INTRODUCTION
As a species, cats are frequently afflicted with immunosuppressive states that put them at risk for serious infections. The retroviruses feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are the most common causes of immunosuppression in the cat.\textsuperscript{21,22} Neutropenia, a specific deficiency of the immune system, can result from a variety of causes. These include primary diseases such as panleukopenia virus and complications of disease treatment, such as that caused by chemotherapy. Immunodeficiency states of newborn kittens are believed to contribute to neonatal sepsis, a leading cause of death in kittens. Inherited and congenital defects in the immune system occur in cats, but these appear to be much less common than in the dog.

Regardless of the cause of immunosuppression, certain clinical principles apply to the treatment of all affected cats. An effort should be made to diagnose the precise cause of immune dysfunction, so that the most appropriate treatment can be given. Special effort should be made to protect immunosuppressed cats from infection, whether it be by isolation and increased hygiene for hospitalized cats or by recommending a low-risk lifestyle at home. This paper will focus on the specific treatment of the most common states of immunosuppression in the cat.

HEREDITARY AND CONGENITAL IMMUNODEFICIENCIES
Hereditary and congenital immunodeficiencies are less common in the cat than in the dog.\textsuperscript{9} Thymic aplasia accompanied by hypotrichosis resembling the nude condition in mice has been reported to occur as an autosomal recessive defect in a family of Birman kittens.\textsuperscript{9} Thymic and lymphoid atrophy have been observed in Ragdoll kittens and also appears in mixed breed kittens. Thymic aplasia or atrophy is typically associated with neonatal deaths or fading syndromes resulting in kitten losses.\textsuperscript{9} Thymic atrophy can occur as a result of systemic sepsis or viral infection, so it is not always possible to determine whether the condition is due to primary immunodeficiency or is secondary to overwhelming infection.

Several inherited defects of neutrophils have been reported in cats, but most are limited to morphologic rather than functional defects. A granulation defect of neutrophils is widespread in Birman cats and is transmitted as an autosomal recessive trait. Although the neutrophils appear toxic, the syndrome is not associated with any defects in neutrophil number or function. The Pelger-Huet anomaly has been observed in mixed breed cats, in which granulocytes are hyposegmented, resembling immature band forms. Although the leukogram appears to have a degenerate left-shift in affected cats, the condition is benign and is not associated with increased risk of infection. The anomaly is transmitted as an autosomal dominant trait, and homozygote fetuses are often lost in utero. A third inherited abnormality of neutrophil morphology is the cytoplasmic granulation found in neutrophils of Siamese cats with the lysosomal storage disease mucopolysaccharidosis type VI. Similar to the granulation defect in Birman cats, neutrophils in MPS VI appear toxic, but are not associated with infection. MPS VI is transmitted as an autosomal recessive defect and is associated with characteristic abnormalities in the shape of ears and head, skeletal defects, and progressive paresis. Chediak-Higashi syndrome is an autosomal recessive syndrome reported in Persian cats that is associated with pigmentary defects resulting in a diluted smoke coat color, yellow-green irises, photophobia, and large eosinophilic cytoplasmic granules in leukocytes. Although most cats do not appear to be clinically affected, neutropenia and depressed neutrophil function have been associated with the syndrome.\textsuperscript{30}

FAILURE OF PASSIVE TRANSFER
Neonatal kittens are dependent upon passive transfer of maternal antibodies for protection against infectious diseases during the first weeks of life. In the cat, 95% of antibodies are acquired postnatally via ingestion of colostrum on the day of birth.\textsuperscript{4} Sepsis is a well-recognized cause of neonatal morbidity and mortality in kittens.\textsuperscript{17} In large animal species, failure of passive transfer (FPT) is strongly correlated with risk of sepsis, and serum IgG concentration is the best predictor of outcome. Surprisingly, although infection is a common cause of morbidity and mortality in kittens from birth to weaning, studies of the correlation between susceptibility to infection and FPT in kittens have not been published. Kittens at risk for FPT include those that are orphaned or rejected before nursing, kittens from very large litters, small or weak kittens,
Neutrophils play a critical role in the prevention and control of infections, especially bacterial invaders. Neutrophils are a primary component of the innate, nonspecific immune response and are activated immediately upon pathogen exposure. A decrease in circulating neutrophil number below 2000/µl is associated with an increased risk of bacterial infection, commonly from organisms that are normal inhabitants of the skin, respiratory tract, and gastrointestinal tract. Neutropenia can be caused by inadequate production of neutrophils in the bone marrow, increased rate of consumption in sites of infection, or destruction in immune-mediated reactions.

