
Penicillin V	15,000 IU/kg or 8–10 mg/kg, PO, tid-qid
Cloxacillin	10–25 mg/kg, IM or PO, qid
Ampicillin	5–10 mg/kg, IV, IM, or SC, bid-tid; 10–25 mg/kg, PO, bid-qid
Amoxicillin	4–10 mg/kg, IM, once to twice daily; 10–20 mg/kg, PO, bid-qid (dogs)
Sodium carbenicillin	10–20 mg/kg, IV or IM, bid-qid
Potassium clavulanate:amoxicillin (1:4)	10–20 mg/kg (amoxicillin) and 2.5–5 mg/kg (clavulanate), PO, bid-qid
Probenecid (prolongs blood concentrations of penicillins that have short plasma half-lives or that are costly)	1–2 mg/1,000 IU penicillin G (dogs), PO, qid
Amoxicillin-clavulanic acid	10–20 mg/kg, PO, bid-qid
Imepenem	1–7 mg/kg, IV or IM, bid-tid
Meropenem	12–24 mg/kg, IV or SC, bid-tid
Ticarcillin (with or without clavulanic acid)	40–110 mg/kg, IM or IV, tid-qid

Special Clinical Concerns

Adverse Effects and Toxicity:

Organ toxicity is rare. Hypersensitivity reactions to penicillin as a hapten reflects, in part, formation of penicillinoic acid. Hypersensitivity (particularly in cattle) includes skin reactions, angioedema, drug fever, serum sickness, vasculitis, eosinophilia, and anaphylaxis. Cross-sensitivity among penicillins is well recognized. Intrathecal administration may result in convulsions. Guinea pigs, chinchillas, birds, snakes, and turtles are sensitive to procaine penicillin. The use of broad-spectrum penicillins may lead to superinfection, and GI disturbances may occur after PO administration of ampicillin. Potassium penicillin G should be administered IV with some caution, especially if hyperkalemia is present. The sodium salt of penicillin G may also contribute to the sodium load in congestive heart failure.

Interactions:

Active renal tubular secretion is delayed in the presence of selected organic ions, including salicylates, phenylbutazone, sulfonamides, and other weak acids. Gut-active penicillins potentiate the action of anticoagulants by depressing vitamin K production by gut flora. Absorption of ampicillin is impaired by the presence of food. β-lactams in general interact chemically with the aminoglycosides and should not be mixed in vitro. Ampicillin and penicillin G are incompatible with many other drugs and solutions and should not be mixed.

Effects on Laboratory Tests:

Laboratory determinations may be altered, depending on the penicillin used. Alkaline phosphatase, AST, ALT, and eosinophil count may be increased. A false-positive Coombs' test may also result after penicillin therapy. A positive test for urine glucose and protein is also possible. Procaine is detectable in the urine of horses for several days after administration of procaine penicillin; withdrawal time before competition may be up to 6 days.

Cephalosporins and Cephamycins

The cephalosporins, and the closely related cephamycins, are similar to penicillins in several respects, sharing pharmacologic group features.

Classes and Antibacterial Spectra

Cephalosporins include cephamycins, the latter of which differ from other cephalosporins in that they contain a 7-alpha-methoxy group, which imparts resistance to extended-spectrum β-lactamases.. The early cephalosporins differed mainly with respect to pharmacokinetic characteristics. Whereas penicillins were classified based on source (natural versus semisynthetic) and spectra, cephalosporins are classified by generations (1–4). Later generations are more resistant to β-lactam destruction and are often characterized by extended but variable spectra.

First-generation Cephalosporins:

This group includes cephalothin (no longer marketed in the USA), cephaloridine, cephapirin, cefazolin, cephalexin, cephradine, and cefadroxil. Cephalosporins in this group are usually quite active against many gram-positive bacteria but are only moderately active against gram-negative organisms. They are ineffective against enterococci. Susceptible gram-negative bacteria include *Escherichia coli* and *Proteus*, *Klebsiella*, *Salmonella*, *Shigella*, and *Enterobacter* spp. Cefazolin is more effective against *E coli* than cephalexin, the latter of which is minimally susceptible. Although generally less susceptible to β-lactamase destruction than penicillins, they are susceptible to cephalosporinases. They are not as effective against anaerobes as are the penicillins.

Second-generation Cephalosporins:

This group includes cefamandole, cefoxitin (a cephamycin), cefotiam, cefachlor, cefuroxime, and ceforanide. These agents are generally active against both gram-positive and gram-negative bacteria. Moreover, they are relatively resistant to β-lactamases compared with first-

generation drugs. They are ineffective against enterococci, *Pseudomonas aeruginosa* (with the frequent exception of cefoxitin), *Actinobacter* spp, and many obligate anaerobes (again, cefoxitin is an exception).

Third- and Fourth-generation Cephalosporins:

The third-generation cephalosporins include ceftiofur, ceftriaxone, cefsulodin, cefotaxime, cefoperazone, moxalactam (not a true cephalosporin), and several others, including cefpodoxime and cefovecin, approved for use in dogs and for use in dogs and cats, respectively. Cefepime is a fourth-generation cephalosporin. The spectrum of third- and fourth-generation cephalosporins varies and should be confirmed based on culture and susceptibility testing before use. The spectrum of veterinary third-generation cephalosporins should not be considered extended in that efficacy often does not include *Pseudomonas* or other problematic coliforms. Ceftiofur has been specifically approved for use in cattle with bronchopneumonia, especially if caused by *Mannheimia haemolytica* or *Pasteurella multocida*. Although it is approved for use in dogs to treat urinary tract infections (injectable), other more convenient drugs are generally used. Cefpodoxime and cefovecin are particularly effective against *Staphylococcus pseudintermedius*, while retaining fair efficacy toward gram-negative organisms such as *E coli*, *Klebsiella*, and *Proteus*. Some drugs approved for use in people have only moderate activity against gram-positive bacteria (again, enterococci are resistant) but have extensive activity against a wide variety of gram-negative bacteria, including *Pseudomonas* spp, *Proteus vulgaris*, *Enterobacter* spp, and *Citrobacter* spp (eg, cefotaxime, ceftazidime). Third- and fourth-generation cephalosporins were designed to be increasingly resistant to β-lactamases. However, differences in chemical structure have been overcome by the formation of extended-spectrum β-lactamases that target third- and fourth-generation drugs (but not, as a general rule, cephamycins). Ceftiofur is a third-generation cephalosporin with a gram-negative spectrum that is more similar to that of first-generation cephalosporins.

General Properties

The physical and chemical properties of the cephalosporins are similar to those of the penicillins, although the cephalosporins are somewhat more stable to pH and temperature changes. Cephalosporins are weak acids derived from 7-aminocephalosporanic acid. They are used either as the free base form for PO administration (if acid stable) or as sodium salts in aqueous solution for parenteral delivery (sodium salt of cephalothin contains 2.4 mEq sodium/g). Cephalosporins also contain a β-lactam nucleus susceptible to β-lactamase (cephalosporinase) hydrolysis. These β-lactamases may or may not also target penicillins. Modifications of the 7-aminocephalosporanic acid nucleus and substitutions on the sidechains by semisynthetic means have produced differences among cephalosporins in antibacterial spectra, β-lactamase sensitivities, and pharmacokinetics.

Antimicrobial Activity

Bacterial Resistance:

Resistance to the cephalosporins includes mechanisms described in general for β-lactams). Cephalosporins generally are stable against the plasmid-mediated β-lactamases produced by gram-positive bacteria such as *Staphylococcus aureus*. Several types of inducible β-lactamases produced by gram-negative organisms may be mediated by either plasmids or

chromosomally and may hydrolyze either or both penicillins and cephalosporins (cross-resistance). Second- and particularly third-generation cephalosporins have greater stability against gram-negative β-lactamases. However, third- and fourth-generation drugs are susceptible to extended-spectrum β-lactamases, the presence of which on susceptibility testing is indicated based on resistance to these drugs but susceptibility to clavulanic acid.

Pharmacokinetic Features

Limited information regarding the pharmacokinetics of cephalosporins in animals is available.

Absorption:

Only a few cephalosporins are acid stable and thus effective when administered PO (eg, cephalexin, cephradine, cefadroxil, cefpodoxime, and cefachlor). They are usually well absorbed, and bioavailability values are 75%–90%. There is no information regarding bioavailability of human generic products when used off-label in veterinary patients. The others are administered either IV or IM, with plasma concentrations peaking ~30 min after injection. Ceftiofur is available in a sustained-release form; its duration of action is extended by administration at the base of the ear in food animals.

Distribution:

Cephalosporins are distributed into most body fluids and tissues, including kidneys, lungs, joints, bone, soft tissues, and the biliary tract, but in general, the volume of distribution is <0.3 L/kg. However, poor penetration into the CSF, even in inflammation, is a notable feature of the standard cephalosporins. Cephalosporins are substrates for P-glycoprotein efflux from the CNS. The third-generation cephalosporins (eg, moxalactam) may achieve good penetration into the CSF. The degree of plasma-protein binding is variable (eg, 20% for cefadroxil and 80% for cefazolin). The high degree of protein binding of cefovecin (90% dogs, 99% cats) contributes to its long elimination half-life (5.5 days in dogs, 6.9 days in cats). However, drug concentrations in transudate remain above the MIC_{90} of both *Staphylococcus intermedius* and *E coli* for up to 14 days. Third- or fourth-generation cephalosporins are often able to penetrate the blood-brain barrier and are frequently indicated in bacterial meningitis caused by susceptible pathogens.

Biotransformation:

Several cephalosporins (such as cephalothin, cephapirin, ceftiofur, cephacetrile, and cefotaxime) are actively deacetylated, primarily in the liver but also in other tissues. The deacetylated derivatives are much less active, with the exception of ceftiofur. Ceftiofur is metabolized to several active metabolites, including an acetylated metabolite, that can contribute significantly to efficacy. Few of the other cephalosporins are metabolized to any appreciable extent.

Excretion:

Most cephalosporins, including cefpodoxime and cefovecin, are renally excreted. Tubular secretion predominates, although glomerular filtration is important in some cases (cephalexin and cefazolin). In renal failure, dosages might be reduced, although the need for doing so is not clear. Biliary elimination of the newer cephalosporins (eg, cefoperazone) may be

significant. Generally, these β-lactam antibiotics maintain effective blood concentrations for only 6–8 hr. Exceptions include ceftiofur, cefpodoxime, and cefovecin.

Pharmacokinetic Values:

Plasma half-lives of cephalosporins are quite variable, being as short as 30–120 min, but generally are longer than those of penicillins. For example, the half-life of the approved cephalexin product in dogs is 7.3 hr (9 hr if given with food). Third-generation cephalosporins tend to have longer plasma half-lives in people, but this is not always the case in other animals—substantial species differences exist. A selection of pharmacokinetic values for cephalosporins is listed in Elimination, Distribution, and Clearance of Cephalosporins to serve as a guide. Dosage modifications are often required in hepatic and renal disease.

Table. Elimination, Distribution, and Clearance of Cephalosporins

Cephalosporin	Species	Elimination Half-life (min)	Volume of Distribution (mL/kg)	Clearance (mL/kg/min)
Cefazolin	Horses	45	188	5.5
Cefotaxime	Sheep	25	134	9.0
Cefpodoxime	Dog	300	150	
Cefovecin	Dog	5.5 days	90	
Cephalexin	Dogs	7.3–9 hr	—	—
Cefadroxil	Dogs	120	—	—
	Cats	150–180	—	—
Ceftiofur	Cattle	~360	—	—

Therapeutic Indications and Dose Rates

First-generation cephalosporins have proved useful, particularly for infections involving *Staphylococcus* spp (eg, oral cephalexin for dermatitis) and for surgical prophylaxis (eg, cefazolin). However, their efficacy appears to be declining because of emerging resistance, including methicillin-resistant organisms. Ceftiofur is approved for use in a variety of food animals. It is approved for bovine respiratory disease principally caused by *Pasteurella* spp and in urinary tract infections in dogs. Use of ceftiofur for treatment of soft-tissue infections in dogs is not recommended, because proper dosages and safety have not been documented. Cefpodoxime (PO) and cefovecin (SC) also have been approved for use in dogs and in dogs and cats, respectively. Cephalosporins are particularly useful to treat infections of soft tissue and bone due to bacteria that are resistant to other commonly used antibiotics. Cefazolin (IV) has been used prophylactically 1 hr before surgery. More than most penicillins, cephalosporins may penetrate tissues and fluids sufficiently (CSF being an exception for most) to be effective in management of osteomyelitis, prostatitis, and arthritis. Oral cephalosporins can be effective in management of urinary tract infections, except those due to *Pseudomonas aeruginosa*. Cephalexin should be anticipated to be ineffective against *E coli*. Cephapirin benzathine is used for dry-cow therapy, and cephapirin sodium is used to treat mastitis. Except for cephapirin, extra-label use of cephalosporins is banned in major food animal species.

A selection of general dosages for some cephalosporins is listed in Dosages of Cephalosporins. The dose rate and frequency should be adjusted as needed for the individual animal.

Table. Dosages of Cephalosporins

Cephalosporin[a]	Dosage, Route, and Frequency
Cephalexin	20–60 mg/kg, PO, bid-tid
Cephapirin	30 mg/kg, IM or IV, every 4–6 hr
Cefazolin	20–25 mg/kg, IM or IV, tid-qid
Cefpodoxime	5–10 mg/kg, PO, once to twice daily
Cefovecin	8 mg/kg, SC, every 14 days
Cephalexin	10–30 mg/kg, PO, tid-qid
Cefadroxil	22 mg/kg, PO, bid
Ceftiofur	1.1–2.2 mg/kg/day, IM

[a] All for use in small animals, except ceftiofur, which is for use in cattle.

Special Clinical Concerns

Adverse Effects and Toxicity:

The approved cephalosporins are relatively nontoxic. IM injections can be painful, and repeated IV administration may lead to local phlebitis. Nausea, vomiting, and diarrhea may occasionally be seen. Hypersensitivity reactions of several forms have been seen, with cross-reactivity to penicillin allergies possible. Superinfection may arise with the use of cephalosporins, and *Pseudomonas* or *Candida* spp are likely opportunistic pathogens.

Interactions:

In vitro incompatibilities are quite common for cephalosporin and cephamycin preparations; an exception exists when mixing with weak bases such as aminoglycosides. Potential pharmacokinetic interactions are similar to those of the penicillin group.

Effects on Laboratory Tests:

Several laboratory determinations may be altered by the cephalosporins. Alkaline phosphatase, AST, ALT, lactate dehydrogenase, and BUN may be increased. A false-positive Coombs' test and a false-positive urine glucose may occur. Hypernatremia may be caused by the sodium salts of various cephalosporins.

Aminoglycosides (Aminocyclitols)

Aminoglycosides are mostly bactericidal drugs that share chemical, antimicrobial, pharmacologic, and toxic characteristics.

Classes

Narrow-spectrum Aminoglycosides:

Included in this group are streptomycin and dihydrostreptomycin, which are mainly active against aerobic, gram-negative bacteria.

Expanded-spectrum Aminoglycosides:

Neomycin, framycetin (neomycin B), paromomycin (aminosidine), and kanamycin have broader spectra than streptomycin that includes many gram-negative aerobic bacteria, as well as synergistic activity toward selected gram-positive organisms. Gentamicin, tobramycin, amikacin (synthesized from kanamycin), sisomicin, and netilmicin are aminoglycosides with extended spectra that include *Pseudomonas aeruginosa*.

Miscellaneous Aminoglycoside Antibiotics:

The chemical structure of apramycin differs somewhat from that of the typical aminoglycosides but is similar enough to be included in this class. The structure of spectinomycin is unusual, but it is fairly comparable to other aminocyclitols with regard to its mechanism of action and antibacterial spectrum.

General Properties

Chemically, the aminoglycoside antibiotics are characterized by an aminocyclitol group, with aminosugars attached to the aminocyclitol ring in glycosidic linkage. Because of minor differences in the position of substitutions on the molecules, there may be several forms of a single aminoglycoside. For example, gentamicin is a complex of gentamicins C_1 and C_2, and neomycin is a mixture of neomycins B and C and fradiomycin. The amino groups contribute to the basic nature of this class of antibiotics, and the hydroxyl groups on the sugar moieties contribute to high aqueous solubility and poor lipid solubility. If these hydroxyl groups are removed (eg, tobramycin), antibiotic activity is markedly increased. Differences in the substitutions on the basic ring structures within the various aminoglycosides account for the relatively minor differences in antimicrobial spectra, patterns of resistance, and toxicities. Aminoglycosides are typically quite stable. When the water solubility of an aminoglycoside is marginal, it is usually the sulfate salt that is used for PO or parenteral administration. The pK_as of these drugs are generally between 8 and 10, and as a result, they tend to be ionized at physiologic pH, which may limit drug movement, particularly in acidic environments.

