The Travelling Pet: What are the Risks?

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It is important for owners to realise that the PETS scheme is primarily focused at stopping imported zoonotic diseases entering the United Kingdom. There is no statutory provision under PETS to reduce the likelihood of animals being exposed to diseases that are currently not endemic within the United Kingdom. The area to which the animal has travelled largely dictates which diseases will be important risks. For example travel around the Mediterranean basin leading to potential exposure to mosquitoes carrying heartworm (dirofilaria) and travel to the United States (more recently included in the PETS scheme) possibly leading to exposure to fungal diseases such as Blastomycosis. The main diseases encountered in mainland Europe include Babesia, Leishmania, Ehrlichiosis and Dirofilariasis.

Leishmaniosis

Leishmaniosis is a serious and fatal protozoan disease of dogs, and occasionally cats, and is endemic though the Mediterranean areas of Europe, South America and the Middle East. In southern Europe Leishmania infantum is the causative species and is carried by its vector the Phlebotomus sand fly. The specific habitat and climate requirements for the sand fly vector, limits endemic Leishmaniosis to southern Europe. It is estimated that at least two and a half million dogs have Leishmaniosis in south west Europe, with climate change has allowed the vector and the disease to move slowly north. Although the risk of zoonotic infection is low, sand flies are considered the main route for L. infantum transmission to people from dogs and wild canids. Children and immunosuppressed adults, such as those with HIV, are particularly susceptible.

Sand flies are not present with in United Kingdom (UK); however reported cases of canine Leishmaniosis are increasing as a result of animals travelling to, and being imported from, endemic areas in Europe. Since the introduction of the Pet Travel Scheme (PETS) in 2000 close to one million dogs have entered the UK under the scheme. Although PETS is designed to keen the UK free from Rabies and Echinococcus multilocularius there is no statutory requirement for preventative measures to be taken against exotic disease during travel. Similarly Leishmaniosis is not notifiable in the UK and the prevalence of the disease in dogs entering the UK is largely unknown. A national reporting scheme known as DACTARI (Dogs and Cat Travel and Risk Information) was set up by DEFRA in March 2003, allowing surveillance of exotic disease (including Leishmaniosis) and to date 51 cases of Leishmaniosis have been reported. However, this scheme is voluntary and does not accurate reflection of case numbers seen.

A recent study reviewing cases with a laboratory diagnosis of Leishmaniosis, documented 257 cases in the UK over the three year period between 2005 & 2007. The majority of these dogs had spent at least six months in an endemic area (96%), with the most commonly reported countries of origin being Spain (57%), Greece (14%), Portugal (9%) or Italy (9%). Worryingly two cases of Leishmania have been reported in un-travelled dogs co-housed with infected imported animals and three dogs obtained from UK rehoming centres were confirmed to have Leishmaniosis having no history of travel. Mechanical dog to dog transmission, or another as yet undetermined vector, is postulated as the route of transmission in these cases.

The life cycle involves the sand fly and a vertebrate host. Female sand flies harbour Leishmania promastigotes in their gut and transmit them during feeding. These promastigotes are injected with saliva into the host's skin, where they are phagocytosed by macrophages. Within the macrophage

multiplication occurs by binary fission to amastigotes. Division ruptures the macrophage freeing amastigotes to penetrate adjacent cells and disseminate to the visceral organs. The cycle is completed when cells containing amastigotes are taken up by the sand fly during feeding. Amastogotes transform into promastigotes and multiply, ready to be injected into a naïve host. Vertical transmission in utero is reported and in North America transmission L. infantum has been transmitted between dogs via blood transfusion.

Not all dogs that are infected with Leishmania will develop clinical signs, as the immune response mounted determines whether the infection will be cleared, whether generalised symptoms develop or when the infection progresses from an asymptomatic to a symptomatic state. Studies in endemic areas show 60-70% of dogs are infected with Leishmania, but the prevalence of disease is much lower, around 10%. There appears to be two peaks in age prevalence in dogs less than three years and then later around eight to ten years of age.

Whether dogs develop clinical signs or not depends largely on their immune response. A humoral Th2 response to infection generally leads to chronic and progressive disease, whereas a Th1 cell mediated response usually leads to clearance of the disease. There is a direct genetic influence on the immune response for example some breeds, such as the German Shepherd, Boxer, Cocker Spaniel and Rottweiler appear to be more susceptible than average to developing symptomatic disease, whereas others, such as the Ibizan hound, only rarely develop disease. Specific MHC class II genes also appear to confer susceptibility to Leishmaniosis. Producing an effective Th1 response is the focus of vaccination strategies and therapeutic options such as domperidone.

