

The A-Z's of Tick Borne Disease

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Objectives

- (1) Review important pathogens and their diagnosis and treatment.
- (2) Discuss new developments and future trends in tick-borne disease.

A is for *Anaplasma*

There are two important species that cause disease in dogs: *Anaplasma phagocytophilum* and *Anaplasma platys*. *A. phagocytophilum* is the agent of canine granulocytic anaplasmosis and is found in the upper Midwest, northeast and western states. It is primarily transmitted by the tick *Ixodes ricinuspersulcatus* in the nymph and adult stages following a tick feeding on a wild animal reservoir as larvae or nymphs. After transmission the organism hijacks neutrophils and inhibits their activity. The organism delays neutrophil apoptosis and persists longer in the host. The vast majority of dogs infected with *A. phagocytophilum* develop no or very mild clinical signs. Clinical animals typically present with fever, lethargy, inappetance and lameness. Additional signs may include bleeding, enlarged lymph nodes and neurologic abnormalities. Diagnosis can be achieved by PCR or acute and convalescent serology. Point-of-care ELISA technology is widely used. Positive tests are suggestive but not definitively diagnostic of infection. This technology does not differentiate between *A. phagocytophilum* and *A. platys*. The treatment of choice is doxycycline 5 mg/kg q12 for 14 days. Dogs positive on point-of-care serologic tests typically do not warrant treatment in the absence of clinical signs but complete blood count should be recommended to monitor for hematologic changes.

Reference: Sykes Ch. 29

B is for *Babesia*

Dogs are infected by three main species: *Babesia canis*, *Babesia gibsoni* and *Babesia conradae*. Cats are infected by: *Babesia felis* and *Babesia felis*. Several other unnamed species likely cause disease. They are transmitted by a variety of tick species and are distributed worldwide. General clinical signs include lethargy, pallor (anemia) and splenomegaly. *Babesia canis* is the most commonly diagnosed form of canine babesiosis. There are three main subspecies (*vogeli*, *canis* and *rossi*). The main tick that transmits *B. canis vogeli* is the brown dog tick/kennel tick. Kenneled dogs are at higher risk (i.e. greyhounds). *Babesia gibsoni* is mainly transmitted by *Haemophysalis spp.* and fighting behavior. American Pitbull Terriers are overrepresented. Perinatal transmission may also play a role. Feline babesiosis is poorly understood and is mainly diagnosed in southern Africa. Treatment of choice is combination atovaquone (15 mg/

kg PO q8 for 10 days) combined with Azithromycin (10 mg/kg PO q24 for 10 days). Diagnosis is typically by cytologic examination and PCR assays. Other options include imidocarb (for *Babesia canis*) and combinations of antimicrobial therapies.

Reference: Sykes Ch. 75

C is for *Cytauxzoon* (also CATS!)

Cytauxzoon felis is a protozoal parasite of felids (bobcat is reservoir species). It is transmitted by *Amblyomma americanum* (Lone Star Tick) in the southern USA. Cases have been reported in the midatlantic region. The parasite infects mononuclear cells which distend and obstruct venules and capillaries until they undergo schizogony. The piroplasts release from mononuclear cells infect RBC's which are then transmitted back to the ticks. Clinical signs include severe anemia, icterus, dyspnea, fever and lethargy. Treatment of choice is combination atovaquone (15 mg/kg PO q8 for 10 days) combined with Azithromycin (10 mg/kg PO q24 for 10 days). Diagnosis is typically by cytologic examination and PCR assays.

Reference: Sykes Ch. 76

D is for Doxycycline

Doxycycline is a tetracycline antibiotic that reaches high intracellular concentrations. It's mechanism of action is inhibition of the 30s subunit of the bacterial ribosome. Use is contraindicated in young animals (<4 weeks) due to potential enamel hypoplasia. Cats are predisposed to esophagitis/esophageal stricture. Typically dosed 5 mg/kg BID. Doxycycline is also thought to have anti-inflammatory effects which may play a role in therapy as well. Mainly excreted in the bile.

