Infection with *Ehrlichia canis* (Ehrlichiosis)

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Purpose

This information is intended to help veterinarians diagnose and manage cases of canine monocytic ehrlichiosis.

Contents

Acknowledgements: The Department of Industry, Tourism and Trade wishes to acknowledge the assistance and expertise of Emeritus Professor Peter Irwin of the School of Veterinary Medicine, Murdoch University, in the preparation of these guidelines. Information regarding clinical diagnosis, laboratory abnormalities, disease progression and treatment has been generously provided by Professor Irwin.

Background

Ehrlichia canis (*E. canis*) is an obligate intracellular rickettsia-like bacterium transmitted by the brown dog tick *Rhipicephalus sanguineu* which causes a severe and potentially life-threatening tick fever disease of dogs called canine monocytic ehrlichiosis (CME). The disease occurs worldwide, particularly in tropical and subtropical regions. It was first detected in Australia in May 2020, and to date has been detected in most locations across the Northern Territory (NT), as well as many communities in northern Western Australia and northern South Australia.

In rare cases, people may become infected with *E. canis* after being bitten by an infected brown dog tick. However, despite widespread evidence of the disease in dogs, and household situations where people live in close proximity to infected dogs and infected ticks, there have been no cases of human infection with *E.canis* in Australia to date.

Nature of the disease

The brown dog tick is widely distributed worldwide, including Australia, and acts as the primary vector of *E. canis*, spreading the pathogen between hosts during blood meals. The tick retains the pathogen through its life stages (transstadial transmission) and can infect hosts in both nymphal and adult stages.

Brown dog ticks use canine species as a primary host, and as such CME is predominately associated with dogs. Unexposed ticks acquire the organism after feeding on an infected dog, then transmit the infection to other dogs during successive life stages. *E. canis* can be transmitted from infected ticks to uninfected dogs within a few hours of attachment[1]. The organism can also be transmitted through blood transfusions.

E. canis infection in dogs may be referred to as CME, canine tropical pancytopenia, tracker dog disease, canine haemorrhagic fever and canine typhus.

Susceptible species

Domesticated or wild animals in the family *Canidae* including dogs and foxes are susceptible to *E. canis* infection. It is plausible that the dingo is a suitable host for *R. sanguineus* and is susceptible to infection by *E. canis*. The pathogenicity and virulence of an *E. canis* infection in dingoes is not known but is likely to be similar to disease seen in domestic dogs or other canids.

Several published reports suggest cats may also become infected, though the natural transmission pathway has not been established and infection is considered uncommon.

Infected dogs do not transmit *E. canis* to people. In rare cases, people may become infected with *E. canis* after being bitten by an infected brown dog tick. There have been no reported cases of infection with *E. canis* in humans in Australia.

Clinical signs

The disease is recognised from experimental studies to develop through three phases; acute, sub-clinical, and chronic/end stage, however the phase of infection may not be apparent based on clinical signs alone. In practice veterinarians will encounter dogs showing a range of signs, from none in the sub-clinical phase to the following:

- Fever
- Lethargy
- Anorexia
- Epistaxis
- Petechiae & ecchymosis
- Lymphadenomegaly
- Splenomegaly
- Oedema
- Muscle pain
- Vestibular disease
- Hyphema, uveitis & retinal haemorrhages
- Corneal oedema
- Weight loss
- Seizures
- Polyarthritis

[1] Fourie, J. J., Stanneck, D., Luus, H. G., Beugnet, F., Wijnveld, M., & Jongejan, F. (2013). Transmission of Ehrlichia canis by Rhipicephalus sanguineus ticks feeding on dogs and on artificial membranes. *Veterinary parasitology*, 197(3-4), 595-603.

Concurrent infection with other tick fever agents such as *Anaplasma platys* and *Babesia (canis) vogeli* are common. Infection with *E. canis* is immunosuppressive and therefore a wide variety of other co-morbidities may be present.

Laboratory abnormalities

Blood tests (haematology, serum biochemistry) and urine analysis are indicated to investigate the systemic signs of illness, bleeding diatheses and weight loss. Regardless of the stage of infection, most (if not all) dogs have thrombocytopenia, which can range from moderate to severe. In fact, dogs with a normal platelet count are very unlikely to have CME. Veterinarians suspecting ehrlichiosis are encouraged to make and examine blood smears to confirm the presence of thrombocytopenia.

