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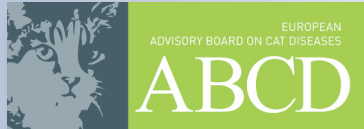
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LEISHMANIOSIS IN CATS

ABCD guidelines on prevention and management



Maria Grazia Pennisi, Katrin Hartmann, Albert Lloret, Diane Addie, Sándor Belák, Corine Boucraut-Baralon, Herman Egberink, Tadeusz Frymus, Tim Gruffydd-Jones, Margaret J Hosie, Hans Lutz, Fulvio Marsilio, Karin Möstl, Alan D Radford, Etienne Thiry, Uwe Truyen and Marian C Horzinek

Overview: *Leishmania* infection is less known in cats than in dogs and humans; felids were traditionally considered a resistant species, and canids as the main reservoir. Only sporadic cases of feline disease have been reported worldwide, mainly caused by *L. infantum*.

Epidemiological investigations have confirmed, however, that feline infections are not rare and that disease occurrence might be underestimated in endemic areas.

Infection: Cats are infected by the same *Leishmania* species that infect dogs and humans in tropical and subtropical areas worldwide. Sand fly vectors take blood meals from cats and are competent vectors for *L. infantum*, as shown experimentally.

Disease signs: Skin lesions (ulcerative, crusty, nodular or scaly dermatitis) are the most frequent clinical manifestations and sometimes the only findings on physical examination. Lymph node enlargement, weight loss, ocular involvement (nodular blepharitis, uveitis, panophthalmitis), decreased appetite, chronic gingivostomatitis and lethargy are the most frequent non-cutaneous findings, alone or in combination.

Diagnosis: Direct confirmation can be obtained by cytology, histology, isolation or polymerase chain reaction (PCR) on samples of skin, lymph nodes, blood or any affected tissue. Serology using a validated immunofluorescence test, ELISA, direct agglutination or Western blot has been used to assess infection frequencies.

Disease management: Little information is available about treatment with follow-up reports. Long-term administration of allopurinol (10–20 mg/kg q12h or q24h) is usually clinically effective. Vaccines are licensed for dogs only.

Agent

After malaria and lymphatic filariasis, leishmaniasis is the third most important vector-borne disease of humans; it is caused by several *Leishmania* species, most of zoonotic concern.¹ In veterinary medicine, canine leishmaniosis caused by *L. infantum* is of primary interest, because dogs are the main reservoir of the parasite for humans, and management of the canine disease may be challenging.²

Cats are naturally infected by the same *Leishmania* species that affect dogs and humans in tropical and subtropical areas worldwide: *L. infantum* in the Mediterranean basin, Iran and Brazil; *L. mexicana* in Texas, USA; *L. braziliensis* in Brazil and French Guiana; *L. amazonensis* in Brazil; *L. venezuelensis* in Venezuela.^{3–10}

The susceptibility of cats has been confirmed by experimental studies [EBM grade III].^{11,12}

Life cycle and transmission

Leishmania species are protozoan parasites, the natural history of which involves two hosts: the phlebotomine sand fly and a vertebrate. The vector harbours flagellated extracellular promastigote forms and transmits them to a vertebrate host; there, the parasite changes into the amastigote form that is able to survive and replicate in intracellular vacuoles within macrophages. Haematophagous female sand flies transmit the promastigotes or may take up amastigotes from an infected vertebrate host.

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.

The latest version of the leishmaniosis in cats guidelines is available at www.abcd-vets.org

There is no evidence that ticks and fleas are involved in natural *Leishmania* transmission.^{1,2} The risk of transmission in the absence of sand flies is negligible, but transplacental infection occurs as a rare event in both dogs and humans.^{1,2} Venereal transmission is a potential means of infection.¹³ Other types of direct transmission have been suggested to explain the spread of the infection among kennel dogs in the USA in the absence of sand fly vectors.^{1,2} The risk of transmission by blood transfusion is important for humans and dogs in endemic areas.^{1,2,14}

Many studies have demonstrated that sand flies take blood meals from cats; experimentally, sand flies have been found to be competent vectors for *L. infantum* in cats [EBM grade III].^{15,16}

Epidemiology

Leishmaniosis caused by *L. infantum* is an emerging disease globally.^{1,2} Using molecular diagnostic techniques on dogs in endemic areas, it was shown that the prevalence of the infection is much higher than that of the disease.¹⁷ The same is true for people: in some endemic areas, latent infections approach 30% of the population, based on a positive leishmanin skin test.¹⁴ Leishmaniosis in cats is sporadically reported worldwide, usually from the same areas where the disease occurs in dogs or humans.³ Cases have been seen in Switzerland, in cats imported from Spain; increased pet movement throughout Europe will lead to more disease, including in non-endemic areas [EBM grade IV].¹⁸

