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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 small 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 not horizontally 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.

European Advisory Board on Cat Diseases The European Advisory Board on Cat Diseases (ABCD) is a body of experts in immunology, vaccinology and clinical feline medicine that issues guidelines on prevention and management of feline infectious diseases in Europe, for the benefit of the health and welfare of cats. The guidelines are based on current scientific knowledge of the diseases and available vaccines concerned.

> An extended version of the feline leukaemia guidelines presented in this article is available at www.abcd-vets.org

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 against common pathogens should be maintained. Inactivated vaccines are recommended. The virus does not survive for long outside the host.

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.

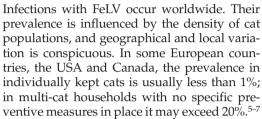


European Advisory Board on Cat Diseases www.abcd-vets.org Corresponding author: Hans Lutz Email: hlutz@vetclinics.uzh.ch



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



Over the past 25 years, the prevalence and importance of FeLV infection in Europe has greatly decreased – thanks to reliable tests, 'testand-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



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%. 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.¹⁷ 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.¹⁸

Clinical signs

The most common disease consequences of persistent FeLV viraemia are immune suppression, anaemia and lymphoma.⁸

The prognosis for persistently FeLVviraemic cats is poor, and most will develop disease. Of these, 70–90% will have died within 18 months to 3 years.⁸ Some may remain healthy for many years before one of the FeLV-related diseases develops, and occasional cases remain permanently healthy [EBM grade III].¹⁹ 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].²⁰ Viral and host factors, such as the virus subgroup and the cell-mediated immune response, influence the pathogenesis.

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

EBM ranking used in this article

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

Roudebush P, Allen TA, Dodd CE, Novotny BJ. Application of evidence-based medicine to veterinary clinical nutrition. *J Am Vet Med Assoc* 2004; **224**: 1765–71.

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.



CD4+ cells and – more importantly – loss of CD8+ lymphocytes have been reported.²¹

Whether or not showing clinical signs, every FeLV-viraemic cat is immune suppressed, with delayed and decreased primary and secondary antibody responses.²² 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, Crypto*coccus* 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.²³ Some clinical problems, such as chronic rhinitis and subcutaneous abscesses, may take much longer to resolve in FeLVinfected cats and may recur.

Anaemia

Cats infected with FeLV may develop different types of anaemia, mainly of the nonregenerative type. Regenerative anaemias associated with haemolysis are rare and may be related to secondary infections (eg, with *M haemofelis*) or to immune-mediated destruction.^{24,25} The FeLV-C subtype can interfere with a haem transport protein, which directly results in a non-regenerative anaemia (Fig 1).^{26,27} Other cytopenias may be present, in particular thrombocytopenia and neutropenia, probably caused by virus-induced immune-mediated mechanisms and myelosuppression.



FIG 1 Pale mucous membranes due to anaemia in a cat with persistent feline leukaemia virus infection. Courtesy of Tadeusz Frymus



FIG 2 Thoracic radiograph showing a cranial mediastinal mass, diagnosed as thymic lymphoma, in a cat with feline leukaemia. Courtesy of Julia Beatty

Lymphoma

Feline leukaemia virus causes mainly lymphoma and leukaemia, but other nonhaematopoietic malignancies are also encountered. Feline leukaemia virus-induced lymphomas are among the most frequent tumours in cats; myeloproliferative disorders are less common and not always associated with FeLV infection.28

Lymphomas have been classified according to their preferred anatomical location into the:

- Thymic or mediastinal form (Fig 2);
- Alimentary form, with tumours in organs of the digestive tract (Fig 3);
- Multicentric or peripheral form, affecting the lymph nodes;
- Atypical or extranodal form, presenting with solitary tumours in the kidneys (Fig 4), central nervous system (CNS) or skin.

Lymphoma is sometimes disseminated, with multiple organ and site involvement.²⁹ When the liver, spleen, bone marrow, blood and/or non-lymphoid organs are affected, the prognosis is poor, whereas forms without detectable FeLV infection carry a better prognosis.30

Different types of acute leukaemia have been described and classified according to the

neoplastic cell type.

Multiple fibrosarcomas in young viraemic cats have occasionally been associated with feline sarcoma virus (FeSV) infection; this virus is an in vivo recombinant resulting from the integration of cellular oncogenes into the FeLV-A genome.³¹ However, solitary fibrosarcomas or feline injection site sarcomas are related to neither FeLV nor FeSV infection.



