

LEPTOSPIROSIS IN CATS

Current literature review to guide diagnosis and management



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Global importance: Leptospirosis is the most widespread zoonosis worldwide. Mammals (eg, rats, horses, cows, pigs, dogs, cats and aquatic species, such as sea lions and northern elephant seals) can all be infected by leptospires. Infection in animals occurs through contact with urine or water contaminated with the bacteria. In people, the disease is acquired mainly from animal sources or through recreational activities in contaminated water.

Practical relevance: Literature on the clinical presentation of leptospirosis in cats is scarce, although it has been demonstrated that cats are susceptible to infection and are capable of developing antibodies. The prevalence of antileptospiral antibodies in cats varies from 4% to 33.3% depending on the geographical location. Urinary shedding of leptospires in naturally infected cats has been reported, with a prevalence of up to 68%. Infection in cats has been associated with the consumption of infected prey, especially rodents. Thus, outdoor cats have a higher risk of becoming infected.

Clinical challenges: Clinical presentation of this disease in cats is rare and it is not known what role cats have in the transmission of leptospirosis. Ongoing work is needed to characterise feline leptospirosis.

Audience: This review is aimed at all veterinarians, both general practitioners who deal with cats on a daily basis in private practice, as well as feline practitioners, since both groups face the challenge of diagnosing and treating infectious and zoonotic diseases.

Evidence base: The current literature on leptospirosis in cats is reviewed. To date, few case reports have been published in the field, and information has mostly been extrapolated from infections in people and dogs. This review is expected to serve as a guide for the diagnosis and management of the disease in cats.

Keywords: Leptospirosis; microscopic agglutination test; real-time PCR; zoonosis

Aetiology

Leptospirosis is caused by spirochetal bacteria of the genus *Leptospira*. These are highly motile, elongated and helically coiled bacteria that differ morphologically from other spirochetes by having a 'question mark' or hook-shaped end.^{1–3} The genus *Leptospira* was originally divided into two species: *Leptospira interrogans*, containing the pathogenic serovars, and *Leptospira biflexa*, containing the non-pathogenic saprophytic serovars.⁴ However, this phenotypic classification has been largely superseded by genetic classification, based on genotypic identification techniques, that includes all serovars of *L. interrogans* sensu lato and *L. biflexa* sensu lato (sensu lato is a Latin phrase meaning 'in the broad sense' and is often used taxonomically to indicate a species complex).³

Currently, 22 species of *Leptospira* have been identified;⁴ at least 10 of these are pathogenic. There are also seven saprophytic species and five species of indeterminate pathogenicity.⁵ It is likely that more species will be described in the future. Pathogenic *Leptospira* species are divided into serovars,

each with distinct antigenic compositions; to date, over 260 pathogenic serovars, arranged into 26 serogroups, have been identified. This serological classification, based on determining antigenic characteristics, is more useful diagnostically and also better serves epidemiological purposes.

All mammals may be susceptible to *Leptospira* infection.³ There are primary (definitive) or carrier hosts for some serovars (eg, dogs are hosts for Canicola; cows and sheep for Hardjo; pigs for Pomona and Bratislava; and rats for Icterohaemorrhagiae and Copenhageni). These contribute to a greater extent to the spread of bacteria in the environment compared with incidental or dead-end hosts (ie, that suffer acute disease and are unlikely to serve as a source of transmission; eg, humans). The definitive host is typically infected at a young age and commonly exhibits minimal clinical disease, whereas animals infected with non-host-adapted serovars are expected to exhibit more severe clinical signs.³

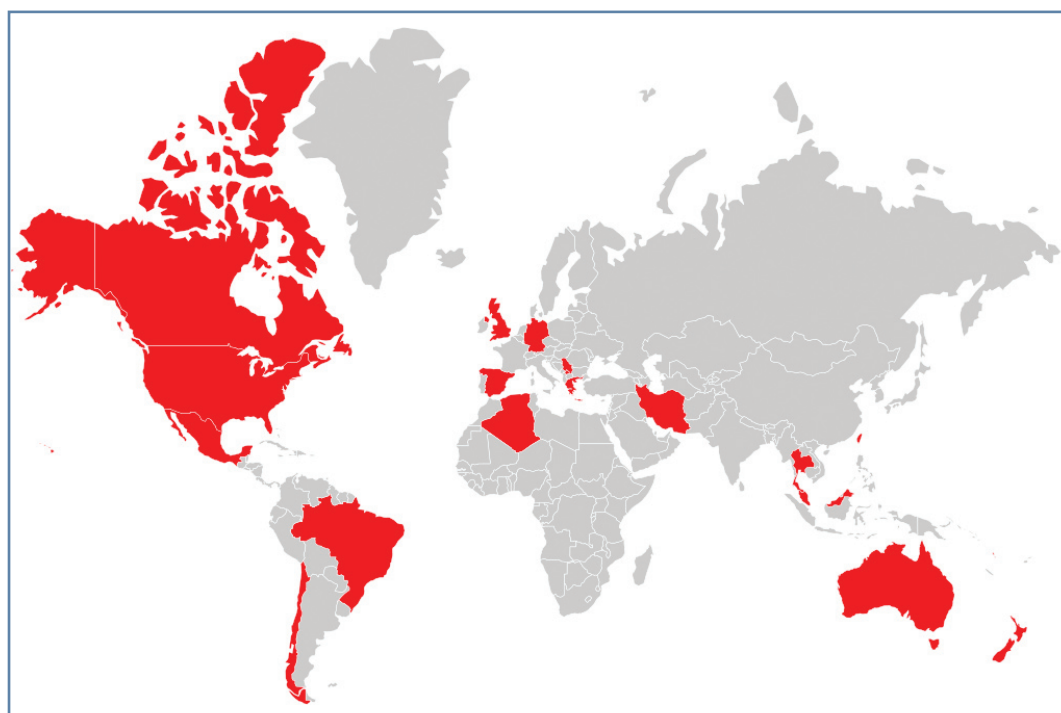



Figure 1 Map indicating (in red) the countries where the prevalence of leptospirosis in cats has been reported, based on microscopic agglutination test (MAT) and/or urinary and blood PCR



Outdoor cats have an increased risk of leptospirosis, through contact with reservoir hosts.

