GUIDELINE for Leptospira spp. infection in cats

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Key points

- *Leptospira* species (spp.) infection can cause leptospirosis, a bacterial disease affecting a variety of domestic and wild animals and humans worldwide that has been reported in over 150 mammalian species.
- Leptospirosis is considered an emerging infectious disease in humans and in dogs.
- Subclinically infected wild and domestic animals serve as reservoir hosts and are a potential source of infection for incidental hosts, including humans.
- *Leptospira* infection in cats is common, and cats usually acquire the infection from hunting rodents.
- The disease leptospirosis in cats is considered rare, but the number of reports on field cats with clinical signs caused by*Leptospira* infection increases, and the disease has recently been seen more commonly.
- In addition, the fact that cats can shed*Leptospira* with their urine, and thus serve as a potential source of infection, has gained increasing attention.
- Antibodies against*Leptospira* are commonly present in the feline population, and *Leptospira* spp. shedding in cats with outdoor exposure has been demonstrated now in different regions worldwide.
- The role of healthy carrier cats as a source of contamination as well as the role of leptospires as a pathogen in cats likely has been underestimated in the past.

Agent properties

Leptospires are mobile, thin, filamentous bacteria of a size of 6.0-25.0 mm length and 0.1-0.2 mm width, that appear as fine spirals often with hook-shaped ends (Fig. 1) (Bharti et al., 2003; Adler and de la Pena Moctezuma, 2010). They actively move by rotating around their axes, with clockwise rotation resulting in hook-shaped ends and counterclockwise rotation resulting in spiral-shaped ends (Wolgemuth et al., 2006). Leptospires can remain infectious for several months under optimal environmental conditions, such as at temperatures around 25 °C, moisture, and a neutral soil pH (Sykes et al., 2011; Schuller et al., 2015).

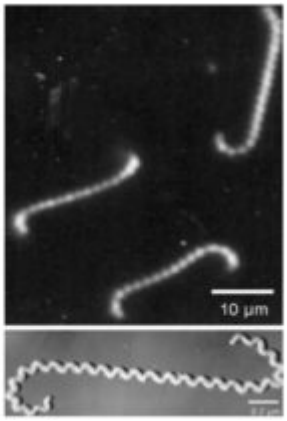

Fig. 1 Dark field photomicrograph (a) and shadowed electron micrograph (b) of Leptospira spp. (courtesy of Ben Adler, Australian Research Council Centre of Excellence in Structural and Functional Microbial Genomics, Monash University, Clayton, Australia).

The genus *Leptospira* belongs to the order *Spirochaetales*. There are over 250 pathogenic serovars of leptospires, based on differences in the carbohydrate component of the bacterial lipopolysaccharide. Serovars are grouped into antigenically related serogroups. Immunity to leptospires is serogroup-specific. Different serovars are adapted to different wild or domestic animal reservoir hosts. Leptospirosis in dogs and humans is caused primarily by pathogenic serovars of the species *Leptospira interrogans* sensu lato. Several of those serovars also have been reported to cause infections in cats (Sykes et al., 2011; Dorsch et al., 2020; Sprißler et al., 2019; Weis et al., 2017).

In dogs, serovars Icterohaemorrhagiae and Canicola were responsible for most cases of canine leptospirosis before 1960. Since the widespread use of a bivalent serovar-specific vaccine against Canicola and Icterohaemorrhagiae, there has been an apparent shift to other serovars that are now more commonly identified in dogs suffering from leptospirosis. This has subsequently led to an increase in canine cases (Sykes et al., 2011; Schuller et al., 2015). In the last ten years, new vaccines for dogs have reached the market in USA and several European countries, which contain not only Canicola and Icterohaemorrhagiae, but also Grippotyphosa, and in some vaccines additionally Bratislava (or Australis which is in the same serogroup) or Pomona, and this has now again decreased the incidence of leptospirosis in dogs in countries where new vaccines are used (Francey et al., 2018).

Epidemiology

Leptospires can cause infections in many animal species, and have been identified in more than 150 mammalian species as well as in bird, fish, amphibian, and reptile species (Everard et al., 1985; Pappas et al., 2008). Subclinically and often chronically infected wild and domestic animals serve as reservoir hosts and shed leptospires mainly through urine, and thus, are a potential source for contamination of the environment (Adler and de la Pena Moctezuma, 2010; Sykes et al., 2011; Schuller et al., 2015). Mainly rodents serve as reservoir hosts, but companion and production animals, such as dogs, cats, pigs, and cattle, can also act as reservoir hosts (Adler and de la Pena Moctezuma, 2010; Mayer-Scholl et al., 2014; Llewellyn et al., 2016; Weis and Hartmann, 2017).

