FELINE INFECTIOUS DISEASES: WHAT'S NEW?

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FELINE RHINOTRACHEITIS VIRUS: CALICIVIRUS AND HERPESVIRUS

Calicivirus and herpesvirus are the two major causes of infectious upper respiratory tract disease in cats, with over 80% of cases being caused by one or both of these viruses; they are collectively referred to as feline rhinotracheitis virus. Other viral agents, including reovirus, cowpox virus, feline coronavirus, and influenza A virus can also cause upper respiratory symptoms in cats, although this is less common. Infection with these viruses occurs most often in cats that are housed together, such as in shelter situations, as well as in young cats at the time that protection from maternal antibodies declines.

FELINE CALICIVIRUS (FCV)

Feline calicivirus (FCV) is a small, non-enveloped single-stranded RNA virus of the caliciviridae family. It is genetically distinct from canine calicivirus, however it is suspected that the two are antigenically linked. There are many FCV isolates, each with significant genetic sequence variability; this is a feature of many RNA viruses, and allows for the rapid generation of viral variants. This sequence variability is particularly pronounced in the key regions of the capsid protein, which is responsible for the antigenic structure of the virus. FCV can mutate within groups of cats as well as within individual cats. Following nasal, oral and conjunctival routes of infection, the virus replicates predominantly in oral and upper respiratory tissues, although rarely strains may have a predilection for lung or synovial tissue. Oral ulcers are the most consistent pathologic feature. The ulcers begin as vesicles, which will often rupture and progress to necrosis of the overlying epithelium with the infiltration of neutrophils. Ulcers may involve the tongue, hard palate, soft palate and pharynx, and usually heal within 2-3 weeks. Pulmonary lesions are less common, and result initially from focal alveolitis, which progresses to acute exudative and proliferative interstitial pneumonia. If the joints are involved, an acute synovitis can occur, with thickening of the synovial membrane and joint effusion.

Cats will begin showing clinical signs of calicivirus following a short incubation period of 2-5 days. There may be a wide range of clinical symptoms, which reflect the genetic variability of the virus. Most common clinical signs include: sneezing, conjunctivitis, ulcers of the tongue, lips and nose, oculonasal discharge, fever and depression. Rarer signs include skin lesions, dyspnea, abortions and shifting-leg lameness. Typically signs will resolve within 7-10 days. For animals with joint involvement, there does not tend to be long-lasting effects on the joints.

VIRULENT SYSTEMIC CALICIVIRUS

Overall, patients with calicivirus tend to be less systemically ill than patients with herpesvirus. The exception to this is the rare patient with virulent systemic calicivirus. In 1998, there was an outbreak of infection with a highly virulent, vaccine-resistant strain of calicivirus; the name of the strain responsible for this outbreak is FCV-Ari. The organism was highly contagious, and spread through the facility via contaminated fomites. Since this first reported outbreak, there have been several other outbreaks in various geographic regions, including Pennsylvania, Massachusetts, Tennessee and Nevada. Outbreaks
have also been reported in the UK and France. Each outbreak has been caused by genetically distinct viral strains, suggesting that the mutations causing these outbreaks are unique in each case. The majority of the outbreaks trace back to a hospitalized shelter cat. Adult cats, who are often vaccinated against calicivirus, are infected more often than kittens, and adult cats are at a significantly higher risk than kittens for severe disease or death. Outbreaks occur most often in the spring or summer, and often last approximately 2 months. Cats may continue to shed virus following recovery, however there have been no reports of transmission of virulent systemic calicivirus from recovered cats. Clinical signs of virulent systemic calicivirus can include anorexia, pyrexia, subcutaneous edema and ulcerative dermatitis (especially on the nose, lips, pinnae, periorbital region and distal limbs), oral ulcers, nasal discharge, respiratory distress, icterus, GI signs, signs of coagulopathy and sudden death.

**FELINE HERPESVIRUS (FHV-1)**

Feline herpesvirus is a double-stranded DNA virus of the herpesvirus family. FHV-1 is closely related, both antigenically and genetically, to canine herpesvirus-1. The domestic cat is the main host, however herpesvirus can also be seen in nondomestic cats, particularly cheetahs. FHV-1 isolates exhibit less variability than FCV. Cats are infected via nasal, oral and conjunctival exposure. The virus targets tissues of the upper respiratory tract, including the soft palate, tonsils, turbinates, conjunctiva and trachea. Rarely, viremia can occur, resulting in generalized disease; this is more likely to occur in young or immunosuppressed patients. Pneumonia is also an uncommon sequelae to FHV-1 infection. Viral shedding starts approximately 24 hours following infection, and persists for 1-3 weeks.

FHV-1 tends to cause more consistent and severe upper respiratory and conjunctival disease than FCV. Initially, infected cats will be depressed, with sneezing, inappetence, fever, serous oculonasal discharge and ptalism. Conjunctivitis may cause a change from serous to mucopurulent ocular discharge; nasal discharge often also becomes mucopurulent. Oral ulcers can occur, however this is occurs must less frequently than with FCV. Other rarely observed clinical signs include: dyspnea, uveitis, skin ulcers and dermatitis. Viral replication within the nasal turbinates can cause chronic damage to the nasal mucosa and nasal turbinates. In rare cases, this can lead to either chronic rhinitis or recurrent upper respiratory infections in the future. Clinical signs of FHV-1 tend to resolve over 2-3 weeks.

**DIAGNOSIS OF FCV, FHV-1**

It can be difficult to differentiate between FCV and FHV-1, as there are many symptoms in common. Patients with FHV-1 tend to be more systemically ill with more severe conjunctivitis and rhinitis than patients with FCV. If a patient has oral ulcers or lameness, then FCV should be suspected. A definitive diagnosis requires viral isolation or PCR of an oropharyngeal swab. False negatives are possible in acute disease when lower quantities of virus are being shed. False positives are also possible in carrier animals whose clinical signs are not due to viral infection. FHV-1 DNA can be found in the conjunctival cells of up to 25% of healthy cats, so this test has a relatively low positive predictive value. Additionally, the currently used PCR assays also can detect vaccine strains of FHV-1, so vaccinated cats may be PCR positive. Serology does not tend to be helpful, as elevated results can be due to the presence of immunity from previous exposure or vaccination. PCR can be used to diagnose FCV and to differentiate between FCV isolates. PCR is highly sensitive and specific, however it has lower positive and negative predictive values. It will only detect viral DNA present at the area sampled at the moment that it is sampled, thus
false negatives are possible. Additionally, a positive PCR does not prove a causative relationship between the virus and a patient’s clinical signs.