Epidemiology

Leptospirosis is endemic in almost all regions of the world.² Its incidence usually increases at the end of the summer months, while in the tropics most infections occur during and after periods of rainfall.^{1,2} Pathogenic *Leptospira* species experience optimal growth at temperatures of 28–30°C. Although they do not replicate outside of the host, they can survive for months in moist soil saturated with urine,^{1,3} and this can lead to significant environmental contamination. In people, there are three main factors associated with the risk of disease transmission: (1) water exposure; (2) exposure to carrier rodents; and (3) transmission from livestock or pets.⁶

Feline leptospirosis was first described in 1972,⁷ and prevalence studies show the main serovars belong to serogroups Australis, Autumnalis, Canicola and Sejroe,^{8–18} although there are geographical variations. The most frequent serovars involved in feline leptospirosis in Europe – according to the European consensus statement on leptospirosis, and based on the prevalence of antibodies measured by the microscopic agglutination test (MAT) – belong to serogroups Australis, Autumnalis, Ballum, Canicola, Grippityphosa, Icterohaemorrhagiae, Pomona and Sejroe.¹⁹ The most commonly reported serovars in cats in the USA belong to serogroups Australis, Autumnalis, Grippityphosa and Pomona.^{8,20} Figure 1 shows the countries where the preva-

At present, it is not completely understood which serovars cause incidental infections in cats and which have developed adaptation to feline species.



lence of leptospirosis in cats has been reported, based on MAT and/or urinary and blood PCR. Table 1 summarises previous research on feline leptospirosis prevalence by MAT diagnosis. Overall seropositivity reported in these studies ranged from 4% to 33.3%, with no clear association with clinical disease.

Leptospiral infection in cats has been associated with the consumption of infected prey,²⁹ involving serovars of the Autumnalis and Ballum serogroups.³ Outdoor cats have an increased risk of becoming infected with leptospires since they are in close contact with reservoir hosts. In rural areas, cats can also become infected via urine from pigs and cows.^{12,15,28–30} The presence of another cat in the household significantly increases the risk of seropositivity for leptospirosis.¹⁴

At present, it is not completely understood which serovars cause incidental infections in cats. Based on previously published reports of acute leptospirosis in cats, serovars belonging to Autumnalis, Australis, Icterohaemorrhagiae, Grippityphosa, Pomona and Sejroe serogroups are involved.^{14,18,30–32} Several studies have confirmed renal carriage of *Leptospira* species by PCR, and these cats had antibodies mainly against serovars belonging to Australis, Canicola, Icterohaemorrhagiae and Pomona serogroups. Given this fact, cats could be a chronic reservoir host for the bacteria and a possible risk factor for human infection.^{10,11,13,14,16,26,30,33,34}

Table 1 Prevalence data for leptospirosis in cats diagnosed by microscopic agglutination test

Location	n	Positive serovar(s)	Negative serovar(s)	Prevalence (%)	Reference
Malaysia – Johor and Selangor	110	Ballum, Bataviae*, Copenhageni and Javanica	Australis, Autumnalis, Canicola, Celledoni, Cynopteri, Djasiman, Grippotyphosa, Hardjo, Hardjo-bovis, Hebdomadis, Icterohaemorrhagiae, Lai, Malaysia, Pomona, Pyrogenes and Tarassovi	18.1	9
Thailand – 13 locations	260	Anhoa, Autumnalis, Celledoni, Copenhageni, Djasiman, Icterohaemorrhagiae and Patoc*	Australis, Ballum, Bataviae, Bratislava, Broomi, Canicola, Coxi, Cynopteri, Grippotyphosa, Haemolytica, Khorat, Paidjan, Pomona, Pyrogenes, Rachmati, Saxkoebing and Sejroe	5.4	10
USA – Iowa	139	Bratislava*, Grippotyphosa, Hardjo, Icterohaemorrhagiae and Pomona	Canicola	8.6	8
Germany – Munich	215	Australis*, Autumnalis, Bratislava, Copenhageni and Grippotyphosa	Canicola, Pomona and Saxkoebing	17.9	11
Caribbean island of St Kitts	50	Cynopteri and Pomona	Alexi, Australis, Autumnalis, Bataviae, Ballum, Borincana, Bratislava, Canicola, Celledoni, Cynopteri, Djasiman, Georgia, Grippotyphosa, Hardjo, Icterohaemorrhagiae, Javanica, Mankarso, Pomona, Pyrogenes, Tarassovi and Wolffi	4	21
Brazil – Lago Grande	43	Andamana and Patoc	Autumnalis, Australis, Bataviae, Bratislava, Butembo, Canicola, Castellonis, Copenhageni, Cynopteri, Grippotyphosa, Guaricura, Hardjo-prajitno, Hebdomadis, Icterohaemorrhagiae, Javanica, Panama, Pomona, Pyrogenes, Shermani, Tarassovi, Whitcombi and Wolffi	4.7	22
Mexico – Mérida	13	Australis and Canicola*	Autumnalis, Bratislava, Grippotyphosa, Hardjo, Icterohaemorrhagiae, Pyrogenes, Panama, Pomona, Tarassovi and Wolffi	23.2	23
Iran – Mashhad	147	Hardjo*, Icterohaemorrhagiae and Pomona	Autumnalis, Ballum, Canicola and Grippotyphosa	12.9	12
Taiwan – Southern Taiwan	225	Australis, Icterohaemorrhagiae, Javanica, Pyrogenes and Shermani*	Autumnalis, Bataviae, Canicola, Panama, Pomona and Tarassovi	9.3	13
Canada – Quebec	240	Bratislava, Grippotyphosa, Icterohaemorrhagiae and Pomona*	Canicola and Hardjo	10.8	14
Chile – Valdivia, Osorno, Paillaco and San Pablo	124	Autumnalis*, Bataviae and Canicola	Ballum, Hardjo, Icterohaemorrhagiae and Pomona	25.2	15
Serbia – Belgrade	161	Australis*, Bratislava, Canicola, Grippotyphosa Pomona* and Pyrogenes	Autumnalis, Bataviae, Icterohaemorrhagiae and Sejroe	26.7	24
Canada – Quebec	40	Autumnalis and Bratislava*	Canicola, Grippotyphosa, Icterohaemorrhagiae and Pomona	25	25
Reunion Island	30	Panama	Australis, Autumnalis, Bataviae, Canicola, Castellonis, Cynopteri, Grippotyphosa, Hardjo-bovis, Hebdomadis, Icterohaemorrhagiae, Copenhageni, Pomona, Pyrogenes, Sejroe and Tarassovi	26.6	26
Iran – Ahvaz	102	Australis and Ballum*	Canicola, Grippotyphosa, Hardjo, Icterohaemorrhagiae and Pomona	4.9	27
USA – Massachusetts	63	Autumnalis*, Bratislava, Icterohaemorrhagiae and Pomona	Canicola, Grippotyphosa and Hardjo	4.8	20
Spain – Andalucia	53	Ballum and Icterohaemorrhagiae*	Australis, Autumnalis, Bataviae, Bratislava, Canicola, Grippotyphosa, Hardjo, Hebdomadis, Pomona, Saxkoebing, Sejroe and Tarassovi	14	16
Greece – Thessaloniki	99	Ballum, Bataviae, Bratislava, Canicola, Panama, Pyrogenes and Rachmati*	Hebdomadis, Panama and Pomona	33.3	17
Scotland – Glasgow	87	Autumnalis, Hardjo-bovis* and Icterohaemorrhagiae	Autumnalis, Bratislava, Ballum, Canicola, Cynopteri, Grippotyphosa, Javanica, Pomona and Tarassovi	9.2	18
New Zealand – North Island	225	Balkanica, Ballum, Canicola, Copenhageni*, Hardjo* and Pomona	Australis, Bataviae, Javanica, Pyrogenes and Tarassovi	8.8	28