Laboratory abnormalities associated with ehrlichiosis include:

- Thrombocytopenia (moderate to severe)
- Leukocytosis (early), leukopenia (late)
- Monocytosis
- Lymphocytosis (early), lymphopenia (late)
- Anaemia (mild to severe in late infection)
- Pancytopenia (late)
- Hyperglobulinaemia
- Hypoalbuminaemia
- Mild elevations in liver enzyme activities
- Mild to moderate azotaemia

Dark-staining clusters of bacteria (morulae) may be observed as intracytoplasmic inclusions in monocytes during early stages of infection. However this is rarely seen and is therefore not considered to be a reliable diagnostic indicator.

Differential diagnosis

The clinical signs above are non-specific and occur in many systemic diseases of an infectious and/or inflammatory nature, including immune-mediated diseases and neoplasia. Differential diagnoses may include anaplasmosis, babesiosis, lymphoma, multiple myeloma and immune-mediated thrombocytopenia.

Veterinarians should consider infection with *E. canis* in sick dogs with a history of tick exposure, especially in the absence of effective prevention of *tick attachment*.

Disease progression

Dogs infected recently may show a combination of signs, or the infection may go unnoticed, after which a period of asymptomatic (sub-clinical) infection lasts for several months, or potentially even years.

Later (chronic) stages of infection are associated with clinical signs and laboratory abnormalities of increasing severity and tend to be terminal in their outcome. As the infection progresses, a range of immune-complex pathologies including vasculitis, uveitis and glomerulonephritis develop as a consequence of excessive immunoglobulin production, however these antibodies are non-protective. Polyclonal and (less commonly) monoclonal gammopathies are noted and terminal bone marrow failure is associated with pancytopenia and sepsis.

Sample collection and testing

While the disease remains on the notifiable disease list, suspect cases will be tested free of charge at the Berrimah Veterinary Laboratory on a weekly basis. Please contact specimen reception on 08 8999 2249 or bvl@nt.gov.au to notify of incoming samples and confirm testing days. If the disease is removed from the notifiable disease list, testing will remain available on a fee for service basis.

Testing for notifiable diseases, including infection with *E. canis*, is not recommended using point of care tests in veterinary clinics or at non-government veterinary laboratories.

The best means of diagnosis of CME is combined polymerase chain reaction (PCR) and serology. Suitable specimens for laboratory testing include:

- EDTA blood (ideally at least 2mL) for detection of bacterial DNA by PCR testing; and
- Whole blood or serum (ideally at least 2ml) for antibody testing (serology) by enzyme-linked immunosorbent assay (ELISA). Sample may be centrifuged to obtain serum only, particularly if there is likely to be a delay in arrival at the laboratory.

There is no value in submitting tick samples for ehrlichiosis testing.

Samples should be sent to Berrimah Veterinary Laboratory - Department of Industry, Tourism and Trade, 29 Makagon Road, Berrimah NT 0828. A completed specimen advice note[2] must accompany all submissions.

Interpretation of results

Patient infection status should be interpreted based on laboratory results, clinical signs and response to previous treatment. The following matrix may be used as a guide:

PCR test result	Serology ELISA test result	
	Positive	Negative
Positive	*Acute Infection*	*Acute Infection*
Negative	*Subacute/chronic infection or recovered*	*Not infected*

Where results are indeterminate or borderline, resampling and retesting at least 14 days from first sample collection is recommended. Persistently borderline antibody results can be tested with a referral quantitative immunofluorescent antibody test (IFAT) as fee for service.

Positive PCR results indicate that there is detectable DNA of the target organism within the sample tested. It should be noted that acute infections are more likely to result in PCR positive blood samples. PCR may be negative in subacute or chronic cases of CME, as the organism may be present in circulation at very low (undetectable) levels, or be sequestered in tissue (spleen or bone marrow). The current PCR diagnostic sensitivity and specificity for *E. canis* is estimated to be greater than 90%.

Serology ELISA is a non-quantitative test which detects host antibody to *E. canis*. Antibody may take 2-3 weeks to develop from the time of infection, and this is also the usual time period for clinical signs to develop; therefore, acute, subacute, chronic and recovered infections are likely to result in ELISA positive results. The longevity of antibody varies between individuals but may remain at detectable levels for years after infection. A single antibody titre result does not indicate where in the disease process the animal is. The diagnostic sensitivity and specificity of this test is estimated at 95% sensitivity and 97% specificity.

