Tick-borne Infections: Fact and Fiction

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I acknowledge that today’s activity is certified for CME credit and thus cannot be promotional. I will give a balanced presentation using the best available evidence to support my conclusions and recommendations.
Objectives

• At the conclusion of this session, the participant will be able to:
  – Review the geographic distribution of tickborne diseases
  – Define the symptoms of tickborne diseases
  – Identify the serologic tests used to diagnose tickborne diseases
  – Describe the appropriate use of antibiotics in treating tickborne diseases
Leading Tick-borne Diseases in the U.S.

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

For information on other tick-borne diseases, visit www.cdc.gov/ticks
Selected Tick Vectors

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

- **Lone Star Tick** (*Amblyomma americanum*):

- **Dog Tick** (*Dermacentor variabilis*):

**Transmit pathogens that cause the following diseases:**

- Lyme disease
- Anaplasmosis
- Babesiosis
- Powassan virus disease
  - *Borrelia miyamotoi* disease
- Ehrlichiosis
  - STARI
  - Tularemia
- Rocky Mtn. Spotted Fever
  - Tularemia
Distribution of Key Tick-borne Diseases, 2014

Diseases are reported to CDC by county of residence. Each dot represents one case. The county where the disease was diagnosed is not necessarily the county where the disease was acquired.

- Lyme disease
- Rocky Mountain spotted fever
- Anaplasmosis
- Ehrlichiosis
- Babesiosis
- Tularemia
Lyme Disease

• Caused by spirochete *Borrelia burgdorferi*
• Transmitted by blacklegged ticks
• ~30,000 cases reported annually in US
• All ages can be affected
  – incidence highest among children 5 through 9 years of age and adults 55 through 59 years of age
Reported Lyme Disease Cases, 2014

Diseases reported to CDC by county of residence. Each dot represents one case. The county where the disease was diagnosed is not necessarily the county where the disease was acquired.
Transmission of Lyme Disease

Seasonal Pattern Of Lyme Disease Cases

Human Cases

Seasonal Activity Of Deer Tick Life Stages

- Adult Deer Tick: Abundant October to May
- Nymphal Deer Tick: Abundant May to Late July
- Larval Deer Tick: Abundant August to October
To Get Lyme Disease

• Tick must be infected with the Lyme disease bacteria

• Infected ticks in the Northeastern U.S.
  – 20% of deer tick nymphs
  – 50% of adult females
  – risk of infection from a recognized tick bite <3%
  – If the tick is engorged risk may be up to 25%
Transmission of Lyme Disease

• Ticks can attach to any part of the human body
  – often found in hard-to-see areas such as the groin, armpits, and scalp
Transmission of Lyme Disease

- If the tick is infected, the chances of transmission increases with time of attachment.

![Bar chart showing transmission rates over time](chart.png)
Clinical Manifestations of Lyme Disease

- Clinical manifestations of Lyme disease are divided into 3 stages:
  - Early localized
  - Early disseminated
  - Late
Clinical Manifestations of Lyme Disease in Children

Gerber MA, et al. NEJM 335:1270, 1996
Early Localized Disease
7 to 14 days after tick bite

Erythema migrans rash

Gerber MA, et al. NEJM 335:1270, 1996
Erythema Migrans (EM)

- 70-80% of cases
- Expands over days to weeks
- Annular but can vary greatly in shape
- Rarely perfectly round
- Rarely painful or pruritic
- Must distinguish from allergic reaction
Tick Bite Hypersensitivity Reaction

- Present while tick is still attached or develops within 48 hours of detachment
- Appearance
  - Usually <5 cm
  - Sometimes urticarial
- Disappears within 24 to 48 hours after tick removal
Erythema Migrans

- Untreated the rash expands to form a large annular erythematous lesion

- Most commonly uniformly erythematous

- Bull’s eye rash less common
Atypical EM Presentations
Sites of Erythema Migrans Rash in Children

Head & neck – most common site in younger children
Extremities – most common site in older children

