FELINE LEUKAEMIA
ABCD guidelines on prevention and management

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Virus properties

Feline leukaemia virus (FeLV) is a gammaretrovirus that infects domestic cats and other felids including the wildcat Felis silvestris, and European and Iberian lynxes. Retroviruses are enveloped RNA viruses that rely on a DNA intermediate for replication. The single-stranded RNA genome is reverse transcribed by the reverse transcriptase enzyme into DNA, which is usually integrated into the host cell genome. Infection of a cell by a retrovirus does normally not lead to cell death.

The FeLV genome contains three genes: the envelope (env) gene, coding for the surface (SU) glycoprotein gp70 and the transmembrane (TM) protein p15E; the polymerase (pol) gene, coding for reverse transcriptase, protease and integrase; and the group specific antigen (gag) gene, coding for internal virion proteins including the nucleocapsid (N) protein p27.1 The domestic cat harbours two gammaretroviruses, which are nothorizontally transmitted: an endogenous feline leukaemia virus (enFeLV) and the RD114 virus.2,3

Feline leukaemia virus exists in the subtypes A, B, C and T, which are defined by their host cell spectrum; antigenically they are closely related.4 Subtype A is ubiquitous and is involved in every infection. Subtype B originates from recombination of FeLV-A with enFeLV. Subtype C is the result of mutations in the env gene, and subtype T is defined by its T lymphotropism.

Feline leukaemia virus does not survive for long outside the host and is readily inactivated by disinfectants, soap, heating and drying. Transmission via fomites is unlikely. However, FeLV will retain infectivity if kept moist at room temperature, and iatrogenic transmission can occur via contaminated needles, surgical instruments or blood transfusions.

Overview Feline leukaemia virus (FeLV) is a retrovirus that may induce depression of the immune system, anaemia and/or lymphoma. Over the past 25 years, the prevalence of FeLV infection has decreased considerably, thanks both to reliable tests for the identification of viraemic carriers and to effective vaccines.

Infection Transmission between cats occurs mainly through friendly contacts, but also through biting. In large groups of non-vaccinated cats, around 30–40% will develop persistent viraemia, 30–40% show transient viraemia and 20–30% seroconvert. Young kittens are especially susceptible to FeLV infection.

Disease signs The most common signs of persistent FeLV viraemia are immune suppression, anaemia and lymphoma. Less common signs are immune-mediated disease, chronic enteritis, reproductive disorders and peripheral neuropathies. Most persistently viraemic cats die within 2–3 years.

Diagnosis In low-prevalence areas there may be a risk of false-positive results; a doubtful positive test result in a healthy cat should therefore be confirmed, preferably by PCR for provirus. Asymptomatic FeLV-positive cats should be retested.

Disease management Supportive therapy and good nursing care are required. Secondary infections should be treated promptly. Cats infected with FeLV should remain indoors.

Vaccination recommendations All cats with an uncertain FeLV status should be tested prior to vaccination. All healthy cats at potential risk of exposure should be vaccinated against FeLV. Kittens should be vaccinated at 8–9 weeks of age, with a second vaccination at 12 weeks, followed by a booster 1 year later. The ABCD suggests that, in cats older than 3–4 years of age, a booster every 2–3 years suffices, in view of the significantly lower susceptibility of older cats.

An extended version of the feline leukaemia guidelines presented in this article is available at www.abcd-vets.org
Feline leukaemia virus will retain infectivity if kept moist at room temperature, and iatrogenic transmission can occur via contaminated needles, surgical instruments or blood transfusions.

**Epidemiology**

Infections with FeLV occur worldwide. Their prevalence is influenced by the density of cat populations, and geographical and local variation is conspicuous. In some European countries, the USA and Canada, the prevalence in individually kept cats is usually less than 1%; in multi-cat households with no specific preventive measures in place it may exceed 20%.5-7

Over the past 25 years, the prevalence and importance of FeLV infection in Europe has greatly decreased – thanks to reliable tests, ‘test-and-removal’ programmes of viraemic carriers, an improved understanding of FeLV pathogenesis and the introduction of effective vaccines.

Viraemic cats are the source of infection; FeLV is shed in saliva, nasal secretions, faeces and milk.8,9 Risk factors are young age, high population density and poor hygiene. Transmission occurs mainly through friendly contacts, such as mutual grooming, but also through bites. In pregnant queens, viraemia usually leads to embryonic death, stillbirth or viraemic kittens, which will fade rapidly. In latently infected queens, virus is usually not transmitted to the fetuses, but single kittens in a litter may become viraemic after birth.9

In these cases, transmission has taken place from individual mammary glands, where sequestered virus remains latent until the mammary gland develops during the last period of pregnancy.