Research is being undertaken to investigate development of a suitable point of care test option for Australia. However, this is not yet complete and use of patient-side tests is not currently recommended. State or territory government laboratories that use validated tests should be used for diagnosis of notifiable diseases. These services will continue to be recommended for diagnosis of

[2] https://industry.nt.gov.au/__data/assets/pdf_file/0011/597431/BVL-san.pdf

ehrlichiosis if the disease is declared endemic, unless or until an appropriate point of care test alternative is commercially available.

Case management

Treatment

This section has been generously provided by Emeritus Professor Peter Irwin of the School of Veterinary Medicine, Murdoch University.

Doxycycline at 10mg/kg q24h (or 5mg/kg q12h) PO, for 28 days is the recommended treatment for CME.

The stage of infection in a patient is not always clear in clinical situations, and cases treated later in the course of infection do not appear to respond so well. This can result in persistent infections and apparent failures in antimicrobial efficacy. The reason for this is not clear but may be associated with bacterial sequestration in the spleen and/or bone marrow. The earlier the infection can be treated the better the likely outcome.

Most other antibiotics are ineffective, however rifampicin at 15mg/kg PO q12h for 7 days appears to be efficacious in limited studies and would be a suitable choice if doxycycline fails to clear infection. It should be noted that rifampicin is not registered for use in animals, and under guidelines for antimicrobial stewardship, should not be used other than in exceptional circumstances, for dogs with laboratory confirmed, persistent infection with *E.canis*.

Imidocarb dipropionate can be used to treat concurrent babesiosis at a dose of 5-6mg/kg IM, repeated 14 days later, but recent literature reports reduced efficacy for CME.

The other main consideration during treatment of CME is to manage the immune-complex pathology, described above, which itself can cause significant morbidity. A short (7-10 day) course of prednisolone at anti-inflammatory dose (1mg/kg q24h PO), although untested in controlled studies, appears to help recovery and reduce complications associated with CME.

Supportive treatments (e.g. blood transfusion, fluid therapy) may be considered as indicated, however chronic ehrlichiosis associated with pancytopenia carries a grave prognosis and recovery is unlikely.

Response to treatment

Unfortunately there is no straightforward test to monitor treatment success. A positive PCR test post treatment may indicate the dog is still bacteraemic and treatment was unsuccessful, however, given the ability of the organism to sequester in tissues and be absent from circulation, a negative result does not indicate if the dog has successfully cleared the infection. Similarly serology ELISA after treatment is not useful, as antibody titres can be expected to stay high for months to years after treatment.

Additional recommendations

Dogs with suspected or confirmed ehrlichiosis should be immediately treated with a registered systemic acaricide, even where there is no visible tick burden. The owner should be informed of the future disease risk to other dogs, including the need to maintain the dog on long term effective tick control, and advised to consider treatment of the dog's home environment by a pest controller.

Owners should be provided with a copy of the Factsheet Ehrlichiosis: treatment for your dog[3].

Movement controls

Dogs with suspected or confirmed ehrlichiosis, or pending test results, may not be allowed to move interstate. Owners should be advised to check with the state biosecurity body of their destination prior to moving their dog.

Jurisdiction	Further information
Queensland	See Biosecurity Queensland website[4] or call 13 25 23.
Western Australia	See WA Department of Primary Industries and Regional Development website[5] or call (08) 9368 3929
South Australia	See SA Department of Primary Industries and Regions website[6]
Victoria	See Agriculture Victoria website[7] or call 136 186
New South Wales	See NSW Department of Primary Industries website[8]
Australian Capital Territory	Call the Biosecurity Veterinary Officer on 13 22 81
Tasmania	See Biosecurity Tasmania website[9] or call 1300 368 550

Prevention

In relation to *E. canis* there are two major categories of acaricides for dogs:

- **Topically acting products that repel and kill**: These products are applied topically (collar or spot-on) and the acaricidal active ingredients (flumethrin or permethrin) enter and remain within the lipid layer of the dog's skin and hair. These products do not need the ticks to feed, but instead they affect ticks rapidly on coming into contact with the treated dog's hair. Most ticks are repelled and will not bite the dog but will die following short exposure to the active ingredient. Two products are efficacious for the prevention of transmission of canine ehrlichiosis - Seresto® (long-lasting collar) and Advantix® (spot-on). In Australia, Seresto ® is registered to reduce the risk of transmission of *E. canis* by brown dog ticks, but Advantix ® is not. Tick repellent products are essential to protect individual dogs from infection with *E. canis*, but their use may be problematic if collar retention or regular spot-on application is difficult.

