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CHAPTER 7

# Antiviral and Immunomodulatory Drugs

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## KEY POINTS

- Most antiviral drugs available for treatment of canine and feline viral infections are nucleoside analogues with greatest activity against herpesvirus and retrovirus infections.
- Because antiviral drugs also affect the function of host cell machinery, they have considerable potential for toxicity.
- Antiviral drugs are widely used in human medicine for treatment of herpesvirus, HIV and other viral infections. Much less is known about these medications in dogs and cats and there are few diseases of dogs and cats for which efficacy has been demonstrated.
- Because of important differences between human and animal virus infections, one should never assume that an antiviral agent used in people should be used in animals unless there is proof of safety and efficacy.
- Antiviral drugs used to treat feline herpesviral infections include famciclovir, idoxuridine, and cidofovir. Zidovudine is the only antiretroviral drug that has demonstrated efficacy for treatment of cats, primarily for FIV infections.
- Antiviral drugs can act synergistically with immunomodulators.
- Immunomodulators include microbial products, plant-derived immunomodulators, naturally occurring mammalian proteins, glucocorticoids, and synthetic compounds such as pentoxifylline and opioids. The effect of many of these drugs on outcome in dogs and cats with infectious diseases has not been fully evaluated using large, prospective, randomized, masked, controlled clinical trials.
- The parenteral use of natural or recombinant human protein immunomodulators in dogs and cats may result in the formation of neutralizing antibodies after 1 to 2 weeks of treatment, which can cross-react with endogenous proteins.

## INTRODUCTION

The purpose of this chapter is to describe the mechanisms of action, spectrum of activity, and adverse effects of the major antiviral and immunomodulatory drugs that have exhibited utility or have potential for treatment of companion animal infectious diseases. An enormous number of different compounds have been considered or evaluated in vitro and in vivo with variable success. Only those currently in use for treatment of dogs and cats with naturally occurring infections, those that show considerable promise for the future, or those evaluated in controlled clinical trials are discussed in this chapter.

### Antiviral Drugs

Antiviral agents interfere with virus-specific events in replication, including viral attachment, uncoating, assembly, and virus-directed macromolecular synthesis. As a result, antiviral agents typically have a restricted spectrum of activity. In contrast to most antibacterial drugs, antiviral drugs can also affect the function of host cell machinery and thus antiviral drugs have a greater risk of toxicity. In addition to acute toxicities such as marrow suppression, many antiviral agents are immunosuppressive, carcinogenic, and teratogenic. Many are given topically in order to minimize systemic toxicity. Antiviral agents are more likely to be effective when an intact host immune response is present. Combinations of antiviral drugs with different mechanisms of action and combinations of antiviral and immunomodulatory drugs are increasingly being used to treat human viral infections, especially HIV infection, with an associated decrease in toxicity and reduction in selection for drug-resistant mutants.

Although all antiviral drugs used to treat small animals were originally developed for treatment of human viral infections, the application of these drugs to treat viral infections of small animals has not proven straightforward. This relates to differences in the composition of human and companion animal viruses (which affect their susceptibility to inactivation by antiviral drugs), or problems relating to toxicity of human antiviral drugs in dogs and cats.

Antiviral drugs can be classified based on their spectrum of activity (i.e., family of viruses that are inhibited) and their mode of action. Antiviral drugs used in small animal medicine are primarily effective against herpesviruses or retroviruses, and most are *nucleoside analogues*. Nucleoside analogues resemble host nucleosides, which are nitrogenous bases with an attached sugar molecule used as a building block for the formation of DNA or RNA (Figure 7-1). Use of nucleoside analogues by viruses during replication leads to the formation of abnormal nucleic acids or termination of nucleic acid synthesis. Latent viral infections are not affected because the replication of latent virus is suspended. However, reactivation of these infections can be reduced in frequency or prevented. Examples of nucleoside analogues and their spectrum of activity are shown in Figure 7-1 and Table 7-1. Other antiviral drugs that have been used in clinical veterinary medicine include *amino acids* (L-lysine) and *neuraminidase inhibitors* (oseltamivir). The value of other treatments such as small inhibitory RNA molecules for viral infections of small animals is also under investigation.[1]

#### Antiherpesviral Drugs

The standard antiviral treatments for herpesviral infections in human patients are the nucleoside analogues acyclovir and

penciclovir, and their prodrugs valacyclovir and famciclovir, respectively. These drugs are activated by the herpesviral enzyme thymidine kinase (TK), which phosphorylates them to a monophosphate form. Host cell enzymes then phosphorylate the drugs further to triphosphate forms, which concentrate in virus-infected cells and interfere with viral DNA replication via inhibition of the viral DNA polymerase enzyme. Because the DNA polymerases of different herpesviruses are inhibited to varying degrees by acyclovir triphosphate, not all herpesviral infections are equally susceptible. Drug resistance results from reduced viral TK activity, altered viral TK, or altered viral DNA polymerase. The antiherpesviral drugs cidofovir, idoxuridine, trifluridine, and vidarabine are not dependent on viral TK for phosphorylation and so have greater host cell toxicity. In small animal medicine, these four drugs have been used topically to treat ocular feline herpesviral infections.

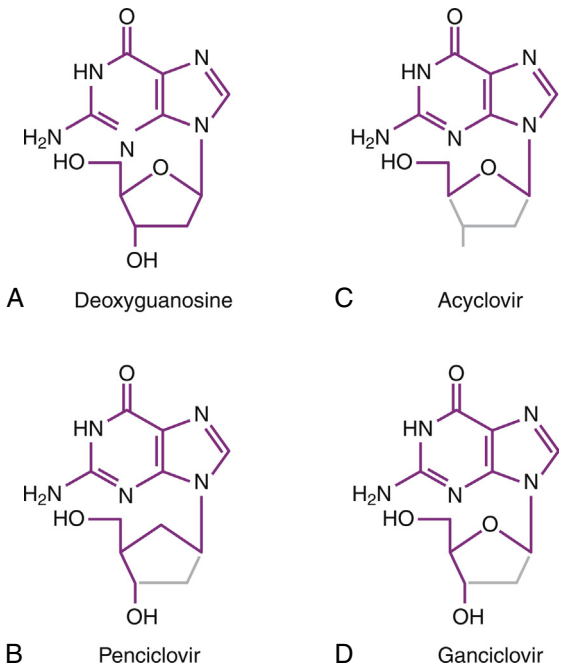


**FIGURE 7-1** Chemical structures of deoxyguanosine (a nucleoside) and antiherpesviral nucleoside analogues. the grey portion is missing in the nucleoside analogues. **A,** Deoxyguanosine. **B,** Acyclovir. **C,** Penciclovir. **D,** Ganciclovir.

