Chapter 15

Antimicrobial Drugs

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I. INTRODUCTION

A. **Selection of an antimicrobial drug.** Antimicrobial therapy is based upon the selective toxicity of the drug for invading organisms rather than mammalian cells. It is important to select an agent to which the organism is sensitive and to maintain the effective tissue concentrations (above the minimal inhibitory concentration or MIC) until the infection is eliminated. A practical approach is to select an antimicrobial agent where the measured MIC is less than the concentration known as the breakpoint concentration. Sensitivity tests using either sensitivity disks or sensititer micro-well plates can be used to estimate the MIC of specific bacteria and then tables are consulted to see if the MIC is below the breakpoint. If the MIC is below the breakpoint, it is predicted that the microbe will be Susceptible (S) to therapy; if it is equal to the breakpoint, it is predicted that the microbe will be Intermediate (I)—where high therapeutic doses may work; if the MIC is above the breakpoint, it is predicted that the microbe will be Resistant (R). The breakpoint concentrations have been determined by groups like the Clinical and Laboratory Standards Institute (CLSI) following review of clinical and laboratory data. The pharmacokinetic data on data labels of more recently introduced antimicrobials contain breakpoint information. It is pointed out that the sensitivity tests and breakpoints are useful indicators for the clinical outcome, but in the whole animal, additional factors like drug binding, drug distribution, and an active immune system affect the outcome so that clinical experience is still essential.

Extra-label use of specific antimicrobial drugs in food animals is prohibited for reasons of safety or limitation of resistance spread. These drugs include the fluoroquinolones, chloramphenicol, nitroimidazoles, furazolidone, nitrofurazone and other nitrofurans, and sulfonamide drugs in lactating dairy cattle (except approved use of sufadimethoxine, glycopeptides, and vancomycin).

There are six selection questions that are helpful to use routinely to aid selection:

1. **Is an antimicrobial agent required—is there an infection that will respond to your treatment?** Avoid: "Just in case."
2. **Where is the infection (which organ/tissue)—what are the access problems to be overcome?**
3. **Which pathogen(s) are usually found at the location of the infection?**
4. **Which antimicrobial agent has the necessary pharmacokinetic properties to get to the location and also will get there at a concentration above the MIC so that the MIC is below the breakpoint?**
5. **What dose and route is necessary to achieve the desired effect?**
6. **How long should the treatment be for?**

There are 4 additional factors to help the selection:

1. **A bactericidal compound is preferable to a bacteriostatic compound.**
2. **Toxicity and cost limit the selection of an antimicrobial drug.**
3. **In food-producing animals, residues in milk and meat requiring the need for withdrawal times before slaughter (preslaughter withdrawal times) are very important and limit the use of specific antimicrobial drugs. Animals must not be slaughtered for meat or their milk used within the preslaughter period (see appendix for the withdrawal period for each drug).**
4. **It should be appreciated that the plasma concentration governs the dose intervals on a treatment regimen but it is the tissue residence times that govern the preslaughter withdrawal times in production animals.**

B. Resistance to antimicrobials

1. **Mechanisms by which bacteria manifest resistance:**
   a. **Organisms may produce enzymes**, constitutive or inducible, which inactivate the drug.
   b. **The permeability to or uptake of the drug by organisms** may be decreased or transport out of the cell may be increased.
   c. **Alteration of the drug receptor or binding site** may result in reduced drug affinity at target loci.
   d. **The organism may develop alternate metabolic or synthetic pathways** to bypass or repair the effects of the antimicrobial.
2. **Mechanisms by which bacteria develop resistance**
   a. **Mutation.** Within a large population of bacteria, chromosomal mutations may occur, which confer resistance either slowly, in a step-wise fashion with each succeeding generation of the mutant more resistant or rapidly, in a single step in which the bacterium is resistant after the initial mutation. Mutation is a random event. Antimicrobials do not induce mutations but may exert a selecting out of resistant strains by suppression of susceptible bacteria.
   b. **Conjugation.** Certain Gram(–) bacteria undergo conjugation, a type of reproduction in which genetic material is transferred from cell to cell via a pilus that is encoded by a resistance transfer factor (RTF) on a plasmid. Resistance factors (R-factors) from plasmid DNA and/or chromosomal DNA may encode for resistance to multiple drugs and may be rapidly transferred to the bacterial population. This is termed **infectious drug resistance or transferable drug resistance** and has been observed clinically in enteric infections with *Salmonella* spp., *Shigella* spp., and *Escherichia coli*.
   c. **Transduction.** The process of transference of drug resistant genes by bacteriophage is termed transduction. It may be important in the development of resistant strains of *Staphylococcus aureus*.
   d. **Transformation.** Bacteria may incorporate DNA encoding for drug resistance from their environment after its secretion or release by resistant organisms. Acquisition of resistance by this mechanism is relatively infrequent.

II. SULFONAMIDES

A.

Chemistry. The sulfonamides are derivatives of *p*-aminobenzene sulfonic acid (Figure 15-1) and are structurally similar to *p*-aminobenzoic acid (PABA), an intermediate in bacterial synthesis of folic acid. They behave as weak organic acids which are poorly water soluble unless prepared as sodium salts. Concentrated solutions of the sodium salts of most sulfonamides are very alkaline and may be corrosive. The solubility of a sulfonamide is not influenced by the presence of other sulfonamides in the solution. This is termed the law of independent solubility and is the primary reason for the use of sulfonamide mixtures in order to increase the combined total sulfonamide concentration to prevent renal precipitation and thus reduce toxicity.

B.

Mechanism of action. Sulfonamides competitively inhibit dihydropteroate synthase, the enzyme which catalyzes the incorporation of PABA into dihydrofolic acid (Figure 15-2). Folic acid is required for purine and DNA synthesis and thus bacterial growth is inhibited. Mammalian cells and bacteria that use preformed folic acid are not affected. Sulfonamides are broad spectrum (including protozoa) and bacteriostatic.

C.

Therapeutic uses. Sulfonamides were widely used in the prevention and treatment of local and systemic infections in all species but now resistance is common. Examples of sulfonamides used in veterinary medicine include the following:

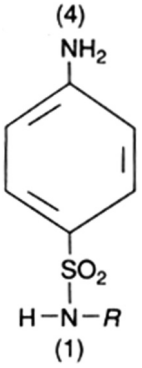

FIGURE 15-1. General structure of the sulfonamides. The *p*-amino group at position 4 must be free for antimicrobial activity to occur. Substitution with a heterocyclic ring (e.g., thiazole, pyrimidine, pyridine) at the *R* position on position 1 distinguishes the various sulfonamides. Replacement of the hydrogen with sodium at position 1 greatly increases the water solubility of the sulfonamide. (Adapted from Figure 11-1, *NVMS Pharmacology*, by Ahrens, F. A. 1996.)

1. **Sulfamethazine is used in cattle, sheep, and swine.** It is slowly excreted and therapeutic levels are maintained in plasma for 24 hours with a single dose.
2. **Sulfadimethoxine is a long-acting sulfonamide.** It is more soluble and less toxic than sulfamethazine. The plasma $t_{1/2}$ is 10–15 hours.
3. **Sulfachlorpyridazine is a rapidly absorbed and rapidly excreted sulfonamide used orally in calves under 1 month of age and in swine for the treatment of respiratory and enteric infections,** especially colibacillosis. Peak levels occur in 1–2 hours in nonruminants and in preruminant calves. The plasma $t_{1/2}$ is 1.2 hours.
4. **Sulfamethoxazole is used to treat urinary tract infections in small animals.** It is rapidly excreted and very soluble. Thus high concentrations may be attained in urine with minimal danger of renal crystalluria.
5. **Sulfacetamide is the only sulfonamide that can be prepared as the sodium salt at neutral pH and thus can be used in ophthalmic preparations.**
6. **Sulfasalazine is an "enteric" sulfonamide employed in the therapy of colitis and inflammatory bowel disease in dogs and cats.** It consists of a molecule of sulfapyridine linked to a molecule of 5-aminosalicylic acid (5-ASA) by a diazo bond. This prevents absorption in the small intestine and allows drug transit to the large bowel where it is cleaved by gut bacteria to sulfapyridine and 5-ASA. These have antibacterial and anti-inflammatory actions, respectively.
7. **Other sulfonamides used in veterinary medicine are** sulfathiazole and sulfaquinoxaline.

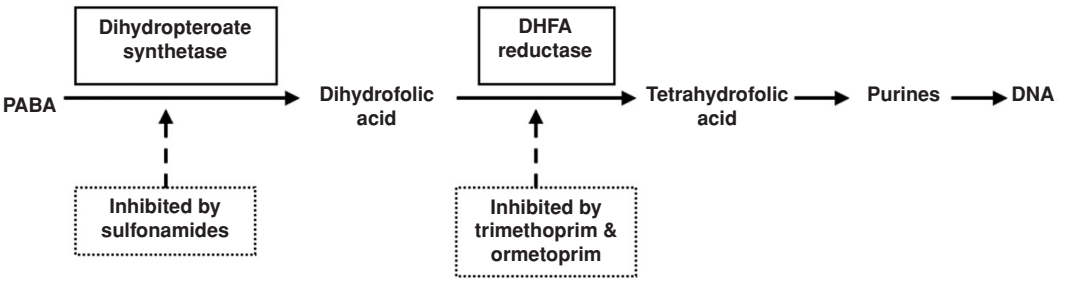

FIGURE 15-2. Mechanism of action of sulfonamides. Sulfonamides block dihydrofolic acid synthesis by competing with *p*-aminobenzoic acid (PABA) for binding sites on dihydropteroate synthetase. Dihydrofolic acid is necessary for the synthesis of tetrahydrofolic acid, and ultimately, purines and DNA. Trimethoprim and ormetoprim inhibit dihydrofolic acid (DHFA) reductase, which is necessary for tetrahydrofolic acid synthesis. Therefore, potentiated sulfonamides (i.e., those combined with trimethoprim or ormetoprim) block the second step of protein synthesis.