With age, cats become increasingly resistant to FeLV; however, at high challenge doses, they can still be infected.10

**Pathogenesis**

Infection usually starts in the oropharynx, where FeLV infects lymphocytes, which travel to the bone marrow. Once the rapidly dividing bone marrow cells become infected, virions are produced at high rates and viraemia develops within a few weeks. Often viraemia develops several months after constant exposure to shedding cats.11 It eventually leads to infection of the salivary glands and intestinal linings, and virus is then shed in large quantities in saliva and faeces.12

A functioning immune system will frequently control both the development and maintenance of viraemia, which then is termed ‘transient’. These ‘regressor’ cats are generally not at risk of developing disease. In a multi-cat household in which there is no control of FeLV infection, 30–40% of the cats will become persistently viraemic, 30–40% will exhibit transient viraemia, and 20–30% will seroconvert without ever having been detectably viraemic. About 5% will follow an atypical course of infection, with antigenaemia but no viraemia.11 A cat that has overcome viraemia remains latently infected; infectious virus can be recovered from some provirus-positive cells (eg, when bone marrow cells are kept in culture for several weeks).14 This virus reactivation also takes place in vivo, when latently infected cats experience immune suppression or chronic stress.15 It is not clear how often this happens, but it is believed to be rare.

Up to 10% of all feline blood samples submitted to a laboratory may prove to be provirus-positive and p27-negative; because FeLV may be reactivated in some of these cats, they should be considered latently infected.15 Cats probably cannot completely clear an FeLV infection, which might explain why virus neutralising antibodies (VNA) persist in recovered cats for many years without any new exposure. The risk of such latent persistence leading to eventual FeLV re-excretion and/or development of disease must be extremely low, since recovered cats have the same life expectancy as naive cats. Local foci of infection or latent virus may also be the source of p27-antigenaemia in cats from which infectious virus cannot be isolated – the so-called ‘discordant’ cats.37

The clinical signs of FeLV infection usually develop in viraemic cats, sometimes after several years of viraemia.8

**Immunity**

**Passive immunity**

Experimentally, susceptible kittens can be protected from FeLV infection by injections of high-titred antisera.13 Once persistent viraemia has become established, however, treatment with neutralising monoclonal antibodies to FeLV is ineffective.16
Active immune response
Cats that have overcome FeLV viraemia usually possess antibody at high titres. In most of these cats, VNA can be detected. However, since not all immune cats develop high titres, cytotoxic T lymphocytes are probably also important in FeLV immunity.

Clinical signs
The most common disease consequences of persistent FeLV viraemia are immune suppression, anaemia and lymphoma.

The prognosis for persistently FeLV-viraemic cats is poor, and most will develop disease. Of these, 70–90% will have died within 18 months to 3 years. Some may remain healthy for many years before one of the FeLV-related diseases develops, and occasional cases remain permanently healthy [EBM grade III]. The cat’s age at the time of infection is the most important determinant of the clinical outcome: with increasing age, cats become less and less susceptible [EBM grade III].

Immune suppression
Immune suppression in FeLV infections is more complex and severe than the more selective effects caused by feline immunodeficiency virus (FIV). Thymic atrophy, lymphopenia, neutropenia, neutrophil function abnormalities, loss of CD4+ cells and – more importantly – loss of CD8+ lymphocytes have been reported.

Whether or not showing clinical signs, every FeLV-viraemic cat is immune suppressed, with delayed and decreased primary and secondary antibody responses. The immune suppression may lead to infection with agents to which cats would normally be resistant, such as Salmonella species. In addition, disease caused by other pathogens may be exacerbated: poxvirus, Mycoplasma haemofelis, Cryptococcus species and infections that are normally inconspicuous in cats, such as Toxoplasma gondii, may surface. Concurrent FeLV infection may also predispose to chronic stomatitis and rhinitis. Some clinical problems, such as chronic rhinitis and subcutaneous abscesses, may take much longer to resolve in FeLV-infected cats and may recur.

Anaemia
Cats infected with FeLV may develop different types of anaemia, mainly of the non-regenerative type. Regenerative anaemias associated with haemolysis are rare and may be related to secondary infections (eg, with M haemofelis) or to immune-mediated destruction. The FeLV-C subtype can interfere with a haem transport protein, which directly results in a non-regenerative anaemia (Fig 1).

Other cytopenias may be present, in particular thrombocytopenia and neutropenia, probably caused by virus-induced immune-mediated mechanisms and myelosuppression.