Epidemiological studies have been performed during the past 15 years in endemic areas using serological (immunofluorescence, ELISA, Western blot, direct agglutination) and/or parasitological methods (cytology, immunohistochemistry, PCR). The rates of infection vary widely, which may be due to the methodology used, the geographic area and population under study. Positive blood PCR rates range between 0.43 and 61% of the population tested, and antibody prevalence between 3 and 59%.³

Pathogenesis

Disease development is influenced by immunological factors, which are linked to the complex genetic background of the hosts, as demonstrated by studies in laboratory animals, dogs and humans.² In people, *L. infantum* can induce anything between a local skin lesion and a severe visceral disease. The latter form is the typical presentation in immune-incompetent patients.¹⁴ In dogs, leishmaniosis is a multisystemic disease with a wide

Leishmaniosis caused by *L. infantum* is an emerging disease globally. In cats, disease is sporadically reported worldwide, usually in the same areas where it occurs in dogs or humans.



spectrum of severity that reflects the balance between the protective cell-mediated and the non-protective humoral immune response. In both humans and dogs there is a dynamic range from subclinical infection to self-limiting mild and non-self-limiting severe disease.^{1,2}

In all host species, macrophages play a central role in the control of the infection. Cytokines such as IFN- γ , IL-2 and TNF- α , secreted by activated T cells, stimulate intracellular killing of *Leishmania* amastigotes by macrophages. The presence of *Leishmania*-infected macrophages is usually associated with a granulomatous inflammatory reaction.² Lymphoid hyperplasia is also common. A massive antibody response is responsible for immune complex deposition in the kidney, with glomerulonephritis and subsequent renal failure.^{1,2}

Histopathology of feline skin lesions mainly shows a diffuse granulomatous dermatitis with macrophages containing many *Leishmania* parasites, or a granulomatous perifolliculitis and lichenoid tissue reaction/interface dermatitis, with a lower parasite load.^{19,20} Granulomatous inflammation has also been seen in the liver and kidney.²⁰

Epidemiological studies have shown that *Leishmania* infection of cats is more common than the associated disease; cats may remain PCR and antibody positive for a long time.³ Cats may be more resistant than dogs to developing disease.

Clinical signs

Canine leishmaniosis is usually chronic and progressive, with an incubation period lasting for months or even years. Any tissue or organ may be involved, but skin lesions are most suggestive, and renal disease is most important prognostically.¹

Feline leishmaniosis caused by *L. infantum* has been documented mainly in the past 20 years in Europe and Brazil.³ Cases have been reported in cats of all ages, almost all domestic shorthair, with no gender predilection. Skin lesions are the most frequent clinical manifestation, and sometimes the only finding on physical examination. Ulcerative, crusty, nodular or scaly dermatitis is found mainly on the head and neck (Figures 1 and 2), less often on the trunk and legs. Pruritus is usually absent; alopecia or a poor coat condition are reported. Lymph node enlargement, weight loss, ocular involvement (nodular blepharitis, uveitis, panophthalmitis), decreased appetite, chronic gingivostomatitis and lethargy are the most frequent non-cutaneous findings. Dehydration, pale mucous membranes, vomiting, hepatomegaly, fever, jaundice, polyuria/polydipsia, spleen enlargement,



Figure 1 *L. infantum*-associated ulcerative dermatitis in a cat. Courtesy of Maria Grazia Pennisi



Figure 2 *L. infantum*-associated haemorrhagic nodule in a cat. Courtesy of Maria Grazia Pennisi

nasal discharge, recurrent abortion and dyspnoea are also found, although less often.

Information on clinicopathological abnormalities is scarce; in a few cases followed up until death or euthanasia, glomerular disease and chronic renal failure have been seen to develop [EBM grade IV].²¹

Data from complete blood counts and serum protein electrophoresis are available but the results may have been influenced by concurrent disease as well as retroviral infection. Various haematological abnormalities have been described in three cats suffering from pancytopenia; in one of them, a retrovirus-negative patient with myelofibrosis, 4% of the circulating neutrophils contained *Leishmania* parasites.²² Hyperglobulinaemia and gammopathy are found in most investigated cases [EBM grade III].³

Immunity

Leishmania immunity is complex. In the dog, a susceptible species, protective immunity against *L. infantum* is CD4 T cell mediated, and the release of gamma-interferon, IL2 and TNF- α is associated with anti-*Leishmania* activation of macrophages. A combination of high antibody levels and a reduced cellular, mixed Th1 and Th2 response is found in dogs developing the disease.^{1,2}

All sick cats possess specific antibodies, and hyperglobulinaemia is often found. As reported for dogs, *Leishmania* PCR-positive healthy cats may be seronegative for anti-*Leishmania* antibodies.^{3,23}

Infection experiments with *L. braziliensis* have shown that the development of skin lesions precedes antibody appearance, and seroconversion occurs when the lesions are healing.¹²

An association between feline immunodeficiency virus (FIV) and *L. infantum* infections was found in endemic areas. Most cats developing clinical signs are suspected to have an

