Feline Leukaemia (2012 edition)

Virus
Feline leukaemia virus (FeLV) is a gamma retrovirus affecting domestic cats worldwide; it was first detected in 1964 by electron microscopy, after experimental transmission of cell-free material (Jarrett et al. 1964). FeLV also infects small wild cats including Felis silvestris and European and Iberian lynxes. Retroviruses are enveloped RNA viruses and rely on a DNA intermediate for replication. The single-stranded RNA genome is reverse transcribed into DNA, which is usually incorporated into the host cell genome through an integrase (Temin & Mizutani 1970). The integrated DNA is known as the "provirus". After reverse transcription, synthesis of viral proteins occurs according to the conventional mechanisms of transcription, with virion assembly taking place near the cytoplasmic membrane and budding from the cell surface (Coffin 1979).

Infection by a retrovirus usually does not lead to cell death. The FeLV genome contains three genes: envelope (env) gene coding for the glycoprotein gp70 (SU) and the transmembrane protein p15 E (TM); the polymerase (pol) gene coding for the reverse transcriptase, protease and integrase; and the group specific antigen (gag) gene coding for the structural proteins of the virus including p27 (Coffin 1979). Besides this "exogenous" FeLV, in the domestic cat two forms of endogenous gamma retroviruses are known: the endogenous feline leukaemia virus (enFeLV) (Soe et al., 1983) and the RD114 virus (Sarma et al., 1973).

The enFeLV is thought to have originated hundred thousands of years ago in cats that had eaten mice viraemic with a murine leukaemia virus (MuLV), which was able to incorporate its genome into the germ line DNA of the predator. This MuLV was then inherited by all offspring. The amount of enFeLV varies between breeds of cats, including Felis silvestris, suggesting that this recombination with MuLVs is a continuing phenomenon (Tandon et al., 2007). The enFeLV genome is incomplete and therefore does not replicate (Soe et al., 1983).

The RD114 virus is of primate origin, replication competent, and thought to have originated hundred thousands of years ago from an ancestor cat that had preyed on an early primate infected with this virus. Feline cells are not susceptible to infection with the RD114 virus, which is not pathogenic for cats. (Barbacid et al., 1977).

FeLV exists in the subtypes A, B, C, and T (Anderson et al., 2000; Russell & Jarrett 1978). The subtypes are defined by their host cell spectrum; antigenically they are closely related. The subtype A is ubiquitous and involved in every infection, whereas subtype B originates from recombination of FeLV A with enFeLV. Subtype C is the result of mutations in the env gene, and subtype T has a tropism for T lymphocytes.

FeLV does not survive for long outside the host as it is destroyed readily by disinfectants, soap, heating and drying. Transmission via fomites is unlikely. The virus will survive, however, if it is kept moist at room temperature so that there is
potential for iatrogenic transmission to occur via contaminated needles, surgical instruments or blood transfusions.

**Epidemiology**

FeLV occurs worldwide. Its prevalence may be influenced by the density of cat populations, and there may be noticeable geographical and local variation. There is little reliable information on the current prevalence of FeLV in different countries. In some European countries, the USA and Canada, the prevalence of FeLV infection in individually kept cats seems to be very low, usually less than 1\% (Hosie et al., 1989; Levy et al., 2006; Lutz et al., 1990). In large multi-cat households without specific preventive measures for introduction of FeLV, the prevalence may be greater than 20\%.

Over the last 25 years, the prevalence and importance of FeLV infection in Europe has greatly diminished due to the availability of reliable tests, the test and removal programmes initiated, improved understanding of the pathogenesis and the introduction of highly efficacious FeLV vaccines.

Cats with FeLV viraemia act as a source of infection. Virus is shed from an infected cat in saliva, nasal secretions, faeces, and milk (Hardy et al., 1976; Pacitti et al., 1986). Risk factors for infection are young age, high population density and poor hygiene. FeLV infection is transmitted mainly by mutual grooming, but also through bites. In viraemic queens, pregnancy usually results in embryonic death, stillbirth or in viraemic kittens which fade away rapidly. In latently infected queens, usually transmission does not take place during pregnancy. However rarely, some (but not all) kittens may become viraemic after birth (Pacitti et al., 1986). In these instances, transmission takes place from individual mammary glands where the virus can remain latent until the mammary gland develops during the last period of pregnancy. Young kittens are especially susceptible to FeLV infection while with age, cats become increasingly resistant to infection (Hoover et al., 1976; Grant et al. 1980). Although aged cats are generally accepted to be more resistant to infection, they can still be infected providing the challenge is sufficiently severe. Usable FeLV infection while with age, cats become increasingly resistant to infection (Hoover et al., 1976; Grant et al. 1980). Although aged cats are generally accepted to be more resistant to infection, they can still be infected providing the challenge is sufficiently severe.