Evidence-based medicine (EBM) is a process of clinical decision-making that allows clinicians to find, appraise and integrate the current best evidence with individual clinical expertise, client wishes and patient needs (see Editorial on page 529 of this special issue, doi:10.1016/j.jfms.2009.05.001).

This article uses EBM ranking to grade the level of evidence of statements in relevant sections on clinical signs, diagnosis, disease management and control, as well as vaccination. Statements are graded on a scale of I to IV as follows:

- EBM grade I: This is the best evidence, comprising data obtained from properly designed, randomised controlled clinical trials in the target species (in this context cats);
- EBM grade II: Data obtained from properly designed, randomised controlled studies in the target species with spontaneous disease in an experimental setting;
- EBM grade III: Data based on non-randomised clinical trials, multiple case series, other experimental studies, and dramatic results from uncontrolled studies;
- EBM grade IV: Expert opinion, case reports, studies in other species, pathophysiological justification. If no grade is specified, the EBM level is grade IV.

Further reading
Other diseases linked to FeLV infection

Immune-mediated diseases may follow a FeLV infection, including haemolytic anaemia, glomerulonephritis and polyarthritits. Antigen–antibody complex deposition and loss of T suppressor activity may be the main contributing factors.

Benign peripheral lymphadenopathy has been diagnosed in FeLV-infected cats, a clinical picture that may be confused with a peripheral lymphoma.32

Chronic enteritis with degeneration of intestinal epithelial cells and crypt necrosis has been found in association with FeLV infection, as has inflammatory and degenerative liver disease.33,34

Fetal resorption, abortion, neonatal death and the ‘fading kitten syndrome’ are the predominant manifestations of FeLV-associated reproductive disorders,8 but are observed rarely today.

Neurological disease (distinct from CNS lymphoma) occurs mainly as peripheral neuropathies, presenting as anisocoria, mydriasis, Horner’s syndrome, urinary incontinence, abnormal vocalisation, hyperaesthesia, paresis and paralysis.35 Indeed, FeLV may be directly neuropathogenic.36

Diagnosis

Direct detection methods

✜ ELISA for p27 This assay indicates the presence of p27, which is a marker of infection but not always of viraemia, as the test would also detect soluble p27 alone. ELISA procedures have the advantage of high diagnostic sensitivity and specificity – although this depends on which ‘gold standard’ is used for comparison.37,38

About 10% of cats tested and found to be PCR-positive are not recognised by the p27 ELISA due to the fact that they are not
antigenaemic.47 By contrast, the test specificity is close to 100%, in that none of the p27-positive samples is PCR-negative [EBM grade I].39

- **Immunochromatography** The diagnostic sensitivity and specificity of immunochromatography tests are comparable to those of the ELISA [EBM grade I].40,41

- **Immunofluorescent assay** Immunofluorescent assay (IFA) has allowed FeLV detection in viraemic cats under field conditions. It was based on the observation that granulocytes, lymphocytes and platelets in viraemic cats contain Gag components, which would be detected in blood smears. When compared with virus isolation as the gold standard, the diagnostic sensitivity is much lower than 100%, but IFA-positive cats are usually persistently viraemic [EBM grade I].42 If a viraemic cat is leukopenic, or if only few peripheral leukocytes are infected, an FeLV infection may be overlooked using IFA. Furthermore, eosinophils have a tendency to bind the fluorescent conjugates used for IFA, which may result in false-positive results if slides are not read carefully.43

- **Virus isolation** Since it detects viral infectivity, FeLV isolation in cell culture has been considered as the ultimate diagnostic criterion.44,45 In view of the complex logistics, however, this test is no longer used routinely.

- **PCR for the detection of provirus (DNA PCR)** Since every feline cell carries 12–15 copies of endogenous FeLV, determination of sequences that would allow only detection of exogenous provirus proved to be difficult.46 The value of PCR was greatly enhanced when its real-time variant became available, which not only allows detection but also quantitation of FeLV proviral DNA.47 DNA PCR may be useful for clarifying inconclusive p27 antigen tests.

- **PCR for the detection of viral RNA** Detection of viral RNA added a new dimension to the diagnosis of FeLV infection.48 Whole blood, serum, plasma, saliva or faeces are used. This technique permits the detection and quantitation of free virus, in the absence of cells. RNA PCR does not always provide the same information as DNA provirus PCR: cats that have overcome FeLV antigenaemia (ie, have become FeLV p27-negative) remain provirus-positive but often are negative for FeLV RNA. In some cats small amounts of viral RNA can be found in plasma, saliva or faeces, although the p27 test remains negative.49 Usually, cats are tested for FeLV individually. However, if the cost of testing is a limiting factor, pooled saliva samples can be used for screening, as PCR is sensitive enough to detect a single infected cat in a pool of up to 30 samples. This approach may be chosen when screening shelters and multi-cat households.50

**Indirect detection methods**

The results of FeLV serology are difficult to interpret, because many cats develop antibodies to their own endogenous FeLV. The tests for VNA are not widely available (mainly restricted to the UK) and are used only infrequently.

