When life gives you Lyme(s)
Addressing seropositive dogs in your practice

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Lyme Disease
- History of Lyme
- Epidemiology
- Introduction to Borrelia burgdorferi
- Pathogenesis and Clinical Signs of Lyme
  - Humans
  - Dogs
- Diagnosis
- Treatment
- Prevention

Lyme, CT 1975-1976
- Two mothers report clusters of children with RA diagnoses
- Most live near or play in wooded areas
- Symptoms began in the summer
  - Many recall tick bite
  - Many also remember a rash at the bite site

NIAID – Rocky Mountain Lab

Lyme disease and Borrelia
Yale School of Medicine Rheumatologist
Allen Steere, MD

Natl’l Institute of Allergy and Infectious Disease Jorge Bensch, Ph.D.
Natl’l Institute of Allergy and Infectious Disease Willy Burgdorfer, Ph.D.

Discovery of Borrelia burgdorferi
Just the beginning
- 1984: Serology testing widely available in Connecticut
- 1987: Lyme disease became a reportable disease
  - All physicians were required to report any and all cases of the disease
- 1988: News of Lyme disease spread and national media attention began
- 1991: First federal funding for Lyme disease surveillance, education, and research available
Lyme disease today

- Most commonly reported vector-borne illness in humans in the US
- Fifth most common Nationally Notifiable Disease
  - Anthrax, West Nile Virus, Listeriosis, etc.

Ixodes spp. today

2013: 95% cases from 14 states

Where do dogs come in?

- Canine seroprevalence <1% associated with very low human illness rates
  - State-wide and county analyses
- Canine seroprevalence >5% associated with above average human disease incidence in state-level analyses

Dogs as sentinels for human Lyme

15% of counties canine seroprevalence >5% but not higher than average human incidence

“In more than half of these counties, incidence increased to above average rates in the following 3 years…”


Canine Lyme emergence and spread


Lyme in dogs: capcvet.org

Lyme in Illinois dogs

Lyme in Illinois dogs
Lyme risk assessment in dogs

Borrelia burgdorferi

- Spirochete bacteria
- Practically invisible with light microscopy
- Cannot survive freely
  - Host-associated with vertebrate reservoirs
- Two main groups
  - LB Borreliae
  - RF Borreliae

Lyme borreliosis players

Organism: B. burgdorferi

Vector: Ixodes scapularis

Reservoir hosts: Small mammals, birds, lizards (maybe), deer and other mammals (adults)

Domestic hosts: human, dog, cat

Pathogenesis: Borrelia burgdorferi

Transmission

- Attachment
  - 1-2 days
- OspA in tick midguts
- OspC induced by attachment changes
  - Over 30 distinct OspC genotypes identified
  - Important prevention implications
Transmission: OspA to OspC

Pathogenesis
- Enters host
- Replicates and migrates through mammalian skin and connective tissue
- Able to colonize many tissues (joints)
  - Can also evade immune system (cystic form)

Clinical signs - humans
- Early localized
  - Erythema migrans
  - 3-30 days post bite
- Early Disseminated
  - Days to weeks post bite
- Late Disseminated
  - Months later
  - 60% untreated patients

Possible clinical manifestations:
- Tendons, muscle, bones
- Ocular manifestations

Clinical signs: Initial systemic signs
- Systemic signs
  - Fever
  - Shifting leg lameness
  - Joint swelling
  - Lymphadenopathy
  - Anorexia
  - Malaise

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Post-treatment Lyme Disease Syndrome

Clinical signs: Polyarthropathy

- Arthritis: most commonly documented syndrome
  - Seen 2-6 mo. Post experimental infection
- Polyarthritis
  - 2-5 day duration
  - Recurrence weeks later
  - Increased synovial fluid cell count

Lyme Nephritis

- Difficult to prove
  - <1-2% of dogs
- Acute progressive azotemia
  - Nonregenerative anemia, thrombocytopenia, inflammatory leukogram, hypoalbuminemia
- Membranoproliferative glomerulonephritis
  - Labradors, Goldens, Bernese Mountain Dogs

