





# **DR. KATHRYN REIF**

Dr. Kathryn Reif is an assistant professor at the Department of Diagnostic Medicine/Pathobiology in the College of Veterinary Medicine at Kansas State University. Her primary research interests center around the control and prevention of ticks and tick-borne diseases important to companion animal, livestock and human health. Current research projects include evaluation of antimicrobial treatment efficacy for anaplasmosis, tick-borne pathogen vaccine development, assessment of tick-borne pathogen genetic diversity, and development of novel techniques to study tick feeding and pathogen transmission. In addition to research pursuits, Dr. Reif enjoys outreach opportunities with the general public and health professionals to discuss the risks of ticks and tick-borne pathogens and tick safety.











Canine borreliosis (Lyme disease), caused by *Borrelia burgdorferi* sensu lato species, is the most common tick-borne disease of dogs and humans in the temperate northern hemisphere.

# Geography

The primary factor driving the geographic distribution of this disease is distribution of the tick vector species which favor temperate climates. The geographic distributions of tick vectors responsible for transmitting canine borreliosis extend over expansive ranges in **North America** and **Eurasia**.

Within a given geographic area the following factors collectively influence the risk of canine borreliosis:





# Local environment

Within a local environment, tick vector populations have a heterogenous distribution. These tick vector species are most commonly encountered in deciduous or mixed-wood areas that provide favorable habitat for ticks (ambient temperatures and humidity) as well as tick host and *B. burgdorferi* s.l. reservoir species.





# Favorable climate conditions

Canine borreliosis is most commonly reported in temperate global regions with climates suitable for supporting the associated tick vector species.

Humidity and host species availability are factors that greatly influence the population density of the primary tick vector species as these vectors are easily susceptible to desiccation and require hosts to feed upon to progress through their life cycle, respectively.









# **Evidence of infection/disease spread**

Increasing and expanding populations of tick vector species are contributing to the increasing spread of canine borreliosis. For example, in North America, geographic distribution of the primary tick vector has more than doubled over the last 20 years. In North America, historic endemic regions included New England and the upper mid-west in the United States; however, the disease is now endemic in most northeastern and mid-Atlantic states and is moving into the Southern Midwest region and westward towards the Great Plains.

Historically endemic areas are experiencing seroprevalence stabilization in dogs or even reduction, however, seroprevalence rates in these areas are still high. Canine borreliosis is now well-established in Southern Canada...





In Europe, tick vector populations have expanded northward into Scandinavia and into higher altitudes in southern regions, also beyond their historic ranges.

Variables contributing to disease spread include:



The increasing distribution of tick vector species

Host species abundance





Climate change







# An introduction to the causative agent(s)

Canine borreliosis (Lyme disease, Lyme borreliosis) is a disease caused by pathogenic tick-borne spirochetal bacteria within the lyme borreliosis group of the genus *Borrelia* in the family Spirochaetaceae.

These bacteria are highly mobile, propelling themselves through the host using periplasmic axial filaments. They are slow-growing, microaerophilic spirochetes with a complex outer membrane composed of lipoproteins and a peptidoglycan layer which classifies them as Gram-negative. Both the ability to move within the host and the ability to vary the composition of their outer surface lipoproteins are important mechanisms these spirochetes use to evade host immune responses.

Borrelia burgdorferi. Stained, culture propagated *B. burgdorferi* spirochetes (40X).



At least 53 species have been described within the genus *Borrelia* and these can be classified in three groups:

Agents of lyme borreliosis: approximately 22 species)

Agents of relapsing fever: approximately 29 species)

A third genetically distinct and largely uncharacterized group: approximately 2 species, found in reptiles.

Lyme borreliosis bacteria belong to the *Borrelia burgdorferi* sensu lato (s.l.) complex which contains approximately 19 genospecies, with multiple strains comprising each genospecies (Table 1).





# Vector (lifecycle)

Ticks in the genus *Ixodes* are the most common vectors of *B. burgdorferi* s.l. Over 18 *Ixodes* species contribute to the maintenance of *B. burgdorferi* s.l. species in nature; however, a handful of species serve as primary transmission vectors of these pathogens to dogs and people. Deer are perhaps the most important wildlife host species maintaining tick populations. Rodents are perhaps the most important wildlife species for maintaining *Borrelia* spp.