8. **Potentiated sulfonamides are fixed combinations of a sulfonamide with trimethoprim or ormetoprim.** This results in a synergistic action via sequential blockade of folate synthesis (Figure 15-2).
   - **a.** Trimethoprim and ormetoprim inhibit dihydrofolate reductase in bacteria (but not mammalian cells) and thus block the formation of tetrahydrofolic acid essential for purine and DNA synthesis.
   - **b.** Potentiated sulfonamides have a broader spectrum of action and a reduced rate of development of bacterial resistance.
   - **c.** Preparations include sulfadiazine plus trimethoprim, sulfamethoxazole plus trimethoprim, and sulfadimethoxine plus ormetoprim. They are used in the treatment of susceptible infections in all species.
   - **d.** Trimethoprim and ormetoprim are organic bases in contrast to the organic acid nature of the sulfonamides. They accumulate by ion-trapping in acidic environments and will concentrate differently in the tissues to the sulfonamides. Trimethoprim plasma $t_{1/2}$ is 2–3 hours in most species.

D. Pharmacokinetics

1. Sulfonamides are well absorbed orally and widely distributed to tissues. Transcellular fluid concentrations are 80% of plasma concentration. Binding to plasma albumin varies with each sulfonamide but is generally 50–75%.
2. Metabolism by acetylation at N_4 and glucuronide conjugation occurs in most species. Acetylation does not occur in the dog. Oxidation of the benzene and heterocyclic rings to quinone derivatives also occurs, especially in dogs. The type and extent of metabolism varies with the sulfonamide and the animal species.
3. Renal excretion of unchanged drug and metabolites is via glomerular filtration, active secretion, and passive tubular reabsorption. Reabsorption is pH–p*K*a dependent.

E. Administration. Sulfonamides and potentiated sulfonamides can be administered orally or by injection, depending on species. Frequency of dosing varies with the individual sulfonamides.

F. Bacterial resistance. Bacteria develop resistance by mechanisms, which include increased PABA production, decreased binding of sulfonamide to dihydropteroate synthase, and bacterial metabolism of sulfonamide. Bacteria which are resistant to one sulfonamide are resistant to all. Resistance to the potentiated sulfonamide does occur but is less common than to the sulfonamide. The spectrum of action of the potentiated sulfonamides is broader and the combination is considered bactericidal rather than bacteriostatic.

G. Adverse effects

1. **Renal crystalluria** due to precipitation of sulfonamides in neutral or acidic urine may occur with large or prolonged doses or inadequate water intake, especially with the older, less soluble sulfonamides such as sulfathiazole. Therapeutic regimens generally do not extend beyond 5 days and renal crystalluria is rare.
2. **Keratoconjunctivitis sicca (KCS) may be observed in dogs treated with sulfonamides**, such as sulfadiazine, which contain the pyrimidine nucleus. The mechanism of the toxic effect on lacrimal acinar cells is unknown.
3. **Hypoprothrombinemia, thrombocytopenia, and anemia occur rarely** and are probably immune-mediated reactions. Sulfonamides should not be used in animals with preexisting bleeding disorders.

III. FLUOROQUINOLONES

A. Chemistry. The fluoroquinolones consist of a quinoline ring to which is attached a carboxyl group, fluorine atom, and piperazine ring. They are weak acids and are lipophilic. Water-soluble salts are used in parenteral preparations.

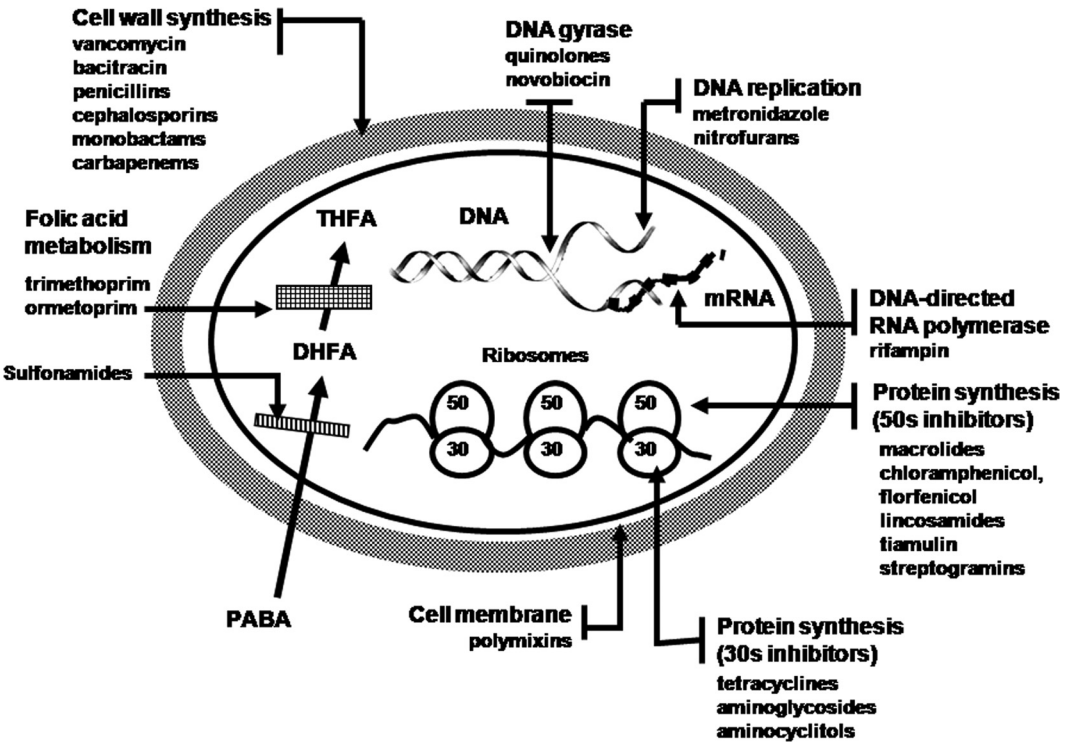

FIGURE 15-3. Mechanisms of action of antibacterial drugs. The five general mechanisms are (1) inhibit synthesis of cell wall, (2) damage outer membrane, (3) modify nucleic acid/DNA synthesis, (4) modify protein synthesis, and (5) modify energy metabolism in the cytoplasm (at folate cycle). (Modified from Figure 46.2, *Human Pharmacology*, 2nd ed., by Brody, T. M., Larner, J., Minneman, K. P., and Neu, H. C. 1994.)

B. **Mechanism of action.** The fluoroquinolones inhibit bacterial DNA gyrase, an enzyme which controls DNA supercoiling as the replicating strands separate. Inhibition of gyrase results in degradation of chromosomal DNA at the replicating fork. Fluoroquinolones are broad spectrum and bactericidal. Anaerobes tend to be resistant (Figure 15-3).

C. **Therapeutic uses**

1. **Enrofloxacin** is used in the treatment of dermal, respiratory, and urinary tract infections (including prostatitis) in dogs, cats, and birds and in respiratory infections in cattle.
2. **Danofloxacin** is used for the treatment of bovine respiratory infections including *Mannheimia* species.
3. **Difloxacin** is used for treatment of dermal, respiratory, and urinary tract infections in dogs.
4. **Orbifloxacin** and Marbofloxacin are used for the treatment of dermal, respiratory, and urinary tract infections of dogs and cats. Orbifloxacin is used for susceptible Gram(–) infections in horses.
5. **Extralabel use of fluoroquinolones in food animals is prohibited.**

D. **Pharmacokinetics.** Oral absorption of the fluoroquinolones is rapid with peak plasma concentrations at 1 hour in dogs. Distribution is wide and includes the CNS, bone, and prostate. Some hepatic metabolism occurs and both parent drug (15–50%) and metabolites are excreted in urine and bile. Renal tubular active secretion results in high urinary concentrations. The plasma $t_{1/2}$ for enrofloxacin is 3–5 hours in dogs and

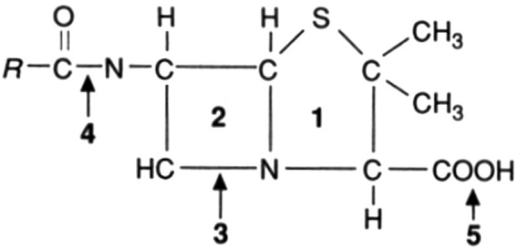

FIGURE 15-4. General structure of penicillins. Substituents at *R* distinguish the various penicillins. (1) Thiazolidone ring. (2) β-Lactam ring. (3) Site of action of β-lactamases (penicillinases). (4) Site of amidase cleavage to yield 6-aminopenicillanic acid (6-APA) nucleus for semisynthetic penicillins. (5) site of salt formation (e.g., sodium, procaine). (Adapted from Figure 11-3, *NVMS Pharmacology*, by Ahrens, F. A. 1996).

6 hours in cats and horses. The elimination $t_{1/2}$ for difloxacin and marbofloxacin is 9–12 hours in dog and cats and for orbifloxacin is 6 hours in dogs and cats and 9 hours in horses.

E. **Administration.** Fluoroquinolines are administered orally or parenterally once or twice a day in all species. Enrofloxacin is administered SC once a day for treatment of respiratory infections in cattle.

F. **Resistance.** Development of bacterial resistance is relatively rare. Long periods of subtherapeutic levels may allow the growth of mutants in which fluoroquinolones are not bound to DNA gyrase.

G. **Adverse effects.** Toxicity associated with fluoroquinolones is **erosion of articular cartilage** in young dogs and foals, particularly, if they are used at high doses for longer than 14 days in rapid growth phase. Enrofloxacin has also been reported to produce **seizures** in dogs on phenobarbital for epilepsy; other quinolones evoke headaches in humans. **Retinal degeneration** has been reported due to acute and diffuse retinal damage in cats.

IV. PENICILLINS

A. **Chemistry.** The structure of penicillins includes a β-lactam ring and a thiazolidone ring (Figure 15-4). Cleavage of the β-lactam ring destroys antibiotic activity. Amidase cleavage of the amide bond side chain yields the 6-amino-penicillanic acid (6-APA) nucleus used in producing semisynthetic penicillins. The carboxyl group attached to the thiazolidone ring is the site of salt formation (sodium, potassium, procaine, etc.) which stabilizes the penicillins and affects solubility and absorption rates.

B. **Mechanism of action.** Penicillins bind to and inhibit the transpeptidase involved in the cross-linking of the bacterial cell wall, the third and final step in cell-wall synthesis (Figure 15-3). The weakened cell wall ruptures, resulting in lysis and cell death. Penicillins also inhibit other peptidases (penicillin-binding proteins) involved in cell wall synthesis and block the inhibition of autolysins. Rapidly growing bacteria are most susceptible to the bactericidal effect of penicillin. The penicillins are primarily effective against Gram(+) aerobes and anaerobes. The broad-spectrum, semisynthetic penicillins are also effective against some Gram(–) pathogens.