Antimicrobial Activity

Mode of Action:

Aminoglycosides are more effective against rapidly multiplying organisms, and they affect and ultimately destroy bacteria by several mechanisms. They need only a short contact with bacteria to kill them and, as such, are concentration dependent in their actions. Their main site of action is the membrane-associated bacterial ribosome through which they interfere with protein synthesis. To reach the ribosome, they must first cross the lipopolysaccharide (LPS) covering (gram-negative organisms), the bacterial cell wall, and finally the cell membrane. Because of the polarity of these compounds, a specialized active transport process is required.

The first concentration-dependent step requires binding of the cationic aminoglycoside to anionic components in the cell membrane. The subsequent steps are energy dependent and involve the transport of the polar, highly charged cationic aminoglycoside across the cytoplasmic membrane, followed by interaction with the ribosomes. The driving force for this transfer is probably the membrane potential. These processes are much more efficient if the energy used is aerobically generated. The efficacy of the aminoglycosides is markedly curtailed in an anaerobic environment. Aminoglycosides are associated with a postantibiotic effect in a number of bacteria, principally gram-negative (eg, *E coli, Klebsiella pneumoniae, P aeruginosa*). The effect generally lasts 2–8 hr after exposure and allows for dosing intervals longer than the half-lives of the drugs.

Several features of these mechanisms are of clinical significance: 1) The antibacterial activity of the aminoglycosides depends on an effective concentration of antibiotic outside the cell. 2) Anaerobic bacteria and induced mutants are generally resistant, because they lack appropriate transport systems. 3) With low oxygen tension, as in hypoxic tissues, transfer into bacteria is diminished. 4) Divalent cations (eg, calcium and magnesium) located in the LPS, cell wall, or membrane can interfere with transport into bacteria because they can combine with the specific anionic sites and exclude the cationic aminoglycosides. 5) Passive movement of aminoglycosides across bacterial cell membranes is facilitated by an alkaline pH; a low pH may increase membrane resistance more than 100-fold. 6) Changes in osmolality also can alter the uptake of aminoglycosides. 7) Some aminoglycosides are transported more efficiently than others and thus tend to have greater antibacterial activity. 8) Synergism is common when aminoglycosides and β-lactam antibiotics (penicillins and cephalosporins) are used in combination. The cell-wall injury induced by the β-lactam compounds allows increased uptake of the aminoglycoside by the bacteria because of easier accessibility to the bacterial cell membrane.

The intracellular site of action of the aminoglycosides is the ribosome, which is irreversibly bound by aminoglycosides, particularly at the 30 S but also the 50 S subunits (which comprise the 70 S subunit). Variability occurs between aminoglycosides with respect to their affinity and degree of binding. The number of steps in protein synthesis that are affected also varies. Spectinomycin cannot induce misreading of the mRNA and often is not bactericidal, in contrast to the other bactericidal members. However, at low concentrations, all aminoglycosides may be only bacteriostatic.

A cell-membrane effect also occurs with aminoglycosides. The functional integrity of the bacterial cell membrane is lost during the late phase of the transport process, and high

concentrations of aminoglycosides may cause nonspecific membrane toxicity, even to the point of bacterial cell lysis.

Efficacy of aminoglycosides is enhanced if peak plasma or tissue drug concentrations exceed MIC by 10–12 times. Once-daily dosing has been used to enhance both efficacy and safety.

Bacterial Resistance:

Several mechanisms of resistance to the aminoglycoside antibiotics have been described. These may be plasmid or chromosomally mediated.

Impaired transport across the cell membrane is an inherent mechanism of nonplasmid-mediated resistance that occurs in anaerobic bacteria (eg, *Bacteroides fragilis* and *Clostridium perfringens*), because the transport process is active and oxygen-dependent. Facultative anaerobes (eg, enterobacteria and *Staphylococcus aureus*) are more resistant to the aminoglycosides when in an anaerobic environment. Impaired transport can be induced by exposure to sublethal concentrations of these antibiotics. Examples include streptomycin resistance among strains of *P aeruginosa*, low-level aminoglycoside resistance among enterococci, and gentamicin resistance in *Streptococcus faecalis*.

Impaired ribosomal binding may not be a clinically important form of single-step resistance, because generally the drugs bind to multiple sites on the ribosomes. Exceptions include *E coli* strains in which a single-step mutation prevents the binding of streptomycin to the ribosome. The same mechanism has been described in *P aeruginosa*.

Enzymatic modification of aminoglycosides may be either plasmid-encoded or chromosomally mediated. Enzymes occur in both gram-negative and gram-positive bacteria. More than 50 enzymes have been identified, with three major types, each including several subclasses: acetylating enzymes (acetyltransferases), adenylating enzymes (nucleotidyltransferases), and phosphorylating enzymes (phosphotransferases). The susceptibility of each aminoglycoside to specific enzymatic attack varies among each subclass. Although cross-resistance is common, there are differences in susceptibility patterns. Chemical modification stabilizes the drug, which decreases susceptibility to enzymatic destruction. For example, chemically modified kanamycin yields amikacin, which is more resistant to enzymatic hydrolysis.

Other mechanisms of resistance include 1) increased concentration of divalent cations (especially Ca^{2+} and Mg^{2+}), which act to repel ionized drug from the microbe, and 2) increased production by *P aeruginosa* mutants of the outer cell membrane protein, H1, resulting in resistance to gentamicin. Note that efficacy will be reduced in the presence of decreased pH (eg, acidic urine or abscesses), which increases resistance to relatively high concentrations of aminoglycosides.

Antibacterial Spectra:

Streptomycin and dihydrostreptomycin (no longer available in the USA) are characterized by narrow spectra, and efficacy is limited by bacterial resistance. Gram-negative bacilli are still susceptible, including strains of *Actinomyces bovis*, *Pasteurella* spp, *E coli*, *Salmonella* spp, *Campylobacter fetus*, *Leptospira* spp, and *Brucella* spp. *Mycobacterium tuberculosis* is also sensitive to streptomycin.

The spectra of neomycin, framycetin, and kanamycin are broader, with clinical use targeting gram-negative organisms, including *E coli* and *Salmonella*, *Klebsiella*, *Enterobacter*, *Proteus*, and *Acinetobacter* spp. Aminoglycosides with spectra that include *Pseudomonas aeruginosa* (gentamicin, tobramycin, amikacin, sisomicin, and netilmicin) are also often highly effective against a wide variety of aerobic bacteria. Because of their efficacy against *P aeruginosa*, aminoglycosides might be considered higher-tier drugs. Selected staphylococci are susceptible, but treatment should be based on synergistic effects, ie, combination with other antimicrobials (eg, β-lactams). With such combination therapy, generally low doses of aminoglycosides are used. Because oxygen is necessary for active transport of drug into the microbe, caution is recommended when treating facultative anaerobes in a low-oxygen environment. Obligate anaerobic bacteria and fungi are not appreciably affected; streptococci are usually only moderately sensitive or quite resistant.

Pharmacokinetic Features

The pharmacokinetic features of the aminoglycosides are similar in most species.

Absorption:

Aminoglycosides are poorly absorbed (usually <10%) from the healthy GI tract. However, permeability may be increased in the neonate and in the presence of enteritis and other pathologic changes, allowing absorption to be significantly greater. In the presence of renal failure, toxic (trough) concentrations may accumulate. Aminoglycosides can be administered slowly by bolus IV injection or SC or IM routes. Absorption from IM injection sites is rapid and nearly complete (>90% availability), except in severely hypotensive animals. Blood concentrations usually peak within 30–90 min after IM administration. Absorption after SC injection may be protracted. Absorption after IP administration can be rapid and substantial. Short dosing intervals, including continuous infusions, are contraindicated for all aminoglycosides. Once-daily therapy is indicated for safety considerations. Serum concentrations of aminoglycosides may reach bactericidal levels after repeated intrauterine infusion, particularly in endometritis.

Distribution:

Aminoglycosides are polar at physiologic pH, limiting distribution to extracellular fluids, with minimal penetration into most tissues. Exceptions include the renal cortex of the kidneys and the endolymph of the inner ear, sites at which aminoglycosides increasingly accumulate as ionization increases. The extracellular fluid compartment normally approximates 25% of body weight, but this volume can change substantially, which leads to indirectly proportional changes in the concentration of an aminoglycoside. For example, extracellular fluid space contracts with dehydration and during gram-negative sepsis, causing concentrations to increase, whereas the distribution volume of aminoglycosides increases with congestive heart failure or ascites, causing concentrations to decrease. Concentrations tend to be lower in neonates, which have a large extracellular fluid compartment relative to body weight. Aminoglycosides are not appreciably bound to plasma proteins (usually <20%). Therapeutic concentrations (~10 times the MIC of the infecting microbe) can be achieved in the synovial, pleural, and even peritoneal fluids, especially if inflammation is present. However, effective concentrations are not reached in CSF, ocular fluids, milk, intestinal fluids, or prostatic secretions. Fetal tissue and amniotic fluid concentrations are very low in most species.

Biotransformation, Excretion, and Pharmacokinetic Values:

The aminoglycosides are excreted unchanged in the urine by glomerular filtration, with 80%–90% of administered drug recoverable from the urine within 24 hr of IM administration. A variable fraction of filtered aminoglycoside is absorbed onto the brush border of the proximal tubule and loop of Henle cells. Binding is facilitated by ionization. After binding, the drug is transported into the cell, sequestered in lysosomes. Rupture of lysozymes results in release into the cytosol. Excessive accumulation (mainly in the renal cortex) leads to a characteristic tubular cell necrosis. Glomerular filtration rates differ between species and are often less in neonates, which may explain the greater sensitivity to aminoglycosides in newborn foals and puppies.

Elimination varies with glomerular filtration changes associated with cardiovascular and renal function, age, fever, and several other factors. Half-life also will vary directly and proportionately with the volume of the extracellular fluid compartment. The aminoglycosides have relatively short plasma half-lives (~1 hr in carnivores and 2–3 hr in herbivores). The elimination kinetics often follow a three-compartment model, indicating a “deep” compartment that reflects binding of drug in the renal tubular cell. Approximately 90% of the injected drug, including that within therapeutic concentrations, is excreted unchanged through the kidneys during the β phase of elimination. The remaining deep or γ phase is excreted over a protracted period, probably due to the gradual release of the antibiotic from renal intracellular binding sites (terminal elimination half-life often 20–200 hr). Concentrations in plasma during this phase are generally below what would be considered therapeutic. The limited selection of pharmacokinetic values for two typical aminoglycosides (see Table: Elimination, Distribution, and Clearance of Aminoglycosides) serves as a basis for any required dosage modifications that may be necessary because of age or renal insufficiency. The best way to alter a dosage regimen of aminoglycosides is to monitor plasma concentrations to assure that 10 times the MIC is achieved at peak concentrations, and concentrations less than target (generally <2 mcg/mL) are achieved before the next dose ("trough" concentrations).

Table. Elimination, Distribution, and Clearance of Aminoglycosides

Aminoglycoside	Species	Elimination Half-life (min)	Volume of Distribution (mL/kg)	Clearance (mL/kg/min)
Gentamicin	Dogs	75	335	3.10
	Horses	110	190	1.23
	Foals	200	300	1.04
Amikacin	Dogs	60	300	3.50
	Horses	45	207	0.75
	Sheep	115	200	0.70

Therapeutic Indications and Dose Rates

Despite their potential to cause nephrotoxicity, the aminoglycosides are commonly used to control local and systemic infections caused by susceptible aerobic bacteria (generally gram-negative). Several aminoglycosides are used topically in the ears and eyes and via intrauterine infusion to treat endometritis. Aminoglycosides occasionally may be infused into the udder to treat mastitis. In general, because of their concentration dependency and potential for

nephrotoxicity, aminoglycosides are administered once daily (same total daily dose; "high" dose), thus minimizing the risk of nephrotoxicity. If used at lower doses for synergistic activity against gram-positive organisms, such as staphylococci, lower doses (30%–50% of the higher dose) might be given at more frequent intervals.

A selection of general dosages for some aminoglycosides is listed in Dosages of Aminoglycosides. The dose rate and frequency should be adjusted as needed for the individual animal.

Table. Dosages of Aminoglycosides

Aminoglycoside	Dosage, Route, and Frequency
Gentamicin	6–12 mg/kg/day, IM or SC
Kanamycin	25–30 mg/kg/day, IM or SC
Streptomycin/dihydrostreptomycin	15–25 mg/kg/day, IM or SC
Amikacin	15–22 mg/kg/day, IM or SC
Netilmicin	6–12 mg/kg/day, IM or SC
Neomycin	15 mg/kg, PO, once to twice daily
	0.5–1 g/day/quarter (intramammary)

If monitoring, two time points (a peak and a second sample 4 hr later) is ideal such that an extrapolated peak concentration can be determined, along with an elimination half-life. The peak should be collected after distribution into tissues is complete, or ~1 hr. The "trough" in this scenario should be collected 2–3 half-lives later (eg, 4–6 hr after dosing) such that concentrations will still be detectable. If a single sample is collected to determine safety, a trough concentration (just before the next dose) is indicated. Trough concentrations generally should be <2 mcg/mL. For efficacy, a 1.5–2 hr peak concentration might be collected; peak concentrations should be 10–12 times the MIC of the infecting organism. For renal function, both a peak and detectable trough (taken well before the next dose, because concentrations may not otherwise be detectable) are indicated so that a half-life, and, if IV administration is used, clearance might be calculated. As a precaution, the following general guidelines may be followed in cases of renal failure in which plasma creatinine values are increased (see Table: Dosage Modifications of Aminoglycosides in Renal Failure).

Table. Dosage Modifications of Aminoglycosides in Renal Failure

Increase in Normal Serum or Plasma Creatinine (mg/dL)	Dose and Dosage Interval
<1	Full dose at usual dosage interval
2-fold increase	Full dose at usual dosage interval or increased to 50% plus usual dosing interval (eg, 36 hr)
3- to 4-fold increase	Full dose, doubling usual dosage interval
>4-fold increase	Aminoglycosides contraindicated

The treatment interval should be increased in neonates (especially puppies and foals), in renal failure, and in obese animals. Doses may be increased in neonates or pediatric animals, in which the volume of distribution is greater than in adults, and in animals with edema, hydrothorax, or ascites, provided their renal function is unimpaired.

Special Clinical Concerns

Adverse Effects and Toxicity:

Ototoxicity, neuromuscular blockade, and nephrotoxicity are reported most frequently; these effects may vary with the aminoglycoside and dose or interval used, but all members of the group are potentially toxic. Nephrotoxicity is of major concern and may result in renal failure due to acute tubular necrosis with secondary interstitial damage. Aminoglycosides accumulate in proximal tubular epithelial cells, where they are sequestered in lysosomes and interact with ribosomes, mitochondria, and other intracellular constituents to cause cell injury. The greater the ionization (eg, the more the amine groups and the lower the pH), the greater the active uptake. Kidneys must have a drug-free period to eliminate accumulated drugs. As such, persistence of aminoglycosides in plasma and thus urine is likely to predispose the tubular cells to toxicity, and the risk may by reduced by allowing plasma drug concentrations to drop below recommended concentrations (generally 1–2 mcg/mL) before the next dose. Nonoliguric renal failure is the usual observation; it is generally reversible if damage is not sufficiently extensive to harm the basement membrane, although recovery may be prolonged.

Renal function should be monitored during therapy; however, no indicator of renal disease is sufficiently sensitive to prevent continued damage once nephrotoxicity is detected. Polyuria, decreased urine osmolality, enzymuria, proteinuria, cylindruria, and increased fractional sodium excretion are indicative of aminoglycoside nephrotoxicity. Later, BUN and creatinine concentrations may be increased. Early changes or evidence of nephrotoxicity can be detected in 3–5 days, with more overt signs in 7–10 days. Several factors predispose to aminoglycoside nephrotoxicosis, including age (with young [especially the newborn foal] and old animals being sensitive), compromised renal function, total dose, duration of treatment, dehydration and hypovolemia, aciduria, acidosis, hypomagnesemia, severe sepsis or endotoxemia, concurrent administration of furosemide, and exposure to other potential nephrotoxins (eg, methoxyflurane, amphotericin B, cisplatinum, and perhaps some cephalosporins). In renal insufficiency, generally the interval between doses is prolonged (rather than reducing the dose) to minimize toxicity, while avoiding a negative impact on efficacy. Dosing in the morning may decrease toxicity in diurnal animals. The risk of toxicity is less in alkaline urine. Nephroactive drugs, including those that alter renal vascular response (eg, autoregulation) should be avoided or used cautiously (eg, NSAIDs, diuretics). Treatment with *N*-acetylcysteine should be considered (see ototoxicity, below).