Classic signs of Leishmania follow a very chronic and often variable course, with clinical signs including weight loss, lymphadenopathy, lameness and cutaneous signs. Most dogs develop cutaneous signs and may occur in the absence of other systemic signs. Cutaneous signs are very varied, but include exfoliative dermatitis, with a classic silvery scale around the muzzle, and peri-orbital areas; peri-ocular alopecia and abnormal nail growth. Due to chronic immune system stimulation polyclonal gammopathies are often seen. Proteinuria secondary to glomerular nephritis is also commonly reported.

In a sick dog with overt signs of Leishmaniosis, diagnosis should be relatively straight forward, by documenting the presence of the organisms (cytology of lymph node, bone marrow or spleen, or by PCR of blood, bone marrow or tissue) or by detecting an immune response to the presence of the organism (Serology). For native British dogs that have travelled to endemic areas, Leishmaniosis should be considered in cases showing any potential clinical signs. Diagnosis in these cases can be made on the basis of these signs and confirmed by documenting the presence of Leishmania organisms. Cytological examination of fine needle aspirates obtained from enlarged lymph nodes or a bone marrow is a very specific way to document Leishmania promastigotes. PCR is also a very specific way of diagnosing infection, although the sensitivity depends tissue submitted (bone marrow > lymph node > skin > conjunctiva > buffy coat > peripheral blood). PCR is most sensitive in acute infection (88%), and declines with chronicity as organisms are sequestered into tissue (50-70%).

The diagnosis of chronic Leishmaniosis in dogs from endemic areas, such as those imported by rescue societies, can be more challenging. The chronic insidious nature of the disease, coupled with vague clinical signs, is compounded by the fact that the presence of the organisms may not be the

cause of the clinical signs seen. In these cases looking for direct evidence of infection, by cytology and/or PCR, should be the starting point, but the negative results do not completely exclude the presence of the disease. In these causes serology is very helpful, as high antibody titres suggest the disease is present.

Treatment for Leishmaniosis is rarely curative, thus therapy is aimed at controlling the clinical signs rather than curing the disease. Treatment is protracted and is of variable success. Allopurinol is the mainstay of treatment and is usually used in combination with meglumine antimoniate or miltefosine. Meglumine antimoniate is a pentavalent antimony compound that selectively inhibits leishmanial glycolysis and fatty acid oxidation and is used in both human and veterinary medicine. Miltefosine was developed as an anti-cancer drug and is now used to treat Leishmania. It is an alkylphosphocholine which inhibits cell signalling and membrane synthesis leading to cell death. Neither meglumine antimoniate (Glucantime) nor miltefosine (Miltefosine) is licenced for use in the UK thus a Special Import Certificate is needed from the Veterinary Medicines Directorate.

Allopurinol is a purine analogue that is incorporated in to the Leishmania parasites RNA and interrupts protein synthesis. Used alone it will help reduce the effects of Leishmaniosis, but improvement is less marked and generally slower (2-3 months compared to 2-3 weeks), than when used in combination therapy. It is relatively cheap, safe and easily available, the main side effect being the risk of xanthine urolithiasis.

Studies comparing the clinical outcome of either meglumine antimoniate or miltefosine, as adjunct to allopurinol have shown similar outcomes that are superior to allopurinol used alone. There are advantages and disadvantages to both drugs. Meglumine antimoniate has to be administered by regular injections, whereas miltefosine is an oral treatment which aids administration for owners. Injections of the meglumine antimoniate are sometimes painful, but are associated with few other side effects, whereas miltefosine can cause gastrointestinal side effects but these are usually brief, transient and self-limiting. Meglumine antimoniate is excreted mainly by the renal route and its heavy metal components may be nephrotoxic, whereas miltefosine is metabolised solely by the liver, potentially helping preserve renal function. Depending on the weight of the animal miltefosine may be the more expensive option. Lastly some drug resistance to both meglumine antimoniate and miltefosine has been reported in people.