**Pathogenesis**

In most cases, infection starts in the oropharynx where FeLV infects individual lymphocytes that are transported to the bone marrow. Once the rapidly dividing bone marrow cells become infected, large amounts of virions are produced and as a consequence viraemia develops within a few weeks of infection. Often, viraemia may develop several months after constant exposure to shedding cats (Lutz et al., 1983b). Viraemia leads to the infection of salivary glands and intestinal linings, and virus is shed in large quantities in saliva and faeces (Rojko
et al., 1979).
Frequently, the development of viraemia as well as established viraemia may be overcome by a functioning immune system (transient viraemia) (Lutz et al., 1980a). Such cats (so-called “regressor” cats) are generally not at risk of developing disease. In a multicat household without control of FeLV infection, 30-40 % of the cats develop persistent viraemia, 30-40 % exhibit transient viraemia and 20-30 % seroconvert without ever being detectably viraemic. A smaller proportion (~5 %) exhibits an atypical course of infection showing antigenaemia but no viraemia (Hoover et al. 1977). A cat that has overcome viraemia remains latently infected, i.e. from some cells that remain provirus-positive infectious virus can be recovered when for instance bone marrow cells are kept in cell culture for several weeks (Rojko et al., 1982). Reactivation may also take place in vivo when latently infected cats experience immune suppression or chronic severe stress (Boretti et al., 2004). It is not clear how often this happens but it is generally believed to be a rare occurrence. Generally, up to 10 % of all feline blood samples submitted to a laboratory prove to be provirus-positive and p27 negative, and as in some of these cats, FeLV may be reactivated, they should be considered latently infected (Boretti et al., 2004). It appears likely that no cat can completely clear FeLV infection from all cells. This might explain why virus neutralising antibodies persist in recovered cats for many years in the absence of overt infection, or exposure to viraemic cats. If this is the case, the risk of such latent persistence leading to re-excretion of virus or the development of disease, must be extremely low since recovered cats appear to have the same life expectancy as cats that have never been exposed to FeLV. However, proviral DNA has been found in the tumours of ostensibly FeLV-free cats (Jackson et al., 1993), suggesting that the virus might be involved in an early event in the pathogenesis of the tumour and then persist only as a provirus, possibly in a defective form. Local foci of infections or latent virus may also be the source of the FeLV p27 antigen that is sometimes found in the plasma of cats from which infectious virus cannot be isolated, the so-called ‘discordant’ cats. of the tumour and then persist only as a provirus, possibly in a defective form. Local foci of infections or latent virus may also be the source of the FeLV p27 antigen that is sometimes found in the plasma of cats from which infectious virus cannot be isolated, the so-called ‘discordant’ cats.
The typical clinical signs of FeLV infection usually develop in viraemic cats, sometimes not until after several years of viraemia (Hardy et al., 1976).

**Immunity**

**Passive immunity**

Experimentally, susceptible kittens can be protected from FeLV infection following passive immunisation with high titred antisera against FeLV (Hoover et al., 1977). Once persistent viraemia has become established, treatment with virus neutralizing monoclonal antibodies to FeLV is ineffective (Weijer et al.,
Active immune response
Most cats that overcome FeLV viraemia exhibit high antibody titres to the virus (ELISA or VN) (Lutz et al., 1980a; Russel & Jarrett, 1978); antibodies are directed against all components of the virus (Lutz et al., 1980a). In most – but not all – cats that overcame viraemia, virus neutralising antibodies can be detected (Flynn et al., 2002). Since not all immune cats develop high antibody titres, it was concluded that cytotoxic T-lymphocytes (CTLs) are also important in FeLV immunity (Lutz et al., 1980a). Indeed, CTLs specific for FeLV appear before virus neutralising antibodies, and following adoptive transfer of FeLV specific CTLs stimulated in vitro, the viral load in FeLV viraemic cats could be lowered (Flynn et al., 2002).