Prevalence

Antibodies against *Leptospira* spp. are commonly present in the feline population, and *Leptospira* spp. shedding in cats with outdoor exposure has been demonstrated now in different regions worldwide (Fenimore et al., 2012; Rodriguez et al., 2012; Dorsch et al., 2020; Sprißler et al., 2019; Weis et al., 2017).

Antibodies have been detected in cats worldwide (Larsson et al., 1985; Batza and Weiss, 1987; Dickeson and Love, 1993; Agunloye and Nash, 1996; Luciani, 2004; Mylonakis et al., 2005; Markovich et al., 2012; Rodriguez et al., 2012; Lapointe et al., 2013; Rodriguez et al., 2014; Talebkhan Garoussi et al., 2015; Rose et al., 2016; Sprißler et al., 2019; Weis et al., 2017; Palerme et al., 2019; Alashraf et al., 2019; Khalili et al., 2020; da Silva et al., 2020; Lehtla et al., 2020; Murillo et al., 2020; Žákovská et al., 2020). Antibody prevalence varies depending on geographical area and climate, and ranged from 4.8% in the United States (Markovich et al., 2012) to 59.3% in

Portugal (da Silva et al., 2020). Two studies in Germany detected antibodies in 14.6% of cats in the Berlin (Rose et al., 2016) and 17.9% of cats in the Munich area (Weis et al., 2017). In the Lisbon area in Portugal 9.5% of 243 cat sera tested by ELISA were found IgG positive to *Leptospira* spp.; however, when the ELISA cut-off was decreased and data were analysed by the best different mixture model, antibody prevalence was re-estimated at 59.3% (da Silva et al., 2020).

Reactivity to many different serovars has been identified in cats based on MAT, including reactivity against serovars Anhoa, Australis, Autumnalis, Ballum, Bratislava, Canicola, Djasiman, Celledoni, Copenhageni, Grippotyphosa, Hardjo, Icterohaemorrhagiae, Pomona, Pyrogenes, and Saxkoebing (Larsson et al., 1984; Batza and Weiss, 1987; Dickeson and Love, 1993; Agunloye and Nash, 1996; Mylonakis et al., 2005; Markovich et al., 2012; Rodriguez et al., 2012; Rose et al., 2016; Sprißler et al., 2019; Weis et al., 2017). Prevalence of serovars differs significantly between geographical regions. Most studies based on antibody detection have used MAT. However, cross-reactions between serovars can occur, and therefore, serovar prevalence studies are difficult to interpret.

A few studies have also looked into shedding of *Leptospira* spp. in the urine of cats using PCR in a few countries. Prevalence ranged from 0.8% in Thailand (Sprißler et al., 2019), 1.7% in Spain (Murillo et al., 2020), 3.3% in Germany (Weis et al., 2017), 3.4% in Canada (Rodriguez et al., 2012) to 11.7% in the United States (Fenimore et al., 2012) and 13.0% in Chile (Dorsch et al., 2020). In a study in Taiwan, a prevalence of *Leptospira* spp. urinary shedding of 67.8% was detected (Chan et al., 2014), but sampling had occurred following a natural disaster that had caused an unusual epidemic of leptospirosis in humans (Su et al., 2011). It was also possible to prove that cats not only shed leptospiral DNA, as detected by PCR, but also truly viable leptospires. This was demonstrated in two studies in Chile; in one study, in which viable leptospires were cultured in the urine of outdoor cats (in 1.3% of the tested cats) (Dorsch et al., 2020) and in one report of interspecies transmission between a cat and a dairy cattle farm (Ojeda et al., 2018). In addition, in one study from Malaysia, culture of kidney tissues revealed growth of *Leptospira* spp. in four of 82 healthy shelter cats, and in one of those four cats the urine was also culture-positive (Alashraf et al., 2020). It is important to realize that some cats also shed lesptospires without having detectable antibodies (Shophet, 1979; Sprißler et al., 2019; Alashraf et al., 2020), and that some cats might shed over a long period of time. In one of the shedding cats in Germany, a follow-up urine sample eight months after the first sampling was positive again for leptospiral DNA, indicating a chronic carrier state or reinfection (Weiss et al., 2017). Prevalence of urinary shedding is comparable to that of dogs in the same areas (Fenimore et al., 2012; Llewellyn et al., 2016; Weis et al., 2017). However, while dogs in Europe most commonly have *Leptospira* spp. infection in late summer and autumn/fall (Schuller et al., 2015), in cats no seasonal peak was found (Weis et al., 2017). The reason for this likely is the difference in transmission of leptospires, which in dogs is more dependent on the outside temperature (see below).

