Introduction to Tick Borne Rickettsial Disease Surveillance in North Carolina

Spotted Fever Group Rickettsia/RMSF

Carl Williams, DVM, DACVPM
State Public Health Veterinarian
TBRD Learning Objectives

• Describe the ecology for RMSF / SFR
• Know the importance of paired serum samples for surveillance
• Know that treatment is NOT dependent on lab tests and should be initiated if illness due to TBRD is suspected
Tick Biology

• They have four stages of development — the egg, larval, nymph, and adult stages
• After hatching from the egg, the tick must take a blood meal to complete each stage in its life cycle
• Each stage of the tick usually takes a blood meal from a different host.
• After feeding, the adult female hard ticks lay one batch of thousands of eggs and then die.
Questing

• Hard ticks seek hosts by a behavior called "questing."
• Questing ticks crawl up the stems of grass or perch on the edges of leaves on the ground in a typical posture with the front legs extended.
• Certain biochemicals such as carbon dioxide serve as stimuli for questing behavior.
• Subsequently, these ticks climb on to a potential host which brushes against their extended front legs.
Human-Biting Ticks in NC
Dog Tick

- Blacklegged Tick (*Ixodes scapularis*)
  - adult female
  - adult male
  - nymph
  - larva

- Lone Star Tick (*Amblyomma americanum*)

- Dog Tick (*Dermacentor variabilis*)
Spotted Fever Rickettsia, in addition to classic RMSF

- **R. parkeri**
  - Vector: *A. maculatum* (gulf coast tick)
  - Clinical: generally less severe than RMSF, causes eschar formation

- **R. amblyomii**
  - Vector: *A. americanum*

Paddock, et. al. Clinical Infectious Diseases 2008; 47:1188–96
RMSF → SFR Case Definition Change

• 2010
  • Spotted fever rickettsioses are responsible for several diseases with similar clinical presentation
  • Serology cannot be reliably used for specific diagnosis due to cross-reactivity of rickettsial antigens resulting in group-specific rather than species-specific antibody production
  • Thus report SFR as opposed to RMSF
Geographic Distribution of RMSF

Cases per million

- NN
- 0.2-1.5
- 1.5-19
- 19-63
SFGR Cases by Month of Symptom Onset, NC
5 YR Average 2008-12
Ongoing surveillance is necessary to monitor the geographic and temporal occurrence of disease to so that clinicians can maintain a high awareness of the disease and the public kept adequately informed about their risk of contracting the disease.
RMSF Classic Clinical Triad

- During the first 3 days of illness the proportion of patients with these symptoms is less than 5%
- By the second week after tick exposure the proportion of patients with these symptoms increases to 60 or 70%

Case Definition Clinical Criteria: Any reported fever and one or more of the following: rash, eschar, headache, myalgia, anemia, thrombocytopenia, or any hepatic transaminase elevation
RMSF / SFR Laboratory Testing

• Paired acute and convalescent sera
  IgG by IFA is the gold standard
  Fourfold rise
    • e.g., 1:64 → 1:256
  Acute = within 10 days of symptom onset
  Convalescent = 2 to 4 weeks after symptom onset

• Single serology is meaningless
RMSF: diagnosis

• The diagnosis of RMSF should be based completely on the probability that individual clinical features represent RMSF in the appropriate epidemiological setting.

✓ Treatment should be initiated on clinical suspicion and not wait for the results of diagnostic tests.

- PCR
- In Vitro culture from blood or CSF
- Serology (Paired sera for IgG)

Necessary to fulfill case definition for surveillance.
North Carolina

Spotted Fever Rickettsiosis Surveillance Algorithm

Lab created in NCEDSS

Request records from Physician

Records received

Follow LHD CD investigation policy. Received records after multiple attempts (# attempts defined by LHD Policy)

Close as Suspect

Yes

Does the patient have a fever?

No

Does not Meet

Yes

Does the pt have at least one additional symptom: Rash, eschar, headache, myalgia, anemia, thrombocytopenia, elevated liver enzymes.

Yes

Is there laboratory evidence?

No

Does not Meet

Yes

Is the laboratory evidence one or more of the following:

- Positive serum IgG IFA test followed by a second IgG IFA test performed 2-4 weeks later with a 4-fold change in titer
- Positive PCR in serum
- Isolated culture of Spotted Fever Group organism
- Spotted fever group antigen in a biopsy or autopsy by IHC