Clinical signs
FeLV infection can cause variable and multiple clinical signs. The most common disease consequences of persistent FeLV viraemia are: immune suppression, anaemia, and lymphoma (Hardy et al., 1976; Hardy et al., 1973). The prognosis for persistently FeLV viraemic cats is poor and most will develop an FeLV related disease. 70-90% of these cats will be dead within 18 months to three years (Hardy et al., 1976). Some persistently viraemic cats may remain healthy for a prolonged period (many years) before FeLV related disease develops and occasional cases remain healthy indefinitely (Hofmann-Lehmann et al., 1995). Some persistently viraemic cats may remain healthy for a prolonged period (many years) before FeLV related disease develops and occasional cases remain healthy indefinitely (Hofmann-Lehmann et al., 1995; EBM grade III). Age of the cat at the time of the infection is the most important factor determining the clinical outcome (Hoover et al., 1976; EBM grade III). Viral and host factors, including the virus subgroup and cell-mediated immune response, influence the pathogenesis of infection within individual infected cats.

Immune suppression
Immune suppression in FeLV is more complex and severe than the more selective one caused by FIV infection. Several abnormalities have been reported including thymic atrophy, lymphopenia, neutropenia, neutrophil function abnormalities, loss of CD4+, and more importantly loss of CD8+ (Ogilvie et al., 1988). Whether recognisable clinical signs are present or not, every FeLV-viraemic cat is immune suppressed (Orosz et al., 1985a; Orosz et al., 1985b; Perryman et al., 1972), with delayed and decreased primary and secondary antibody responses. The immune suppression can have many clinical consequences and may lead to infection with other primary infectious agents to which cats would be normally resistant, such as Salmonella spp. In addition, there may be exacerbation of disease caused by other pathogens, such as pox virus, Mycoplasma haemofelis.
and Cryptococcus, and infections normally not pathogenic in cats, e.g. due to Toxoplasma gondii. Concurrent FeLV infection may also predispose to chronic refractory disease such as stomatitis and chronic rhinitis (Knowles et al., 1989; Tenorio et al., 1991). Some clinical problems such as chronic rhinitis and subcutaneous abscesses may take much longer to resolve in FeLV-infected cats and unexpected recurrences may arise.

Anaemia
FeLV-infected cats may develop many different types of anaemia, which are mainly non-regenerative and rarely regenerative. Regenerative anaemias, associated with haemolysis may be related to secondary opportunistic infections, for example by Mycoplasma haemofelis, or to immune-mediated destruction (Scott et al., 1973; Kociba, 1986). FeLV-C can interfere with a haem transport protein (Cotter, 1979; Quigley et al., 2000), which directly results in a non-regenerative anaemia. Non-regenerative anaemias may be caused by chronic inflammatory mechanisms, myelodestruction, myelosuppression (either pancytopenia or pure erythrocyte aplasia) and myeloproliferative disease. Other cytopenias may be present, in particular thrombocytopenia and neutropenia, probably caused by virus-induced immune-mediated mechanisms and myelosuppression. in particular thrombocytopenia and neutropenia, probably caused by virus-induced immune-mediated mechanisms and myelosuppression.

Lymphoma
FeLV may cause different tumours in cats, mainly lymphoma and leukaemia, but also other non-haematopoietic malignancies. FeLV-induced lymphomas are among the most frequent tumour forms of the cat; myeloproliferative disorders are less common and not always associated with FeLV infection (Francis et al., 1979a; Louwerens et al., 2005). Different forms of lymphoma have been classified according to its most frequent anatomic location:
- The thymic or mediastinal form;
- The alimentary form, where tumour cells are associated with organs of the digestive tract;
- The multicentric or peripheral form, which affects lymph nodes;
- The atypical or extranodal form, presenting with solitary tumours in kidneys, CNS, or skin;
In some cases, lymphoma is disseminated with multiple organ and site involvement. (Hardy et al., 1970; Reinacher & Theilen 1987). Liver, spleen, bone marrow, blood and/or non-lymphoid organ involvement are associated with a poor prognosis (Vail & Thamm, 2005)
It is also possible for cats to develop some forms of lymphoma with no known or detectable association with FeLV infection, which carries a better prognosis (Vail & Thamm, 2005).
Different types of acute leukaemia have been described depending on the
neoplastic transformed cell type. Multiple fibrosarcomas in young viraemic cats have occasionally been associated with infection with FeSV (feline sarcoma virus), a recombinant virus developing from recombination of the FeLV-A genome with cellular oncogenes (Hardy, 1981; Donner et al., 1982; Besmer, 1983). However, solitary fibrosarcomas or feline injection site sarcomas are related to neither FeLV nor FeSV infection.