C. **Therapeutic uses**

1. **Natural penicillins**
   a. **Penicillin G (benzylpenicillin)** is used in all species for the treatment of infections caused by Gram(+), nonpenicillinase producing pathogens. It is the most potent penicillin for these organisms.
   b. **Penicillin V** now used infrequently for long-term oral therapy of Gram(+) bacterial infections in dogs, cats, and horses.
2. **Penicillinase-resistant penicillins** include methicillin, oxacillin, and cloxacillin. Their use is suited for severe staphylococcal infections caused by β-lactamase-producing

organisms (some bovine mastitis) but they are less effective against *Streptococcus* than the natural penicillins.

3. **Broad-spectrum penicillins**
   a. **Aminopenicillins.** Ampicillin and amoxicillin are active against many Gram(–) aerobes (*E. coli*, *Proteus, Haemophilus* spp.) as well as Gram(+) pathogens. They are used in all species for the treatment of susceptible infections. They are acid-stable but are not penicillinase stable. GI absorption of amoxicillin is better than ampicillin.
   b. **Carbenicillin and ticarcillin** are carboxypenicillins that have antipseudomonal actions when used alone or in combination with or gentamicin or tobramycin. They are useful for ear and skin infections in dogs caused by *Pseudomonas* spp.
   c. **Piperacillin** is an ureidopenicillin that has an extended Gram(–) spectrum including *Pseudomonas, Enterobacter*, and *Klebsiella* spp. Cost limits its use to the treatment of severe Gram(–) bacterial infections in dogs and cats.
4. **Potentiated penicillins.** Clavulanic acid has minimal antibacterial action but it inhibits many of the β-lactamases produced by penicillin-resistant organisms. It is combined with amoxicillin or ticarcillin in commercial preparations. Sulbactam has an action similar to clavulanic acid and is combined with ampicillin. The potentiated penicillins are used in small animals for extended spectrum antimicrobial action. Tazobactam is another β-lactamase inhibitor.

D. **Pharmacokinetics.** Many penicillins are broken down by gastric HCl and are thus poorly absorbed orally. These include penicillin G, methicillin, and ticarcillin. Acid stable penicillins are well absorbed orally. These include penicillin V, ampicillin, amoxicillin, oxacillin, cloxacillin, and the indanyl salt of carbenicillin. The distributions of penicillins are confined mostly to the extracellular spaces occur, but clinically effective concentrations in most tissues except for the CNS, bones, prostate, and eye. More than 90% of an administered dose is excreted unchanged in the urine by glomerular filtration and active tubular secretion. The remainder is metabolized by the liver to penicilloic acid derivatives, which may act as antigenic determinants in penicillin hypersensitivity.

E. **Administration.** Penicillins are generally administered IM. The acid-stable penicillins are administered orally 2–3 times a day. Procaine penicillin G is slowly absorbed from IM sites and may provide therapeutic levels for 24 hours with a single dose. Benzathine penicillin G is even more slowly absorbed over 48–72 hours but blood levels attained are relatively low. Sodium or potassium salts of penicillin G may be administered IV or IM every 4–6 hours.

F. **Resistance.** Inactivation of penicillins by bacteria-producing penicillinases (β-lactamases) is the most common mechanisms of resistance. Failure of the drug to bind to penicillin-binding proteins (PBPs) may also occur.

G. **Adverse effects.** Allergic reactions to penicillin may occur in animals, especially cattle. Signs include skin eruptions, angioedema, and anaphylaxis. Procaine salts of penicillin should not be used in birds, snakes, turtles, guinea pigs, or chinchillas because these species are sensitive to procaine. Procaine penicillin G should not be used in race horses 30 days before racing. Release of procaine due to high levels of plasma esterases in horses may produce CNS effects. Hyperkalemia and cardiac arrhythmias may result from IV administration of potassium penicillin in all species.

V. CEPHALOSPORINS

A. **Chemistry.** Cephalosporins are β-lactam antibiotics, which have a 7-amino-cephalosporanic acid nucleus analogous to the 6-APA nucleus of penicillins. They are weak acids and are administered as the sodium salt, monohydrate, or free base.

B. **Mechanism of action.** Cephalosporins inhibit the third stage of bacterial cell wall synthesis—the cross-linking of the peptidoglycan chain, by the same mechanism as the penicillins (Figure 15-3). Cephalosporins are bactericidal.

C. **Therapeutic uses.** Cephalosporins may be used in penicillin-intolerant patients, but this should be done with caution since cross-reactivity can occur.

1. **First generation cephalosporins** include cephalexin (oral), cefadroxil (oral), cephapirin (parenteral), and cephalothin (parenteral). They are effective against Gram(+) aerobes. **Cephalosporins are frequently employed for antibiotic prophylaxis because of their ability to penetrate tissues. They are a first alternate to penicillins in the treatment of many infections caused by Gram(+) pathogens.**
2. **Second-generation cephalosporins** include cefaclor (oral) and cefoxitin (parenteral). Their antibacterial spectrum is broader than that of first-generation cephalosporins and includes some Gram(–) pathogens. They are not widely used in veterinary medicine.
3. **Third-generation cephalosporins** include ceftiofur, cefoperazone, cefotaxime, cefixime, and cefpodoxime (Simplicef®). They have an extended spectrum of action against Gram(–) organisms, are resistant to β-lactamases cephalosporinases), and penetrate the blood–brain barrier. Ceftiofur is used in the treatment of respiratory disease in cattle, horses, sheep, and swine following IM injection and for intramammary treatment of mastitis in cattle. It is also used for treating urinary tract infections and soft tissue infections in dogs and cats. Cefoperazone is used in dogs to treat soft tissue infections and Gram(–) bacteremia. Cefotaxime is used in dogs, cats, and foals to treat Gram(–) sepsis, soft tissue infections meningitis, and CNS infections. Cefpodoxime proxetil is the prodrug marketed for use in the treatment of skin infections in dogs and cats. Cefixime is used in the treatment of urinary tract infections and respiratory infections in dogs and cats and for bacterial endocarditis in dogs.
4. **Fourth-Generation cephalosporins** include cefepime and cefquinone and have more activity against bacteria, particularly *Pseudomonas*, showing resistance to other cephalosporins. Some manufacturers have implied incorrectly that their third-generation cephalosporins are fourth generation.

D. **Pharmacokinetics.** Most cephalosporins are unstable in gastric acid and must be given parenterally. Cephalexin and cefadroxil, cefachlor, and cefixime are acid stable and are well absorbed orally. Cephalosporins are distributed in the extracellular fluid and penetrate body tissues except the CSF. Metabolism is minimal except for a few cephalosporins such as cephalothin, which is deacetylated by the liver. The plasma $t_{1/2}$ for most cephalosporins is 1–2 hours. The $t_{1/2}$ for cefixime in dogs is 7 hours. The elimination $t_{1/2}$ for ceftiofur in cattle is 8–12 hours following IM administration. Ceftiofur tissue concentration fall in food animals below tolerance levels in liver and kidney after 4 days. Renal excretion is by glomerular filtration and active tubular secretion like penicillins.

E. **Administration.** The acid-stable cephalosporins (cephalexin, cefadroxil, cefachlor, and cefixime) are administered orally every 8–12 hours in dogs and cats. Parental cephalosporins are administered IM, IV, or SC every 8–12 hours in all species. An exception is ceftiofur, which is administered once a day in cattle, horses, sheep, dogs, and cats.

F. **Resistance.** Bacterial β-lactamase production may confer resistance, although cephalosporins tend to retain efficacy in contrast to the penicillins.

G. **Adverse effects.** Side effects are rare and **cephaolsporins are considered to be among the safest antimicrobials in use.** Prolonged treatment or high doses may produce **hemopoietic effects with anemia and bone marrow depression**. **Hypersensitivity and allergic reactions** may occur.

VI. CARBAPENEMS

A. **Chemistry.** Carbapenems are β-lactams with a structure similar to penicillin but the –S- in the thiazolidine is replaced by a methyl group.

B. **Mechanism of action** is similar to other β-lactam antimicrobial drugs but the carbapenems bind to more penicillin-binding proteins so that **they have a very broad spectrum of action, one of the widest spectrum antimicrobials** (Figure 15-3).

C. **Therapeutic uses.** The carbapenems are used to treat very serious infections like peritonitis associated with ruptured GI tract or intestinal spillage during surgery. They are effective against Gram(+) and Gram(–) aerobic and anaerobic bacteria including *Pseudomonas* and *Enterobacteriaciae*.

D. **Pharmacokinetics. Oral administration is not possible because of acid hydrolysis and poor absorption**. Imipenem is given IV over a period of 15–30 minutes and elimination in humans is governed by a $t_{1/2}$ of 2 hours where 75% is eliminated by renal filtration and metabolism in the renal tubules. No information on $t_{1/2}$ is available for animals. Imipenem undergoes extensive metabolism by the kidney dehydropeptidase (DHP-1) in the brush border of the proximal tubule. The metabolite is nephrotoxic and exhibits antimicrobial action in the urine. Imepenem is used with a DHP-1 inhibitor, cilastatin, to decrease toxicity and increase elimination $t_{1/2}$. Meropenem is a more recent derivative that is more DHP-1 stable that does not need cilastatin to inhibit kidney metabolism.

E. **Adverse effects.** Side effects may include anorexia, vomiting, and diarrhea; CNS toxicity including seizures and tremors; and hypersensitivity reactions including pruritis, fever, and rarely, anaphylaxis.

VII. MONOBACTAMS

A. **Chemistry.** Monobactams have a β-lactam ring but the adjacent thiazolidine ring has been replaced.

B. **Mechanism of action.** Aztreonem binds to penicillin binding proteins present in Gram(–) aerobic bacteria and disrupt cell wall synthesis (Figure 15-3). **It is stable to most β-lactamases**.

C. **Therapeutic uses.** Aztreonem is used in humans to replace aminoglycosides, which are more toxic when used with macrolides and lincosamides. **It may be used as a reserve antibiotic in veterinary medicine to treat severe Gram(–) infections.**

D. **Pharmacokinetics.** When given parenterally, aztreonem has a similar distribution to penicillin G. Penetration of CSF is good. It is excreted by the kidneys with an elimination $t_{1/2}$ of 1.2 hours in humans. No other information is available for animals.

E. **Adverse effects.** Hypersensitivity reactions may occur but cross-allergy with penicillins or cephalosporins has not been observed.

