

GUIDELINE for Babesiosis

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Synopsis

Babesiosis is a tick-borne protozoal disease affecting domestic and wild animals and humans worldwide. Babesiosis is caused by parasites of the genus *Babesia* belonging to protozoan piroplasmids (Alvarado-Rybak et al., 2016). The disease is named after the Romanian bacteriologist Victor Babes, and was also known as piroplasmosis (from Latin *pirum*, meaning “pear”, and *plasma*, meaning “image, formation”) (Alvarado-Rybak et al., 2016). *Babesia* species are common blood parasites of mammals. Human babesiosis is relatively uncommon, but an increasing number of cases has been reported (Madison-Antenucci et al., 2020), likely because of increased awareness. Babesiosis is relatively common in dogs in many countries worldwide, but is only rarely found in cats (Birkenheuer, 2012).

Babesia species infection of domestic cats has been reported only sporadically from various countries, but it appears to be common and to cause significant disease in cats in South Africa (Penzhorn et al., 2004; Bosman et al., 2013). Feline babesiosis in South Africa is usually caused by *Babesia felis* sensu stricto, and this disease is well documented in case reports (Jackson and Dunning, 1937), studies on signalment, clinical manifestation, pathology (Futter et al., 1980; Futter et al., 1981; Jacobson et al., 2000; Schoeman et al., 2001), as well as treatment studies (Potgieter, 1981; Penzhorn et al., 2000). Lethargy, anorexia, and anaemia generally occur, while icterus is only occasionally seen; elevated body temperature is not a typical feature of South African feline babesiosis (Futter et al., 1980).

In Europe, different *Babesia* species (e.g., *Babesia canis* sensu stricto, *Babesia vogeli*, *Babesia gibsoni*, *Babesia microti*) can cause disease in dogs (Solano-Gallego et al., 2016), and the same *Babesia* species are sometimes found in cats in Europe, but rarely cause disease (Vilhena et al., 2013; Maia et al., 2014; Spada et al., 2014; Pennisi et al., 2015; Persichetti et al., 2016; Persichetti et al., 2018).

Agent properties

Babesia species belong to the piroplasmids, tick-borne protozoan parasites that infect blood cells (erythrocytes, lymphocytes, or other leukocytes) or endothelial cells of different wild and domestic vertebrates worldwide. They can cause severe disease in livestock, dogs, cats, wild mammals and, occasionally, in humans. There are several recognized species of *Babesia*, *Theileria*, *Cytauxzoon*, and *Rangelia* infecting captive and wild carnivores, including members of Canidae, Felidae, Mustelidae, Procyonidae, Ursidae, Viverridae, Hyaenidae, and Herpestidae, and the number of piroplasmid species is likely even higher than previously anticipated.

In domestic cats, as well as in wild felids, several different *Babesia* species have been described so far, and with the advancement of molecular analyses, several new species have been discovered in recent years (Criado-Fornelio et al., 2004; Alvarado-Rybak et al., 2016; Bosman et al., 2019). Many *Babesia* species infections in cats remain asymptomatic, with the exception of infection with *Babesia felis* sensu stricto, a small *Babesia* species that commonly causes disease in cats in South Africa. Occasionally, disease in cats is caused by other *Babesia* species; as an example, *Babesia lengau* originally found in clinically healthy cheetahs (Bosman et al., 2010), was detected also in two domestic cats with severe disease (Bosman et al., 2013).

A comprehensive review on the literature summarizing the molecular characterization of *Babesia* species found in cats all over the world has been published recently (Penzhorn and Oosthuizen, 2020). Molecular characterization revealed that cats can harbour a variety of species belonging to four clades within the genus *Babesia*. Feline babesiosis is most prevalent in South Africa, where four *Babesia* species have been described, *Babesia felis* sensu stricto and the closely related *Babesia leo* (clade I), *Babesia lengau* (clade II), and *Babesia* species Cat Western Cape (clade VI) (Penzhorn and Oosthuizen, 2020). Clade VI also includes *Babesia canis* subspecies *presentii*, *Babesia hongkongensis* (Penzhorn and Oosthuizen, 2020), and *Babesia panickeri* (Panicker et al., 2020).

Seven other *Babesia* species have been found in domestic cats: the dog-associated *Babesia canis sensu stricto*, *Babesia gibsoni*, and *Babesia vogeli*, as well as *Babesia lohiae*, *Babesia microti*, *Babesia vulpes* (Penzhorn and Oosthuizen, 2020).