The predominant vectors of borreliosis are:

In North America

Click on **H** for more information

#### VECTOR BORNE DISEASE

The broad host range and expansive geographic distribution of these major *Ixodes* species underpin their success as *B. burgdorferi* s.l. transmission vectors.



*Ixodes species.* Attached *Ixodes scapularis* female and male.



# **Proportion of infected vectors**

The proportion of ticks infected with *B. burgdorferi* in a given area is heterogeneous and can vary dramatically from <1% to almost 100%. The number of bloodmeals a tick has taken

is **positively correlated** with infection risk.

These ticks generally feed once per life stage, therefore a host-seeking nymph has had one opportunity to acquire the pathogen during its larval blood meal while a host-seeking adult has had two prior opportunities to acquire the pathogen during its larval and nymphal blood meals.





U.S. areas with high proportions of *B. burgdorferi*-infected ticks tend to be in the mid-Atlantic, upper Midwest, and New England areas. In Europe, countries with high proportions of *B. burgdorferi* s.l.-infected ticks tend to be in Central and Eastern Europe.

Factors that influence the proportion of infected vectors:

VECTOR BORNE DISEASE

# Reservoirs

Canine borreliosis agents are maintained in nature in enzootic cycles involving competent tick vectors and wildlife reservoirs (see table 1).

Dogs and humans are accidental and most often dead-end hosts and do not contribute to maintaining these agents in nature. Multiple vertebrate species serve as reservoirs for *B. burgdorferi* s.l. including numerous mammals, birds and reptiles.



Infection with *B. burgdorferi* s.l. has been observed in over 300 vertebrate species; however, not all these vertebrates are equally important in maintaining *B. burgdorferi* s.l. in nature. Depending on the *B. burgdorferi* genospecies, some vertebrate hosts are more important in maintenance than others. Some genospecies have developed highly specialized host preferences and can only infect certain vertebrate species, whereas other genotypes are more 'generalists' in their reservoir species use.



# **Probability of transmission and routes of transmission**

The longer an infected tick is attached, the greater the probability of *B. burgdorferi* s.l. transmission.

Although transmission time may vary, transmission of B. *burgdorferi* s.l. is significantly greater once the infected tick has been attached for 36-48 hours.





> 90%

if the tick feeds completely

#### VECTOR BORNE DISEASE

Transmission appears to occur a little more quickly with for some European *B. burgdorferi* s.l. genospecies and strains compared to North American strains. Most *B. burgdorferi* s.l. transmission studies used *B. burgdorferi* sensu stricto, and transmission timing information on other genospecies or strains is lacking.

Factors that may influence transmission timing:

*B. burgdorferi* s.l. genospecies/strain differences

- Interrupted tick blood meal
- Simultaneous feeding of multiple-infected ticks
- Co-infecting microbes in the tick



# **Transmission mechanisms**

life cycle stage.

Click on **H** for more information

#### VECTOR BORNE DISEASE

#### Borreliosis agents are typically acquired by ticks during their larval or nymphal blood meals when feeding on an infected wildlife host. Once infected, *Ixodes* ticks can transmit *B. burgdorferi* s.l. during their next blood meal which typically occurs in their next



# **WHAT BEHAVIORS** PUT A DOG AT RISK FOR THE DISEASE?



# CAN A DOG BE INFECTED AND NOT SHOW SIGNS?



#### Infection *vs* disease



#### VECTOR BORNE DISEASE



Risk to the population from subclinically diseased dogs



Tests that reveal a subclinically infected dog



# Pathogenesis

*B. burgdorferi* inoculated via tick saliva into skin disseminate in the blood stream from the tick bite site to distal, typically collagen-rich, tissues. Some *B. burgdorferi* genospecies have a greater predilection for certain host tissues compared to others.

Infection is recognized by the host's immune response and the extent of the response correlates with the amount of pathologic change. **Excessive innate and adaptive immune responses** can occur in the infected tissue (e.g. joint).

#### VECTOR BORNE DISEASE

Excessive innate immune responses can lead to increased disease severity associated with overproduction of proinflammatory cytokines and chemokines upon recognition of bacterial surface proteins by Toll-like receptors. An excessive adaptive immune response also contributes to disease pathogenesis where accumulation of pathogen specific antigen/antibody immune complexes in tissues (e.g. joint, kidney) promote inflammation and immune-mediated disease at these sites.