FIG 3 Mesenteric lymphadenopathy in a cat with alimentary lymphoma associated with feline leukaemia. Courtesv of Julia Beatty

Other diseases linked to FeLV infection

Immune-mediated diseases may follow a FeLV infection, including haemolytic anaemia, glomerulonephritis and polyarthritis. 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.

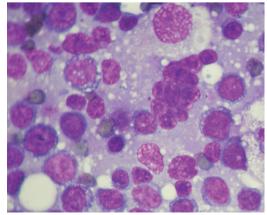
Neurological disease (distinct from CNS lymphoma) occurs mainly as peripheral neuropathies, presenting as anisocoria, mydriasis, Horner's syndrome, urinary incontinence, abnormal vocalisation, hyperaesthesia, paresis and paralysis.³⁵ Indeed, FeLV may be directly neuropathogenic.36

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

FIG 4 Lymphoblasts in a renal fine needle aspirate from a cat with renal lymphoma associated with feline leukaemia. Courtesy of Albert Lloret



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 immune chromatography 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

Interpret with care!

Virus isolation usually produces a positive result first after FeLV infection, followed within a few days by DNA and RNA PCR, ELISA, and still later by IFA.⁵¹ Persistently viraemic cats are usually positive in all tests.

In veterinary practice, antigen ELISA and immunochromatography are used most commonly. As the prevalence of FeLV infection has decreased in many European countries, the potential for false-positive results increases. A doubtful positive result in a healthy cat should therefore always be confirmed, preferably using provirus PCR (DNA PCR) offered by a reliable laboratory. A positive test result in a cat showing clinical signs that are consistent with FeLV infection is more reliable – in these cats the prevalence of viraemia is higher.

Cats testing positive may overcome their viraemia after 2–16 weeks; in rare cases it takes even longer. Therefore, every test-positive cat without clinical signs should be separated and retested; depending on the owner's compliance, this can be done for up to 1 year. By this stage, there is little chance that the cat will clear its viraemia.

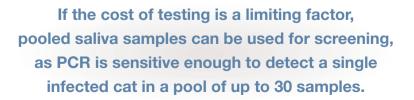
Cats that turn negative for virus isolation, ELISA, immunochromatography, IFA and RNA PCR may remain positive for DNA PCR, probably for life [EBM grade I].⁴⁹ These cats should be considered latently infected. The clinical significance of this state is low in most cats, but, in rare instances, chronic stress, immune suppression or co-infection with other viruses may lead to reactivation. Such cats should be considered as potential sources of infection.⁵²

In summary, cats should be initially tested for p27. If the result is inconclusive for any reason, the test should be repeated by a reliable laboratory, using an alternative method, preferably DNA PCR for provirus.

> 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.



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 immunesuppressed, 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. **Routine vaccination**

Both male and female retrovirus-infected healthy cats should be neutered to minmaintained. However, FeLV-infected cats may not imise the risk of virus mount adequate immune responses, as has been transmission. Surgery is found with rabies vaccines.54 Protection by vaccination generally well tolerated. may therefore not be comparable with that in healthy, Virus transmission in the uninfected cats. If these cats are allowed to roam - which is strongly advised against, certainly in rabies-endemic hospital can be avoided areas - more frequent vaccinations should be considered. by simple precautions Inactivated vaccines are generally recommended as, and routine cleaning. in immune-suppressed cats, modified-live virus may The virus is infectious only regain pathogenic potential and cause disease. 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 retrovirusnegative 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

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.



of FeLV-infected cats

Vaccination programmes to prevent

common infectious diseases should be

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 interferonomega 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].⁵⁹ 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.

Vaccination recommendations

The vaccines

The first commercial FeLV vaccine was introduced in the USA in 1984. It was based on conventionally prepared FeLV antigens, and it protected cats from viraemia.⁶¹ Several FeLV vaccines are now available in Europe, some of them obtained through recombinant DNA technology. One such vaccine contains the viral envelope glycoprotein and part of the transmembrane protein expressed in *Escherichia coli* – it was the first genetically engineered vaccine for companion animals.⁶²

A more recent preparation uses a canarypox virus vector that carries the genes for the envelope glycoprotein gp70, and the nucleocapsid protein p27.⁶³ After injection, there is a single round of poxvirus replication, which is sufficient for expression of the inserted FeLV genes. The protective effect is achieved by stimulating cellular immunity, which leads to rapid development of neutral-ising antibodies when vaccinated cats encounter the field virus.⁵¹

General considerations

The differences between the various brands of FeLV vaccines are more conspicuous than for vaccines against other feline infectious diseases: there are demonstrable differences in achieving protection. However, the results of comparative vaccine efficacy studies can be misleading, because of differences in the protocols used – such as the route of challenge, the challenge strain used and the criteria for defining protection.⁶⁴ Different studies of the same vaccine have produced contrasting results. The early FeLV vaccines, which are no longer on the market, performed poorly in some independent vaccine efficacy studies.