Confirmed Event

Yes

Positive IgG or IgM antibody by IFA, ELISA, or latex agglutination

Probable Event

No

Does not Meet
North Carolina

Spotted Fever Rickettsiosis Surveillance Algorithm

1. Lab created in NC EDSS
2. Request records from Physician
3. Follow LHD CD investigation policy. Received records after multiple attempts (# attempts defined by LHD Policy)
4. Does the patient have a fever?
   a. Yes
      i. Does the patient have at least one additional symptom: Rash, eschar, headache, myalgia, anemia, thrombocytopenia, elevated liver enzymes.
         i. Yes
            1. Is there laboratory evidence?
               a. Yes
                  1. Is the laboratory evidence one or more of the following:
                     a. Positive serum IgG IFA test followed by a second IgG IFA test performed 2-4 weeks later with a 4-fold change in titer
                     b. Positive PCR in serum
                     c. Isolated culture of Spotted Fever Group organism
                     d. Spotted fever group antigen in a biopsy or autopsy by IHC
                        1. Yes
                           1. Confirmed Event
                        1. No
                           1. Does not Meet
               a. No
                  1. Probable Event
               a. Yes
                  1. Positive IgG or IgM antibody by IFA, ELISA, or latex agglutination
         i. No
            1. Close as Suspect
   a. No
      1. Does not Meet

5. No

Does not Meet

NC Communicable Disease Manual/Spotted Fever Group Surveillance Algorithm
May 2013
Page 1 of 1
Introduction to Lyme Disease Surveillance in North Carolina
Lyme disease Learning Objectives

- Describe the basic ecology of LD
- Know the surveillance case definition
- Describe the case classification process
- Characterize the degree to which under-reporting occurs
What is Lyme Disease

• The most common vector borne disease in the US
• Tick borne illness due to infection with *Borrelia burgdorferi* sensu stricto and is transmitted by the bite of an infective *Ixodes scapularis* tick.
Human-Biting Ticks in NC
Blacklegged Tick

Blacklegged Tick (Ixodes scapularis)
- adult female
- adult male
- nymph
- larva

Lone Star Tick (Amblyomma americanum)

Dog Tick (Dermacentor variabilis)
LD Cases by Year of Symptom Onset, NC

- Probable
- Confirmed
LD Cases by Year of Report, US
Confirmed Lyme disease cases by age and sex--United States, 2001-2010

Mean Annual LD Incidence Rate (2008-2011) Stratified by Age, NC
Why conduct Surveillance for LD?

• Ongoing surveillance is needed to monitor the demographic geographic and temporal patterns of disease, identify risk factors for transmission and evaluate prevention and control strategies.

• CSTE position statement 10 – ID – 06
Geographic Distribution

- The overall average reported incidence rate for NC for the four-year period of evaluation is 0.81 cases per 100,000 population. Seventy counties reported at least one case during the time period 2008 to 2011 and 30 counties reported zero cases.

1. Orange  5.16
2. Camden  5.04
3. Jones    4.84
4. Gates   4.19
5. Perquimans  3.69
6. Ashe    3.65
7. Chatham  3.10
8. Pasquotank  3.09
9. Sampson  2.75
10. Carteret 2.59
North Carolina
Lyme Disease Confirmed and Probable Rates*
by County of Residence
2008-2011

Rate per 100,000 Population
- 0.2 - 0.9
- 1.0 - 1.9
- 2.0 - 2.9
- 3.0 - 5.2
- None

*Average four year rate.

n=315
North Carolina
Lyme Disease Confirmed and Probable Rates* by County of Residence
2008-2011

Rate per 100,000 Population
- 0.2 - 0.9
- 1.0 - 1.9
- 2.0 - 2.9
- 3.0 - 5.2
- None

n=315

*Average four year rate.
LD Case Classification Based on Three Surveillance Criteria

• Clinical Component
• Acaralogical Risk
• Laboratory Component
LD Surveillance Criteria: Clinical

• Early manifestation of LD:
  – **Dermatologic**: Erythema Migrans rash

• Late manifestations of LD are:
  – **Musculoskeletal system**: Pain or swelling in large joints
  – **Nervous system**: Bells palsy
  – **Cardiovascular system**: AV heart block
LD Surveillance Criteria: Acarological Risk

• Known exposure is defined as having been (less than or equal to 30 days before onset of EM) in wooded, brushy, or grassy areas (i.e., potential tick habitats) in a county in which Lyme disease is endemic. A history of tick bite is not required.

• A county in which Lyme disease is endemic is one in which at least two laboratory confirmed cases have been acquired in the county or in which established populations of a known tick vector are infected with B. burgdorferi.

• Wake, Guilford and Haywood are endemic
LD Surveillance Criteria: Laboratory

• Positive culture for *B. burgdorferi*
• Positive two-tier testing interpreted using established criteria
• Positive single-tier IgG immunoblot seropositivity interpreted using established criteria.
Two-Tiered Testing for Lyme Disease

First Test
- Enzyme Immunoassay (EIA)
- Immunofluorescence Assay (IFA)
  OR
Positive or Equivocal Result
  OR
Negative Result

Second Test
- Signs or symptoms ≤ 30 days
  - IgM and IgG Western Blot
- Signs or symptoms > 30 days
  - IgG Western Blot ONLY

Consider alternative diagnosis
OR
If patient with signs/symptoms consistent with Lyme disease for ≤ 30 days, consider obtaining a convalescent serum
Understanding Test Results for Infectious Diseases
Consider the likelihood of disease before performing laboratory testing

The likelihood that a patient has a disease depends on many factors:
- Has the patient been in an area where the disease is found?
- Does the patient have signs and symptoms typical of the disease?
- Does the patient have risk factors for contracting or developing the disease?