Neutropenia in cats is frequently a consequence of viral infection, especially FeLV, FIV, or panleukopenia virus, which can both decrease the production and increase the consumption of neutrophils. Primary bone marrow disease such as myelodysplastic and myeloproliferative diseases may suppress production of neutrophils from the bone marrow. Overwhelming demand due to sepsis may increase consumption of neutrophils, and other infections, such as toxoplasmosis, histoplasmosis, cytauxoonosis, and cryptococcosis are occasionally reported to be associated with neutropenia in cats. Neutropenia is a well-described dose-limiting reaction to many commonly used chemotherapeutic drugs in cats. Uncommon idiosyncratic reactions to certain drugs, such as chloramphenicol, can suppress bone marrow activity in cats, leading to neutropenia. Severe neutropenia has also been reported to occur in FIV-infected cats treated with griseofulvin, so this drug is contraindicated in cats with FIV. Immune-mediated reactions to drugs or vaccines and unknown causes may also result in severe neutropenia, but these appear to be rare in cats. Neutropenia in cats is less common than in dogs, primarily due to the high rate of parvovirus-associated neutropenia in dogs. In one report, the most common cause of neutropenia in cats was FeLV or FIV infection, followed by primary bone marrow diseases and myelodysplasia. A cause of the neutropenia was not determined in almost half of the cases.

Best outcomes are expected when the underlying cause of the neutropenia can be identified and corrected. Neutropenia secondary to chemotherapy is managed by withholding further treatment until the neutrophil count has recovered. Patients with previous adverse reactions to chemotherapy may be treated by alternate drugs or by reducing the dose or frequency of administration. Corticosteroid therapy is usually contraindicated for cats that are immunosuppressed due to neutropenia, but in certain instances, such as the treatment of immune-mediated reactions, lymphosarcoma, and some FeLV-related conditions, judicious use of corticosteroids may improve neutrophil counts. Overwhelming bacterial infections are treated aggressively with appropriate antibiotics and surgical debridement if indicated, but the use of antibiotics in asymptomatic neutropenic cats is controversial. There is no evidence that prophylactic antibiotic therapy prevents serious infections. It is possible that overzealous use of antibiotics may disrupt the normal flora inhabiting the skin, respiratory tract, and gastrointestinal tract, leading to invasion of more resistant and dangerous organisms. Antibiotics are clearly indicated for febrile neutropenic cats, or cats that have other signs of infection. Ideally, cultures of blood, urine, or other sites would be obtained prior to initiating antibiotic therapy, but that is not always practical. Antibiotics should be selected for broad spectrum and bactericidal activity. Neutrophils survive only a few hours in circulation, so it is not feasible to treat neutropenia by blood transfusion.

Granulocyte colony stimulating factor (G-CSF) is a cytokine required for the differentiation of mature neutrophils from bone marrow progenitor cells. G-CSF also enhances the function of circulating mature neutrophils. Recombinant human G-CSF (rhG-CSF) is commercially available and has been shown to induce a rapid increase in neutrophil counts in both normal and neutropenic cats. Despite a high degree of homology between human and feline G-CSF sequences, there is enough difference that normal cats recognize the human preparation as foreign and produce antibodies against it after 17–21 days of continuous administration. This limits the duration that rhG-CSF can be used in cats. There is some
withheld from 24 hours prior to 24 hours following the administration of chemotherapy. Alternatively, G-CSF can be
administered only when significant neutropenia develops. One published protocol suggests the use of G-CSF during
febrile neutropenia (< 500/µl for more than 3 days), or a history of febrile neutropenia following previous chemotherapy. A dose of 5 µg/kg is administered subcutaneously once daily until the neutrophil count exceeds 3000/µl for 2 days.15