E is for *Ehrlichia*

There are three important species that cause disease in dogs: *Ehrlichia ewingii*, *Ehrlichia canis* and *Ehrlichia chaffeensis*. *Ehrlichia canis* is the agent of canine monocytic ehrlichiosis but chronic infection can progress to a severe form often referred to as "tropical canine pancytopenia." It is found worldwide but is most prevalent in tropical and subtropical environments. It is primarily transmitted by the tick *Rhipicephalus sanguineus* (Brown Dog Tick). Clinical signs of acute infection typically occur 8-20 days after infection. It has a tropism for mononuclear phagocytes. It ruptures infected cells and can spread to new cells in the host. Immune mediated mechanisms contribute greatly to clinical signs such as fever, lethargy, inappetance and lameness. These animals may also have bleeding tendencies secondary to thrombocytopenia and platelet dysfunction. Dogs typically spontaneously recover within 2-4 weeks and either clear the infection or become subclinically infected for months to years. Chronic infection is rare and only develops in some dogs. The presence of pancytopenia is typical of chronic infection. Marked granular lymphocytosis may occur and dogs with persistent

lymphocytosis should be checked for *E. canis*. Diagnosis can be achieved by PCR for acute infection. Chronic infection is typically diagnosed by detection of extremely high IFA titers. Treatment of CME has variable success and should be based on improvement of clinical signs. Doxycycline is the mainstay of therapy but chloramphenicol and imidocarb have been used with varying success.

Ehrlichia ewingii (more common in dogs) and *Ehrlichia chaffeensis* (more common in people and unknown role in dogs) both infect granulocytes (neutrophils). Both are transmitted primarily by *Amblyomma americanum* (Lone Star Tick). They typically cause fever, lethargy and polyarthritis. Point-of-care ELISA technology is widely used for diagnosis. Positive tests are suggestive but not definitively diagnostic of infection. This technology does not differentiate between *E. canis* and other species. The treatment of choice is doxycycline 5 mg/kg q12 for 14 days for *E. ewingii/ chaffeensis* and 21 days for *E. canis*. Treatment of seroreactive animals with normal bloodwork is controversial but not currently recommended. Yearly monitoring should be instituted for animals with positive *Ehrlichia* tests if *E. ewingii* infection is not confirmed.

Reference: Sykes Ch. 28

F is for Fever from the Rocky Mountain that is Spotted

Rocky Mountain Spotted Fever (RMSF) is an acute illness of dogs and people caused by the agent *Rickettsia rickettsia*. It is transmitted by several different ticks (*Dermacentor*, *Rhipicephalus*, *Amblyoma*) and is therefore distributed throughout North America. The organism infects endothelial cells and leads to a clinical syndrome consistent with vasculitis. Signs include fever, vomiting, ocular signs, peripheral edema, cutaneous hyperemia and necrosis. This can be life threatening and therapy (doxycycline) should be begun before laboratory diagnosis by PCR or serology.

Reference: Sykes Ch. 30

G is for Galactose-alpha-1, 3-galactose

Fun fact: Mammalian Meat Allergy is linked to bites from the Lone Star Tick. Transmitted carbohydrate after a tick bites an animal and then a human. Human develops antibodies against "alpha-gal." Unlikely to occur in dogs since alpha-gal is a self-antigen.

H is for Hepatozoon

H. americanum and *H. canis* are the main agents of domestic dog disease. Only *H. americanum* is endemic to the USA. Clinical signs include lethargy, fever, weight loss, locomotor abnormalities and signs of protein losing nephropathy. Transmission occurs to dogs after ingestion of an infected tick. Sporozoites of the protist are released into the GI tract and they infect host cells and they migrate to muscles and encyst. Matured "meront" ruptures and releases "gamonts." These move into canine blood which are ingested by ticks where sexual

reproduction occurs. Paratenic hosts (rodents/lagomorphs) may also play a role in the disease cycle. Diagnosis includes cytologic examination, PCR assays or muscle histopathology. Therapy is referred to as "TCP": TMS (15 mg/kg PO q12 for 14 days), Clindamycin (10 mg/kg q8 for 14 days) and Pyrimethamine (0.25 mg/kg PC q24 for 14 days). Two years of decoquinatate (coccidiostat) is recommended following therapy.