Aminoglycosides can cause ototoxicity, which may manifest as either auditory or vestibular dysfunction. Binding or damage to mitochondria plays a prominent role in ototoxicity. Vestibular injury leads to nystagmus, incoordination, and loss of the righting reflex. The lesion is often irreversible, although physiologic adaptation can occur. Ototoxicity is not unusual in people, but relevance to veterinary patients is not clear. Cats are particularly sensitive to the toxic vestibular effects, although occurrence at therapeutic concentrations after systemic administration is unlikely. However, aminoglycosides should not be administered topically into the ear unless the tympanic membrane is intact. Hearing impairment reflects permanent damage and loss of the hair cells in the organ of Corti. Loss of

high-frequency hearing is followed by deafness, which may not be complete if sufficiently low doses or durations were used. Aminoglycosides should be avoided in working dogs that depend on hearing (eg, guide dogs). Factors increasing the risk of vestibular and cochlear damage are the same as for nephrotoxicity but also include preexisting acoustic or vestibular impairment and concurrent treatment with potentially ototoxic drugs. The ototoxic potential is greatest for gentamicin, sisomicin, and neomycin, and least for netilmicin. In people, treatment with *N*-acetylcysteine has deceased the risk of aminoglycoside ototoxicity.

All aminoglycosides, when administered in doses that result in high plasma concentrations, have been associated with muscle weakness and respiratory arrest attributable to neuromuscular blockade. The effect is more pronounced when aminoglycosides are used with other drugs that cause neuromuscular blockade and with gas anesthetics. Neomycin, kanamycin, amikacin, gentamicin, and tobramycin are listed in order of most to least potent for these neuromuscular effects. The effect is due to the chelation of calcium and competitive inhibition of the prejunctional release of acetylcholine in most instances (there are some differences among aminoglycosides). The blockade is antagonized by calcium gluconate and somewhat less consistently by neostigmine.

CNS disturbances rarely include convulsions or collapse after rapid IV administration. Other adverse effects include superinfection when used topically or PO, a malabsorption syndrome due to attenuation of intestinal villous function when used PO in neonates, occasional hypersensitivity reactions, contact dermatitis, cardiovascular depression, and inhibition of some WBC functions (eg, neutrophil migration and chemotaxis and even bactericidal activity at high concentrations).

Interactions:

Enhanced nephrotoxicity may become evident with concurrent administration of aminoglycosides and other potentially nephroactive (such as diuretics) or nephrotoxic (such as NSAIDs) agents. Neuromuscular blockade is more likely when aminoglycosides are administered at the same time as skeletal muscle relaxants and gas anesthetics. Aminoglycoside ototoxicity is enhanced by the loop-acting diuretics, especially furosemide. Cardiovascular depression may be aggravated by aminoglycosides when administered to animals under halothane anesthesia. High concentrations of carbenicillin, ticarcillin, and piperacillin inactivate aminoglycosides because of direct interactions both in vitro and in vivo in the presence of renal failure. Synergistic interactions that enhance antibacterial efficacy have been documented when aminoglycosides are administered with other antimicrobials, particularly β-lactams.

Effects on Laboratory Tests:

BUN, serum creatinine, serum transaminases, and alkaline phosphatase values may be increased. Proteinuria is a significant laboratory finding.

Miscellaneous Aminocyclitol Antibiotics

Apramycin (administered orally) is used to control enteric gram-negative infections, particularly *E coli* and salmonellae in calves and piglets. It also is active against *Proteus*, *Klebsiella*, *Brachyspira*, and *Mycoplasma* spp. There is little cross-resistance within the aminoglycosides, and plasmid-mediated resistance is yet to be confirmed. Apramycin is

poorly absorbed after administration PO (<10%). It is rapidly absorbed from parenteral injection sites. Plasma concentrations peak within 1–2 hr of IM administration. Apramycin distributes only into the extracellular fluid and is excreted unchanged in the urine (95% within 4 days). The elimination half-life in calves is ~4–5 hr. Apramycin is toxic in cats but considered safe in most other species (3–6 times the recommended oral dose rarely produces toxicity). The oral dose rate is 20–40 mg/kg/day, for 5 days. The parenteral dose rate is 20 mg/kg, bid. The withdrawal time in pigs and calves (in Europe) is 28 days after oral use.

The structure of spectinomycin differs from that of the aminoglycosides, but it also binds to bacterial ribosomes and interferes with protein synthesis. However, the effect is bacteriostatic rather than bactericidal. Spectinomycin can be inactivated by an enzyme coded for by an R factor, but mutant resistance due to diminished ribosomal binding is perhaps more common. It is active against several strains of streptococci, a wide range of gram-negative bacteria, and *Mycoplasma* spp; most *Chlamydia* spp are resistant. It is poorly absorbed from the GI tract but is rapidly absorbed after IM administration, with blood concentrations peaking within 1 hr. Like aminoglycosides, spectinomycin penetrates tissues rather poorly and distributes principally into extracellular fluid. Metabolic transformation of spectinomycin is limited, and 80% can be recovered unchanged in the urine over 24–48 hr; ~75% is eliminated by glomerular filtration in ~4 hr. At usual doses, no major toxic reactions have been reported. It is administered both PO at 20 mg/kg, bid, and IM at 5–10 mg/kg, bid. Withdrawal time for pigs is usually ~3 wk.

Quinolones, including Fluoroquinolones

Quinolone carboxylic acid derivatives are synthetic antimicrobial agents. Nalidixic acid and its congener oxolinic acid have been used for treatment of urinary tract infections for years, whereas flumequine has been used successfully in several countries to control intestinal infections in livestock. Many broad-spectrum antimicrobial agents have been produced by modification of the various 4-quinolone ring structures.

Classes

Known generically as quinolones or 4-quinolones, these drugs are derived from several closely related ring structures that have certain common features. Nalidixic acid, considered a first-generation drug, is the earliest of the quinolones. In general, subsequent generations are based on spectrum, but this often reflects similar changes in chemical structure. Subsequent drugs contain a fluorine group and, as such, are referred to as fluoroquinolones. Most veterinary drugs and many human drugs, including ciprofloxacin, are considered second generation. Pradofloxacin is an example of a later-generation drug approved for use in cats (USA) or dogs and cats (European Union).

Table. Quinolones and Species Approvals in the USA and EU.

Quinolone	Species
Ciprofloxacin	Dogs, cats
Danofloxacin	Dogs, cattle
Difloxacin	Dogs
Enrofloxacin	Dogs, cats, cattle, swine
Marbofloxacin	Dogs, cats
Norfloxacin	Dogs, cats
Orbifloxacin	Dogs, cats
Pradofloxacin	Cats
Sarafloxicin	Voluntarily withdrawn

General Properties

Within the diversity of their various ring structures, the quinolones have a number of common functional groups essential for their antimicrobial activity. For example, the quinolone nucleus contains a carboxylic acid group at position 3 and an exocyclic oxygen at position 4 (hence the term 4-quinolones), which are believed to be the active DNA-gyrase binding sites. Various modifications have produced compounds with differing physical, chemical, pharmacokinetic, and antimicrobial properties. For example, the side chain attached to the nitrogen at position 1 affects potency. Replacement of the ethyl group at this position with a bulkier group (eg, the cyclopropyl group of ciprofloxacin and similar drugs) enhances gram-negative and positive spectra. Addition of a fluorine atom at position 6 profoundly enhances the gram-positive spectrum, whereas the addition of a (heterocyclic nitrogen-containing) piperazyl ring at position 7 enhances bacterial penetration and potency, including toward *Pseudomonas aeruginosa*. Substitutions on the piperazyl (eg, ofloxacin and its L isomer, levofloxacin; sparfloxacin) enhance gram-positive penetration, whereas substitutions at position 8 enhance anaerobic activity (eg, sparfloxacin, pradofloxacin, moxifloxacin). If the substitution is with a methoxy group (rather than a halogen), the risk of phototoxicity is reduced.

The quinolones are amphoteric and, with a few exceptions, generally exhibit poor water solubility at pH 6–8. Although the impact on therapeutic efficacy is not clear, they appear to act as weak bases in that they are much less effective in acidic than in nonacidic urine pH. In concentrated acidic urine, some quinolones form needle-shaped crystals, although this apparently has not been reported with clinical use. Liquid formulations of various quinolones for PO or parenteral administration usually contain freely soluble salts in stable aqueous solutions. Solid formulations (eg, tablets, capsules, or boluses) contain the active ingredient either in its betaine form or, occasionally, as the hydrochloride salt.

Antimicrobial Activity

Mode of Action:

The quinolones inhibit bacterial enzyme topoisomerases, including topoisomerase II (otherwise known as DNA gyrase) and topoisomerase IV. Bacterial DNA supercoils and then uncoils during replication. Supercoiling requires transient nicks that are subsequently sealed after DNA polymerase passes. Topoisomerase II allows for single strand nicks in the DNA that support coiling and uncoiling. Topoisomerase IV supports disentanglement of DNA as chromosomes separate. Inhibition of topoisomerases reduces supercoiling, resulting in disruption of the spatial arrangement of DNA, and reduces DNA repair. Mammalian topoisomerase enzymes fundamentally differ from bacterial gyrase and are not susceptible to quinolone inhibition. The quinolones are usually bactericidal; susceptible organisms lose viability within 20 min of exposure to optimal concentrations of the newer fluoroquinolones. Typically, clearing of cytoplasm at the periphery of the affected bacterium is followed by lysis, rendering bacteria recognizable only as "ghosts."

Quinolones are associated with a postantibiotic effect in a number of bacteria, principally gram-negative (eg, *E coli*, *Klebsiella pneumoniae*, *P aeruginosa*). The effect generally lasts 4–8 hr after exposure.

Efficacy of the fluorinated quinolones depends on concentrations in plasma that exceed the MIC of the infecting organism by 10- to 12- fold. As such, the drugs are concentration dependent. However, efficacy also is correlated to the magnitude of the area under the inhibitory curve (AUC:MIC); as such, efficacy also takes into account elimination half-life.

The fluoroquinolones can have significant antibacterial activity at extraordinarily low concentrations, although efficacy toward some organisms (eg, *E coli*) is bimodal: some isolates are very susceptible (MIC <0.01–0.5 mcg/mL), whereas the MIC for a significant number of other isolates is very high (>64 mcg/mL). In general, MIC for most susceptible microbes, including *E coli*, *Klebsiella*, *Proteus*, *P aeruginosa*, and *Staphylococcus* have increased since the approval of the quinolones in the early 1990s.

Bacterial Resistance:

Chromosomal mutational resistance to the original fluoroquinolones was considered to be low in frequency, and plasmid-mediated resistance nonexistent. However, resistance is increasingly being recognized, indicating that therapy based on culture and susceptibility is prudent. In general, cross-resistance should be anticipated among the more closely related members of this class.

Gram-negative bacteria more commonly target DNA gyrase; emerging resistance is more often associated with changes in the GyrA compared to the GyrB subunit. In contrast, the primary target of gram-positive organisms tends to be topoisomerase IV, with resistance mechanisms targeting it, followed by changes in DNA gyrase. Use of the drug selects for resistance. High-level resistance (3–4 times the breakpoint MIC) generally reflects a second-step mutation that leads to changes in the amino acid sequence of subsequent topoisomerase targets. However, even with this second step of resistance, MIC are often below the resistant breakpoint range on which susceptibility testing is based. With the second increase in MIC,

mutations in efflux pump regulators also emerge, causing marked increase in expression. As a result, high-level, multidrug resistance emerges.

Another mechanism of resistance is the combined effect of increased efflux pumps and decreased porins that act in concert to reduce intracellular concentrations. Virulence of refractory mutants may not diminish.

Note that if resistance does emerge to one fluoroquinolone, it is likely to impact all fluoroquinolones. However, resistance may be slower to emerge to newer drugs, including gemifloxacin, trovafloxacin, gatifloxacin, or pradofloxacin, because of larger side chains that facilitate binding to either DNA gyrase or topoisomerase IV.

Antimicrobial Spectra:

The fluoroquinolones are active against a wide range of gram-negative organisms and several gram-positive aerobes. This includes *E coli*, *Salmonella*, *Klebsiella*, *Enterobacter*, *Proteus*, and generally *Pseudomonas aeruginosa*. The fluoroquinolones are active against intracellular pathogens, including, eg, *Brucella* spp. Quinolones also have significant activity against *Mycoplasma* and *Chlamydia* spp. Obligate anaerobes tend to be resistant to most quinolones, as are most enterococci (previously group D *Streptococcus* spp (*Enterococcus faecalis* and *Enterococcus faecium*). *Nocardia* and atypical mycobacteria may also be susceptible.

The newer third- and fourth-generation fluorinated quinolones, such as pradofloxacin, are often characterized by an effective anaerobic spectrum.

A synergistic effect has been demonstrated in vitro between quinolones and β-lactams, aminoglycosides, clindamycin, and metronidazole.

Pharmacokinetic Features

Among the few quinolones that have been studied to any degree in domestic animals, pharmacokinetic differences can markedly differ. Because of the physicochemical nature of the group, this is to be expected. A general overview follows, but some diversity should be anticipated.

Absorption:

Quinolones are commonly administered PO, although forms of enrofloxacin and ciprofloxacin are available for IV, IM, and SC (enrofloxacin) administration. Absorption into the blood after IM or SC delivery is rapid; after administration PO, blood concentrations usually peak within 1–3 hr. Bioavailability is often >80% for most quinolones, except for ciprofloxacin and in ruminants with functional forestomachs, in which bioavailability may be as low as 0–20%. The presence of food may delay absorption in monogastric animals, which may impact efficacy. The bioavailability of ciprofloxacin after administration PO in dogs is variable and can be as little as 40%; it is 0–20% in cats and horses. Marbofloxacin oral bioavailability is almost 100%.

Distribution:

With few exceptions, the quinolones penetrate all tissues well and quickly. Particularly high concentrations are found in organs of elimination (kidneys, liver, and bile), but concentrations found in prostatic fluid, bone, endometrium, and CSF are also quite notable. Most quinolones also cross the placental barrier. The apparent volume of distribution of most quinolones is large. The degree of plasma-protein binding is extremely variable, from ~10% for norfloxacin to 30% for enrofloxacin in dogs and >90% for nalidixic acid. Fluorinated quinolones as a group accumulate in phagocytic WBCs.

Biotransformation:

Some quinolones are eliminated unchanged (eg, ofloxacin), some are partially metabolized (eg, ciprofloxacin, enrofloxacin), and a few are completely degraded. Metabolites are sometimes active; enrofloxacin is de-ethylated to form ciprofloxacin. Characteristically, phase I reactions result in a number of primary metabolites (up to six have been described for some quinolones) that retain some antibacterial action. Conjugation with glucuronic acid then ensues, followed by excretion. In contrast, only ~10% of marbofloxacin is metabolized.

Excretion:

Renal excretion is the major route of elimination for most quinolones. Both glomerular filtration and tubular secretion are involved. Urine concentrations are often high for 24 hr after administration, and crystals may form in concentrated acidic urine. The clinical significance of this finding is unclear. In renal failure, clearance is impaired, and reductions in dose rates are essential. Biliary excretion of parent drug, as well as conjugates, is an important route of elimination in some cases (eg, ciprofloxacin, marbofloxacin, difloxacin, pefloxacin, nalidixic acid). Quinolones appear in the milk of lactating animals, often at high concentrations that persist for some time.

Pharmacokinetic Values:

The clearance and volume of distributions of the drugs vary among species, resulting in differences in plasma half-lives. Plasma concentrations attained are usually directly proportional to the dose administered but also vary with volume of distribution and oral bioavailability. Package inserts should be consulted for C_{max} for those drugs approved for use in the target species.

Table. Pharmacokinetics of Selected Fluoroquinolones

Drug	Species	Elimination Half-life (hr)	Volume of Distribution (L/kg)	Clearance (mL/min/kg)
Enrofloxacin	Cats	7		4.3
	Dogs	4.4	3.7	11
	Mares	4–7	2	0.5–4
Marbofloxacin	Dogs	12	2	1.5
Orbifloxacin	Cats	4.5	1.3	
	Dogs	5.4	1.2	

Therapeutic Indications and Dose Rates

Quinolones are indicated for the treatment of local and systemic infections caused by susceptible microorganisms, particularly against deep-seated infections and intracellular pathogens. Therapeutic success has been obtained in respiratory, intestinal, urinary, and skin infections, as well as in bacterial prostatitis, meningoencephalitis, osteomyelitis, and arthritis. Because of their lipid solubility and ability to accumulate in phagocytic WBCs, quinolones should be considered for use in infections located in tough to penetrate tissues. Therapeutic failure is likely to result with multidrug-resistant organisms; this coupled with their emerging adverse events should cause these drugs to be considered second tier for dogs and cats.