**Disease is Common**

- 1% False Negative
  - 1 of 60 people who tests negative has the disease

**Disease is Rare**

- 67% False Positive
  - 2 of 3 people who test positive do not have the disease

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**Key**
- Red: people with disease
- Blue: people without disease

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* 40 out of 100 patients in this area have the disease
† 1 out of 100 patients in this area have the disease
# Lyme disease WB ➔ Tier Two

**IgM:** 2 of the 3 following bands must be present to be considered positive

<table>
<thead>
<tr>
<th>24 kDa (OspC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 kDa (BmpA)</td>
</tr>
<tr>
<td>41 kDa (Fla)</td>
</tr>
</tbody>
</table>

A positive IgM immunoblot is only meaningful during the first 4 weeks of illness.

By 4 – 6 weeks post infection the IgG WB is virtually always positive.

**IgG:** 5 of the following 10 bands must be present to be considered positive

<table>
<thead>
<tr>
<th>18 kDa</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 kDa (OspC)</td>
</tr>
<tr>
<td>28 kDa</td>
</tr>
<tr>
<td>30 kDa</td>
</tr>
<tr>
<td>39 kDa (BmpA)</td>
</tr>
<tr>
<td>41 kDa (Fla)</td>
</tr>
<tr>
<td>45 kDa</td>
</tr>
<tr>
<td>58 kDa (not GroEL)</td>
</tr>
<tr>
<td>66 kDa</td>
</tr>
<tr>
<td>93 kDa</td>
</tr>
</tbody>
</table>
**What is Laboratory Evidence of Infection for Surveillance?**

- Two tier positive is lab evidence of infection
- IgG WB alone is lab evidence of infection
- EIA alone is NOT
- IgM WB alone is NOT

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Tests and Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quest Diagnostics (Chantilly VA)</td>
<td>Test Number 10672; CPT Code 86618 (EIA &amp; WB)</td>
</tr>
<tr>
<td>LabCorp</td>
<td>Test Number 258004; CPT Code 86618(x2) (EIA &amp; WB)</td>
</tr>
<tr>
<td>Mayo Medical Laboratories</td>
<td>Test ID: LYME (9129); CPT Code 86618 (EIA) &amp; Test ID: LYWB (9535); CPT Code 86617x2 (WB)</td>
</tr>
</tbody>
</table>
Note PCR is NOT an Accepted Test for LD Surveillance

- *B. burgdorferi* initially disseminates from the site of an infected tick bite via the blood, but the bloodborne phase is relatively brief and the concentration of spirochetes is quite low.
- This test is not clinically useful for LD diagnosis
- There are no PCR-based assays for the diagnosis of Lyme disease cleared by the US FDA
- Two-tiered serology remains the mainstay of laboratory testing for Lyme disease
LD Case Classification

• **Confirmed:**
  1. a case of EM *with* a known exposure, or
  2. a case of EM *with* laboratory evidence of infection and without a known exposure or
  3. a case with at least one late manifestation *with* laboratory evidence of infection.

• **Probable:** any other case of physician-diagnosed Lyme disease that has laboratory evidence of infection (non-objective manifestations)

• **Suspect:** a) a case of EM where there is no known exposure and no laboratory evidence of infection, or b) a case with laboratory evidence of infection but no clinical information available (e.g. a laboratory report).
What’s in NCEDSS

• NCEDSS for the time period 1/1/2008 → 12/31/2011
• 4201 LD events were created for investigation as potential cases of LD.
  3955 events created by receipt of a laboratory report
    • ONLY 7% of these events resulted in a confirmed or probable case
    • 3586 from automatic Electronic Laboratory Report (ELR) feed
    • 369 from manual entry of paper lab report

Remainder from traditional case report form submission
Is laboratory evidence* of infection present?

Yes

Are objective early or late manifestations of LD present?

Yes

Has the clinician diagnosed LD in the absence of objective early or late manifestations?

Yes

Confirmed

No

Probable

No

Suspect

Is EM present?

Yes

Confirmed

No

Not a Case

No

Is there known exposure?

Yes

Confirmed

No

Suspect

No

Not a Case
What’s in NCEDSS

• Of the 4201 “events” for 2008 → 2011 there were
• 315 cases (75 confirmed & 240 probable) identified.

NOTE that only 7.5% of all LD events actually become confirmed or probable cases.

For purposes of comparison, during the same time period, approximately 25% of Rocky Mountain Spotted Fever (RMSF) events and 31% of Human Monocytic Ehrlichiosis events actually become confirmed or probable cases.
Summary

• Lyme disease is frequently tested for in NC patients
• It is essential to use the appropriate testing algorithm to reduce the likelihood of false positives
• The incidence rate in NC is lower than classically endemic areas
• Cases of LD are likely very under-reported
• Areas of high incidence may be expanding