All these studies show that outdoor cats might be a reservoir or incidental hosts for the transmission of leptospires. Likely, urinary shedding and the role of cats as a source of infection have been underestimated in the past.

Wild felids can also be infected with *Leptospira* spp. In two of 57 healthy captive felids in Brazil, antibodies against *Leptospira* spp. were detected (Ullmann et al., 2012). In addition, jaguars in various areas in Brazil had antibodies against different *Leptospira* serovars (Furtado et al., 2015). In a wildlife safari park in South Italy, three of 15 tigers were antibody-positive by MAT (Iatta et al., 2020). Antibodies against *Leptospira* spp. were also detected in wildcats in a natural park in Serranía de Cuenca in Central Spain (Candela et al., 2019).

Predisposing factors

No correlation was found between the presence of antibodies and sex or breed. However, an association with age has been reported, with older cats being more likely to possess antibodies (Larsson et al., 1984; Mylonakis et al., 2005; Rodriguez et al., 2012). Antibodies are more common in outdoor cats, those living in urban areas, and those that are known hunters (Rodriguez et al., 2012; Lehtla et al., 2020). In a study in Portugal, being infected with feline immunodeficiency virus (FIV) was identified as a significant risk factor associated with the presence of anti-*Leptospira* IgG antibodies in ELISA when using a low cut-off value (da Silva et al., 2020).

Concerning predisposing factors for shedding, in one study two factors, the health status (being sick compared to healthy), and having received previous vaccination against core vaccine components, were associated with leptospiruria (Dorsch et al., 2020).

Transmission

Leptospires are transmitted by direct contact or indirectly. Direct transmission between hosts occurs through urine, venereal routes, placental transfer, bites, or ingestion of infected animals or tissues. *Spirochaetales* have also been demonstrated to survive in insects and other invertebrates, but their role as vectors of *Leptospira* spp. is unknown. In dogs and humans, indirect transmission is more frequent than direct transmission and occurs through exposure to contaminated environment, e.g., soil, food, bedding. Thus, water contact is most important in dogs and humans, and habitats with stagnant or slow-moving warm water favour survival of the organism. Leptospires in contaminated water invade the host through skin wounds but also through intact mucous membranes (Sykes et al., 2011; Schuller et al., 2015). In cats indirect transmission through water contact is less likely (Hartmann et al., 2013; Weis et al., 2017) due to cats' aversion to swimming in water, but they might be infected by drinking out of natural water sources. Cats are thought to most

commonly get infected through direct rodent contact. It has been shown experimentally that feeding on rodents harbouring leptospires can lead to infection in cats (Shophet and Marshall, 1980). Rodents are the natural reservoir for many serovars, and prey-predator transmission between cats and rodents seems to occur commonly (Shophet, 1979). In Germany, in almost 10% of rodents, DNA of pathogenic leptospires was detected (Mayer-Scholl et al., 2014). On the Reunion Island, DNA of pathogenic *Leptospira* spp. was found in kidney samples of more than 50% of rodents (Desvars et al., 2013), although the antibody prevalence in 172 feral cats was low (0.6%) (Gomard et al., 2019). In France, 44% of wild rats tested positive by PCR or culture (Ayral et al., 2015). The risk of infection for cats hunting rodents is therefore considered relatively high (Desvars et al., 2013).

As pigs and cattle can shed leptospires subclinically, farms are another source of infection for cats (Everard et al., 1985; Harkness et al., 1970; Truong et al., 2013). In one study in Iran, cats in contact with dairy cattle herds were significantly more commonly infected than cats in urban areas (Talebkhan Garoussi et al., 2015). In one study in Chile, interspecies transmission of pathogenic *Leptospira* spp. between livestock and a domestic cat dwelling in a dairy cattle farm was demonstrated. The cat was physically healthy but had leukocytosis with neutrophilia, monocytosis, and hyperproteinaemia. Urinary shedding was detected by PCR, and the cat had microagglutination test (MAT) titres against serovars Pomona and Autumnalis. The cattle herd in contact with the cat also had evidence of *Leptospira* spp. infection (Ojeda et al., 2018). Dogs also can be chronic shedders of *Leptospira* spp. (Harkin et al., 2003a; Rojas et al., 2010; Gay et al., 2014; Llewellyn et al., 2016; Boonciew et al., 2020; Altheimer et al., 2020). Due to the low pH, *Leptospira* spp. can only survive for a short time in the urine of dogs. Nevertheless, infection of cats by direct contact with urine from dogs or other cats is likely possible (Hartmann et al., 2013).