**TREATMENT OF FCV, FHV-1**

Nursing care is the most important component of therapy for feline rhinotracheitis. If oral ulcers are severe, patients may require appetite stimulants or feeding tubes. Nebulization and mucolytics may be helpful if severe congestion is present. Antibiotics should be considered in cases where a secondary bacterial infection is suspected, or in immunosuppressed patients. Ideally, antibiotic choices should be based on culture and sensitivity results. However, if this is not available, a broad-spectrum antibiotic should be chosen that is effective against bacteria commonly found in the feline oropharynx. Antivirals that are effective in treating human herpes infections, such as Acyclovir, have not been effective in treating FHV-1 and FCV. L-lysine reduces viral replication through the antagonism of arginine, and may suppress the clinical manifestations of viral upper respiratory infections.¹ L-lysine does not seem to be effective in preventing upper respiratory infections from developing, however.² Interferon has been suggested for use in acute viral disease, for its immunomodulatory properties.

**EPIDEMIOLOGY OF FELINE RHINOTRACHEITIS VIRUS**

Historically, FCV and FHV-1 were isolated in nearly equal frequencies. In recent years, however, FCV seems to be more common than FHV-1. These viruses exist most commonly in groups of cats that are housed together; the viruses will circulate and maintain themselves in a group of cats. FCV and FHV-1 are transmitted easily either by direct transmission, via aerosol and/or direct contact with eyes, noses and mouths, or through fomites. Most cats will shed FCV in oropharyngeal secretions for 30 days following infection, but up to 50% of cats will continue to shed the virus for up to 75 days. Approximately 25% of recovered cats may become long-term viral carriers, and may shed the virus either continuously or intermittently. Cats that clear the virus are susceptible to re-infection in the future. Similar to other herpesviruses, cats that are infected with FHV-1 will be infected for life. Following acute infection, most cats will shed large quantities of virus for 2-3 weeks. At this time, most cats will stop shedding, however the virus will remain latent in the trigeminal ganglia. After a variable period of time, these cats may against develop clinical signs of infection, and will again start shedding the virus. This is more likely to occur if a patient is immunosuppressed or stressed.

A case control study was performed, which looked at 573 cats in 8 shelters in California.³ FCV and FHV-1 were the most commonly isolated viruses, and were present in 13-36% and 3-38% of cats, respectively. Rarely, Bordetella bronchiseptica, Chlamydophila felis, and Mycoplasma spp were identified (2-14% of cats).

**FCV, FHV-1 IMMUNITY**

Infected cats develop some degree of immunity following natural infection with FCV and FHV-1, however this immunity may be incomplete or short-lived. Maternal antibodies may persist for 10-14 weeks for FCV and 2-10 weeks for FHV-1. However, low levels of maternal antibodies do not necessarily protect against subclinical infections. Thus, kittens infected at these ages may become carriers.

**FCV, FHV-1 PREVENTION**

FCV is more resistant to disinfection than FHV-1, which is readily destroyed outside of the host. There are many different types of vaccines against feline rhinotracheitis viruses, including live, attenuated,
inactivated adjuvanted, and modified live intranasal vaccines. Most of these vaccines are relatively effective against disease, however not necessarily against infection with the viruses. The vaccinations are designed to be broadly cross-reactive, however the great antigenic diversity of FCV can make vaccination less successful against this virus. Newer vaccines against FCV that incorporate a number of different FCV strains have been found to offer broader heterologous protection against infection, based both on higher neutralizing antibodies and improved clinical protection and reduction of virus shedding post-infection. Rarely, clinical signs of respiratory disease have been reported following vaccination with modified live vaccines.

**BORDETELLA BRONCHISEPTICA**

Bordetella organisms are gram negative, aerobic coccobacillus, which are best known for causing canine infectious tracheobronchitis, or kennel cough. The role of bordetella as a primary agent of respiratory disease in cats is unknown. Bordetella is known to reside in the respiratory tract of cats, and has been isolated from kittens and occasionally adult cats with clinical signs of lower respiratory disease. This bacteria also, however, has the potential to cause disease in cats. Bordetella possesses intrinsic mechanisms for evading host defenses, including fimbriae, which recognize specific receptors within the respiratory tract, allowing for colonization of ciliated epithelial cells. Once colonized, bordetella organisms release exo and endotoxins, which impair the function of the respiratory epithelium. Additionally, this bacteria has the unique ability to invade host cells. By existing intracellularly, organisms are able to evade immune defense mechanisms.

In experimentally infected cats, clinical signs of bordetella include fever, sneezing, nasal discharge, and submandibular lymphadenopathy. In rare cases, pneumonia can develop. This is a more likely sequelae in kittens, and mortality rates in patients with bordetella pneumonia can be high. Signs of bordetella infection generally resolve within 10 days.

There is no feline vaccine against *Bordetella bronchiseptica*, however modified-live vaccines marketed for dogs are likely effective.

**CHLAMYDIA FELIS**

Chlamydiae are obligate intracellular parasites, which, similar to bacteria, have a cell wall, DNA and RNA. However, they lack the metabolic machinery necessary to survive and replicate on their own. Therefore they live and multiply in cytoplasmic vacuoles of host cells. Chlamydiae are commensals of ocular, respiratory, gastrointestinal and genitourinary mucosae.

Acute, chronic and recurrent conjunctivitis are the most commonly reported symptoms with chlamydial infection. Experimental inoculation of chlamydial organisms into the gastrointestinal, respiratory or genitourinary tracts has led to clinical disease, however it is unknown if this organism plays a role in causing disease in naturally-infected cats. Cats with concurrent FIV infection have been documented to have prolonged symptoms and shedding when compared to uninfected cats.