### Acyclovir and Valacyclovir

Acyclovir is a synthetic analogue of the purine nucleoside deoxyguanosine (see Figure 7-1). In human patients, acyclovir is widely used to treat herpes simplex and varicella-zoster virus infections, both of which are α-herpesviruses. In small animal medicine, acyclovir has primarily been used to treat feline herpesvirus-1 (FHV-1) infections, although FHV-1 has a much lower susceptibility to the drug compared with the human herpesviruses.[2] Acyclovir has also been used to treat canine herpesvirus-1 (CHV-1) infections in puppies (see Chapter 16). Other nucleoside analogues (trifluridine, idoxuridine, cidofovir, ganciclovir, and penciclovir) show much greater activity than acyclovir against FHV-1 in vitro.[2-4]

Topical acyclovir has been used with limited success to treat feline herpetic dermatitis[5] and keratitis.[6] Topical treatment requires frequent (>4 times a day) application for beneficial effect.[6] The oral bioavailability of acyclovir is low in cats, and high doses are required to achieve adequate serum drug concentrations.[7] Valacyclovir, the prodrug for acyclovir, is rapidly converted to acyclovir by a first-pass effect after oral administration, and administration of the prodrug results in improved oral bioavailability of acyclovir. Unfortunately, administration of high doses of acyclovir or valacyclovir to cats has resulted in significant toxicity, including myelosuppression, renal tubular

**TABLE 7-1**

**Antiviral Drugs in Use in Small Animals**

| Antiviral Drug | Mechanism of Action | Human Applications | Small Animal Applications |
|---|---|---|---|
| Acyclovir/ valacyclovir | Guanosine analogue; interferes with viral DNA polymerase and DNA synthesis. Activity requires viral TK. | Herpesviruses, especially HSV and varicella-zoster virus | Poorly effective against FHV-1 |
| Penciclovir/ famciclovir | See acyclovir | Herpesviruses, especially HSV and varicella-zoster virus | FHV-1 infections |
| Cidofovir | Deoxycytidine monophosphate analogue. Activity independent of viral TK. | Systemically to treat cytomegalovirus retinitis; topically to treat papillomavirus infections | Topical treatment of FHV-1 ocular infections |
| Idoxuridine | Iodinated thymidine analogue. Interferes with viral DNA synthesis. | Topical treatment of HSV keratoconjunctivitis | Topical treatment of FHV-1 keratitis |
| Trifluridine | Fluorinated thymidine analogue. Interferes with viral DNA synthesis. | See idoxuridine | See idoxuridine |
| Vidarabine | Adenosine analogue. Interferes with viral DNA synthesis. | See idoxuridine | See idoxuridine |
| Zidovudine | Thymidine analogue. Interferes with viral DNA synthesis. | Systemic treatment of HIV infections | Systemic treatment of FIV and FeLV infections |

FHV-1, feline herpesvirus-1; HSV, herpes simplex virus; TK, thymidine kinase.

necrosis, and hepatic necrosis, without effective suppression of viral replication.[8] Thus the use of systemic acyclovir and valacyclovir to treat cats with herpesvirus infections is not recommended.

### Penciclovir and Famciclovir

Of all antiviral drugs used to treat small animal patients, penciclovir and famciclovir have shown the greatest promise. Penciclovir is another guanosine analogue (see Figure 7-1). It is present at much higher concentrations and for longer duration in cells than is acyclovir, which permits less frequent dosing. In humans, the prodrug famciclovir is well absorbed orally and rapidly converted to penciclovir, leading to increased oral bioavailability of penciclovir. Most of the drug is eliminated unchanged in the urine, and so dose reduction may be required for animals with decreased kidney function. In human patients, the concurrent administration of food decreases peak plasma concentrations without affecting overall bioavailability. In humans with herpes simplex virus and herpes zoster infections, famciclovir is as effective as acyclovir. In contrast, penciclovir (and thus famciclovir) have been shown to be potent inhibitors of FHV-1 replication (which is not the case for acyclovir). Penciclovir-resistant mutants of FHV-1 with altered TK enzymes have been described.[9]

Administration of famciclovir to cats at dosages comparable to those used in other species results in much lower plasma concentrations and a longer time to development of peak plasma concentrations of penciclovir when compared with other animal species, which suggests altered absorption or metabolism of famciclovir in cats.[10] High doses of famciclovir have been required to achieve adequate plasma drug concentrations. Nevertheless, famciclovir is well tolerated when administered orally to cats at doses that produce clinical responses.[5,10,11] Treatment of cats with experimentally induced FHV-1 conjunctivitis with famciclovir at 90 mg/kg PO q8h for 21 days resulted in lower clinical and pathologic disease scores and decreased viral shedding when compared with placebo-treated cats.[11] Clinical responses also occur in naturally infected cats with both acute and chronic manifestations of disease with negligible adverse effects.[5] Because of saturation of the metabolism of famciclovir to penciclovir, equivalent serum and tear penciclovir concentrations can be achieved in cats with 40 or 90 mg/kg PO q8h of famciclovir, so 40 mg/kg PO q8h is considered equally efficacious.[12,13] Clinical improvement often occurs within a week of treatment.

### Ganciclovir

Ganciclovir resembles acyclovir except that it has an additional hydroxymethyl group on its acyclic side chain (see Figure 7-1). In human patients, ganciclovir is widely used specifically for the treatment of human cytomegalovirus infections, which can be life threatening in the immunocompromised. Cytomegaloviruses are β-herpesviruses. Systemic administration of ganciclovir to human patients is associated with a high prevalence of adverse drug reactions, especially cytopenias and central nervous system (CNS) signs, and so the use of ganciclovir is limited to patients with life-threatening or sight-threatening infections. A topical ophthalmic gel formulation of ganciclovir (0.15%) is now available for treatment of keratitis caused by herpes simplex virus-1. Ganciclovir is highly inhibitory to FHV-1 replication in vitro.[4,14] Pharmacokinetic, safety, and efficacy studies in cats have not yet been performed, but topical ganciclovir holds promise for treatment of feline ocular herpesviral infections.

### Cidofovir

Cidofovir is a nucleotide analogue of deoxycytidine monophosphate. Because the drug already has a monophosphate group, its metabolism to the active diphosphate form by host cellular enzymes is not dependent on viral TK, and so it has been used to treat acyclovir- and penciclovir-resistant infections. In human patients, cidofovir is primarily used to treat cytomegalovirus retinitis. Cidofovir also has efficacy against other DNA virus infections, such as poxvirus and papillomavirus infections, and has been used topically as a cream to treat viral warts in people. Because the oral bioavailability of cidofovir is extremely low (<5%), it is always administered intravenously, intravitreally, or topically. Cidofovir has a prolonged intracellular half-life, which enables infrequent parenteral dosing regimens in human patients (once weekly, and then every other week for maintenance therapy).