Before the advent of molecular characterization, the usual approach for identifying *Babesia* species was based on morphological descriptions leading to the classification of “large” or “small” *Babesia* species. This approach is no longer considered useful because *Babesia* species undergo morphological changes during their development in erythrocytes, and there is substantial overlap between measurements of “large” and “small” *Babesia* species. A second approach was to characterise *Babesia* species based on their host specificity, but this approach was also not ideal as there is significant overlap between host species. Molecular characterization has now led to the description of various well-known but also new *Babesia* species in domestic cats (Panicker et al., 2020; Penzhorn and Oosthuizen, 2020); however, the classification of different *Babesia* species remains a challenge. Today, characterisation of variations in the 18S rRNA gene is widely used as a taxonomic and phylogenetic tool for classifying *Babesia* species. There is, however, no universal criterion on sequence identity for classifying organisms at the species level (Penzhorn and Oosthuizen, 2020).

Babesia felis sensu stricto (clade I) was the first molecularly characterized *Babesia* species from a domestic cat by sequencing genome parts of an isolate used for experimental infection to test efficacy of different drugs for treatment of feline babesiosis (Potgieter, 1981; Penzhorn et al., 2000). *Babesia felis sensu stricto* was also found in 2.9% of 34 healthy cats in Qatar (Alho et al., 2017). In a study in Lahore, Pakistan, 45% of 100 domestic cats showing signs of anaemia and lethargy had piroplasms in their blood smears, and *Babesia felis sensu stricto* was detected by loop-mediated isothermal amplification (LAMP), although no sequencing was performed (Salim et al., 2018).

Babesia leo (clade I) was detected in lions in Kruger National Park, South Africa (Penzhorn et al., 2001), and was suspected to be the cause of disease in six cats (one in Port Elizabeth and four in KwaZulu-Natal, South Africa, and one in Maputo, Mozambique) (Würth and Zahler-Rinder, 2004; Bosman et al., 2019). The genomic sequences of the parasites detected in four of these cats shared 100% identity to *Babesia leo*, and the sequences of the parasite of the fifth cat shared 99% identity to *Babesia leo* (Bosman et al., 2019).

Babesia lengau (clade II) was found in cheetahs in South Africa (Bosman et al., 2010), and was associated with two cases of feline babesiosis in South Africa, one being the first reported case of cerebral babesiosis in a cat (Bosman et al., 2013).

***Babesia* species Cat Western Cape** (clade VI) was recently discovered in South Africa as a new species within clade VI. Seven cats with this infection were reported, six from the vicinity of Cape Town and one from Durban, KwaZulu-Natal (Bosman et al., 2019).

Babesia canis subspecies presentii (clade VI) was described in two cats in Israel (Baneth et al., 2004). This subspecies showed a very high genetic similarity to *Babesia canis sensu stricto* isolates, detected in cats in Spain and Portugal (Criado-Fornelio et al., 2003).

Babesia hongkongensis (clade VI), a new species, genetically and geographically distinct from other previously described *Babesia* species, was found in blood and kidney specimens collected from a free-ranging cat in Hong Kong. Phylogenetic analysis of the 18S rRNA gene sequence showed that *Babesia hongkongensis* falls into a distinct branch of the Babesiidae, and the 18S rRNA gene sequence had 97% identity to various *Babesia* sequences found in feral raccoons and dogs (Wong et al., 2012).

Babesia panickeri (clade VI) was recently described in a 3-month-old cat in India that showed clinical signs of babesiosis (Panicker et al., 2020).

Babesia canis sensu stricto was identified in cats in Spain and Portugal (Criado-Fornelio et al., 2003). A short fragment of the 18S rRNA gene was highly similar to fragments of *Babesia canis* subspecies *presentii* (Criado-Fornelio et al., 2003). In another study in Portugal, gene sequences from samples from 1.3% of 320 cats had 100% identity to *Babesia canis sensu stricto* (Vilhena et al., 2013).

Babesia gibsoni was identified in 4.2% of 119 apparently healthy cats from St. Kitts in the Caribbean. The partial 18S rRNA sequence showed 100% identity to *Babesia gibsoni* (Kelly et al., 2017).