VIII. AMINOGLYCOSIDES

A. **Chemistry.** Aminoglycosides consist of two or three amino sugars joined to a hexose (aminocyclitol) by glycosidic bonds. Numerous amino groups contribute to their very polar and basic character. Sulfate salts are water soluble.

B. **Mechanism of action.** The aminoglycosides bind to the 30S ribosomal fragment and inhibit the rate of protein synthesis and the fidelity of mRNA translation which results in the synthesis of abnormal proteins (Figure 15-3). Their uptake by bacteria includes an energy-dependent step (EDP_1), which is oxygen linked and is inhibited by an anaerobic or acidic environment and by Ca^{2+} or Mg^{2+}. They are bactericidal against Gram(–) aerobes and are synergistic with β-lactams against many Gram(+) pathogens.

C. **Therapeutic uses.** The aminoglycosides are used in the treatment of Gram(–) infections in all species.

1. **Streptomycin and dihydrostreptomycin** are the oldest members of this class of antibiotics. Their use has declined with the advent of broader spectrum aminoglycosides such as gentamicin and amikacin.
2. **Neomycin** is used orally for the treatment of enteric infections and topically for treating skin, ear, and eye infections.
3. **Gentamicin and amikacin** are expanded spectrum aminoglycosides with activity against *Pseudomonas, Proteus, Staphylococcus*, and *Corynebacterium* spp., as well as Gram(–) aerobes. They are used in all species for the treatment of susceptible infections of the skin, respiratory tract, ear, eye, urinary tract, and septicemia. Tobramycin is similar to gentamicin but has more potent antipseudomonal activity and reduced nephrotoxicity.
4. **Kanamycin** has an antimicrobial spectrum similar to gentamicin except it is not effective against *Pseudomonas* spp. It is currently used in veterinary medicine only as an oral preparation combined with bismuth subcarbonate and aluminum magnesium silicate for the treatment of bacterial enteritis in dogs and for symptomatic relief of the associated diarrhea.

D. **Pharmacokinetics. Aminoglycosides are not absorbed from the GI tract because of their high polar nature.** They are distributed to the extracellular fluid and to transcellular fluids such as pleural and peritoneal fluids. Distribution is limited with penetration of the CNS or ocular tissue being minimal. **Aminoglycosides tend to accumulate in the renal cortex and otic endolymph, which predisposes these tissues to their toxicity.** They are excreted unchanged in the urine by glomerular filtration. The plasma $t_{1/2}$ is 1–3 hours for most species. **The prolonged residues values in kidney severely limits the use of aminoglycosides in production animals to label use only.**

E. **Administration.** Aminoglycosides are administered IM or SC for systemic infections. Because the bactericidal effects of aminoglycosides are concentration-dependent for systemic infections, some clinicians advocate a high dose once daily (pulse therapy, rather than twice daily) to allow full clearance to reduce renal and cochlear toxicity. For enteric infections, an oral dose twice a day may be used.

F. **Resistance.** Inactivation of aminoglycosides by bacterial enzymes is the most common form of resistance. **The numerous amino and hydroxyl side groups are sites of attack by acetylases, phosphorylases, and adenylases**. Resistance may be plasmid-mediated and develop quickly. Amikacin is more resistant to enzymatic degradation than other members of this class.

G. **Adverse effects**

1. **The aminoglycosides are relatively more toxic than other classes of antimicrobials.** Toxicity is reversible if the treatment is stopped early. Dosage regimens must be adjusted in animals with decreased renal function and they should not be used with other ototoxic or nephrotoxic drugs such as furosemide or amphotericin B.
2. **Ototoxicity** is due to progressive damage to cochlear sensory cells and/or vestibular cells of the inner ear resulting in deafness and ataxia, respectively.
3. **Nephrotoxicity** is due to the damage of the membranes of proximal tubular cells resulting in a loss of brush border enzymes, impaired absorption, proteinuria, and decreased glomerular filtration rate.

4. **Neuromuscular blockade** is a relatively rare adverse effect of aminoglycosides. It is caused by prejunctional blockade of acetylcholine (ACh) release and decreased postsynaptic sensitivity to ACh. Muscle paralysis and apnea are treated with calcium gluconate.

IX. TETRACYCLINES

A. **Chemistry.** The tetracyclines are polycyclic compounds that are amphoteric and that fluoresce when exposed to ultraviolet light. Most are prepared as the hydrochloride salt. They form insoluble chelates with cations such as Ca^{2+}, Mg^{2+}, Fe^{3+}, and Al^{3+}. They accumulate in growing teeth and bones.

B. **Mechanism of action.** Tetracyclines reversibly inhibit bacterial protein synthesis by binding to the 30S ribosome and preventing attachment of aminoacyl tRNA to the mRNA-ribosome complex (Figure 15-3). They block the addition of amino acids to the growing peptide chain. They are bacteriostatic and broad spectrum. Their antimicrobial spectrum includes Gram(+) and Gram(–) aerobes and anaerobes, *Rickettsiae*, *Spirochetes*, *Chlamydiae*, *Mycoplasma*, and some protozoans such as *Anaplasma* spp. and *Haemobartonella* spp.

C. **Therapeutic uses**

1. **Large animals.** Tetracycline, chlortetracycline, and oxytetracycline are used in the treatment of local and systemic bacterial, chlamydial, rickettsial, and protozoal infections in cattle, sheep, horses, and swine and as feed additive/growth promoters in cattle and swine.
2. **Small animals.** Doxycycline, minocycline, and tetracycline are used in the treatment of respiratory and urinary tract infections in dogs and cats and as specific therapy for *Borrelia* (Lyme disease), *Brucella*, *Haemobartonella*, and *Ehrlichia* spp. infections. They are also effective in the treatment of psittacosis in birds.

D. **Pharmacokinetics.** Oral absorption of tetracyclines ranges from 60–90% of the administered dose except for chlortetracycline, which is only 35% absorbed. Divalent or trivalent cations impair absorption and thus milk, antacids, or iron salts should be avoided 3 hours before and after oral administration. Distribution is wide and includes all tissues except those of the CNS. **Doxycycline and minocycline are more lipid soluble than tetracycline, chlortetracycline, or oxytetracycline and penetrate the CNS, eye, and prostate at therapeutic concentrations.** Metabolism is minimal in domestic animals, except for minocycline, which is extensively metabolized by the liver. Renal excretion by glomerular filtration is the major route of elimination for most tetracyclines, but small amounts are excreted into feces via bile and/or diffusion from the blood into the intestine. **Doxycycline is unique in that intestinal excretion is the major route of elimination (75%)**. The plasma $t_{1/2}$ ranges from 6–12 hours for most tetracyclines. A recent derivative of the glycylcyclines, **tigecycline**, has been developed that has an effect against methicillin-resistant *S. aureus* (MRSA).

E. **Administration.** Tetracyclines are administered orally or IV every 8–12 hours. IM injections produce pain, irritation, and sterile abscesses unless special buffered solutions are used. **Oral therapeutic doses should be avoided in adult ruminants and used with caution in horses because of the danger of disrupting ruminal or colonic microflora, respectively**.

F. **Resistance** is now common because of widespread use. Resistance may be plasmid-mediated and is usually due to decreased drug uptake or active transport of the tetracycline out of the bacterial cell.

G. Preslaughter withdrawal of oxytetracycline in food animals

1. The Food Animal Residue Avoidance Databank (FARAD) recommends, in cattle, an extralabel withdrawal of 28 days for intrauterine treatment. It also recommends testing milk after intrauterine treatment, as there is inter-cow variability in the residue elimination profiles in milk.
2. FARAD recommends an extralabel preslaughter withdrawal of 28 days in sheep and goats after IM or SC oxytetracycline administration. A milk withdrawal of 96 hours is recommended for sheep and goats.
3. For swine, FARAD recommends an extralabel preslaughter period of 14 days following administration of tetracycline product in feed or water to swine.

H. Adverse effects

1. **The tetracyclines (except doxycycline and minocycline) are potentially nephrotoxic** and should be avoided if renal function is impaired.
2. **Permanent staining of unerupted teeth may occur in young animals** due to the formation of a tetracycline-calcium phosphate complex in enamel and dentine.
3. **Suprainfections of fungi, yeast, or resistant bacteria** may occur in the GI tract with prolonged administration of broad-spectrum antibiotics such as the tetracyclines. GI adverse effects are seen frequently in cats. **Oral tetracyclines should not be used with herbivores because of serious effects on ruminant digestion.**
4. **Antianabolic effects are seen at high doses** because of binding to mitochondrial ribosomes. This may result in an elevated blood urea nitrogen (BUN) especially with preexisting renal disease.
5. **Photosensitivity and hepatotoxicity are rare side effects in animals.**

X. CHLORAMPHENICOL GROUP

A.

Chemistry. Chloramphenicol is an unusual natural compound because it contains dichloracetate and nitrobenzene moieties as part of its structure. Palmitate salts are water insoluble and are administered orally. Chloramphenicol sodium succinate is water soluble for parenteral use. Florfenicol is a fluorinated derivative where the $-NO_2$ group has been replaced by $-SO_2CH_3$ to treat respiratory infections in beef cattle. It does not leave the toxic residues in meat that chloramphenicol does.

B.

Mechanism of action. Chloramphenicol and florfenicol bind to the bacterial 50S ribosome unit to inhibit peptide bond formation and protein synthesis (Figure 15-3). They are bacteriostatic and broad spectrum and are effective against most anaerobic bacteria.

C.

Therapeutic uses. Chloramphenicol is not allowed for use in food-producing animals because the potential danger of residue-induced toxicity in humans (see below). It is used in dogs, cats, horses, and birds for local and systemic infections, inducing respiratory, CNS, and ocular infections, and infections caused by anaerobes and *Salmonella* spp. Florfenicol is approved for use only in cattle for the treatment of bovine respiratory disease (BRD) caused by *Pasteurella* spp. and *Haemophilus somnus*. It is used in dogs and cats for treating susceptible infections when the myelotoxic potential of chloramphenicol must be avoided.

D. Pharmacokinetics

1. **Chloramphenicol** is rapidly absorbed from the GI tract and widely distributed to all tissues including the CNS and eye. Hepatic metabolism by glucuronide conjugation occurs slowly for 75% of the administered drug in cats, but faster to 90% in dogs. The elimination $t_{1/2}$ is 1–1.5 hours for dogs and horses and 4–5 hours in cats.

2. **Florfenicol** is absorbed orally in dogs and cats and from IM sites in cattle. It is widely distributed, including the CNS, similar to chloramphenicol. The serum $t_{1/2}$ is 18 hours in cattle and 4–6 hours in dogs and cats. In cattle, two-thirds of a dose is excreted as the parent drug in the urine and one-third is metabolized by the liver.