G-CSF has also been used to treat neutropenia associated with infectious diseases in humans.14,39 Conflicting reports exist about the efficacy of using G-CSF for both canine and feline parvoviral (feline panleukopenia virus) neutropenia, but most of the evidence suggests that there is not a significant response.31 Feline parvovirus was shown to block the stimulatory effect of G-CSF on bone marrow cultures, providing further evidence that parvoviral infection induces a neutropenia that is resistant to G-CSF therapy.20

There is a theoretical basis for the use of G-CSF in septic patients, regardless of whether neutropenia is present. Experimental studies in animals and observational studies in human patients suggest that G-CSF improves both number and function of neutrophils in the presence of infection.10 rhG-CSF was shown to reduce bacteremia and endotoxin levels in dogs with experimental sepsis. Despite the theoretical benefits, there is no published information on the use of G-CSF in cats with bacterial infections, so its use would be considered speculative at this time.

Multiple studies of human patients with HIV-related neutropenia report improved neutrophil number, neutrophil function, and clinical outcomes when G-CSF was administered.1,19,26,28,29 HIV shares many of the same immune deficiencies HIV, including chronic neutropenia and neutrophil dysfunction. Although the use of G-CSF in retrovirus-infected cats has not been reported, in the author’s experience, some cats with neutropenia associated with FeLV or FIV infection respond favorably to rhG-CSF administration.

RETROVIRAL INFECTION
Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are present worldwide and are among the most common infectious diseases of cats. The individual response to infection with either retrovirus is so varied as to make predictions about the course of disease in individual cats impossible. Host factors such as the age of the cat at the time of infection, genetic variables, immune function, and concurrent diseases are as important as viral factors such as strain, dose, and route of infection in determining the clinical outcome.

Both viruses have been shown to induce multiple defects in immune function of both the humoral and cell mediated immune systems.21,22 Although immune dysfunction is believed to underlie many of the clinical problems that develop in infected cats, blood dyscrasias, neoplasia, and chronic inflammatory conditions are more common than overt secondary infections.6 Following FIV infection, most cats experience a prolonged asymptomatic period (years) following seroconversion. The most common disease syndromes diagnosed in these FIV+ cats were stomatitis, neoplasia (especially lymphoma and cutaneous squamous cell carcinoma), ocular inflammation (uveitis and chorioretinitis), anemia or leukopenia, opportunistic infections, renal insufficiency, and lower urinary tract disease.6,22 Although FeLV-infected cats may also experience a period of good health, it is often shorter (a few months to a few years) than for FIV-infected cats. The most common diseases associated with FeLV infection were anemia, lymphoma, upper respiratory infections, myeloproliferative diseases, hemobartonellosis, and stomatitis.6,21

The first concern for the care of asymptomatic retrovirus-infected cats is to promote a healthy lifestyle. Keeping such cats indoors reduces both the risk of spreading the infection to other cats and of exposing the infected cats to the infectious and traumatic risks of outdoor life. A healthy diet (avoiding raw foods), stress-free lifestyle, and regular veterinary examinations help prevent the development of disease and aid early detection of problems that do occur. Routine vaccination according to the guidelines of the American Association of Feline Practitioners is generally recommended, but the use of killed vaccines may be preferred.

Despite a positive test result, it is important to understand that these patients are often capable of responding to treatment as well as negative cats. Not all diseases in FeLV or FIV positive cats are related to the virus infection. The essential aspect of treating sick FeLV+ or FIV+ cats is diagnosing the precise cause of illness. In many cases, the illness is not virus-related, and treatment should mirror what is offered to cats that are free of viral infection. In other cases, the disease is related to the viral infection, but is still treatable. For example, anemia is the most common problem affecting
FeLV+ cats. Primary bone marrow suppression due to certain strains of FeLV carries a poor prognosis for recovery, whereas anemia due to hemobartonellosis carries an excellent prognosis. Determining the cause of anemia may require a complete blood count, reticulocyte count, coagulation tests, bone marrow examination, or other diagnostics. Primary virus-associated anemia in FeLV+ cats generally does not respond to erythropoietin treatment, whereas anemia in FIV+ cats often does.