Other diseases
Immune-mediated diseases associated to FeLV infection have been reported, including haemolytic anaemia, glomerulonephritis and polyarthritis. Antigen-antibody complex deposition and loss of T-suppressor activity may be the main factors contributing to immune-mediated diseases. T-suppressor activity may be the main factors contributing to immune-mediated diseases.

Benign peripheral lymphadenopathy has been diagnosed in FeLV-infected cats (Moore et al., 1986); a clinical picture with potential to be mistaken as peripheral lymphoma. Chronic enteritis associated with degeneration of intestinal epithelial cells and crypt necrosis has been associated with FeLV-infection in cats in which virus is present in intestinal crypt cells (Reinacher, 1987). Inflammatory and degenerative liver disease has also been described associated with FeLV infection (Reinacher, 1989).

Reproductive disorders and fading kitten syndrome have been also reported. Foetal resorption, abortion and neonatal death are the main manifestations (Hardy et al., 1981). Fading kittens and other reproductive disorders are rarely observed these days, largely as a result of the very low prevalence of infection in pedigree breeding cats, achieved by routine testing.

Neurological disease not associated to CNS lymphoma or opportunistic CNS infections has been described, mainly peripheral neuropathies presenting as anisocoria, mydriasis, Horner’s syndrome, urinary incontinence, abnormal vocalization, hyperesthesia, paresis and paralysis (Haffer et al., 1987). Neuropathogenicity has been investigated as a possible direct effect of the virus (Dow & Hoover, 1992).

Diagnosis
ELISA (p27)
The first p27 ELISA tests were based on polyclonal antibodies; such tests had the advantage of allowing quantitation of p27 but had a tendency to produce false-positive results as the antibodies did not detect only viral proteins but occasionally also non-viral components (Lutz et al., 1980b; Lutz et al., 1980c). Improved ELISA tests based on monoclonal antibodies to p27 were introduced later to detect p27 capsid protein of exogenous FeLV present in blood or serum (Lutz et al., 1983a; Lutz et al., 1983b). This assay utilises a single monoclonal antibody specific for an epitope (A) of p27 fixed to a solid phase. The serum sample to be tested is mixed with one or two additional monoclonal antibodies
specific for epitopes B and C of p27, and the mixture is then added to the solid phase. Hence the presence of p27 leads to insolubilisation of the enzyme-conjugated antibodies and the resulting colour change is indicative for the presence of p27, a marker of infection (but not always of viraemia as soluble p27 may be detected in the absence of infectious virus). ELISA procedures have the advantage of high diagnostic sensitivity and specificity – which, however, depends on the gold standard used for comparison. soluble p27 may be detected in the absence of infectious virus). ELISA procedures have the advantage of high diagnostic sensitivity and specificity – which, however, depends on the gold standard used for comparison.

In a field study in which the gold standard was proviral PCR, the diagnostic sensitivity was found to be 90 %, i.e. about 10 % of all 597 cats tested and found to be PCR positive were not recognised by p27 ELISA due to the fact that they are not antigenaemic; the specificity was very close to 100 % in that none of the p27 positive samples turned out to be PCR-negative (Hofmann et al. 2001). If the gold standard is virus isolation, the diagnostic sensitivity is in the range of 90 % and the diagnostic specificity of >98 % (Hartmann et al. 2001).

Immune chromatography
These tests are based on the same principle as the ELISA but small beads less than one micron in size are coated to the revealing antibodies rather than enzymes. The diagnostic sensitivity and specificity of immune chromatography tests was shown to be comparable to those of the ELISA (Hartmann et al., 2007; Hartmann et al., 2001; Pinches et al., 2007; Robinson et al., 1998; EBM grade I).