Reference Sykes Ch. 77

I is for Infectious *Bartonella*

Canine and feline bartonellosis can present in a variety of ways including: endocarditis, lymphadenopathy and uveitis. *Bartonella vinsonii* is one of the most commonly identified organisms in dogs. It appears to be transmitted by *R. sanguineus*. Diagnosis is typically by PCR detection. Galaxy Diagnostics offers a culture enrichment step prior to PCR and is currently and widely considered the gold standard. Combination therapy with a fluoroquinolone and doxycycline is considered gold standard for therapy.

References: Sykes Ch. 52

<https://cvm.ncsu.edu/wp-content/uploads/2016/05/Bartonellosis.pdf>

K is for Ko-Infections

It is important to note that co-infections often occur and this complicates understanding the relevance of infections on clinical presentation. A good example is that *Bartonella vinsonii* is commonly co-transmitted with *Ehrlichia canis*.

L is for Lyme Borreliosis

Transmitted by the tick *Ixodes scapularis*, the pathogen *Borrelia burgdorferi* is a common agent of tick-borne disease in the United States. Clinical infection typically presents as fever, lethargy, inappetance and lameness due to polyarthropathy. It has been estimated that only 10% of dogs infected with the bacterium show clinical signs. Signs typically occur 2-5 months following tick bite. Lyme nephritis is a manifestation associated with Bb exposure. Golden Retrievers and Labrador Retrievers are overrepresented. Dogs are typically younger (<5 years). Immune-mediated mechanisms have been proposed. IgM, IgG and C3 deposits can be detected in affected kidneys. Clinical signs include PU/PD, proteinuria and renal failure. Treatment with doxycycline or amoxicillin is recommended for 4 weeks. Immunosuppressive therapy may need to be instituted in conjunction with antibiotics to treat Lyme nephritis.

Reference: Sykes Ch. 51

M is for *Mycoplasma*

Mycoplasma haemocanis (hemoplasma) is suspected to be transmitted by a tick (*R. sanguineus*) which has been demonstrated experimentally and is associated with hemolytic anemia in splenectomized dogs. Diagnosis is by cytologic examination or PCR assays. Treatment of choice would be doxycycline or fluoroquinolone therapy.

Reference: Sykes Ch. 41

N is for New Tick in New Jersey

Fun Fact: *Haemaphysalis longicornis* is an Asian tick that has been recently discovered in New Jersey. In China it has been linked to Severe Fever with Thrombocytopenia Syndrome (SFTS) fever virus (bunyavirus). This tick has been shown to harbor *Borrelia*, *Rickettsia* and *Babesia gibsoni*.

O is for Other *Borrelia*

The role of other *Borrelia* spp. is poorly understood in dogs and cats. In people, *Borrelia miyamotoi* has been associated with similar syndromes to Lyme disease and a variety of *Borrelia* are associated with relapsing fever.

P is for Preventatives

Tick preventatives is a huge topic that could be its own subject for a CE lecture. The “hottest topic” is the use of Isoxazolines for ectoparasite prevention. These ORAL tick preventatives inhibit ligand-gated chloride channels (GABA and glutamate) of ticks at a novel binding site from historical agents.

Q is for Q fever

Very uncommon diagnosis in dogs and infections is typically subclinical. Abortion, premature birth and stillbirth may occur. Diagnosis is typically by PCR or serology performed at reference labs. Tick transmission likely plays a small role, but the organism has been shown to replicate in the mid gut of several tick species.

Reference: Sykes Ch. 32

R is for Rapid Molecular Diagnostics

PCR allows for the specific amplification of DNA sequences that are unique to a given organism and this makes it possible to detect the presence of that particular organism. Diagnosis of infection with organisms that are difficult, or that take a long time, to grow can be facilitated using specific PCR assays. In particular, specific PCR lends itself to the detection of organisms such as *Leptospira*. Whole genome shotgun (WGS) metagenomics has been recognized as a method of choice for unbiased, culture-independent, and high-resolution characterization of

microbial communities. The limitation of these techniques for clinical and regulatory applications is that WGS sequencing and bioinformatics analyses must be both rapid and accurate. Recent advances in next-generation sequencing technologies have increased the throughput with a significant reduction in production and it is now possible to obtain a more complete picture of a microbial community in 48 hours from sample receipt. They may also play a role in detection of pathogens with low burden such as those discussed in this session. This technology may play a role in the discovery of new pathogens as well.