**If the cost of testing is a limiting factor, pooled saliva samples can be used for screening, as PCR is sensitive enough to detect a single infected cat in a pool of up to 30 samples.**
**Disease management**

**General management**
In any feline community, FeLV-infected cats should be kept separate from uninfected individuals. They should also be confined strictly indoors to prevent virus spread in the neighbourhood. Preventing exposure of an immune-suppressed, retrovirus-infected cat to infectious agents carried by other animals offers additional health benefits. This is true in the home environment as well as in the veterinary hospital. Although test-positive cats can be housed in the same ward as other hospitalised patients, they should be kept in individual cages, and not in a ‘contagious ward’ with cats suffering from infections such as viral respiratory disease. Also, it may be prudent to avoid feeding uncooked meat, which may pose a risk of bacterial or parasitic infections.

Healthy FeLV-infected cats should be examined regularly. A complete blood count, biochemistry profile and urinalysis should be performed periodically, ideally every 6–12 months.

Both male and female retrovirus-infected healthy cats should be neutered to minimise the risk of virus transmission. Surgery is generally well tolerated. Virus transmission in the hospital can be avoided by simple precautions and routine cleaning. The virus is infectious only for a short while outside the host and is sensitive to all disinfectants including common soap.53

**Supportive treatment**
If FeLV-infected cats are sick, prompt and accurate diagnosis is important to allow early intervention. Many respond well to appropriate medication, although a longer or more aggressive course of therapy (eg, with antibiotics) may be needed than in retrovirus-negative cats. Corticosteroids, other immunosuppressive or bone marrow suppressive drugs should generally be avoided, unless used as a treatment for FeLV-associated malignancies or immune-mediated disease.

Good veterinary care is important – many FeLV viraemic cats may need fluid therapy. Secondary bacterial infections, especially with *M haemofelis*, will often respond to doxycycline. If stomatitis/gingivitis is present, corticosteroids should be considered to increase the food intake. Blood transfusions may be useful in anaemic cats and, in leukopenic cases, granulocyte colony-stimulating factor can be considered [EBM grade IV].55

Treatment regimes for lymphomas, particularly based on chemotherapeutic drugs, are now well established. Some cases of lymphoma respond well to chemotherapy, with remission expected in most cases, and some cats showing no recurrence within 2 years. Chemotherapy of FeLV-positive lymphomas will not resolve the persistent viraemia, and the prognosis for such cats is poor.56

**Immunomodulation**
Although reports of uncontrolled studies of immunomodulators frequently suggest dramatic clinical improvement (eg, when using poxvirus-based ‘paramunity inducers’), these effects were not confirmed in a controlled study [EBM grade I].57

**Antiviral therapy**
The efficacy of antiviral drugs is limited, and many have severe side effects in cats.58 There are only a few controlled studies that have demonstrated some effect. Feline interferon-omega inhibits FeLV replication in vitro, and treatment of viraemic cats with this cytokine has been shown to significantly improve clinical scores and extend survival times [EBM grade I].58 However, no viral parameters were measured throughout this study to support the hypothesis that interferon-omega actually exerted an antiviral effect.

An anti-retroviral compound routinely used is 3’-azido-2’,3’-dideoxythymidine (AZT). It effectively inhibits FeLV replication in vitro, and in vivo in experimental infections. It can reduce plasma virus load, improve the immunological and clinical status, increase quality of life, and prolong life expectancy in some FeLV-infected cats. It should be used at a dosage of 5–10 mg/kg q12h PO or SC. The higher doses should be used carefully as side effects (eg, non-regenerative anaemia) may develop [EBM grade I].60

**Vaccination**
The ABCD considers FeLV to be a non-core vaccine component (see box on page 571). In most circumstances, however, FeLV immunisation should be part of the routine vaccination programme for pet cats. It provides good protection against a potentially life-threatening infection, and the benefits outweigh any risk of adverse effects.
The best method of preventing the spread of infection is to isolate the infected individuals and to prevent interaction with uninfected housemates. It is realised, however, that it is not realistic to expect such quarantine enforcement from a cat owner.

Although protection conferred by the current vaccines is good, the ABCD does not recommend reliance on vaccination to protect FeLV-negative cats living together with FeLV-positive cats.