A selection of general dosages for some quinolones is listed in Dosages of Quinolones. The dose rate and frequency should be adjusted as needed for the individual animal and the MIC of the infecting organisms. Plasma drug concentrations should approximate 10 times the MIC of the infecting microbe. Higher doses are encouraged unless mitigating circumstances preclude the increase; in such instances, unless the MIC is very low, alternative antimicrobials might be considered. In dogs and cats, use ideally is based on culture and susceptibility testing when possible. Extra-label use of fluoroquinolones is prohibited in food animals.

Table. Dosages of Quinolones

Quinolone[a]	Species	Dosage, Route, and Frequency
Nalidixic acid	Cats, dogs	3 mg/kg, PO, qid
Enrofloxacin	Dogs	5–20 mg/kg, PO, once to twice daily
		2.5 mg/kg, SC, once, then PO
	Beef cattle (not veal or dairy)	7.5–12.5 mg/kg, SC, once
		2.5–5 mg/kg/day, SC
	Pigs	2.5–5 mg/kg/day, PO or IM
	Preruminant calves	2.5–5 mg/kg/day, PO or SC
Marbofloxacin	Cats, dogs	2.75–5.5 mg/kg/day, PO
Difloxacin	Dogs	5–10 mg/kg/day, PO
Orbifloxacin	Cats, dogs	2.5–7.5 mg/kg/day, PO
Pradofloxacin	Cats	7.5 mg/kg/day, PO

[a] Extra-label use of fluorinated quinolones in food-producing animals is prohibited in the USA.

Special Clinical Concerns

Adverse Effects and Toxicity:

Although adverse effects with the older quinolones (nalidixic and oxolinic acids) were relatively common, the newer ones seem to be well tolerated. However, several adverse effects can limit use in selected species. Retinal degeneration may occur acutely in cats, with the risk greatest for enrofloxacin; because these drugs are concentration dependent,

enrofloxacin probably should not be used in cats. The presence of renal disease may increase this risk. Pradofloxacin may be the least retinotoxic, followed by marbofloxacin and orbifloxacin, but each of these appears to be safe in cats at doses that would be necessary to achieve targeted C_{max}:MIC ratios for susceptible organisms. The mechanism is not known. Quinolones tend to be neurotoxic, and convulsions can occur at high doses. Vomiting and diarrhea rarely develop with fluoroquinolones. Dermal reactions and photosensitization have been described in people, but the occurrence seems low. Hemolytic anemia has also been seen. Administering large doses of quinolones for any length of time during pregnancy has resulted in embryonic loss and maternal toxicity. Because high prolonged dosages in growing dogs have produced cartilaginous erosions leading to permanent lameness, excessive use of quinolones should be avoided in immature animals. Quinolone administration in horses has not yet been extensively studied, but there is some indication that damage to the cartilage in weightbearing joints may be seen.

In 2008, the FDA added a "black-box" warning for seven fluoroquinolones that increased the risk of tendinitis and a tendon rupture.

An emerging toxicity associated with fluoroquinolones is mitotoxicity, ie, damage to mitochondrial topoisomerase or other mitochondrial structures. Mitochondrial effects may not emerge until some time after fluoroquinolone therapy is instituted. Although the entirety of the clinical impact of this toxicity is not known, nor its relevance to veterinary medicine, adverse events ranging from neurologic to musculoskeletal to cardiovascular may ultimately be attributed to this effect.

Interactions:

The fluorinated quinolones may be involved in a number of drug interactions. Antacids or other drugs containing multivalent cations and sucralfate appear to interfere with the GI absorption of the quinolones. Nitrofurantoin impairs the efficacy of quinolones if used concurrently for urinary tract infections. Quinolones inhibit the biotransformation of methylxanthines, with theophylline being the most clinically relevant, but also including caffeine and theobromine. This is a class effect, with the risk varying among the fluoroquinolones in people. A similar ranking of risk is not available for veterinary medicine. In people, cyclosporine concentrations may also be increased by concurrent administration with fluoroquinolones, leading to prolonged and potentially toxic plasma concentrations.

Effects on Laboratory Tests:

AST, ALT, alkaline phosphatase, and BUN may be increased. Urine glucose may be altered, and urinalysis may reveal needle-shaped crystals.

Sulfonamides and Sulfonamide Combinations

Sulfonamides are the oldest and remain among the most widely used antibacterial agents in veterinary medicine, chiefly because of low cost and their relative efficacy in some common

bacterial diseases. The synergistic action of sulfonamides with specific diaminopyrimidines renders these drugs much more effective than sulfonamides alone.

Classes

The many available sulfonamides and sulfonamide derivatives can be categorized into several types, based mainly on their indications and duration of action in the body. Probably the most common classification is based on water versus lipid solubility or duration of effect. Although there are many sulfonamide antimicrobials, only a few are used clinically in animals.

Standard Use Sulfonamides:

In most species, members of this large group are administered 1–4 times/day, depending on the drug, to control systemic infections caused by susceptible bacteria. In some instances, administration of the sulfonamide can be less frequent if the drug is eliminated slowly in the species being treated. Sulfonamides included in this class, depending on the species, are sulfathiazole, sulfamethazine (sulfadimidine), sulfamerazine, sulfadiazine, sulfapyridine, sulfabromomethazine, sulfaethoxypyridazine, sulfamethoxypyridazine, sulfadimethoxine, and sulfachlorpyridazine.

Highly Soluble Sulfonamides Used for Urinary Tract Infections:

A few very water-soluble sulfonamides, eg, sulfisoxazole (sulfafurazole) and sulfasomidine, are rapidly excreted via the urinary tract (>90% in 24 hr) mostly in an unchanged form; because of this, they are primarily used to treat urinary tract infections.

Poorly Soluble Sulfonamides Used for Intestinal Infections:

Some sulfonamide derivatives, such as sulfaguanidine, are so insoluble that they are not absorbed from the GI tract (<5%). Phthalylsulfathiazole and succinylsulfathiazole undergo bacterial hydrolysis in the lower GI tract with the consequent release of active sulfathiazole. Salicylazosulfapyridine (sulfasalazine) is also hydrolyzed in the large intestine to sulfapyridine and 5-aminosalicylic acid, an anti-inflammatory agent that might be used for management of ulcerative colitis in dogs.

Potentiated Sulfonamides:

A group of **diaminopyrimidines** (trimethoprim, methoprim, ormetoprim, aditoprim, pyrimethamine) inhibit dihydrofolate reductase in bacteria and protozoa far more efficiently than in mammalian cells. Used alone, these agents are not particularly effective against bacteria, and resistance develops rapidly. However, when combined with sulfonamides, a sequential blockade of microbial enzyme systems occurs with bactericidal consequences. Examples of such potentiated sulfonamide preparations include trimethoprim/sulfadiazine (co-trimazine), trimethoprim/sulfamethoxazole (co-trimoxazole), trimethoprim/sulfadoxine (co-trimoxine), and ormetoprim/sulfadimethoxine. Sulfonamides are used in combination with pyrimethamine to treat protozoal diseases such as leishmaniasis and toxoplasmosis.

Topical Sulfonamides:

Several sulfonamides are used topically for specific purposes. Sulfacetamide is not highly efficacious but is occasionally used to treat ophthalmic infections. Mafenide and silver sulfadiazine are used on burn wounds to prevent invasion by many gram-negative and gram-positive organisms. Sulfathiazole is commonly included in wound powders for the same purpose.

General Properties

The sulfonamides are derivatives of sulfanilamide, which is the nucleus common to all. The addition or substitution of various functional groups to the amido group or in which various substitutions on other amino groups result in compounds with varying physical, chemical, pharmacologic, and antibacterial properties. Although amphoteric, sulfonamides generally behave as weak organic acids and are much more soluble in alkaline aqueous solutions than in acidic solutions. Those of therapeutic interest have pK_a values of 4.8–8.6. Water-soluble sodium or disodium salts are used for parenteral administration. Such solutions are highly alkaline, somewhat unstable, and readily precipitate with the addition of polyionic electrolytes. In a mixture of sulfonamides (eg, the sulfapyrimidine group), each component drug has its own solubility; therefore, a combination of sulfonamides is more water soluble than a single drug at the same total concentration. This is the basis of triple sulfonamide mixtures used clinically. The N-4 acetylated sulfonamides, except for the sulfapyrimidine group (sulfamethazine, sulfamerazine, sulfadiazine), are less water soluble than their nonacetylated forms. This has bearing in the development of sulfonamide crystalluria. The highly insoluble sulfonamides (phthalylsulfathiazole and succinylsulfathiazole) are retained in the lumen of the GI tract for prolonged periods and are known as “gut-active” sulfonamides. Trimethoprim and ormetoprim are basic drugs.

Antimicrobial Activity

Mode of Action:

The sulfonamides are structural analogues of para-aminobenzoic acid (PABA) and competitively inhibit dihydropterate synthetase, an enzyme that facilitates PABA as a substrate for the synthesis of dihydrofolic acid (folic acid). Dihydrofolate is a precursor for formation of tetrahydrofolate (folinic acid), an essential component of the coenzymes responsible for single carbon metabolism in cells. Sulfonamides are antimetabolites that substitute for PABA, resulting in blockade of several enzymes needed for the biogenesis of purine bases and other metabolic reactions necessary for formation of RNA. Protein synthesis, metabolic processes, and inhibition of growth and replication occur in organisms that cannot use preformed (eg, dietary) folate. The effect is bacteriostatic, although a bactericidal action is evident at the high concentrations that may be found in urine. Diaminopyrimidines such as trimethoprim inhibit dihydrofolate reductase, which is further into the folic acid synthesis pathway. The combination of a sulfonamide and a diaminopyrimidine results in synergistic, bactericidal actions on susceptible organisms; as such, the combination is referred to as a "potentiated" sulfonamide.

The optimal ratio in vitro for the combination of trimethoprim or ormetoprim and a sulfonamide depends on the type of microorganism but is usually ~1:20. However, the

commercially available preparations use a ratio of 1:5 because of pharmacokinetic considerations that presumably result in the optimal ratio at the site of infection.

Sulfonamides are most effective in the early stages of acute infections when organisms are rapidly multiplying. They are not active against quiescent bacteria. Typically, there is a latent period before the effects of sulfonamide therapy become evident. This lag period occurs because the bacteria use existing stores of folic acid, folinic acid, purines, thymidine, and amino acids. Once these stores are depleted, bacteriostasis occurs. Bacterial growth can resume when the concentration of PABA increases or when the level of sulfonamide falls below an enzyme-inhibitory concentration. Because of the bacteriostatic nature of sulfonamides, adequate cellular and humoral defense mechanisms are critical for successful sulfonamide therapy when used as sole agents. Even potentiated sulfonamides, which are bactericidal, are time dependent in their antibacterial efficacy.

Although all of the sulfonamides have the same mechanism of action, differences are evident with respect to activity, pharmacokinetic fate, and even antimicrobial spectrum at usual concentrations. The differences are due to the variety of physiochemical characteristics seen among the sulfonamides.

The efficacy of sulfonamides can be reduced radically by excess PABA, folic acid, thymine, purine, methionine, plasma, blood, albumin, tissue autolysates, and endogenous protein-degradation products.

Bacterial Resistance:

Resistance to sulfonamides is both chromosomally and plasmid mediated. Altered proteins such that affinity is reduced appears to be the most common mechanism of resistance. For example, in staphylococci, chromosomally mediated resistance reflects mutations in genes encoding for dihydropterate synthetase and plasmid-mediated resistance reflects mutations in dihydrofolate reductases, with the latter causing high-level resistance to trimethoprim. Staphylococci may have acquired some mechanisms of sulfonamide resistance from enterococci. Because sulfonamides act in a competitive fashion, overproduction of PABA can also preclude inhibition of dihydropterate synthetase. Alternate pathways of folic acid synthesis may also contribute to low-level resistance. Cross-resistance between sulfonamides is common. Resistance emerges gradually and is widespread in many animal populations. Plasmid-mediated sulfonamide resistance in intestinal gram-negative bacteria is often linked with ampicillin and tetracycline resistance.

Antimicrobial Spectra:

The spectrum of all sulfonamides is generally the same. Sulfonamides inhibit both gram-positive and gram-negative bacteria, *Nocardia*, *Actinomyces* spp, and some protozoa such as coccidia and *Toxoplasma* spp. More active sulfonamides may include several species of *Streptococcus*, *Staphylococcus*, *Salmonella*, *Pasteurella*, and even *Escherichia coli* in their spectra. Strains of *Pseudomonas*, *Klebsiella*, *Proteus*, *Clostridium*, and *Leptospira* spp are most often highly resistant, as are rickettsiae, mycoplasmas, and most *Chlamydia*.

Pharmacokinetic Features

There are notable differences among the many sulfonamides with respect to their pharmacokinetic fate in the various species. The standard classification of short-, medium-, and long-acting sulfonamides used in human therapeutics is usually inappropriate in veterinary medicine because of species differences in disposition and elimination.

Absorption:

Sulfonamides may be administered PO, IV, IP, IM, intrauterine, or topically, depending on the specific preparation. Except for the poorly absorbed sulfonamides intended for local treatment of intestinal infections, most are rapidly and completely absorbed from the GI tract of monogastric animals. Absorption from the ruminoreticulum is delayed, especially if ruminal stasis is present. Therapeutic doses of sulfonamides are usually administered PO except in acute life-threatening infections when IV infusions are used to establish adequate blood concentrations as rapidly as possible. Sulfonamides are frequently added to drinking water or feed either for therapeutic purposes or to improve feed efficiency. A few highly water-soluble preparations may be injected IM (eg, sodium sulfadimethoxine) or IP (some irritation of the peritoneum can be seen). Absorption is rapid from these parenteral sites. Generally, sulfonamide solutions are too alkaline for routine parenteral use.

Trimethoprim is rapidly absorbed after administration PO (plasma concentrations peak in ~2–4 hr) except in ruminants, in which it tends to be trapped in the ruminoreticulum and appears to undergo a degree of microbial degradation.

Absorption occurs readily from parenteral injection sites; effective antibacterial concentrations are reached in <1 hr, and peak concentrations in ~4 hr.

Distribution:

Sulfonamides are distributed throughout all body tissues. The distribution pattern depends on the ionization state of the sulfonamide, the vascularity of specific tissues, the presence of specific barriers to sulfonamide diffusion, and the fraction of the administered dose bound to plasma proteins. The unbound drug fraction is freely diffusible. Sulfonamides are bound to plasma proteins to a greater or lesser extent, and concentrations in pleural, peritoneal, synovial, and ocular fluids may be 50%–90% of that in blood. Sulfadiazine is ≥90% bound to plasma proteins. Concentrations in the kidneys exceed plasma concentrations, and those in the skin, liver, and lungs are only slightly less than the corresponding plasma concentrations. Concentrations in muscle and bone are ~50% of those in the plasma, and those in the CSF may be 20%–80% of blood concentrations, depending on the particular sulfonamide. Low concentrations are found in adipose tissue. After parenteral administration, sulfamethazine is found in jejunal and colonic contents at about the same concentration as in blood. Passive diffusion into milk also occurs; although the concentrations achieved are usually inadequate to control infections, sulfonamide residues may be detected in milk. Trimethoprim and ormetoprim are basic drugs that tend to accumulate in more acidic environments such as acidic urine, milk, and ruminal fluid.

Trimethoprim diffuses extensively into tissues and body fluids. Tissue concentrations are often higher than the corresponding plasma concentrations, especially in lungs, liver, and kidneys. Approximately 30%–60% of trimethoprim is bound to plasma proteins. The extent of

metabolic transformation of trimethoprim has not yet been established, although there is a suggestion that hepatic biotransformation can be extensive, at least in ruminants. This may not be the case in all species; >50% of a dose is excreted unchanged in many instances. Trimethoprim is largely excreted in the urine by glomerular filtration and tubular secretion. A substantial amount may also be found in the feces. Concentrations in milk are often 1–3.5 times higher than those in plasma.

Biotransformation:

Sulfonamides are usually extensively metabolized, mainly by several oxidative pathways, acetylation, and conjugation with sulfate or glucuronic acid. Species differences are marked in this regard. The acetylated, hydroxylated, and conjugated forms have little antibacterial activity. Acetylation (poorly developed in dogs) reduces the solubility of most sulfonamides except for the sulfapyrimidine group. The hydroxylated and conjugated forms are less likely to precipitate in urine.

