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REVIEW

Arthropod-transmitted infectious diseases of cats

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The emergence of new, and the re-emergence of previously controlled, arthropod-transmitted microparasitic diseases are challenges for human and veterinary medicine. Both arthropods and arthropod-transmitted infections are expanding their zoogeographic range due to climate change and increased accessibility to niche environments. In addition, the relatively unimpeded movement of companion animals to and from countries with a high prevalence of arthropod-transmitted diseases has introduced both the arthropods and the diseases they carry to previously non-endemic areas. For example, in 2000–2001, the compulsory requirement for a 6 month quarantine period for dogs and cats travelling from specified European countries and rabies-free islands to the United Kingdom (UK) was eliminated under the conditions of the Pet Travel Scheme (PETS). The scheme has encouraged considerable movement of domestic pets and in the first 14 months of its operation 17 465 dogs and cats entered the UK, many from areas with arthropods and arthropod-transmitted diseases that are not currently found in the UK.

Changes in land and water management are also encouraging increases in arthropod populations and their more widespread distribution. The expansion of domestic housing and pets into sylvatic environments has resulted in increased association of wildlife reservoir host and vector species with human and pet activity. Domesticated cats in particular, prey on the wild small mammals which are also important reservoirs for arthropod-borne infections and some arthropod vectors have now adapted to a peri-domicillary cycle involving cats.

Finally, there is an increased recognition of arthropod-transmitted diseases due to application of molecular techniques, in particular polymerase chain reaction (PCR) analysis, to diagnosis and pathogen identification. Organisms that are difficult to culture and so previously unidentified, are now the subject of active research.

The arthropod parasites most commonly recognised as vectors of feline diseases are fleas of the family *Pulicidae* and ticks of the family *Ixodidae*. The potential of fly, mite or lice species for disease transmission in cats has not been determined.

Ctenocephalides felis, the cat flea, is the predominant species of flea found on cats throughout the world and is recognised as a transmission vector for *Bartonella henselae* infection, yersiniosis, coxiellosis and several rickettsial diseases. *Ct felis* has also been anecdotally incriminated in

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the transmission of *Haemobartonella felis* although arthropod transmission has never been confirmed. Adult *Ct felis* are obligate, haemophagous ectoparasites that spend several months feeding in the stable environment on the skin surface of a single cat; the length of time being dependent on host grooming (Rust 1994). A percentage (2–15%) of *Ct felis*, particularly males, may move from one cat to another. The intermediate stages of *Ct felis* do not develop on their host, but rather in close proximity to its resting place (Kern et al 1992). During these stages, *Ct felis* is more tolerant of temperature and humidity extremes than other flea species. With their serrated mouth parts, adult *Ct felis* produce cutaneous micro-wounds from which they feed. Disease transmission occurs through contamination of micro-wounds with flea saliva and/or faeces, the latter being produced in voluminous quantities at the time of feeding (Silverman & Appel 1994). A percentage of cats develop allergic inflammatory reactions to components of flea saliva or salivary glands but the effect of these on disease transmission is unknown. The domestic habitats in which most pet cats live provide optimal environmental requirements for *Ct felis* development. The free-roaming, hunting behaviour of cats encourages exchange between domestic and potentially infected sylvatic flea populations, an important factor in the ecology of several emerging or re-emerging zoonotic diseases (Azad et al 1997).

Cats appear to be less predisposed than dogs to the common tick-transmitted micro-parasitic diseases such as babesiosis, ehrlichiosis, borreliosis, tick-transmitted rickettsioses and hepatozoonosis. This does not appear to be a function of the suitability of cats as hosts for tick attachment as, despite grooming behaviour, heavy infestations are not uncommon among cats in geographical areas endemic for tick-transmitted infections (Larsen et al 2001). However, cats may have innate resistance or adaptation to infection that limits the development of disease, or compromises tick-to-cat transmission of infectious agents. Alternatively, the non-specific nature of clinical signs in infected cats may have resulted in under-diagnosis of these diseases. In addition, the association of disease with tick infestation may be less obvious in long-haired cats or when cats are not examined closely for the presence of ticks. However, cats appear to be more susceptible to some tick-borne infections, notably tularaemia (*Francisella tularensis*) and cytauxzoonosis (*Cytauxzoon felis*). There is limited information on the species of ticks capable of attaching to and transmitting infectious diseases to cats. In the cool temperate areas of the northern Europe, the most common species found attached to cats are *Ixodes hexagonus* (the hedgehog tick), *I ricinus*, *I canisuga* and *I ventalloi* (Hillyard 1996, Ogden et al 2000). *I hexagonus* was found to be the most common tick infesting cats in recent surveys in the UK and France (Pichot et al 1997, Ogden et al 2000). In warmer regions, cats have been found infested with *Dermacentor* spp, *Rhipicephalus sanguineus* and *Haemaphysalis* spp.

There have been limited studies on the process of transmission of infectious agents by arthropod parasites to cats, and even fewer determining the factors that underlie vector competency. Most studies relate to experimental infections with *Bartonella henselae*. The immunological reaction of cats to ticks has not been studied in any depth and the degree of resistance to infestation is not known. However, arthropod-transmitted pathogens are often associated with the induction of immunological abnormalities. Animals that are unable to mount a protective immune response may develop persistent sub-clinical infection which recrudesces with stress or concurrent disease. Chronic antigen exposure may result in exuberant non-protective antibody responses and the induction of polysystemic immune-mediated disease. The role of arthropod-transmitted diseases in chronic, relapsing syndromes with fever and signs of immune-mediated disease in cats deserves further investigation.

Even though the infectious organisms discussed in this review are dealt with as individual causative agents of arthropod-borne disease, there is potential for co-infection to occur. Multiple infections can occur when several arthropod species and a susceptible host share the same biohabitat. Similarly, multiple species and multiple genotypes of the same pathogenic species can occur in an individual animal. Cats with dual infections of *B henselae* and *B clarridgeiae* have been reported, as have dual infections with different strains of *B henselae* (Gurfield et al 1997). Significant association between *Bartonella henselae* and *Borrelia burgdorferi* seropositivity has also been reported in UK cats (Barnes et al 2000). The same arthropod species may be a vector for several pathogens and coinfection of individual ticks can occur (Schouls et al 1999). Coinfection may partially explain variations in classic clinical presentation, pathogenicity and response to

therapy, and the role of active co-infection rather than sequential exposure, can now be clarified by polymerase chain reaction (PCR) analysis (Kordick et al 1999b).

