Tickborne Diseases: A Springtime Review of Diagnosis, Treatment and Prevention

Clinician Outreach and Communication Activity (COCA) Conference Call
April 10, 2014
Objectives

At the conclusion of this session, the participant will be able to accomplish the following:

- Discuss the geographic distribution of Lyme disease, Southern tick-associated rash illness (STARI), Rocky Mountain spotted fever, ehrlichiosis, and anaplasmosis.
- Explain the signs and symptoms of tickborne diseases.
- Describe the appropriate use of serologic tests for confirming diagnoses of tickborne diseases.
- State the appropriate use of antibiotics in treatment of tickborne diseases.
Continuing Education Disclaimer

In compliance with continuing education requirements, CDC, our planners, our presenters, and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. Planners have reviewed content to ensure there is no bias.

The presentation will not include any discussion of the unlabeled use of a product or a product under investigational use.

CDC does not accept commercial support.
Accrediting Statements

CME: The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Continuing Medical Education (ACCME®) to provide continuing medical education for physicians. The Centers for Disease Control and Prevention designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CNE: The Centers for Disease Control and Prevention is accredited as a provider of Continuing Nursing Education by the American Nurses Credentialing Center’s Commission on Accreditation. This activity provides 1.0 contact hours.

IACET CEU: The CDC has been approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), 1760 Old Meadow Road, Suite 500, McLean, VA 22102. The CDC is authorized by IACET to offer 0.1 ANSI/IACET CEU’s for this program.

CECH: Sponsored by the Centers for Disease Control and Prevention, a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is designated for Certified Health Education Specialists (CHES) and/or Master Certified Health Education Specialists (MCHES) to receive up to 1.0 total Category I continuing education contact hours. Maximum advanced level continuing education contact hours available are 0. CDC provider number GA0082.

CPE: The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is a designated event for pharmacists to receive 0.1 CEUs in pharmacy education. The Universal Activity Number is 0387-0000-14-093-L04-P and enduring 0387-0000-14-093-H04-P. This program is knowledge based.

AAVSB/RACE: This program was reviewed and approved by the AAVSB RACE program for 1.0 hours of continuing education in jurisdictions which recognize AAVSB RACE approval. Please contact the AAVSB RACE program if you have any comments/concerns regarding this program’s validity or relevancy to the veterinary profession.
Christina Nelson, MD, MPH
Medical Epidemiologist
Bacterial Diseases Branch
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Naomi Drexler, MPH
Epidemiologist
Rickettsial Zoonoses Branch
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Leading Tickborne Diseases in US

- Lyme disease (*Borrelia burgdorferi*)
- Rocky Mountain spotted fever (*Rickettsia rickettsii*)
- Ehrlichiosis (*Ehrlichia chaffeensis*, others)
- Anaplasmosis (*Anaplasma phagocytophillum*)
- Babesiosis (*Babesia microti*)

For information on other tickborne diseases, visit [www.cdc.gov/ticks](http://www.cdc.gov/ticks)
Distribution of Key Tickborne Diseases, 2012

NOTE: In 2012, no cases of tickborne illness were reported from Hawaii. In 2012, Alaska reported ten travel-related cases of Lyme disease.

Diseases reported to CDC by state health departments. Each dot represents one case. The county where the disease was diagnosed is not necessarily the county where the disease was acquired.
Number of Selected Tickborne Disease Cases Reported to CDC, 2012

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyme disease</td>
<td>30,831</td>
</tr>
<tr>
<td>Spotted Fever Rickettsiosis</td>
<td>4,470</td>
</tr>
<tr>
<td>Anaplasmosis</td>
<td>2,389</td>
</tr>
<tr>
<td>Ehrlichiosis</td>
<td>1,128</td>
</tr>
</tbody>
</table>

Source: Notifiable Diseases and Mortality Tables, August 23, 2013 / 62(33);669-682

1 Confirmed and probable cases
2 Includes Rocky Mountain spotted fever
3 *Ehrlichia chaffeensis*
Selected Tick Vectors

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

Primary diseases transmitted:
- Lyme disease
- Anaplasmosis
- Babesiosis
- Powassan disease

Lone Star Tick (*Amblyomma americanum*)

Ehrlichiosis
- STARI
- Tularemia

Dog Tick (*Dermacentor variabilis*)

Rocky Mtn Spotted Fever
- Tularemia
Lyme disease

- Caused by spirochete *Borrelia burgdorferi*
- Occurs in areas of North America, Europe, and Asia
- ~30,000 cases reported annually in US
- Transmitted in US by *Ixodes* ticks
Life cycle of *Ixodes scapularis*