E. Administration. Chloramphenicol is administered orally, IM, IV, or SC every 6–8 hours to dogs, birds, or horses and every 12 hours to cats. Florfenicol is administered IM in cattle and repeated 48 hours later for a total of two doses of the slow-release preparation. It is administered IM or SC every 8 hours in dogs and every 12 hours in cats.

F. Resistance. Resistant bacteria inactivate chloramphenicol by production of an acetyltransferase and other metabolizing enzymes. Similar inactivation is expected with florfenicol.

G. Adverse effects

1. **Anemia,** which is dose-related, may occur in animals and humans. Chloramphenicol may inhibit the uptake of iron by erythrocytes and their rate of maturation in bone marrow. A second type of anemia may occur in humans treated with chloramphenicol. **It is non-dose-related and rare but the resulting aplastic anemia is often fatal and this is the reason for the drug's ban in food-producing animals.**
2. **Anorexia and diarrhea** may occur especially in cats with high or prolonged dosage.
3. **Florfenicol is not known to produce aplastic anemia** and its use is permitted in beef cattle.

XI. MACROLIDES

A. Chemistry. The macrolide antibiotics include erythromycin, azithromycin, clarithromycin, tulathromycin, tylosin, and tilmicosin. They are basic, lipid-soluble compounds consisting of a lactone ring to which are attached deoxy sugars. They are prepared as sulfate salts or as esterified salts of stearate, tartrate, estolate, or lactobionate.

B. Mechanism of action. Macrolides are bacteriostatic by inhibiting bacterial protein synthesis (Figure 15-3). They bind to the 50S ribosome to prevent translocation of amino acids to the growing peptide chain. Binding sites on the 50S ribosome overlap with binding sites of chloramphenicol and the lincosamides (especially clindamycin) and combination therapy should be avoided. Their antimicrobial activity is primarily against Gram(+) aerobes and anaerobes and *Mycoplasma* spp. Tylosin and tiamulin are effective against some Gram(–) pathogens, including *Pasteurella* and *Haemophilus* spp.

C. Therapeutic uses

1. **Erythromycin** is an alternate to penicillin for infections caused by Gram(+) aerobes and anaerobes in dogs, cats, and horses. It is a drug often chosen for the treatment of enteritis caused by *Campylobacter jejuni* in dogs and foals and for *Rhodococcus equi* pneumonia in foals.
2. **Tylosin** is used in cattle, sheep, and swine for the treatment of local and systemic infections caused by *Mycoplasma* and Gram(+) bacteria. It is also added to feed as a growth promotant in these species. Tylosin is used in dogs and cats for the treatment of chronic colitis.
3. **Tilmicosin** is used in cattle for the treatment of respiratory disease caused by *Pasteurella* spp. It has potentially fatal toxic effects in horses and humans.
4. **Azithromycin** is used in dogs, cats, and horses and is effective against *Staphylococcus, Streptococcus*, and *Mycoplasma.* It is used as an alternative for erythromycin for *R. equi* pneumonia in foals

5. **Tulathromycin** is used for the treatment of bovine and swine respiratory diseases. It is effective against *Mannheimia*, *Mycoplasma*, and *Haemophilus*; it is concentrated in leucocytes and lung tissue.
6. **Clarithromycin** is used in dogs and cats for the treatment of mycobacterial infections including canine leproid granuloma, feline leprosy, and for *Helicobacter* spp. in cats and ferrets, and for *R. equi* in foals.

D. **Pharmacokinetics.** Macrolides are absorbed orally if protected from gastric acid destruction by enteric coated preparations or administration of the stable, esterified salts. They are weak organic bases that are widely distributed to all tissues except those of the CNS. They are concentrated in acidic environments like the respiratory secretions, milk, and leukocytes. Tilmicosin concentrates in lung tissue at levels 60-fold higher than serum. Erythromycin is mainly excreted unchanged in bile but a fraction is metabolized by *N*-demethylation in the liver. Tylosin, tilmicosin, and azithromycin are excreted unchanged in bile and urine. The plasma $t_{1/2}$ for the macrolides are erythromycin—1–3 hours in most species; azithromycin—20 hours in cats and 35 hours in foals; tilmicosin—1 hour in cattle and 25 hours in pigs; tylosin—1 hour in dogs and cattle and 4 hours in sheep, pigs, and goats; tulathromycin—90 hours in cattle and pigs. Information is not available for the $t_{1/2}$ of clarithromycin.

E. **Administration**

1. **Erythromycin** is administered orally or IM three times a day to dogs, cats, and foals, and IM once a day in cattle, sheep, and swine.
2. **Tylosin** is administered IM or orally once or twice a day to swine, calves, lambs, dogs, and cats.
3. **Tilmicosin** is administered SC to cattle every 72 hours.
4. **Tulathromycin**. A single IM injection is claimed to be effective against bovine and swine respiratory infections.
5. **Azithromycin** is administered orally once a day to dogs, cats, and foals.
6. **Clarithromycin** is administered orally twice a day to dogs, cats, ferrets, and foals.

F. **Resistance.** Bacterial resistance to macrolide antibiotics may be chromosomal or plasmid mediated and is due to decreased drug binding by the 50S ribosome. Less frequently, active efflux, or enzymatic inactivation by resistant bacteria may occur.

G. **Adverse effects.** Erythromycin, tylosin, azithromycin, clarithromycin, and tulathromycin have relatively few side effects. Mild GI upset with oral doses and pain and irritation at IM injection sites may occur. Erythromycin is recognized to be an agonist of the motilin (a peptide that stimulates contraction of GI smooth muscle) receptor and acts on the stomach, ileum, cecum, and pelvic flexure and can produce abdominal pain and diarrhea. Edema of the rectal mucosa with mild anal prolapse may be seen in swine following IM administration of tylosin. Erythromycin should not be administered orally to adult ruminants or tylosin, orally or parenterally, to adult horses because of the danger of severe diarrhea. Tilmicosin produces cardiovascular toxicity in species other than cattle by increasing myocardial Ca^{2+} concentrations. Side effects are rare for others in the group.

XII. LINCOSAMIDES

A. **Chemistry.** Lincomycin, clindamycin, and pirlimycin are derivatives of a sulfur-containing octose with an amino acid-like side chain and are highly lipid soluble. They are prepared as HCl or phosphate salts, which are water soluble, or clindamycin palmitate for oral administration.

B. **Mechanism of action.** The lincosamides bind to the bacterial 50S ribosome to inhibit protein synthesis (Figure 15-3). Since this is the same binding site of chloramphenicol

and the macrolides, combined therapy should be avoided. Lincomycin and clindamycin are bacteriostatic and are active against Gram(+) aerobes and obligate anaerobes, *Toxoplasma* spp. *Neospora canis*, and *Mycoplasma* spp. The antibacterial activity of clindamycin is greater than that of lincomycin, especially against anaerobes.

C. **Therapeutic uses.** Lincomycin is used in swine for the control and treatment of swine dysentery, and the treatment of staphylococcal, streptococcal, and mycoplasmal infections. Clindamycin is used in dogs and cats for periodontal disease, osteomyelitis, dermatitis, and deep soft tissue infections caused by Gram(+) organisms. It is used for treating toxoplasmosis in dogs and cats and neosporosis in dogs. Pirlimycin is prepared and used for the treatment of bovine mastitis.

D. **Pharmacokinetics.** Oral absorption is 50% for lincomycin and 90% for clindamycin. Distribution is wide with excellent penetration of bone and soft tissues, including tendon sheaths. CNS levels are low unless the meninges are inflamed. Lincosamides are metabolized by the hepatic microsomal enzymes into sulfoxide and other metabolites (60%, lincomycin; 90%, clindamycin). Parent drug and metabolites are excreted in urine, bile, and feces. The elimination $t_{1/2}$ is 3–5 hours in dogs and cats. No information is available for other species.

E. **Administration.** Lincomycin is administered IM to swine once a day or added to the drinking water. Clindamycin is administered orally or IM twice a day to dogs and cats. Pirlimycin is given by intramammary infusion.

F. **Resistance.** Altered drug binding by bacterial ribosomes is the usual form of resistance. **Cross-resistance between lincosamides and macrolides is common.**

G. **Adverse effects. Lincosamides are contraindicated in horses, rabbits, hamsters, and guinea pigs because they may produce a severe, often fatal, diarrhea due to altered GI flora.** Side effects are rare in dogs, cats, cattle, and swine except for neuromuscular blockade at high doses or when used with anesthetics.

XIII. MISCELLANEOUS ANTIBACTERIAL DRUGS

A. Aminocyclitols

1. **Mechanism of action.** Spectinomycin and apramycin are **chemically related to the aminoglycosides but are bacteriostatic, not bactericidal.** They bind to the 30S ribosome and inhibit protein synthesis (Figure 15-3). They are active primarily against Gram(–) aerobes and *Mycoplasma* infections.
2. **Therapeutic uses.** Spectinomycin is used in dogs, cats, horses, swine, calves, and poultry for the treatment of enteric and respiratory infectious disease. Apramycin is used to treat enteric infections, especially colibacillosis in swine and calves.
3. **Pharmacokinetics.** The pharmacokinetics of aminocyclitols is similar to that of the aminoglycosides. Less than 10% is absorbed orally. Parenterally administered spectinomycin distributes to the ECF and is excreted unchanged by the kidney. Other information is not available for animals.
4. **Administration.** Spectinomycin is administered orally or parenterally twice a day in all species. Apramycin is administered to swine and cattle in the drinking water once a day.
5. **Adverse effects.** No significant toxicity is associated with clinical use of spectinomycin.

B. Metronidazole

1. **Chemistry.** The nitroimidazoles include metronidazole, ipronidazole, dimetridazole, and ronidazole. They are heterocyclic compounds containing a five-membered ring similar to the nitrofurans. Only metronidazole is used in veterinary medicine.