Babesia vogeli infection in cats was first reported in 1.4% of 1490 stray cats tested in Bangkok, Thailand (Simking et al., 2010). The sequenced target amplicons had 98% identity with a *Babesia vogeli* sequence detected in dogs in Brazil (Passos et al., 2005). In a survey in Portugal, 8.1% of 320 cats tested positive for *Babesia vogeli* (Vilhena et al., 2013). Samples from three of these cats that had clinical signs (Vilhena et al., 2013) and from eight cats from another study (Vilhena et al., 2017) were identical to *Babesia vogeli*. In a survey in southern Portugal, 6.6% of 649 cats were found to be infected with *Babesia* species, possibly also *Babesia vogeli* (Maia et al., 2014). In Brazil, 16.2% of 37 free-ranging cats in a zoo in Sao Paulo tested positive for *Babesia* species with sequence identity of 99% to *Babesia vogeli* (Andre et al., 2014), and 6.7% of 30 cats in Rio Grande do Sul State were infected with *Babesia* species with 100% sequence identity to *Babesia vogeli* (Malheiros et al., 2016). On the island of St. Kitts in the Caribbean, *Babesia vogeli* was found in 12.6% of 119 apparently healthy cats with all sequences being 100% identical to 19 *Babesia vogeli* sequences (Kelly et al., 2017). In Qatar, 2.9% of 34 healthy cats tested positive for *Babesia vogeli* with 100% identity (Alho et al., 2017). Infection with *Babesia vogeli* was recently also detected in 1.5% of 203 pet cats in Shenzhen, China (Zhang et al., 2019).

Babesia lohae was identified in an *Ixodes holocyclus* tick removed from a cat as well as in an *Ixodes tasmani* tick collected from a brushtail possum in Queensland, Australia. Phylogenetically, *Babesia lohae* groups within the *Babesia canis* sensu stricto clade and with other *Babesia* species from Australian marsupials and ticks from marsupials. It is therefore possible that brushtail possums are a reservoir host of *Babesia lohae* (Greay et al., 2018).

Babesia microti has been detected in cats in several countries. In a survey of stray cats in Milan, Italy, 0.8% of 260 cats were positive for *Babesia microti* DNA by PCR, and 18S rDNA sequencing confirmed *Babesia microti* with 100% identity to *Babesia microti* sequenced from *Ixodes ricinus* ticks removed from dogs in Poland (Spada et al., 2014). In Sicily, Italy, 26.1% of 23 cats were positive for *Babesia microti* DNA by PCR (Pennisi et al., 2007). One cat with clinical signs in Cape Town, South Africa, was infected with both *Babesia felis* sensu stricto and *Babesia microti*, and this *Babesia microti* strain was almost identical to *Babesia microti* strains of Japan and Germany (Bosman et al., 2019). In a survey in Pakistan, 13.2% of 159 cats that were presented at veterinary clinics were infected with *Babesia microti* based on PCR amplification of a 238-bp amplicon specific for the 18S rRNA gene of *Babesia microti* (Akram et al., 2019).

Babesia vulpes (referred to as *Theileria annae* at the time) was found in two clinically healthy cats with immunosuppressive viral infections in Portugal; the sequence was 100% identical to a dog isolate (Zahler et al., 2000; Criado-Fornelio et al., 2003). *Babesia vulpes* (referred to as *Babesia annae* at the time) was also identified in a cat in France (Fritz and Derré, 2011).

Epidemiology

Historically, the first report of feline babesiosis was published in 1904 in tame and wild cats in India (Lingard and Jennings, 1904), but this description remains dubious, since the authors also included humans and chickens in their list of affected hosts. In 1929, Davis described a *Babesia* species in a wild cat in Sudan and named it *Babesia felis* (now *Babesia felis* sensu stricto) (Davis, 1929). Fourteen domestic cats were inoculated with blood from this wild cat and became persistently infected, but did not develop clinical signs (Davis, 1929). In 1933, two cougars shipped from San Francisco arrived at the Cairo Zoological Gardens, Egypt, where they were housed in close proximity to other large felids. Within two to three weeks, both animals developed clinical signs of babesiosis (Carpano, 1934), and trophozoites resembling those of dog-associated *Babesia gibsoni* were found (Patton, 1910). In 1937 in India, small intraerythrocytic piroplasms were detected in blood smears of an anaemic cat at necropsy, although merozoite tetrads were not seen; thus, it was assumed that the organism was different from *Babesia felis* sensu stricto (Mangrulkar, 1937). In 1950, a similar small organism seen in blood smears from an apparently healthy Indian wild cat was named *Babesia cati*; however, attempts to transmit this organism to domestic cats were unsuccessful (Mudaliar et al., 1950). In 1967, a large *Babesia* species was detected in a neotropical jaguarundi. This *Babesia* species was used to experimentally infect domestic cats, which however did not develop clinical signs (Dennig, 1967). The species was named *Babesia herpailuri* (Dennig, 1969). In 1972, *Babesia pantherae* from leopards, an organism smaller than *Babesia herpailuri*, was used to experimentally infect splenectomised domestic cats (Dennig and Hebel, 1969; Dennig and Brocklesby, 1972). A small piroplasm matching the morphological description of *Babesia felis* sensu stricto was also transmitted experimentally from leopards to domestic cats (Dennig and Brocklesby, 1972).