Diagnosis of arthropod-transmitted diseases

Although history and clinical signs may suggest one of the arthropod-transmitted infectious diseases, diagnosis should be supported by laboratory techniques which include combinations of direct microscopic visualisation or immunodetection of infective organisms in blood or infected tissue, microbial culture, serological testing, immunoblotting, and PCR.

In endemic areas and in acute disease, direct visualisation (using the light microscope) of *Babesia*, *Ehrlichia*, *Cytauxzoon* and *Hepatozoon* species in Giemsa stained blood smears and *Leishmania* species in lymph node, bone marrow aspirates or skin biopsies is valuable. However, in chronic disease, low-grade exposure or subclinical infection, levels of bacteraemia/parasitaemia may be low and direct visualisation does not allow intra-species differentiation. In *Yersinia* infection, Gram-negative organisms may be visualised in impression smears from lymph node aspirates although in bartonellosis, demonstration of organisms in lymph node smears or biopsy samples is extremely difficult, and requires Warthin Starry staining. The use of direct immunohistochemical or immunocytochemical methods on biopsy samples and cytological preparations from infected animals may increase both sensitivity and specificity but these techniques are currently only available from research laboratories.

Although culture is still considered the definitive test for the presence of infection, there are considerable challenges associated with culture of arthropod-borne organisms which limit its availability as a diagnostic method in practice. As a group, these organisms are often fastidious and may require long periods of culture, special media (*Bartonella*, *Borrelia*, *Francisella*) or eukaryotic cell co-culture systems (*Rickettsia*, *Ehrlichia*, *Leishmania*, *Babesia*). In addition, the collection and transport of material for culture may represent a considerable zoonotic hazard and Category 2 or 3 containment facilities are commonly required for culturing (*Ehrlichia*, *Borrelia*, *Yersinia*, *Francisella*, *Rickettsia*, *Coxiella*). Microbiological laboratories should be consulted prior to sample submission and sample package and transport should fulfil all biosafety requirements.

Serological testing is the most practical and commonly employed diagnostic methodology for arthropod-borne infectious diseases, and the indirect fluorescent antibody (IFA) and enzyme-linked immunosorbent assay (ELISA) tests are most widely used. However, serological testing in cats is severely limited by poor availability of feline-specific test kits, in addition to the more general disadvantages of reduced ability to identify acute infection, difficulty in differentiating infection from prior exposure or vaccinal titres, and antigenic cross-reactivity between organisms. A rise in immunoglobulin G titre is required to confirm active infection and there is considerable inter-laboratory variation in interpretation of significant titres. Serological testing can be supported by western immunoblotting to characterise and distinguish the different species involved in disease, but immunoblotting has limited availability in practice.

Many of the problems of serological diagnosis are circumvented by the use of the PCR, and methods employing PCR have been reported for most of the arthropod-borne infections affecting cats. The more routine availability of dedicated molecular laboratories for diagnostic work and the advent of real-time PCR now minimises the risk of contamination and PCR analysis for *Bartonella*, *Ehrlichia*, *Borrelia*, *Leishmania*, *Hepatozoon*, and *Babesia* among others, is now commercially available. Advantages of PCR include its sensitivity and specificity, particularly in the early phases of disease, and its versatility. It can be applied to blood, bone marrow, splenic and lymph node aspirates, body fluids such as joint and cerebrospinal fluid and formalin fixed tissue biopsy samples. Small diagnostic samples can be screened for several pathogens simultaneously and PCR can be used to monitor the progress of therapy. However, the sensitivity of PCR produces its own problems in interpretation. The presence of microbial DNA although indicative of current infection, is not diagnostic for disease unless it is present with compatible clinical signs. The use of quantitative PCR may well help to solve this problem in the future.

Bacterial diseases transmitted by arthropods

Bartonellosis

Bartonellosis is caused by fastidious, Gram-negative, intraerythrocytic, arthropod-transmitted

bacteria of the genus, *Bartonella*. Several species have been identified in wild and domestic cats: *Bartonella henselae*, *B koehlerae, B clarridgeiae* and '*B weissii*' although *B henselae* is the most prevalent and geographically widespread (Breitschwerdt & Kordick, 2000). Asymptomatic infection with *B henselae* or *B clarridgeiae* is common in cats, which are therefore considered to be a major reservoir for human infection. In humans, *B henselae* and *B clarridgeiae* have been shown to be the agents of the common, but usually self-limiting cat scratch disease (CSD) (Kordick et al 1997b, 1999a). However, less frequently, *B henselae* has been associated with more profound syndromes such as the vasculoproliferative disorders bacillary angiomatosis and peliosis hepatis, as well as endocarditis, prolonged bacteraemia and various ocular disorders including Perinaud oculoglandular syndrome, neuroretinitis and chorioretinitis (Cunningham & Koehler, 2000).

Genotypic and phenotypic (serological) variations have been demonstrated among strains of *B henselae*. At present, the most significant division within the species delineates strains into one of two subtypes on the basis of their 16SrRNA gene sequence (Bergmans et al 1995). This delineation also manifests as serological variation (Drancourt et al 1996), and it has been suggested that these two groups may represent subspecies or different serogroups. *B henselae* strain variation has also been observed among isolates from domestic and wild cats (Yamamoto et al 1998) and between those from different geographic areas (Baneth et al 1995b). However, as yet there is no indication that strains recovered from human infections possess any specific virulence determinants or form a consistent subgroup within the spectrum of genotypes observed among strains isolated from cat reservoirs. Indeed, an epidemiological survey found that in each case of CSD studied, the genotypic profile of the human-infecting strain was indistinguishable from that of the strain infecting the cat or cats to which the human was exposed (Koehler et al 1997).

The major vector of *B henselae* in cats is the flea, *Ct felis* (Chomel et al 1996). *B henselae* can be visualised in and cultured from *Ct felis* for up to 9 days after an infected blood meal (Higgins et al 1996a); however the role of the cat flea as a biological vector has not been fully determined. Cat-to-cat transmission of *B henselae* occurs via intradermal inoculation of infected faeces from *Ct felis* (Flexman et al 1995, Foil et al 1998). However, the role of the cat flea in the transmission of *B henselae* from cats to humans has not been proven.