Lyme Nephritis

Search for *Borrelia burgdorferi* in Kidneys of Dogs with Suspected “Lyme Nephritis”

**Discussion**

Utilizing advanced molecular diagnostic techniques, we found *Borrelia burgdorferi* in the kidneys of 2 dogs with Mystopathies, but the clinical relevance of these findings remains unknown. Our results indicate that **Borrelia burgdorferi** is a transient, asymptomatic pathogen in some dogs and may play a role in the development of renal disease in canines. Although no evidence exists to support the causative role of *Borrelia burgdorferi* in canine renal disease, our findings suggest that further study is warranted to evaluate the potential impact of this organism on canine health.

Unique presentations

- Rheumatoid arthritis
- Cardiac myositis

Uncertain if *Borrelia* was causative agent

Many dogs show no signs at all

**Diagnosis**

- Bacterial culture or PCR
- Serology
  - ELISA
  - C6 antibody testing
  - Multiplex testing
Bacterial culture

- Most definitive way to diagnose!
- Difficult
  - Not in the blood
  - Requires special medium (BSK)
  - Examined every two weeks for 6 weeks

PCR

- Transiently in blood, so can’t used blood-based PCR tests
  - Need to test tissues where you think organism might be located
  - Skin, synovial fluid (viability!), etc.
- Low numbers of organisms in naturally infected dogs = False negatives

Serology: ELISA

- Early tests detected antibodies against whole cell antigen
- These did NOT differentiate between vaccination and infection
  - Follow with confirmatory test

Serology: C6 antibody testing

- C6 protein is expressed only in natural infection
  - Should be positive in dogs infected by tick and negative in vaccinated dogs

Quantitative C6 Antibody

- What to do with this information?
Quantitative C6 Antibody

- May be useful for monitoring for assessment of Lyme nephritis risk (CICs)
- Magnitude of the decrease in CICs was correlated to the decrease in quant C6 in treated dogs
  - Repeated serology may be a method of predicting decreased CICs following treatment of infected dogs

Cornell Multiplex Lyme

- Detects antibodies to three Osp Ag
  - OspA: vaccination typically (recall where OspA is expressed)
  - OspC: recent infection
  - OspF: chronic infection
- Limited studies on this test just like C6

Antech AccuPlex 4

- Dirofilaria immitis, Ehrlichia canis (specific), Anaplasma phagocytophilum (specific)
- Borrelia burgdorferi
  - OspA, Osp C, Osp F
  - Synthetic peptide

What to do with a positive dog?

ACVM Consensus Statement

Four Criteria for Diagnosing Lyme Disease

1. Evidence of exposure
2. Consistent clinical signs
3. Consideration of other differentials
4. Response to treatment

Diagnosing Lyme: Sick or Proteinuric

Proteinuric dogs need attention too

ACVM Consensus Statement

Consensus Recommendations for the Diagnostic Investigation of Dogs with Suspected Glomerular Disease

<table>
<thead>
<tr>
<th><strong>Disease</strong></th>
<th><strong>SNAP 4Dx</strong></th>
<th><strong>Diagnosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplasma</td>
<td>+</td>
<td>Positive</td>
</tr>
<tr>
<td>Borrelia</td>
<td>-</td>
<td>Negative</td>
</tr>
<tr>
<td>Ehrlichia</td>
<td>+</td>
<td>Positive</td>
</tr>
<tr>
<td>Dirofilaria</td>
<td>+</td>
<td>Positive</td>
</tr>
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Diagnosing Lyme: Positive Test Result