Immunofluorescence assay (IFA)
The first method that allowed FeLV detection in viraemic cats under field conditions was the indirect IFA, introduced in 1973 (Hardy et al., 1973). It was based on the observation that granulocytes, lymphocytes, and platelets in viraemic cats contain gag components, which may be detected by IFA in blood smears. The diagnostic sensitivity of IFA compared to virus isolation as the gold standard is significantly lower than 100 %; but positive cats are usually persistently viraemic (Hawks et al., 1991; EBM grade I). If a viraemic cat has leukopenia or if only a small percentage of peripheral leukocytes are infected, the presence of FeLV infection may be overlooked using IFA tests. Furthermore, all eosinophils have a tendency to bind the FITC conjugates used for IFA resulting in false positive tests if slides are not read carefully (Floyd et al., 1983).

Virus isolation
Virus isolation in cell culture has been considered to be the ultimate criterion for FeLV infection. (Jarrett 1980; Jarrett et al., 1982). Indeed, in the early phase of infection, detection of infectious FeLV is often the most sensitive parameter (Lehmann et al. 1991). In view of difficult logistics, this test is no longer considered for routine testing.
PCR for the detection of provirus (DNA PCR)
Since every cat cell carries between 12 and 15 copies of endogenous FeLV, it proved difficult to determine sequences specific for detecting exogenous provirus (Jackson et al., 1996). The value of PCR techniques was greatly enhanced by the development of real-time PCR that not only allows detection but also quantitation of FeLV provirus (Hofmann-Lehmann et al., 2001). PCR procedures have the highest analytical and diagnostic sensitivity and a high specificity – provided the tests are run with precautions of clean work, in separate labs, with all necessary controls and under conditions of "good laboratory practice". PCR for the detection of provirus may be useful for the clarification of inconclusive p27 antigen tests.

PCR for the detection of viral RNA
The detection of viral RNA added a new aspect to the diagnosis of FeLV infection (Tandon et al., 2005). Viral RNA present in whole blood, serum, plasma, saliva or faeces is extracted, reverse transcribed into cDNA, which is then amplified by real-time PCR. This technique permits the detection and quantitation of virus in the absence of cells. RNA PCR does not provide the same information as DNA provirus PCR. Many cats that have overcome FeLV viraemia remain provirus-positive but do not possess detectable viral RNA in plasma, saliva or faeces (Gomes-Keller et al., 2006a). However, detection of viral RNA is a reliable parameter of viraemia.
In most situations, individual cats are tested for FeLV. However, in circumstances where the cost of testing is a limitation, pooled saliva samples can be used, as the RNA PCR is sufficiently sensitive to detect a single infected cat in a pool of up to 30 samples. This approach may be advantageous when screening multicat households (Gomes-Keller et al., 2006b).

Serology
Although antibodies against FeLV can be measured, the results are difficult to interpret because many cats develop antibodies to their endogenous FeLV. Therefore such tests are currently of little clinical value. In some research laboratories, the so-called FOCMA (feline oncornavirus-associated cell membrane antigen) test was used to detect antibodies to what was believed to be a tumour-associated antigen. It was later found that FOCMA was indeed a combination of several viral components; as this test is difficult to establish and to standardise, is not considered to be of clinical value. Virus neutralising antibodies can be measured, but this test is not widely available (except in the UK) and is used infrequently.

Test interpretation
The first test that becomes positive after FeLV infection is usually virus isolation, followed within a few days by DNA and RNA PCR, ELISA, and later by IFA
Persistently viraemic cats are usually positive in all tests. The most widely used in-practice tests are antigen ELISA and immunochromatography. As the prevalence of FeLV infection has decreased in many European countries, also false positive test results tend to increase. Therefore, a doubtful positive result in a healthy cat should always be confirmed, preferably using provirus PCR (DNA PCR) offered by a reliable laboratory. A positive test in a cat with clinical signs consistent with FeLV infection is more reliable, as in sick cats the prevalence of FeLV is considerably higher. Cats testing positive may overcome viraemia after two to sixteen weeks - in rare cases even later. Therefore, every test-positive healthy cat should be separated and retested after several weeks or months; depending on compliance of the owner, retesting can be done still later (up to one year) when it is highly unlikely that the cat will clear the viraemia.