Culture-based surveys of cats for *Bartonella* have been performed in several countries throughout the world and bacteraemia may occur in the absence of detectable antibody (Kordick & Breitschwerdt 1997, Pretorius et al 1999). The prevalence of bacteraemia reported although variable, is often high (9–90%) (Breitschwerdt & Kordick 2000). Variability may be a consequence of small survey sizes, differences in cat population characteristics (cattery, stray, feral and captive wild cats) and seasonal variation in prevalence as well as true differences in geographic prevalence. The prevalence of infection appears to be higher in young to middle-aged cats but there is no breed or gender predisposition (Kordick et al 1999c). Although geographic environments with warm temperatures and high humidity are reportedly associated with the highest exposure rates (Breitschwerdt & Kordick 2000), the prevalence in cool temperate climates is also relatively high. In recent UK surveys for *B henselae*, 11% of cats surveyed were culture positive (Laycock et al 2001) and 41% of cats were seropositive (Barnes et al 2000). The effect of climatic factors on the ecology of *Bartonella* infection may be blurred as in colder countries, animals are kept in heated domestic or confined environments, facilitating the maintenance of the flea life cycle.

Disease association with naturally occurring *Bartonella* infection is difficult to determine because of its high prevalence in apparently asymptomatic cats. Clinical disease is characterised by fever, lethargy, transient anaemia, lymphadenomegaly, neurological dysfunction or reproductive failure has been reported following experimental infections with *B henselae* and *B clarridgeiae* (Guptill et al 1997, Guptill et al 1998, Kordick & Breitschwerdt 1997, O'Reilly et al 1999, Mikolajczyk & O'Reilly 2000). However, the validity of the extrapolation of data resulting from experimentally induced infections to those which occur naturally, remains debatable. Moreover, differences in experimental method (organism passage, routes of infection, inoculation doses, age of cats infected) also make direct comparisons between data produced as a result of experimental infections difficult (Karem 2000). Most importantly, there are limited reports of clinical disease in naturally infected cats. There is a statistical correlation between cats naturally infected with *B henselae* infection, stomatitis and

urinary tract disease (Glaus et al 1997). Uveitis associated with intraocular *Bartonella* DNA and ocular IgG production has also been reported in cats (Lappin and Black 1999, Lappin et al 2000). Although *Bartonella* infection has been associated with other clinical syndromes such as endocarditis based on positive blood culture (Malik et al 1999), the association is difficult to evaluate unless the presence of lesional organisms is confirmed. Pathological abnormalities documented in experimentally infected cats have included lymphocytic-plasmacytic myocarditis, lymphocytic cholangiohepatitis, lymphocytic interstitial nephritis and lymph node and splenic hyperplasia (Guptill et al 1997). However, although *Bartonella* DNA was amplified from lesional tissue, this is not necessarily associated with causality. Strain variation in *B henselae* virulence has also been reported in experimental infection (O'Reilly et al 1999).

Co-infection with different species (*B henselae* and *B clarridgeiae)* and strains (*B henselae* Types I and II) of *Bartonella* have been reported (Gurfield et al 1997). The effect of co-infection with FIV and *B henselae* has been investigated and there is no direct association between FIV and *B henselae* seropositivity. However, in cats which have serological evidence of both infections, there is an increased risk of lymphadenopathy and gingivitis (Ueno et al 1996). A significant correlation between *Bartonella henselae* and *Borrelia burgdorferi* seropositivity has also been reported in UK cats (Barnes et al 2000) which may reflect multiple vector exposure. Alternatively both *Bartonella* and *Borrelia* spp have been identified in *Ixodes ricinus* and *I scapularis* tick populations in the US and the Netherlands (Hofmeister et al 1998, Schouls et al 1999).

Of the feline arthropod-borne infectious diseases, the immune response to *Bartonella* infection has been best studied. Following experimental intradermal infection, both SPF neonatal kittens (Mikolajezyk & O'Reilly 2000, Guptill et al 1999) and adult cats (O'Reilly et al 1999) make a serum IgM and IgG antibody response as assessed by IFA or ELISA. By western blotting, the serum antibodies from experimentally infected cats recognise at least 24 distinct *Bartonella* antigens (Freeland et al 1999), although a more restricted range of immunodominant epitopes (of molecular weight 15–80 kD) are recognised with sera from naturally-infected cats (Haimerl et al 1999, Barnes at al 2000). In experimental infection, serum antibody develops during the period of bacteraemia (Regnery et al 1996). Maternal antibody specific for *B henselae* is transferred to neonates in colostrum and persists for a period of 10 weeks (Guptill et al 1998). There is serological cross-reaction between *B henselae* and *B quintana*, but antibody specific for *B henselae* may be demonstrated by pre-absorption of serum with a suspension of this bacterium (Haimerl et al 1999, Freeland et al 1999, Baneth et al 1995b).

In contrast to the numerous studies of the humoral response in feline bartonellosis, there are few reported studies of the *Bartonella*-specific cell-mediated immune response. Positive delayed cutaneous hypersensitivity reactions in cats following exposure and challenge with live *B henselae* have been reported (Karem 2000). In one long-term experimental infection study, cats failed to make a response following intradermal administration of 'cat scratch disease' antigen (Kordick et al 1999c), and the *Bartonella*-specific in vitro lymphocyte proliferative response has been examined in one further study (Guptill et al 1997).

The diagnosis of *Bartonella* infection is best made by culture and/or PCR because of the high prevalence of seropositivity in normal cats. The association of infection and clinical disease is difficult to confirm and requires identification of *Bartonella* organisms within tissues such as lymph node showing compatible pathology.

Treatment of bartonellosis and elimination of bacteraemia is problematic. Doxycycline, amoxicillin, amoxicillin/clavulanate used at higher than recommended dose rates have been successful in suppressing bacteraemia in experimental infections. Rifampicin and enrofloxacin are also reportedly effective (Regnery et al 1996, Greene et al 1996, Kordick et al 1997a) (Table 1). However, total elimination of infection may be impossible despite the use of combination therapy such as rifampicin and doxycycline (Table 2), and prolonged duration (4–6 weeks) of therapy. In addition, the risk of re-exposure is high.