In addition to anemia, other diseases commonly affecting both FeLV+ and FIV+ cats include lymphoma and stomatitis. FIV-associated lymphomas are unique in that most are B cell tumors, compared to the predominance of T cell tumors in FeLV+ cats and cats that have neither virus. The location of lymphoid malignancies is also unique for FIV, and many are found in extranodal sites such as the eye, nasal cavity, and kidney. Chemotherapy usually induces a rapid and complete remission in both FeLV+ and FIV+ cats, and these remissions may last as long as those achieved in virus-free cats with lymphoma.21,22

Ulceroproliferative stomatitis is one of the most frequently encountered conditions in cats with long-term FIV and FeLV infection. Concurrent calicivirus infection is often identified in the oral cavity of cats with FIV or FeLV associated stomatitis and may be an important infectious co-factor. The proliferative mucosal lesions characteristically originate in the faucae and progress rostrally, especially along the maxilla. The lesions are usually painful and infected, and tooth loss is common. Histologically, the mucosa is invaded by plasma cells and lymphocytes, with variable degrees of neutrophilic and eosinophilic inflammation. Although the etiology of the syndrome is uncertain, the histologic findings suggest chronic antigenic stimulation or immune dysregulation. Palliation is often possible with dental cleaning, antibiotics, or corticosteroids, but these treatments rarely resolve the lesions or prevent further tooth loss. The most effective treatment is extraction of the molars and premolars, paying careful attention to removal of all of the roots. In almost all cases of stomatitis in these cats, long-term resolution of inflammation is achieved, and cats return to eating a normal diet, including kibble. When lesions persist or recur, dental radiographs should be made to rule out incompletely removed root fragments. In some cats, complete resolution requires the removal of the canines and incisors as well.22

Immunomodulating drugs are the most widely used medications in FeLV and FIV infected cats. Immunomodulators are suggested to benefit retrovirus-infected cats by restoring compromised immune function, thereby allowing the patient to control viral burden and recover from associated clinical syndromes.38 In contrast, antiviral drugs, such as AZT, target the virus directly.12 Unfortunately, neither immunomodulators nor antiviral drugs have received thorough evaluation in multiple large controlled studies of naturally infected cats. Most of the reports that do appear in the veterinary literature are difficult to interpret due to unclear diagnostic criteria, lack of clinical staging or follow-up, the natural variability of the course of disease, the lack of placebo control groups, small numbers of cats used, and additional supportive treatments given. In one of the few controlled studies reported on immunomodulating drugs, FeLV+ cats treated with interferon alpha, *Staphylococcus* protein A, or both failed to show any objective improvements compared with cats treated by placebo.36

Acemannan (Carrisyn, Carrington Laboratories) is a complex carbohydrate (mannan) polymer derived from the aloe vera plant. In one uncontrolled open-label trial, 50 cats with natural FeLV infection were treated with acemannan (2 mg/kg IP q week x 6 weeks). Whether concurrent supportive care was permitted was not described. Of the remaining 41 cats that completed the 12-week study, 29 (71%) were known to be alive. All cats remained ELISA-positive for FeLV antigen, and there was no significant change in clinical or hematologic scores from baseline.33 In another uncontrolled open-label study, 49 naturally FIV-infected cats were treated with acemannan (2 mg/kg IV or SQ q week x 12 weeks, then monthly, or 100 mg PO q 24 hour). Concurrent supportive care with antibiotics and fluids was permitted. Survival was 82% at 12 weeks and 64% at one year. There was no change in clinical score from baseline, but the cats experienced an increase in median lymphocyte count, and a decrease in median PCV and neutrophil counts. The administration of acemannan by IV bolus was associated with acute collapse in some cats.40 Because neither study included a control group, and because clinical and laboratory evaluations failed to document improvement from pretreatment evaluations, it is difficult to determine whether the use of acemannan improved the outcome of infection in these cats. The survival rates reported for treated cats are commonly observed without the use of immunomodulators, so it is possible that the cats were responding to supportive care or simply would have survived without medical care at all.