# Early signs

There are no pathognomonic canine borreliosis clinical signs and only about 5-10% of infected dogs develop overt clinical signs.

#### **Most common signs:**



#### VECTOR BORNE DISEASE

Unlike the disease in people, dogs generally do not develop clinical signs until several weeks (>4 weeks) to several months post-infection. They are also largely non-specific, making diagnosis difficult based on clinical signs alone. The most common clinical presentation of canine borreliosis is an acute mono- or polyarticular lameness (shifting leg lameness) with joint swelling and fever. Dogs do not develop the characteristic bull's eye rash (*erythema migrans*) reported frequently in people.





# Progression

Most dogs that experience subclinical disease or mild to moderate clinical disease will resolve the infection with or without treatment; however, antimicrobial treatment can greatly facilitate recovery.

Progression to more severe disease occurs in a small percentage (< 2%) of infected dogs.

Disease progression is linked to the degree of the individual animal's immune response to infection leading to immune-mediated tissue injury. This is most common in joint tissues (arthritis) and hypothetically in kidneys (nephritis). The specific tissue affected in severe disease is heavily influenced by the infecting *B. burgdorferi* s.l. genospecies. There are experimental studies examining *B. burgdorferi* s.s. disease pathology in dogs, but disease development in dogs caused by other *B. burgdorferi* genospecies is not described.





# **Prognostic factors**

A small percentage of dogs develop clinical signs of disease and seropositive clinically healthy dogs have a good chance of resolving infection with or without treatment.

Seropositive dogs displaying mild to moderate signs of infection (e.g. fever, arthralgia, lameness, anorexia) have a good **recovery prognosis** and tend to rapidly respond to antimicrobial treatment.

Seropositive dogs with signs of immune-mediated inflammation, possibly a result of *B. burgdorferi* antigen/host antibody complexes in kidney or other tissues, have a poorer prognosis even with antimicrobial treatment.





# **Recovery indications**

Clinical recovery assessment based on observation of reduced pathogen infection level is difficult because clinical signs are more associated with the animal's immune response to the pathogen rather than the pathogen. Quantitative serology assays are available to monitor titers, which should decrease if the animal is not re-exposed or infected during the recovery or treatment period – and re-exposure is likely for dogs living in endemic areas. Seroconversion does not make a dog immune from re-infection or disease, and seropositive dogs remain susceptible to infection with other *B. burgdorferi* s.l. genospecies or heterologous strains of the same genospecies. Dogs experiencing severe immune-mediated disease signs suspected to be caused by *B. burgdorferi*-s.l. infection have a poorer prognosis.





# WHAT DIAGNOSTIC TESTS SHOULD BE RUN IN A DOG THAT IS SUSPECTED TO HAVE THE INFECTION/DISEASE?

# Rapid, table-side

They are the most common assays used to diagnose canine borreliosis.

These table-side tests are frequently administered during routine annual health assessments to monitor exposure/ infection of dogs to *Borrelia* and other vector-borne pathogens. Multiple commercial table-side assays are available, with assays differing in the specific pathogen antigens for which they recognize antibody.

# In hospital using microscope or similar equipment

**Direct detection** of *B. burgdorferi* (e.g. evaluation of thin blood smears, etc.) is not recommended. When spirochetes are observed on a thin blood smear, these are more likely a relapsing fever *Borrelia* species rather than a *B. burgdorferi* s.l. species.

Detection in histological preps or using molecular assays is also inefficient as the number of organisms in host tissues is low. Growing borreliae from infected host tissue is an option to confirm the infection; however, most hospitals or labs are not set up to conduct these labor and time intensive cultures.





### WHAT DIAGNOSTIC TESTS SHOULD BE RUN N A DOG THAT IS SUSPECTED TO HAVE THE INFECTION/DISEASE?

# Laboratory testing

There are multiple additional commercial and in-house serologic-based diagnostic assays available from commercial, government, and university diagnostic laboratories.

- These assays may test for antibodies against single antigens or a combination or antigens to evaluate B. *burgdorferi* s.l. exposure/infection.
- Diagnosis by direct observation of the pathogen (biopsy) culture) or pathogen DNA (molecular-based tests such as PCR) is difficult, especially at later stages of infection, because the pathogen migrates quickly away from the initial site of inoculation through the bloodstream into favored collagen-rich tissues.