2. **Mechanism of action.** Metronidazole is taken up by anaerobic bacteria and protozoa and reduced to a cytotoxic metabolite, which disrupts DNA (Figure 15-3). It is bactericidal against most obligate anaerobes and is active against protozoa, including *Giardia* and *Trichomonas* spp.
3. **Therapeutic uses.** Nitroimidazoles have demonstrated carcinogenicity in laboratory animals and their use is banned in food-producing animals. Metronidazole is used in dogs, cats, and horses for the treatment of severe infections caused by anaerobic pathogens, especially brain abscesses and pelvic, genitourinary tract, and respiratory infections. Metronidazole is also used to treat protozoal infections such as giardiasis and trichomoniasis in dogs and cats.
4. **Pharmacokinetics.** Metronidazole is well absorbed orally and widely distributed, including the CNS. Hepatic metabolism by oxidation and conjugation occurs for one-third to one-half of administered drug. Metabolites and unchanged drug are excreted in urine and feces. The elimination $t_{1/2}$ in dogs and horses are 3–5 hours.
5. **Administration.** Metronidazole is administered orally twice a day in dogs, cats, and horses.
6. **Adverse effects.** High or prolonged dosage may produce neurotoxicity with signs that include nystagmus, ataxia, and seizures.

C. Rifampin

1. **Mechanism of action.** Rifampin inhibits DNA-dependent RNA polymerase, which prevents initiation of RNA synthesis (Figure 15-3). It is bactericidal for mycobacteria and Gram(+) pathogens. It is effective against intracellular infections.
2. **Therapeutic uses.** Rifampin is combined with erythromycin in the treatment of *R. equi* infections in foals. Rifampin is also used in combination with other antifungal agents to treat fungal infections such as aspergillosis or histoplasmosis in dogs and cats when infection involves the CNS.
3. **Pharmacokinetics.** Rifampin is absorbed orally and rapidly distributed to cells and tissues. Rifampin is metabolized in the liver to a deacetylated form that also has antibacterial activity. Both this metabolite and parent drug are excreted primarily in the bile, but up to 30% may be excreted in the urine. The parent drug is substantially reabsorbed in the gut, but the metabolite is not. Reported elimination $t_{1/2}$ for various species are 6–8 hours in horses, 8 hours in dogs, and 3–5 hours in sheep. Because rifampin can induce hepatic microsomal enzymes, elimination rates may increase with repeated doses.
4. **Administration.** Rifampin is administered orally three times a day in foals, dogs, and cats.
5. **Adverse effects.** Side effects are rare. **Hepatotoxicity** may occur in animals with preexisting liver disease. Rifampin may produce red-orange colored urine, sweat, and saliva but this is not harmful.

D. Tiamulin

1. **Mechanism of action.** Tiamulin binds to the 50S bacterial ribosome to inhibit protein synthesis (Figure 15-3). Its mechanism of action and antibacterial spectrum are similar to macrolides such as tylosin. It is active against Gram(+) cocci, *Mycoplasma*, *spirochetes*, and some Gram(–) pathogens such as *Haemophilus* spp.
2. **Therapeutic uses.** Tiamulin is administered in medicated feed or water in swine for the control and treatment of *Haemophilus* pneumonia and swine dysentery.
3. **Pharmacokinetics.** Tiamulin is well absorbed orally, widely distributed, and metabolized by the liver. Elimination of metabolites occurs in feces (70%) and urine (30%). The $t_{1/2}$ is 4–12 hours in pigs.
4. **Adverse effects.** Dermatitis with erythema and pruritus may be observed if pigs are overcrowded and is due to the irritant metabolites in urine.

E. Vancomycin

1. **Mechanism of action.** Vancomycin blocks the second step of bacterial cell wall synthesis by inhibiting polymer release from the cell membrane (Figure 15-3). It is bactericidal for Gram(+) organisms.

2. **Therapeutic uses.** Vancomycin is a reserve antibiotic administered IV over 30–60 minutes every 6–8 hours for methicillin-resistant staphylococcal infections of bone and soft tissue in dogs and cats. It is administered orally every 6–8 hours in dogs for the treatment of multidrug-resistant enteric infection.
3. **Pharmacokinetics.** Vancomycin is not absorbed orally. It distributes to the ECF and transcellular fluids and is excreted unchanged by glomerular filtration. It has a plasma $t_{1/2}$ of 2 hours.
4. **Adverse effects.** Ototoxicity and nephrotoxicity occur with large or prolonged dosage.

F. Bacitracin

1. **Mechanism of action.** Bacitracin inhibits the second step of cell wall synthesis (Figure 15-3). It is bactericidal for Gram(+) bacteria and *Spirochetes*.
2. **Therapeutic uses.** Bacitracin is used in topical ointments and solutions and is frequently combined with polymixin B and/or neomycin in these preparations. It is also added to swine and poultry rations for the prevention and treatment of clostridial enteritis and as a growth promotant.
3. **Pharmacokinetics.** Bacitracin is not absorbed orally. It is too nephrotoxic for systemic use.
4. **Adverse effects.** Systemic toxicity does not occur with topical or oral administration of bacitracin.

G. Polymyxin B

1. **Mechanism of action.** Polymyxin B interacts with phospholipids in the bacterial cell membrane to produce a detergent-like effect and membrane disruption (Figure 15-3). It is rapidly bactericidal to Gram(–) organisms.
2. **Therapeutic uses.** Polymyxin B is used topically to treat Gram(–) bacterial infections of the skin, eye, and ear in all species. It is usually combined with bacitracin for broad-spectrum antibacterial effects. Polymyxin B is administered orally to cattle and swine for the treatment of Gram(–) enteric infections.
3. **Pharmacokinetics.** Polymyxin B is not absorbed orally. **It is too nephrotoxic for parenteral use.**
4. **Adverse effects.** Polymyxin B does not produce systemic toxicity when administered topically or orally, since it is not absorbed systemically using these routes of administration.

H. Nitrofurans

1. **Mechanism of action.** The nitrofurans are reduced by bacteria to reactive intermediates that inhibit nucleic acid synthesis (Figure 15-3). They produce DNA fragmentation and may also block mRNA translation. They are broad spectrum and bacteriostatic.
2. **Therapeutic uses.** Nitrofurantoin is occasionally used in the treatment of lower urinary tract infections in dogs and cats. It is administered orally every 6–8 hours and is most effective in acid urine. Nitrofurazone is used topically as an antibacterial ointment, powder, and water-soluble wound dressings in all species.
3. **Pharmacokinetics.** Nitrofurantoin is absorbed orally and rapidly excreted by glomerular filtration and active secretion. Peak urine levels are achieved less than 1 hour after administration. The plasma $t_{1/2}$ is 20 minutes in humans; no information is available for animals.
4. **Adverse effects.** Side effects are rare. Nausea, vomiting, and diarrhea may occur in dogs and cats following oral administration. Nitrofurans may not be used in food-producing animals (include topically) because they have been shown to be potential carcinogens in laboratory animals.

I. Novobiocin

1. **Chemistry.** Novobiocin is a coumarin antibiotic and is acidic.

2. **Mechanism of action.** It blocks binding of ATP to DNA gyrase to inhibit supercoiling of bacterial DNA (Figure 15-3). It is bacteriostatic for Gram(+) cocci, especially *S. aureus*.
3. **Therapeutic uses. Novobiocin** is used for wound treatment and the treatment of mastitis particularly *Staphylococcus* infections. It is less potent against *Streptococcus* infections.
4. **Pharmacokinetics.** Novobiocin is absorbed orally with peak levels in 2–4 hours. Tissue penetration is relatively poor. It is excreted primarily into bile and feces. The plasma $t_{1/2}$ after oral administration in humans is ~6 hours; no information is available for animals.
5. **Administration.** Novobiocin is given by intramammary infusion usually combined with procaine penicillin to limit the development of resistance. Novobiocin is combined with tetracycline in a proprietary preparation (AlbaPlex®) for oral administration twice a day in dogs for susceptible infections.
6. **Adverse effects.** Novobiocin does not produce systemic toxicity when administered topically or orally

J. Streptogramins

1. **Chemistry.** Virginiamycin is used for poultry and is a mixture of streptogramin B, a macrolide (virginiamycin M), and streptogramin A, a cyclic hexadepsipeptide (virginiamycin S). The human preparation Synercid® is a mixture of the macrolide, dalfopristin, and the cyclic hexadepsipeptide, quinupristin.
2. **Mechanism of action.** Streptogramins bind to the 50S ribosome to inhibit protein synthesis (Figure 15-3). Virginiamycin is bactericidal against Gram(+) aerobic and anaerobic bacteria.
3. **Therapeutic uses.** Virginiamycin is administered as a medicated feed additive in broiler chickens and swine as a growth promotant and for the prevention of necrotic enteritis in broiler chickens and for the control of swine dysentery in pigs weighing up to 120 lbs. It is also used as a feed additive in cattle to increase feed efficiency and to reduce the incidence of liver abscesses. Synercid® is used in humans for the treatment of vancomycin-resistant enterococcal infection and methicillin-resistant *S. aureus.*

   There is concern that the use of virginiamycin in poultry may lead to transferable resistance to humans and limit the value of Synercid®.
4. **Pharmacokinetics.** Virginiamycin is administered orally. Since it is not absorbed, its antibacterial effects are limited to the GI tract.

K. Ionophore antibiotics

1. **Chemistry.** Ionophores are polyether antibiotics derived from *Streptomyces* used primarily in poultry and swine for feed efficiency and anticoccidial activity. They include monensin, lasalocid, laidlomycin, salinomycin, and narasin.
2. **Mechanism of action.** Ionophores act as alkali metal ionophores. They complex with Na^+ in the cell membrane to produce passive extracellular transport of K^+ and intracellular influx of H^+, which kills bacteria and coccidian by lowering intracellular pH. In the rumen, ionophores selectively affect Gram(+) organisms resulting in a shift to Gram(–) populations in the rumen microflora. This increases the production of propionic acid and decreases the production of acetic and butyric acids by rumen bacteria. This change in volatile acids (VFA) increases feed efficiency by reducing bacterial energy losses to CO_2 and methane, thereby increasing the energy content per unit of feed.
3. **Therapeutic uses.** Monensin, lasalocid, and laidlomycin are administered as premixes or medicated feed for growth promotion, feed efficiency, and control of coccidiosis in cattle and broiler chickens. Salinomycin and narasin are administered as medicated feed to broiler chickens for prevention of coccidiosis.
4. **Pharmacokinetics.** Ionophores are absorbed orally. Monensin absorption is 50% in ruminants. They are rapidly and extensively metabolized by the liver and the numerous metabolites are excreted by bile and eliminated in the feces. Absorption

is more complete and metabolism is slower in monogastric animals, especially horses, which may explain the greater toxicity in this species.