The development of a feline vaccine to reduce the prevalence of *B henselae* bacteraemia and the risk of human transmission has been proposed. Experimental studies have shown that intradermally infected cats develop resistance (abacteraemia) only following challenge with an homologous species of *Bartonella* or an homologous strain of *B henselae* (Yamamoto et al 1998, Regnery et al 1996). This lack of cross-protection suggests that any vaccine would require incorporation of multiple *Bartonella*

Table 1. Drugs recommended for treatment of arthropod-borne infectious diseases in cats

Drug	Infection	Dose rate (mg/kg)	Dose frequency (h)	Route
Antibiotic				
Amoxicillin	Bartonellosis, borreliosis	10–20	12	IV, SC, PO
Amoxicillin/clavulanate	Bartonellosis	10–20	12	IV, SC, PO
Doxycycline	Ehrlichiosis, yersiniosis, borreliosis	5–10	12 decrease to 24	PO, IV
Oxytetracycline	Ehrlichiosis, yersiniosis, borreliosis	10–25	8	PO, IV
Erythromycin	Coxiellosis	10 622	8	PO, IV
Azithromycin†	Coxiellosis, borreliosis	7–15	12	PO
Chloramphenicol	Yersiniosis, tularaemia	25–50	12	IV, IM, SC, PO
Fluoroquinolones* eg, enrofloxacin	Bartonellosis, coxiellosis, yersiniosis, tularaemia	5–15	8–12	IV, IM, SC, PO
Aminoglycosides eg, gentamycin	Yersiniosis, tularaemia	2–4	12–24	IM
Rifampicin*†	Bartonellosis, coxiellosis	5–10	24	PO
Trimethoprim/sulphonamide/pyrimethamine	Coxiellosis	15–60	24	PO
Anti-protozoal				
Imidocarb diproprionate†	Cytauxzoonosis	5–6.6	Once. Repeat in 2 weeks	SC, IM
Primiquine sulphate†	Babesiosis	1 mg/cat	Every 36 h for 6 days, then once weekly for 4 weeks	IM
Diminazene aceturate†	Cytauxzoonosis	3.5	Once. Repeat in 7 days	IM
Meglumine antimonate†	Leishmaniosis	5	24 for 20–30 days	SC

*Used in combination with other antibiotics. See Table 2.
†Not licensed for cats.

Table 2. Antibiotic combinations used for treatment of arthropod-borne infectious diseases in cats

Infection	Antibiotics
Bartonellosis	Rifampicin and doxycycline, Amoxycillin clavulanate and enrofloxacin
Coxiellosis	Rifampicin and doxycycline, Rifampicin and fluoroquinolones

epitopes, particularly as coinfection with more than one *Bartonella* species or strain is recognised in naturally infected cats (Gurfield et al 1997). It is likely that cellular immunity is also important in protection of cats against *B henselae*. Cats vaccinated with killed *B henselae* develop a non-protective IgG response while live challenge prevents subsequent reinfection (Karem 2000).

Even though the mechanism of transmission of *Bartonella* infection from cats to humans has not been determined, the prevalence of *Bartonella* bacteraemia in cats and the risk of *Bartonella*-associated disease in pet owners, is decreased by a vigorous integrated flea control programme. When uninfected cats are housed with *B henselae* bacteraemic SPF cats in an ectoparasite-free environment, there is no evidence of *Bartonella* transmission between cats (Chomel et al 1996). Furthermore, when continuous preventative treatment for fleas and ticks was given to two cats and one dog persistently infected with *Bartonella* species in a single household, the in-contact humans remained serologically negative (Kordick & Breitschwerdt 1998).

Ehrlichiosis

Feline ehrlichiosis is caused by tick-transmitted intracellular bacteria of the genus *Ehrlichia.* For many years, *Ehrlichia*-like inclusions have been detected in monocytes, lymphocytes and granulocytes of cats with febrile illness and thrombocytopenia in many countries (Buoro et al 1989, Bouloy et al 1994, Beaufils et al 1999, Bjoersdorff et al 1999), as has serological evidence of *Ehrlichia* infection (Peavy et al 1997, Matthewman et al 1996, Beaufils 1999). However, only recently have the ehrlichial species infecting cats been characterised at the molecular level. Three genogroups of ehrlichiae causing disease in animals and humans are recognised following phylogenetic analysis using the 16SrRNA gene sequences (Drancourt & Raoult 1994, Walker & Dumler 1996). Cats are susceptible to experimental infection with members of the *Ehrlichia phagocytophila* genogroup (Genotype II) including *E equi* (Lewis et al 1975). Granulocytic ehrlichiosis caused by *Ehrlichia phagocytophila* infection has been identified and characterised in a cat from Sweden (Bjoersdorff et al 1999), and illness in cats associated with molecular evidence of *E phagocytophila* infection has recently been identified in Denmark, UK and the USA (Shaw et al 2001, Shaw 2001, Lappin et al 2001). Feline ehrlichiosis associated with inclusions in mononuclear cells has been reported in cats with seropositivity to *Ehrlichia canis* (Genogroup III) (Matthewman et al 1996, Peavy et al 1997, Beaufils et al 1999). Recently molecular evidence has confirmed the occurrence of *E canis* infection in North American cats with clinical signs compatible with monocytic ehrlichiosis (Breitschwerdt et al 2001). Cats are susceptible to experimental infection with *E risticii* (Genogroup I) (Dawson et al 1988) and serological evidence of *E risticii* infection has been reported in cats (Peavy et al 1997, Stubbs et al 1998).

As in other species, ehrlichiosis in cats is presumed to be tick-transmitted. Infestation with *Ixodes* species ticks (Sweden) and *Haemaphysalis leachii* (Kenya) has been found on infected cats (Bjoersdorff et al 1999, Buoro et al 1989). However, definitive evidence for the route of transmission is lacking. Risk factors associated with positive serology for *E canis* and/or *E risticii* have been studied (Stubbs et al 2000). Cats with outdoor exposure were more likely to have positive *E canis* and/or *E risticii* serology and cats with positive *E canis* serology were more likely to be female. There was no association with breed or age.