Cats that clear infectious virus from the plasma will be negative by VI, ELISA, immunochromatography, IFA, and RNA PCR, but will remain positive by DNA PCR (Gomes-Keller et al., 2006a; EBM grade I). These cats should be considered latently infected, although the clinical significance is low in most cats. However, in rare instances, chronic stress, immune suppression or infection with other viruses may lead to reactivation. The mean proviral load in cats that have overcome viraemia is several hundred times lower than in cats with persistent viraemia. A small proportion (2-3 %) of cats remain positive by ELISA and immunochromatography although no infectious virus can be isolated from the plasma. These cats have foci of infection outside the bone marrow from which soluble p27 is released into the circulation; such cats are potential sources of infection (Lutz et al., 1980c).

In summary, cats can be initially tested for p27. If the result is inconclusive for any reason, the test should be repeated by a qualified laboratory, using an alternate format, preferably PCR for provirus.

**Infection management**

FeLV-infected cats should be strictly confined indoors, to prevent spread to other cats in the neighbourhood. There may also be benefits in preventing exposure of the immune-suppressed retrovirus-infected cat to infectious agents carried by other animals. This is true for the home environment as well as for the veterinary hospital. Although they can be housed in the same ward as other hospitalised patients, they should be kept in individual cages. Since they may be immune-suppressed, they should be kept separated from cats with other infectious diseases. They should not be placed in a "contagious ward" with cats suffering from e.g. viral respiratory disease.

Management should be aimed at minimising potential exposure to other infectious agents. As well as confining the cat indoors it may be prudent to avoid feeding uncooked meat, which may pose a risk of bacterial or parasitic infections to which FeLV-positive cats are more susceptible.
Asymptomatic FeLV-infected cats should receive clinical check-ups at least every six months. A complete blood count (CBC), biochemistry profiles and urinalyses should be performed periodically, ideally every six to twelve months. Intact male and female retrovirus-infected cats should be neutered to minimise the risk of virus transmission and for health benefits. Surgery is generally well tolerated by asymptomatic FeLV-infected cats. The virus is infectious only for a short while outside the host (Francis et al., 1979b), and is sensitive to all disinfectants including common soap; simple precautions and routine cleaning procedures will prevent transmission in the hospital.

Routine vaccination in FeLV-infected cats is a matter of discussion. Vaccination programmes to prevent common infectious diseases should be maintained in FeLV-infected cats, although they may not mount an adequate immune response to e.g. rabies vaccination (Franchini, 1990). Therefore, protection of a FeLV-infected cat may not be as good as that of an uninfected animal. If these cats are allowed outside – which is not recommended, certainly never in rabies-endemic areas – more frequent vaccination may be considered. Inactivated vaccines are recommended whenever available, because modified live virus vaccines may cause symptoms in immune-suppressed cats.

Treatment
If FeLV-infected cats are sick, prompt and accurate diagnosis is important to allow early therapeutic intervention and successful treatment. Therefore, more intensive testing should be implemented earlier in the course of illness than in uninfected cats. Many cats with retrovirus infection respond well to appropriate medications although a longer or more aggressive course of therapy (e.g., antibiotics) may be needed than in retrovirus-negative cats. Corticosteroids, other immune-suppressive or bone marrow-suppressive drugs should generally be avoided, unless used as a treatment of FeLV-associated malignancies or immune-mediated disease. Good veterinary care is important for FeLV-viraemic cats. Many may need fluid therapy. Some specific complications of FeLV infection may respond to treatment, such as secondary bacterial infections, especially with Mycoplasma haemofelis, which often responds 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 the case of leukopenia, granulocyte colony-stimulating factor (G-CSF) can be considered (Fulton et al., 1991; EBM grade IV). 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 show no recurrence within two years. Chemotherapy of FeLV-positive lymphomas will not resolve the persistent viraemia and the outlook for such cats is not good (Ettinger, 2003).

Immune-modulators
There is little evidence from controlled studies to support the efficacy of immune modulators on the health or longevity of FeLV-infected cats. Nevertheless, it has been suggested that some of these agents may benefit infected animals by restoring compromised immune function, thereby allowing the patient to control its viral burden and recover. Although uncontrolled studies have suggested dramatic clinical improvement (e.g., when using preparations known as “paramunity inducers”), these effects were not observed in carefully controlled studies (Hartmann et al., 1998; EBM grade I).