Drug combination	Dose	Possible side effects
Meglumine antimonite & Allopurinol	75-100mg/kg SC every 24 hours for 4 weeks 10mg/kg PO every 12 hours	Possible nephrotoxicity Pain on injection Injection site reactions Xanthine urolithiasis
Miltefosine & Allopurinol	2mg/kg PO every 24 hours for 4 weeks 10mg/kg PO every 12 hours	Vomiting Diarrhoea Xanthine urolithiasis

Recently attention has been focused on treatment that may help encourage a cell mediated Th1 immune response to infection. Domperidone is a dopamine receptor antagonist which is usually used for its gastric prokinetic and anti-emetic actions. Its anti-dopaminergic effect results in the release of serotonin, which in turn leads to the release of prolactin, which in a pro-inflammatory cytokine, thought to help modulate the Th1 response. A recent study using domperidone clinically found it helped reduce clinical signs and antibody titres in affected dogs, with no reported side effects.

Supportive treatment for renal dysfunction such as ACE inhibitors for protein loosing nephropathy and antibiotics for secondary bacterial pyoderma may also be needed.

Clinical signs associated with feline Leishmaniosis are rarely described, although PCR and serological studies from southern Europe suggest infection might be more widespread than the clinical manifestation suggests. Cutaneous nodular or ulcerative lesions, similar to those seen in dogs, are most common however a wide variety of symptoms are reported. An increased prevalence in cats with immunosuppressive viruses, such as FIV and FeLV, has not been confirmed.

For naïve dogs traveling to endemic areas, reducing possible exposure to sand flies is essential in trying to prevent Leishmaniosis. Sand flies are crepuscular, meaning they are most active at dawn and dusk. Keeping animal housed during those times and using fine mesh screens to keep sand flies out of kennel areas will limit exposure. Deltamethrin-impregnated collars are also very effective at reducing bites from Phlebotomus flies. Recently a canine vaccination against Leishmania has been brought to the UK market. This utilises cutting edge vaccine technology to combine a specific mixture of Leishmania surface proteins (known as excreted-secreted proteins or ESP) with a specific saponin adjuvant, to direct the immune system to a Th1 cell mediated response by the induction of cytotoxic T-cells. Studies have shown that the vaccine is extremely promising and appears to greatly reduce the risk of infection. In a field trial performed between two sites, both in highly endemic areas, the vaccine was shown to reduce the risk of infection by fourfold in dogs housed outside without any other preventative treatment. It is thought that vaccination is likely to have a greater protective effect in less endemic areas. As with any vaccine it is important to remind clients that the vaccination compliments rather than replaces other preventatives measures. The induction course is 3 injections at 3 weekly intervals, with annual boosters thereafter. Transient mild injection site reactions have been reported with a slightly higher frequency than for standard canine vaccinations.

Dirofilariosis

Adult Dirofilaria immitis reside in the pulmonary arteries and the right ventricle and usually lead to little obstruction to the vasculature. These worms produce microfilariae which are released into the bloodstream. Microfilariae are ingested by mosquitos in which development to the L3 larval stage occurs, this is infectious when the mosquito feeds. These migrate to the pulmonary arteries and mature to adults, moving to the right ventricle at this stage. If both sexes are present microfilariae are produced 6-7 months after exposure. The dog is the primary host for D.immitis and zoonotic infections are rare.

Currently D.immitis is not endemic in the UK, however it is widespread through most of North America and Southern Europe. Native mosquito vectors have been shown to be able to transmit the L3 larvae in laboratory conditions; however outside the laboratory, ambient temperatures are not warm enough for larval development, preventing heartworm becoming established.

Most infected dogs have few clinical signs, however disease come from pulmonary arterial disease. Irritation to the pulmonary endothelium leads to pulmonary thromboembolism and hypertension, causing signs such as coughing, dyspnoea and exercise intolerance. The severity of these signs depends on the number of worms present, the duration of infection and the host immune response.

Diagnosis is based on clinical signs and demonstrating the presence of microfilariae, which can be seen on blood films or documenting the presence of antigen. Treatment of adult infections is not without risk as dead worms will be swept into the pulmonary tree and vascular removal is a possible alternative. Preventing infection with chemoprophylaxis is therefore a much better strategy, with monthly milbemycin or selemectin having proven efficacy.

Babesiosis

Babesia is a tick borne disease which can cause severe and life threatening anaemia in dogs. It is particularly prevalent in France, with increasing incidence in the south (particularly south of the Loire valley), however tick vectors are wide spread and the disease in endemic in most of mainland Europe. High levels of babesia sporozoites within tick saliva are passed into the host's circulation when the tick feeds; the tick must feed for a minimum of 48-72 hours for transmission to occur. The life cycle is continued in the host by the production of merozoites within erythrocytes. These either infect further erythrocytes or the life cycle is completed by infecting ticks during feeding. Babesia infection results in an array of clinical signs which vary between the strains present. Most signs result from haemolytic anaemia or the systemic inflammatory response this generates and multiple organ failure which results.