Clinical signs reported in cats with naturally occurring ehrlichiosis are extremely varied. For monocytic ehrlichiosis, these include intermittent fever, anorexia, weight loss, vomiting, diarrhoea, upper respiratory signs and muscle pain. Clinicopathological findings include anaemia, thrombocytopenia, leucopenia and hyperglobulinaemia (Bouloy et al 1994, Peavy et al 1997, Stubbs et al 1998, Beaufils et al 1999). However, in a study by Stubbs et al (2000), statistically significant associations between clinical signs and positive

serology for *E canis* and/or *E risticii*, were more limited. Ocular discharge, uveitis and polyarthritis were significantly more common in cats with positive *E canis* and/or *E risticii* serology; vomiting and hyperglobulinaemia were more common in cats with positive *E risticii* and *E canis* serology respectively. There was a negative association between thrombocytopaenia and *E canis* and/or *E risticii* positive serology (Stubbs et al 2000). However, as some cats may be sero-negative for *E canis* but positive by PCR for ehrlichial DNA (Breitschwerdt et al 2001), disease associations suggested by serological data alone may be inadequate. Cats with *E phagocytophila* infection on PCR analysis presented with fever, lethargy, weight loss and joint pain (Bjoersdorff et al 1999, Shaw 2001, Lappin et al 2001). Further investigation of species and strain variation of ehrlichiae infecting cats as well as co-infection, may well explain the wide spectrum of clinical presentation.

Whether cats become persistently infected or develop immune-mediated sequelae as a result of chronic infection as occurs in dogs is unknown. However, prolonged elevation of antibody levels in cats seropositive for *E canis* and organisms of the *E phagocytophila* genogroup is reported (Bjoersdorff et al 1999, Beaufils et al 1999, Stubbs et al 2000). No association with FIV or FeLV has been reported, and although one case had concurrent *Haemobartonella felis* infection, the presence of co-infection with other arthropod-borne pathogens has not been investigated.

Definite diagnosis of feline ehrlichiosis is made by demonstration of intra-leucocytic inclusions in, or PCR of, a peripheral blood sample. However, the presence of inclusions in infected cats is variable (Stubbs et al 2000, Bjoersdorff et al 1999). Serological (IFA) testing is available for both *E risticii* and *E canis* infections in cats (Stubbs et al 2000) but considerable cross-reaction occurs between ehrlichial species and a rising titre is required to confirm active infection.

Although controlled therapeutic trials are lacking, administration of doxycycline or tetracycline (Table 1) is the treatment of choice for feline ehrlichiosis and clinical response is reported to be excellent (Peavy et al 1997, Bjoersdorff et al 1999, Beaufils et al 1999). Antibiotic therapy should be administered for a minimum period of 21–28 days.

Rickettsial infections

These arthropod-transmitted, intracellular infections are rarely reported to cause clinical disease in cats. However, as domestic cats are susceptible to infection with a number of rickettsial species and are hosts for their arthropod vectors, they may play an increasingly important role in the epidemiology of these diseases in humans.

Two causes of flea-transmitted human typhus are now recognised; *Rickettsia typhi* transmitted by rodent fleas with a world-wide distribution and the recently characterised and closely related *R. felis* in south-western USA (Schriefer et al 1994a, 1994b, Higgins et al 1996b). *Ct felis* is now also a recognised vector for typhus and will support infections with both rickettsial species (Noden et al 1998). This vector has a catholic host range and is particularly well adapted to feed on opossums and cats. In endemic areas of the USA, peri-urban opossums are major reservoir hosts for *R felis* (Schriefer et al 1994b) but the reservoir potential of cats has not been determined. Experimental infection of cats with *R felis* has been demonstrated (Wedincamp & Foil 2000) as has seropositivity to *R typhi* (Sorvillo et al 1993, Matthewman et al 1997b). The pathogenic potential of either rickettsial species for cats is unknown. What is in no doubt, is that cats will transport *Ct felis* into domestic surroundings and as transovarial and trans-stadial transmission of *R felis* has been shown (Azad et al 1992), a domestic focus of infection for humans could be established.

Seropositivity indicates cats are also susceptible to infection with the tick-transmitted rickettsial species *Rickettsia rickettsiae* (Greene & Breitschwerdt 1998) and *R conorii* (Matthewman et al 1997b). Clinical disease associated with infection has not been identified in cats, but *R rickettsiae* infection in dogs and humans in the Americas causes Rocky Mountain spotted fever. Similarly, in southern Europe, the Middle east and southern Africa, infection with the species *R conorii* causes Boutonneuse or Mediterranean spotted fever in humans. Whether cats play a role in the epidemiology of these diseases through interaction with the wild rodent reservoir of infection and ticks is unknown.

Coxiellosis

Coxiella burnetii is an extracellular, arthropod-transmitted, spore-forming bacterium which in cats produces subclinical infection but in humans causes Q fever, a disease associated with fever, arthralgia, myalgia, hepatitis and respiratory symptoms. A wide range of wild and domesticated animals including cats are considered

reservoir hosts for human infection. In wildlife reservoir cycles, *C burnetii* is commonly transmitted by arthropod vectors, including ticks. In addition, the sporulated form of *C burnetii* is highly resistant to environmental extremes and can be spread between hosts by ingestion or aerosol dissemination of infected fluids such as milk, urine and vaginal/uterine secretions, or by ingestion of infected tissues such as placental material (Nagaoka et al 1998).

Seropositivity to *C burnetii* ranges from 16–20% in populations of stray and companion cats in the USA, Canada and Japan (Randhawa et al 1974, Higgins & Marrie 1990, Htwe et al 1992, Morita et al 1994) while lower seroprevalences are reported from Africa (Matthewman 1997a). Cross-reactivity between *C burnetii* and *B henselae* has been reported in human studies (LaScola & Raoult 1996) and although this has not been investigated in cats, it may inflate seroprevalence figures for *Coxiella.*

Infected cats are considered important reservoirs for human coxiellosis. *C burnetii* appears to be frequently carried in the vagina of healthy cats in endemic areas (Nagoaka et al 1998) and contact with infected parturient cats is a risk factor for human infection (Pinsky et al 1991, Morita et al 1994).