Excretion:

Most sulfonamides are excreted primarily in the urine. Bile, feces, milk, and sweat are excretory routes of lesser significance. Glomerular filtration, active tubular secretion, and tubular reabsorption are the main processes involved. The proportion reabsorbed is influenced by the inherent lipid solubility of individual sulfonamides and their metabolites and by urinary pH. Urinary pH, renal clearance, and the concentration and solubility of the respective sulfonamides and their metabolites determine whether solubilities are exceeded and crystals precipitate. This can be prevented by alkalinizing the urine, increasing fluid intake, reducing dose rates in renal insufficiency, and using triple-sulfonamide or sulfonamide-diaminopyrimidine combinations.

Pharmacokinetic Values:

There are great differences between the pharmacokinetic values of various sulfonamides in animals, and extrapolation of these values is rarely appropriate; for example, the plasma half-life of sulfadiazine is 10.1 hr in cattle and 2.9 hr in pigs. The recommended dose rates and frequencies reflect this disparity in elimination kinetics.

The plasma half-life of trimethoprim is quite prolonged in most species; effective concentrations may be maintained for >12 hr, with the result that the frequency of administration is usually 12–24 hr. The elimination rates of trimethoprim in sheep seem to be much shorter than in monogastric species.

Therapeutic Indications and Dose Rates

The sulfonamides are commonly used to treat or prevent acute systemic or local infections. Disease syndromes treated with sulfonamides include actinobacillosis, coccidiosis, mastitis, metritis, colibacillosis, pododermatitis, polyarthritis, respiratory infections, and toxoplasmosis.

Sulfonamides are more effective when administered early in the course of a disease. Chronic infections, particularly with large amounts of exudate or tissue debris present, often are not responsive. In severe infections, the initial dose should be administered IV to reduce the lag

time between dose and effect. For drugs with a long elimination half-life, the initial dose should be double the maintenance dose. Adequate drinking water should be available at all times, and urine output monitored. A course of treatment should not exceed 7 days under usual circumstances. If a favorable response is seen within 72 hr, treatment should be continued for 48 hr after remission to prevent relapse and the emergence of resistance. The ability to mount an immune response must be intact for successful sulfonamide therapy.

A selection of general dosages for some sulfonamides is listed in Dosages of Sulfonamides. The dose rate and frequency should be adjusted as needed for the individual animal.

Table. Dosages of Sulfonamides

Sulfonamide	Species	Dosage, Route, and Frequency
Sulfathiazole	Horses	66 mg/kg, PO, tid
	Cattle, sheep, pigs	66 mg/kg, PO, every 4 hr
Sulfamethazine	Cattle	220 mg/kg/day, PO or IV (initial dose; half for subsequent doses)
Sulfadiazine	All	50 mg/kg, PO, bid
Sulfadimethoxine	All	55 mg/kg/day, PO (initial dose; half for subsequent doses)
Sulfaethoxypyridazine	Cattle	55 mg/kg/day, PO
	Pigs	110 mg/kg/day, PO (initial dose, half for subsequent doses)
Sulfapyridine	Cattle	132 mg/kg, PO, bid (initial dose, half for subsequent doses)
Succinylsulfathiazole	All	160 mg/kg, PO, bid (initial dose; half for subsequent doses)

Table. Dosages of Potentiated Sulfonamides

Combination Sulfonamide	Dosage, Route, and Frequency
Trimethoprim/sulfadiazine	15–60 mg/kg/day, PO, IV, or IM
Ormetoprim/sulfadimethoxine	55 mg/kg/day, PO (initial dose; half for subsequent doses)

Special Clinical Concerns

Adverse Effects and Toxicity:

Adverse reactions to sulfonamides may be due to hypersensitivity or direct toxic effects. Possible hypersensitivity reactions include urticaria, angioedema, anaphylaxis, skin rashes, drug fever, polyarthritis, hemolytic anemia, and agranulocytosis. Keratitis sicca is a recognized adverse effect. The allergic response targets, in part, metabolites of the aryl amine of sulfonamides. Because dogs are deficient in acetylation, they may be at risk of increased formation of phase I metabolites associated with adverse effects. Crystalluria with hematuria, and even tubular obstruction, is not common in veterinary medicine. Acute toxic manifestations may be seen after too rapid IV administration or if an excessive dose is injected. Clinical signs include muscle weakness, ataxia, blindness, and collapse. GI disturbances, in addition to nausea and vomiting, may occur when sulfonamide concentrations are sufficiently high in the tract to disturb normal microfloral balance and vitamin B

synthesis. Sulfonamides depress the cellulolytic function of ruminal microflora, but the effect is usually transient (unless excessively high concentrations are reached). Several adverse effects have been reported after prolonged treatment, including bone marrow depression (aplastic anemia, granulocytopenia, thrombocytopenia), hepatitis and icterus, peripheral neuritis and myelin degeneration in the spinal cord and peripheral nerves, photosensitization, stomatitis, conjunctivitis, and keratitis sicca. Mild follicular thyroid hyperplasia may be associated with prolonged administration of sulfonamides in sensitive species such as dogs, and reversible hypothyroidism can be induced after treatment with high doses in dogs. Several sulfonamides can lead to decreased egg production and growth. Topically, the sulfonamides retard healing of uncontaminated wounds.

Up to 10 times the recommended dose of trimethoprim has been given with no adverse effects. Prolonged administration of trimethoprim at reasonably high concentrations leads to maturation defects in hematopoiesis due to impaired folinic acid synthesis. This effect is readily reversible by supplementation with folinic acid.

Interactions:

Sulfonamide solutions are incompatible with calcium- or other polyionic-containing fluids as well as many other preparations. Sulfonamides may be displaced from their plasma-protein-binding sites by other acidic drugs with higher binding affinities. Antacids tend to inhibit the GI absorption of sulfonamides. Alkalinization of the urine promotes sulfonamide excretion, and urinary acidification increases the risk of crystalluria. Some sulfonamides act as microsomal enzyme inhibitors, which may lead to toxic manifestations of concurrently administered drugs such as phenytoin.

Effects on Laboratory Tests:

Bilirubin, BUN, bromsulphthalein (BSP®), eosinophils, methemoglobin, AST, and ALT may be increased. Platelet, RBC, and WBC counts are often decreased. Urinalysis may show a change in color, glucose, porphyrins, and urobilinogen. Sulfonamide crystals may also be found.

Tetracyclines

The tetracyclines are broad-spectrum antibiotics with similar antimicrobial features, but they differ somewhat from one another in terms of their spectra and pharmacokinetic disposition.

Classes

There are three naturally occurring tetracyclines (oxytetracycline, chlortetracycline, and demethylchlortetracycline) and several that are derived semisynthetically (tetracycline, rolitetracycline, methacycline, minocycline, doxycycline, lymecycline, etc). Elimination times permit a further classification into short-acting (tetracycline, oxytetracycline, chlortetracycline), intermediate-acting (demethylchlortetracycline and methacycline), and long-acting (doxycycline and minocycline). The newest class of tetracycline-related antimicrobials are the glycylcyclines, represented by tigecycline, which contains a bulky side chain compared with minocycline.

General Properties

All of the tetracycline derivatives are crystalline, yellowish, amphoteric substances that, in aqueous solution, form salts with both acids and bases. They characteristically fluoresce when exposed to ultraviolet light. The most common salt form is the hydrochloride, except for doxycycline, which is available as doxycycline hyclate or monohydrate. The tetracyclines are stable as dry powders but not in aqueous solution, particularly at higher pH ranges (7–8.5). Preparations for parenteral administration must be carefully formulated, often in propylene glycol or polyvinyl pyrrolidone with additional dispersing agents, to provide stable solutions. Tetracyclines form poorly soluble chelates with bivalent and trivalent cations, particularly calcium, magnesium, aluminum, and iron. Doxycycline and minocycline exhibit the greatest liposolubility and better penetration of bacteria such as *Staphylococcus aureus* than does the group as a whole. This may contribute to their efficacy in treatment of gingival diseases that may be associated with bacterial glycocalyx. Tigecycline is a glycylcycline derivative of minocycline; its large side chain decreases the risk of resistance.

Antimicrobial Activity

Mode of Action:

The antimicrobial activity of tetracyclines reflects reversible binding to the bacterial 30S ribosomal subunit, and specifically at the aminoacyl-tRNA acceptor ("A") site on the mRNA ribosomal complex, thus preventing ribosomal translation. This effect also is evident in mammalian cells, although microbial cells are selectively more susceptible because of the greater concentrations seen. Tetracyclines enter microorganisms in part by diffusion and in part by an energy-dependent, carrier-mediated system responsible for the high concentrations achieved in susceptible bacteria. The tetracyclines are generally bacteriostatic, and a responsive host-defense system is essential for their successful use. At high concentrations, as may be attained in urine, they become bactericidal because the organisms seem to lose the functional integrity of the cytoplasmic membrane. Tetracyclines are more effective against multiplying microorganisms and tend to be more active at a pH of 6–6.5. Antibacterial efficacy is described as time dependent.

Bacterial Resistance:

The most common mechanism by which microbes become resistant to tetracyclines is decreased accumulation of drug into previously susceptible organisms. Two mechanisms include 1) impaired uptake into bacteria, which occurs in mutant strains that do not have the necessary transport system, and 2) the much more common plasmid- or transposon-mediated acquisition of active efflux pumps. The genomes for these capabilities may be transferred either by transduction (as in *Staphylococcus aureus*) or by conjugation (as in many enterobacteria). A second mechanism of resistance is the production of a "protective" protein that acts by either preventing binding, dislodging the bound drug, or altering the negative impact of binding on ribosomal function. Among the tetracyclines, tigecycline is characterized by less resistance due to efflux or ribosomal protection. Rarely, tetracyclines can be destroyed by acetylation. Resistance develops slowly in a multistep fashion but is widespread because of the extensive use of low concentrations of tetracyclines.

Antimicrobial Spectra:

All tetracyclines are about equally active and typically have about the same broad spectrum, which comprises both aerobic and anaerobic gram-positive and gram-negative bacteria, mycoplasmas, rickettsiae, chlamydiae, and even some protozoa (amebae). Tetracyclines generally are the drug of choice to treat rickettsiae and mycoplasma. Among the susceptible organisms is *Wolbachia*, a rickettsial-like intracellular endosymbiont of nematodes, including *Dirofilaria immitis*. Strains of *Pseudomonas aeruginosa*, *Proteus*, *Serratia*, *Klebsiella*, and *Trueperella* spp frequently are resistant, as are many pathogenic *Escherichia coli* isolates. Even though there is general cross-resistance among tetracyclines, doxycycline and minocycline usually are more effective against staphylococci.

Pharmacokinetic Features

Absorption:

After usual oral dosage, tetracyclines are absorbed primarily in the upper small intestine, and effective blood concentrations are reached in 2–4 hr. GI absorption can be impaired by sodium bicarbonate, aluminum hydroxide, magnesium hydroxide, iron, calcium salts, and (except for the lipid-soluble tetracyclines doxycycline and minocycline) milk and milk products. Oral bioavailability, however, can vary markedly among drugs, with chlortetracycline being the least and doxycycline the most orally bioavailable. Tetracyclines at therapeutic concentrations should not be administered PO to ruminants: they are poorly absorbed and can substantially depress ruminal microfloral activity. Specially buffered tetracycline solutions can be administered IM and IV. Through chemical manipulation (especially choice of carrier and high magnesium content), the absorption of oxytetracycline from IM sites may be delayed, which produces a long-acting effect. Tetracyclines can also be absorbed from the uterus and udder, although plasma concentrations remain low.

Distribution:

Tetracyclines distribute rapidly and extensively in the body, particularly after parenteral administration. They enter almost all tissues and body fluids; high concentrations are found in the kidneys, liver, bile, lungs, spleen, and bone. Lower concentrations are found in serosal fluids, synovia, CSF, ascitic fluid, prostatic fluid, and vitreous humor. The more lipid-soluble tetracyclines (doxycycline and minocycline) readily penetrate tissues such as the blood-brain barrier, and CSF concentrations reach ~30% of the plasma concentrations. Doxycycline is the most extensively distributed. Because tetracyclines tend to chelate calcium ions (less so for doxycycline), they are deposited irreversibly in the growing bones and in dentin and enamel of unerupted teeth of young animals, or even the fetus if transplacental passage occurs. Drug bound in this fashion is pharmacologically inactive. Tetracyclines are bound to plasma proteins to varying degrees (eg, oxytetracycline, 30%; tetracycline, 60%; doxycycline, 90%).

Biotransformation:

Biotransformation of the tetracyclines seems to be limited in most domestic animals, and generally about one-third of a given dose is excreted unchanged. Rolitetracycline is metabolized to tetracycline. Doxycycline and minocycline may be more extensively biotransformed than other tetracyclines (up to 40% of a given dose).

Excretion:

Tetracyclines are excreted via the kidneys (glomerular filtration) and the GI tract (biliary elimination and directly). Generally 50%–80% of a given dose is recoverable from the urine, although several factors may influence renal elimination, including age, route of administration, urine pH, glomerular filtration rate, renal disease, and the particular tetracycline used. Biliary elimination is always significant, commonly being ~10%–20%, even with parenteral administration. Doxycycline appears to be eliminated through feces predominantly through intestinal cells, rather than bile. Only ~16% of an IV dose of doxycycline is eliminated unchanged in the urine of dogs. A portion of doxycycline is also renally excreted in active form in some species. For minocycline, bile appears to be the major route of excretion. Tetracyclines are also eliminated in milk; concentrations peak 6 hr after a parenteral dose, and traces are still present up to 48 hr later. Concentrations in milk usually attain ~50%–60% of the plasma concentration and are often higher in mastitic milk. Tetracyclines also are excreted in saliva and tears.

Pharmacokinetic Values:

The plasma half-lives of tetracyclines are 6–12 hr and can be longer depending on age (slower elimination in animals <1 mo old), disease, and the tetracycline itself (see Table: Elimination, Distribution, and Clearance of Tetracyclines). In large animals, daily injections of standard dosages usually are sufficient to maintain effective inhibitory concentrations. Long-acting formulations of oxytetracycline, when injected IM, generally produce plasma concentrations >0.5 mcg/mL for ~72 hr. Tetracyclines usually are administered PO bid-tid (every 12–24 hr for doxycycline and minocycline).

Table. Elimination, Distribution, and Clearance of Tetracyclines

Tetracycline	Species	Elimination Half-life (hr)	Volume of Distribution (mL/kg)	Clearance (mL/kg/min)
Oxytetracycline	Dogs	6	3,000	4.23
	Calves (<3 mo old)	10–13	1,500–2,400	3.45
	Cattle	7–10	800–1,000	3.33
	Horses	8–10	1,100	2.89
Minocycline	Dogs	7	2,000	3.21
Doxycycline	Dogs	7–10	930	1.7
	Cats	5	340	1.0
	Horses	9		

Therapeutic Indications and Dose Rates

The tetracyclines are used to treat both systemic and local infections. However, resistance and their bacteriostatic nature suggest caution with empirical use for bacterial infections, particularly in dogs and cats. Specific conditions include infectious keratoconjunctivitis in cattle, chlamydiosis, heartwater, anaplasmosis, actinomycosis, actinobacillosis, nocardiosis (especially minocycline), ehrlichiosis (especially doxycycline), *Wolbachia*, eperythrozoonosis, and haemobartonellosis. Minocycline and doxycycline are often effective to a somewhat lesser degree against resistant strains of *Staphylococcus aureus*.

In addition to antimicrobial chemotherapy, the tetracyclines are used for other purposes. As additives in animal feeds, they serve as growth promoters. Because of the affinity of tetracyclines for bones, teeth, and necrotic tissue, they can be used to delineate tumors by fluorescence. Demethylchlortetracycline has been used to inhibit the action of antidiuretic hormone in cases of excessive water retention. Because of either their metalloproteinase-inhibiting effects or their binding of calcium, they are used to "stretch" flexor digital tendons in neonatal foals. Finally, they are being used to reduce the risk of adverse events and to enhance killing of adult heartworms and/or microfilaria before adulticide therapy.

A selection of general dosages for some tetracyclines is listed in Dosages of Tetracyclines. The dose rate and frequency should be adjusted as needed for the individual animal.