Pathogenesis

The pathogenesis of feline leptospirosis is not well known but is likely similar to that in dogs and humans. Infection occurs *via* direct contact with a host or its urine, or indirectly *via* contaminated soil or water (e.g., drinking or bathing). After penetration through mucous membranes, abraded or scratched skin, leptospires multiply rapidly upon entering the blood vascular space as early as one day after infection and can circulate up to seven days in the blood. They invade the kidneys, liver, spleen, central nervous system (CNS), eyes, and genital tract amongst others, and can damage these organs by replicating and causing inflammation (Adler and de la Pena Muctezuma, 2010). Initial replication mainly causes damage to kidneys and liver. The extent of damage is variable and depends on the virulence of the organism and host susceptibility. The immune response can clear the leptospires from most organs except from the kidneys, where the agent can persist (Levett, 2001; Schuller et al., 2015). In dogs, shedding can continue for weeks to months (Adler and de la Pena Muctezuma, 2010; Sykes et al., 2011) and this might be the case in cats as well (Weis et al., 2017).

Immunity

Immunity after infection with *Leptospira* spp. is considered to be only short-lived. In dogs, true duration of immunity after natural infection is unclear, and it is unknown whether or not life-long immunity can develop after natural infection. So far, there are no reports of reinfection of dogs with *Leptospira* spp. after successful treatment. Immunity to leptospires is serogroup-specific, with little cross-protection between different serogroups (Schuller et al., 2015).

Passive immunity

Not much is known about passively acquired (maternally derived) antibodies against *Leptospira* spp. in cats or in dogs. However, two studies found that in pigs, vaccinated mothers transferred antibodies to their piglets (Millar et al., 1987; Martins Soto et al., 2008). In one study, mean neutralizing antibodies titers were low and passive immunity was of short duration (Martins Soto et al., 2008). In the other study, antibodies titres varied greatly from piglet to piglet. Titres declined between 4 and 10 weeks of age, with an uncorrected half-life of 15.5 days. Colostrum-derived antibody protected four of eight pigs from intravenous challenge at 8 weeks of age (Millar et al., 1987).

Active immunity

Recovery from infection depends upon production of specific antibodies. Antibodies are usually detectable three to ten days after the presence of first clinical signs (Merien et al., 1995; Levett, 2001; Sykes et al., 2011). In an experimental study, cats developed antibodies detectable in MAT three weeks after infection (Shropshire et al., 2016). As antibodies increase, leptospires are cleared from most tissues, except from the kidneys. Renal colonization occurs in most infected animals, and the organism usually persists in the tubular epithelial cells causing shedding for months to years after clinical recovery (Sykes et al., 2011; Greene et al., 2012; Schuller et al., 2015).

Clinical signs

Although *Leptospira* spp. infection and shedding in cats seems to be as common as in dogs, clinical disease is less frequently observed. However, some cases of clinical manifestation of feline *Leptospira* spp. infection have been described. During an outbreak of

leptospirosis in dogs in UK, several cats with clinical signs of leptospirosis were identified (Murphy, 2015).

There are few experimental studies in which cats have been infected with pathogenic *Leptospira* spp. Disease after experimental infection was usually mild, or infection remained subclinical (Dickeson and Love, 1993; Agunloye and Nash, 1996; André-Fontaine, 2006). Some cats showed mild clinical signs, such as polyuria/polydipsia, mild diarrhoea, and a slight increase in body temperature (Semmel, 1954; Fessler and Morter, 1964; Larsson et al., 1985). Laboratory diagnostics revealed a mild leukocytosis (Semmel, 1954). Six of seven experimentally infected cats had an enlarged liver at necropsy, and histopathological degenerative changes of the liver were noted. Five of seven cats showed non-purulent interstitial nephritis (Fessler and Morter, 1964).

