TICK-BORNE DISEASE – EIGHT KEY QUESTIONS ANSWERED

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1. Which ticks, which pathogens, which areas?

Hard bodied (Ixodid) ticks (Kidd, 2003)

- *Ixodes scapularis, Ixodes pacificus* – Transmits *Anaplasma phagocytophilum* and *Borrelia burgdorferi*
- *Amblyomma americanum* – Transmits *Ehrlichia ewingii*
- *Dermacentor variabilis* – Transmits *Ehrlichia canis*
- *Rhipicephalus sanguineus* – Transmits *Ehrlichia canis, Anaplasma platys*
- Life stages – egg, larva, nymph, adult

2. What are the transmission times for each pathogen and why do they vary? (Kidd, 2003)

- A window of opportunity generally exists between tick attachment and the transmission of a disease-causing agent from the tick to the host. During this window, transmission can be prevented by repelling, removing or killing the tick.
- **Pathogen factors** –
    - Organisms that exist in the salivary glands of unfed ticks (e.g. *Anaplasma*) can be transmitted faster than those that do not (e.g. *Borrelia burgdorferi*). Some pathogens undergo reactivation, multiplication, or migration before they are transmitted to the mammalian host
    - There can be different transmission times for different species of the same pathogenic genus.
- **Host factors** - There can be different transmission times according to the host species.
- **Immunological factors** - Host immunity against *Borrelia burgdorferi* can prevent tick transmission because antibodies are ingested with the blood meal and kill *Borrelia burgdorferi* in the midgut. If the tick vector is partially fed and interrupted, it can transmit *Borrelia burgdorferi* much faster to a second host on which it attaches.

  The outer membrane of *B. burgdorferi* is composed of outer surface proteins (Osp). Osp are expressed by *B. burgdorferi* at different stages of the life cycle. Outer surface protein A (OspA) is required for the tick vector to become infected and is expressed during the part of the *Borrelia* life cycle that occurs in the midgut of the tick. The next stage of the *Borrelia* life cycle occurs when the bacteria move from the midgut of the tick to the salivary glands. At this stage, outer surface protein expression moves from Osp A to OspC. Once *B. burgdorferi* has been transmitted to a susceptible mammal, expression of OspA is minimal or absent and another outer surface protein, OspC, dominates. OspC is required for *B. burgdorferi* to infect mammals. Anti-Osp C antibodies are capable of killing *Borrelia*, while anti-Osp A antibodies can only prevent transmission.

  Natural infection with *B. burgdorferi* does not induce long-lasting protective immunity. Vaccination provides protection against infection by inducing antibodies against *Borrelia* outer surface proteins. Anti-Osp C antibodies are capable of killing *Borrelia*, while anti-Osp A antibodies can only prevent transmission of infection to mammals.

  Vaccine protection against *Borrelia burgdorferi*

  Outer surface protein A (Osp A)

  All current vaccines induce antibodies against outer surface protein A (OspA). OspA expression is required for *Borrelia* to infect ticks and is found in *Borrelia* that are located in the

midgut of the tick. OspA expression is reduced soon after tick attachment to mammals and OspA immunity appears to be effective only during a narrow window at the beginning of a blood meal, but it helps prevent further transmission of *B. burgdorferi* from ticks feeding on vaccinated dogs. A recently published controlled clinical trial demonstrated that an OspA-only vaccine was unable to provide complete protection against infection when a challenge infection with *Borrelia burgdorferi* was administered. In that study, 2 of 15 dogs in the vaccinated group became infected after challenge, and 1 of those 2 dogs showed evidence of joint inflammation on histopathology at the end of the 6-month study period (Grosenbaugh et al., 2016).

Outer surface protein C (Osp C)

OspC expression is required for *Borrelia* to infect mammals. This is the main immunogenic protein of *B. burgdorferi* and is located in the tick salivary glands and in the dog's body during natural infection. There are approximately 15 OspC types in the USA and 30 OspC types have been identified worldwide. Until recently, it was thought that a single 'universal' OspC type could induce antibodies that would cross-protect against the other OspC types. This has recently been disproven (Oliver et al., 2016), emphasizing the importance of inducing antibodies against a number of different OspC types to help provide optimal protection from *Borrelia* infection in mammals.