Diagnosis of active infection with *Coxiella* is made by demonstration of a rising antibody titre, PCR or immunohistochemical techniques. Treatment of cats may be required in households where there is increased risk of human infection. *Coxiella* infections are variably susceptible to single agent therapy with macrolides (erythromycin, azithromycin), potentiated sulphonamides and fluoroquinolones (Table 1) for 2–4 weeks duration. Combination therapy (Table 2) of doxycycline and fluoroquinolones with rifampicin may be more effective (Levy et al 1991).

Yersiniosis

Plague is caused by the non-spore-forming bacterium, *Yersinia pestis*. Localised foci of disease occur in temperate, semi-arid areas throughout the world and infection is maintained in reservoir rodent populations by flea transmission. Epizootic outbreaks of disease occur when *Y. pestis* infection expands into more highly susceptible small mammal populations. With semi-urban development now extending into endemic areas of plague, there is increasing risk of domestic cats being infected by bites from rodent fleas acquired during hunting, or more commonly by ingestion of infected small mammals. *Ct felis* is a relatively ineffective vector for plague transmission. Bacteraemic cats are a source for human infection either directly through aerosol spread, bites or scratches or indirectly by transporting infected fleas into the domestic environment (Macy 1998, Gage et al 2000).

Both domesticated and wild cats are more susceptible to clinical yersiniosis than dogs. In experimentally infected cats, most develop mild to moderately severe clinical disease with subsequent recovery, although some develop an acute fulminating and fatal syndrome (Gasper et al 1993). Two main clinical syndromes are recognised in naturally infected cats (Eidson et al 1991, Carlson 1996). Bubonic plague is associated with fever, dehydration, weight loss and lymphadenopathy with abscessation and draining tracts affecting the cervical, retropharyngeal and submandibular lymph nodes. Recovery may occur following this stage or there is haematogenous spread with progression to the often fatal, septicaemic syndrome. Multiple organ involvement, endotoxic shock, oedema and disseminated intravascular coagulation (DIC) with marked leucocytosis are characteristic. In cats, pneumonic involvement during this stage is common and dissemination by aerosol may occur to in-contact humans. Primary pneumonic plague in cats is rare. Less commonly reported clinical signs are vomiting, diarrhoea, tonsillar and lingual lymph node enlargement and necrotic stomatitis (Eidson et al 1991, Carlson 1996).

Fluorescent antibody testing and rising serological titres provide a presumptive diagnosis. Confirmation of diagnosis is made by demonstration of bacteria in affected tonsillar tissue or lymph node aspirates with appropriate Gram and Giemsa staining characteristics, followed by culture. Stringent biosafety procedures should be carried out in collection and transport of specimens and culture requires a containment laboratory. The decision to treat cats with plague should always take into consideration the zoonotic risk. In particular, the potential for aerosol spread from pulmonary lesions in infected cats should be evaluated by thoracic radiology. Appropriate protective clothing and gloves should be worn and all contaminated material or surfaces should be disinfected. *Yersinia pestis* is sensitive to routine disinfectants and a variety of antibiotics including aminoglycosides, doxycycline, chloramphenicol and

fluoroquinolones (Bonacorsi et al 1994) (Table 1). Therapy should be continued for a minimum of 21 days. Doxycycline is most commonly used in the bubonic syndrome and can be used for prophylaxis in exposed, subclinical cats (Macy 1998).

Tularaemia

The aetiological agent of tularaemia in mammals and birds is the tick-transmitted bacterium, *Francisella tularensis*. These organisms are distributed throughout the temperate and sub-Arctic areas of the northern hemisphere and there is geographic variation in strain, the species of tick vector and reservoir hosts involved. Two biovars are recognised and cats are susceptible to both (Baldwin et al 1991). *F tularensis tularensis* is distributed throughout North America and is associated with a tick-rabbit cycle. *F tularensis palearctica* has a broad distribution throughout the northern hemisphere and has a more complex epidemiology involving a hare/rabbit reservoir-tick/mosquito cycle. Tick vectors include species of *Dermacentor*, *Ambylomma*, *Ixodes* and *Haemaphysalis*. Cats may also be infected by ingesting infected rodent or lagomorph prey. Infected domestic cats may transmit tularaemia to humans by bites and scratches (Capellan & Fong 1993, Rodon et al 1998, Arav-Boger 2000).

Cats appear more susceptible to naturally occurring clinical tularaemia than dogs and younger cats appear more predisposed. Clinical signs include fever, marked lethargy, anorexia, regional or generalised lymphadenopathy with abscessation, splenomegaly and/or hepatomegaly with abscessation, oral ulceration, leucopenia, icterus and in some cases death (Baldwin et al 1991, Gliatto et al 1994, Woods et al 1998). Presumptive diagnosis may be made serologically but confirmation requires culture of infected tissue or body fluids using rigorous biosafety procedures to prevent human infection.

Therapeutic regimes for feline tularaemia have not been thoroughly investigated and are adapted from human cases. Aminoglycoside, tetracycline, chloramphenicol and fluoroquinolone antibiotics have been advocated for 2–4 weeks duration (Enderlin et al 1994) (Table 1).

Borreliosis

Borreliosis is caused by a tick-borne extracellular spirochete, *Borrelia burgdorferi sensu lato* which is transmitted by ticks of the genus *Ixodes*. At least four genospecies with geographical distributions primarily in the northern hemisphere, cause disease in humans (Fillipuzzi-Jenny 1993). Much of the published borreliosis research in dogs and cats relates to the Genogroup I species, *B burgdorferi sensu stricto*, which is the main cause of borreliosis in humans and dogs in the USA. However, *B garinii* and *B afzelii* are the major pathogenic species for humans in Europe and in Japan, *B japonica* causes human disease (Dressler et al 1994, Wilske et al 1996, Hubalek & Halouzka 1997). At this time, there have been no surveys to determine the degree to which these *Borrelia* species contribute to infection and disease in dogs and cats.