A few case reports about cats with leptospirosis in the field have described the disease in outdoor and hunting cats (Bryson and Ellis, 1976; Arbour et al., 2012; Murphy, 2015). The most common clinical manifestation after natural infection seems to be an interstitial nephritis (Hemsley, 1956; Rees, 1964; Fessler and Morter, 1964; Arbour et al., 2012), and affected cats are presented with acute polyuria/polydipsia, anorexia, and lethargy (Arbour et al., 2012). In one case series of three cats with leptospirosis, all cats had renal disease without liver involvement (Arbour et al., 2012). In an older case description, a cat with ascites, enlarged liver, and impaired hepatic function, but without icterus, had antibodies against serovar Hardjo (Agunloye and Nash, 1996). Leptospires also have been isolated from thoracic fluid, aqueous humour, and kidneys of a cat, which, at necropsy, had widespread haemorrhages and straw-coloured fluid in the thoracic and peritoneal cavities (Bryson and Ellis, 1976).

It has been discussed whether *Leptospira* spp. infection in cats might play a role as a factor in the commonly occurring syndrome of feline chronic kidney disease (Hartmann et al., 2020). A relation between polyuria and polydipsia and the presence of antibodies against *Leptospira* spp. has been suggested (Luciani, 2004; André-Fontaine, 2006). Two studies indeed described an association between the presence of antibodies against *Leptospira* spp. and chronic kidney disease (Luciani, 2004; Rodriguez et al., 2014). While 14/16 cats with polyuria/polydipsia (87.5%) had antibodies against leptospires, only 32/80 healthy cats (40.0%) were antibody-positive (Luciani, 2004). In another study, 17/114 cats with renal disease (14.9%) had antibodies, while only 9/125 healthy cats (7.2%) were antibody-positive, which represented a significant difference (Rodriguez et al., 2014). However, other studies have found no association between chronic kidney disease and the presence of antibodies against leptospires. While 4/66 azotaemic cats had antibodies (6.1%), 8/75 cats without azotaemia (10.7%) were antibody-positive (Shropshire et al., 2016). In a German study, there was also no correlation; 5/24 clinically healthy cats (20.8%) and 8/28 chronically ill cats (28.6%) had antibodies (Weis et al., 2017). A correlation between excretion of leptospires and chronic kidney disease in cats was also investigated in a study which found that 2/125 (1.6%) clinically healthy cats and 6/113 (5.3%) cats with chronic kidney disease were urine PCR-positive; however, this difference was not significant (Rodriguez et al., 2014).

Laboratory and diagnostic imaging findings

Many cats are infected with leptospires, but do not develop clinical signs (Hartmann et al., 2013). Consequently, the diagnosis “feline leptospirosis” should only be made when associated clinical signs and clinico-pathological abnormalities are present (Weis and Hartmann, 2017).

Laboratory changes

Usually *Leptospira* spp.-infected cats do not show laboratory changes (Weis and Hartmann, 2017; Weis et al., 2017). If clinical manifestation occurs, laboratory changes might be similar to those commonly seen in dogs with leptospirosis.

In dogs, the majority presents with a leukocytosis, with WBC counts reaching 40,000/µl or even up to 80,000/µl. Differential cell counts often reveal neutrophilia, sometimes with a left shift, lymphopenia, and monocytosis. Mild to severe thrombocytopenia is common. Approximately half of dogs with leptospirosis are presented with an anaemia, which is mostly mild to moderate (Schuller et al., 2015). Blood urea and creatinine are increased in the majority of dogs. Hepatic injury, as evidenced by increases in the activity of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and hyperbilirubinemia, almost exclusively occur in conjunction with azotaemia (Goldstein et al., 2006; Geisen et al., 2007). Electrolyte abnormalities, such as hypo- and hyperkalaemia, hyper- and hypophosphataemia, hyponatraemia, and hypochloraemia, are also common in canine leptospirosis and usually parallel the degree of renal and gastrointestinal dysfunction. Increases of creatine kinase (and AST) activity and troponin I were reported in about 50% of dogs, and suggest skeletal and myocardial injury (Mastrorilli et al., 2007). Various abnormalities of haemostatic parameters can be present indicating that both hyper- and hypocoagulable states can occur (Mastrorilli et al., 2007).

Urinalysis shows isosthenuria in the majority of dogs with leptospirosis, but hyposthenuria has also been described, glucosuria secondary to acute tubular injury, haematuria, pyuria and granular casts can be present, and proteinuria occurs in the majority of dogs (Birnbaum et al. 1998; Adin and Cowgill, 2020; Mastrorilli et al., 2007).

Diagnostic imaging findings

Most cats with *Leptospira* spp. infection will not show diagnostic imaging abnormalities, but those with clinical disease might show changes that are similar to those described in dogs.