Babesia species infection of domestic cats has been reported in various countries, including South Africa (Dunning, 1937; Penzhorn et al., 1999; Jackson and Jacobson et al., 2000; Penzhorn et al., 2004; Bosman et al., 2007; Bosman et al., 2013), Sudan (Davis, 1929), Zimbabwe (Stewart et al., 1980), Mozambique (Bosman et al., 2019), Qatar (Alho et al., 2017), Iraq (Suliman, 2009), Israel (Baneth et al., 2004), India (Mangrulkar, 1937), Pakistan (Ahmad et al., 2011; Akram et al., 2019), Hong Kong (Wong et al., 2012), China (Zhang et al., 2019), Thailand (Jittapalapong and Jansawan, 1993; Passos et al., 2005; Simking et al., 2010), Brazil (Andre et al., 2014; Andre et al., 2015; Malheiros et al., 2016), Caribbean Islands (Kelly et al., 2017), Australia (Greay et al., 2018), and in Europe in France (Bourdeau, 1996), Germany (Moik and Gothe, 1997), Poland (Adaszek et al., 2010), Portugal (Criado-Fornelio et al., 2003), Spain (Criado-Fornelio et al., 2003), and Italy (Spada et al., 2014; Pennisi et al., 2015; Persichetti et al., 2016; Persichetti et al., 2018). In all countries besides South Africa, infections are generally only sporadic and their course is mild, in contrast to the situation in South Africa, where infection is common and causes significant disease in cats.

Most clinical cases of feline babesiosis have been reported in **Africa**, particularly **South Africa**. The first cats with the clinical feline babesiosis were described in 1937 and originated from the vicinity of Cape Town, South Africa (Jackson and Dunning, 1937; McNeil, 1937). This first case was a cat with fever and anaemia that recovered after administration of quinuronium sulfate (Jackson and Dunning, 1937). The second description was a report on babesiosis in free-ranging cats that had fever and anaemia and were successfully treated with quinuronium sulfate or trypan blue (McNeil, 1937). Subsequently, feline babesiosis was reported in Knysna, a coastal town approximately 430 km east of Cape Town, South Africa (Robinson, 1963). The first larger study included 70 cats from veterinary clinics in South Africa, and the organism found was named *Babesia felis* (now *Babesia felis* sensu stricto) (Futter and Belonje, 1980). The blood of one sick cat was used to experimentally infect 20 cats that subsequently developed clinical signs, including lethargy, anorexia, and anaemia, but rarely fever. In contrast to earlier reports, trypan blue and quinuronium sulfate were not effective in treating these experimentally infected cats (Futter and Belonje, 1980). Since first been described, feline babesiosis is now relatively

common in South Africa, and occurs primarily along the eastern and southern coastlines as well as in isolated foci along the eastern escarpment of Mpumalanga and Limpopo provinces (Penzhorn et al., 1999; Jacobson et al., 2000; Penzhorn et al., 2004). Outside of South Africa, a large *Babesia* species was described in blood smears of a sick cat with high fever from the suburbs of Harare, Zimbabwe, that was treated with diminazene, and whose clinical signs resolved. The organism was tentatively classified as *Babesia herpailuri* (Stewart et al., 1980). In Mosul, **Iraq**, in blood smears of 26.0% of 50 cats *Babesia* species were seen, but they were not further characterized (Suliman, 2009). *Babesia canis* subspecies *presentii* was described in two cats in **Israel**; one was sick, and the other a subclinical carrier. The sick cat, which was coinfecting with feline immunodeficiency virus and 'Candidatus Mycoplasma haemominutum', showed icterus and anaemia. It responded rapidly to treatment with imidocarb and doxycycline and fully recovered (Baneth et al., 2004). In Jerusalem, Israel, *Babesia vogeli* was detected in 0.2% of cat fleas, *Ctenocephalides felis*, collected from 185 infested stray cats (Kamani et al., 2018).