No FeLV vaccine provides 100% efficacy of protection and none prevents infection. Cats that overcome p27 antigenaemia without exception become provirus-positive in the blood and also positive for viral RNA in plasma, although at very low levels compared with persistently viraemic cats. These experiments confirm that FeLV vaccination neither induces sterilising immunity nor protects from infection [EBM grade III].⁶⁵

Long-term observations of vaccinated cats after experimental challenge indicate that low levels of RNA viraemia and of proviral DNA are not clinically impor-

tant, and these cats can be regarded as protected.

Non-core vaccine The ABCD considers vaccines that protect against FeLV infections as being non-core.

To vaccinate – or not?

In most circumstances, 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. If the possibility of exposure to FeLV can be excluded, vaccination is not required. Geographical variations in the prevalence of FeLV may therefore influence the decision as to whether or not to vaccinate. In some European countries, FeLV has

disappeared, whereas in others it is still a significant health issue. However, owners' circumstances – and their cats' lifestyle – might change, leading to potential exposure, particularly when

moving house. This possibility should be considered, especially in kittens presented for primary vaccination.

Primary course

All cats at risk of exposure should be vaccinated – kittens at the age of 8–9 weeks and again at 12 weeks, together with core vaccine components.⁶⁶ As the combination of different immunogens within one syringe is only legal when the company has registered it for the country of interest, the local veterinary regulations should be consulted.

If the FeLV status of a cat is unknown, it should be tested for FeLV antigenaemia before vaccination in order to avoid 'vaccine failures'; these are likely when cats already infected before vaccination develop FeLV-related clinical signs. If FeLV infection before vaccination is unlikely, testing may not be needed; for example, kittens from a FeLV-negative mother and father (an infected male cat may transmit infection during mating through biting), without contact with other cats.

Booster vaccinations

No published data support a duration of immunity of longer than 1 year after primary vaccination, and most vaccine producers therefore recommend annual boosters. However, in view of the significantly lower susceptibility of adult cats to FeLV infection, the ABCD suggests that a booster

> every 2–3 years is sufficient for cats older than 3–4 years of age.

No FeLV vaccine provides 100% efficacy of protection and none prevents infection.

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 testand-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].¹⁹ 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

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 marrowsuppressive 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.

Immunocompromised cats with FIV infection should be vaccinated against FeLV, – but only if they are at risk of infection.

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.