In dogs radiographic, as well as computerised tomography (CT), pulmonary changes can reflect leptospiral pulmonary haemorrhage syndrome (LPHS), although changes can be present in the absence of respiratory signs (Baumann and Fluckiger, 2001). Thoracic radiography might underestimate lesion type and severity as compared to thoracic CT (Gendron et al., 2014).

The most common abdominal sonographic examination findings in dogs relate to the kidneys and include cortical hyperechogenicity, renomegaly, mild pyelectasia, a medullary band of hyperechogenicity, and mild perirenal fluid accumulation. Other findings include hepatomegaly, splenomegaly, evidence of ascites, enlargement and hypoechogenicity of the pancreas, thickening of the gastric and (rarely) intestinal wall, and mild lymphadenomegaly (Birnbaum et al., 1998; Adin and Cowgill, 2020; Mastrorilli et al., 2007).

Diagnosis

Direct detection of *Leptospira* spp. (especially from urine samples) in cats is particularly important to assess a potential zoonotic risk (Weis et al., 2017). Indirect detection of antibodies using MAT (which has been validated for cats) is the most common diagnostic method to predict infection.

Detection of the infectious agent

Direct identification of the organisms can be achieved by several techniques, including visualization in fresh urine by dark-field microscopy or in tissue sections or on air-dried smears by light microscopy, culturing of the organism, or detection of DNA by PCR. All direct methods, however, are only reliable if a positive result is obtained, and a negative result never excludes the presence of the infectious agent due to the fact that leptospires are only shed intermittently and sometimes in low numbers (Levett, 2001). Sensitivity of direct detection methods can be increased when an immunomagnetic separation-coupled technique is used (Dorsch et al., 2020), but this is not for routine use but only research purposes.

Direct identification of viable leptospires by dark field microscopy is not reliable and thus not recommended (Levett, 2001; Hartmann et al., 2013). A more reliable method is antibody staining (by immunofluorescence or immunoperoxidase), which can be used to identify leptospiral agents in body fluids and cytological samples of organs, such as liver or kidneys (Fig. 2), if appropriate samples are available (Adler and de la Pena Moctezuma, 2010).

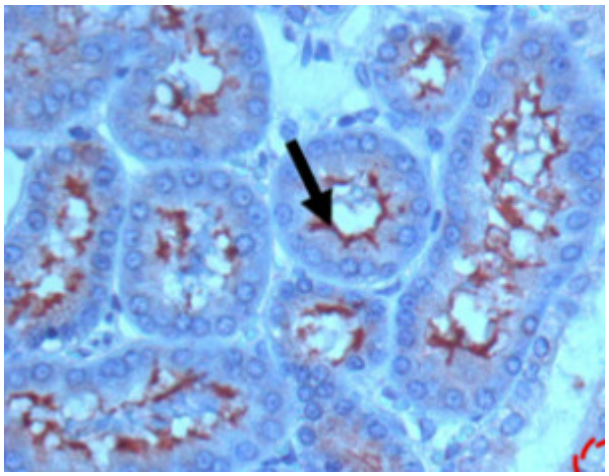

Fig. 2. Immunohistology staining of leptospires in the kidneys of an infected hamster. Leptospires stained with specific antiserum (arrow) are seen lining the proximal renal tubules (courtesy of Ben Adler, Australian Research Council Centre of Excellence in Structural and Functional Microbial Genomics, Monash University, Clayton, Australia).

Leptospires can be cultured from the urine, blood, and cerebrospinal fluid (CSF), but grow very slowly. Cultures usually take weeks to months before becoming positive (Dorsch et al., 2020), and reliable results can only be expected when the animal had not been pretreated with antibiotics. Thus generally, in most cases culture is not a useful option in practice.

PCR methods are available to detect leptospiral DNA in body fluids, including urine, blood, CSF, and aqueous humour (Bal et al., 1994; Merien et al., 1995; Harkin et al., 2003a; Harkin et al., 2003b) and have been shown to be applicable to cats (Fenimore et al., 2012; Rodriguez et al., 2012; Sprißler et al., 2019; Weis et al., 2017; Dorsch et al., 2020). In humans, PCR was shown to be more reliable in early diagnosis than antibody testing or culture (Brown et al., 1995). PCR to identify DNA from organisms in urine, where it reaches high concentrations, has been experimentally shown to be sensitive and specific, and it allows a diagnosis at an early stage of infection. However, PCR is only useful in animals not previously treated with antibiotics and can be negative in infected cats due to intermittent shedding (Levett, 2001).