Diagnosis of *Chlamydia felis* can be made via cell culture, cytology or PCR from swabs from infected tissue surfaces. A diagnosis based on cytology may reveal intracytoplasmic inclusions composed of clusters of coccoid bodies within phagocytes or epithelial cells. Fluorescent antibody techniques using monoclonal antibodies may aid in the identification of chlamydial organisms. As with many feline
infectious diseases, serology is not very helpful in diagnosing chlamydial infections, as it only proves exposure.

Treatment for infection with *Chlamydia felis* is with tetracyclines. Oral treatment with doxycycline for 3-4 weeks is generally recommended. If only ocular infection is present, tetracycline ophthalmic ointment can be used.

Kittens have maternal antibody protection against *Chlamydia felis* until they are 7-9 weeks old. Both inactivated and modified live vaccines exist for protection against chlamydial infections. Vaccination is not completely effective at preventing infection and shedding, however does decrease replication of the organisms, therefore reducing clinical signs in infected cats. Rarely post-vaccinal reactions have been reported 7-21 days after vaccination, consisting of fever, anorexia, lethargy and occasional lameness. It is important to remember that *Chlamydia felis* has the rare potential to cause conjunctivitis in humans. Therefore it is important to instruct owners to take precaution when medicating their cats with chlamydial conjunctivitis.

**MYCOPLASMA FELIS**

Mycoplasmas are the smallest free-living microorganisms. They are prokaryotes, which are able to exist extracellularly, however they depend on nutrients from their environment. Mycoplasmas exist on the mucous membranes of the respiratory and urogenital tracts of many animal hosts. These organisms lack cell walls, and so are fragile outside of the host. However, this unique characteristic allows them to be intrinsically resistant to cell wall-inhibiting antibiotics, including penicillins, cephalosporins and vancomycin. Mycoplasmas are considered normal flora in dogs and cats of many mucosal and serosal surfaces. However, they also have the potential to cause disease of the respiratory tract, urogenital tract, joints, mammary glands and conjunctiva. Additionally, some mycoplasma species can become intracellular, resulting in chronic, persistent infections.

*Mycoplasma felis* infection can cause conjunctivitis. Clinical signs, including serous to mucoid ocular discharge, can last for 60 days if untreated. While mycoplasma organisms can exist as normal flora in the upper respiratory tract of cats, their presence in the lower respiratory tract often causes clinical disease. Patients with impaired pulmonary clearance as a result of viral or bacterial infection or asthma, may be more prone to developing lower respiratory tract infections with inhaled mycoplasma organisms. Pulmonary mycoplasma infections may result in suppurative inflammation of the conducting airways.

The diagnosis of *Mycoplasma felis* can be difficult, since it can exist as normal flora in healthy patients. Mycoplasma organisms should not be isolated from the lower airways, however, so their presence in a cat with respiratory disease likely indicates true infection. Exudates can be examined, and occasionally mycoplasma organisms can be identified using an electron microscope. Alternatively, mycoplasma can be cultured, however due to their fragile nature, a specific culture must be requested. PCR for mycoplasma also exists.

Several antibiotics can be used to treat *Mycoplasma felis* infection, including macrolides (tylosin, erythromycin, tiamulin), tetracyclines, chloramphenicol, clindamycin, nitrofurantoin, aminoglycosides (gentamicin, amikacin), and azithromycin.
PREVENTION OF FELINE UPPER RESPIRATORY INFECTIONS

Prevention of feline upper respiratory diseases in household cats involves routine vaccination, and a booster prior to entering high-risk situation (boarding, exposure to other cats, stressful events). In an attempt to decrease the risk of upper respiratory tract infection outbreaks in boarding catteries, all cats entering a facility should be up to date on vaccines, cats should be housed individually, cats with known upper respiratory infections should be isolated, and hands and equipment should be disinfected between cats.

FELINE LEUKEMIA VIRUS

PREVALENCE AND PATHOGENESIS

FeLV exists worldwide. While some slight geographic and local variations exist, overall infection rates are relatively similar, ranging from 1-8% of healthy cats, and up to 21% of sick cats. Kittens (especially < 4 months old) are at increased risk for infection; resistance develops with age. However, adult cats may still be at risk. A recent study revealed 67% of adult cats developed persistent FeLV infection after challenge. FeLV negative cats living with FeLV-infected cats are at increased risk for contracting the virus. Males and females are infected with FeLV with equal frequency; however, outdoor cats are more likely to be infected. Cats with abscesses are another high-risk population for FeLV.

Following infection, FeLV replicates in many tissues, including bone marrow, respiratory epithelium, and salivary glands. Social behaviors (eg, grooming and sharing food bowls) are effective means of transmission. While virus may enter other body fluids and secretions, transmission via urine and feces is less likely. Iatrogenic transmission, via contaminated fomites and blood transfusions can occur. Vertical transmission is possible by transplacental spread or spread through the milk.

Acute infection with FeLV may follow 1 of 2 main courses. An effective immune response can eliminate antigenemia after a few weeks (prior to bone marrow involvement); this is called a regressive infection. Historically, it was believed these patients had cleared the virus, however, new research suggests most actually remain infected for life. While these cats have no serologic evidence of infection, the virus persists in circulation, and provirus can be detected by PCR. These cats are unlikely to develop FeLV-associated diseases or shed virus in saliva, but could be infectious to other cats via blood transfusion or organ transplantation. Rarely, regressor cats may have a recurrence of viremia, resulting in clinical disease.

The second main outcome is progressive infection, which results from an ineffective immune response. In this case, there is extensive virus replication, first in the lymphoid, mucosal, and glandular epithelial tissues, followed by the bone marrow. These cats remain persistently viremic and antigenemic, thus positive by all testing methods (ELISA, IFA, PCR), and are infectious to other cats. Many go on to develop FeLV-associated diseases, often within the first few years following infection. Two very rare stages of FeLV infections also exist: abortive infections, characterized by the absence of virus, antigen, and provirus after initial infection, and focal
infections, which are restricted to tissues such as the spleen, lymph nodes, small intestine, or mammary gland.