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References

- Coffin JM. Structure, replication, and recombination of retrovirus genomes: some unifying hypotheses. J Gen Virol 1979; 42: 1–26.
- 2 Soe LH, Devi BG, Mullins JI, Roy-Burman P. Molecular cloning and characterization of endogenous feline leukemia virus sequences from a cat genomic library. *J Virol* 1983; 46: 829–40.
- 3 Sarma PS, Tseng J, Lee YK, Gilden RV. Virus similar to RD114 virus in cat cells. *Nat New Biol* 1973; **244**: 56–9.
- 4 Anderson MM, Lauring AS, Burns CC, Overbaugh J. Identification of a cellular cofactor required for infection by feline leukemia virus. *Science* 2000; 287: 1828–30.
- 5 Hosie MJ, Robertson C, Jarrett O. Prevalence of feline leukaemia virus and antibodies to feline immunodeficiency virus in cats in the United Kingdom. *Vet Rec* 1989; **125**: 293–97.
- 6 Levy JK, Scott HM, Lachtara JL, Crawford PC. Seroprevalence of feline leukemia virus and feline immunodeficiency virus infection among cats in North America and risk factors for seropositivity. J Am Vet Med Assoc 2006; 228: 371–76.
- 7 Lutz H, Lehmann R, Winkler G, et al. Feline immunodeficiency virus in Switzerland: clinical aspects and epidemiology in comparison with feline leukemia virus and coronaviruses. *Schweiz Arch Tierheilkd* 1990; **132**: 217–25.
- 8 Hardy WD Jr, Hess PW, MacEwen EG, et al. Biology of feline leukemia virus in the natural environment. *Cancer Res* 1976; 36: 582–88.
- 9 Pacitti AM, Jarrett O, Hay D. Transmission of feline leukaemia virus in the milk of a non-viraemic cat. Vet Rec 1986; 118: 381–84.
- 10 Grant CK, Essex M, Gardner MB, Hardy WD, Jr. Natural feline leukemia virus infection and the immune response of cats of different ages. *Cancer Res* 1980; **40**: 823–29.
- 11 Lutz H, Pedersen NC, Theilen GH. Course of feline leukemia virus infection and its detection by enzyme-linked immunosorbent assay and monoclonal antibodies. *Am J Vet Res* 1983; 44: 2054–59.
- 12 Rojko JL, Hoover EA, Mathes LE, Olsen RG, Schaller JP. Pathogenesis of experimental feline leukemia virus infection. *J Natl Cancer Inst* 1979; 63: 759–68.
- 13 Hoover EA, Schaller JP, Mathes LE, Olsen RG. Passive immunity to feline leukemia: evaluation of immunity from dams naturally infected and experimentally vaccinated. *Infect Immun* 1977; **16**: 54–9.
- 14 Rojko JL, Hoover EA, Quackenbush SL, Olsen RG. Reactivation of latent feline leukaemia virus infection. *Nature* 1982; 298: 385–88.
- 15 Boretti FS, Ossent P, Bauer-Pham K, et al. Recurrence of feline leukemia virus (FeLV) and development of fatal lymphoma concurrent with feline immunodeficiency virus (FIV) induced

immune suppression. Proceedings of the 7th International Feline Retrovirus Research Symposium, Pisa, Italy, 2004.

- 16 Weijer K, UytdeHaag FG, Jarrett O, Lutz H, Osterhaus AD. Postexposure treatment with monoclonal antibodies in a retrovirus system: failure to protect cats against feline leukemia virus infection with virus neutralizing monoclonal antibodies. *Int J Cancer* 1986; **38**: 81–7.
- 17 Lutz H, Pedersen N, Higgins J, Hubscher U, Troy FA, Theilen GH. Humoral immune reactivity to feline leukemia virus and associated antigens in cats naturally infected with feline leukemia virus. *Cancer Res* 1980; 40: 3642–51.
- 18 Flynn JN, Dunham SP, Watson V, Jarrett O. Longitudinal analysis of feline leukemia virus-specific cytotoxic T lymphocytes: correlation with recovery from infection. J Virol 2002; 76: 2306–15.
- 19 Hofmann-Lehmann R, Holznagel E, Aubert A, Ossent P, Reinacher M, Lutz H. Recombinant FeLV vaccine: long-term protection and effect on course and outcome of FIV infection. *Vet Immunol Immunopathol* 1995; 46: 127–37.
- 20 Hoover EA, Olsen RG, Hardy WD Jr, Schaller JP, Mathes LE. Feline leukemia virus infection: age-related variation in response of cats to experimental infection. J Natl Cancer Inst 1976; 57: 365–69.
- 21 Ogilvie GK, Sundberg JP, O'Banion MK, Badertscher RR 2nd, Wheaton LG, Reichmann ME. Clinical and immunologic aspects of FeLV-induced immunosuppression. *Vet Microbiol* 1988; 17: 287–96.
- 22 Perryman LE, Hoover EA, Yohn DS. Immunologic reactivity of the cat: immunosuppression in experimental feline leukemia. *J Natl Cancer Inst* 1972; **49:** 1357–65.
- 23 Tenorio AP, Franti CE, Madewell BR, Perdersen NC. Chronic oral infections of cats and their relationship to persistent oral carriage of feline calici-, immunodeficiency, or leukaemia viruses. *Vet Immunol Immunopathol* 1991; **29:** 1–14.
- 24 Scott DW, Schultz RD, Post JE, Bolton GR, Baldwin CA. Autoimmune haemolytic anemia in the cat. *J Am Anim Hosp Assoc* 1973; **9:** 530–47.
- 25 Kociba GJ. Hematologic consequences of feline leukaemia virus infection. In: Kirk RW, ed. Current veterinary therapy, Vol XIII. Philadelphia: WB Saunders, 1986: 448.
- 26 Cotter SM. Anaemia associated with feline leukemia virus infection. J Am Vet Med Assoc 1979; 175: 1191–94.
- 27 Quigley JG, Burns CC, Anderson MM, et al. Cloning of the cellular receptor for feline leukemia virus subgroup C (FeLVC), a retrovirus that induces red cell aplasia. *Blood* 2000; **95**: 1093–99.
- 28 Louwerens M, London CA, Pedersen NC, Lyons LA. Feline lymphoma in the postfeline leukemia virus era. J Vet Intern Med 2005; 19: 329–35.
- 29 Reinacher M, Theilen G. Frequency and significance of feline leukemia virus infection in necropsied cats. *Am J Vet Res* 1987; 48: 939–45.
- 30 Vail DM, Thamm D. Hematopoietic tumors. In: Ettinger SJ, Feldman EC, eds. Textbook of veterinary internal medicine. Missouri: Elsevier Saunders, 2005: 732–47.
- 31 Donner L, Fedele LA, Garon CF, Anderson SJ, Sherr CJ. McDonough feline sarcoma virus: characterization of the molecularly cloned provirus and its feline oncogene (vfms). *J Virol* 1982; 41: 489–500.
- 32 Moore FM, Emerson WE, Cotter SM, DeLellis RA. Distinctive peripheral lymph node hyperplasia of young cats. *Vet Pathol* 1986; 23: 386–91.
- 33 Reinacher M. Feline leukemia virus-associated enteritis a condition with features of feline panleukopenia. *Vet Pathol* 1978; 24: 1–4.