Detection of antibodies

Antibodies can be detected using the MAT or an enzyme-linked immunosorbent assay (ELISA). MAT is the most common diagnostic method to detect antibodies in dogs and humans. It is also the antibody test of choice in cats and has been validated for cats (Larsson et al., 1984; Batza and Weiss, 1987; Agunloye and Nash, 1996; Dickeson and Love, 1993; Mylonakis et al., 2005; Markovich et al., 2012; Rodriguez et al., 2012; Shropshire et al., 2016; Sprißler et al., 2019; Weis et al., 2017). However, as shown in dogs, the MAT has marked limitations with regards to sensitivity, specificity, and repeatability, especially if single titres are interpreted (Miller et al., 2011; Fraune et al., 2013). MAT is not serovar-specific (Sykes et al., 2011; Schuller et al., 2015), and cross-reactions make identification of the infecting serovar difficult. Infected animals can be antibody-negative in the acute phase of the disease, due to the normal delay in appearance of serum antibodies. In addition, different serogroup antigens are included in the assay, and false-negative results will occur when the infecting serogroup is not included. In dogs, widespread use of vaccines also limits usefulness of the MAT. Non-infected dogs vaccinated with whole cell anti-leptospiral vaccines, especially with the new ones that contain four serovars, can have post-vaccinal titres of 1:6400 or higher to both, vaccinal and non-vaccinal serovars (Barr et al., 2005; Midence et al., 2012; Martin et al., 2014), and vaccinal titres can even persist for twelve months in some dogs (Martin et al., 2014). Reactivity of anti-leptospiral antibodies with multiple serogroups often prevents the determination of the infecting serogroup. Moreover, the serogroup with the highest MAT titre can vary over time, indicating that the MAT does not reliably predict the infecting serogroup in infected animals (Miller et al., 2011). Although there is so far no vaccine in cats and thus, diagnostic interference with vaccine antibodies can be excluded, in cats variation of results between laboratories and differences in humoral immune responses can make correct interpretation of MAT results problematic.

In-house tests to detect immunoglobulin G (IgG) or IgM antibodies in dogs are now available. However, although potentially useful in dogs (Lizer et al., 2017; Lizer et al., 2018), such tests have not been evaluated in cats.

Treatment

Treatment of dogs consists of supportive therapy and antibiotics, and the same should be done in cats with leptospirosis.

Antimicrobial treatment

Antimicrobial therapy usually consists of two stages. The first stage is aimed to immediately inhibit multiplication of the organism and rapidly reduce fatal complications of infection, such as hepatic and renal failure. Penicillin and its derivatives are the antibiotics of choice for terminating *Leptospira* spp. replication. Initially, ampicillin (20 mg/kg q 8 h IV) or amoxicillin, if available for IV use (20 mg/kg q 12 h IV), should be given parenterally to a vomiting, uraemic, or hepatically compromised animal. These drugs prevent shedding and transmission of the organism within 24 hours of initiation of therapy. They are neither able to clear the infection from the kidneys nor to prevent a carrier state with chronic shedding. In the second stage, other drugs should be administered to address the carrier state. Doxycycline (5 mg/kg q 12 h PO for three weeks) is the drug of choice, and treatment should start as soon as the clinical condition allows its oral application (Sykes et al., 2011; Schuller et al., 2015). Intravenous application of doxycycline (e.g., of human preparations that are available in some countries) is not recommended in cats because it can cause shock and vomiting, and subcutaneous injection can lead to development of abscesses in cats. Doxycycline can also cause liver toxicity. Thus, it should only be started after the animal has stopped vomiting, and liver enzyme activities are in the reference range. In cats, use of doxycycline suspension is preferred over tablets or capsules to lower the risk of oesophagitis and secondary oesophageal strictures, especially with some doxycycline salts (hyclate) (German et al., 2005; Trumble, 2005). Administration of the hyclate preparation of doxycycline should always be followed by food or water because of the possibility of it inducing oesophagitis in cats with incomplete swallowing. In animals without clinical signs or with only mild signs, doxycycline can be used for both, initial and elimination therapy (Sykes et al., 2011; Schuller et al., 2015).

If healthy cats are identified to shed leptospires, treatment with doxycycline (5 mg/kg q 12 h PO for three weeks) should be initiated to control the carrier state (Weis and Hartmann, 2017). This minimizes the risk of infection for other animals and humans. However, in

hunting cats, reinfection with leptospires is possible. Testing for *Leptospira* spp. shedding in healthy cats might be indicated if the owner is immunosuppressed or if an animal or human being in the household is diagnosed with leptospirosis.