- **Systemically acting products:** These products are given to dogs either orally (tablets or chewables) or topically (spot-on application). Regardless of the method of action, the acaricidal active ingredient of these products (isoxazolines are most common) will reach the dog's bloodstream. These products require the tick to feed and ingest a lethal dose of acaricide prior to being killed, with the time from attachment to kill being from 8 to 48 hours. It is crucial to highlight that *E. canis* can be transmitted within 3 hours of tick attachment, which is faster than most isoxazolines kill ticks. Consequently, systemically-acting products are not able to prevent the transmission of *E. canis* to dogs from the tick, and are not registered for the prevention of canine ehrlichiosis. While isoxazolines are highly effective acaricides and are useful to kill the brown dog tick vector in settings where reducing the

[3] https://nt.gov.au/__data/assets/pdf_file/0005/899501/ecanis-treatment-for-your-dog-information-sheet.pdf
[4] https://www.business.qld.gov.au/industries/farms-fishing-forestry/agriculture/livestock/animal-welfare/pests-diseases-disorders/canine-ehrlichiosis
[5] https://www.agric.wa.gov.au/ehrlichiosis
[6] https://pir.sa.gov.au/biosecurity/animal_health/ehrlichiosis_disease_in_dogs
[7] https://agriculture.vic.gov.au/biosecurity/animal-diseases/general-livestock-diseases/ehrlichiosis
[8] https://www.dpi.nsw.gov.au/biosecurity/animal/humans/ehrlichia-canis
[9] https://dpipwe.tas.gov.au/biosecurity-tasmania/animal-biosecurity/animal-health/ehrlichiosis

rate of community transmission of ehrlichiosis is important, these products are not recommended as the sole method of tick control to prevent ehrlichiosis.

Dogs that live in high-risk situations may benefit from the application of both repel and kill and systemically acting products. However, the majority of dogs can be efficiently protected from ehrlichiosis with the use of repel and kill products only. It is important to keep in mind that no product can offer 100% efficacy against ticks, and therefore, no topically acting tick repellent can provide 100% protection from ehrlichiosis.

A summary of acaricidal options for dogs is provided below, however please note this list is not exhaustive and there may be additional registered products available.

Acaricide type	Active acaricide	Brand name	Route	Frequency of administration	>90% proven efficacy for prevention of ehrlichiosis?
Isoxazoline	Sarolaner	Simparica (Zoetis)	Oral	Monthly	No
	Afoxolaner	Nexguard (Boehringer Ingelheim)	Oral	Monthly	No
	Fluralaner	Bravecto (Intervet)	Topical or oral	3-monthly	No
	Lotilaner	Credelio (Elanco)	Oral	Monthly	No
Repel and kill	Flumethrin	Seresto (Bayer-Elanco)	Collar	8-monthly	Yes[10]
	Permethrin	Advantix (Bayer-Elanco)	Spot-on	Monthly	Yes[11]
	Delamethrin	Scalibor (Intervet)	Collar	6-monthly	No

The combined use of a repel and kill product **and** a systemic isoxazoline may provide broader spectrum protection for an individual dog, reduce individual tick burden and minimise the spread of disease.

In summary, it is recommended that dog owners use an integrated tick control strategy which includes:

- Keeping dogs up to date a tick control program which includes registered tick repellents (primary protection) and tick control products (secondary protection).
- Avoiding taking dogs into tick-infested areas.
- Having any tick infestations in the house or yard managed by a pest controller.
- Inspecting dogs daily for ticks, especially if they live or have visited a tick-infested area.

[10] Stanneck, D., & Fourie, J. J. (2013). Imidacloprid 10%/flumethrin 4.5% collars (Seresto®, Bayer) successfully prevent long-term transmission of Ehrlichia canis by infected Rhipicephalus sanguineus ticks to dogs. *Parasitology Research*, 112, 21-32.
[11] Fourie, J. J., Luus, H. G., Stanneck, D., & Jongejan, F. (2013). The efficacy of Advantix® to prevent transmission of Ehrlichia canis to dogs by Rhipicephalus sanguineus ticks. *Parasite*, 20.