CLINICAL SIGNS

FeLV infection can cause variable clinical signs. In a study of over 8,000 FeLV positive cats, the most common presenting signs were various infections, followed by anemia, lymphoma, leukopenia or thrombocytopenia, and leukemia or myeloproliferative disorders. FeLV infection can also cause various malignancies; most commonly lymphoma and leukemia, however other tumors have been reported as well. Hematopoietic disorders, particularly cytopenias, can occur as a result of bone marrow suppression. Approximately 10% of FeLV-associated anemias are regenerative, most often resulting from immune-mediated hemolytic anemia or concurrent mycoplasma infection, but most are nonregenerative, resulting from myelosuppression, myelodestruction, myeloproliferative disease, neoplasia, or chronic inflammatory disease. Immunosuppression resulting from FeLV infection accounts for a large portion of the morbidity and mortality of infected cats, due either to lymphopenia or abnormal lymphocyte function. Other disorders, such as glomerulonephritis and reproductive disorders, have also been reported.

DIAGNOSIS

Available diagnostic tests for FeLV have a high negative predictive value (99-100%), but a lower positive predictive value (91-100%). Thus, a negative result is more reliable than a positive result; it is important to consider the history and clinical signs when interpreting all results.

The ELISA test, which detects free soluble FeLV-p27 antigen in plasma or serum, is the recommended screening test. Cats become ELISA positive in the first phase of viremia, which is within the first weeks following infection; experimentally, most test positive within 28 days. The ELISA test is very sensitive, but can yield false positive results. Additionally, regressive cats or cats with acute infection can test negative.

Immunofluorescent antibody testing (IFA) detects cell-associated p27 antigen in blood cells, primarily neutrophils and platelets. Cats become positive only after bone marrow infection, which occurs after at least 3 weeks of viremia. A positive IFA result indicates bone marrow infection, thus progressive infection. Negative IFA results can be seen either with regressive infection or initial stages of viremia. PCR can be used to detect the FeLV virus, and is currently being offered by several commercial laboratories. Technical errors, which can result from a lack of standardization of current reagents and testing protocols, can significantly decrease the sensitivity and specificity of this test. PCR is most useful in patients with suspected regressive infection, as this is the only method that will confirm the presence of DNA without the presence of antigen.

Based on AAFP guidelines, any sick cats should be tested for FeLV, regardless of previous test results, age, or vaccine status. All cats should be tested prior to adoption, especially those entering households with uninfected cats, as should be currently owned cats prior to admission of a new, uninfected cat. Any cat recently exposed to an infected cat, or cats with exposure to the
outdoors, should be tested. All cats with unknown FeLV status, or cats that will be blood or tissue donors, should be tested.

MANAGEMENT

It is important to treat secondary diseases in cats with FeLV, as these patients are often immunosuppressed. Blood transfusions are an important part of therapy for those with anemia. If the anemia is regenerative, and there is evidence of immune-mediated destruction, immunosuppression is indicated. If mycoplasma infection is suspected, antibiotic therapy with doxycycline is warranted. While erythropoietin concentrations are often elevated in cats with FeLV-related anemia, treatment with human recombinant erythropoietin has anecdotally been helpful in some cases. Cats with lymphoma and FeLV should be treated with chemotherapy, however FeLV infection is a negative prognostic indicator.

PREVENTION

The AAFP now recommends vaccinating all kittens against FeLV, regardless of risk for infection. There are currently several vaccines available, with variable preventable fractions. All of the vaccines induce immunity for at least 12 months. Of the commercially available vaccines, the Fel-O-Vax (Boehringer Ingelheim) and Fevaxyn FeLV (Schering) demonstrated 100% preventable fractions. One recent paper showed the risk of FeLV in unvaccinated cats to be >8 times higher than in vaccinated cats, lending clinical support for vaccination. Vaccination against FeLV does not interfere with testing, as the available diagnostic tests are for antigen.

FELINE IMMUNODEFICIENCY VIRUS
PREVALENCE AND PATHOGENESIS

Feline immunodeficiency virus (FIV) prevalence varies significantly worldwide, with rates reported at 4.3%, 28.9%, 47%, and 2.5% in Canada, Japan, the UK, and the United States, respectively. The prevalence of FIV is significantly higher in male cats than in females, and it most commonly affects adults. As with FeLV, cats presenting to a veterinary clinic with a wound or abscess are also more likely to test positive for FIV.

In the acute phases of infection the virus exists in salivary epithelium, lymphocytes, plasma, and serum. Experimentally, FIV is easily transmitted by all parenteral routes. However, in natural settings, FIV transmission occurs primarily by bite or fight wounds. Vertical transmission is also possible, and some kittens will acquire infection in utero or via nursing.

Pathogenesis of FIV is influenced by a number of factors, including age at time of infection (young animals develop clinical signs faster), properties of the FIV isolate, amount of virus involved with infection, and route of infection. The hallmark of FIV pathogenesis is progressive disruption of normal immune function.

CLINICAL SIGNS

Clinical signs of FIV infection are nonspecific. In the acute phase, cats may show fever, lethargy, acute gastrointestinal signs, stomatitis, dermatitis, conjunctivitis, or respiratory signs. In experimentally infected cats, enlarged lymph nodes are present in the acute phase. This phase
may last from several days to a few weeks, after which cats will appear clinically healthy. The duration of this asymptomatic phase is variable; FIV production continues in cells and tissues and cats are still prone to complications, thus it is not a true latent period.

In later stages of disease, clinical signs often reflect opportunistic infections, neoplasia, myelosuppression, and neurologic disease. Ocular abnormalities, including uveitis, glaucoma, and retinal hemorrhages may be observed. Chronic renal insufficiency has been reported in FIV positive patients, potentially due to immune complex deposition. Neoplasia has been associated with FIV infection, and FIV positive cats are more likely to develop lymphoma or leukemia compared to noninfected cats. Stomatitis is a common finding during any stage of infection. The cause is unknown; however, histopathology suggests either an immune response to chronic antigenic stimulation or immune dysregulation.