- **Peak risk**
  - May-July

- Stages:
  - Eggs
  - Nymph
  - Larva
  - Adults

Seasons:
- Spring
- Summer
- Fall
- Winter
Confirmed Lyme Disease Cases by Month of Disease Onset--United States, 2001-2010
Reported Lyme Disease Cases, 2012

NOTE: Cases are reported based on patient's county of residence, which may be different from where they were infected.
Erythema Migrans (EM)

- 70-80% of cases
- ~7-14 days after tick bite
- Expands over days
- Rarely painful
- Distinguish from allergic reaction
Atypical EM Presentations

Disseminated and Late Lyme Disease

- Facial palsy
  - Summer months
  - May be bilateral
  - $\pm$ CSF pleocytosis
- Arthritis
  - Intermittent
  - Oligoarticular
- Late-stage neurologic
  - Peripheral neuropathy
  - Encephalopathy
Clinical Signs of Confirmed Lyme Disease Cases—United States, 2001-2010

- **Erythema migrans**: 70%
- **Arthritis**: 30%
- **Bells palsy**: 8%
- **Radiculoneuropathy**: 4%
- **Meningitis/Encephalitis**: 2%
- **Cardiac**: 1%

Number of cases

N = 213,515
Two-Tiered Testing for Lyme Disease

First Test
- Enzyme Immunoassay (EIA)
  OR
- Immunofluorescence Assay (IFA)

Positive or Equivocal Result
- Signs or symptoms $\leq$ 30 days
  - IgM and IgG Western Blot
- Signs or symptoms $>$ 30 days
  - IgG Western Blot ONLY

Negative Result

Consider alternative diagnosis

OR

If patient with signs/symptoms consistent with Lyme disease for $\leq$ 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*

100 people tested for the disease‡

**NEGATIVE TESTS**
- True Negatives
- False Negatives

**POSITIVE TESTS**
- False Positives
- True Positives

- **1% FALSE NEGATIVE**
  1 of 60 people who tests negative has the disease

- **3% FALSE POSITIVE**
  1 of 40 people who tests positive does not have the disease

### DISEASE IS RARE†

100 people tested for the disease‡

**NEGATIVE TESTS**
- True Negatives
- False Negatives

**POSITIVE TESTS**
- False Positives
- True Positives

- **0% FALSE NEGATIVE**
  None of the 97 people who tests negative has the disease

- **67% FALSE POSITIVE**
  2 of 3 people who test positive do not have the disease

---

*40 out of 100 patients in this area have the disease.
† 1 out of 100 patients in this area have the disease.
‡ Test specificity = 98% (high) and test sensitivity = 98% (high)
## Sensitivity of Two-Tiered Serologic Testing

<table>
<thead>
<tr>
<th>Lyme Disease Stage</th>
<th>Sensitivity (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM rash (acute)</td>
<td>38</td>
</tr>
<tr>
<td>EM rash (convalescent)</td>
<td>67</td>
</tr>
<tr>
<td>Early neurologic</td>
<td>87</td>
</tr>
<tr>
<td>Late neurologic</td>
<td>100</td>
</tr>
<tr>
<td>Arthritis</td>
<td>97</td>
</tr>
</tbody>
</table>

*Specificity of two-tiered testing is generally > 95%

**Bottom line:**
- Good in later stages of disease
- Testing of EM patients not generally necessary

Bacon et al. JID 2003; 187:1187–99
**Additional Tests: Questionable Utility**

- Single-tier IgM or IgG immunoblot tests without a previous EIA/IFA
- In-house criteria for interpretation of immunoblots
- Capture assays for antigens in urine
- Tests for “cystic forms” of *B. burgdorferi*
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- Measurements of antibodies in joint fluid (synovial fluid)
- Novel culture techniques

More info on [www.cdc.gov/Lyme](http://www.cdc.gov/Lyme)
Red Flags for Alternative Labs

- Tests offered are not FDA approved
- Laboratory claims to “specialize” in Lyme and other tick-borne disease testing
- Do not accept insurance → patient pays out of pocket ($500 - $1,000++)
Treatment – Adults

- **Tick bite prophylaxis** – doxycycline 200 mg po x1 (only in certain circumstances)

- **Erythema migrans:**
  - Doxycycline 100 mg po bid x 14 days or
  - Amoxicillin 500 mg po tid x 14 days or
  - Cefuroxime 500 mg po bid x 14 days

- **Patients with multiple EMs, facial palsy, and/or arthritis can be treated with the same oral regimens**
  - Duration 14-28 days, depending on clinical picture

From: The Clinical Assessment, Treatment and Prevention of Lyme disease, Human Granulocytic Anaplasmosis and Babesiosis: Clinical Practice Guidelines from the Infectious Diseases Society of America; CID; 2006.
Treatment – Adults Continued

- Carditis can be treated with oral or IV antibiotics x 14 days.