*Most prevalent serovar reported in the study

Table 2 summarises the scant research that has been carried out in cats in different countries to determine the prevalence of *Leptospira* DNA shedding in urine. In these studies, the prevalence ranged from 0% to 67.8%, with no clear association with clinical disease. The prevalence may differ depending on the geographical location and the PCR-selected primers, among other factors.

Pathogenesis

Depending on the host and infecting serovar, leptospiral infection may cause a spectrum of syndromes from asymptomatic carriage to fulminant, acute disease.³ Reports of clinical disease due to *Leptospira* species in pet cats are scarce.

Leptospire can enter the body through cuts and abrasions, mucous membranes, such as the conjunctiva, or through moist, weakened skin. The bacteraemia lasts around 7 days. The pathogenesis of the disease in cats remains unknown, although it is assumed to be similar to that in humans and dogs³⁷ (Figure 2). Acute clinical disease occurs with the bacteraemic phase of the disease.^{1,2,38} It is seen mainly in young incidental hosts and is usually associated with haemolysin-producing bacteria, such as the *Ictero-haemorrhagiae* or *Pomona* serogroups, which cause haemolytic disease, haemoglobinuria, jaundice and, in severe cases, death.³ After leptospire have reached a critical level in the blood, clinical signs appear due to the action of leptospiral toxins or toxic cellular components.^{1,2,38} Organ damage occurs as a result of leptospire replicating and inducing cytokine production and by direct invasion of inflammatory cells.³

The primary lesions develop in the endothelium of the small blood vessels, leading to localised ischaemia, and resulting in renal tubular necrosis, among other target organ damage (Figure 2). Renal colonisation occurs in most infected animals because the bacteria replicate and persist in the cells of the renal tubule epithelium. This multiplication process causes the release of cytokines and the recruitment of inflammatory cells, which trigger nephritis.^{1,2,38} Chronic interstitial nephritis, which may result in chronic renal damage, has been described in cats infected with leptospire.¹⁶ After 10 days of infection, leptospire enter the tubular lumen and are eliminated in the urine over a period of days to months.^{1,2,38}

Table 2 Summary of current research on prevalence of urinary shedding of *Leptospira* DNA in cats

Location	n	Gene target/primer set	Prevalence (%)	Reference
Reunion Island	172	<i>rrs2</i> , <i>lipL32</i> and <i>lipL41</i>	0.6	35
Thailand – 13 locations	260	<i>lipL32</i>	0.8	10
Algeria – Algiers	107	<i>rrs</i> (16S) and <i>hsp</i>	0	36
Germany – Munich	215	<i>lipL32</i>	3.30	11
Australia – Christmas Island	59	23S	42.4	33
Canada – Quebec	240	G1 and G2 and B64-I/B64-II	3.33	14
Réunion Island	30	<i>lipL32</i>	26.6	26
Taiwan – Southern Taiwan	225	G1/G2 and <i>Leptospira rrs</i> (16S)	67.8	13

Cats can act as carrier hosts, not developing clinical disease, but shedding bacteria into the environment in their urine.



The duration of elimination via the urine and its intensity varies from species to species and animal to animal, and depends on the infecting serovar;³ precise information on these aspects is currently unavailable in cats.

As mentioned earlier, cats can act as carrier hosts, not developing clinical disease, but shedding bacteria into the environment in their urine. An epidemiological study has confirmed the presence of leptospiral DNA in the urine of cats for more than 8 months after infection, with little or no association with disease.¹¹ However, this does not rule out the possibility that infected animals could develop kidney disease at a later stage. The development of the carrier state and the specific mechanisms required for leptospire to enter the lumen of the proximal renal tubules, adhere to renal epithelial cells, evade antibodies in the filtrate and acquire the nutrients they need to replicate are not well understood.³

Leptospiral pulmonary haemorrhage syndrome (LPHS) has been recognised in people and dogs. This syndrome may be present in 70% of dogs infected with leptospire.³⁹ The clinical signs associated with canine LPHS are mainly acute and findings correspond to severe alveolar and subpleural



Although the pathogenesis of feline leptospirosis is not yet well understood, it is assumed to be very similar to that in humans and dogs.