S is for Serology

Typically used for detection of pathogen EXPOSURE. Results are reported often as “titers.” A titer is the highest dilution of an assay to give a positive reaction. Detecting a four-fold rise in titer requires acute and convalescent titers (typically 2 weeks apart). This is the only way to definitively diagnose a disease by serology that does not differentiate immunoglobulin classes. Assays that detect IgM may also suggest recent infection. High titers may also be suggestive of infection (>1:64 is suggested for Tick-Borne pathogens (NCSU VBDDL).

T is for Tularemia

Gram negative bacterium *Francisella tularensis* is the agent of Tularemia or Rabbit Fever. Dermacentor and Amblyomma ticks have been implicated as important vectors of this disease in the Eastern USA. Biting flies are implicated in the west. The bacterium has several terrestrial and aquatic reservoirs. Clinical signs include fever, lethargy, inappetance, subcutaneous abscesses, splenomegaly and hepatomegaly. Cases are most common in Oklahoma and Kansas in dogs. It is likely underdiagnosed. Seroprevalence in the NE of cats was 12% in one study. Dogs and cats typically ingest dead rabbits as main source of infection, but tick-borne may be an important route.

Reference: Sykes Ch. 56

U is for Use of Prophylaxis

When owners find an engorged tick it may be tempting to prescribe prophylactic antibiotics however, according to the CDC, this is not indicated to prevent anaplasmosis, ehrlichiosis, RMSF or babesiosis. A single dose of doxycycline can be considered to prevent borreliosis if ALL of the following circumstances are true:

- a. Doxycycline is not contraindicated.
- b. The attached tick can be identified as an adult or nymphal *I. scapularis* tick.
- c. The estimated time of attachment is ≥ 36 h based on the degree of engorgement of the tick with blood or likely time of exposure to the tick.

- d. Prophylaxis can be started within 72 h of tick removal.
- e. Lyme disease is common in the county or state where the patient lives or has recently traveled, (i.e., CT, DE, MA, MD, ME, MN, NH, NJ, NY, PA, RI, VA, VT, WI).

Reference: <https://www.cdc.gov/ticks/tickbornediseases/tick-bites-prevention.html>

V is for Viruses

Several viruses are transmitted to humans by tick. One important disease is TBEV (Tick-Borne Encephalitis Virus) which is currently limited to Europe and Asia. Subclinical infection is widespread in dogs in Europe. Rare cases of clinical disease have been reported (possibly predisposition in Rottweillers?). Powassan virus reports have been increasing in the USA but natural infection has never been reported in dogs.

Reference: Sykes Ch. 27

W is for Websites

There are great resources for tick-borne disease information for veterinarians including:

NCSU Diagnostic Lab:

<https://cvm.ncsu.edu/research/labs/clinical-sciences/vector-borne-disease/>

ACVIM Consensus Statements

https://onlinelibrary.wiley.com/page/journal/19391676/homepage/free_reviews_and_consensus_statements.htm

Bayer Companion Vector-Borne Disease:

<http://www.cvbd.org/en/tick-borne-diseases/>

X is for Xenodiagnosis (You didn't think I could do it?!)

Xenodiagnosis is a diagnostic method where potentially infected tissues are exposed to naïve vectors and detection in the vector leads to definitive diagnosis.

Y is for Your Role

Prevention! Diagnostics (passive surveillance)! Treatment!

Z is for Zebra or Horse?

Incidence of tick-borne disease is increasing and they are a common diagnosis (or suspected diagnosis) in veterinary medicine. It should be considered for any “nebulous” disease, patients with thrombocytopenia or hemolytic anemias or fever of unknown origin.