Some cases of feline babesiosis have been described in **Asia**. The first report was a cat from **India** that was anaemic, and a small *Babesia* species was detected at necropsy (Mangrulkar, 1937). Also in India, organisms resembling *Babesia felis* sensu stricto were seen in a blood smear from a kitten with fever, lethargy, and anorexia that recovered after administration of primaquine phosphate (Bendangla and Varshney, 2006). In another sick cat in India, infection with a large *Babesia* species was successfully treated with diminazene (Sabu et al., 2013). In Lahore, **Pakistan**, feline babesiosis was diagnosed in 3.1% of 163 cats presented at a university veterinary hospital (Ahmad et al., 2011). Cases also have been described from Hongkong (Wong et al., 2012) and Thailand (Jittapalapong and Jansawan, 1993; Simking et al., 2010). Recently, infection with *Babesia vogeli* was detected in 1.5% of 203 pet cats in Shenzhen, China (Zhang et al., 2019).

There have been a few reports of feline babesiosis in **South and Central America**; in **Brazil** (Andre et al., 2014; Andre et al., 2015; Malheiros et al., 2016), and the **Caribbean Islands** (Kelly et al., 2017), but no cases have been reported in North America.

In **Australia**, *Babesia lohiae* was identified in a female *Ixodes holocyclus* tick collected from a cat in Queensland, Australia (Greay et al., 2018), but no clinical cases have been described.

Feline babesiosis is considered rare in **Europe**. The first clinical case, reported in 1992 in **France**, was an anaemic eight-year-old cat in which a small *Babesia* species was found on blood smear examination (Leger et al., 1992). There was also a report of a large *Babesia* species in a blood smear from a cat from Paris, France (Leger et al., 1992), and it was hypothesized that the small organisms were *Babesia divergens* or *Babesia microti*, whereas the large organisms were *Babesia canis* sensu stricto or *Babesia vogeli* (Bourdeau, 1996). A subsequent case from France was attributed to *Babesia vulpes* (referred to as *Babesia annaei* at the time) infection (Fritz and Derré, 2011). The only clinical case in **Germany**, reported in 1997, was a ten-month-old cat imported from Northern Sweden. Blood smears showed a large *Babesia* species. Clinical signs included fever and anaemia. The cat responded to treatment with imidocarb (Moik and Gothe, 1997). In **Poland**, a ten-year-old cat showed anaemia, fever, and haematuria and recovered fully after administration of imidocarb. The organisms on blood smear resembled *Babesia canis*, but sequencing of a 559-bp fragment of the 18S rRNA gene only demonstrated 95% homology with *Babesia canis* sensu stricto (Adaszek et al., 2010). In the **United Kingdom**, 541 ticks infesting stray cats were investigated by molecular analysis; *Babesia* species were found in 1.1% of the ticks and identified as *Babesia vulpes* sp. nov./*Babesia microti*-like and *Babesia venatorum* (Davies et al., 2017). In **Spain**, *Babesia canis* sensu stricto was found in a cat with clinical signs (Criado-Fornelio et al., 2003). In one study in **Portugal**, *Babesia* species infection was detected in 6.6% of 652 stray cats, and *Babesia vogeli* was identified by DNA sequencing (Maia et al., 2014). In another Portuguese study involving 320 cats, 1.3% were infected with *Babesia canis* and 8.1% with *Babesia vogeli* (Vilhena et al., 2013). *Babesia vogeli* and *Babesia microti* infections in cats were also detected in **Italy** (Spada et al., 2014; Pennisi et al., 2015; Persichetti et al., 2016; Persichetti et al., 2018). In Southern Italy, 23.8% of 42 investigated cats had antibodies against *Babesia microti*, but *Babesia* species DNA could not be identified in any of the cats (Persichetti et al., 2016). *Babesia vogeli* DNA was found in 0.8% of 132 adult ticks removed from cats living in Southern Italy (Pennisi et al., 2015). In Northern Italy, *Babesia microti* DNA was detected in blood samples of 0.8% of 260 stray cats (Spada et al., 2014). However, in two recent studies, no *Babesia* species were identified in 286 randomly selected healthy cats from catteries and colonies in central Italy (Morganti et al., 2019) and in 958 client-owned cats living in the North (n = 556), Centre (n = 173), or South (n = 229) of Italy (Latrofa et al., 2020).