**DIAGNOSIS**

Clinical screening is performed by detecting circulating antibodies against the virus, most commonly using the ELISA test which detects FIV specific antibodies and is very sensitive. Kittens up to 12 weeks of age may test positive due to the presence of maternal antibodies. For this reason it is advised to retest cats at 6 months, at which time they should test negative unless truly infected. Additionally, cats in the acute phase of infection may test negative; thus, cats with a recent history of exposure should be retested in 8 weeks.

Confirmatory tests for FIV include western blot, IFA and PCR. The ELISA, western blot, and IFA tests can all yield false positive results in FIV vaccinated cats. PCR detects viral DNA, therefore vaccinated cats should not test positive. An ELISA test that detects antibodies against formalin-treated FIV whole virus and untreated transmembrane peptide exists, which can differentiate uninfected from infected cats, regardless of vaccination status. Developed in Japan, this test is not currently available in the US. One study demonstrated this discriminant ELISA was very effective at detecting positively infected cats, regardless of vaccination status, with very high sensitivity (97.1%) and specificity (100%) rates. While PCR is very sensitive and specific, false positive and negative results are possible. Additionally, the marked variability of the viral genome raises concerns about the ability of PCR to detect all FIV variants. Methods for this test are not yet standardized; results from different laboratories have shown widely variable results, with misdiagnosis of both uninfected and infected cats.

**MANAGEMENT**

It is important to keep cats with FIV indoors. These patients should visit the veterinarian at least twice yearly, for a physical examination, basic bloodwork, and a urinalysis. When underlying infections are present, cultures should be considered to determine the most appropriate antibiotic therapy. It is recommended that intact animals be spayed or neutered.

While the immune deficiency often associated with this disease can affect response to vaccines, it is important to protect these patients against diseases for which vaccines exist. It is generally recommended that killed vaccines be used to eliminate the potential of cats developing illness from modified live vaccines.

**PREVENTION**
FIV prevention includes minimizing risk of transmission and vaccination. Currently, only one vaccine against FIV is licensed in the US (Fel-O-Vax, www.bi-vetmedica.com). Two studies demonstrated 100% protection against infection with 2 subtype B strains in vaccinated cats.\textsuperscript{18} Published preventable fractions range from 82-100%.\textsuperscript{19} Duration of efficacy is 12 months, thus annual vaccination is recommended. Vaccination can cause false positive results using the ELISA test for at least 1 year.\textsuperscript{20}

The risk versus benefit of vaccination for each individual cat should be strongly considered. The existing vaccine affords significant protection for individual cats against FIV infection, from which at-risk patients may benefit. The difficulty in yielding false positive results in vaccinated cats may be mitigated by microchip implantation at the time of vaccination, as well as future improvements in diagnostic testing for FIV.
FELINE DIABETES MELLITUS

Diabetes mellitus (DM) in humans is most commonly characterized as being either type 1 or type 2. Type 1 diabetes accounts for 10% of human patients, and results from an absolute deficiency of insulin secretion, due to T-cell mediated autoimmune destruction of beta cells. Type 2 diabetes accounts for 90% of diabetic humans, and results from insulin resistance and beta cell dysfunction. Rarely, type 3 DM can occur as a result of the non-specific destruction of pancreatic tissue, due to conditions such as pancreatic neoplasia, hyperadrenocorticism or acromegaly. The main difference between type 1 and type 2 DM is a difference in the severity of beta cell loss, and the severity and reversibility of concurrent insulin resistance. In dogs and cats, the terms insulin-dependent (IDDM) and non insulin-dependent (NIDDM) are more commonly used, with IDDM being most similar to type 1 DM and NIDDM being similar to type 2 DM. Dogs most often suffer from IDDM, while cats are more prone to NIDDM. This terminology can be somewhat confusing in cats, as some cats can initially appear to have type 2 DM, which then progresses to type 1 as the beta cell function is exhausted, or cats may flip back and form between the two types as the severity of insulin resistance and impairment of beta cell function waxes and wanes.

There are clinically important differences between canine and feline diabetics. Cats often have a significant population of residual functional beta cells, which allows some cats to oscillate between an insulin-dependent and non-insulin-dependent state, and may provide the opportunity for the use of an oral hypoglycemic agent in some cats. Cats are considered very sympathoadrenal animals, and have a rapid catecholamine response during times of stress, excitement, fear or aggression; this is why we can’t rely on single blood glucose readings in the hospital to monitor therapy the way we may be able to in dogs. Cats are more prone to the development of hypoglycemia and the Somogyi phenomenon at doses of insulin that may be assumed to be safe for the treatment of DM.

Feline DM has a multifactorial pathogenesis, including pancreatic islet amyloidosis, vacuolar degeneration of beta cells, and islet hypoplasia. Insulin dependency may be present initially, or may develop as beta cells are destroyed; this is dependent on the degree of insulin resistance and the severity of pancreatic islet pathology. The more severe and the less reversible the cause of the insulin resistance, the more likely a cat with mild islet pathology will be insulin dependent, and vice versa.

Chronic hyperglycemia can cause glucose toxicity, which leads to beta cell dysfunction, suppressing insulin secretion and causing peripheral insulin resistance. The chronic hypersecretion of insulin is accompanied by the secretion of amylin, or islet-amyloid polypeptide. Amylin has several functions that complement those of insulin, including the promotion of gluconeogenesis, stimulation of muscle glycogen breakdown, and maintenance of blood glucose. Chronic hypersecretion of insulin and amylin, which are both secreted by the pancreatic beta cells, leads to the deposition of amyloid in the pancreatic islets. Amyloid is
cytotoxic, and deposits lead to islet cell destruction. Over time, this can lead to DM. Glucotoxicity leads to peripheral insulin resistance through the down-regulation of glucose transport systems and a defect in post-transport insulin action. Glucose toxicity is potentially reversible with treatment, which is the basis for diabetic remission. Studies have shown that increased fatty acids have a similar effect on pancreatic beta cells as increased glucose, suppressing insulin secretion. This is known as lipotoxicity.