- Nervous system disease is treated with IV antibiotics x 14 days.

- Patients with recurrent arthritis should be retreated with oral antibiotics (28 days) or IV antibiotics (14 days).

- NOTE: This is a summary of treatment options. See published guidelines for more details and special situations. Available at: IDSA website (www.idsociety.org).

The Clinical Assessment, Treatment and Prevention of Lyme disease, Human Granulocytic Anaplasmosis and Babesiosis: Clinical Practice Guidelines from the Infectious Diseases Society of America; CID; 2006
Prognosis

- Most patients treated with antibiotics recover completely.

- In patients with persistent or recurrent joint swelling, re-treatment with a second 4-week course may be needed.

- Some patients – particularly those diagnosed with later stages of disease – may have persistent symptoms of fatigue, muscle aches, reduced concentration.
  - Preferred term for this is Post-Treatment Lyme Disease Syndrome (PTLDS).
  - Studies have not shown that long-term antibiotic treatment is beneficial.
Death from Prolonged Antibiotic Therapy for Lyme Disease

- 30-year-old woman received 27 months IV ceftriaxone through catheter

- Death due to embolization of large *Candida* septic thrombus

- Record provided no clear evidence for diagnosis of Lyme disease

*Figure 1.* Opened right atrium from a patient who died because of inappropriate therapy for Lyme disease. The photo shows a large infected thrombus on the fractured tip of the patient’s Groshong catheter.

Patel et al. CID 2000: 31:1107-9
STARI or Lyme Disease?

- Southern Tick-Associated Rash Illness (STARI)
  - Rash indistinguishable from Lyme disease EM
  - May be accompanied by fatigue, fever, headache, muscle and joint pains
  - Follows bite of lone star tick, *Amblyomma americanum*

- Also known as Master’s disease
- Cause of STARI is not known
Southern Tick-associated Rash Illness (STARI)

Life stages of lone star tick (Amblyomma americanum)
Treatment of STARI

- It is not known whether antibiotic treatment is necessary or beneficial for patients with STARI.

- STARI has not been linked to arthritis, neurologic disease, or chronic symptoms.

- Nevertheless, because STARI resembles early Lyme disease, physicians will often treat patients with oral antibiotics:
  - Lantos et al. model → observe is preferred strategy in places where Lyme disease is rare.

Prevention – Talk About It!

- Avoid tick habitat
- Use DEET (at least 20%) or wear permethrin-treated clothing
- Shower soon after being outdoors
  - Washes away unseen nymphs and gets tick infested clothing off of the body
- Daily tick checks—remove attached ticks ASAP
- Treat pets appropriately for ticks year-round
- Call your provider if you develop a fever or rash
Tick-borne rickettsial diseases

Including Rocky Mountain spotted fever (RMSF), Ehrlichiosis, and Anaplasmosis

- Severe and potentially fatal
- Rapidly progressing
- Similar clinical presentation

But…

- Are all treated with doxycycline
- Use similar laboratory diagnostics
Reported Cases of Rocky Mountain spotted fever, 2012

One dot placed randomly within county of residence for each confirmed case. Cases are reported from the infected person's county of residence, not necessarily the place where they were infected.
RMSF—Seasonal distribution

Percent of RMSF Cases Reported each Month, 1993-2011

Month of Onset
RMSF—Primary tick vectors

*Dermacentor variabilis*
American dog tick

*Dermacentor andersoni*
Rocky Mountain wood tick

*Rhipicephalus sanguineus*
Brown dog tick
Rocky Mountain spotted fever

- Tick-borne intracellular bacteria *Rickettsia rickettsii*

- Infects endothelial cells, causes vasculitis
  - Non-specific symptoms
  - Multi-system organ failure

- No “classic” presentation

- Rapidly fatal
  - Median time to death 8 days
  - >20% case fatality rate in untreated cases
RMSF: early clinical manifestations (Day 1-4)

- **Day 1-2**: fever, headache, myalgia (*may be responsive to OTC pain/fever meds*)
- **Day 2-4**: May develop respiratory signs (cough, community-acquired pneumonia) and/or gastrointestinal signs (nausea, vomiting, abdominal pain)
- **Day 2-4**: light maculopapular rash *may* appear
- **Day 2-4**: Thrombocytopenia, hyponatremia, elevated liver enzymes (AST, ALT) *may* occur
RMSF: late clinical manifestations (Day 5 or later)