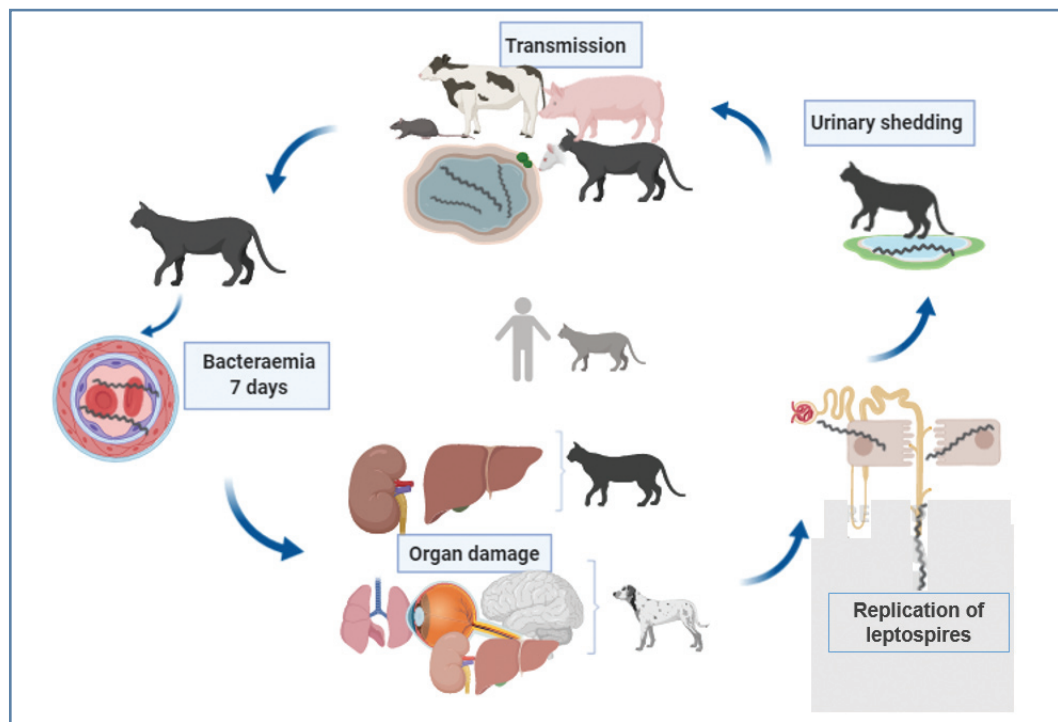


Figure 2 Proposed pathogenesis of leptospirosis in cats. The figure depicts the transmission mechanisms through which a cat can become infected by *Leptospira* species: preying on rodents, sharing the environment with farm animals that shed the bacteria in urine, or through standing water containing bacteria. Once the animal has become infected it suffers a period of bacteraemia of approximately 7 days and leptospires can be identified in blood. The main target organs in cats are the kidney and the liver; lungs, brain and eyes may also be affected, especially in dogs. Replication of leptospires occurs in the kidney leading to urinary bacterial shedding. Image ©Biorender

The presence of another cat in the household significantly increases the risk of seropositivity for leptospirosis.



haemorrhages, which cause an associated dyspnoea. While, to date, LPHS has not been described in cats, chronic liver inflammatory infiltration, fibrosis and multifocal hepatic

necrosis have been reported.^{14,16,31} Damage to organs including the spleen, eyes, meninges, muscle and placenta has also been reported in species other than cats.^{2,3,40}

Virulence mechanisms and host factors

The virulence mechanisms of leptospires and the intrinsic factors of the host that determine the result of infection remain poorly understood. Recent mutagenesis studies in animal models of acute infection and of renal colonisation have demonstrated that specific genes and proteins, among them lipoproteins LipL32 and LipL41 and LigB adhesin, are present in pathogenic *Leptospira* species, but are not necessary for virulence.^{3,41,42} Loa22, an outer membrane protein containing a C-terminal OmpA domain, plays an indirect role in the virulence of *Leptospira* species.⁴³ Changes in motility through modifications in or mutations of genes involved in flagellar structure also play a role in the specific virulence of leptospires.^{44,45}

Adhesion to host tissues appears to be a pre-requisite for successful infection; however, genetic studies have not confirmed a definitive role for many adhesins in the pathogenesis of *Leptospira* species.³ With regard to the survival of leptospires in vivo, it has been suggested that pathogenic leptospires undergo receptor-mediated endocytosis^{46,47} and are able to survive inside macrophages.⁴⁸ Production of pro-inflammatory

cytokines and chemokines is more prolific in animal species susceptible to severe leptospirosis compared with resistant animal species.⁴⁹ Pathogenic leptospires are resistant to the bactericidal activity of complement, while saprophytic leptospires are highly susceptible.^{41,50,51} The ability to acquire iron in vivo is a key virulence property for most bacterial species. Pathogenic leptospires possess haemoxygenase (HemO), which facilitates the acquisition of iron from heme, the major source of iron in the mammalian host.^{52,53} However, no conclusive results were obtained in relation to attenuation of virulence of leptospires in a study using a HemO mutant.⁵⁴

Mutagenesis studies have also demonstrated that several stress response genes, which are upregulated with bacterial transition from the environment to the host, increase their susceptibility to oxidative stress and therefore render the bacteria less virulent.^{55–57} In the same way, the inactivation of Mce, a homologue of the mycobacterial mammalian cell entry protein in leptospires, has been found to result in a significant reduction in virulence.⁵⁸

Table 3 Clinical signs of leptospirosis in cats based on published studies of acute disease

	Reference	Serovar(s)	Clinical signs	Diagnosis	MAT	PCR
Prospective study	11	Australis	Seizures	Not reported	+	+
	11	Australis, Bratislava and Copenhageni	Acute diarrhoea	Not reported	+	+
	14	Bratislava, Grippotyphosa, Icterohaemorrhagiae and Pomona	Not reported	AKI	4+	NP
	18	Autumnalis, Hardjo, and Icterohaemorrhagiae	Not reported	AKI	8+	NP
Case report	32	Saxkoebing	Vomiting and diarrhoea, hyperaesthesia and painful on handling	AKI – leptospirosis	+	+
	31	Grippotyphosa, Hardjo, Icterohaemorrhagiae and Pomona	Polyuria and polydipsia	AKI – leptospirosis	+	NP
	31	Bratislava, Grippotyphosa and Pomona	Polyuria, polydipsia, haematuria and lameness	AKI – leptospirosis	+	NP
	31	Autumnalis, Bratislava, Grippotyphosa and Pomona	Comatose	AKI – leptospirosis	+	+
	30	Autumnalis and Pomona	Haematuria	Leptospirosis	+	+

MAT = microscopic agglutination test; + = positive; – = negative; AKI = acute kidney injury; NP = not performed; 4+, 8+ = number of positive cats in the study

Clinical signs in cats are mild or absent despite the presence of leptospires in the blood and urine.



Diagnosis

Clinical signs

In cats, clinical signs are, at most, mild, despite the presence of leptospires in the blood and urine.

Clinical signs reported in infected cats (based on confirmation by MAT and/or PCR) include polyuria, polydipsia, haematuria, uveitis, lameness, lethargy, anorexia, weight loss, ascites, vomiting, diarrhoea, pain on handling, and inflammatory lesions on the skin and digits.^{11,14,17,18,25,30–32,59} Pathological findings reported in these animals include the presence of haemorrhagic or straw-coloured thoracic and peritoneal fluids.^{31,18} Some cats

with antibodies against *Leptospira* species have been found to have signs associated with renal disease and/or histopathological evidence of renal inflammation.^{14,16,30,35,59} As in dogs, leptospirosis in cats can cause acute kidney injury that leads to chronic kidney disease.^{19,60} Lesions in the liver of affected cats have been reported less commonly than in dogs.^{11,18,29,31,32}

Tables 3–5 collate information from several papers that detail the clinical signs in cats at the time of presentation, the laboratory test used for diagnosis and the *Leptospira* serovars involved. The cases have been divided into cats with acute disease (Table 3), those identified as chronic carriers (Table 4) and those with a history of exposure (Table 5).