Gerber MA, et al. NEJM 335:1270, 1996
History of Tick Bite

• Most EM rashes result from an unrecognized tick bite
  – Only 36% of children in a community study reported a tick bite in the prior 4 weeks
  – In 38% the bite was at another site from the EM rash

• History of prior tick bites is evidence of potential tick exposure

Gerber MA, et al. NEJM 335:1270, 1996
Early Disseminated Lyme Disease
3 to 5 weeks after the tick bite

- Multiple EM
- Other manifestations may occur with or without a skin lesion
  - Palsies of the cranial nerves
  - Lymphocytic meningitis
  - Carditis
- Systemic symptoms, such as low-grade fever, arthralgia, myalgia, headache, and fatigue may be present
Multiple EM

- Result of hematogenous dissemination
  - Not caused by multiple tick bites
Bell’s Palsy

- Bilateral pathognomonic
- Associated factors
  - Onset between June and October
  - Fever
  - Headache
  - No history of herpetic lesions
- Usually resolves completely with or without antibiotics
- Need LP only if signs of meningitis
Lyme Meningitis

• Lymphocytic meningitis
  – PMNs in the CSF usually <10 %

• Differentiating between enteroviral and Lyme meningitis
  – Children with Lyme tend to
    • Be older (median age of 10.5 versus 5.5 years)
    • Have a longer duration of symptoms before Dx (12 versus 1 day)
  – Strong association with Lyme
    • EM rash
    • Cranial nerve palsy
    • Papilledema
Lyme Carditis

• Less common in children than in adults
  – young adult males appear to be most prone
• Usually manifests as various degrees of AV block
  – Partial heart block more common
  – Complete heart block rare
• Usually self-limited
• Affected children may need a temporary pacemaker
Late Lyme Disease (Weeks to Months)

- Relapsing arthritis
  - usually pauciarticular
  - affects large joints, particularly knees

- Compared with septic arthritis
  - joint swelling/effusion out of proportion to pain or disability
  - lower peripheral WBC and ESR

- Children treated with appropriate antibiotics in the early stage of disease almost never develop late disease
Nonspecific Symptoms
Should You Test for Lyme Disease?

• Frequency of nonspecific symptoms without EM rash or other manifestations of Lyme disease as sole presentation of Lyme disease is not known
  – Information from clinical trials of Lyme vaccine suggests it is uncommon (<0.3%)

• Serologic testing for Lyme disease should not be performed for children without
  – Symptoms or signs suggestive of Lyme disease
  – AND plausible geographic exposure
"Chronic Lyme Disease" in Children

• There is no evidence that such an entity exists
• Most patients labeled as having “chronic Lyme disease”
  – Have no evidence of Lyme disease by either history or serologic testing
• Long-term treatment with antimicrobials
  – Not associated with benefit
  – Associated with a variety of potential deleterious effects
  – Often prevents treatment of underlying illness or relief of symptoms
Diagnostic Testing for Lyme Disease

- Recognition of a consistent clinical illness in people who have had plausible geographic exposure
- Early Lyme disease in patients with EM rash is diagnosed clinically
  - recognition of the characteristic appearance of this skin lesion
  - serologic testing is not recommended
Two-Tiered Testing for Lyme Disease

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

**Second Test**
- IgM and IgG Western Blot
- IgG Western Blot ONLY

**Positive or Equivocal Result**
- Signs or symptoms ≤ 30 days
- Signs or symptoms > 30 days

**Negative Result**

Consider alternative diagnosis

**OR**

If patient with signs/symptoms consistent with Lyme disease for ≤ 30 days, consider obtaining a convalescent serum
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 patients with EM and exposure in an endemic area is not generally necessary

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

• Single-tier Western blot tests without a previous EIA
• In-house criteria for interpretation of Western blots
• Capture assays for antigens in urine
• Tests for “cystic forms” of *B. burgdorferi*
• Lymphocyte transformation tests
• Quantitative CD57 lymphocyte assays
• Novel culture techniques