- Worsening systemic illness (cough, dyspnea, arrhythmias, hypotension, severe abdominal pain)
- Petechial rash may develop
- Thrombocytopenia, hyponatremia, elevated liver enzymes (AST, ALT) usually present
- Onset of neurologic signs (photophobia, altered mental status, seizures)
RMSF treatment

- Treat early, based on clinical suspicion and exposure history
  - Do not wait for lab results – may be negative early during the course of infection
  - Use exposure history as a guide- keep in mind tick bite only reported in 60% of cases

- Doxycycline is the drug of choice for adults and children of all ages
  - Improvement often seen in 24-72h
  - Other broad-spectrum antibiotics are not effective
  - Sulfas, fluoroquinolones may cause more severe disease
Doxycycline and RMSF in children

- Recent studies have shown that health care providers hesitate to use doxycycline in children under 8 years.
- Not shown to cause dental staining at the recommended dose and duration, even multiple courses.
- **OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED**
- CDC and the American Academy of Pediatrics (AAP) recommend doxycycline as first line treatment for RMSF in children.
Doxycycline dose/duration for RMSF

**Adult or child ≥45 kg**
- Doxycycline 100 mg bid p.o. or i.v., 5-10 days

**Child <45 kg**
- Doxycycline 2.2 mg/kg/day bid p.o. or i.v.
- 5 days (or 3 days past defervescence)

**Pregnant adult or Life-threatening tetracycline allergy**
- *Consult with infectious disease specialist

*In rare cases, chloramphenicol may be considered as an alternative, but patients have higher risk of fatal outcome.*
Testing for RMSF

- Testing is used for surveillance and public health (magnitude of cases, confirm risks)
- No early diagnostic test can definitively rule RMSF in or out
- Do not base treatment decisions on (or wait for) test results
RMSF diagnostic tests

- PCR or IHC of whole blood, serum, tissue
  - Most accurate for severely ill/fatal cases
  - Unlikely to be positive for mild RMSF or samples taken early (day 1-4 of illness)

- Serology (IFA)
  - Detects antibodies
  - Testing of paired sera (acute, convalescent 2-4 weeks later) recommended
  - Can be difficult to interpret
    - Often negative during acute illness
    - Antibodies from prior infections may persist for years
New developments in RMSF

- Brown dog tick has been implicated as a vector for RMSF on American Indian Reservations in the Southwestern United States and Mexico.
- More peridomestic and domestic exposures associated with the brown dog tick.
- Associated with high case fatality rate and unusually high incidence.
- Children are especially vulnerable to infection.
Ehrlichiosis and Anaplasmosis—epidemiology, diagnosis, and treatment

Female lone star tick—transmits *Ehrlichia chaffeensis*

Female blacklegged tick—transmits *Anaplasma phagocytophilum*
One dot placed randomly within county of residence for each confirmed case. Cases are reported from the infected person's county of residence, not necessarily the place where they were infected.
Symptoms—Ehrlichiosis

- Fever / chills
- Headache / malaise
- Muscle pain
- Nausea / vomiting / diarrhea
- Confusion
- Rash
  - In up to 60% of children, less than 30% of adults
  - Macular, maculopapular (early) or petechial (late)
- Thrombocytopenia, leukopenia and elevated liver enzymes

Severe clinical presentation may include multiple organ failure, septic shock, or respiratory failure.
One dot placed randomly within county of residence for each confirmed case. Cases are reported from the infected person's county of residence, not necessarily the place where they were infected.
Symptoms—Anaplasmosis

- Fever / chills
- Headache/ malaise
- Muscle pain
- Nausea / abdominal pain
- Cough
- Confusion
- Rash (rare with anaplasmosis)
- Thrombocytopenia, leukopenia and elevated liver enzymes

Severe clinical presentations may include respiratory failure, renal failure or toxic-shock-like syndrome.
Note on blood transfusions and organ transplants

- Both *ehlichia* and *anaplasma* species infect the leukocytes
- Transfusion-associated and solid-organ transplant transmissions have been reported in the US
- Donors may be asymptomatic
- Leukoreduced blood products may reduce the risk of transmission, but does not eliminate it altogether
- Patients who develop either disease within a month of blood or organ donation should be reported to state health departments
Treatment—Ehrlichiosis and Anaplasmosis