In addition to beta cell dysfunction, insulin resistance is the other most significant factor in feline DM. Insulin resistance leads to an increased demand for insulin secretion, which can be problematic for cats with islet cell dysfunction. The resulting hyperglycemia may act to suppress the function of the remaining beta cells, leading to hypoinsulinemia and hyperglycemia. Cats with DM have been found to be 6 times less sensitive to insulin than non-diabetic cats. The 3 main sites of insulin action, and therefore potential insulin resistance, are hepatocytes, muscle cells and adipocytes. The most common causes for insulin resistance are obesity, pancreatitis, endocrinopathies (hyperadrenocorticism, hyperthyroidism, acromegaly), various infections, chronic inflammatory conditions and chronic glucocorticoid administration. There may be a genetic component to insulin resistance and therefore DM in that Burmese cats are over-represented in populations of diabetic cats in Australia.

Obesity is the most common cause for insulin resistance in cats. It induces reversible insulin resistance through the down-regulation of insulin receptors, impaired receptor binding affinity for insulin and post-receptor defects in the actions of insulin. Adipocyte-specific hormones, including leptin and adiponectin, play a role in obesity-induced insulin resistance. Leptin functions as an adipostat, which senses and regulates body energy stores. Obese patients have a tendency toward higher body leptin contents, while an inverse relationship between body leptin concentrations and insulin sensitivity has been reported. Adiponectin is associated with an increase in insulin sensitivity, via increased insulin sensitivity through decreased hepatic glucose production and increased glucose utilization by muscle. Obesity is correlated with decreased adiponectin secretion.

**DIAGNOSIS:**

The diagnosis of DM is straight-forward, and requires documentation of persistent hyperglycemia and glucosuria. The hallmark clinical signs of DM include polyuria and polydipsia, polyphagia, weight loss, lack of grooming/unkempt haircoat and lethargy, while less common signs can include a peripheral neuropathy, decreased interactions with the owners and clinical signs from a complicating disease (e.g. icterus, vomiting, dehydration etc.). Diabetic patients can be obese (especially in the early stages of disease), or can be thin if they have been untreated as weight loss is common.

Stress hyperglycemia is common in cats, and if significant, can result in glucosuria. The renal threshold for glucose is approximately 270-280 mg/dL, and stress hyperglycemia can
frequently yield higher blood glucose values than this. This can yield the diagnosis of DM based on a blood and urine from a single clinic visit difficult. Fructosamine values can aid in the diagnosis of DM, as they reflect the mean blood glucose over the previous 1-2 weeks, and therefore can eliminate the variable of stress hyperglycemia. Fructosamine is the product of an irreversible reaction between glucose and the amino groups of plasma proteins. Limitations of a fructosamine are that it can be normal in a patient with a recent onset of DM, and it can be reduced in patients with hypoproteinemia or hyperthyroidism.

Approximately 8% of diabetic cats will develop a peripheral neuropathy. Electrophysiological testing in such patients reveals prominent demyelination at all levels of motor and sensory peripheral nerves and their nerve roots. Diabetic neuropathy is characterized by a plantigrade stance, progressive paraparesis, distal limb muscle atrophy and pelvic limb hyporeflexia; the thoracic limbs are rarely involved. Clinical improvement over weeks to months may be seen with adequate treatment of the DM, however complete recovery is rare.

Any recently diagnosed diabetic cat should have baseline lab work performed, including a CBC, biochemical profile, urinalysis and urine culture. It is important to run a urine culture even if a UA is normal, as urinary tract infections are common in diabetic patients, and patients can often be asymptomatic without urinary sediment changes. Additional lab work and imaging (T4, f-PLI, thoracic radiographs, abdominal ultrasound) may be indicated if a patient has additional clinical signs or a concurrent condition is suspected.

TREATMENT GOALS:

The main therapeutic goal of DM include adequate glycemic control, ideally as quickly as possible following the diagnosis of DM. Good glycemic control can act to reverse glucose toxicity, maximizing the preservation of beta cell function and increase the changes of diabetic remission. Other goals include the eliminations of clinical signs (weight loss, PU/PD, polyphagia), the maintenance of a stable, healthy body weight, and avoidance of the complications of DM (DKA, hypoglycemia, diabetic neuropathy).

TREATMENT MODALITIES:

The mainstay of DM treatment is proper insulin administration, while other treatments include proper diet, exercise, and the control of concurrent disorders that can lead to insulin resistance. Insulin therapy should be initiated as soon as possible to prevent diabetic complications, and to increase the chance of diabetic remission by reversing the effects of glucose toxicity. While diet alone or oral hypoglycemic agents can be attempted, insulin therapy provides the most reliable means for achieving rapid diabetic control and increasing the chances for remission. Which regimen is most effective, however, depends on the number of remaining functional beta cells and the response of the individual patient to therapy.
It is important to realize that cats can be unpredictable in their response to exogenous insulin, and that individual cats may vary significantly in their insulin requirements.

The recommended insulin types for the majority of diabetic cats include intermediate and long-acting insulins, including protamine zinc insulin (PZI), glargine insulin, detemir insulin, or lente insulin. The current PZI insulin on the market is ProZinc™ by Boehringer Ingelheim. This product has more protamine than NPH insulin, resulting in longer duration. This is a recombinant human insulin, which is FDA approved for use in cats. Prozinc was evaluated in a prospective clinical trial of 133 diabetic cats. This study revealed that PZI/Prozinc was effective for controlling BG levels and clinical signs within 45 days of initiating treatment in 85% of these cats. The feline population evaluated in this study included both newly diagnosed diabetics and existing diabetics who were poorly controlled on their current insulin.22

Glargine insulin (Lantus™ by Sanofi Aventis) has a 2 amino acid substitution in the beta chain of the insulin molecule, which alters the isoelectric point. As a result, the insulin remains in solution at an acidic pH, but precipitates at a normal pH (in the subcutaneous tissue). As a result, following the injection of this insulin subcutaneously there is a slow release from microprecipitates, yielding a long duration of action. In humans, Lantus is marketed as a “peakless” insulin, and it is recommended for once daily dosing. Studies in healthy cats have revealed that the action of glargine insulin peaks at 14-16 hours, and twice daily dosing is recommended in most diabetic cats.

Detemir insulin (Levemir® by Novo Nordisk) is a long-acting insulin that acts by causing reversible binding between albumin and insulin, resulting in the gradual release of the bound fraction of insulin from albumin and prolonged action. In general, detemir has similar pharmacokinetic and pharmacokinetic properties to glargine, but has a slightly longer duration. Detemir tends to have a higher potency in cats than other types of insulin, and therefore dosing is more conservative.