Babesia species are commonly detected in **wild felids** in Africa (Alvarado-Rybak et al., 2016), such as in lions in South Africa (Lopez-Rebollar et al., 1999; Penzhorn et al., 2001; Penzhorn, 2006; Bosman et al., 2007), Eswatini (previously Swaziland) (Bosman et al., 2007), Tanzania (Munson et al., 2008), Zambia (Williams et al., 2014), and Botswana (McDermid et al., 2017), in cheetahs in South Africa (Bosman et al., 2010) and Namibia (Bosman et al., 2007), in other wild felids in Kenya (Githaka et al., 2012) and Zimbabwe (Kelly et al., 2014), and have also been occasionally detected in wild felids outside of Africa, such as in European wild cats in Bosnia and Herzegovina (Hodzic et al., 2018), in Iberian lynx in Spain (Luaces et al., 2005), in cougars in Florida (Yabsley et al., 2006), and in wild felids in Brazil (Andre et al., 2011).

In felids other than domestic cats, *Babesia felis* does not seem to cause disease. *Babesia felis* was detected in 18.6% of 97 clinically healthy captive cheetahs in South Africa and in 7.5% of 40 free-ranging cheetahs in Namibia, as well as in a lion and a serval in South

Africa (Bosman et al., 2007). In addition, several other *Babesia* species, including *Babesia herpailuri* and *Babesia pantherae*, have been detected in wild felids, such as in lions, cheetahs, and Florida cougars (Yabsley et al., 2006). These *Babesia* species from wild felids can be transmitted experimentally to domestic cats, but their infectivity and pathogenicity under natural circumstances is unknown. *Babesia leo* is genetically similar to *Babesia felis sensu stricto* and is common in lions of the Kruger National Park, South Africa, and in Eswatini (previously Swaziland) (Bosman et al., 2007) but also present in domestic cats in these areas.

Pathogenesis

Feline Babesiosis is a vector-borne disease that is usually transmitted by ticks. The vectors for most *Babesia* species in cats have not yet been identified. Apart from the usual transmission by ticks, *Babesia* species can be transmitted iatrogenically, e.g., through blood transfusions (Birkenheuer, 2012).

Babesia replicate in erythrocytes, where they produce merozoites. In some *Babesia* species, these structures appear as inclusions attached to each other at their tips, thereby forming tetrads. These so-called “Maltese Cross formations” are pathognomonic for infection with some *Babesia* species. Ticks are infected by ingesting merozoites during feeding, and replication of the parasite within their salivary cells results in sporozoite formation. When infected ticks feed, the sporozoites are regurgitated into the bloodstream of the host (Birkenheuer, 2012).

Most *Babesia* species found in cats do not seem to cause disease, with the exception of *Babesia felis sensu stricto*, the most important pathogenic *Babesia* species in cats (Penzhorn et al., 2004) found in South Africa. Although babesiosis in domestic cats has been reported sporadically in other countries, the disease appears to be a distinctly South African phenomenon (Davis, 1929). South African feline babesiosis usually occurs in cats less than three years of age, without any sex or breed predilection (Schoeman et al., 2001). Most other *Babesia* species found in domestic cats seem to be less pathogenic (Birkenheuer, 2012).

Clinical signs

Severe disease has been described in cats infected with *Babesia felis sensu stricto* in South Africa (Penzhorn et al., 2004). This species has not been reported in Europe, apart from in cats imported from South Africa (Wells et al., 2012). Feline babesiosis caused by other *Babesia* species presents rather as a mild chronic disease (Baneth et al., 2004).