*Propionibacterium acnes* (ImmunoRegulin, ImmunoVet) is a killed bacterial product. No prospective studies have been reported on its in retrovirus-infected cats, but practitioners have described their clinical experience in published round-table discussions and in anecdotal reports. In one discussion, a practitioner reported having treated 76 clinically ill cats with FeLV infections with ImmunoRegulin (0.25–0.5 ml IV twice weekly, then every other week for 16 weeks) and supportive care including prednisone, antibiotics, and vitamins. Although no specific clinical and laboratory evaluations were discussed, the practitioner reported that 55 (72%) of the cats became seronegative for FeLV. In another discussion, a veterinarian recalled treating 700 FeLV-infected cats with ImmunoRegulin (0.5 ml IV q 3 days, then q week for 6+ weeks) in conjunction with antibiotics, fluids, and other supportive care. He estimated that 50% of cats improved, although seroconversion to negative was rare.24
Staphylococcus protein A (SPA, Sigma) is a bacterial polypeptide product purified from the cell wall of Staphylococcus aureus Cowan I. A variety of SPA sources and treatments have been used in FeLV-infected cats. Interest was first generated when plasma from FeLV-infected lymphosarcoma-bearing cats was passed over SPA or S. aureus columns to remove circulating immune complexes and then returned to the cats. More than 100 cats were treated in this manner, generally undergoing twice weekly treatments for 10–20 weeks. In some studies, a high rate of tumor remission and conversion to FeLV-negative status was observed, while in others, responses were less dramatic and short-lived.

Subsequently, it was determined that SPA and other products may have leached from the filters and columns used for immunosorption and been returned to the cats as contaminants in the plasma. The possibility that these products exerted a positive immunomodulatory effect caused investigators to treat cats with small doses of SPA. Again, the lack of placebo-treated controls in any of these reports makes it difficult to determine the true effect of SPA therapy.

PIND-ORF (Baypamun, Bayer) is derived from an inactivated parapox ovis virus and is proposed to induce nonspecific or “para” immunity. Following reports of eliminating disease and viral infection from hundreds of FeLV+ cats, quickly became the most commonly used treatment for FeLV infections in Europe. In the only double blind, placebo-controlled clinical trials of an immunomodulator reported to date, more than one hundred FeLV+ cats were randomized to receive Baypamun (1.0 ml SQ twice in one week, then q week x 6 weeks) or placebo. Neither the owners nor the investigators were aware of the treatment group. There were no significant differences in clinical score, hematology score, lymphocyte subsets, FeLV p27 concentration, pterin concentration, reversion to negative status, or survival between the groups. This study demonstrates the marked differences that can be observed in uncontrolled or retrospective case studies compared to randomized, controlled clinical trials. The ability of clinicians to select the most effective treatments for their retrovirus-infected patients is severely hampered by the predominance of anecdotal reports compared to controlled trials in the veterinary literature.