### WHAT DIAGNOSTIC TESTS SHOULD BE RUN IN A DOG THAT IS SUSPECTED TO HAVE THE INFECTION/DISEASE?

# **Test interpretation**

Serologic assays, the most common tests used to diagnose canine borreliosis, detect pathogen-specific antibody in the dog, not the pathogen. Seroconversion occurs approximately four weeks after initial infection, therefore recently infected dogs may test seronegative (*B. burgerdorferi* s.l.-infected dogs rarely display clinical signs before serocoversion).

Based on the serologic assay antigen target, tests may differ in their ability to differentiate:

- **Exposed versus infected dogs**
- Infected versus vaccinated dogs
- Active versus past infection (IgM versus IgG)
- *B. burgdorferi* versus other *Borrelia* species (e.g. relapsing fever *Borrelia* species)

#### VECTOR BORNE DISEASE

Most serologic-based tests are qualitative and provide a yes/no response; however, laboratory-based quantitative serologic assays are available (that can be useful in monitoring antibody titer changes to determine infection progression, treatment response, or re-infection).

For **seropositive dogs,** other laboratory tests (e.g. CBC, serum chemistry, urinalysis to test for proteinuria) are useful to facilitate treatment decisions.

*B. burgdorferi*-specific antigen/antibodies complexes may be the cause of protein-limiting nephropathy in seropositive dogs; however, no staining techniques are validated for identification of these immune complexes and confirmation of *B. burgdorferi* s.l. instigated nephritis is difficult.



#### WHAT DIAGNOSTIC TESTS SHOULD BE RUN N A DOG THAT IS SUSPECTED TO HAVE THE INFECTION/DISEASE?

# Acute vs convalescent

Titer changes can be used to help discern whether a dog is actively infected or recovering from a previous infection. Monitoring antibody titers can be used to assess treatment response, infection relapse, or re-exposure – which is common for dogs in endemic areas. The best antibodies used for assessing convalescence are against antigens expressed after the borreliae infects the vertebrate host, such as the VIsE C6 antigen or OspF, both of which wane upon successful treatment or natural resolution of infection.







# WHAT GENERAL TREATMENT STRATEGY IS RECOMMENDED FOR SICK DOGS?

## Types of drugs to use

Tetracycline and beta-lactam antimicrobials are the primary drug classes used to treat canine borreliosis.

# Monotherapy or combination therapy

Mono therapy with a tetracycline or beta-lactam antibiotic is usually successful for treating canine borreliosis. Doxycycline and minocycline, at 10 mg/kg for 30 days, are the most frequently used antimicrobial regimens. Several other antimicrobial treatment options including beta-lactams have also been successful. A list of antimicrobial treatment options provided in the ACVIM Consensus is included (Table 2). *B. burgdorferi* s.l. replicate slowly and owner compliance with administering the full antimicrobial regimen is important for successful infection control. Combination therapies may be indicated when a dog is coinfected with other pathogens or supportive care may be needed to manage associated chronic disease symptoms (e.g arthritis or glomerulonephritis) (Table 2). Treatment is generally recommended for seropositive dogs displaying canine borreliosis clinical signs or asymptomatic dogs with evidence of protein-limiting nephropathy. However, treatment of seropositive, non-clinical, non-proteinuric dogs is more controversial.



#### WHAT GENERAL TREATMENT STRATEGY IS RECOMMENDED FOR SICK DOGS?

# Supportive treatment strategies

Dogs with suspected *B. burgdorferi* s.l.-related arthritis may benefit from:

Analgesics (preferred)



S Glucocorticosteroids (if immune-mediated arthritis is suspected).

In addition to antimicrobial treatment, **supportive treatment** of seropositive dogs with protein-limiting nephropathy or glomerulonephritis should follow recommendations for immune-complex glomerulonephritis standard of care guidelines.







#### WHAT GENERAL TREATMENT STRATEGY **S RECOMMENDED FOR SICK DOGS?**

# Monitoring for response to treatment

In general, dogs that experience mild to moderate borreliosis clinical signs and receive treatment have a good recovery prognosis and signs generally resolve within the first few days after treatment initiation.



Treatment response in symptomatic dogs, including dogs with lameness, is often observed within the first few (1-3) days of treatment.