5. **Adverse effects.** Toxicity of ionophores when used in species for which they are approved is uncommon, unless mixing errors occur. Ionophore toxicity is due to cellular electrolyte imbalances, increased extracellular K^+, and intracellular Na^+ and Ca^{2+} concentrations, resulting in cellular damage and death. The increased intracellular Ca^{2+} concentration is due to the exchange of Na^+ for Ca^{2+} by Na^+–Ca^{2+} exchanger; this exchange is particularly prominent in cardiac and skeletal muscles and these are usually the most severely affected. Horses are the most susceptible species to toxic effects when accidentally exposed to ionophore-containing feeds.

XIV. ANTIFUNGAL AGENTS

A. Griseofulvin

1. **Chemistry.** Griseofulvin is a cyclohexane benzofuran antibiotic derived from Penicillium griseofulvin. It is insoluble in water.
2. **Mechanism of action.** Griseofulvin is actively taken up by growing dermatophytes (ringworm). It binds to microtubules to inhibit spindle formation and mitosis. It is fungistatic for dermatophytes such as *Microsporum* spp. and *Trichophyton* spp. Its action is slow as infected cells are shed and replaced with uninfected cells.
3. **Therapeutic uses.** Griseofulvin is used in dogs, cats, and horses for multifocal dermatophyte infections.
4. **Pharmacokinetics.** The GI absorption rate varies from 25–70%. The absorption is increased by high-fat foods and by preparations consisting of micronized particles. It distributes to keratin precursor cells of skin, hair shafts, and nails. It is metabolized by the liver by demethylation and glucuronide conjugation and excreted in urine. Griseofulvin's plasma $t_{1/2}$ in dogs is less than 6 hours, but is stored in the growing keratin cell producing skin, hair, and horn.
5. **Administration.** Griseofulvin is administered orally twice a day to dogs and cats and once daily to horses for 4–6 weeks.
6. **Adverse effects.** Untoward effects are rare. Leucopenia and anemia may occur as an idiosyncratic reaction in kittens.

B. Nystatin and Natamycin

1. **Chemistry.** Nystatin and natamycin are polyene antibiotics derived from *Streptomyces* spp.
2. **Mechanism of action.** Nystatin and natamycin are fungicidal to yeast infections caused by *Candida* spp. and *Malassezia* spp. They act by binding to erogsterol of the protoplast membrane of fungi to alter permeability and allow leakage of cell contents.
3. **Therapeutic uses.** Nystatin and natamycin are too toxic for parenteral use. They are administered topically for yeast infections of the eye, ear, and skin, and administered orally for treating mucosal yeast infections of the mouth and GI tract. Nystatin is used as a feed additive in poultry to prevent crop mycosis and mycotic diarrhea. Nystatin is a component of topical proprietary preparations such as Panalog®, which also include thiostrepton, a polypeptide antibiotic, and triamcinolone, a glucocorticoid.
4. **Pharmacokinetics. Nystatin is** not absorbed orally and is excreted in the feces.
5. **Administration.** Nystatin is administered orally every 6–8 hours for Candidal infections in dogs and cats. Natamycin is used topically primarily for ocular mycotic infections and is the drug of choice for treating fungal keratitis in horses.
6. **Adverse effects.** Adverse effects are rare since the drugs are not supposed to enter the systemic circulation. Occasional GI upset may be observed with high dose.

C. Azoles

1. **Chemistry.** Ketoconazole, itraconazole, and fluconazole are imidazole antifungals for systemic use. Other imidazoles used only topically for dermatophyte, *Aspergillus* or yeast infections include miconazole and clotrimazole.
2. **Mechanism of action.** The azoles inhibit the synthesis of ergosterol in fungal cytoplasmic membranes by blocking cytochrome P450 enzymes and increasing cellular permeability. At high doses, mammalian steroid synthesis (corticosteroids and sex steroids) is inhibited. Azoles are fungistatic for most pathogenic fungi causing systemic infections such as *Blastomyces*, *Coccidioides*, *Cryptococcus*, and *Histoplasma* spp. They are also effective against candidiasis and griseofulvin-resistant dermatophytes.
3. **Therapeutic uses.** Ketoconazole is used in dogs, cats, horses, and birds for systemic mycoses and for severe yeast infections. It is also used in dogs and cats at high dosage for the treatment of hyperadrenocorticism (see Chapter 12, III E 4 b). Fluconazole and itraconazole have replaced ketoconazole in most treatment regimens for the systemic mycoses because of their longer $t_{1/2}$, greater activity, and lower toxicity. Clotrimazole and miconazole are used topically in the treatment of *Candida*, *Aspergillus*, and dermatophyte infections.
4. **Pharmacokinetics**
   - **a.** Following oral administration, azoles are well absorbed in the presence of food that stimulates bile flow.
   - **b.** They are widely distributed, particularly in tissues high in lipid content; however, minimal amounts are found in cerebrospinal fluid (~10% of other tissue levels).
   - **c.** They are metabolized by microsomal enzymes of the liver and excreted in bile.
   - **d.** The $t_{1/2}$ of ketoconazole in dogs is 1–6 hours. In humans, fluconazole's plasma $t_{1/2}$ is ~30 hours and itraconazole's $t_{1/2}$ is 20–60 hours. Because of their long $t_{1/2}$, these two azoles do not reach steady state plasma levels for 6–14 days after beginning therapy, unless loading doses are given. **Patients with impaired renal function may have $t_{1/2}$ extended significantly and dosage adjustment may be required.**
5. **Administration.** Ketoconazole is administered orally twice a day for 3–6 months for systemic mycotic infections. Fluconazole and itraconazole are administered orally or IV once a day to dogs and cats for systemic mycoses for periods of 1–3 months, depending on the type of pathogenic fungi being treated. Clotrimazole and miconazole are applied topically for the treatment of yeast or dermatophyte infections or via nasal infusion for treating nasal aspergillosis.
6. **Adverse effects.** Anorexia, vomiting, and diarrhea may occur, especially in cats, treated with ketoconazole. Suppression of adrenal or gonadal steroids may also occur but the effects are transient at doses employed in antifungal therapy. Adverse effects are rare with fluconazole or itraconazole therapy, unless in patients with impaired renal function.

D. Amphotericin B

1. **Chemistry.** Amphotericin B is a polyene macrolide that is stabilized with sodium desoxycholate as a colloidal suspension.
2. **Mechanism of action.** Amphotericin B binds to ergosterol of fungal cell membranes to form pores or channels, which result in leakage of cell contents. It is fungicidal against most organisms causing systemic mycoses, including *Aspergillus*, *Blastomyces*, *Coccidioides*, *Cryptococcus*, and *Histoplasma* spp.
3. **Therapeutic uses.** Amphotericin B is used to treat systemic fungal infections in dogs, cats, horses, and birds. Combined therapy with ketoconazole, fluconazole, itraconazole (to reduce toxicity), or flucytosine (for CNS, bone, or ocular infections) is common.
4. **Pharmacokinetics.** Amphotericin B is not absorbed from the GI tract. After IV administration, it slowly distributes to most tissues except the CNS, eye, and bone. Elimination is biphasic with plasma $t_{1/2}$ of 24–48 hours and 1–2 weeks.

Approximately 65% of amphotericin B is excreted unchanged into urine (20%) and feces (45%).

5. **Administration.** Amphotericin B is diluted in 5% dextrose and administered IV. Treatment frequency and duration vary with the type of infection.
6. **Adverse effects.** Renal toxicity is a serious side effect. Amphotericin B produces renal vasoconstriction, decreased GFR, and damage to tubular epithelium. BUN must be monitored weekly during therapy.

E. Flucytosine

1. **Chemistry.** Flucytosine (5-FC) is a fluorinated pyrimidinethat is deaminated by fungi (not mammalian cells) to 5-fluorouracil, a potent antimetabolite.
2. **Mechanism of action.** Flucytosine inhibits thymidylate synthase and DNA and RNA synthesis in susceptible fungi. It is fungicidal against *Cryptococcus*, *Candida*, and *Aspergillus* spp.
3. **Therapeutic uses.** Flucytosine is combined with amphotericin B for synergistic action in the treatment of cryptococcosis (especially meningeal cryptococcosis) in dogs and cats. It is used alone in treating aspergillosis and candidiasis in psittacine birds.
4. **Pharmacokinetics.** Flucytosine is well absorbed orally and widely distributed, including the CNS. It is excreted unchanged in urine. The plasma $t_{1/2}$ in humans is 3–6 hours. No information is available for animals. The $t_{1/2}$ may be prolonged in patients with compromised renal function.
5. **Administration.** Flucytosine is administered orally 3–4 times a day for a minimum of 4 weeks.
6. **Adverse effects.** Toxicity is low. Mild GI disturbances and, more rarely, bone marrow suppression have been reported.

F. Terbinafine

1. **Chemistry.** Terbinafine is an allylamine derivative.
2. **Mechanism of action.** Terbinafine inhibits the synthesis of ergosterol—a component of fungal cell membranes. By blocking the enzyme squalene monooxygenase (squalene 2,3-epoxidase), terbinafine inhibits the conversion of squalene to sterols (especially ergosterol) and causes accumulation of squalene. Both these effects are thought to contribute to its antifungal action. Unlike azoles, **terbinafine does not block cytochrome P450 enzymes. It is fungicidal against dermatophytes and fungistatic against yeast.**
3. **Therapeutic uses.** When administered orally (30 mg/kg/day) or topically, terbinafine is useful for treating dermatophytic infections in dogs and cats. It is also useful for treating birds for systemic mycotic infections such as aspergillosis.
4. **Pharmacokinetics.** No information is available for animals. In humans, it is readily absorbed (>70%) when given orally. Since terbinafine is lipophilic, food may enhance GI absorption of the drug by increasing bile secretion. Terbinafine is distributed to skin and into the sebum. Over 99% of drug in the plasma is bound to albumin. Drug in the circulation is metabolized in the liver into demethylated, deaminated, and dealkylated conjugates, which are excreted into urine. The elimination $t_{1/2}$ is ~36 hours. The drug may persist in adipose tissue and skin for more than 30 days.
5. **Adverse effects.** Terbinafine appears to be well tolerated by animals.

XV. ANTIVIRAL AGENTS

A. Amantadine

1. **Chemistry.** Amantadine is 1-aminoadamantane.
2. **Mechanism of action.** When influenza viruses replicate within the host cell, a viral membrane protein known as M_2 forms an ion-channel for H^+ influx from the

endosome into the virion prior to fusion of the viral membrane with the endosomal membrane. Amantadine binds to M_2 protein and blocks its ion channel activity and thus inhibits viral uncoating and replication.