- 34 Reinacher M. Diseases associated with spontaneous feline leukaemia virus (FeLV) infection in cats. *Vet Immunol Immunopathol* 1989; **21:** 85–95.
- 35 Haffer KN, Sharpee RL, Beckenhauer W, Koertje WD, Fanton RW. Is the feline leukaemia virus responsible for neurologic abnormalities in cats? *Vet Med* 1987; 82: 802–5.
- 36 Dow SW, Hoover EA. Neurologic disease associated with feline retroviral infection. In: Kirk RW, Bonagura JD, eds. Current veterinary therapy, Vol XI. Philadelphia: WB Saunders, 1992: 1010.
- 37 Lutz H, Pedersen NC, Harris CW, Higgins J. Detection of feline leukemia virus infection. *Feline Pract* 1980; **10**: 13–23.
- 38 Lutz H, Pedersen NC, Durbin R, Theilen GH. Monoclonal antibodies to three epitopic regions of feline leukemia virus p27 and their use in enzyme-linked immunosorbent assay of p27. J Immunol Methods 1983; 56: 209–20.
- 39 Hartmann K, Werner RM, Egberink H, Jarrett O. Comparison of six in-house tests for the rapid diagnosis of feline immunodeficiency and feline leukaemia virus infections. *Vet Rec* 2001; **149**: 317–20.
- 40 Hartmann K, Griessmayr P, Schulz B, et al. Quality of different in-clinic test systems for feline immunodeficiency virus and feline leukaemia virus infection. *J Feline Med Surg* 2007; **9:** 439–45.
- 41 Pinches MD, Diesel G, Helps CR, Tasker S, Egan K, Gruffydd-Jones TJ. An update on FIV and FeLV test performance using a Bayesian statistical approach. *Vet Clin Pathol* 2007; **36**: 141–47.
- 42 Hawks DM, Legendre AM, Rohrbach BW. Comparison of four test kits for feline leukemia virus antigen. *J Am Vet Med Assoc* 1991; **199:** 1373–77.
- 43 Floyd K, Suter PF, Lutz H. Granules of blood eosinophils are stained directly by anti immunoglobulin fluorescein isothiocyanate conjugates. *Am J Vet Res* 1983; **44**: 2060–63.
- 44 Jarrett O. Feline leukaemia virus diagnosis. Vet Rec 1980; 106: 513.
- 45 Jarrett O, Golder MC, Weijer K. A comparison of three methods of feline leukaemia virus diagnosis. *Vet Rec* 1982; **110**: 325–28.
- 46 Jackson ML, Haines DM, Taylor SM, Misra V. Feline leukemia virus detection by ELISA and PCR in peripheral blood from 68 cats with high, moderate, or low suspicion of having FeLV-related disease. *J Vet Diagn Invest* 1996; **8**: 25–30.
- 47 Hofmann-Lehmann R, Huder JB, Gruber S, Boretti F, Sigrist B, Lutz H. Feline leukaemia provirus load during the course of experimental infection and in naturally infected cats. *J Gen Virol* 2001; 82: 1589–96.
- 48 Tandon R, Cattori V, Gomes-Keller MA, et al. Quantitation of feline leukaemia virus viral and proviral loads by TaqMan realtime polymerase chain reaction. *J Virol Methods* 2005; **130**: 124–32.
- 49 Gomes-Keller MA, Gonczi E, Tandon R, et al. Detection of feline leukemia virus RNA in saliva from naturally infected cats and correlation of PCR results with those of current diagnostic methods. *J Clin Microbiol* 2006; 44: 916–22.
- 50 Gomes-Keller MA, Tandon R, Gonczi E, Meli ML, Hofmann-Lehmann R, Lutz H. Shedding of feline leukemia virus RNA in