Diagnosis of canine Babesia is most convincingly made by demonstrating the presence of organisms within infected erythrocytes, with Babesia canis usually forming pairs of pyriform organisms. The level of parasitism is often low, especially in chronic cases, which can make detection difficult. Collecting blood from peripheral capillary beds (e.g. the ear tip or nail bed) can yield a higher number of infected cells. PCR is the most sensitive and specific way of diagnosing infection, and also allows determination of the species present.

Treatment for babesiosis relies on parasite clearance and supportive care. In general, imidocarb (two doses of 5 mg/kg/IM given at a 14-day interval) is suggested as the most effective drug for parasite clearance and improvement is normally seen within 24 hours of treatment. Clindamycin is suggested until definitive treatment is available (25 mg/kg q 12h). Supportive care usually consists of intravenous fluid therapy and symptomatic treatment of clinical signs such as vomiting and diarrhoea. In cases of severe haemolytic anaemia, oxygen therapy and blood transfusions can be required.

Babesia is carried by Dermacentor reticulates and Rhipicephalus sanguineus (the Brown dog tick). Although D.reticulates is present within the United Kingdom, it is not thought to harbour babesia.

The brown dog tick (Rhipicephalus sanguineus) is only rarely found within the UK, however recent studies indicate the climate and habitat suggest it is likely to increase in prevalence. This raises the concerns that the babesia could become established in the endogenous tick population and that climate changes could favour proliferation of suitable vectors. Worryingly there are reported cases of babesia in untraveled dogs; one fatal case in Kent was postulated to have become infected after possibly encountering an infected tick entering the UK on a goods lorry (Holm and others 2006). Feline Babesiosis is rarely seen, although B. pantherea is endemic in wild cats of Africa and could be seen in zoo animals in the UK. Clinical signs are generally more subtle and cats rarely develop a haemolytic crisis.

Ehrlichia

Ehrlichia canis is a tick-borne intracellular rickettsial parasite found in southern Europe and the Mediterranean basin and leads to monocytic ehrlichiosis. Ehrlichia is transmitted by the brown dog tick (Rhipicephalus sanguineus) and disease mirrors the prevalence of this vector. Although Ehrlichia is not currently considered endemic in the UK, patients are occasionally imported with the disease and a recent case in an untraveled dog has been reported (Wilson and others, 2013) and if Rhipicephalus sanguineus becomes more prevalent (which is likely with climate change) a potential disease reservoir would be created. The organism is not passed transovarially in the tick so unexposed ticks must feed on an infected dog in the acute phase to become infected. Accurate information on the disease prevalence is not known, however cases are particularly concentrated around the south coast of France, Corsica, Greece and the southern half of Italy.

Once infected, three phases of ehrlichoisis are seen; acute, subclinical and chronic. The acute phase has an incubation period of 8-20 days and consists of non-specific signs such as fever, anorexia and lymphadenomegaly. CBC will usually reveal thrombocytopenia, leucopenia and anaemia. Dogs usually recover spontaneously before entering a period of sub clinical infection. Some dogs clear the organism at this stage, however in some dogs the organism persists leading to chronic infection. Chronic infection leads to leukopenia, thrombocytopenia and platelet dysfunction leading to severe bleeding in some cases (sub-mucosal haemorrhage and epistaxis). In this phase biochemistry will usually reveal a marked increase in globulins. German Shepherd dogs are particularly susceptible to infection, especially in younger animals.

Diagnosis can be made on the basis of PCR which is very sensitive and is effective at confirming that animal shave cleared the infection after treatment. Identification of Ehrlichia morulae in leucocytes is also diagnostic, but can be difficult and is time consuming. Blood collected from a peripheral capillary vessel is most rewarding, however morulae can also be seen in lymph node and lung aspirates.

Doxycycline is the treatment of choice (5mg/kg BID or 10mg SID for 14 to 21 days) however imidocarb can be useful in resistant infection. Supportive therapy with fluid therapy and blood transfusions may be required, depending on the patient. Steroids should also be considered if there is a life threating thrombocytopenia as it is likely that immune mediated destruction is part of its pathogenesis. A vaccine is not available and prophylactic tetracycline has been suggested for dogs at

risk, but is generally not recommended. Good tick control and prompt tick removal is essential in endemic areas.

The effects of feline Ehrlichia are not well documented, although Erhlichia like organisms have been seen in sick cats in several countries, including France. Clinical signs include fever, joint pain, anaemia, dyspnoea and lymphadenopathy.

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