**Skin lesions
are the most
frequent clinical
manifestation
of feline
leishmaniosis.
Most cats
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system.**



impaired immune system because of concurrent FIV infection, FIV plus feline leukaemia virus (FeLV) infection, cancer (squamous cell carcinoma), diabetes mellitus, autoimmune disease (pemphigus foliaceus), and treatment with corticosteroids or other immunosuppressive drugs [EBM grade IV].²³⁻²⁵

Diagnosis

The diagnosis can be accomplished by parasitological (cytology, histology, PCR, isolation) and serological methods (immunofluorescence test, ELISA, direct agglutination, Western blot). In most feline cases where cytology, isolation and PCR were performed, they confirmed the diagnosis obtained using lymph node, skin, bone marrow or blood samples (Figure 3). Ocular disease caused by *L. infantum* was diagnosed by histology after enucleation of the affected eye. On post-mortem examination, parasitological evidence of infection was also obtained from samples of spleen, liver, kidney, pancreas and gastrointestinal organs.³ Immunohistochemistry has been used on skin biopsies.^{19,20}

Serological tests for leishmaniosis are not commercially available. Recently, immunofluorescence testing has been validated for use in feline samples [EBM grade III].²³

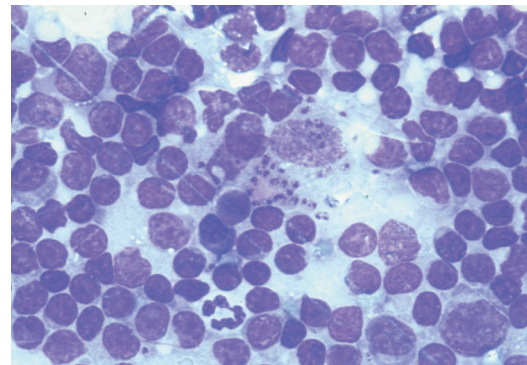


Figure 3 Lymph node smear from a cat, showing *Leishmania* amastigotes in a macrophage (MG-G stain; x64 objective). Courtesy of Maria Grazia Pennisi

Treatment

The available information on treatment is mostly based on single case reports, not always with an appropriate follow-up (EBM grade IV).³ Long-term administration of allopurinol (10–20 mg/kg q12h or q24h) is usually clinically effective, even in FIV-positive cats. However, the infection is not cleared and clinical signs may recur after stopping therapy, as is the case in dogs.^{3,26} Meglumine antimoniate (5–50 mg/kg or 375 mg/cat q24h SC or IM under different protocols), used for therapy in four cases, produced a good clinical response [EBM grade IV].³ Surgical excision of nodules performed in two cats was followed by recurrence.^{18,27}

Prevention

Information is not available on the prevention of feline leishmaniosis. In dogs, the disease is prevented by means of application of repellent agents against sand flies and, more recently, also by vaccination.¹

Zoonotic risk

Leishmania species reported in cats are of zoonotic concern but no information is available on the risk associated for owners of infected cats. Vectorial transmission is considered the principal route for *L. infantum* and dogs are considered the main peridomestic reservoir. Only one study, performed in Iran, has found that owners of infected dogs have a higher risk for leishmaniosis caused by *L. infantum*.²⁸

Zoonosis
The *Leishmania* species reported in cats are of zoonotic concern.



EBM grades

The ranking system for grading the level of evidence of various statements within this article is described on page 533 of this Special Issue.

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Conflict of interest

The authors do not have any potential conflicts of interest to declare.

KEY POINTS

- ❖ Cats are naturally infected by the same *Leishmania* species as dogs and humans in tropical and subtropical areas worldwide.
- ❖ Sand fly vectors take blood meals from cats and are competent vectors for *L. infantum*.
- ❖ Leishmaniosis occurs sporadically worldwide in cats, usually in the same areas where dogs or humans are affected, or in cats imported from these areas.
- ❖ The rates of infection vary in cats from endemic areas, dependent on the diagnostic method, geographic area and population under study.
- ❖ Histology of the skin, liver and kidney shows a granulomatous inflammation.
- ❖ Skin lesions (ulcerative, crusty, nodular or scaly dermatitis) are the most frequent clinical manifestations and sometimes the only findings on physical examination.
- ❖ Lymph node enlargement, weight loss, ocular involvement (nodular blepharitis, uveitis, panophthalmitis), decreased appetite, chronic gingivostomatitis and lethargy are the most frequent non-cutaneous findings.
- ❖ Glomerular disease and chronic renal failure are observed in followed-up cases.
- ❖ An association between FIV and *L. infantum* infections is found in endemic areas.
- ❖ Cytology, histology, isolation or PCR on samples of skin, lymph node, blood or any affected tissue are useful for direct diagnosis.
- ❖ Serology using a validated immunofluorescence test, ELISA, direct agglutination or Western blot has been used to assess infection frequencies.
- ❖ Long-term administration of allopurinol (10–20 mg/kg q12h or q24h) is usually clinically effective.
- ❖ Apart from vector control, no preventive measure is known for cats; vaccines are licensed for dogs only.



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