Although *B burgdorferi* seropositivity of 4.8–36% has been reported in cats in the UK (May et al 1994), USA (Omran et al 1997) and Germany (Lindner & Bockel 1995), naturally occurring clinical disease has not been reported. The results of experimental infection of cats with US strains of *B burgdorferi* are contradictory with respect to inducing clinical signs. Burgess (1992) reported no apparent disease following infection while others (Gibson et al 1993, Omran et al 1997) reported some cats with non-specific signs including fever, lethargy, stiffness and arthritis. Clinical and pathological signs referable to hepatic, gastrointestinal, neurological and cardiac disease are also reported (Omran et al 1997). There is some evidence that persistent infection without disease may occur. Cyclical increases in both *B burgdorferi*-specific IgM and IgG levels with associated neutropenia have been reported in experimentally infected cats (Omran et al 1997). However, studies using longitudinal post-infection culture and PCR analyses remain to be published.

Clinical borreliosis has not been fully characterised but techniques used to indicate infection in cats include PCR and serology. Therapeutic protocols have not been specifically described for cats. However, doxycycline, amoxicillin, azithromycin, penicillin, ceftriaxone and cefotaxime are used in human and canine cases (Table 1) and duration of therapy should extend to 30 days.

Protozoal diseases transmitted by arthropods

Cytauxzoonosis

Cytauxzoonosis is caused by a tick-transmitted, haemotropic protozoan parasite, *Cytauxzoon felis*.

It has been reported from both Africa and the USA and appears to be endemic in North American wild cat species such as the Florida panther (*Puma concolor coryi*) and the bobcat (*Lynx rufus*) (Kier et al 1982). The members of the genus *Cytauxzoon* share characteristics with organisms of the genera *Theileria* and *Babesia* and on a molecular level, *C felis* has considerable homogeneity with *Babesia rodhaini* and *Theileria equi* (Allsopp et al 1994). The primary tick vector of the disease in the USA is *Dermacentor variabilis.*

In natural infections with *C felis*, there is apparent variation in pathogenicity which may be associated with geographical distribution. Although mortality rates in domestic cats approaching 50% are described (Kier & Greene 1998), less severe and asymptomatic infections are also reported (Walker & Cowell 1995, Meinkoth et al 2000).

C felis has developmental stages in both macrophages and erythrocytes of infected cats. In experimentally infected cats, proliferation of organisms in mononuclear phagocytic cells particularly in the lungs, results in marked vascular damage and occlusion, release of inflammatory mediators and DIC. The intra-erythrocytic stage induces both intravascular and extravascular haemolysis (Hoover et al 1994). This produces a rapidly progressive syndrome in most cats characterised by acute fever, haemolytic anaemia, lymphadenomegaly, anorexia, dyspnoea, and in severe cases, poor peripheral perfusion followed by hypothermia, coma and death. Pathological findings are dominated by generalised oedema, serous effusions and petechial haemorrhages.

Diagnosis is made by demonstration of intraerythrocytic organisms with appropriate morphology in blood, lymph node, bone marrow or splenic aspirates in combination with compatible clinical signs. No serological tests are routinely available. Anti-protozoal therapy using imidocarb diproprionate or diminazene aceturate is recommended (Table 1). A single injection provides sufficient residual activity in the majority of cases. Supportive fluid therapy is essential and DIC should be managed using heparin. Broad spectrum antibiotic therapy with enrofloxacin or cephalosporins is also recommended.

Babesiosis

Babesiosis is caused by tick-borne, intraerythrocytic protozoan parasites of the genus *Babesia.* Two *Babesia* species infecting domesticated cats have been reported from Africa and Asia; *Babesia cati* and *B felis*. *B felis* is endemic in localised areas of South Africa and is a recognised cause of clinical disease in domestic cats. However, there are limited studies on the epidemiology of the disease and although it is presumed to be tick-transmitted as in other species, the vectors are unknown. In cats treated by veterinary surgeons, Jacobson et al (1999) determined that young to middle aged cats may be more predisposed, as are cats of the Oriental and Siamese breeds. *B pantherae* and *B herpailuri* are endemic in wild cat species and will infect domestic cats under experimental conditions. Recently, a new species of *Babesia* has been reported in lions (LopezRebollar et al 1999).

The pathogenesis of feline babesiosis is presumed to be similar to that in dogs and involves parasite-induced erythrocyte damage with subsequent haemolytic anaemia. However, clinical signs are less severe than in dogs, and cats rarely develop intravascular haemolytic crises (Moik & Gothe 1997, Jacobson et al 1999). Pyrexia and icterus are rarely seen and most signs are related to the severity of anaemia and include anorexia, lethargy, weakness, pallor, tachycardia and tachypnoea. Because of limited studies in this area, the potential for persistent infection despite therapy, as occurs in dogs, is unknown. Co-infections of *B felis* with FeLV, FIV, feline infectious peritonitis virus, *Haemobartonella felis* and respiratory viruses are reported (Jacobson et al 1999) but controlled studies are lacking. There appears to be no information on the prevalence of co-infection with other arthropod-borne diseases.

Diagnosis is made by demonstration of intraerythrocytic protozoal organisms with appropriate morphology in blood, lymph node, bone marrow or splenic aspirates in combination with compatible clinical signs. Sensitivity is limited by low-level parasitaemia in chronic cases or where prevalence is low. No serological tests are routinely available for cats but PCR will provide both an investigational and diagnostic tool in the future. The drug most commonly recommended for treatment of babesiosis in cats is the antimalarial, primiquine phosphate although other anti-babesial drugs may be effective (Jacobson et al 1999) (Table 1). Blood transfusions are rarely required.

Leishmaniosis

Leishmaniosis is caused by an intracellular protozoan parasite of the genus *Leishmania* and is

transmitted by sandflies. *L infantum* infection is common in dogs in endemic areas of Europe, the Middle East and many tropical and subtropical areas of the world and causes serious systemic and cutaneous disease in susceptible animals.

In contrast to dogs, natural infection and clinical disease in domestic cats caused by *Leishmania* species appear to be rare. Whether the low prevalence of infection/disease in endemic areas is due to under-reporting or to the fact that cats have a high degree of natural resistance is unknown. However, cases of systemic clinical disease and asymptomatic infection due to *L infantum* and other species are reported (Passos et al 1996, Ozon et al 1998, Hervas et al 1999) and wild cats have been incriminated as reservoirs for leishmaniosis in endemic Mediterranean countries. Cutaneous lesions alone have been reported in association with *L venezuelensis* (BonfanteGarrido et al 1996) and unspecified *Leishmania* spp in Europe, South America and in the southern USA (Barnes et al 1993). The pathogenesis of the disease in cats has not been investigated. Feline leishmaniosis is presumed to be sandfly-transmitted, however, the vector is unknown and the epidemiology of the disease in cats has not been investigated in detail.