Interferon alpha (IFNα) is one of many interferons that have shown promise as direct antiviral agents (at high doses) and as immunomodulators (at low doses). Anecdotal reports of beneficial responses in cats with either FeLV or FIV infection treated orally with low doses (0.5–30 U PO q day) of various forms of IFNα have been described. The most positive responses are reported with human IFNα in contrast to bovine or feline products. The mechanism by which oral IFNα acts is unknown, but the product is not believed to be present in the blood or oral cavity in concentrations high enough to exert a direct antiviral effect. It is possible IFNα binds to mucosal receptors, triggering an immunologic cascade with advantageous systemic effects. In a study of 6 cats with severe lymphocytic-plasmacytic stomatitis due to chronic (3–4 year) experimental FIV infection, treatment with human IFNα (5 U PO q 24 hour x 5 days every other week) failed to improve clinical, hematologic, or histologic scores, lymphocyte subsets, or viral infection status. In another small study, IFNα failed to improve hematologic or lymphocyte subset abnormalities in cats with chronic FeLV infection. Weiss reported on more than 100 previously reported and unreported cases of FeLV-infected cats treated with various protocols for low-dose IFNα. Many of these cases were also treated with antibiotics, blood transfusions, fluids, and other supportive care, so it is not possible to know what role the IFNα treatment played in the clinical course. Based on the results of these cases, Weiss recommended treating cats with 15–30 U IFNα PO q day for 7 days on alternate weeks (recombinant human IFNα; Roferon, Hoffman LaRoche). Roferon is supplied in 3 million U vials. The protocol for diluting the drug for oral use is: 1) mix stock in 1 liter sterile saline, 2) freeze in 1 or 10 ml aliquots, 3) as needed, thaw aliquots and mix into the working solution by further diluting into 100 ml (1 ml aliquot) or 1000 ml (10 ml aliquot), 4) the final concentration of 30 U/ml is considered an appropriate cat dose. This working solution may be stored in the refrigerator for several months, but repeated freeze-thaws should be avoided. High-dose rhIFNα (10,000–1,000,000 U/kg SC q day), which suppresses growth of both FeLV and FIV in culture, has also been shown to reduce virus levels in experimentally infected cats. However, the cats developed neutralizing antibodies against the human protein after several weeks of the treatment.

There are no reports of responses in naturally infected cats to high-dose IFNα therapy.

AZT/Zidovudine (Retrovir, Glaxo-Wellcome) is the most widely used antiviral agent for both human and feline retroviral infection. It is a nucleoside analog inhibitor of the viral enzyme reverse transcriptase, preventing conversion of viral RNA into DNA, which would then enter the host genome. AZT is so effective that it is often used as the gold standard against which new candidate drugs are compared. FIV-infected cats, particularly those with viral-induced neurologic disease or stomatitis may achieve clinical improvement with AZT treatment (5–15 mg/kg PO or SQ BID). In one study, 33 FIV-infected and 32 FeLV-infected cats, all with chronic oral inflammation (stomatitis), were treated with AZT (5 mg/kg SQ BID or placebo for 3 weeks in a double-blind design. No other treatments were permitted. FIV-infected cats treated with AZT had improved stomatitis score, overall clinical score, and helper T cell counts compared to placebo. FeLV-infected cats also had improved stomatitis score, and decreased FeLV antigenemia compared to placebo. The importance of this study is the clear advantage of AZT treatment for clinical and immunologic recovery compared to placebo. The dose of 5 mg/kg BID, which is lower than previously recommended, offers the advantages of reduced hematologic toxicity and cost. The PCV should be monitored periodically in AZT-treated cats, as anemia is a common side effect. If the PCV drops below 20%, treatment may be stopped for a few days, and then gradually reinstated when the PCV is normal again.
### Medications with possible immunomodulatory or antiviral activity in FeLV and FIV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Proposed mechanism</th>
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<tbody>
<tr>
<td>Interferon alpha</td>
<td>30 units (1 ml) PO daily every other week</td>
<td>Immunomodulation</td>
</tr>
<tr>
<td>Staphylococcus Protein A</td>
<td>10 µg/kg IP twice weekly for 10 weeks, then monthly</td>
<td>Immunomodulation</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>0.5 ml IV twice weekly for 2 weeks, then weekly</td>
<td>Immunomodulation</td>
</tr>
<tr>
<td>Acemannan</td>
<td>2 mg/kg IP once weekly for 6 weeks</td>
<td>Immunomodulation</td>
</tr>
<tr>
<td>AZT</td>
<td>5–15 mg/kg PO or SC BID</td>
<td>Antiviral</td>
</tr>
<tr>
<td>Interferon alpha</td>
<td>100,000 units/kg SC daily for 6–12 weeks</td>
<td>Antiviral</td>
</tr>
</tbody>
</table>

### REFERENCES