Like ganciclovir, cidofovir is highly active in vitro against FHV-1.[4,14,15] Twice-daily administration of a 0.5% cidofovir ophthalmic solution significantly decreases viral shedding and the severity of clinical disease in cats with experimentally induced ocular FHV-1 infection (Table 7-2).[16] Local irritation and scarring of the nasolacrimal duct has been reported with topical administration of cidofovir to humans and rabbits with keratoconjunctivitis.

### Idoxuridine and Trifluridine

Idoxuridine and trifluridine are halogenated thymidine analogues that interfere with the replication of FHV-1 in vitro, although they are more potent inhibitors of herpes simplex virus replication.[2,14] They have been used to treat herpesviral keratitis in humans and in cats.[17] These drugs are highly toxic when given systemically, because host cell and viral DNA synthesis are equally affected. Frequent topical application is required (five to six times daily), and prolonged use can cause corneal irritation or ulceration. Trifluridine has better corneal penetration than idoxuridine and is available as a 1% ophthalmic solution. Unfortunately, trifluridine is expensive, and ocular administration of trifluridine is often extremely irritating to cats.[18] In contrast, topical idoxuridine administration is generally well tolerated.

### Vidarabine

Vidarabine is an adenosine analogue that is phosphorylated by host cellular enzymes to vidarabine triphosphate, which interferes with DNA synthesis by both the virus and host cells. It is effective against idoxuridine-resistant herpesviral strains because its mechanism of action differs from that of idoxuridine. It is reportedly well tolerated by cats when administered five to six times daily to cats as a 3% ophthalmic ointment.[18]

### Lysine

Lysine is an amino acid that interferes with herpesviral replication by a poorly understood mechanism. Antagonism of arginine may somehow be involved, because a high lysine-to-arginine ratio appears to be important for efficacy. However, arginine itself was also shown to interfere with the replication of herpes simplex virus in vitro.[19]

Lysine has shown efficacy when administered as tablets to cats with FHV-1 conjunctivitis[20] and, in another study, it reduced shedding of reactivated virus by latently infected cats.[21]

TABLE 7-2

**Antiviral Drugs Used for Treatment of Feline Herpesvirus Infections**

| Drug | Dose | Interval | Route | Comments |
|---|---|---|---|---|
| Famciclovir | 62.5 mg/cat, 125 mg/cat, or 40-90 mg/kg | q8h | PO | Reduce dose for cats with renal insufficiency. Compound suspensions are bitter and poorly tolerated. Broken tablets are best administered in a gel cap. Safe in kittens. |
| Cidofovir | 0.5% solution | q12h | Topical ophthalmic | Monitor for ocular irritation. Solution prepared from commercial 7.5% intravenous solution by dilution in sterile saline. Store diluted solution up to 6 months at 4°C, –20°C, and –80°C. Can also be obtained from compounding pharmacies. |
| Idoxuridine | 0.1% solution or 0.5% ointment | 5-6 times daily | Topical ophthalmic | Monitor for ocular irritation and ulceration. Compounding may be required. |
| Trifluridine | 1% solution | 5-6 times daily | Topical ophthalmic | May be poorly tolerated. |
| Vidarabine | 3% ointment | 5-6 times daily | Topical ophthalmic | Well tolerated. Compounding may be required. |
| Lysine | 250 mg (kittens)<br>500 mg (cats) | q12h | PO | Questionable efficacy. Bolus administration preferred to dietary supplementation. |
| Zidovudine | 5 to 15 | q12h | PO, SC | Monitor CBC weekly during treatment for the first month, then monthly. Use low end of the dose range in renal failure. Use higher dose with caution. |

When administered as tablets to cats in a shelter, there was no reduction in upper respiratory tract disease.[22] There was concern that the stress of tablet administration may have contributed to disease in these cats. However, in two other studies, dietary supplementation with lysine was not effective for management of upper respiratory tract disease in a shelter.[23,24] In fact, cats that received the lysine-supplemented diet had more severe disease and more frequent viral shedding than cats that received a non-supplemented ration, despite having increased plasma lysine concentrations. The lysine-supplemented diet did not affect plasma arginine concentration, so altered arginine levels did not appear to contribute to the increased severity of disease.

## Antiretroviral Drugs

All antiviral drugs used to treat cats with retrovirus infections have been nucleoside analogues, which inhibit the DNA polymerase function of the retroviral reverse transcriptase (RT) enzyme. Unfortunately, many drugs used for treatment of HIV infections (such as protease inhibitors) are not effective for treatment of feline retrovirus infections, because they only act on HIV enzymes. The only antiretroviral that has shown benefit in naturally infected cats is zidovudine (AZT). At the time of writing, an integrase inhibitor known as raltegravir has shown early promise for treatment of FeLV infections both in vitro and in vivo.[25,26] Many drugs that have activity against feline retroviruses in vitro, such as ribavirin and adefovir (PMEA), are toxic when given to cats, which limits their use in practice.

### Zidovudine and Fozivudine

Zidovudine (azidothymidine; AZT; Retrovir) is a thymidine analogue and was one of the first drugs shown to be effective against HIV. Inside host cells, it is converted to the active triphosphate form. AZT inhibits the replication of FIV, reduces plasma viral load, improves stomatitis, and increases CD4/CD8 ratios in cats naturally infected with FIV.[27,28] Some FIV isolates are resistant as a result of mutations in the RT enzyme. Although AZT is active against FeLV in vitro, when compared with FIV-infected cats, it has not performed as well for treatment of naturally infected, sick cats with chronic FeLV infection. Nevertheless, improvement in stomatitis, reduced antigenemia, and reduction in development of lymphoma have been reported in studies of naturally and experimentally FeLV-infected cats that were treated with AZT.[28,29]

AZT is available as a10 mg/mL syrup and a 10 mg/mL injection. It has good oral bioavailability and is well distributed to tissues, including the CNS. It is metabolized to an inactive form by the liver and excreted by the kidneys. Dosage reduction has been recommended for cats with renal failure. Unfortunately, some cats treated with AZT can develop dose-related hematologic adverse effects, most commonly nonregenerative anemia and neutropenia, so the CBC must be monitored during treatment. Adverse effects may be confused with retrovirus-induced cytopenias. In human patients with HIV infection, cytopenias are more likely to occur when disease is advanced.