More info on www.cdc.gov/Lyme
Antibiotics for Lyme Disease

- *B. burgdorferi* is highly susceptible to
  - tetracyclines
  - penicillins
  - second- and third-generation cephalosporins
- *B. burgdorferi* is resistant to
  - fluoroquinolones
  - rifampin
  - first-generation cephalosporins
- Macrolides may or may not be active depending on the borrelial strain tested
# 2018 Redbook Recommendations

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Drug(s) and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Localized Disease</strong></td>
<td></td>
</tr>
<tr>
<td>EM single or multiple at any age</td>
<td><strong>Doxycycline</strong> 4.4 mg/kg/d orally divided into 2 doses (max 200 mg/day) for 10 days OR <strong>Amoxicillin</strong> 50 mg/kg/d orally divided into 3 doses (max 1.5 g/d) for 14 days OR <strong>Cefuroxime</strong> 30 mg/kg/d orally divided into 2 doses (max 1 g/d) for 14 days (no suspension available) OR For a patient unable to take doxycycline or a beta-lactam – <strong>Azithromycin</strong> 10 mg/kg/d orally once daily for 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extracutaneous Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Isolated facial palsy</td>
<td><strong>Doxycycline</strong> 4.4 mg/kg/d orally divided into 2 doses (max 200 mg/day) for 14 days</td>
</tr>
<tr>
<td>Meningitis</td>
<td><strong>Doxycycline</strong> 4.4 mg/kg/d orally divided into 2 doses (max 200 mg/day) for 14 days OR <strong>Ceftriaxone</strong> 50-75 mg/kg IV once daily (max 2 g/d) for 14 days</td>
</tr>
<tr>
<td>Arthritis</td>
<td>An oral agent as for early localized disease for 28 days</td>
</tr>
<tr>
<td>Persistent arthritis after first course of therapy</td>
<td>Retreat using an oral agent as for first-episode arthritis for 28 days OR <strong>Ceftriaxone</strong> 50-75 mg/kg IV once daily (max 2 g/d) for 14-28 days</td>
</tr>
<tr>
<td>AV heart block or carditis</td>
<td>An oral agent as for early localized disease for 14 days (range 14-21 days) OR <strong>Ceftriaxone</strong> 50-75 mg/kg IV once daily (max 2 g/d) for 14 days (range 14-21 days) for hospitalized patient; oral therapy (as for early localized disease) can be substituted when patient is ready for discharge to complete a 14-21 day course</td>
</tr>
</tbody>
</table>
Doxycycline Tooth Staining Study

- Short term doxycycline use does not:
  - Darken shade of teeth
  - Cause visible staining of teeth
  - Increase risk of enamel hypoplasia

- Doxycycline can be safely administered to children at dose and duration recommended for rickettsial diseases

Prognosis

• Most treated patients recover completely
• Some patients may have persistent symptoms of fatigue, muscle aches, reduced concentration
  – Particularly those with later stages of disease
  – Preferred term for this is Post-treatment Lyme Disease Syndrome (PTLDS) not Chronic Lyme
  – Placebo-controlled trials have not shown a sustained benefit of extended antibiotic treatment

Simultaneous Infection with other Tick-borne Agents

• Patients can also be infected with
  – *Borrelia miyamotoi*
  – Agents of babesiosis and anaplasmosis
  – Powassan virus (deer tick virus)

• Suspect in patients who
  – manifest high fever or hematologic abnormalities
  – do not respond as expected to therapy prescribed for Lyme disease
Tick-borne Rickettsial Diseases

• Nonspecific early clinical signs make them difficult to diagnose
• Some are rapidly progressing and may be fatal
• Increasing incidence

• But...
• Are all treated with doxycycline
• Use similar laboratory methods for diagnostic confirmation
**Rickettsia rickettsii:**
Rocky Mountain spotted fever

- Gram-negative intracellular bacterium
- Infects endothelial cells
- Transmitted by *Dermacentor variabilis*, *Dermacentor andersoni*, and in some areas *Rhipicephalus sanguineus*
**Rickettsia rickettsii:**
Rocky Mountain spotted fever

- Causes widespread vasculitis and multisystem organ failure
- Can be rapidly fatal
  - >20% case fatality rate in untreated cases
- Difficult to diagnose in early stage of illness
Incidence of Spotted Fever Rickettsiosis, 2000-2013