Broader protection is provided if both antibodies against both OspA and OspC are induced. Vaccination can induce a clinically insignificant rise in Lyme disease specific circulating immune complexes. However, studies have not linked canine Lyme-nephritis with vaccination against Lyme disease.

- **Transmission time estimates** –
    - Since *Anaplasma* lives in the tick salivary glands it is transmitted very soon after feeding starts (<24 hours).
    - *E. canis* is transmitted in <24 hours (Fourie et al., 2013. Transmission of Ehrlichia canis by Rhipicephalus sanguineus ticks feeding on dogs and on artificial membranes. Veterinary Parasitology 197(3-4):595-603).
    - Very few *Borrelia burgdorferi* are transmitted within 24-48 hours of attachment and feeding, but if feeding is longer, very efficient transmission occurs.
- Time frame for successful acaricide intervention varies among tick-borne infections depending on transmission times

3. How long after infection can I expect a blue dot, and how long will seropositivity persist? (Little, 2009) -

- *Borrelia burgdorferi* - 4-6 weeks
- *A. phagocytophilum* - 2-3 weeks
- *E. canis* - 3-4 weeks
- Clinical signs can precede seropositive status for *Anaplasma* and *Ehrlichia* infection, so re-test a suspect clinical, seronegative case 1-2 weeks later to see if it has seroconverted.
- Seropositive status for *Anaplasma* and *Ehrlichia* can last for years after exposure; in some areas >50% dogs test positive for *Anaplasma* and up to 15% dogs test positive for *Ehrlichia*
- Doxycycline administration has no impact on the production of antibodies or timing of seroconversion (Sainz, 2015)
- Serologic cross-reactions – While no important cross reaction exists between *Ehrlichia* and *Anaplasma*, potential cross-reactions could occur if titers against one pathogen is very high; there can be cross-reactions between species within each genus

4. Which clinical signs/lab results should I expect? (Sainz, 2015; Little, 2010)

- *A. phagocytophilum* - Incubation period is usually 1-2 weeks; acute stage with fever, anorexia, lethargy, polyarthropathy, bleeding diatheses, epistaxis, vomiting, diarrhea, thrombocytopenia,

lymphopenia, elevated liver enzymes. Most infected dogs either present in the acute stage or remain healthy.

- *A. platys* – Infected dogs can become clinically ill with febrile disease associated with cyclic (every 1-2 weeks) thrombocytopenia. However, in general *A. platys* infection creates a milder course of disease than other *Ehrlichia*/*Anaplasma* agents, although disease may be more severe in dogs that are co-infected with *A. platys* and other rickettsial pathogens.
- *E. canis* - Incubation period is usually 1-3 weeks; 2-4 week acute phase with fever, anorexia, lethargy, bleeding disorders, polyarthropathy, lameness, lymphadenomegaly, neurological signs. Many dogs have subclinical infections, sometimes with mild thrombocytopenia. The chronic infection stage has a grave prognosis and can develop months to years after initial infection. Typical signs include fever, anorexia, weight loss, myalgia, anterior uveitis, severe pancytopenia, and bleeding tendencies. German shepherds are predisposed to the development of chronic ehrlichiosis.

5. What should I do when there's a blue dot in a clinically healthy dog?
***Anaplasma* and *Ehrlichia* (Little, 2010)**

- Revisit tick control with dog owner
- Decision to treat is made when there are clinical signs of disease, not based solely on positive serologic status, which could indicate either past or current infection
- Seropositive asymptomatic dog - Perform CBC and if in reference range may choose to not treat, or to treat with a single course of antimicrobials to avoid potential disease progression