Lente insulin (Vetsulin® by Merck) is a mixture of 30% short-acting amorphous insulin and 70% longer-acting crystalline insulin. Vetsulin is FDA approved for use in cats.

Oral hypoglycemic agents can be considered for use in diabetic cats in situations in which owners are unwilling or unable to give insulin. It is important for the owners to understand, however, that oral hypoglycemic agents are inferior to insulin therapy in regards to reversal of glucose toxicity and induction of diabetic remission. Glipizide is a sulfonylurea that acts to stimulate insulin secretion from the pancreatic beta cells. Based on its mechanism of action, this medication will not be useful in patient with no remaining beta cells, and treatment is only successful in approximately 1/3 of diabetic cats. Suitable potential candidates for glipizide therapy are cats in good body condition, with mild to moderate diabetic symptoms, who are non-ketotic.
Nutritional management is extremely important in the treatment of DM. It is important to remember that cats are true carnivores, that are best adapted to eat a diet composed mainly of protein and fat. Cats have a few unique features by which they metabolize carbohydrates. Cats lack salivary, intestinal and pancreatic amylase, which is the enzyme responsible for initiating carbohydrate digestion. They also have little or no hepatic glucokinase (which is responsible for the phosphorylation of glucose in omnivores), and a high capacity for gluconeogenesis from amino acids. For this reason, high-protein, low-carbohydrate diets are ideal, and have been shown to improve clinical diabetic control and increase rates of diabetic remission. However, it is important to choose a diet that the patient will like, and will predictably eat. Weight management is important in diabetic patients, as most diabetic cats are overweight or obese. Weight loss to reach a healthy weight can help to reverse obesity-induced insulin resistance.

The recommended treatment for a newly diagnosed diabetic patient includes instituting insulin therapy as soon as possible. PZI and glargine insulin are recommended as the first choices, however certain feline patients may end up needing to be tried on other insulin options such as lente or detemir. The initial insulin dosage for the majority of cats should be 1 U/cat BID, however the optimal dosage will depend on an individual cat’s size, degree of hyperglycemia and response to therapy. It is essential that clients of newly diagnosed diabetic patients are properly educated regarding insulin handling and injection techniques.

**DIABETIC MONITORING:**

The most important parameter in diabetic monitoring is the owner’s observations of their cat. I have owners pay close attention to their cat’s body weight, water consumption and urinations, and urine glucose (when the cat permits). Diabetic monitoring should initially consist of recheck visits every 1-2 weeks following diagnosis. It is important to prepare owners for frequent visits in the first couple of months as glycemic control is attained. Important monitoring parameters include: owner’s report of clinical signs, body weight, blood glucose and serum fructosamine values. Blood glucose curves, either in-hospital or at home, can sometimes be helpful in assessing diabetic control.

Urine glucose reflects the average glucose concentration in urine that accumulates in the bladder. It is important to remember that the results can be affected by hydration status and urine concentration. Monitoring urine glucose is most helpful in assessing trends (consistently negative urine glucose may indicate that a lower insulin dose is indicated, or that a patient is in diabetic remission), however insulin dose should not be adjusted according to urine glucose measurements. Monitoring urinary glucose can be very helpful in the diagnosis of diabetic ketoacidosis.

Fructosamine readings can be helpful as an adjunctive tool in monitoring diabetic cats. The fructosamine value can help to assess diabetic control as good (360-450 µmol/L), moderate (450-550 µmol/L) or poor (>600 µmol/L). It is important to remember, however, that these
values may indicate the adequacy of diabetic control, however do no help to identify the underlying problem. For example, a high fructosamine may tell you that a patient’s DM is poorly controlled, however it does not tell you whether a patient may need a higher or lower insulin dose. Furthermore, fructosamine values should dictate a change in insulin dosage only if consistent clinical signs exist. Mild fluctuations between fructosamine readings is to be expected, and this is generally not felt to be significant, unless there is a difference of > 50 µmol/L between 2 fructosamine readings. Additionally, reference ranges for fructosamine values vary depending on lab, and what is considered a “normal” fructosamine in a healthy cat should not be the target for good glycemic control in a diabetic cat.

**BG CURVES:**

I do not routinely perform BG curves in my feline diabetic patients. However, I do recommend them in cats with persistent clinical signs despite appropriate insulin therapy. Given the confounding factor of stress hyperglycemia, in-hospital BG curves don’t tend to be very helpful in overly aggressive or stressed cats. I usually recommend that the owners feed their cat and give insulin as usual, then bring them into the hospital for the curve. We check BG readings every 2 hours for 12-24 hours, in an attempt to determine the glucose nadir and the duration of effect of insulin. An ideal glucose nadir is 100-150 mg/dL, and ideal duration of effect ranges from 8-14 hours. If you are questioning owner compliance, then having them administer the insulin in the hospital, in front of you or one of your staff members can be helpful. It is important to remember that there can be significant day-to-day variability in BG curves generated on consecutive days.²³

If a BG curve is indicated, the issue of stress hyperglycemia, as well as the cost to client of an in-hospital BG curve can be alleviated by having owners perform BG curves at home. Blood can be sampled using a lancet device from the pinna or footpad, and the glucose level can be assessed using a portable glucose monitor. The AlphaTRAK (Abbott Animal Health) has been validated for use in cats. I do not recommend that owners adjust insulin dosages based on individual glucose readings (unless it is to hold off on giving insulin when hypoglycemia is present), or even results of curves, but have them send me the curves for analysis. Even with at-home BG curves, there can be large day-to-day variations in glucose curve results.

**CONTINUOUS GLUCOSE MONITORING SYSTEMS (CGMS):**

Continuous glucose monitoring systems are devices with subcutaneous sensors that measure interstitial glucose (which parallels blood glucose) for up to 72 hours. An electrode is inserted into the subcutaneous space (usually in the intrascapular region), and obtains BG readings every 5 minutes. These devices can be helpful in diabetic patients who are difficult to control, as it allows for the assessment of day-to-day variation in BG. Limitations of continuous glucose monitoring systems are usually technical, in that they require calibration (often every 12
hours), the sensors can become dislodged, some patients may not tolerate wearing them, and they are expensive.