Table. Dosages of Tetracyclines

Tetracycline	Species	Dosage, Route, and Frequency
Tetracycline	Cats, dogs	7 mg/kg, IM or IV, bid
		20 mg/kg, PO, tid
Oxytetracycline	Cats, dogs	7 mg/kg, IM or IV, bid
		20 mg/kg, PO, tid
	Cattle, sheep, pigs	5–10 mg/kg/day, IM or IV
	Calves, foals, lambs, piglets	10–20 mg/kg, PO, bid-tid
	Horses	5 mg/kg, IV, once to twice daily
Doxycycline	Dogs	5–10 mg/kg/day, PO
		5 mg/kg/day, IV
	Before heartworm adulticide therapy	10 mg/kg, PO, bid, for 30 days

Special Clinical Concerns

Adverse Effects and Toxicity:

Because several diverse effects may result from administration of tetracyclines, caution should be exercised. Superinfection by nonsusceptible pathogens such as fungi, yeasts, and resistant bacteria is always a possibility when broad-spectrum antibiotics are used. This may lead to GI disturbances after either PO or parenteral administration or to "persistent infection" when they are applied topically (eg, in the ear). Severe and even fatal diarrhea can occur in horses receiving tetracyclines, especially if the animals are severely stressed or critically ill.

High doses administered PO to ruminants seriously disrupt microfloral activity in the ruminoreticulum, eventually producing stasis. Elimination of the gut flora in monogastric animals reduces the synthesis and availability of the B vitamins and vitamin K from the large intestine. With prolonged therapy, vitamin supplementation is a useful precaution.

Tetracyclines chelate calcium in teeth and bones; they become incorporated into these structures, inhibit calcification (eg, hypoplastic dental enamel), and cause yellowish then brownish discoloration. At extremely high concentrations, the healing processes in fractured bones is impaired.

Rapid IV injection of a tetracycline can result in hypotension and sudden collapse. This appears to be related to the ability of the tetracyclines to chelate ionized calcium, although a depressant effect by the propylene glycol carrier itself may also be involved. This effect can be avoided by slow infusion of the drug (>5 min) or by pretreatment with IV calcium gluconate.

The IV administration of undiluted propylene glycol–based preparations leads to intravascular hemolysis, which results in hemoglobinuria and possibly other reactions such as hypotension, ataxia, and CNS depression.

Because tetracyclines interfere with protein synthesis even in host cells and therefore tend to be catabolic, an increase in BUN can be expected. The combined use of glucocorticoids and tetracyclines often leads to a significant weight loss, particularly in anorectic animals.

Hepatotoxic effects due to large doses of tetracyclines have been reported in pregnant women and in other animals. The mortality rate is high.

The tetracyclines are also potentially nephrotoxic and are contraindicated (except for doxycycline) in renal insufficiency. Fatal renal failure has been reported in septicemic and endotoxemic cattle given high doses of oxytetracycline. The administration of expired tetracycline products may lead to acute tubular nephrosis.

Swelling, necrosis, and yellow discoloration at the injection site almost inevitably are seen. Phototoxic dermatitis may occur in people treated with demethylchlortetracycline and other analogues, but this reaction is rare in other animals. Hypersensitivity reactions occur; for example, cats may develop a “drug fever” reaction, often accompanied by vomiting, diarrhea, depression, inappetence, fever, and eosinophilia.

The tetracyclines can inhibit WBC chemotaxis and phagocytosis when present in high concentrations at sites of infection. This clearly hinders normal host defense mechanisms and compounds the bacteriostatic activity of tetracyclines. The use of immunosuppressive drugs such as glucocorticoids impairs immunocompetence even further.

Doxycycline administered in tablets has been associated with esophageal erosion in cats. The incidence is reduced if administration is followed by a 5-mL volume of fluid. Doxycycline may be associated with GI upset; this might be reduced by administering the drug with food.

Interactions:

Absorption of tetracyclines from the GI tract is decreased by milk and milk products (except for doxycycline and minocycline), antacids, kaolin, and iron preparations. Tetracyclines gradually lose activity when diluted in infusion fluids and exposed to ultraviolet light. Vitamins of the B-complex group, especially riboflavin, hasten this loss of activity in infusion fluids. Tetracyclines also bind to the calcium ions in Ringer’s solution.

Methoxyflurane anesthesia combined with tetracycline therapy may be nephrotoxic. Microsomal enzyme inducers such as phenobarbital and phenytoin may shorten the plasma half-lives of minocycline and doxycycline. Except for minocycline and doxycycline, the presence of food can substantially delay absorption of tetracyclines from the GI tract. The

tetracyclines are less active in alkaline urine, and urine acidification can increase their antimicrobial efficacy.

Effects on Laboratory Tests:

Tetracyclines may increase amylase, BUN, bromsulphthalein (BSP®), eosinophil count, AST, and ALT. Tetracyclines used in combination with diuretics are often associated with a marked rise in BUN. Cholesterol, glucose, potassium, and prothrombin time may be decreased. A false-positive urine glucose test is also possible.

Phenicols

Chloramphenicol is a highly effective and well-tolerated broad-spectrum antibiotic. However, because it causes blood dyscrasias, it is prohibited for use in food-producing animals in several countries, including the USA and Canada. Thiamphenicol is less effective but safer than chloramphenicol; florfenicol, a thiamphenicol derivative, is significantly more active in vitro than chloramphenicol against many pathogenic strains of bacteria. Florfenicol is approved for use in cattle.

General Properties

Chloramphenicol is a relatively simple neutral nitrobenzene derivative with a bitter taste. It is highly lipid soluble and is used either as the free base or in ester forms (eg, the neutral-tasting palmitate for administration PO and the water-soluble sodium succinate for parenteral injection). Chloramphenicol is a relatively stable compound and is unaffected by boiling, provided that a pH of 9 is not exceeded. The nitrophenol group of chloramphenicol is replaced by a methyl sulfonyl group for thiamphenicol and florfenicol; florfenicol also contains a fluorine molecule. These structural changes improve efficacy, reduce toxicity, and for florfenicol, the fluorine molecule reduces bacterial resistance.

Antimicrobial Activity

Mode of Action:

The phenicols inhibit microbial protein synthesis by binding to the 50S subunit of the 70S ribosome and impairing peptidyl transferase activity. Because peptide-bond formation is inhibited, peptides cannot elongate. The effect is usually bacteriostatic but, at high concentrations, chloramphenicol may be bactericidal for some species. Protein synthesis is inhibited in both prokaryotic and eukaryotic (mitochondrial) ribosomes.

Bacterial Resistance:

Resistance against chloramphenicol develops slowly and in a stepwise fashion. In clinical bacterial isolates, high-level plasmid-mediated resistance reflects the production of chloramphenicol acetyltransferase (encoded for by the *cat* gene) and results in acetylation of the molecule, which can no longer bind to the ribosome. Other inactivating enzymes also may be involved. In resistant gram-negative bacteria, chloramphenicol acetyltransferase is a constitutive enzyme; in gram-positive organisms, the enzyme is inducible. The fluorine atom of florfenicol prevents acetylation, thus enhancing the efficacy of this drug. In *Pseudomonas*

aeruginosa and in strains of *Proteus* and *Klebsiella* spp, resistance is also nonenzymatic and is based on an inducible permeability block that is both chromosomal and plasmid-mediated. Reduced permeability contributes to low level resistance. Very rarely, resistance may reflect altered ribosomal subunit structure and binding. Resistance to chloramphenicol often develops together with resistance to tetracycline, erythromycin, streptomycin, ampicillin, and other antibiotics because of multiple genes being carried on the same plasmid.

Antimicrobial Spectra:

Many genera of gram-positive and gram-negative bacteria and several anaerobes such as *Bacteroides fragilis*, as well as *Rickettsia* and *Chlamydia* spp are susceptible. Chloramphenicol is notable for its anaerobic spectrum. Of special note is the efficacy against many *Salmonella* spp but the resistance of most strains of *P aeruginosa*.

Pharmacokinetic Features

Absorption:

Absorption occurs promptly and rapidly from the upper GI tract when chloramphenicol base is administered PO to nonruminant animals. Blood concentrations usually are maximal in 1–3 hr. Because ruminal microflora readily reduce the nitro group, chloramphenicol is inactivated in the ruminoreticulum and is not available for absorption. The larger ester forms of chloramphenicol require hydrolysis by lipases to release the antibiotic for absorption from the GI tract; thus, the systemic availability of chloramphenicol is delayed when the palmitate and other ester preparations are used. Generic inequivalence has been seen with oral dosage forms. The presence of food and intestinal protectants does not interfere with absorption of chloramphenicol, although drugs that depress GI motility do. Florfenicol is rapidly absorbed after administration PO, although milk interferes with absorption.

Chloramphenicol sodium succinate may be injected both IV and IM. However, hydrolysis is required in the body because only free chloramphenicol base is active. The kinetics of this hydrolysis reaction may be slow and incomplete, with considerable individual and species variability. The absorption of chloramphenicol base itself from IM injection sites is notably restricted. For example, in horses, the therapeutic blood concentration of 5 mg/mL is achieved at a dosage of 50 mg/kg body wt, IM, after only 6–8 hr. Chloramphenicol base is absorbed after IP injection. Florfenicol is available as an injectable solution intended for IM use.

Distribution:

Approximately 40%–60% of chloramphenicol in plasma is reversibly bound to albumin, and the free fraction readily diffuses into almost all tissues (including the brain); highest concentrations are reached in the kidneys, liver, and bile. Substantial concentrations (~50% of plasma values) are also reached in many body fluids such as the CSF and aqueous humor. Milk concentrations are ~50% those of plasma but may be higher in mastitis. Transplacental diffusion is seen in all species, with concentrations of ~75% being reached in the fetus as compared with the dam. Chloramphenicol does not attain effective concentrations in normal synovial fluid but does so in septic arthritis. The blood-prostate barrier is an exception to the extensive intracorporeal distribution of chloramphenicol, and concentrations in the inflamed prostate are low to nil. Approximately 15%–20% of peak serum concentrations are seen within abscesses. Florfenicol also penetrates most body tissues, although penetration of CSF

and aqueous humor is less than that of chloramphenicol. Florfenicol does penetrate the milk of lactating cows.

Biotransformation:

Unlike many other antibacterial agents, chloramphenicol undergoes extensive hepatic metabolism. Although some nitroreduction and other phase I reactions occur, free chloramphenicol is biotransformed primarily by glucuronide conjugation. Urinary products after administration of chloramphenicol sodium succinate include inactive forms, mainly the unhydrolyzed sodium succinate and the glucuronide; only 5%–15% appears as biologically active chloramphenicol.

There are several clinical concerns with respect to the biotransformation of chloramphenicol. In cats, a characteristic genetic deficiency in glucuronyl transferase activity leads to plasma half-lives that are often considerably longer than those in other species (eg, cats, 5.1 hr; ponies, 54 min), and dosages need to be adjusted accordingly. Phase I metabolism may also be deficient in cats. Very young animals frequently do not have full microsomal enzyme capabilities, and the plasma half-lives of chloramphenicol in the young (<4 wk old) of many species are often much longer than those of adults. Foals appear to be a notable exception to this generalization. Liver disease also prevents chloramphenicol from undergoing normal metabolic degradation, and active antibiotic accumulates in the body.

Excretion:

The principal route of excretion of parent drug (minor) and glucuronide is renal. Free chloramphenicol and the chloramphenicol sodium succinate dosage form undergo glomerular filtration (5%–10%), whereas the glucuronide metabolite is eliminated by tubular secretion (90%–95%). Only 5%–15% of chloramphenicol is present in the urine in the active, unchanged form. The biliary route also plays a part in excretion, but enterohepatic cycling is often pronounced, and usually only a small amount of chloramphenicol is recoverable in feces. Enterohepatic cycling prolongs blood concentrations to some degree in herbivores.

Pharmacokinetic Values:

The plasma half-life of chloramphenicol varies among species and depends on age in some species. The specific volumes of distribution usually reflect the extensive diffusion into tissues (see Table: Elimination and Distribution of Chloramphenicol and Florfenicol). Dose rates and frequencies are typically adjusted for the species and age of the animal. Florfenicol is eliminated by the kidneys.

Table. Elimination and Distribution of Chloramphenicol and Florfenicol

Drug	Species	Elimination Half-life (hr)	Volume of Distribution (mL/kg)
Chloramphenicol	Cats	5.1	2,360
	Dogs	4.2	1,700
	Calves (<1 wk old)	5.0	1,080
	Cattle	3.0	1,580
	Horses	0.9	950
Florfenicol	Cattle	18.3	700

Therapeutic Indications and Dose Rates

Chloramphenicol is used to treat both systemic and local infections. Salmonellosis and *Bacteroides* sepsis have been specific indications, but use of chloramphenicol has decreased in the absence of an easily accessible, commercially available, approved preparation. Florfenicol is approved for use in treatment of bovine respiratory disease.

General dosages for chloramphenicol and florfenicol are listed in Dosages of Chloramphenicol and Florfenicol. The dose rate and frequency should be adjusted as needed for the individual animal.

Table. Dosages of Chloramphenicol and Florfenicol

Drug	Species	Dosage, Route, and Frequency
Chloramphenicol	Cats	45–60 mg/kg, PO, IV, or IM, bid
	Dogs	45–60 mg/kg, PO, IV, or IM, tid-qid
	Horses	50 mg/kg, PO, tid-qid, or IV, every 2–4 hr
Florfenicol	Cattle	20 mg/kg, IM, repeated in 48 hr

Special Clinical Concerns

Adverse Effects and Toxicity:

In people, chloramphenicol (but not florfenicol) can produce two distinctive syndromes of bone marrow suppression. One form is characterized by nonregenerative anemia (with or without thrombocytopenia or leukopenia), increased serum iron, bone marrow hypocellularity, cytoplasmic vacuolization of blast cells and lymphocytes, and maturation arrest of erythroid and myeloid precursors. This suppression is dose-dependent and reversible. Daily doses of 50 mg/kg for 3 wk can produce similar effects in cats. Milder hematologic effects are evident in dogs at much higher daily dosages (225 mg/kg). Such blood dyscrasias may also be seen in susceptible neonatal animals given standard adult doses of chloramphenicol. This toxic effect is postulated to be due to interference with mRNA and protein synthesis in rapidly multiplying cells.

The second form of bone marrow suppression is an irreversible aplastic anemia that is not related to dose or duration and may appear after the drug has been discontinued. Peripheral

blood showing pancytopenia may be associated with hypoplastic or aplastic bone marrow. The incidence is ~1:25,000–40,000. The aplastic anemia appears to reflect lack of the nitro group and, as such, does not cause aplastic anemia. Because tissue residues in food animals might induce aplastic anemia in people, use of chloramphenicol in food animals is prohibited in the USA and several other countries. A form of aplastic anemia, apparently a type of hypersensitivity reaction to chloramphenicol, has been recognized in dogs and cats.

GI disturbances can develop in all nonruminant animals treated with oral chloramphenicol. Use in neonatal calves leads to a malabsorption syndrome associated with ultrastructural and functional changes of the small-intestinal enterocytes. Anorexia and depression have been seen in cats treated for >1 wk.

Because chloramphenicol can suppress anamnestic immune responses, animals should not be vaccinated while being treated with this antibiotic. Because of the ability of chloramphenicol to inhibit protein synthesis, excessive topical application on wounds may delay healing.

In both male and female rats, chloramphenicol has adversely affected the structure and functions of the gonads. In large animals, adverse signs are most often associated with propylene glycol–based preparations that, when infused rapidly IV, may result in collapse, hemolysis, and death.

Notwithstanding the severity of the chloramphenicol-associated adverse effects noted above, chloramphenicol is relatively safe, provided overdosage is avoided, courses of therapy are limited to 1 wk, the dose is reduced for newborn animals and for animals with impaired liver function, and there is no evidence of a preexisting bone marrow depression.

Interactions:

Chloramphenicol is a potent noncompetitive microsomal enzyme inhibitor that can substantially prolong the duration of action of several drugs administered concurrently. Frank toxic effects are likely if administration is repeated. Examples of such drugs include pentobarbital, codeine, phenobarbital, phenytoin, NSAIDs, and coumarins.

In combination with sulfamethoxypyridazine, chloramphenicol can cause hepatic damage. Chloramphenicol also delays the response of anemia to iron, folic acid, and vitamin B_{12}. It interferes with the actions of many bactericidal drugs, such as the penicillins, cephalosporins, and aminoglycosides, and such combinations should not be used under most circumstances. Aqueous solutions of chloramphenicol sodium succinate should not be mixed with other preparations before administration because of a high incidence of incompatibility.

Chloramphenicol should not be administered concurrently with other antibacterial agents that bind to the 50S ribosomal subunit (eg, the macrolides and lincosamides).