Fozivudine is a thioether lipid-zidovudine conjugate that undergoes intracellular cleavage to zidovudine monophosphate and subsequent phosphorylation to the active triphosphate form. Cleavage preferentially occurs in lymphocytes and monocytes compared with RBC and marrow stem cells, and so hematologic toxicity is less likely to occur. Fozivudine reduces viremia in cats experimentally infected with FIV, without significant adverse effects.[30] Further study is required to evaluate this drug for treatment of chronic FIV and FeLV infections in cats.

### Lamivudine

Lamivudine (3TC), a cytidine analogue, is synergistic when combined with AZT for treatment of HIV infection, and the combination is in common use in human medicine. AZT/3TC prevented FIV infection when given to cats shortly after experimental inoculation, but did not appear to be beneficial for treatment of cats with chronic FIV infection.[31] In addition, severe hematologic adverse effects and fever occurred in some cats.

### Other Antiretroviral Drugs

Raltegravir inhibits the retroviral integrase enzyme. Integrase incorporates transcribed viral DNA into the host chromosome. In human patients, raltegravir is approved for treatment of HIV infections and is used in combination with other antiretroviral drugs. Although expensive, raltegravir has shown great promise for treatment of FeLV infections in vitro and also in vivo.[25,26] Other drugs that have shown promise in vitro for treatment of FeLV infections, with no evidence of toxicity to cell cultures, are the nucleoside analogues tenofovir, decitabine, and gemcitabine.[26] Tenofovir is used as part of combination therapy to treat HIV infections. It is administered as a prodrug. Decitabine and gemcitabine are cytidine analogues used in human patients to treat myelodysplastic syndromes and carcinomas, respectively. The use of combinations of gemcitabine and carboplatin to treat carcinomas in cats has been reported, but cytopenias and gastrointestinal toxicity occurred in some of the cats.[32]

Plerixafor is a bicyclam derivative that selectively blocks the chemokine receptor, CXCR4. This receptor is used by FIV to enter cells (see Chapter 21). In a placebo-controlled, masked clinical trial, administration of plerixafor to cats with FIV infection for 6 weeks reduced proviral load but did not lead to improvement in clinical or immunologic variables.[33]

## Antiinfluenza Viral Drugs

The main drugs used in human medicine to treat influenza virus infections are neuraminidase inhibitors, such as oseltamivir and zanamivir, and the tricyclic amines amantadine and rimantadine, which inhibit the M2 ion channel protein that is present in influenza A viruses (Figure 7-2). Only oseltamivir has been used to any great extent in small animals. Amantadine, which also has antagonistic effects at the NMDA (*N*-methyl-D-aspartate) receptor, has been used to treat osteoarthritis in animals in combination with other drugs.[34]

### Oseltamivir

Oseltamivir (Tamiflu) is the prodrug of oseltamivir carboxylate (GS4071), a potent inhibitor of influenza virus neuraminidase. Oseltamivir was developed because of the poor oral bioavailability of zanamivir, a neuraminidase inhibitor that is structurally similar to GS4071. Neuraminidase is a surface glycoprotein of both influenza A and influenza B viruses (see Figure 7-2). The viral neuraminidase cleaves sialic acid residues on the surface of infected cells, which allows new virus particles to be released from host cells. It also prevents aggregation of virus particles after they are released and facilitates spread of the virus through the mucus of the respiratory tract by cleaving sialic acid residues in mucin.

In humans and dogs, oseltamivir has high oral bioavailability.[35] Esterase enzymes in the liver then convert oseltamivir to its active form, which is well distributed to most body fluids, including surface epithelial cells throughout the upper and lower respiratory tract. Elimination of the drug relies on renal excretion. The drug is well tolerated in humans, with gastrointestinal signs being the most frequently reported adverse effects.

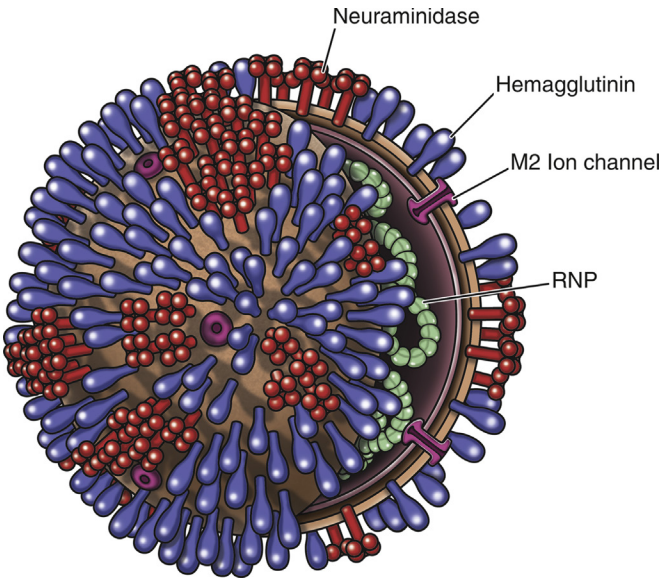


**FIGURE 7-2** Structure of an influenza virus. The M2 protein, which is only present in influenza A viruses, is inhibited by tricyclic amines such as amantadine. Oseltamivir inhibits the viral neuraminidase.

The prevalence of resistance to oseltamivir among influenza virus isolates is generally low (<5%). High-level resistance results from mutations in the viral neuraminidase. Neuraminidase inhibitors could play a critical role in prevention of mortality in human influenza virus pandemics, so strategies that minimize the selection of resistant mutants are important. The Centers for Disease Control and Prevention recommends prioritizing antiviral treatment to human patients at risk of complications of influenza, such as the very young and very old.[36]

Oseltamivir has been used to treat canine parvovirus (CPV) enteritis in puppies, with anecdotal reports of improved outcome. A single prospective, randomized, masked, placebo-controlled trial of 35 dogs with CPV enteritis showed that dogs treated with oseltamivir (2 mg/kg PO q12h) had no significant drop in their white blood cell count, whereas untreated dogs had a significant drop in their white blood cell count in the first 5 days of hospitalization.[37] Treated dogs also gained weight during hospitalization, whereas untreated dogs lost weight. However, there was no difference in hospitalization time, treatments needed, clinical scores, morbidity, or mortality between the two groups, and the number of dogs in each group was small. No significant adverse drug effects were observed, but oseltamivir was administered as a 1:1 dilution with water, in order to reduce reactions to the taste of the drug and vomiting shortly after drug administration. The authors acknowledged that there were potential concerns that related to administration of an oral medication to dogs with enteritis, with variability in drug absorption.