Table 4 Clinical signs of leptospirosis in cats according to published studies of chronic carrier cases

	Reference	Serovar(s)	Clinical signs	Diagnosis	MAT	PCR
Prospective study	11	Australis and Bratislava	Asymptomatic	Incidental infection (routine health check)	+	+
	11	Grippotyphosa	Not reported	Mast cell tumour in spleen and liver	+	+
	11	Not determined	Not reported	Foreign body in pharynx (grass)	–	+
	11	Grippotyphosa	Not reported	CKD and abdominal mass	+	+
	11	Australis, Autumnalis, Bratislava and Copenhageni	Chronic diarrhoea	Not reported	+	+
	14	Bratislava, Copenhageni, Grippotyphosa and Pomona	Not reported	CKD	13+	6+
	14	Bratislava, Grippotyphosa, Icterohaemorrhagiae and Pomona	Not reported	Incidental infection (routine health check)	9+	2+
	16	Icterohaemorrhagiae	Kidney: Chronic interstitial nephritis. Chronic inflammatory infiltrate (macrophages and lymphocytes) Liver: Chronic inflammatory infiltration	Not reported	+	NP
	16	Canicola	Asymptomatic	Not reported	+	NP

MAT = microscopic agglutination test; + = positive; – = negative; CKD = chronic kidney disease; NP = not performed; 13+, 6+, etc = number of positive cats in the study

Table 5 Clinical signs of leptospirosis in cats based on published studies of animals with a history of exposure

	Reference	Serovar(s)	Clinical signs	Diagnosis	MAT	PCR
Prospective study	9	Ballum, Bataviae and Javanica	Not reported	Feline upper respiratory disease	+	NP
	15	Autumnalis, Bataviae, Canicola and Grippotyphosa	Asymptomatic	Incidental infection (routine health check)	10+	NP
	24	Australis, Bataviae, Bratislava, Canicola, Grippotyphosa, Icterohaemorrhagiae, Pyrogenes, Pomona and Sejroe	Asymptomatic	Incidental infection (neutering)	43+	NP
	25	Autumnalis and Bratislava	Not reported	CKD	+	NP
	25	Autumnalis and Bratislava	Polyuria and polydipsia	Not reported	+	NP
	25	Autumnalis and Bratislava	Not reported	Hepatic lipidosis	2+	NP
	25	Autumnalis and Bratislava	Asymptomatic	Not reported	3+	NP
	27	Australis and Ballum	Asymptomatic	Not reported	5+	NP
	16	Icterohaemorrhagiae	Kidney: Chronic interstitial nephritis. Chronic inflammatory infiltrate (macrophages, lymphocytes and plasma cells). Proliferative glomerulonephritis Liver: Multifocal hepatic necrosis. Chronic inflammatory infiltrate (lymphocytes and plasma cells)	Not reported	+	NP
	16	Ballum	Kidney: Chronic interstitial nephritis. Chronic inflammatory infiltrate (macrophages and plasma cells)	Not reported	+	NP
	16	Ballum	Asymptomatic	Not reported	+	NP
	16	Icterohaemorrhagiae	Kidney: Chronic interstitial nephritis. Chronic inflammatory infiltrate (macrophages and lymphocytes)	Not reported	+	NP
	17	Rachmati	Asymptomatic	Not reported	15+	NP
	17	Rachmati	Not reported	Various chronic diseases	18+	NP
Retrospective study	59	Bratislava and Icterohaemorrhagiae	Not reported	CKD – azotaemia	4+	NP
	59	Bratislava and Icterohaemorrhagiae	Not reported	CKD – non-azotaemia	8+	NP

MAT = microscopic agglutination test; + = positive; – = negative; CKD = chronic kidney disease; NP = not performed; 10+, 43+, etc = number of positive cats in the study

Polyuria, polydipsia, haematuria, uveitis, laminitis, lethargy, anorexia, weight loss, vomiting and diarrhoea, painful handling, and inflammatory lesions on skin and foot digits are some of the clinical signs reported in affected cats.

Clinicopathological data

Table 6 summarises some of the most common clinicopathological abnormalities associated with leptospirosis in cats.

Complete blood count

Leukocytes can fluctuate according to the stage and severity of infection. Leukopenia is a possibility during leptospiraemia, evolving to leukocytosis owing to neutrophilia with a left shift. In advanced states, leukocyte counts may be in the range of $16.5\text{--}45 \times 10^9/\text{l}$ (reference interval $2.75\text{--}11.75 \times 10^9/\text{l}$).^{18,19,60,61}

Serum biochemistry

Urea and creatinine concentrations are increased in 80–90% of cases of canine leptospirosis.⁶⁰ Most infected cats present



with azotaemia at the time of diagnosis. The increase is usually moderate to severe.^{11,14,25,31,32,59} In affected dogs, serum liver enzyme (alkaline phosphatase [ALP] more commonly than alanine aminotransferase [ALT]) and total bilirubin increases are associated with liver dysfunction.^{38,40,60} Conversely, in feline leptospirosis these increments are not as characteristic, and only slight increases have been reported.^{11,18,25,31,32} Leptospire toxins inhibit $\text{Na}^+\text{K}^+\text{-ATPase}$ activity in the epithelial cells of the renal tubules in cats and dogs, which can lead to significant renal losses of electrolytes, resulting in severe hypokalaemia.⁶⁰ In cats, increases in serum phosphorus concentration have been reported, probably associated with a decrease in the glomerular filtration rate.³¹

Urine analysis

Findings in dogs include isosthenuria or occasionally hyposthenuria, glycosuria, proteinuria, bilirubinuria, haematuria, pyuria and the presence of casts in fresh urine sediment.^{38,60} In cats, hyposthenuria, haematuria and proteinuria have been reported.^{30,31} Leptospire are not visible on routine fresh urinary sediment examination, as the size of the bacteria is below the resolution of light microscopy.¹⁹

Ultrasonographic findings

The few published reports of feline leptospirosis describe renal ultrasonographic findings that are similar to those in canine leptospirosis, including a granular appearance of the kidney, enlarged kidneys with a cortex that is thinner than the medulla, a slightly hyperechogenic renal cortex and a decrease in the definition of the corticomedullary junction.^{31,32} Heterogeneity in the pancreatic and liver parenchyma has also been reported in one case.³²

Specific testing

Laboratory diagnosis of leptospirosis in veterinary medicine is usually based on the demonstration of serum antibodies by MAT and ELISA, and/or isolation of *Leptospira* DNA from blood and urine by PCR. Bacterial culture of blood and/or urine is not widely used because it is time consuming. Specific diagnostic tests that are available for cats are MAT and PCR.