In addition to its antiviral activity, amantadine antagonizes the *N*-methyl-D-aspartate (NMDA) receptor in the CNS. NMDA receptors are important in pain sensation, especially chronic pain. Amantadine combined with other analgesics such as opiates or NSAIDs alleviates chronic pain.

3. **Therapeutic uses.** The primary use of amantadine in veterinary medicine is as an adjunct to NSAIDs for the treatment of chronic pain in dogs and cats. It is effective for treating some, but not all, influenza viruses. Because oral absorption in horses is variable, it has been used IV to treat equine-2 influenza but its potential for inducing seizures when administered by this route limits its use.
4. **Pharmacokinetics.** Given orally, ~50% of the dose of amantadine is absorbed in horses and high levels are attained in secretions. It is excreted unchanged by the kidneys. The elimination $t_{1/2}$ in horses is ~3.5 hours. The information for dogs and cats is not available.
5. **Administration.** As an adjunct to chronic pain therapy, amantadine is administered orally once a day to dogs and cats.
6. **Resistance.** Develops quite rapidly.
7. **Adverse effects.** Infrequently, the following signs are seen: agitation, loose stools, flatulence, or diarrhea, particularly early in therapy.

B. Acyclovir

1. **Chemistry.** Acyclovir is a guanosine derivative with selectivity for particular herpes viruses.
2. **Mechanism of action.** Acyclovir is metabolized to the monophosphate by thymidine kinase, which is more active in the virus than in the host cell. The host cell then converts the monophosphate to the triphosphate that inhibits the viral DNA polymerase, ending the nucleotide chain prematurely.
3. **Therapeutic uses.** Acyclovir is used to treat ocular and respiratory infections of herpes virus 1 of cats. Although acyclovir is active against equine herpes virus type-l in vitro, oral absorption is poor in horses and therapeutic levels are not attained
4. **Pharmacokinetics.** Acyclovir is poorly absorbed (~20%) after oral administration. It is widely distributed throughout body tissues and fluids, including the brain, semen, and CSF. It has low protein binding and crosses the placenta. Acyclovir is primarily metabolized by the liver and has a $t_{1/2}$ of ~3 hours in humans. No information is available for animals.
5. **Administration.** Acyclovir is administered orally twice a day to cats.
6. **Adverse effects.** Leucopenia and anemia may occur. These are reversible if therapy is discontinued.

C. Zidovudine (AZT)

1. **Chemistry.** Zidovudine is an analog of thymidine.
2. **Mechanism of action.** Zidovudine is phosphorylated by host cell enzymes to AZT 5′-triphosphate, which competes with host 5′-thymidine, which is essential for proviral DNA formation by reverse transcriptase of the virus. The incorporation of the 5′-triphosphate zidovudine into the viral DNA chain produces the termination of viral DNA synthesis. Mammalian α-DNA polymerase does not incorporate the zidovudine.
3. **Therapeutic uses.** Zidovudine may be used in cats to treat FIV infection where it produces temporary alleviation of the clinical signs and increase in quality of life and survival time in most cats, particularly when clinical signs of immunodeficiency are evident. It does not inhibit the viremia. Clinical improvement occurs 14 days after the start of treatment. Zidovudine is not effective against feline leukemia virus at nontoxic doses
4. **Pharmacokinetics.** Zidovudine is well absorbed orally and has a $t_{1/2}$ of ~2 hours in cats. It is metabolized in the liver by glucuronide conjugation and excreted in urine. $t_{1/2}$ may be extended in cats that have low levels of glucuronyl transferase.

TABLE 15-1. Websites for Antimicrobial Information

VIN	http://www.vin.com/
FDA—human	http://www.accessdata.fda.gov/scripts/cder/drugsatfda
Compendium veterinary product	http://www.bayerdvm.com/Resources/cvp_main.cfm?CFID=307632&CFTOKEN=61494892
Merck veterinary manual	http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/toc_191200.htm

5. **Administration.** Zidovudine is administered orally 2–3 times a day for a minimum of 4 weeks.
6. **Resistance.** Mutation of virus target sites may result rapidly and resistance to zidovudine is expected with long-term use.
7. **Adverse effects.** Anemia and reduction in hemoglobin are the most common side effects observed in cats. Diarrhea and weakness may also occur. Reduced dosage should be employed in cats with renal or hepatic insufficiency.

D. Cat omega interferon

1. **Chemistry. Interferons are cytokines**, proteins produced by host cells when they are attacked by viruses. Cat omega interferon is produced by genetic engineering and is a type 1 interferon closely related to alpha interferon. **It has a $t_{1/2}$ of 1–2 hours in dogs and cats.**
2. **Mechanism of action.** Interferon's mechanism of action is not a direct attack on the virus but by altering host cell metabolism to induce proteins that protect against viral invasion by several methods including destruction of mRNA and blockade of translational proteins resulting in the inhibition of viral replication.
3. **Therapeutic uses.** Feline omega interferon can be used to treat cat viral infections, including calci virus, FeLF, FIV, and other feline viral infections as well as canine parvovirus.
4. **Administration.** Interferons may be given SC or by other parenteral routes (depending on the virus to be treated) once a day.
5. **Adverse effects.** Transient anorexia and weight loss may occur in cats. Fever, myelotoxicity, and myalgia may develop with parenteral administration at higher dosages (Tables 15-1 and 15-2).

TABLE 15-2. Generic and Trade Names for Antimicrobial Drugs

Class	Generic Name	Trade Name
Penicillins		
Old penicillins		
	Penicillin G—benzylpenicillin	Many
	Penicillin V—Phenoxymenthyl Penicillin	Many
	Benzathine penicillin G	Many
	Procaine penicillin G	Many
	Penicillin G potassium	Many
Penicillinase resistant		
	Methicillin	Staphcillin®
	Nafcillin	Nafcillin®
	Oxacillin	Oxacillin®
	Cloxacillin	Orbenin®, Dry-Clox®
Aminopenicillins		
	Ampicillin	Polyflex®
	Amoxicillin	Amoxi-Tab®, Biomax®
Carboxypencillins		
	Carbenicillin	Geopen®, Geocillin®
	Ticarcillin	Ticar®
Ureidopenicillins		
	Piperacillin	Pipercil®
Potentiated penicillins		
	Amoxicillin-clavulanate	Clavamox®
	Ticarcillin-clavulanate	Timentin®
	Ampicillin-sulbactam	
Cephalosporins		
First generation		
Oral	Cefadroxil	Cefa-Drops®
Oral	Cephalexin	Keflex®
Parenteral	Cephaparin	
	Cefazolin	Ancef®, Kefzol®
Second generation		
Oral	Cefachlor	Ceclor®
Parenteral	Cefoxitin	
Third generation		
Parenteral	Ceftiofur	Naxcel®
Fourth generation		
Parenteral	Cefapime	Maxipime®
Carbapenems		
	Imipenem	Primaxin®
	Meropenem	Merrem®
Monobactams		
	Azetreonem	Azactam®
Polypeptids		
	Bacitracin	Many
Aminoglycosides		
	Streptomycin	Streptomycin Bulk®
	Neomycin	Neomix, Biosol®
	Kanamycin	Kantrim® Amforal®
	Amikacin	Amiglyde-V®
	Gentamicin	Gentavet®, Gentocin®

(*continued*)

TABLE 15-2. (*Continued*)

Class	Generic Name	Trade Name
Aminocyclitols		
	Spectinomycin	Adspec®
	Apramycin	Apralan®
Tetracyclines		
	Chlortetracycline	Aureomycin®
	Oxytetracycline	Terramycin®
	Tetracycline	Panmycin®
	Doxycycline	Doxyrobe®
	Minocycline	Minocin®
Macrolides		
14-molecule ring	Erythromycin	Galimycin®, Ery-Tab®
15-molecule ring	Azithromycin	Zithromax®
	Tulathromycin	Draxxin®
16-molecule ring	Tylosin	Tylan®
	Tilmicosin	Micotil®
Lincosamides		
	Lincosamides	Lincosin®
	Clindamycin	Antirobe®, Clinsol®
	Pirlimycin	Pirsue®
Amphenicols		
	Chloramphenicol	Chloromycetin®
	Florfenicol	Nuflor®
Streptogramins		
	Streptogramin A and B Virginiamycin M and A	Stafac®
	Dalfopristin and quinupristin	
Polymixins		
	Polymixin B	Aerosporin®
	Polymixin E	Colistin®
Mupirocins		
	Mupirocin	Bactroban®
Sulfonamides		
	Sulfamethoxazole + trimethoprim	Bactrim®, Septra®
	Sulfadiazine Sulfadimethoxine	Albon®
Diaminopyridazines		
	Trimethoprim + sulfadiazine	Tribrissen®
	Ormethoprim + sulfadimethoxine	
Methenamine		
	Methenamine	Hiprex®, Mandelamine®
Fluoroguinolones	Enrofloxacin	Baytril®
	Sarafloxacin	Saraflox®
	Difloxacin	Dicural®
	Orbifloxacin	Orbax®
	Marbofloxacin	Zeniquin®
Novobiocins		
	Novobiocin	Albamycin®
	Novobiocin + tetracycline	Albaplex®

(*continued*)

TABLE 15-2. (*Continued*)

Class	Generic Name	Trade Name
Nitroimidazoles		
	Metronidazole	Flagyl®
Nitrofurans		
	Nitrofurantoin	Furadantin®
	Furazolidone	Topazone®
	Nitrofurazone	NFZ Puffer®
Isoniazid		
	Isoniazid	Nidrazid®
Rifampin		
	Rifampin	RiFadin®
Pleuromutilins		
	Tiamulin	Denagard®
Glycopeptides		
	Vancomycin	Vancocin®
Ionophores		
	Monensin	Rumensin®
	Lasalocid	Bovatec®
	Narasin	Monteban®
	Salinomycin	Biocox®
	Laidlomycin	Cattlyst®
Antifungals		
	Griseofulvin	Fulcin®
	Flucytosine	5-FC®, Ancoban®
	amphotericin	Amphocin®, Fungizone®
	Terbinafine	Lamisil®
Azoles	Clotrimazole	Lotrimin®, Mycelex®
	Fluconazole	Diflucan®
	Itraconazole	Sporanox®
	Ketoconazole	Nizoral®
	Miconazole	Many
Topical Antifungals	Nystatin natamycin	Natacyn®, Mycostatin®

SUGGESTED READING

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