As CPV has no neuraminidase, it was hypothesized that oseltamivir instead may act on the neuraminidases of bacteria that are normally responsible for secondary bacterial infections in CPV enteritis, which are primarily those of the gastrointestinal tract. The role of bacterial neuraminidases in the pathogenesis of enteric bacterial infections and bacterial translocation is unknown. Bacterial neuraminidase enzymes may play a role in biofilm formation and help bacteria to invade mucin layers of the respiratory tract.[38] It has been suggested that gut bacteria

may use neuraminidase enzymes to cleave sialic acid residues on gastrointestinal epithelial cells, which exposes receptor sites for bacterial adherence.

A major concern that relates to treatment of CPV enteritis with oseltamivir is the possibility of selection for resistant mutants among influenza viruses if widespread use of the drug occurs in veterinary clinics. Given the restrictions on the use of this drug for treatment of human influenza virus infections, further investigation is required before the use of oseltamivir can be recommended for treatment of CPV enteritis.

### Other Antiviral Drugs

Although not useful for treatment of cats because of toxicity, the nucleoside analogue ribavirin has shown promise in vitro for treatment of canine distemper virus (CDV) infections. Another drug, 5-ethynyl-1-beta-D-ribofuranosylimidazole-4-carboxamide (EICAR), has also shown activity against CDV in vitro[39] and for treatment of measles virus, which is closely related to CDV.[40] Ribavirin is primarily used to treat hepatitis C virus infections in humans. The pharmacokinetics and toxicity of ribavirin and EICAR in dogs require further study.

Nelfinavir is a protease inhibitor used to treat HIV infection. It also limits the replication of severe acute respiratory syndrome (SARS) coronavirus in vitro,[41] but its mode of action against coronaviruses is poorly understood. Nelfinavir was not effective in a mouse model of SARS.[42] Although nelfinavir alone was not completely effective, a combination of nelfinavir and *Galanthus nivalis* agglutinin (GNA) inhibited the replication of feline coronavirus in vitro and may have application for the treatment of feline infectious peritonitis (FIP).[43] GNA appears to bind the viral outer envelope glycoproteins and prevent cellular entry. The use of nelfinavir was reported in a few cats with naturally occurring coronavirus infections,[43,44] but the toxicity and pharmacokinetics of nelfinavir and GMA in cats and efficacy of these drugs for treatment of FIP remains unknown.

## Immunomodulators

An immunomodulator is any drug that alters immune system function. Immunomodulators are also referred to as *biologic response modifiers*. Their use for treatment of infectious diseases may be beneficial when compromise of the immune system impairs effective antimicrobial drug treatment. Alternatively, immunomodulators can be used to dampen an excessive host inflammatory response.

A variety of immunomodulators have been used to treat feline retroviral infections, FIP, FHV-1 infections, and canine and feline parvoviral enteritis (Table 7-3). Immunomodulators used in veterinary medicine can be divided into six main groups: (1) microbial products; (2) plant-derived biologic response modifiers; (3) naturally occurring cytokines, such as colony-stimulating factors, and interferons; (4) immunoglobulins; (5) glucocorticoids; and (6) synthetic compounds with immunomodulatory activity, such as pentoxifylline.

Treatment of canine and feline viral infections with immunomodulators has frequently been associated with disappointing results, and data from large, prospective, controlled clinical trials are generally not available. Frequently, an immunomodulator shows antiviral activity in vitro but this does not correlate with treatment responses in vivo. Sometimes, mild to moderate clinical improvement is observed, but treatment does not result in cure. The use of human recombinant cytokines beyond 1 or 2 weeks of treatment has been associated with the development of antibodies against the cytokines, which have the potential to cross-react with endogenous cytokines. In the absence of data from randomized, placebo-controlled clinical trials to support their use, immunomodulators should be used with caution, because they may have the potential to accelerate disease. This may occur for viruses that are dependent on rapidly dividing cells for replication (such as parvovirus) or those that replicate only in activated lymphocytes (such as FIV). Promotion of an inflammatory response may also have detrimental effects if immune-mediated processes play an important role in the pathogenesis of disease (such as for FIP).

### Microbial Products

Microbial products with immunomodulatory activity include bacillus Calmette-Guérin extract (a mycobacterial cell wall extract from *Mycobacterium bovis*), purified staphylococcal protein A, killed *Propionibacterium acnes* (ImmunoRegulin, ImmunoVet), *Staphylococcus aureus* phage lysate (Staphage Lysate, Delmont Laboratories, USA), *Serratia marcescens* abstract, and inactivated poxviruses (Baypamun, Bayer). To date, controlled clinical trials with these products have not demonstrated significant efficacy for treatment of viral infections in dogs and cats. Staphylococcal phage lysate, which contains components of *S. aureus* and a bacteriophage, and *Propionibacterium acnes* immunotherapy have shown efficacy for treatment of pyoderma in dogs and are available commercially for this purpose (see Table 7-3; also see Chapter 84).[45]

### Plant-Derived Biologic Response Modifiers

*Acemannan* (Carrisyn, Carrington Laboratories, Irving, TX) is a mucopolysaccharide derived from aloe vera plant leaves that induces cytokine production and dendritic cell maturation. It stimulates macrophages to secrete a variety of cytokines, including IFN-γ, TNF-α, prostaglandin E2, Il-1, and Il-6. It has been used to treat FIV and FeLV infections, either by oral or parenteral administration,[46,47] and a veterinary product is available for treatment of canine and feline fibrosarcomas. Controlled trials are needed to understand the efficacy of this treatment in naturally infected cats.

*Polyprenyl immunostimulant* (Sass & Sass, Inc., Oakridge, TN) is a plant-derived investigational veterinary biological that is made up of phosphorylated, linear polyisoprenols. In vitro, it upregulates synthesis of Th1 cytokines and has antiviral properties. Cats with experimentally induced FHV-1 infection had a decreased severity and duration of upper respiratory tract signs when treated with polyprenyl immunostimulant, in comparison to placebo-treated cats.[47a] Long-term (>2 years) survival has been reported in a few cats with noneffusive FIP that were treated with polyprenyl immunostimulant. The response in cats with effusive FIP has been disappointing.[48]

### Naturally Occurring Mammalian Proteins

#### Colony-Stimulating Factors

Colony-stimulating factors (CSFs) are naturally occurring glycoproteins that stimulate production, differentiation, survival, and activation of white blood cells. Examples include erythropoietin; thrombopoietin; Il-5 (which stimulates eosinophil and basophil production); Il-3; stem cell factor; and macrophage CSF, granulocyte CSF (G-CSF), and granulocyte-macrophage CSF (GM-CSF). Recombinant G-CSF has been used most