Symptomatic treatment

Symptomatic and supportive treatment depends on the severity of clinical signs and the presence of renal or hepatic dysfunction and other complicating factors. Treatment of acute kidney injury is the most critical aspect in dogs and the same is likely true for cats. Medical management comprises of assessing volume status and correcting fluid deficits, evaluating for signs of volume overload throughout, and addressing any hyperkalaemia or uraemic acidosis. Severe acute kidney injury with anuria often requires renal replacement therapy with haemodialysis that is life saving for many animals with severe anuric leptospirosis and early referral to facilities with haemodialysis should be considered, although haemodialysis currently exists only in specialised referral centres and might not be available for small cats. Haemodialysis is indicated in animals with inadequate urine output that are developing volume overload, hyperkalaemia, or signs of uraemia that are not responsive to medical management. After stabilisation, ongoing medical treatment comprises carefully matching the input volumes of fluid therapy with the cat's requirements for maintenance and its ongoing losses (including urine) – so-called measuring fluid 'ins and outs'. The extent of renal damage after treatment determines the overall prognosis (Sykes et al., 2011; Schuller et al., 2015).

Management of infected patients

Infected cats are a potential risk for veterinarians and the veterinary staff handling the cat as well as for the cat's owners.

Management in the clinic

In order to minimize the risk for people handling *Leptospira* spp.-shedding cats, e.g., in a veterinary clinic, the same precautions should be taken as if handling a *Leptospira* spp.-infected dog, such as wearing gloves and goggles and taking specific measures when handling urine-contaminated areas and objects, such as litter boxes.

Management at home

Veterinarians should advise owners of cats with suspected *Leptospira* spp. infection to seek medical advice if they become ill and to advise their own medical doctor of their cat's illness. Owners should be instructed to wash hands after handling their cat and to wear gloves when cleaning up urine spills until the course of antimicrobial drug therapy is completed. Routine household disinfectants should be used to clean urine-contaminared areas.

Prognosis

In dogs, prognosis of leptospirosis generally depends on the severity of the kidney injuries, and the same is likely true for cats. In more severe cases, prognosis largely depends on the availability of, and suitability of the patient to, renal replacement therapy that is often necessary to survive the time to recovery from renal failure in animals with severe acute kidney injury. In dogs, approximately 50% of those surviving the acute phase of the disease display impairment of their renal function more than one year after hospital discharge.

Vaccination

Although several vaccines are on the market for dogs, no vaccine is available for cats.

Prevention

To avoid cats getting infected with *Leptospira* spp., cats should be prevented from feeding on (potentially infected) rodents and be kept away from stagnant water. Cats that are kept indoors only have a very low risk of infection (Weis and Hartmann, 2017).

Zoonotic risk

The number of people suffering from leptospirosis worldwide is estimated at over 1 million per year. The number of people that die from the disease is estimated to be around 60,000 per year (Costa et al., 2015).

The role of cats in the transmission of leptospires to humans is unclear. Since cats can shed viable leptospires in their urine, they are considered to have a zoonotic potential, and appropriate precautions should be taken when handling cats potentially infected, such as disinfection of hands after contact with urine or prey, antibiotic treatment of cats shedding leptospires (Weis and Hartmann, 2017). One study investigated the role of introduced feral cats as a reservoir for infecting humans on a tropical Christmas Island, where a recent case of human leptospirosis had been detected. Pathogenic leptospires were found by PCR in kidney samples of 42.4% of investigated cats (Dybing et al., 2017). The risk of infection is especially high if outdoor cats that can be potentially infected still use an indoor litter box, and owners of outdoor cats should generally be advised to wear gloves during litter box cleaning.

On the other hand, cats might reduce their owners' risk of infection by eliminating reservoir hosts (e.g., rodents) and thus, minimizing the continuous environmental spread of leptospires (Childs et al., 1992). Especially in tropical countries, cats also reduce the direct contact of humans with rodents by minimizing rodent density. In a study in Nakhon Ratschasima, Thailand, twice as many people of an uninfected control group (25/129, 19.7%) owned cats compared to people that were infected with leptospires (5/49; 10.2%) (Tangkanakul et al., 2001). Also, in a study in Baltimore, USA, people living with cats were less likely to have antibodies against leptospires than people without cat contact. Keeping cats as pets was determined as a protective factor for leptospiral infection (Childs et al., 1992).

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