- Treat as soon as the disease is suspected
- Adult – Doxycycline 100mg BID until 3 days after fever resolves
- Pediatric – Doxycycline 2.2 mg/kg BID until 3 days after fever resolves
- This treatment regimen has not been proven to cause dental staining, even with repeated use
- If anaplasmosis is suspected, patients should be treated with doxycycline for 10-14 days to provide appropriate length of therapy for possible incubating co-infection with Lyme disease
Testing for Ehrlichiosis and Anaplasmosis

- Testing is used for surveillance and public health (magnitude of cases, confirm risks)
- No early diagnostic test can definitively rule ehrlichia/anaplasma in or out
- Do not base treatment decisions on (or wait for) test results
During acute illness test using PCR on whole blood. 
  - Most sensitive in the first week of illness, and quickly decreases in sensitivity following the administration of appropriate antibiotics
  - PCR is currently the only diagnostic test able to adequately distinguish between ehrlichia and anaplasma species
  - PCR far more sensitive for Ehrlichiosis and Anaplasmosis
  - Even so, a negative result does not completely rule out the diagnosis
Serology—Ehrlichiosis and Anaplasmosis

- The gold standard serologic test is the indirect immunofluorescence assay (IFA) using species-specific antigen, performed on acute and convalescent sera
  - The first sample should be taken in the first week of symptoms
  - The second sample should be taken 2 to 4 weeks later.
  - Positive samples should demonstrate a significant (four-fold) rise in antibody titers
  - IgM antibodies are less specific than IgG antibodies and more likely to result in a false positive
For more information...

- MMWR March 31, 2006/Vol. 55/No. RR-4
  - Updates coming soon!
Thank you!

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
To Ask a Question

- **Using the Webinar System**
  - “Click” the Q&A tab at the top left of the webinar tool bar
  - “Click” in the white space
  - “Type” your question
  - “Click” ask

- **On the Phone**
  - Press Star (*) 1 to enter in the queue to ask a question
  - State your name
  - Listen for the operator to call your name
  - State your organization and then ask your question
CME: The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Continuing Medical Education (ACCME®) to provide continuing medical education for physicians. The Centers for Disease Control and Prevention designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CNE: The Centers for Disease Control and Prevention is accredited as a provider of Continuing Nursing Education by the American Nurses Credentialing Center’s Commission on Accreditation. This activity provides 1.0 contact hours.

IACET CEU: The CDC has been approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), 1760 Old Meadow Road, Suite 500, McLean, VA 22102. The CDC is authorized by IACET to offer 0.1 ANSI/IACET CEU’s for this program.

CECH: Sponsored by the Centers for Disease Control and Prevention, a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is designated for Certified Health Education Specialists (CHES) and/or Master Certified Health Education Specialists (MCHES) to receive up to 1.0 total Category I continuing education contact hours. Maximum advanced level continuing education contact hours available are 0. CDC provider number GA0082.

CPE: The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is a designated event for pharmacists to receive 0.1 CEUs in pharmacy education. The Universal Activity Number is 0387-0000-14-093-L04-P and enduring 0387-0000-14-093-H04-P. This program is knowledge based.

AAVSB/RACE: This program was reviewed and approved by the AAVSB RACE program for 1.0 hours of continuing education in jurisdictions which recognize AAVSB RACE approval. Please contact the AAVSB RACE program if you have any comments/concerns regarding this program’s validity or relevancy to the veterinary profession.
Continuing Education guidelines require that the attendance of all who participate in COCA Conference Calls be properly documented. All Continuing Education credits/contact hours (CME, CNE, CEU, CECH, ACPE and AAVSB/RACE) for COCA Conference Calls/Webinars are issued online through the CDC Training & Continuing Education Online system http://www.cdc.gov/TCEOnline/.

Those who participate in the COCA Conference Calls and who wish to receive CE credit/contact hours and will complete the online evaluation by May 11, 2014 will use the course code WC2286(SC). Those who wish to receive CE credits/contact hours and will complete the online evaluation between May 12, 2014 and April 9, 2015 will use course code WD2286(SC). CE certificates can be printed immediately upon completion of your online evaluation. A cumulative transcript of all CDC/ATSDR CE’s obtained through the CDC Training & Continuing Education Online System will be maintained for each user.
Thank you for joining!
Please email us questions at coca@cdc.gov

Centers for Disease Control and Prevention
Atlanta, Georgia
http://emergency.cdc.gov/coca
Join Us on Facebook

CDC Facebook page for Health Partners! “Like” our page today to receive COCA updates, guidance, and situational awareness about preparing for and responding to public health emergencies.

http://www.facebook.com/CDCHealthPartnersOutreach