saliva is a consistent feature in viraemic cats. *Vet Microbiol* 2006; **112:** 11–21.

- 51 Hofmann-Lehmann R, Tandon R, Boretti FS, et al. Reassessment of feline leukaemia virus (FeLV) vaccines with novel sensitive molecular assays. *Vaccine* 2006; **24:** 1087–94.
- 52 Lutz H, Pedersen NC, Higgins J, Harris HW, Theilen GH. Quantitation of p27 in the serum of cats during natural infection with feline leukemia virus. In: Hardy WD, Essex M, McClelland A, eds. Feline leukemia virus, Development in cancer research 4. North Holland: Elsevier, 1980: 497–505.
- 53 Francis DP, Essex M, Gayzagian D. Feline leukemia virus: survival under home and laboratory conditions. *J Clin Microbiol* 1979; **9**: 154–56.
- 54 Franchini M. Die Tollwutimpfung von mit felinem leukämivirus infizierten katzen. Vet Diss Zürich Univ, 1990.
- 55 Fulton R, Gasper PW, Ogilvie GK, Boone TC, Dornsife RE. Effect of recombinant human granulocyte colony-stimulating factor on hematopoiesis in normal cats. *Exp Hematol* 1991; **19**: 759–67.
- 56 Ettinger SN. Principles of treatment for feline lymphoma. *Clin Tech Small Anim Pract* 2003; **18**: 98–102.
- 57 Hartmann K, Block A, Ferk G, Vollmar A, Goldberg M, Lutz H. Treatment of feline leukemia virus-infected cats with paramunity inducer. *Vet Immunol Immunopathol* 1998; 65: 267–75.
- 58 Hartmann K. Antiviral and immunodulatory chemotherapy. In: Greene CE, ed. Infectious diseases of the dog and cat. 3rd edn. St Louis, USA: Elsevier Saunders, 2006: 10–25.
- 59 de Mari K, Maynard L, Sanquer A, Lebreux B, Eun HM. Therapeutic effects of recombinant feline interferon-omega on feline leukemia virus (FeLV)-infected and FeLV/feline immunodeficiency virus (FIV)-coinfected symptomatic cats. J Vet Intern Med 2004; 18: 477–82.
- 60 Hartmann K. FeLV treatment strategies and prognosis. Compend Contin Educ Pract Vet 2005; 27 (suppl): 14–26.
- 61 Lewis MG, Mathes LE, Olsen RG. Protection against feline leukemia by vaccination with a subunit vaccine. *Infect Immun* 1981; 34: 888–94.
- 62 Kensil CR, Barrett C, Kushner N, et al. Development of a genetically engineered vaccine against feline leukemia virus infection. *J Am Vet Med Assoc* 1991; **199:** 1423–27.
- 63 Tartaglia J, Jarrett O, Neil JC, Desmettre P, Paoletti E. Protection of cats against feline leukemia virus by vaccination with a canarypox virus recombinant, ALVAC-FL. J Virol 1993; 67: 2370–75.
- 64 Sparkes AH. Feline leukaemia virus and vaccination. J Feline Med Surg 2003; 5: 97–100.
- 65 Hofmann-Lehmann R, Cattori V, Tandon R, et al. Vaccination against the feline leukaemia virus: outcome and response categories and long-term follow-up. *Vaccine* 2007; **25**: 5531–39.
- 66 Brunner C, Kanellos T, Meli ML, et al. Antibody induction after combined application of an adjuvanted recombinant FeLV vaccine and a multivalent modified live virus vaccine with a chlamydial component. *Vaccine* 2006; **24**: 1838–46.

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