Microscopic agglutination test

Determination of antibody titre by MAT is the recommended technique for leptospirosis diagnosis, as MAT reactivity to a serovar suggests exposure to a serovar belonging to the corresponding serogroup (though not necessarily to the specific serovar tested).⁶² The selection of the serogroups and the serovars to be evaluated depends on the geographical location of the patient's likely exposure. Antibodies (IgM and IgG) are detected at around 15 days post-infection by MAT.³ Little information is available on the duration of these antibodies in the blood of cats. Clinical interpretation should always be based on the results of paired serum titres, and it is worth noting that some infected animals may produce a result that is lower than the widely accepted minimum significant titre result of 1:100.³ It is even possible that seroconversion in cats is expressed at a lower titre compared with dogs.⁵⁹

Table 6 Clinicopathological findings in 19 cats diagnosed with leptospirosis^{11,18,30–32}

	Finding	Clinical course	Affected/sampled cats
Haematology	Non-regenerative anaemia	Chronic carrier	2/19 (10.5%)
	Haemoconcentration	Acute disease	2/19 (10.5%)
	Neutropenia	Acute disease	1/19 (5.2%)
	Neutrophilia	Acute disease	2/19 (10.5%)
	Leukocytosis with left shift	Acute disease	2/19 (10.5%)
	Thrombocytopenia	Acute disease	1/19 (5.2%)
Biochemistry	Hypoalbuminaemia	Acute disease	2/2 (100%)
	Azotaemia	Acute disease and chronic carrier	9/19 (47.4%)
	Liver enzymes increased	Acute disease	6/8 (75%)
	Hyperglycaemia	Acute disease	1/2 (50%)
	Hyperphosphataemia	Acute disease	1/1 (100%)
	Bicarbonate decreased	Acute disease	1/1 (100%)
Urine analysis	Low USG	Acute disease and chronic carrier	3/5 (60%)
	Proteinuria	Acute disease	3/6 (50%)
	Haematuria	Acute disease	2/6 (33.3%)
	Renal and red cell casts	Acute disease	1/5 (20%)
Serological test	FeLV/FIV negative	Acute disease	5/5 (100%)

USG = urine specific gravity; FeLV = feline leukaemia virus; FIV = feline immunodeficiency virus

Several studies have confirmed renal carriage of *Leptospira* species in cat populations, which means cats could be a chronic reservoir host for the bacteria and a possible risk factor for human infection.



MAT results are strongly dependent on laboratory quality control, and there is considerable inter-laboratory variability.⁶³ Practitioners are encouraged to submit diagnostic samples to laboratories that adhere to a proficiency scheme.⁶⁴ Test interpretation may be more reliable in cats than in dogs because no interference with vaccine antibodies exists as cats are not vaccinated.³⁷ Furthermore, laboratory-reared young adult specific pathogen-free cats infected with *Borrelia burgdorferi* did not form antibodies against *Leptospira* species as a cross-reaction.⁵⁹ The authors of that study suggest that positive *Leptospira* species MAT results from cats in the field are likely to reflect antibodies against leptospire and not *B burgdorferi*.

MAT results are strongly dependent on quality control procedures in the laboratory. Practitioners are encouraged to submit diagnostic samples to laboratories that adhere to a proficiency scheme.

ELISA and rapid immunodiagnostic screening tests

ELISAs used for leptospirosis identify the presence of leptospiral antibodies (specific IgM class antibodies) earlier than MAT, at between 4–6 days post-infection.³ The main advantages of ELISA compared with MAT are, in the authors' opinion, the stability of antigenic preparations and the genus specificity, meaning all types of leptospires can be diagnosed with a single antigenic preparation, irrespective of the causal serovar.⁶⁵ In dogs, a combination of ELISA plus MAT is recommended for leptospirosis diagnosis.¹⁹

Rapid patient-side tests for leptospirosis diagnosis were developed almost a decade ago.⁶⁶ Curtis et al performed a recombinant LipL32-based rapid in-clinic ELISA (SNAP Lepto) for the detection of antibodies against *Leptospira* species in dogs in 2015.⁶⁷ Neither of the tests distinguish between serovars, nor do they provide a titre magnitude. The first test⁶⁶ is based on the detection of *Leptospira*-specific IgM and has demonstrated a sensitivity and specificity of 100% and 95.3%, respectively. It can therefore detect dogs with clinically suspected acute leptospirosis. Dogs previously vaccinated or suffering from an acute but subclinical infection can also produce positive results. A LipL32-based in-clinic ELISA for the rapid detection of *Leptospira*-specific antibodies in dogs is not IgM specific, but the study authors considered it a convenient tool to assess *Leptospira* antibody status in dogs.⁶⁷

Neither rapid test techniques, nor ELISA, to diagnose leptospirosis in cats have yet been developed.

ELISA and rapid patient-side tests for *Leptospira* species diagnosis in cats have not yet been developed.