TABLE 7-3

**Commercially Available Immunomodulators That May Have Benefit for Treatment of Infectious Diseases of Dogs and Cats**

| Drug | Dose | Interval | Species | Route | Comments |
|---|---|---|---|---|---|
| Acemannan | 2 mg/kg | Weekly | C | SC | For treatment of fibrosarcomas, efficacy unclear for FIV and FeLV infections |
| Feline recombinant interferon omega | 1 million U/kg | q24h for 5 consecutive days on days 0, 14, and 60 | C, D | SC | For FeLV infections |
| | 0.1 million U/kg | q24 | C | Oromucosal | For refractory caudal stomatitis associated with FCV infection |
| Filgrastim | 5 µg/kg | q24h | C, D | SC | Monitor CBC weekly during treatment. Long-term use (>2 weeks) can lead to development of neutralizing antibodies. |
| Lactoferrin | 200 mg powder or 40 mg/kg solution | q24h | C | Topical | For refractory gingivitis and stomatitis. Must be purchased from chemical suppliers |
| Lymphocyte T-cell immunomodulator | 1 mL | Weekly | C | SC | For treatment of FeLV and FIV infections |
| Human recombinant interferon alpha | $10^4$ to $10^6$ U/kg | q24h | C | SC | Monitor CBC weekly during parenteral treatment. Long-term parenteral use can lead to development of neutralizing antibodies |
| | 1 to 50 U/cat | q24h | | PO | |
| Pentoxifylline | 15 mg/kg | q8h | D | PO | Benefits for treatment of FIP unclear. Co-administration of cytochrome P450 inhibitors may increase serum drug concentrations |
| | ¼ of a 400 mg tablet | q8h | C | | |
| Polyprenyl immunostimulant | 3 mg/kg | Three times weekly | C | PO | Possible benefit for treatment of noneffusive FIP |
| Prednisolone | 1 to 2 mg/kg | q24h | C | PO | For FIP |
| *Propionibacterium acnes*, killed | 0.1 mg dogs <7 kg<br>0.2 mg 7-20 kg<br>0.4 mg 20-34 kg<br>0.8 mg > 34 kg | Twice weekly. After 14 d, weekly until remission, and monthly thereafter to maintain remission | D | IV | For pyoderma. Available as a 0.4 mg/mL solution |
| *Staphylococcus aureus* phage lysate | 0.5 mL | Once or twice weekly | D | SC | For pyoderma |

*C*, Cats; *D*, dogs.

widely in veterinary medicine as an immunomodulator. The use of these drugs may be limited by their cost and immunogenicity.

**Granulocyte colony-stimulating factor.** Granulocyte CSF stimulates growth and differentiation of the neutrophil cell line. It also stimulates neutrophil function, including chemotaxis, phagocytosis, antibody-dependent cellular cytotoxicity, and superoxide production. Nonglycosylated, recombinant human G-CSF is available under the trade name Neupogen. Pegfilgrastim (Neulasta) is a pegylated form with a long half-life and single-dose administration. Lenograstim is a glycosylated form available outside the United States. These three forms have similar efficacy and adverse effects in humans. G-CSF is approved for use in humans for treatment of chemotherapy-induced myelosuppression, for treatment of severe chronic neutropenia, for mobilization and collection of peripheral blood stem cells for bone marrow transplantation, and to accelerate myeloid reconstitution after hematopoietic stem cell transplantation.[49] G-CSF and GM-CSF have been used to treat pneumonia and severe sepsis in humans without neutropenia, but significant benefit has not been identified.[50,51]

When G-CSF is administered as a daily subcutaneous injection to dogs and cats, the neutrophil count increases over several days. This results from an enhanced rate of granulopoiesis and a shortened neutrophil maturation time. Slight increases in monocyte and lymphocyte counts can also occur.[52] Counts return to normal 5 days after discontinuation of treatment.

In veterinary medicine, filgrastim has been used to treat chemotherapy-induced neutropenia and cyclic neutropenia in gray collies. Filgrastim was not effective for treatment of leukopenia in experimentally induced CPV infection.[53,54] Repeated administration of filgrastim to dogs and cats has been associated with development of antibodies to the protein within 2 to 3 weeks of treatment, which can cross-react with endogenous G-CSF. Thus, although it can increase neutrophil counts in some FIV-infected cats, long-term use of filgrastim is not recommended.[55] Recombinant canine G-CSF (rcG-CSF) may be safer for long-term use in dogs, and possibly also cats. One recombinant canine formulation mobilized neutrophils in dogs within 24 hours of administration.[56] Recombinant canine G-CSF reduces the severity and duration of bone marrow suppression induced by cyclophosphamide in dogs.[57] In a prospective, non-randomized clinical trial for treatment of CPV infection, neutrophil counts were higher and hospital times were shorter in dogs treated with rcG-CSF, but survival times were decreased.[58] Treatment of canine and feline parvovirus infections with G-CSF might cause harm, because the increased cell turnover induced by the drug might promote parvovirus replication. Further studies are required to evaluate the utility of rcG-CSF for treatment of neutropenias associated with canine parvoviral enteritis, feline retrovirus infections, and chronic canine monocytic ehrlichiosis.

In dogs and cats, exogenous G-CSF is well tolerated. In human patients, the main adverse effects of treatment are bone and musculoskeletal pain, headache, anemia, thrombocytopenia, and splenomegaly. Long-term use in humans can be associated with osteopenia as a result of upregulation of osteoclast activity. Rare complications in people include splenic rupture and exacerbation of autoimmune disorders.

**Granulocyte-macrophage colony-stimulating factor.** GM-CSF stimulates growth and function of neutrophils, monocytes, and eosinophils. Commercial GM-CSF formulations available for treatment of hematologic disorders in human patients include sargramostim, molgramostim, and regramostim, which vary slightly in amino acid sequence and degree of glycosylation. When used to treat cats with FIV, viral load increased,[59] and so the use of GM-CSF is not recommended for treatment of FIV-induced cytopenias. Interestingly, sargramostim has been used to treat some human patients with AIDS-associated opportunistic infections, which include oropharyngeal candidiasis and disseminated mycobacterial infections. Administration of recombinant human GM-CSF to dogs was associated with antibody development after 10 days.[60]

## Interferons

Interferons are cytokines with antiviral properties. IFN-α, IFN-β, and IFN-ω are type I interferons, which are produced by leukocytes and fibroblasts in response to a viral infection. Type I interferons activate natural killer (NK) cells, increase expression of major histocompatibility complex (MHC) class I molecules, and have antitumor activity. IFN-γ is the only type II interferon and is produced by T lymphocytes and NK cells in response to antigenic stimulation. IFN-γ plays a critical role in the clearance of intracellular pathogens by macrophages. Recombinant human IFN-γ has been used to treat chronic granulomatous disease in humans as well as chronic infections caused by intracellular bacteria and fungi, but recombinant veterinary preparations are not available.