***Borrelia burgdorferi* (Little, 2009) -**

- Revisit tick control with dog owner
- Vaccinated dogs will not be positive on SNAP4Dx or C6Quant; will be positive on IFA and whole cell ELISA; Western blot is a DIVA test
- Always follow positive serology with UA; can also consider Quant C6
- Treat symptomatic seropositive dogs, but the decision to treat asymptomatic dogs is controversial; balance between lack of evidence-based information on the prevalence of clinical infections and the pathology caused; renal failure is progressive and terminal; arthropathy is a painful condition and clinical signs might not always be noticed/reported by dog owners
- *Anaplasma* and *Borrelia burgdorferi* co-infections are relatively common since they have the same *Ixodes* tick vector; clinical signs are more severe with co-infections and diagnosis might be more difficult since more clinical signs generate a longer DDx list

6. What about antigen detection methods? Blood smears and PCR panels (Sainz, 2015)
Blood smears

- *E. canis* – Morulae only found in 4-6% clinical cases; increased sensitivity if examine monocytes in buffy coat, and if specialist cytologists examine lymph node aspirates using multiple oil immersion fields (50%)
- *A*. *phagocytophilum* – Morulae in neutrophils in up to 60% cases

PCR

- PCR testing is more sensitive than direct microscopic evaluation; use EDTA blood and/or splenic aspirates
- Enables speciation and can provide estimation of bacterial load; tick-borne PCR panels can detect co-infections to facilitate successful management
- False negative results can occur, especially once doxycycline treatment has commenced or at certain stages of infection due to reduced copy numbers – negative test means 'no pathogen detected'
- False positive results can occur in microfilaremic *D. immitis*-infected dogs because of cross-reactions with 16S primers by *Wolbachia* spp. (Little, 2010)

7. **How do I treat clinically infected dogs and what response should I expect from successful treatment? (Little, 2010)**

- *Anaplasma*, *Ehrlichia* – A 28-day course of doxycycline (5mg/kg q12h or 10 mg/kg q24h) should be administered.
  - Acute phase shows marked clinical response to doxycycline within 24-48 hours
  - Platelet count should return to normal in 14 days (up to 2-4 weeks) after successful treatment; don't repeat serologic testing because it just proves exposure
- *B. burgdorferi* - A 28-day course of doxycycline (5mg/kg q12h or 10 mg/kg q24h) should be administered. If the cause of the clinical signs is Lyme disease, there should be a marked clinical response to antimicrobial treatment within 24-48 hours.
- *E. canis* and *B. burgdorferi* infection might persist subclinically even after successful treatment
- Immunity stimulated by natural infection with *E. canis* or *B. burgdorferi* does not prevent re-infection

8. **How do I prevent infection?**

- Annual screening to monitor effectiveness of tick prevention methods such as vaccination against Lyme disease and acaricides, as a guide to local prevalence; as a marker for tick exposure (follow up with dog owner if positive); and as a marker for local *Borrelia* risk to humans.
- *B. burgdorferi* – Annual vaccination after initial primary series. Broad spectrum Osp C plus Osp A protection is essential.
- Landscaping, avoidance of tick habitats
- Acaricides - What should I be looking for?
  - Need for speed because transmission times relatively short for *Anaplasma* and *Ehrlichia*
  - Must remain effective for the full dosing interval. Dryden et al. (2006) demonstrated reversable neurotoxicity rather than tick killing with topical imidacloprid-permethrin treated dogs by Day 21 post-treatment. This resulted in ticks not being killed for the last week of the 1-month dosing interval for the product and being active in the environment of the treated dogs.
  - Year-round protection essential since many ticks are resistant to cold temperatures and *R. sanguineus* prefers to live indoors
  - Safety – Data based on field conditions with very large numbers of dogs

Links to head-to-head studies from *Parasites and Vectors*

Access full paper by clicking on 'Full text links' near the top right of page.