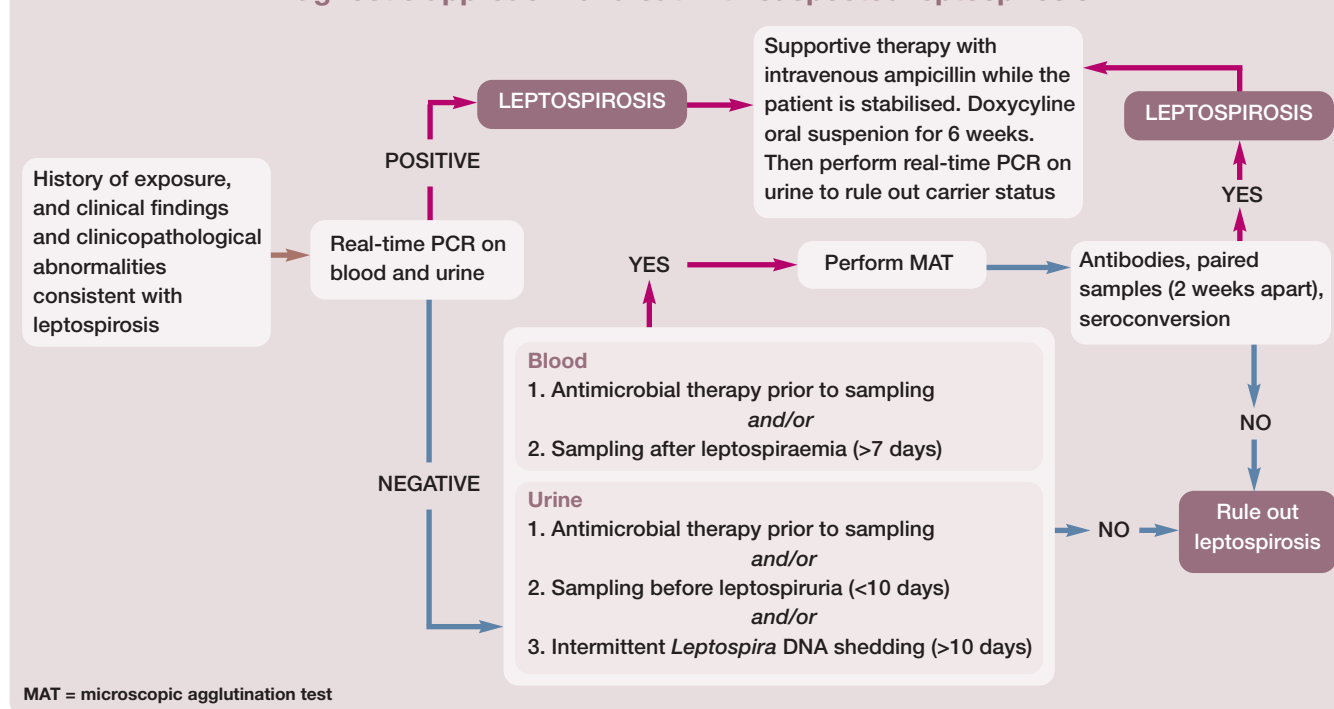


PCR

PCR directly identifies leptospiral DNA. It does not determine the infecting serogroup or serovar, but it can indicate the *Leptospira* species. The test can be performed on blood, urine, cerebrospinal fluid and body tissues. In cases of acute leptospirosis, this would be the test of choice to perform on blood and urine in cats. Compared with culture, PCR gives fast results, contributing to an early diagnosis.⁶⁵ Real-time PCR techniques are recommended, due to their greater sensitivity and specificity. Genes that have more than one copy in the genome, such as *lig* or *rrs*, should be selected with the aim of increasing the sensitivity of the technique. Genes present only in the pathogenic species can also be added as they will increase the specificity of the test.⁶⁸

A positive PCR result means that leptospiral DNA is present in the sample. In acute infections or in chronic carriers, the test would be positive in urine, indicating that bacterial DNA is being shed. However, negative results in blood and urine do not rule out leptospirosis, as leptospiraemia is transient (only occurring in the initial phases of the disease); also results are usually negative if the cat has received antibiotic therapy,^{19,60} and shedding in urine can be intermittent.³ In one report, leptospires were cultured from cat urine and the results were confirmed by PCR,³⁴ suggesting that cats can shed living *Leptospira* bacteria, not just their DNA.

Diagnostic approach for a cat with suspected leptospirosis



Prognosis

The prognosis depends principally on the severity of any organ damage. In dogs that develop LPHS, the prognosis is usually poor since the animal is in acute respiratory failure with associated dyspnoea resulting from damage to the small pulmonary vessels, as described earlier; LPHS is one of the most common leptospiral-associated causes of death in dogs. The prognosis is also poor for affected animals that develop acute renal injury unless haemodialysis is available.⁶⁰

In cats with mild clinical signs and no severe organ damage, response to specific antimicrobial therapy and outcome are good.^{30–32} Cats that survive acute renal failure, and especially those treated in the chronic phase of leptospirosis, may develop renal damage as a consequence of the initial condition, and this may be permanent.

Treatment

Supportive therapy

Intravenous fluids should be given to affected animals to correct the electrolyte fluid imbalance. The use of centrally acting antiemetics and the parenteral administration of gastric protectors is recommended in cats that develop associated renal failure. Pain management is particularly important in the early stages of the disease to treat painful swollen kidneys, muscle, joints and gastrointestinal tissue.¹⁹

Case notes

A 2-year-old intact male domestic shorthair cat, showing lethargy and anorexia for 5 days, was presented for investigation.

Case work-up

The cat was an indoor-outdoor animal with a history of hunting small rodents. Vaccinations were current.

On admission, the cat was quiet and depressed.

On physical examination, body

temperature was 39.7°C

and the cat's mucous

membranes were pale and

dry. Heart rate was 180 beats per minute and pulse strength

was normal; no murmurs or gallop rhythms were detected.

Clinical dehydration was estimated to be 7%. There were no

other remarkable findings upon physical examination. Owing

to the non-specific clinical signs, blood samples were

collected for haematology, biochemistry and feline leukaemia

virus (FeLV)/feline immunodeficiency virus (FIV) testing. A urine

sample was obtained by cystocentesis for complete urine

analysis. Clinical pathology results are shown in the table.

Mild leukocytosis with mature neutrophilia and

thrombocytopenia were observed. Serum biochemistry profile

showed a mild uraemia, increase in ALT and hyperproteinaemia

(mainly due to an increase in the globulin fraction). FeLV

antigen and FIV antibody testing were negative (IDEXX

SNAP Combo Test). Most of the clinical pathological

changes were suspected to be due to dehydration. However,

thrombocytopenia and leukocytosis suggested a possible

infectious origin. Ancillary tests, including an abdominal

ultrasound examination and thoracic radiography, were

performed. The results were unremarkable.

Given the patient's predation habits, leptospirosis was

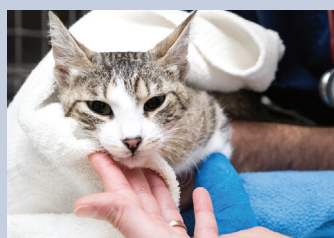
considered and PCR (blood and urine) was performed. In

addition, serum was serologically examined by MAT against

eight *Leptospira* serovars: Australis, Autumnalis, Canicola,

Grippotyphosa, Icterohaemorrhagiae, Javanica, Pomona

and Sejroe. MAT serology for leptospirosis was negative.