The clinical presentation is similar to that seen in dogs although the small number of cases make the association of infection and clinical signs difficult to interpret. Cutaneous lesions include diffuse areas of alopecia and granulomatous dermatitis of the head, scaling and pinnal dermatitis, ulceration and nodules (Barnes et al 1993). Systemic involvement with *L infantum* has been reported in association with jaundice, vomiting, hepatomegaly, splenomegaly, lymphadenomegaly, membranous glomerulonephritis and granulomatous gastroenteritis (Ozon et al 1998). Co-infection with other arthropod-borne agents remains to be investigated but in the small number of cases tested, co-infection with the immunosuppressive viruses (FIV or FeLV) has not been confirmed (Barnes et al 1993, Ozon et al 1998) despite the strong association with human leishmaniosis and HIV infection.

Presumptive diagnosis is most commonly made by the demonstration of protozoal organisms in tissue biopsy specimens using both light and electron microscopic examination. Culture is not routinely available and there are no commercially available serological tests employing feline reagents. PCR, particularly of bone marrow offers a sensitive and specific diagnostic tool for this disease although no reports of its use in feline leishmaniasis have as yet been published. There are no therapeutic agents licensed for leishmaniosis in cats although there is a single report of successful treatment of one cat with cutaneous disease using meglumine antimonate (Hervas et al 1999).

Hepatozoonosis

Hepatozoonosis is a tick-transmitted, protozoal disease caused by species of the intraleucocytic parasite, *Hepatozoon.* Although most commonly reported as a disease of dogs with a wide distribution throughout countries bordering the Mediterranean, Middle East, Africa, Asia and the Americas, as yet uncharacterised *Hepatozoon* species are reported to infect domesticated and wild cats in areas of Israel endemic for canine infection (Baneth et al 1998). Unlike other tick-transmitted diseases, infection with *Hepatozoon* in dogs occurs by ingestion of infected *Rhipicephalus sanguineus* ticks rather than by tick bites, and cats are presumed to be infected by the same route.

As in dogs with *H canis* infection, a characteristic clinical syndrome in cats associated with hepatozoonosis is difficult to define. However, increased serum creatine phosphokinase and aspartate transaminase levels have been associated with infection (Baneth et al 1998) and it is recognised that *H americanum* infection in American dogs is characterised by severe myositis. Co-infection with other micro- and macroparasitic diseases including those that are arthropod-transmitted, is common with *H canis* infection in dogs. Similarly, co-infection with FIV, FeLV and *Haemobartonella felis* has been reported with feline hepatozoonosis (Baneth et al 1998). Diagnosis as in the other arthropod-borne protozoal infections, is by demonstration of intra-leucocytic organisms with characteristic morphology in peripheral blood or bone marrow smears. Response to therapy with doxycycline for 14–21 days has been recommended (Baneth et al 1995a) (Table 1).

Strategies for control

Vector control

The importance of prophylactic flea control in the management of bartonellosis has been demonstrated (Chomel et al 1996, Kordick & Breitschwerdt 1998). This emerging zoonosis is an important reason to maintain routine

Table 3. Drugs recommended for arthropod control in cats

Drug (*Company*)	Arthropod	Species targeted	Route	Dose (mg/kg)
Insecticides/Acaricides				
Fipronil (*Merial*)	Ticks	*Ixodes, Dermacentor, Rhipicephalus sanguineus, Amblyomma, Haemophysalis*	0.25% spray and 10% spot-on	7.5–15
	Fleas	*Ctenocephalides felis*		
Selemectin (*Pfizer*)	Fleas	*Ct felis*	Spot-on	6
Nitenpyram (*Novartis*)	Fleas	*Ct felis*	Oral	2–4
Imidocloprid (*Bayer*)	Fleas	*Ct felis*	10% spot-on	10–20
Insect growth regulators				
Fipronil/Methoprene (*Merial*)	Fleas, ticks	*Ct felis, Ixodes, Dermacentor, Rhipicephalus sanguineus, Amblyomma, Haemophysalis*	10%/9% combined spot-on	7.5–15
Lufenuron (*Novartis*)	Fleas	*Ct felis*	Oral	30
			Subcut	10
Pyriproxifen (*Virbac, Bayer*)	Fleas	*Ct felis*	10% spot-on	12–30

prophylactic flea control measures in cats and safe, effective, residual insecticides are now available for use (Table 3). Control measures should combine both adulticide and insect development inhibitors that are licensed for use in cats.

Tick control in cats is also recommended in endemic areas (Table 3). However, there is a marked deficit of literature concerning the efficacy of acaricides for tick infestation in cats. This may reflect the technical difficulties involved in performing such studies. One obvious problem lies in establishing large enough patent tick infestations in both control and treated groups to ensure reliable estimates of efficacy. A further problem lies in toxicity of pyrethroids in cats which limit their use as acaricides in this species. Fipronil is the only acaricide which has been extensively investigated as an acaricide for use in cats (Wiedemann 2000).

Vaccination

The development of vaccination programmes for control of arthropod-borne infections in cats would benefit both feline and human health. However, there are intrinsic problems with producing vaccines against a group of organisms that can readily evade and manipulate the host immunity. Moreover, vaccine development requires detailed knowledge of the nature of the target species immune response to immunodominant epitopes, and such studies are lacking for these feline micro-parasites. Of the diseases reviewed here, feline vaccination has been proposed only for the control of human CSD and studies of the feline immune response to *Bartonella* are summarised above.

Summary

Arthropod-transmitted microparasitic diseases are emerging problems in cats. Not only do they cause serious disease in their traditional tropical and semi-tropical range but they are now increasingly recognised as causing disease of cats in temperate climates and urban environments. In addition, it is now recognised that subclinically infected cats may provide a reservoir for human arthropod-transmitted infectious disease such as bartonellosis. The emergence of these diseases is due to a number of factors including the expansion of tick range into urban and semi-urban areas world-wide, movement of infected cats into previously non-endemic areas and the revolution produced by the application of molecular techniques to diagnosis and pathogen identification.

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