**Disease control in specific situations**

**Multi-cat households**

If a cat is diagnosed with FeLV in a multi-cat household, all resident cats should be tested. If other positive cats are identified, a test-and-removal programme – involving periodic testing and elimination of positive cats until all test negative – should be applied. The best method of preventing the spread of infection is to isolate the infected individuals and to prevent interaction with uninfected housemates. It is realised, however, that it is not realistic to expect such quarantine enforcement from a cat owner.

Although protection conferred by the current vaccines is good, the ABCD does not recommend reliance on vaccination to protect FeLV-negative cats living together with FeLV-positive cats.
Shelters
There are marked geographical differences in the prevalence of FeLV in rescue shelters in Europe, which may influence the policies on testing and vaccination. In some countries (eg, the UK) the prevalence is very low, while in others it is noticeably higher, with regional differences.

Sick FeLV-positive shelter cats should be euthanased. Some rescue shelters are successful in having confirmed FeLV-positive, healthy cats adopted by selected households. It must be ensured that such cats do not pose a risk to uninfected cats. This may require them being rehomed to environments where they will live in isolation or only with other infected cats.

Feline leukaemia virus transmission within a shelter should be minimised. Ideally, cats should be housed individually. If they are housed in groups, they should be tested, and positive and negative cats should be segregated. Vaccination may be considered.

Breeding catteries
The prevalence of FeLV infection is now very low in pedigree breeding catteries in some European countries. It is recommended that routine testing is maintained once or twice a year. Contact should be limited to cats from establishments that implement a similar screening programme. If any cats are allowed access outside (discouraged for pedigree breeding cats), they should be vaccinated.

Immunocompromised cats
❖ Feline immunodeficiency virus (FIV) positive cats In a long-term study where FIV-infected cats were vaccinated against FeLV infection, a clear benefit was shown [EBM grade III]. Therefore, under field conditions, immunocompromised cats with FIV infection should be vaccinated – but only if they are at risk: indoor-only FIV-positive cats should not be vaccinated against FeLV.

As the immune response in immunocompromised cats is decreased, more frequent boosters may be considered (in asymptomatic cats). The vaccination of FeLV-positive cats against FeLV is of no benefit whatsoever.

❖ Cats with chronic disease Acutely ill cats should not be vaccinated, but those with chronic illness such as renal disease, diabetes mellitus or hyperthyroidism should be vaccinated regularly if they are at risk of infection.

❖ Cats receiving corticosteroids or other immunosuppressive drugs Vaccination should be considered carefully in cats receiving corticosteroids or other immunosuppressive drugs. Depending on the dosage and duration of treatment, corticosteroids may suppress the immune response, particularly its cell-mediated arm. The use of corticosteroids at the time of vaccination should be avoided.

KEY POINTS
❖ Feline leukaemia virus (FeLV) affects cats worldwide.
❖ Over the past 25 years, the prevalence of FeLV infection has dropped considerably, thanks both to reliable tests for identifying viraemic carriers and to vaccines.
❖ Transmission of infection occurs through viral shedding (saliva, nasal secretions, milk, faeces) by FeLV-infected cats.
❖ In large groups of cats, around 30–40% will develop persistent viraemia, 30–40% show transient viraemia and 20–30% seroconvert; a minority (~5%) shows antigenaemia in the absence of viraemia.
❖ In viraemic queens, pregnancy usually results in embryonic death, stillbirth or in viraemic, ‘fading’ kittens.
❖ Young kittens are especially susceptible to FeLV infection.
❖ Most persistently viraemic cats die within 2–3 years.
❖ In low-prevalence areas, there may be a risk of false-positive results: a doubtful positive test result in a healthy cat should be confirmed, preferably by PCR for provirus.
❖ Cats infected with FeLV should remain indoors and receive a regular clinical check-up (every 6 months).
❖ Vaccination against common pathogens should be maintained. Inactivated vaccines are recommended
❖ Corticosteroids, other immunosuppressive or bone marrow-suppressive drugs should be avoided.
❖ All cats with an uncertain FeLV status should be tested prior to vaccination.
❖ All healthy cats at potential risk of exposure (outdoor access, FeLV-endemic area) should be vaccinated against FeLV.
❖ Kittens should be vaccinated at 8–9 weeks of age, with a second vaccination at 12 weeks, followed by a booster 1 year later.
❖ The ABCD suggests that in cats older than 3–4 years of age, a booster every 2–3 years suffices.
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3 Sarma PS, Tseng J, Lee YK, Gilden RV. Virus similar to RD114 virus lines would not have been possible without financial assistance of Christina Espert-Sanchez is gratefully acknowledged.