S Dogs that naturally self-resolve infection or are successfully treated can maintain **serum antibody levels** for several months to several years depending on the specific antibody test.







#### WHAT GENERAL TREATMENT STRATEGY S RECOMMENDED FOR SICK DOGS?

# Management of co-infections

Multiple other **bacterial**, **viral**, and **protozoal** pathogens are carried in the same *lxodes* species vectors.

Therefore, dogs bitten by these ticks can be co-infected with multiple pathogens. Co-infection or successive *B. burgdorferi* s.l. infection(s) can complicate diagnosis and assessment of treatment response.

Doxycycline and similar tetracycline antimicrobials are commonly used for the treatment of most tickborne bacterial diseases, and dogs experiencing **co**infection with multiple tick-borne bacterial **pathogens** should respond to this treatment as well.

VECTOR BORNE DISEASE

**Co-infection of other pathogens such as** *Babesia* **species protozoa**, also transmitted by *lxodes* species, may complicate the clinical picture and dogs may require additional diagnostic tests to confirm coinfection and may require additional therapeutics for disease management.



# **ARE OTHER PETS OR PEOPLE IN THE HOUSE** AT RISK?

# The risks to people from an infected/sick dog

*B. burgdorferi* infected dogs do not pose a direct risk to other people or pets within the household. This pathogen quickly leaves the bloodstream, and blood-to-blood contact between an infected dog and other household members poses virtually no transmission risk.

# Other public health considerations

Owners and dogs share many of the same risk factors for encountering *B. burgedorferi* s.l.-infected ticks, and dogs can serve as sentinels for borreliosis risk in humans. A dog that is seropositive for *B. burgdorferi* s.l. has been in an area with infected ticks. Dogs typically travel with their owners, and it is likely that the owner was in the same area with infected ticks. *B. burgdorferi*infected ticks can be found in urban, suburban, and rural areas as long as suitable environmental microhabitats, reservoir hosts, and tick vector species are present. Owners living in areas of new tick introduction may be less familiar with the hazard that these parasites represent.





# **ARE OTHER PETS OR PEOPLE IN THE HOUSE** AT RISK?

# Can cats get this infection/disease?

Cats experimentally-infected with *B. burgdorferi* did not develop clinical signs, however they seroconverted, and pathogen DNA was recovered from tick inoculation site biopsies.

Cats living in **endemic areas** are susceptible to being bitten by *B. burgdorferi* s.l.-infected ticks.

Feline borreliosis is controversial and some veterinarians in endemic regions report cases of cats with **clinical signs.** Certain *Borrelia* genotypes or strains may be more likely to cause clinical signs in cats; however, additional research is needed.





# How to avoid the vector

**Complete avoidance of vector ticks** eliminates any canine borreliosis risk; however, this is difficult as vector tick populations are increasing in density and distribution in rural, suburban, and urban areas. To reduce exposure to tick vector species, dogs should avoid or limit the amount of time walking in areas with vegetative ground litter under tree canopies or along areas adjacent to unmaintained vegetative areas and avoid resting in treeor shrub-shaded areas where other tick hosts may also rest. Check dogs moving through potential infested areas for ticks, focusing especially around the ears, eyes, collar, paws and groin area. Regular 'tick checks' also help prevent inadvertent transfer of ticks at home where other pets or people may get bitten.



Complete avoidance of *B. burgdorferi* s.l.-infected ticks is difficult and may reduce quality of life, therefore dogs should receive tick-preventive products throughout the year. Safe and effective commercial **acaricidal and** repellent products are available for tick control on dogs and cats.

Products that prevent or rapidly kill attached ticks are preferred to protect dogs from tick-borne pathogens such as *B. burgdorferi* s.l.
Owner compliance is vital for success and the product that is not administered will not work, regardless of product choice. The "best" tick preventive product is the one an owner will compliantly administer. Longer acting products can help to improve owner compliance with recommended treatment schedules.



#### VECTOR BORNE DISEASE

Repellent products that reduce/prevent attachment are primarily synthetic pyrethroid compounds such as permethrin, deltamethrin and flumethrin. These repellent compounds are commonly topically applied and have acaricidal effects that kill ticks upon prolonged contact.



# Is routine testing recommended?

Routine annual testing of dogs living in endemic areas is recommended and is often integrated into annual checkups. Annual evaluation of these tests helps to monitor dog exposure, parasiticide products efficacy, vaccine efficacy, and general disease risk for other household members (e.g. other pets or owners) from vector exposure.