Staphylococcus Protein A is a bacterial polypeptide purified from cell walls of Staphylococcus aureus Cowan I that acts as an immune modulator. In a placebo-controlled study, treatment of ill, client-owned FeLV-infected cats (with 10 g/kg, twice per week for up to ten weeks) did not cause a statistically significant difference in FeLV status. However, in the owners’ impression, the health of their pets had improved (McCaw et al., 2001).

**Antivirals**

The efficacy of antiviral drugs is limited, and many cause severe side effects (Hartmann, 2006). Only a few controlled studies have demonstrated some effect of a few drugs in FeLV-infected cats.

Feline interferon-ω inhibits FeLV replication in vitro. Treatment of FeLV-viraemic cats significantly improved their health and extended their survival time, but it did not resolve the viraemia (de Mari et al., 2004; EBM grade I). In a placebo-controlled field study, 48 FeLV-infected cats were treated with interferon-ω (10^6 IU/kg s.c. q24h on five consecutive days repeated three times with several weeks between treatments; de Mari et al., 2004). A statistically significant difference was found in the survival time of treated versus untreated cats. No viral parameters, however, were measured to support the assumption that interferon exerted an anti-FeLV effect rather than inhibited secondary infections.

An antiviral compound routinely used is 3’-azido-2’,3’-dideoxythymidine (AZT), a nucleoside analogue (thymidine derivative) that blocks retroviral reverse transcriptase. The drug 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 the quality of life, and prolong life expectancy in FeLV-infected cats. It should be used at a dosage of 5-10 mg/kg q12h per os or s.c.. Higher doses should be used carefully, as side effects (e.g. non-regenerative anaemia) can develop (Hartmann, 2005 EBM grade I).

**Vaccination**

After several experimental vaccines had been described (Jarrett et al., 1975; Jarrett et al., 1974; Pedersen et al., 1979), the first FeLV vaccine used in veterinary practice was introduced in the USA in 1984. It was based on conventionally prepared FeLV antigens, and it protected cats from viraemia (Lewis et al., 1981).

A number of FeLV vaccines are now available in Europe. Some used
recombinant DNA technology, like the one consisting of the viral envelope glycoprotein as well as part of the transmembrane protein expressed in E. coli (Kensil et al., 1991); this was the first genetically engineered small animal vaccine.

The most recent product uses a canarypox virus vector that carries the genes for the envelope glycoprotein and the capsid protein (Tartaglia et al., 1993). After injection, there is a single round of replication by the vector poxvirus resulting in the expression of the inserted FeLV genes. In contrast to other cat vaccines, neutralising antibodies do not develop. The protective effect is achieved by stimulating cellular immunity which leads to rapid development of neutralising antibodies if vaccinated cats encounter field virus (Hofmann-Lehmann et al., 2006; Lehmann et al, 1991).

The differences between available FeLV vaccines are more significant than those for other feline infectious diseases - differences in performance, particularly efficacy of protection. Comparison of efficacy studies can be misleading because of differences in the protocols – such as the route of challenge, the challenge strain used and the criteria for defining protection (Sparkes, 2003). Different studies on the same vaccine sometimes led to divergent results. The first FeLV vaccine and some others, which are no longer on the market, have performed poorly, as found in independent efficacy studies with disappointing protection. The European Pharmacopoeia defines the criteria for assessing the efficacy of protection. A common problem is the difficulty to infect healthy control cats with a single experimental challenge. The criteria include a minimum acceptable infectivity rate in controls to confirm that an acceptably strong challenge has been provided. Natural resistance to FeLV challenge is taken into account when calculating the level of protection, which is then expressed as the "preventable fraction" (Scarlett & Pollock, 1991).

Some protocols have been based on a “natural” FeLV challenge – by co-mingling viraemic with trial cats. These protocols are not in agreement with the European Pharmacopoeia, but they mimic the natural mode of virus transmission, which is generally based not on a single large exposure but on chronic exposure over a period of time. Cohabiting infected viraemic cats with vaccinated cats is regarded by clinical experts as a more realistic measure of protection that vaccines would provide in the field.