**Interferon alpha.** Naturally occurring IFN-α represents a group of more than 20 molecules that vary slightly in composition and inhibit viral nucleic acid and protein synthesis. A variety of recombinant human and natural IFN-α preparations are available, including pegylated forms that have prolonged biologic half-lives. In human patients, IFN-α is used in conjunction with antiviral drugs to treat hepatitis B and hepatitis C virus infections, papillomavirus infections, and HIV-associated Kaposi's sarcoma. It is generally administered for 24 or 48 weeks.

Recombinant human IFN-α (rhIFN-α) has been administered parenterally and orally to cats for treatment of feline retroviral infections, feline upper respiratory viral infections, and FIP. It inhibits replication of FeLV, FIV, FHV-1, and feline coronavirus in vitro. Unfortunately, mixed results have been obtained after parenteral and oral administration to cats with retrovirus infections, and parenteral IFN-α was not effective for treatment of FIP.[61] Parenteral administration can lead to the development of neutralizing antibodies and apparent loss of activity after 3 or 7 weeks.[62]

Oral administration of a low dose of rhIFN-α to treat viral infections of animals has been controversial because of proteolytic degradation of rhIFN-α by gastric acid. Nevertheless, beneficial outcomes have been reported in some cats with FHV-1, FeLV, and FIV infections, presumably because immunomodulation follows mucosal absorption of the drug. Topical application of rhIFN-α to the eye has been used to treat FHV-1 keratitis, but controlled studies using this treatment are lacking. With the availability of more effective antiviral drugs such as famciclovir, it is likely that the use of these antiviral drugs may take precedence over, or be used in combination with, treatment with IFN-α.

**Feline recombinant interferon-omega.** IFN-ω is a Type 1 interferon closely related to IFN-α. It is secreted by virus-infected leukocytes. Its precise mechanism of action is not known. In dogs it increases macrophage and NK cell activity, and it has antiviral activity against several feline viruses in vitro, including FeLV, FHV-1, feline calicivirus (FCV), canine and feline parvoviruses, and feline coronavirus. It also has antitumor activity.[63] A recombinant feline formulation of IFN-ω produced in silkworms is available in Europe and Canada for veterinary use (rfIFN-ω, Virbagen omega, Virbac). Because it has similar activity in canine and feline cells, it has potential for treatment of both canine and feline viral infections. The optimal dosing regimen is unknown, but the manufacturer recommends three cycles of treatment, on days 0, 14, and 60, for 5 consecutive days.

Preliminary data suggested that treatment of cats with FIP with rfIFN-ω might increase survival times,[64] but a randomized, placebo-controlled study of naturally infected cats demonstrated no improvement in quality of life or survival time.[65] When cats with naturally occurring FeLV-related disease were treated with rfIFN-ω in a placebo-controlled trial, survival time over a 2-month follow-up period increased.[66] Improvement in clinical scores and laboratory parameters was also documented in some sick cats that were naturally infected with FeLV and FIV, despite no significant changes in viral load.[67] The drug also has been used topically, orally, and parenterally to treat FHV-1 infections, and subcutaneously to treat refractory FCV-associated stomatitis.[68-71] Oromucosal administration of rfIFN-ω to cats with refractory FCV-associated stomatitis led to significant clinical improvement when compared with placebo.[68] Treatment of puppies with naturally and experimentally induced CPV enteritis with rfIFN-ω in a number of placebo-controlled trials was associated with reduced disease severity and, in some studies, significantly reduced mortality. In contrast, there was no improvement in survival in cats from a cattery with feline panleukopenia virus infection that were treated with rfIFN-ω when compared with an untreated control group.[72]

Recombinant fIFN-ω is well tolerated by dogs and cats. Transient lethargy, fever, vomiting, mild diarrhea, and anorexia have been documented in some treated cats, especially at higher doses ($2.5 \times 10^6$ U/kg). Mild neutropenia, eosinophilia, and reversible increases in the activity of serum AST have also been described following treatment.[73] Additional studies of the efficacy and safety of rfIFN-ω in larger numbers of sick cats with retroviral infections and cats and dogs with other viral infections are required.

### Lymphocyte T-cell Immunomodulator

Lymphocyte T-cell immunomodulator (T-cyte Therapeutics, Inc.) is a protein derived from thymus epithelial cells. According to the product brochure, LTCI upregulates Il-2 production in vitro and regulates CD4 T-cell function. It was also reported to stimulate platelet production in mice with chemotherapy-induced thrombocytopenia. LTCI has been conditionally approved by the U.S. Department of Agriculture as an aid for treatment of FIV and FeLV infections, and for the associated signs of cytopenias and opportunistic infections. Controlled independent studies of the efficacy of LTCI in cats are required.

### Immunoglobulins

In human patients, human intravenous immune globulin (IVIG) has been used for treatment of immunodeficiencies, as well as autoimmune disorders (Figure 7-3). A single infusion of human IVIG has been used successfully to treat immune-mediated thrombocytopenia in dogs,[74] but repeated administration to animals may lead to transfusion reactions. Intravenous immunoglobulin preparations have been commercially available for passive immunization of cats or dogs in Europe. These contain antibodies to FPV, FHV-1, and FCV (Feliserin, IDT Biologika GmbH, Rodelben, Germany), or CDV, canine adenovirus, and CPV (Stagloban, IDT Biologika GmbH). The efficacy of these preparations has not been reported. Subcutaneous and intraperitoneal administration of adult cat serum to kittens with failure of passive transfer can provide IgG concentrations equivalent to those in kittens that suckle normally.[75] In general, when given parenterally in high doses, specific immunoglobulins are only effective for prevention, and not treatment of an infectious disease.[76] Oral administration is not effective. Passive administration of antitoxins is also used to treat tetanus (see Chapter 54) and for neutralization of snake venom components. Passive immunization may be associated with allergic reactions, which can be severe, and it has the potential to interfere with subsequent active immunization attempts. Administered antibodies are generally eliminated over a period of 2 to 3 weeks.