- Efficacy of Simparica Trio™, a novel chewable tablet containing sarolaner, moxidectin, and pyrantel against induced hookworm infections in dogs
  https://doi.org/10.1186/s13071-020-3951-4
- Safety and efficacy of a novel oral chewable combination tablet containing sarolaner, moxidectin and pyrantel (Simparica Trio®) against natural flea infestations in client-owned dogs in the USA
  https://doi.org/10.1186/s13071-020-3952-3
- Efficacy of a Novel Orally Administered Combination Product Containing Sarolaner, Moxidectin and Pyrantel (Simparica Trio™) Against Induced Infestations of Five Common Tick Species Infesting Dogs in the United States
  https://doi.org/10.1186/s13071-020-3945-2
- Evaluation of the Speed of Kill of a Novel Orally Administered Combination Product Containing Sarolaner, Moxidectin and Pyrantel (Simparica Trio®) Against Induced Infestations of *Ixodes scapularis* on Dogs
  https://doi.org/10.1186/s13071-020-3953-2
- Efficacy of a new oral chewable tablet containing sarolaner, moxidectin, and pyrantel (Simparica Trio™) against induced ascarid infections in dogs
  https://doi.org/10.1186/s13071-020-3950-5

- Field efficacy and safety of a novel oral chewable tablet containing sarolaner, moxidectin, and pyrantel (Simparica Trio®) against naturally acquired gastrointestinal nematode infections in dogs presented as veterinary patients in Europe and the United States
  https://doi.org/10.1186/s13071-020-3947-0
- Laboratory studies evaluating the efficacy of a novel orally administered combination product containing sarolaner, moxidectin and pyrantel (Simparica Trio®) for the treatment and control of flea infestations on dogs
  https://doi.org/10.1186/s13071-020-3944-3
- Laboratory and field studies to investigate the efficacy of a novel, orally administered combination product containing sarolaner, moxidectin and pyrantel for the prevention of heartworm disease (*Dirofilaria immitis*) in dogs
  https://doi.org/10.1186/s13071-019-3702-6
- Preventive efficacy of oral moxidectin at various doses and dosage regimens against macrocyclic lactone-resistant heartworm (*Dirofilaria immitis*) strains in dogs.
  https://doi.org/10.1186/s13071-019-3685-3

• Evaluation of sarolaner and spinosad oral treatments to eliminate fleas, reduce dermatologic lesions and minimize pruritus in naturally infested dogs in west Central Florida, USA.
https://www.ncbi.nlm.nih.gov/pubmed/28814316

• Comparative speed of kill of sarolaner (Simparica) and afoxolaner (NexGard against induced infestations of *Ixodes scapularis* on dogs.
https://www.ncbi.nlm.nih.gov/pubmed/26876891

• Comparative speed of kill of sarolaner (Simparica™ Chewables) and fluralaner (Bravecto(®)) against induced infestations *of Amblyomma americanum* on dogs.
https://www.ncbi.nlm.nih.gov/pubmed/27430425

• Comparative speed of kill of oral treatments with Simparica™ (sarolaner) and Bravecto®(fluralaner) against induced infestations of *Rhipicephalus sanguineus* on dogs.
https://www.ncbi.nlm.nih.gov/pubmed/26911244

• Comparative speed of kill of sarolaner (Simparica) and afoxolaner (NexGard) against induced infestations of *Amblyomma americanum* on dogs.
https://www.ncbi.nlm.nih.gov/pubmed/26897175

• Comparative speed of kill of sarolaner (Simparica) and afoxolaner (NexGard) against induced infestations of *Rhipicephalus sanguineus* s.l. on dogs.
https://www.ncbi.nlm.nih.gov/pubmed/26896456

• Comparative speed of kill of sarolaner (Simparica) and spinosad plus milbemycin oxime (Trifexis) against induced infestations of *Ctenocephalides felis* on dogs.
https://www.ncbi.nlm.nih.gov/pubmed/26896448

• Comparative speed of kill of sarolaner (Simparica and fluralaner (Bravecto) against induced infestations of *Ctenocephalides felis* on dogs.:
https://www.ncbi.nlm.nih.gov/pubmed/26896436

• Comparative speed of kill of sarolaner (Simparica) and afoxolaner (NexGard) against induced infestations of *Ctenocephalides felis* on dogs.:
https://www.ncbi.nlm.nih.gov/pubmed/26896428

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