Suggested human Lyme treatment

Treatment of Lyme Disease

Suggested human Lyme treatment

Canine Lyme treatment

- Longer duration than humans
- Signs weeks to months after infection
- Options other than doxycycline
Canine Lyme treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Initial Dose</th>
<th>Duration (weeks)</th>
<th>Preferred Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>10-20</td>
<td>PO</td>
<td>10-20</td>
<td>4-6</td>
<td>Erythema, polyarthritis, neural, and neurologic</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>25-50</td>
<td>PO</td>
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<tr>
<td>Penicillin</td>
<td>20-40</td>
<td>IV</td>
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What to do with a positive dog?
- Lyme + with signs: easy, treat it!
  - Doxycycline or amoxicillin for 4+ weeks
  - Consider co-infections like Anaplasma
- BUT – most dogs that are Lyme + will not develop clinical signs (we think)
  - No consensus right now on what to do with these dogs other than:
    - Check for proteinuria
    - Treat before you vaccinate
  - Hard to deny owner of dog that is positive antibiotics

What about prevention?
- AAHA vaccine classification: non-core
  - Variety of vaccine types: whole cell bacterin, OspA (works in the tick), OspA and OspC combination, chimeric OspC
  - Should we be vaccinating?

How do vaccines work?
- Infected unfed nymph 23°C, elevated pH
- 72 hr feeding nymph 37°C, lower pH

Vaccine efficacy
- Levy (JAVMA 1993)
  - Whole cell vaccine
  - 1,969 dogs vaccinated vs 4,498 unvaccinated

  1% (20/1969) positive
  4.7% (211/4498) positive
Vaccine efficacy

- Levy (Vet Therapeutics 2002)
  - C6 ELISA dogs vaccinated annually with a whole-spirochete bacterin had a much lower rate of subsequent infection (5%) than unvaccinated dogs (64%)
  - Preventative fraction of 92%

Vaccine efficacy

One-Year Duration of Immunity Induced by Vaccination with a
Canine Lyme Disease Bacterin


- Vaccine efficacy: 60% skin biopsies + spirochete + 67% developed joint infection, lameness, Bb antibodies

- Vaccine efficacy: 40% skin biopsies + spirochete + 0% signs of disease, subsequent biopsy

Vaccine safety

- Reactions in < 2% of dogs receiving variety of vaccines
  - Levy 1993: 1.9% (38/1969)
  - JAVMA 2005: vaccine-associated adverse events in 0.4% (132/30,201)

- DA2LPP: 86 VAAE / 28,852 doses
  - 0.3% rate of VAAE

- What about Lyme nephritis?

Vaccine safety and Lyme nephritis

- Lyme nephritis (LN) is due to circulating immune complexes (CICs)
- Effect of vaccines on CICs in Lyme negative dogs is low
- Unclear role of vaccines and CICs (and thus LN) in positive dogs
  - Treat positive dogs, then vaccinate
  - What about when the dog is positive again?

Human Prevention

A Novel Multivalent OspA Vaccine against Lyme Borreliosis Is Safe and Immunogenic in an Adult Population Previously Infected with *Borrelia burgdorferi* Senso Lato


- Immunization with a *Borrelia burgdorferi* BB0172-Derived Peptide Protects Mice against Lyme Disease

- Scientists Discover A Second Bacterium That Causes Lyme Disease

New agents of Lyme disease?
New agents of Lyme disease?

- Atypical PCR product in 6 patients from 2012 on
  - 5/6 – fever
  - 4/6 – diffuse rash
  - 3/6 – neurologic signs
  - 1/6 – knee pain/swelling
- Motile spirochetes in one blood sample, cultured spirochetes in two
  - Significantly higher spirochaetaemia
- Found in ticks in area of probable exposure

Summary

- Lyme disease is spreading across the US
- Variety of clinical presentations ranging from no clinical signs to severe and life-threatening
- If positive, check for proteinuria, if present (>0.5 in dogs) pursue workup
  - Consider treating positive dogs prior to vaccine
- Remember 4 qualifications for Lyme diagnosis in sick dogs
- Treat with doxycycline, amoxicillin
- Recommend vaccination in at-risk patients
- Tick prevention!