THE PROBLEM DIABETIC CAT:

Despite following the best medical recommendations, some feline diabetics are extremely difficult to control, and do not improve on insulin and proper diet. If a cat remains persistently hyperglycemic, despite receiving > 1.5 units/kg of insulin, this is cause to take a closer look at this patient. First review insulin handling and administration with the owner, and rule out factors such as expired insulin or improper handling. If insulin is being properly stored and administered, then you should suspect the presence of either insulin resistance or the Somogyi response. In these cases, a BG curve can be helpful to differentiate between these potentials. If insulin resistance is suspected (based on persistent hyperglycemia after insulin), then you should look for concurrent diseases. The most common causes for insulin resistance include: infection (especially urinary tract infections, which can be clinically silent), obesity, pancreatitis, hyperadrenocorticism, acromegaly, hyperthyroidism, neoplasia, or glucocorticoid or progestagen administration.

In contrast to dogs, hyperadrenocorticism is rare in cats. Patients with hyperadrenocorticism exhibit a wide range of clinical signs. Similar to signs of DM, these patients are frequently PU/PD and polyphagic. They also often have alopecia, fragile skin, muscle atrophy and a pendulous abdomen. Approximately 90% of cats with hyperadrenocorticism have concurrent DM, and the main reason for identification of hyperadrenocorticism in cats is the presence of unregulated DM. Acromegaly (hypersomatotropism) is caused by a growth-hormone secreting tumor in the pituitary gland. Excessive growth hormone causes anabolic effects (mediated by IGF-1), yielding proliferation of bone, cartilage and soft tissue, and catabolic effects, causing muscle wasting. The diagnosis of acromegaly is based on consistent clinical signs and elevated IGF-1 levels.

DIABETIC REMISSION

Some diabetic cats are only transiently diabetic, and through effective glycemic control glucotoxicity can be reversed and patients can go into a diabetic remission. Diabetic remission is reported in under 20-40% of diabetic cats. Remission is most often achieved within the first three months of treatment, however technically can occur at any time. Diabetic remission does not equal diabetic cure, and patients who achieve diabetic remission are at risk for relapse in the future if new sources of insulin resistance are encountered. Lifelong weight and dietary management are recommended to minimize the risk of relapse. Cats have the greatest chance of achieving remission when insulin is rapidly started following the diagnosis of DM, patients are switched to a suitable diabetic diet, and intensive monitoring is performed to facilitate the tight maintenance of normoglycemia. Good candidates for diabetic remission are cats who are obese (and can achieve an ideal body weight), cats on glucocorticoids, and cats who are effectively
treated for hyperadrenocorticism. It is likely that cats with transient DM are in a subclinical diabetic state that becomes clinical when the pancreas is stressed by insulin resistance. These cats have some existing abnormality of their pancreatic islets, which impairs their ability to compensate for current insulin resistance, leading to carbohydrate intolerance.

There are several factors that can affect the success of treatment of DM, and the likelihood that diabetic remission may be achieved. They include: the severity of pancreatic beta cell loss, the responsiveness of tissues to insulin (influenced by the presence of concurrent disease), the presence of glucose toxicity, and problems with the absorption or duration of exogenous insulin.
REFERENCES:


Pathogenesis: Stages of FeLV Viremia

- **Ineffective Immune Response**
  - **Progressive Infection**
    - Extensive virus replication in lymphoid tissues, bone marrow
    - Persistent viremia, antigenemia
    - FeLV-associated diseases

- **FeLV Exposure**
  - **Abortive Exposure**
  - **Focal Infection**
    - Virus localized in tissues

- **Effective Immune Response**
  - **Regressive Infection**
    - FeLV antigen, virus detectable in blood for 2-3 wks post-exposure
    - Cats maintain proviral DNA but are not antigenemic long term
    - Unlikely to develop FeLV-associated disease
    - Rare recurrence of viremia, clinical disease
## Diagnosis of FeLV

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Sample</th>
<th>Detects</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>Plasma or serum, tears, saliva</td>
<td>Free soluble p27 antigen</td>
<td>Recommended screening test; can have false +</td>
</tr>
<tr>
<td>IFA</td>
<td>Blood smears, Bone marrow</td>
<td>Cell-associated P27 antigen (cytoplasm)</td>
<td>Confirmatory test; + indicates progressive infection</td>
</tr>
<tr>
<td>PCR</td>
<td>Blood, bone marrow, LN, tissue, saliva</td>
<td>Viral RNA, proviral DNA</td>
<td>Most sensitive test; may be only way to detect regressive infection; lab dependent</td>
</tr>
</tbody>
</table>
FeLV Diagnostic Algorithm

ELISA

- Negative
  - Retest if < 12 weeks old or if recently exposed
  - Consider PCR to rule out regressive or early infection

- Positive
  - IFA or PCR
    - Positive
      - Progressive Infection
    - Negative
      - Retest in 60 days (ELISA, IFA)

- Positive
  - Retest in 6-8 weeks
## Diagnosis of FIV

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Sample</th>
<th>Detects</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>Serum</td>
<td>FIV-specific antibodies (p24)</td>
<td>Very sensitive and specific Vaccination interferes; false - in acute phase, in end-stage disease</td>
</tr>
<tr>
<td></td>
<td>Serum, Plasma</td>
<td>Antibodies</td>
<td>Confirmatory test; vaccine interferes</td>
</tr>
<tr>
<td>Western Blot</td>
<td>Serum, Plasma</td>
<td>Antibodies</td>
<td>Confirmatory test; vaccine interferes</td>
</tr>
<tr>
<td>IFA</td>
<td>Serum, Plasma</td>
<td>Antibodies</td>
<td>Confirmatory test; vaccine interferes</td>
</tr>
<tr>
<td>PCR</td>
<td>Tissue</td>
<td>Viral DNA</td>
<td>Very sensitive and specific; variable results between labs, genomic variability of virus problematic</td>
</tr>
</tbody>
</table>