### Lactoferrin

Bovine lactoferrin is a glycoprotein with immunomodulatory properties that is normally present in exocrine secretions and neutrophils. It reduces cytokine secretion by mononuclear cells and lymphocyte activation in cats infected with FIV. In vitro, bovine lactoferrin has antiviral activity against FCV and FHV-1.[77,78] Topical application (40 mg/kg q24h for 14 days) to the mouth of a small number of FIV-positive and FIV-negative cats with stomatitis was associated with improved appetite and reduced oral inflammation, salivation, and pain, and increased neutrophil phagocytic activity.[79] Chronic oral administration of bovine lactoferrin to a dog with $\beta_2$-integrin-related neutrophil dysfunction was associated with increased neutrophil function and recovery from opportunistic infections.[80]

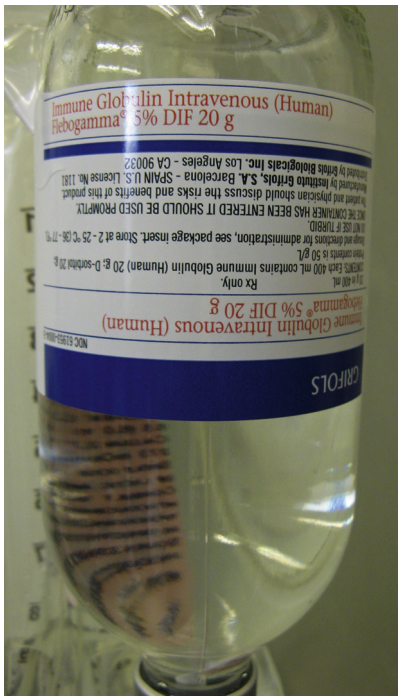


**FIGURE 7-3** Human intravenous immune globulin solution (inverted for administration).

## Glucocorticoids

In animals and humans with infectious diseases, treatment with glucocorticoids is sometimes used to dampen an overzealous immune response that contributes to the pathology of infection. Glucocorticoids have potent antiinflammatory and immunosuppressive properties. They suppress cytokine synthesis, decrease antibody production, cause lymphocytolysis and eosinopenia, decrease neutrophil margination, interfere with cyclooxygenase-2, and reduce the activity of phospholipase A2, and thus initiation of the arachidonic acid cascade. However, glucocorticoid administration also has the potential to worsen outcome through excessive immune suppression, so their use has been advocated only for specific infectious diseases under certain circumstances. Glucocorticoids can also contribute to development of secondary infections even when they are used to treat another disease. For example, it is not unusual in dogs or cats for a latent infection to emerge, or for a secondary infection to develop (e.g., demodicosis, staphylococcal pyoderma, dermatophytosis, systemic mycoses) when glucocorticoids are used to produce immunosuppression.

An example of the beneficial effect of glucocorticoids for treatment of an infectious disease is in FIP, where inflammation plays a major role in pathogenesis. Although controlled clinical trials comparing prednisone treatment with a placebo have not been performed, for many cats, treatment with prednisolone (1 to 2 mg/kg PO q24h) is associated with transient complete or partial remission and as a result is generally accepted as the standard of care for treatment of FIP (see Chapter 20).[65]

A short course of prednisolone using immunosuppressive doses (1 mg/kg PO q12h) has also been used to suppress secondary immune-mediated hemolysis in cats infected with *Mycoplasma haemofelis*,[81] but given that glucocorticoids can reactivate hemoplasma infections, additional studies are needed to determine whether this practice improves outcome. Similarly, glucocorticoid treatment has been used to suppress

immune-mediated consequences of infection with the tick-borne pathogens *Ehrlichia canis* and *Babesia* spp, when antimicrobial treatment alone is not followed by complete resolution of clinical abnormalities. Adjunctive glucocorticoid treatment did not worsen outcome in dogs with Rocky Mountain spotted fever.[82] In contrast, glucocorticoid administration may have a negative impact in dogs with Lyme arthritis.[83] There are anecdotal reports of improved outcome for dogs with suspected Lyme glomerulonephritis that are treated with methylprednisolone sodium succinate in conjunction with other immunosuppressive drugs, such as mycophenolate mofetil or azathioprine (see Chapter 51).

Many large human studies have assessed the role of glucocorticoid treatment in septic shock (see Chapter 86). Treatment with high doses of hydrocortisone for less than 5 days is contraindicated because of secondary infection and gastrointestinal bleeding. Treatment with physiologic doses of glucocorticoids has been advocated to overcome relative adrenal insufficiency, which occurs in severe septic shock in both humans and dogs.[84] Recent consensus guidelines for human patients with septic shock recommend adjunctive hydrocortisone treatment in patients who are unresponsive to fluid resuscitation and treatment with vasopressors.[85]

Infections that generate inflammation within the eye and CNS are frequently treated with anti-inflammatory doses of topical or systemic glucocorticoids, respectively, in conjunction with antimicrobial drugs. The goal of such treatment is to minimize or prevent loss of vision or deterioration of neurologic status, especially when organism death is followed by a profound inflammatory response. For CNS infections, the effect of concurrent glucocorticoid treatment may depend on the specific pathogen present and the immune response of the infected individual. Prospective studies that evaluate outcome after adjunctive glucocorticoid treatment in CNS infections of dogs and cats are lacking. In a retrospective study, treatment of dogs and cats with CNS cryptococcosis with antiinflammatory doses of glucocorticoids increased survival in the first 15 days after starting antifungal drug treatment.[86]

## Other

### Pentoxifylline

Pentoxifylline is a synthetic methylxanthine derived from theobromine. It is a broad-spectrum phosphodiesterase inhibitor with a variety of immunomodulatory properties. In rodents and humans it inhibits TNF-α, Il-1, Il-6, and Il-12 production, as well as the activation of T and B cells, and increases neutrophil mobility and chemotaxis. It increases erythrocyte cAMP levels, which results in increased erythrocyte deformability, lowered blood viscosity, and improved microcirculation and tissue perfusion. Pentoxifylline also decreases platelet aggregation, and increases tissue plasminogen activator in patients with hyperaggregable platelets, so may be useful for treatment of disorders that result in hypercoagulable states. The value of pentoxifylline for treatment of endotoxemia has been primarily studied in horses. Despite significant decreases in TNF and IL-6 activity after incubation of equine monocytes with pentoxifylline in vitro, these effects did not occur in horses in vivo.[87] Beneficial effects of pentoxifylline are limited in horses when administered IV after challenge with endotoxin.[88]

In dogs, pentoxifylline has been used to treat a variety of skin diseases, including canine atopic dermatitis, dermatomyositis, and cutaneous vasculopathies.[89,90] In cats it has been used to treat FIP, but a masked, placebo-controlled study of the related drug propentofylline showed no benefit of treatment.[91]

In dogs, pentoxifylline has a low and unpredictable oral bioavailability and a short half-life, and so three-times-daily administration has been recommended. Adverse effects include vomiting and decreased appetite, which are more likely to occur when the tablets are crushed. Crushed tablets are also unpalatable to cats.

### Antimicrobial Drugs with Immunomodulatory Properties

Antimicrobial drugs with immunomodulatory properties include the macrolides, doxycycline, and metronidazole. The mechanisms of these activities are discussed in Chapter 8.

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