Courtesy of Fundació Hospital Clínic Veterinari, Universitat Autònoma de Barcelona, Spain

Clinical pathology results

Complete blood count

	Result	RI
RBCs ($\times 10^{12}/\text{l}$)	6.2	6–10.2
Hb (g/dl)	10.5	9–15
HCT (l/l)	0.3	0.3–0.5
MCV (fl)	47.2	41–53
MCHC (g/dl)	36	30–34
Leukocytes ($\times 10^9/\text{l}$)	18.2	5.0–15.0
Lymphocytes ($\times 10^9/\text{l}$)	5.8	1.4–6.1
Monocytes ($\times 10^9/\text{l}$)	1.8	0.1–0.6
Band neutrophils ($\times 10^9/\text{l}$)	0	0–300
Segmented neutrophils ($\times 10^9/\text{l}$)	12.0	2.5–11.3
Platelets ($\times 10^9/\text{l}$)*	115	200–600

Serum biochemistry (selected data)

	Result	RI
Albumin (g/l)	24.8	23–34
Globulins (g/l)	44.0	26–38
Total proteins (g/l)	96.9	54–78
Creatinine ($\mu\text{mol/l}$)	91	44.2–132.6
Urea (mmol/l)	8.6	3.32–8.3
ALT (U/l)	51.4	<50

Urine analysis (cystocentesis)

	Result
Specific gravity	>1.050
pH	6
Nitrite	Negative
Protein	Negative
Glucose	Negative
Ketones	Negative
Bilirubin	Negative
Blood	No abnormalities identified
Sediment	Moderate fat droplets
UPC	0.23

*Only mild platelet aggregates were observed on blood smear
RBCs = red blood cells; Hb = haemoglobin; HCT = haematocrit;
MCV = mean cell volume; MCHC = mean cell haemoglobin
concentration; ALT = alanine aminotransferase; UPC = urine
protein:creatinine concentration; RI = reference interval

Diagnosis Blood PCR for leptospirosis was positive and urine PCR was negative.

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Enteral feeding tubes are highly recommended in cats with anorexia, until they can feed themselves in a self-sufficient manner, minimising the risk of secondary complications.³⁸

Antimicrobial therapy

The antimicrobial therapy suggested in cats is based on the treatment recommended for dogs. Intravenous ampicillin may be the antibiotic of choice while the patient is stabilised. Once the animal is stable, 6 weeks of doxycycline oral suspension has been suggested in order to eliminate the carrier state.³⁷ Monohydrate salt of doxycycline, which is less irritating to the cat's oesophagus than hyclate or hydrochloride doxycycline salt, is marketed as tablets or suspension. Doxycycline monohydrate tablets should be administered immediately before a meal or with a treat in order to avoid secondary oesophagitis.^{69,70}

Prevention

There is no commercial vaccine available for cats. However, one study has shown that cats can produce antibodies (of lower titre magnitude than vaccinated dogs) when experimentally inoculated with a commercial dog vaccine (containing four different serovars).⁵⁹ The follow-up time for the animals was 42 days, at which point only one animal maintained antibody levels. The authors of that

Doxycycline is advised to eliminate the carrier state. It should be administered as a monohydrate salt to avoid oesophagitis.



study suggest further work is needed before a vaccine against *Leptospira* species for cats can be considered.

Given the current lack of a vaccine, the best way to avoid infection in cats is via prevention of exposure. Cats that are kept indoors have a lower risk of being infected.³⁷ Prevention of predation opportunities and avoidance of contact with stagnant water, urine from infected animals and dogs at risk of clinical leptospirosis is recommended.^{6,30,31,37} For cats that share an environment with a positively diagnosed animal, doxycycline can be given at 5 mg/kg PO q12h or at 10 mg/kg PO q24h for 2 weeks.^{19,60}

KEY POINTS

- ❖ Cats may act as chronic reservoir hosts of *Leptospira* bacteria and are a possible risk factor in the transmission and maintenance of leptospirosis, the most widespread zoonosis worldwide.
- ❖ Research on leptospirosis should highlight the importance that cats have in the disease maintenance cycle.



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Treatment and outcome The cat was maintained on fluid therapy and antimicrobial therapy with ampicillin (20 mg/kg IV q12h) for 4 days. On day 4 of hospitalisation, ALT, creatinine and urea were re-checked; values were within reference intervals. On discharge, after receiving PCR blood results, doxycycline at 5 mg/kg PO q12h for 6 weeks was prescribed. Instructions were given to keep the animal confined during the next 6 weeks and isolated from other cats and dogs. The owners were advised to wear gloves while

cleaning the litter box during this period, to use routine household disinfectants to clean the litter box and to wash their hands after handling their cat.

Six weeks later, the cat had recovered completely and no abnormalities were observed upon physical examination. A further urine PCR was recommended in order to rule out a chronic carrier state, as well as a further MAT to assess seroconversion, but for economic reasons this was not approved by the owners.

What this case demonstrates:

- ❖ While leptospirosis is an uncommon infectious disease in cats, practitioners should consider leptospirosis as a differential diagnosis in cats that hunt small rodents.
- ❖ At the time of admission, clinical pathological data in sick cats are not always characteristic of the disease, as in this case.
- ❖ For acute infections, PCR on blood and urine is the first-choice test to perform; MAT antibody titres are likely to be negative or low at that point, and seroconversion is not expected until 15 days post-infection.
- ❖ Leptospirosis is a zoonosis and special handling methods are needed in these cases: (1) avoiding contact with the cat's urine and wearing gloves when cleaning the litter box; (2) using disinfectants to clean the cat's litter box as well as any other areas where the cat urinates; (3) preventing the cat from going outside to urinate in the environment; and (4) always washing hands after handling the cat.
- ❖ Owing to the zoonotic potential of leptospires, prophylactic treatment of other pets in the same household that may have been exposed to leptospires in the environment is recommended.
- ❖ When a diagnosis of leptospirosis is made, veterinarians should inform pet owners of the zoonotic risk of *Leptospira* bacteria, and recommend medical attention if any family member develops signs of illness consistent with leptospirosis.

Conflict of interest

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Ethical approval

This work did not involve the use of animals and therefore ethical approval was not required.

Informed consent

This work did not involve the use of animals and therefore informed consent was not required. For any animals individually identifiable within this publication, informed consent for their use in the publication (either verbal or written) was obtained from the people involved.

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