Common clinical signs of *Babesia felis sensu stricto* infection are anorexia, lethargy, weakness, and a rough haircoat (Futter and Belonje, 1980; Penzhorn et al., 2004). Unlike in dogs, fever and icterus are uncommon, and in most cats that present with fever, a concurrent illness is diagnosed (Futter and Belonje, 1980). Most clinical signs are secondary to haemolytic anaemia that results from the infection of erythrocytes by the parasite. Cats usually cope well with the anaemia and show only mild clinical signs. Complications of babesiosis include renal failure, pulmonary oedema, hepatopathy, and neurologic disorders (Futter and Belonje, 1980).

Immunity

The host generates a specific immune response against most *Babesia* species, but this does not eliminate the parasite. Cats that recover from clinical signs usually remain chronic carriers (Birkenheuer, 2012). Immunity in dogs is not long-lasting (Brandao et al., 2003), and the same is expected in cats.

Diagnosis

Direct detection of the organism *via* microscopic examination of blood smears provides a presumptive diagnosis. PCR is the method of choice for detecting *Babesia* species infection in cats (Birkenheuer, 2012).

Complete Blood Count and Serum Biochemistry

The typical laboratory findings in cats with babesiosis are a consequence of haemolytic anaemia, which is usually regenerative, macrocytic, and hypochromic. Haemolysis can be caused by both extravascular and intravascular erythrolysis (Schoeman et al., 2001). Anaemia is most pronounced approximately three weeks after experimental infection (Futter and Belonje, 1980). Blood smears can show increased polychromatophils, Howell-Jolly bodies, nucleated erythrocytes, and anisocytosis (Futter and Belonje, 1980). Erythrophagocytosis by monocytes can occasionally be observed (Futter and Belonje, 1980). Sometimes, intra-erythrocytic parasites can be seen on blood smears (Schoeman et al., 2001). Secondary immune-mediated haemolytic anaemia (IMHA) with anti-erythrocyte antibodies can be detected in some cats, potentially leading to positive auto-agglutination and a positive Coomb's test (Schoeman et al., 2001).

Infected cats usually do not have changes in their white blood cell counts. Thrombocytopenia is common in other animals with babesiosis but is an inconsistent finding in cats (Schoeman et al., 2001). On serum biochemistry, ALT activity is elevated in most cats with babesiosis, likely as a result of liver cell damage due to hypoxia, whereas ALP activity generally remains within reference ranges

(Schoeman et al., 2001; Penzhorn et al., 2004). Total bilirubin concentration is commonly increased (Schoeman et al., 2001), most likely as a result of haemolysis, but secondary hepatocellular injury can also be a contributing factor (Penzhorn et al., 2004). Feline babesiosis usually does not alter urea and creatinine concentrations or blood pH (Futter et al., 1981). Polyclonal gammopathy has been observed, with hypergammaglobulinaemia also leading to increased total protein concentrations (Schoeman et al., 2001). Serum haptoglobin concentrations were significantly increased and paraoxonase-1 concentrations significantly decreased in eleven cats infected with *Babesia vogeli* when compared to ten healthy non-infected cats (Vilhena et al., 2017).

Microscopic detection of the organism

Babesia species infection can be diagnosed when merozoites are detected in blood smears. Parasites are best identified in thin smears examined at maximum magnification under oil, using Romanovski (methylene blue and eosin) or Giemsa stains (Fig. 1). Sometimes the characteristic “Maltese cross” tetrad formation can be seen. The different *Babesia* species and some of the other blood parasites, such as *Cytauxzoon felis*, are morphologically indistinguishable (Yabsley et al., 2006). When the level of parasitaemia is low, which is often the case, detection of the organism in blood smears can be difficult.

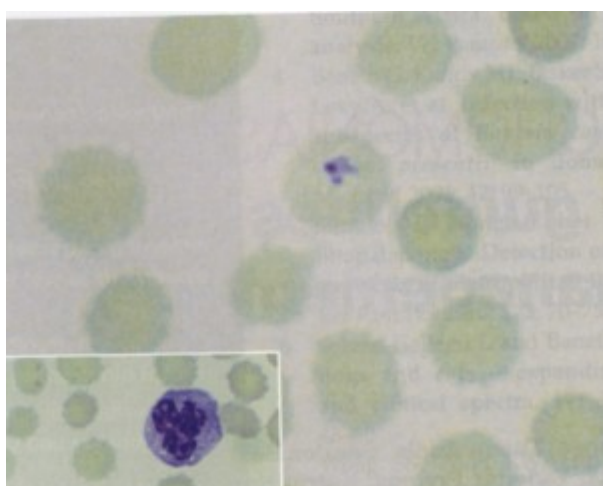


Fig. 1. Blood smear of a cat with *Babesia* species in erythrocytes (courtesy of Katrin Hartmann, Medizinische Kleintierklinik, Ludwig-Maximilians-Universität München, Germany).