Effects on Laboratory Tests:

Chloramphenicol may cause increased alkaline phosphatase concentrations and prothrombin times. WBC and thrombocyte counts may be decreased. Anemia becomes evident in extreme cases. A false glucosuria test is possible.

Macrolides

The macrolide antibiotics typically have a large lactone ring in their structure and are much more effective against gram-positive than gram-negative bacteria. They are also active against mycoplasmas and some rickettsiae.

Classes

Macrolides fall into three classes, depending on the size of the macrocyclic lactone ring. None of the 12-membered ring group is used clinically. Erythromycin and the closely related oleandomycin and troleandomycin belong to the 14-membered ring group. Azithromycin (synthesized from erythromycin) and gamithromycin are 15-ring members, a subclass referred to as azalides. Of the 16-membered ring group, spiramycin, josamycin, tylosin, and tilmicosin (synthesized from tylosin), are used clinically. Tulathromycin contains three amine rings and is classified as a triamilide. Ketolides, which include tylosin and spiramycin, are closely related macrolides.

General Properties

A macrolide is actually a complex mixture of closely related antibiotics that differ from one another with respect to the chemical substitutions on the various carbon atoms in the structure and in the aminosugars and neutral sugars. For example, erythromycin is mostly erythromycin A, but B, C, D, and E forms may also be included in the preparation.

The macrolide antibiotics are colorless, crystalline substances. They contain a dimethylamino group, which makes them basic. Although they are poorly water soluble, they do dissolve in more polar organic solvents. Macrolides are often inactivated in basic (pH >10) as well as acidic environments (pH <4 for erythromycin). The multiple functional groups make it possible for them to undergo a large number of chemical reactions. More stable ester forms, eg, acetylates, estolates, lactobionate, succinates, propionates, and stearates, are commonly used in pharmaceutical preparations.

Antimicrobial Activity

Mode of Action:

The antimicrobial mechanism seems to be the same for all of the macrolides. They interfere with protein synthesis by reversibly binding to the 50S subunit of the ribosome. They appear to bind at the donor site, thus preventing the translocation necessary to keep the peptide chain growing. The effect is essentially confined to rapidly dividing bacteria and mycoplasmas. Macrolides are regarded as being bacteriostatic but demonstrate bactericidal activity at high concentrations. Macrolides are significantly more active at higher pH ranges (7.8–8). Macrolides are considered to be time dependent in terms of antimicrobial efficacy.

The macrolides appear to have immunomodulatory effects useful to treat respiratory infections, in particular, those associated with *Pseudomonas aeruginosa*, based on efficacy at doses (concentrations) considered ineffective against susceptible bacteria.

Bacterial Resistance:

Lack of cell wall permeability renders most gram-negative organisms inherently resistant to macrolides. There are a few exceptions, and gram-negative forms without cell walls are usually susceptible. Resistance to macrolides in gram-positive organisms results from alterations in ribosomal structure (target site methylation or mutation) and loss of macrolide affinity. Post-translational methylation results in cross-resistance to lincosamides and streptogramins. Macrolide resistance may be intrinsic or plasmid-mediated and constitutive or inducible; it may develop rapidly (erythromycin) or slowly (tylosin) and generally results in cross-resistance between macrolides. Efflux from cells is a second important mechanism of resistance for some members of this class, as is, less frequently, drug inactivation.

Antimicrobial Spectra:

Macrolides are active against most aerobic and anaerobic gram-positive bacteria, although there is considerable variation as to potency and activity. In general, macrolides are not active against gram-negative bacteria, but some strains of *Pasteurella*, *Haemophilus*, and *Neisseria* spp may be sensitive. Exceptions include tilmicosin, gamithromycin, and tulathromycin, for which the spectra are characterized as broader and include *Mannheimia haemolytica* and *Pasteurella multocida*, as well as the above-mentioned gram-negative bacteria. *Helicobacter* also is generally included in the spectrum. Azithromycin, derived from erythromycin, includes *Bordetella* in its spectrum. *Bacteroides fragilis* strains are moderately susceptible to macrolides. Macrolides are active against atypical mycobacteria, *Mycobacterium*, *Mycoplasma*, *Chlamydia*, and *Rickettsia* spp but not against protozoa or fungi. In vitro synergism is seen with cefamandole (against *B fragilis*), ampicillin (against *Nocardia asteroides*), and rifampin (against *Rhodococcus equi*).

Pharmacokinetic Features

Absorption:

Macrolides are readily absorbed from the GI tract if not inactivated by gastric acid. Oral preparations are often enteric-coated, or stable salts or esters (such as stearate, lactobionate, glucoheptate, propionate, and ethylsuccinate) are used. Plasma concentrations peak within 1–2 hr in most cases, although absorption patterns may be erratic because of the presence of food and may depend on the salt or ester used. Absorption from the ruminoreticulum is usually delayed and is unreliable. Erythromycin and tylosin may also be administered IV or IM. Tilmicosin, gamithromycin, and tulathromycin are administered SC, except in swine, for which an oral tilmicosin preparation is available. Absorption after injection is rapid, but pain and swelling can develop at the injection sites.

Distribution:

Macrolides become widely distributed in tissues, and concentrations are about the same as in plasma, or even higher in some instances. They actually accumulate within many cells, including macrophages, in which they may be ≥20 times the plasma concentration. WBCs will then facilitate distribution to the site of inflammation. This accumulation accounts in part for the long dosing interval that characterizes some macrolides (eg, tilmicosin). With spiramycin, the tissue concentrations remain especially high, even though plasma concentrations are rather low. Macrolides tend to concentrate in the spleen, liver, kidneys, and

particularly the lungs. They enter pleural and ascitic fluids and concentrate in the eye but do not distribute to the eye or the CSF (only 2%–13% of plasma concentration unless the meninges are inflamed). They concentrate in the bile and milk. Up to 75% of the dose is bound to plasma proteins, and they bind to α1-acid glycoproteins rather than to albumin.

Biotransformation:

Metabolic inactivation of the macrolides is usually extensive, but the relative proportion depends on the route of administration and the particular antibiotic. After administration PO, 80% of an erythromycin dose undergoes metabolic inactivation, whereas tylosin appears to be eliminated in an active form.

Excretion:

Macrolide antibiotics and their metabolites are excreted mainly in bile (>60%) and often undergo enterohepatic cycling. Urinary clearance may be slow and variable (often <10%) but may represent a more significant route of elimination after parenteral administration. For example, in people, 14% of azithromycin and 20%–40% of clarithromycin is excreted unchanged in urine. The concentration of macrolides in milk often is several times greater than in plasma, especially in mastitis.

Pharmacokinetic Values:

Macrolides tend to be characterized by high oral bioavailability, but this is variable among species, drugs, and salts. For example, oral bioavailability for tylosin is 0.35 for the tartrate salt versus 0.14 for the phosphate. For azithromycin, oral bioavailability is 39% in foals 6–10 wk old, 59% in cats, and 97% in dogs. The accumulation of macrolides among different tissues contributes to the large volume of distribution (for azithromycin 12 L/kg in dogs, 23 L/kg in cats, 22 L/kg in foals 6–10 wk old) and long elimination half-life (for azithromycin, 29 hr in dogs, 35 hr in cats, and 20 hr in foals). For tulathromycin, the elimination half-life is 65 hr in calves and 69 hr in pigs 2–3 mo old. Because of these long half-lives, time to steady state may be prolonged, and a loading dose may be indicated for multiple dosing. Tylosin, however, is an exception, with a volume of distribution approximating 1 L/kg and a half-life of 1–2 hr. Another exception is azithromycin, which has a half-life in cats that varies among tissues, reaching >72 hr for some. Effective plasma inhibitory concentrations are maintained for ~8 hr after administration PO and for ~12–24 hr after IM injection. Dosage frequencies are commonly 2–3 times/day, PO, or 1–2 times/day, parenterally.

Therapeutic Indications and Dose Rates

The macrolides are used to treat both systemic and local infections. They are often regarded as alternatives to penicillins for treatment of streptococcal and staphylococcal infections. General indications include upper respiratory tract infections, bronchopneumonia, bacterial enteritis, metritis, pyodermatitis, urinary tract infections, arthritis, and others. Macrolides are indicated for treatment of *Rhodococcus* respiratory tract infections in foals. Formulations to treat mastitis are also available and often have the advantage of a short withholding time for milk. Tilmicosin, gamithromycin, and tulathromycin are approved for use in treatment of bovine respiratory diseases associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*. In swine, tilmicosin phosphate is added to feed or water for control of swine respiratory disease.

A selection of general dosages for some macrolides is listed in Dosages of Macrolides. The dose rate and frequency should be adjusted as needed for the individual animal.

Table. Dosages of Macrolides

Macrolide	Species	Dosage, Route, and Frequency
Erythromycin	Cattle	8–15 mg/kg, IM, once to twice daily
	Cats	15 mg/kg, PO, tid
	Foals	25 mg/kg, IM, tid
Tylosin	Cattle	10–20 mg/kg, IM, once to twice daily
	Pigs	10 mg/kg, IM, once to twice daily
		7–10 mg/kg, PO, tid
	Cats	10 mg/kg, IM, bid
Tilmicosin	Cattle	10 mg/kg, SC, once
Tulathromycin	Cattle	2.5 mg/kg, SC, once
	Swine	2.5 mg/kg, IM, once
Gamithromycin	Cattle	6 mg/kg, SC, once
Azithromycin	Dogs	5–10 mg/kg, PO, once to twice daily

Special Clinical Concerns

Adverse Effects and Toxicity:

Toxicity and adverse effects are uncommon for most macrolides (except tilmicosin), although pain and swelling may develop at injection sites. Hypersensitivity reactions have occasionally been seen. Erythromycin estolate may be hepatotoxic and cause cholestasis; it may also induce vomiting and diarrhea, particularly when high doses are administered. Horses are sensitive to macrolide-induced GI disturbances that can be serious and even fatal. In pigs, tylosin may cause edema of the rectal mucosa, mild anal protrusion with diarrhea, and anal erythema and pruritus. After 5 mg/kg/day, dogs had a greater tendency to develop ventricular tachycardia and fibrillation during acute myocardial ischemia. Tilmicosin is characterized by cardiac toxicity (tachycardia and decreased contractility). Parenteral (but not oral) administration should be avoided in swine, and extra-label use should be avoided. Cattle have died after IV injection of tilmicosin, and human injury is possible after accidental exposure.

Interactions:

Macrolide antibiotics probably should not be used with chloramphenicol or the lincosamides, because they may compete for the same 50S ribosomal binding site, although the in vivo significance of this potential interaction is unclear. Activity of macrolides is depressed in

acidic environments. Macrolide preparations for parenteral administration are incompatible with many other pharmaceutical preparations. Erythromycin and troleandomycin and other macrolides are microsomal enzyme inhibitors that depress CYP3A4 (in people) and thus the metabolism of many drugs. Macrolides also are substrates for and potentially potent inhibitors of P-glycoprotein efflux pumps.

Effects on Laboratory Tests:

Alkaline phosphatase, bilirubin, bromsulphthalein (BSP®), total WBC count, eosinophil count, AST, and ALT may increase. Cholesterol concentrations may decrease.

Streptogramins

The streptogramin antibiotics include two distinct groups. Group A contain a 23-membered unsaturated ring with lactone and peptide bonds, and group B are depsipeptides (lactone-cyclized peptides). These antibiotics are included in the macrolide-lincosamide-streptogramin (MLS) group. However, whereas the individual A and B components act in a bacteriostatic fashion when used as sole agents, together the affinity for the ribosome is enhanced, causing them to be bactericidal. Streptogramins include virginiamycin. Streptogramins are used to treat vancomycin-resistant staphylococci and *Enterococcus faecium*.

Lincosamides

General Properties

Lincosamides are derivatives of an amino acid and a sulfur-containing octose. They are monobasic and more stable in salt forms (hydrochlorides and phosphates).

Antimicrobial Activity

Mode of Action:

Lincomycin and clindamycin bind exclusively to the 50S subunit of bacterial ribosomes and suppress protein synthesis. Lincosamides, macrolides, and chloramphenicol, although not structurally related, seem to act at this same site. The lincosamides are bacteriostatic or bactericidal depending on the concentration. Activity is enhanced at an alkaline pH. Efficacy is considered time dependent.

Bacterial Resistance:

Lincosamides are generally ineffective against facultative anaerobic (but not anaerobic) gram-negative bacteria. Resistance to lincosamides appears slowly, perhaps as a result of chromosomal mutation. Plasmid-mediated resistance has been found in strains of *Bacteroides fragilis*. Resistance appears to be due to plasmid or chromosomally mediated post-transcriptional methylation of the 50S ribosomal subunit. Cross-resistance occurs with macrolides and streptogramins. Other mechanisms include increased activation of an efflux pump and destruction of the drug.

Antimicrobial Spectra:

Lincomycin has a limited spectrum against aerobic pathogens but a fairly broad spectrum against anaerobes. Clindamycin is a more active analogue with somewhat different pharmacokinetic patterns. Many gram-positive cocci, except for enterococci, and *Mycoplasma* are inhibited by lincosamides, but most gram-negative organisms are resistant. Clindamycin is less effective toward ureaplasmas. *Bacteroides* spp and other anaerobes are usually susceptible. *Clostridium difficile* strains appear to be regularly resistant.

Pharmacokinetic Features

Absorption:

Lincomycin is incompletely absorbed from the GI tract, especially if administered soon after feeding; plasma concentrations peak within 2–4 hr. Absorption from IM injection sites is good; plasma concentrations peak in 1–2 hr. Approximately 90% of an oral dose of clindamycin is absorbed, and effective plasma concentrations are achieved more rapidly than with lincomycin. Absorption is not significantly affected by the ingestion of food. Clindamycin palmitate is used PO, and clindamycin phosphate IM; the latter reaches peak plasma concentration in 1–3 hr.

Distribution:

Lincosamides are widely distributed in many fluids and tissues, including bone, but significant concentrations are not attained in the CSF even when the meninges are inflamed. They diffuse across the placenta in many species. Approximately 90% of clindamycin is bound to plasma proteins. It also accumulates in polymorphonuclear WBCs and alveolar macrophages such that concentrations exceed those of plasma 50-fold. Clindamycin is able to penetrate glycocalyx, such as that associated with dental tartar.

Biotransformation:

After administration PO, ~50% of a dose of lincomycin and 80%–90% of a dose of clindamycin are metabolically altered in the liver. Metabolites often retain activity. Liver disease impairs the biotransformation of lincosamides.

Excretion:

Unchanged antibiotic and several metabolites may be excreted in bile and urine. In people, as little as 10% of clindamycin is excreted in the urine. The proportions depend on the route of administration. Concentrations remain high in the feces for some days, and growth of sensitive microorganisms in the large intestine may be suppressed for up to 2 wk. Milk is also an important excretory route.

Pharmacokinetic Values:

The elimination half-life of lincosamides is frequently >3 hr, and the apparent volume of distribution is >1 L/kg. They are usually administered bid. In dogs, clindamycin has an elimination half-life of 3.9 hr and a volume of distribution of 1.4 L/kg.

Therapeutic Indications and Dose Rates

The lincosamides are indicated for infections caused by susceptible gram-positive organisms, particularly streptococci and staphylococci, and for those caused by anaerobic pathogens. Clindamycin is approved for use in cats and dogs for treatment of infected wounds, abscesses, and dental infections. Clindamycin has also been used to treat selected protozoal diseases, including toxoplasmosis, but usually in combination with other antimicrobials.

A selection of general dosages for some lincosamides is listed in Dosages of Lincosamides. The dose rate and frequency should be adjusted as needed for the individual animal.

Table. Dosages of Lincosamides

Lincosamide	Species	Dosage, Route, and Frequency
Lincomycin	Cattle	10 mg/kg, IM, bid
	Pigs	10 mg/kg, IM, bid 7 mg/kg, in-feed
	Dogs	20 mg/kg/day, PO
	Cats	10 mg/kg, IM, bid 25 mg/kg, PO, bid
Clindamycin	Dogs, cats	5–10 mg/kg, PO, bid

Special Clinical Concerns

Adverse Effects and Toxicity:

No serious organ toxicity has been reported, but GI disturbances do occur. Clindamycin-induced pseudomembranous enterocolitis (caused by toxigenic *Clostridium difficile*) or disruption of GI flora is a serious adverse reaction in a number of species and can be lethal; thus, clindamycin is contraindicated for use in some in horses, guinea pigs, hamsters, rabbits, chinchillas, and ruminants. Lincosamides are contraindicated in horses, because severe and even fatal colitis may develop. Skeletal muscle paralysis may be seen at high concentrations. Hypersensitivity reactions occasionally are seen. Lincosamides should not be used in neonates because of their limited ability to metabolize drugs.