#### VECTOR BORNE DISEASE

# General thoughts on preventive treatments

Tick avoidance can be difficult and impractical as a sole prevention method and use of tick preventive products is the best strategy to reduce the likelihood of dogs being bitten by *B. burgdorferi* s.l.infected ticks potentially leading to canine borreliosis (or infection with other tick-transmitted pathogens).

A changing climate and increasing tick populations are increasing the risks for dogs. In areas where monthly temperature highs exceed 4°C (40°F), dogs will benefit from year-round tick control because ticks are commonly active above this temperature. Riskbased decisions based on location, dog breed, travel, vaccine availability and veterinary consultation will help determine whether a dog would additionally benefit from vaccination.



Strategies to encourage owner compliance with tick preventive products:

- Identifying a product that the client will most compliantly administer.
- S Education regarding tick activity.

Increasing awareness about risk of tick-borne pathogens.

Client education on the risks of ticks and tick-borne pathogens in their local area can be very effective to keep clients engaged in practicing active tick prevention strategies (e.g. compliantly using tick preventive **products** or vaccination).



Timely and regionally pertinent information, or links to such information, about ticks and tick-borne diseases in a client's local area are most useful.





# Is there a vaccine?

For dogs living or visiting canine borreliosis endemic areas, vaccination in combination with use of tick preventive products is an effective strategy for further protection against canine borreliosis. These vaccines are available in many areas and consist of either bacterins (whole killed borreliae) or specific recombinant or chimeric outer surface proteins (e.g. OspA, OspC) and may be adjuvanted or non-adjuvanted. Vaccination-induced antibodies against OspA are thought to work by entering the tick during early stages of feeding and killing the borreliae inside the tick before they are transmitted to the dog. Vaccine-induced antibodies against OspC are thought to help kill or control borreliae during early infection in the dog around the tick bite site. However, because *lxodes* ticks can carry other pathogens, for which vaccines are not available, it is not recommended to use vaccine in lieu of tick-preventives as the tick species that transmit B. burgdorferi s.l. also serve as vectors for other pathogens (e.g. A. phagocytophilum, Babesia spp.) that can also infect and cause disease in dogs.



![](_page_38_Picture_5.jpeg)

# WHAT DOES THE FUTURE LOOK LIKE?

# What are the changes being seen with the disease?

- Canine borreliosis is an expanding threat to dogs and Lyme borreliosis is an expanding threat to people as tick vector populations intensify and expand.
- **Information** regarding the prevalence, likelihood of infection, likelihood of disease development, and clinical signs of disease associated with different *B. burgdorferi* genospecies and strains is increasing.
- Studies are needed on how disease manifestations differ in dogs infected with different *B. burgdorferi* s.l. genospecies or strains, and such information would be valuable in further developing strategies for disease intervention and therapy.

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# WHAT DOES THE FUTURE LOOK LIKE?

![](_page_40_Picture_1.jpeg)

![](_page_40_Picture_3.jpeg)

### WHAT DOES THE FUTURE LOOK LIKE?

# Has resistance to prevention or reduced treatment effect been seen?

Tick populations and borreliosis risk are influenced by a multitude of complex and interwoven variables, and an integrated management plan that considers multiple variables (which may be unique to a given area) is necessary to reduce vector tick populations and mitigate disease risk.

**Disease control** 

VECTOR BORNE DISEASE

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#### **Tick control**

![](_page_41_Picture_7.jpeg)

# **FURTHER READING**

#### Websites

Centers for Disease Control: Lyme disease. https://www.cdc.gov/lyme/

Companion Animal Parasite Council. https://capcvet.org/

Companion Vector-Borne Diseases: Lyme borreliosis. http://www.cvbd.org/en/tick-borne-diseases/lyme-borreliosis/

European Centre for Disease Prevention and Control: Borreliosis. https://www.ecdc.europa.eu/en/borreliosis

European Scientific Counsel Companion Animal Parasites: Control of Vector-borne diseases in dogs and cats. https://www.esccap.org/uploads/ docs/znkh6j1d\_0775\_ESCCAP\_Guideline\_GL5\_v8\_1p.pdf

International Renal Interest Society. http://www.iris-kidney.com/

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