No FeLV vaccine provides complete (100 % efficacy) 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 when compared with persistently viraemic cats (Hofmann-Lehmann et al., 2007; EBM grade III). These experiments confirm that FeLV vaccination neither induces sterilising immunity nor does it protect from infection.

Long-term observation of vaccinated cats after experimental challenge indicates that low levels of RNA viraemia and of proviral DNA are not clinically significant, and these cats can be regarded as protected.
FeLV should generally be included in the routine vaccination programme for pet cats. Protection against a potentially life-threatening infection is justified, and the benefit for most cats considerably outweigh any risk of adverse effects. In situations where the probability of exposure to FeLV can be discounted, vaccination is not required. Geographical variations of the prevalence of FeLV may influence the decision. In some European countries FeLV has been almost eliminated, and there may be local variations in the prevalence within countries where the virus is still a significant health issue.

The lifestyle of individual cats may also be a decision factor; if it can be assured that a cat will not be exposed to FeLV, vaccination is unnecessary. However, owners’ circumstances may change, and with them their cats’ lifestyle, particularly when moving house. This possibility should be considered especially in kittens presented for primary vaccination.

Primary vaccination
Vaccination should be carried out in all cats at risk of exposure. It is recommended that kittens be vaccinated at the age of 8 or 9 weeks and 12 weeks, together with the core vaccinations. (Brunner et al., 2006). Combination of different immunogens in one syringe is only legal when the company has registered it for that country, therefore the local veterinary regulations should be carefully consulted.

If its FeLV status is unknown, the cat should be tested for FeLV antigenaemia prior to vaccination in order to avoid “vaccine failures”; these will be obvious when cats infected prior to vaccination develop FeLV-related clinical signs. If FeLV infection prior to vaccination is unlikely, testing may not be needed (e.g. kittens from a FeLV-negative queen and tomcat, which had no contact with other cats).

Booster vaccinations
No data have been published to assume that the immunity lasts longer than 1 year after primo-vaccination. Therefore, most vaccine producers recommend annual boosters. However, considering the significantly lower susceptibility of adult cats to FeLV infection, the ABCD suggests that in cats older than three to four years, a booster every two to three years is sufficient.

Control in specific situations
Multi-cat households
If a cat is diagnosed with FeLV in a multi-cat household, all of them should be tested. If indeed more positive cats are identified, the test and removal system should be implemented, which involves periodic testing and removal of the positive cats until all test negative. The best method of preventing spread of infection is to isolate the infected individuals and to prevent interaction with uninfected housemates. Although protection conferred by FeLV vaccines is good in most situations, the ABCD does not recommend reliance solely on vaccination
to protect negative cats living together with FeLV positive cats.

Shelters
There are marked geographical differences in the prevalence of FeLV in rescued cats in Europe, which may influence policies of testing and vaccination. In some countries, like the UK, the prevalence is low, whilst in others it is noticeably higher, with regional differences within these countries.

Sick shelter cats, which are confirmed FeLV-positive should be euthanised.

Some rescue shelters are successful in offering confirmed FeLV-positive, healthy cats for adoption to selected households, but it must be ensured that such cats do not pose any risk of infection to other cats. This may require positive cats to be re-homed to households where they will live in isolation or only with other infected cats.

To avoid FeLV transmission in a shelter, cats should ideally be housed individually; if they are housed in groups, FeLV-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, largely as a result of routine testing and the removal of infected cats. It is recommended that routine testing is continued once or twice a year in such catteries. Contact should be limited to cats from establishments that implement a similar routine. If any cats are allowed access outside, with the opportunity of contact with neighbouring cats of uncertain FeLV status (discouraged for pedigree breeding cats), they should be vaccinated.

Vaccination of immunocompromised cats
The vaccination of FeLV-positive cats against FeLV is of no benefit.

In a long-term study where FIV-infected cats were experimentally vaccinated against FeLV infection, there was a clear benefit when compared with the non-vaccinated animals (Hofmann-Lehmann et al., 1995). Also under field conditions, FIV-seropositive cats should be vaccinated against FeLV infection (EBM grade III), but only if they are at risk (indoor-only FIV-positive cats should not be vaccinated). As the immune response in immunocompromised cats is decreased, more frequent boosters may be considered (in asymptomatic cats).

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

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