Fig. 1. Blood smear of a cat with *Babesia* species in erythrocytes (courtesy of Katrin Hartmann, Medizinische Kleintierklinik, Ludwig-Maximilians-Universität München, Germany).

Detection of antibodies

Testing for anti-*Babesia* antibodies is widely used in dogs, but is currently not commercially available in cats.

Polymerase chain reaction

Today, the best method for a definitive diagnosis of *Babesia* species infection in cats is detecting the organisms' nucleic acid in blood samples by PCR (Criado-Fornelio et al., 2004). Techniques have been developed for simultaneous detection of several *Babesia* species using sensitive PCR assays with subsequent differentiation between species through 18S ribosomal subunit sequence analysis (Baneth et al., 2004; Criado-Fornelio et al., 2004; Yabsley et al., 2006).

Treatment

Prognosis depends on severity of disease, which is influenced mainly by the *Babesia* species, but also by host factors. Mortality rates of 15 to 20% have been reported with *Babesia felis* sensu stricto infection (Ayoob et al., 2010). Concurrent infection with *Mycoplasma haemofelis*, feline leukaemia virus, or feline immunodeficiency virus has a negative impact on the response to treatment and outcome (Schoeman et al., 2001).

Antiprotozoal drugs and supportive care are the mainstays of therapy. Cats infected with *Babesia felis* sensu stricto should always receive treatment, as the infection is commonly fatal if untreated. In a review of 20 cats with experimental *Babesia felis* sensu stricto infection and 70 naturally infected cats, all untreated animals died (Futter and Belonje, 1980). Response to treatment is generally good, but recurrence of clinical signs and chronic persistent infections are possible (Futter et al., 1981), and repeated or extended treatment might be necessary if the cat does not recover after the first course of treatment (Penzhorn et al., 2004).

Most canine or human anti-*Babesia* drugs are not effective in cats and, when used in experimental studies to treat *Babesia felis* sensu stricto infection, showed variable or disappointing results (Penzhorn et al., 2000; Potgieter, 1981). Currently, the drug of choice is primaquine phosphate, an antimalaria compound. Administration of 0.5 mg/kg orally or intramuscularly has been shown to be effective for resolving clinical signs (Penzhorn et al., 2004; Birkenheuer, 2012). This dose of primaquine phosphate is given one to three times at 72-hour intervals and followed-up with the same dose (0.5 mg/kg) once weekly for three weeks. If there is recrudescence of parasitaemia after two to three weeks, application of primaquine phosphate (0.5 mg/kg) should be repeated if the cat is still showing clinical signs. Although primaquine phosphate is capable of reducing parasitaemia, it does not eliminate the *Babesia* species. It frequently causes vomiting when administered orally. Due to its narrow therapeutic window in cats, it has to be administered carefully, as dosages exceeding 1 mg/kg can be lethal (Potgieter, 1981). Thus, regular monitoring of the cat (physical examination, complete blood count, serum biochemistry) during treatment is recommended.

Other antiparasitics are not recommended for treatment. Rifampicin and sulfadiazine-trimethoprim showed some anti-parasitic effect but were less effective than primaquine phosphate, while buparvaquone, enrofloxacin, and danofloxacin did not show any anti-*Babesia* effect (Penzhorn et al., 2000). Cats infected with *Babesia* species falling in clade VI have responded favourably to treatment with diminazene aceturate or imidocarb.

Supportive treatment is very important. It consists of blood transfusions if necessary, fluid therapy including stabilization of the electrolyte balance, and nutritional support.

Prevention

As *Babesia* species are transmitted by various tick species, tick control is the best way to prevent infection. Since cats do not tolerate permethrin, other compounds (e.g., flumethrin or fipronil) should be used.

A soluble parasite antigen of several *Babesia* species has been used experimentally and commercially as a vaccine against bovine and canine *Babesia* species to prevent clinical manifestations of these infections, with variable success. However, no feline vaccines exist against babesiosis.

Public health considerations

Although there are some *Babesia* species that can infect humans (e.g. *Babesia microti*), humans do not acquire the infection directly from cats.

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