Interactions:

Lincosamides have additive neuromuscular effects with anesthetic agents and skeletal muscle relaxants. Kaolin-pectin prevents their absorption from the GI tract. They should not be combined with bactericidal agents or with the macrolides.

Effects on Laboratory Tests:

Alkaline phosphatase, AST, and ALT may be increased.

Polymyxins

This group of polypeptide antibiotics includes polymyxin B and polymyxin E, or colistin. Because of toxicity, these drugs are most commonly used topically, or PO for treatment of intestinal infections. Colistimethate is a form of colistin intended for parenteral administration. Polymyxins are bactericidal; they interact strongly with phospholipids in bacterial cell membranes and radically disrupt their permeability and function. The polymyxins are more effective against gram-negative than gram-positive bacteria. Their rather narrow spectrum includes *Enterobacter*, *Klebsiella*, *Salmonella*, *Pasteurella*, *Bordetella*, *Shigella*, *Pseudomonas* spp, and *Escherichia coli*. Most *Proteus* or *Neisseria* spp are not susceptible. Although intrinsic bacterial resistance to polymyxins is recognized, resistance is uncommon and is chromosome-dependent only. Polymyxins act synergistically when combined with potentiated sulfonamides, tetracyclines, and some other antibacterials; they also reduce the activity of endotoxins in body fluids and may be beneficial in endotoxemia. Their action is inhibited by divalent cations, unsaturated fatty acids, and quaternary ammonium compounds.

Polymyxins are not absorbed after PO or topical administration; plasma concentrations peak ~2 hr after parenteral administration. Blood concentrations usually are low, because polymyxins bind to cell membranes as well as tissue debris and purulent exudates. The polymixins undergo renal elimination mostly as degradation products, and their plasma half-lives are 3–6 hr. They are notably nephrotoxic and neurotoxic and, as such, systemic therapy at antimicrobial doses should be avoided. Neuromuscular blockade can be seen at higher concentrations. Intense pain at sites of injection and hypersensitivity reactions also can be expected. Polymyxin B is a potent histamine releaser. The main indication for parenteral use of polymyxins is life-threatening infection due to gram-negative bacilli or *Pseudomonas* spp that are resistant to other drugs. Polymyxins are also used PO against susceptible intestinal infections. Anti-endotoxin binding activity is an additional therapy via slow IV bolus. Topical application is common, eg, for otitis externa.

Recommended dose rates for polymyxins vary considerably. A general guideline is 20,000 U/kg, PO, bid; 5,000 U/kg, IM, bid; 50,000–100,000 U by intramammary infusion; 100,000 U intrauterine in cattle. IV administration of polymyxins is potentially dangerous.

Bacitracins

Bacitracins are branched, cyclic, decapeptide antibiotics. Bacitracin A is the most active of the group and the main component of the commercial bacitracin preparations used either topically or PO. These antibiotics are bactericidal. They interfere with cell membrane function, suppress cell wall formation by preventing the formation of peptidoglycan strands, and inhibit protein synthesis. Bactericidal activity requires the presence of divalent cations, such as zinc.

The spectrum of bacitracins is described as broad, but it is used primarily to treat gram-positive infections. Resistance is rare. Bacitracins are often used in combination with neomycin and polymyxins to enhance the antibacterial spectrum.

Bacitracins are not appreciably absorbed from the GI tract and are not used systemically because of their pronounced nephrotoxicity. However, they are used locally in wound powders and ointments, dermatologic preparations, eye and ear ointments, and as feed additives in swine and poultry rations for growth promotion. In antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile* cytotoxin, bacitracin (given PO) is considered an alternative to vancomycin. Hypersensitivity reactions to bacitracins are seen occasionally.

Glycopeptides

Vancomycin is a complex glycopeptide that binds to precursors of the peptidoglycan layer in bacterial cell walls. This effect prevents cell wall synthesis and produces a rapid bactericidal effect in dividing bacteria. Its efficacy is time dependent. Vancomycin is active against most gram-positive bacteria but is not effective against gram-negative cells because of their large size and poor penetrability. Resistance to vancomycin does not readily develop. The drug is widely distributed in the body. Excretion (in active form) is via the kidneys; in renal insufficiency, striking accumulations may develop. The plasma half-life in dogs is 2–3 hr. The only indication for use of parenteral vancomycin is serious infection due to methicillin-resistant *Staphylococcus aureus*. Although poorly absorbed, oral vancomycin is used to treat antibiotic-associated enterocolitis, especially if caused by *Clostridium difficile*. Febrile reactions and thrombophlebitis (because of tissue irritation) at injection sites may be seen. Hypersensitivity reactions are seen infrequently. Ototoxicity and nephrotoxicity were fairly common in the past but are rare today because of fewer impurities in the final form.

Fosfomycin

Fosfomycin, a phosphonic acid that contains a carbon-phosphorus bond, is a natural antibiotic produced by *Streptomyces fradiae*. It is a phosphoenolpyruvate analogue that irreversibly inhibits phosphoenolpyruvate transferase, an enzyme that catalyzes the first step of peptidoglycan synthesis of microbial cell walls. Its in vitro spectrum is broad, with potential efficacy toward isolates expressing multidrug resistance, including *Escherichia coli* and methicillin-resistant staphylococci. As a cell wall inhibitor, fosfomycin is bactericidal when present at the site of infection at therapeutic concentrations. Cell wall inhibition is time dependent, but fosfomycin also exhibits a concentration-dependent effect. Resistance to fosfomycin is uncommon and reflects the FosX or FosA enzyme, which hydrolyzes the drug. The gene for this protein is chromosomally mediated. When resistance occurs, it generally is not associated with multidrug resistance. Studies in people have demonstrated that fosfomycin distributes well to soft tissues, reaching therapeutic breakpoints. Adverse effects of fosfomycin appear to be limited to diarrhea. Approved for human use in the USA as the tromethamine salt, its indication is as a one time (or up to 3 days) treatment of uncomplicated urinary tract infections in people. Fosfomycin has been added to the World Health Organization's list of critically important drugs. Accordingly, its use should be reserved, along with other critically important drugs, to situations in which lower-tier drugs are no longer appropriate.

Rifamycins

Several semisynthetic derivatives (rifamycin SV, rifampin [rifampicin], rifamide) of natural rifamycins have been used as extended-spectrum antibiotics. Rifamycins interfere with the synthesis of RNA in microorganisms by binding to subunits of sensitive DNA-dependent RNA polymerase. They are active against gram-positive organisms, some mycobacteria, a few strains of gram-negative bacteria (mostly cocci; bacilli are more resistant), some anaerobes, and chlamydiae. At high concentrations, they are also active against several viruses. Fungal and yeast infections resistant to rifampin alone often respond when a rifamycin is added to an antifungal agent (eg, amphotericin B). Resistance to rifamycins may develop rapidly as a 1-step process. For this reason, they should be administered in combination with other antimicrobials, such as penicillins, erythromycin, miconazole, and amphotericin B.

The primary use of the rifamycins in people has been to treat tuberculosis. Rifampin has been used in foals to control *Rhodococcus equi* pneumonia. Because rifamycins penetrate tissues and cells to a substantial degree, they are particularly effective against intracellular organisms. Rifampin is readily but incompletely (~40%) absorbed from the GI tract, and plasma concentrations peak within 2–4 hr. Concurrent feeding may reduce or delay absorption. Rifampin may also be administered IM or IV. Approximately 75%–80% of rifampin is bound to plasma proteins. It is widely distributed in body tissues and fluids because of its high lipid solubility. Rifampin is biotransformed to several metabolites, some of which are active, and is primarily excreted in bile (used for cholangitis in people) and to a lesser degree in urine. Enterohepatic cycling of the parent drug and its main metabolite (desacetylrifampin) commonly occurs. The elimination half-life of rifampin is dose dependent: in horses, it is ~6 hr; in dogs, ~8 hr. The plasma half-life progressively shortens by ~40% during the first 2 wk of treatment because of the induction of hepatic microsomal enzymes; conversely, it is increased with hepatic dysfunction.

Rifampin is usually well tolerated and produces few adverse effects. GI disturbances and abnormalities in liver function (icterus) have been reported in people. Hypersensitivity reactions can also result from rifampin administration, and renal failure is a possible consequence when intermittent dosage schedules are followed. Partial, reversible immunosuppression of lymphocytes develops. Urine, feces, saliva, sputum, sweat, and tears are often colored red-orange by rifampin and its metabolites. CNS depression after IV administration and temporary inappetence are seen in horses. The dose range for rifampin in horses is 10–25 mg/kg/day, PO or parenterally.

Nitrofurans

Nitrofurans are synthetic chemotherapeutic agents with a broad antimicrobial spectrum; they are active against both gram-positive and gram-negative bacteria, including *Salmonella* and *Giardia* spp, trichomonads, amebae, and some coccidial species. However, when compared with other antimicrobial chemotherapeutic agents, their potency is not of particular note. The nitrofurans appear to inhibit a number of microbial enzyme systems, including those involved in carbohydrate metabolism, and they also block the initiation of translation. However, their basic mechanism of action has not yet been clarified. Their primary action is bacteriostatic, but at high doses they are also bactericidal. They are much more active in acidic environments (pH 5.5 is optimal for nitrofurantoin activity). Resistant mutants are rare, and clinical resistance emerges slowly. Among themselves, nitrofurans show complete cross-resistance, but there is no cross-resistance with any other antibacterial agents.

Because of very slight water solubility, the nitrofurans are used either PO or topically. No nitrofuran is effective systemically. They are either not absorbed at all from the GI tract or are so rapidly eliminated that they reach inhibitory concentrations only in the urine. Toxic signs seen with excessive doses of nitrofuran derivatives include CNS involvement (excitement, tremors, convulsions, peripheral neuritis), GI disturbances, poor weight gain, and depression of spermatogenesis. Various hypersensitivity reactions can also be seen. Some nitrofurans are carcinogenic, and their future use is in doubt.

Nitrofurans are among the drugs for which extra-label use is prohibited in food animals in the USA.

Nitrofurantoin

The mechanism of action of nitrofurantoin is unique. It is reduced by bacterial flavoproteins to reactive intermediates that inhibit bacterial ribosomes and other macromolecules. Protein synthesis, aerobic energy metabolism, DNA and RNA synthesis, and cell wall synthesis are inhibited. Nitrofurantoin is bactericidal in urine at therapeutic doses. Resistance is rare. Nitrofurantoin is used to treat urinary tract infections caused by susceptible bacteria, such as *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Aerobacter aerogenes*. *Proteus* spp, *Pseudomonas aeruginosa*, and *Streptococcus faecalis* are usually resistant. After administration PO, nitrofurantoin is rapidly and completely absorbed (the macrocrystal form takes longer) and is swiftly eliminated by the kidneys, mainly by tubular secretion (~40% in the unchanged form). Serum concentrations are low, and little unbound drug is available for diffusion into the tissues. The plasma half-life is only ~20 min. Nitrofurantoin is concentrated in acid urine. When the pH reaches ~5, the drug becomes supersaturated without precipitation, and its antibacterial action is maximal. Nitrofurantoin can be administered PO or parenterally. The dosage for dogs and cats is 4.4 mg/kg, PO, tid for 4–10 days. Adverse effects are not common at usual dosages, but nausea, vomiting, and diarrhea can develop. CNS disorders have been seen, and polyneuropathy is a serious effect seen in people. Animals with decreased renal function have a predisposition for polyneuritis. Various manifestations of hypersensitivity reactions can be seen. Yellow discoloration of teeth occasionally has been reported in very young animals.

Nitrofurazone

Nitrofurazone is only slightly soluble in water but, in general, corresponds to nitrofurantoin in terms of its mechanism of action, antimicrobial spectrum, potency, and physicochemical characteristics. Its main indications include the treatment of bovine mastitis, bovine metritis, and wounds. However, pus, blood, and milk reduce the antibacterial activity. Nitrofurazone is also used as a feed additive (0.05%) to control intestinal bacterial and coccidial infections. The withdrawal time for nitrofurazone in pigs is 5 days.

Furazolidone

This is a nitrofuran with a wide range of antimicrobial activity that includes *Clostridium*, *Salmonella*, *Shigella*, *Staphylococcus* and *Streptococcus* spp, and *E coli*. It is also active against *Eimeria* and *Histomonas* spp. It is usually administered PO to treat intestinal infections but may also be applied topically. The usual oral dose of furazolidone in calves is 10–12 mg/kg, bid for 5–7 days. Caution should be exercised when treating small calves (eg,

Jersey breed) to avoid excessive dose rates, lest neurotoxicity result; signs include head tremors, ataxia, visual impairment, and convulsions.

Miscellaneous Nitrofurans

Nifuraldezone, like furazolidone, is used to control bacterial enteritis in calves. Nifurprazine is used only topically as an antibacterial agent. Furaltadone is used both PO to prevent intestinal infections and directly into the teat to treat mastitis.

Nitroimidazoles

The 5-nitroimidazoles are a group of drugs that have both antiprotozoal and antibacterial activity. Nitroimidazoles with activity against trichomonads and amebae include metronidazole, tinidazole, nimorazole, flunidazole, and ronidazole. Metronidazole and nimorazole are effective in treatment of giardiasis, whereas dimetridazole, ipronidazole, and ronidazole control histomoniasis in poultry. Several nitroimidazoles have activity against trypanosomes. Metronidazole, ronidazole, and other nitroimidazoles are active against anaerobic bacteria. Metronidazole is the compound that has been the most studied and is discussed as the prototype of the group. Extra-label use of nitroimidazoles is prohibited in food animals in the USA.

Metronidazole

Metronidazole has been used for many years in therapeutic management of trichomoniasis, giardiasis, and amebiasis. It is active against obligate anaerobic bacteria. It is not active against facultative anaerobes, obligate aerobes, or microaerophilic bacteria other than *Campylobacter fetus*. At concentrations readily attained in serum after PO or parenteral administration, metronidazole is active against *Bacteroides fragilis*, *B melaninogenicus*, *Fusobacterium* spp, and *Clostridium perfringens* and other *Clostridium* spp. It is generally less active against nonsporeforming, gram-positive bacilli such as *Actinomyces*, *Propionibacterium*, *Bifidobacterium*, and *Eubacterium* spp. Metronidazole is also somewhat less active against gram-positive cocci such as *Peptostreptococcus* and *Peptococcus* spp, but the less sensitive strains are usually not obligate anaerobes.

Metronidazole is bactericidal at concentrations equal to or slightly higher than the minimal inhibitory concentration. The precise mode of action is unclear, but reduction in an anaerobic environment yields a compound that then binds to DNA, causing loss of the helical structure, strand breakage, and impairment of DNA function. Only susceptible organisms (bacteria and protozoa) appear to be capable of metabolizing the drug.

The pharmacokinetic pattern of metronidazole generally follows that expected of a highly lipid-soluble basic drug. It is readily but variably absorbed from the GI tract (bioavailability 60%–100%), with serum concentrations peaking within 1–2 hr, and becomes widely distributed in all tissues. Metronidazole penetrates the blood-brain barrier and also attains therapeutic concentrations in abscesses and in empyema fluid. It is only slightly bound to plasma proteins. Biotransformation is quite extensive, and parent drug and metabolites are excreted by both the renal and biliary routes. The elimination half-life in dogs is ~4.5 hr, and in horses, 1.5–3.3 hr.

The principal clinical indications for metronidazole include the treatment of specific protozoal infections (amebiasis, trichomoniasis, giardiasis, and balantidiasis) and anaerobic bacterial infections such as those that may be seen in abdominal abscesses, peritonitis, empyema, genital tract infections, periodontitis, otitis media, osteitis, arthritis, and meningitis, and in necrotic tissue. Metronidazole has been successfully used to prevent infection after colonic surgery. Nitroimidazoles also act as radiosensitizers, and metronidazole has been used as an adjunct to the radiotherapy of solid tumors.

Adverse effects are not commonly associated with metronidazole. High doses may induce signs of neurotoxicity in dogs, such as tremors, muscle spasms, ataxia, and even convulsions. Reversible bone marrow depression has been reported. The drug should not be used in pregnant animals, particularly during the first trimester, although the evidence for carcinogenicity and mutagenicity is still tenuous. Metronidazole may produce a reddish brown discoloration of the urine due to unidentified pigments.

Recommended dose rates for metronidazole in dogs are 44 mg/kg, PO, followed by 22 mg/kg, qid, for anaerobic infections; 25 mg/kg, PO, bid, for giardiasis; and 66 mg/kg/day, PO, for trichomoniasis. Courses of therapy are generally 5–7 days. Both PO and IV preparations are available.