RMSF: Early Clinical Manifestations (Days 1-4)

- **Day 1-2**: Fever, headache, myalgia (*may be responsive to pain/fever meds*)

- **Day 2-4**: May develop respiratory signs (cough) and/or gastrointestinal signs (nausea, vomiting, abdominal pain)

- **Day 2-4**: Faint maculopapular rash (variable)
Initial Rash of RMSF

- Small (1-5 mm), blanching, pink macules, 2 to 4 days after onset of fever
- First appears on wrists, ankles, forearms, spreads centrally
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)
- Death
RMSF Petechiae

Petechiae on palms or soles
– typically do not appear until after 5th day of illness
– indicates advanced disease
Complications of RMSF

- Gangrene
- Cerebral edema
- Pulmonary edema
- Myocarditis

Photos courtesy of Dr. Chris Paddock and Dr. Gerardo Alvarez Hernandez
Risk Factors for Fatal Outcome

• Delayed onset or absence of rash
• Age <10 years or ≥60 years
• Chronic conditions with signs/symptoms that overlap with RMSF (i.e. chronic lung disease)
• G-6-PD deficiency
• Off-season onset (colder months, first and last cases of the year)
• Delay in administration of effective therapy (doxycycline)
Ehrlichiosis

- Most commonly caused by *Ehrlichia chaffeensis* in United States
- Obligate intracellular bacteria which infect the peripheral blood leukocytes
Incidence of *Ehrlichia chaffeensis*, 2000-2013

NOTE: Incidence based on national surveillance data, 2000-2013
Symptoms—Ehrlichiosis

- Fever / chills
- Headache / malaise
- Muscle pain
- Nausea / vomiting / diarrhea
- Confusion
- Rash
  - in up to 60% of children
  - less than 30% of adults
- Thrombocytopenia, leukopenia and elevated liver enzymes

Severe clinical presentation may include multiple organ failure, septic shock, or respiratory failure
Anaplasmosis

- Caused by *Anaplasma phagocytophilum*
- Obligate intracellular bacteria which infect the peripheral blood leukocytes (predilection for granulocytes)
Incidence of Anaplasmosis, 2000-2013

NOTE: Incidence based on national surveillance data, 2000-2013
Symptoms—Anaplasmosis

- Fever / chills
- Headache/ malaise
- Muscle pain
- Thrombocytopenia, leukopenia, elevated liver enzymes and mild anemia
- Gastrointestinal symptoms
- Rash is uncommon

Severe clinical presentations may include respiratory failure, peripheral neuropathies, renal failure or toxic-shock-like syndrome
Treating Rickettsioses—A Race Against Time

• Doxycycline is most effective treatment of RMSF and other rickettsial diseases in patients of all ages

• Treatment should be initiated early in patients of all ages with suspected rickettsial disease, before diagnosis confirmed

• Rapid treatment can prevent death and disability
Confirming a Rickettsial Infection

- Treatment decisions must be made by clinical suspicion
- Do not base treatment decisions on (or wait for) confirmatory test results
- Laboratory test selection will depend on level of disease progression, the suspected agent, and specimen availability
Testing Options

• PCR of whole blood, skin, or tissue
  – Sensitive for ehrlichiosis and anaplasmosis during acute illness
  – Generally insensitive for RMSF during acute illness until late in disease progression

• Serology (IFA)
  – Requires both an acute and a convalescent sample to be interpretable
  – May be difficult to interpret due to cross-reactivity and antibody persistence

• IHC of skin or tissue

• Microscopy for detection of morulae
  – For ehrlichiosis and anaplasmosis only
The Most Important Points

• Early symptoms are non-specific but can progress rapidly
• Early treatment with doxycycline is the best way to prevent severe disease, disability, and death
• Do not wait on confirmatory diagnostic test results to make a treatment decision
Updated guidelines on treatment, diagnosis and management of tick-borne rickettsial diseases:

http://www.cdc.gov/mmwr/volumes/65/rr/rr6502a1.htm?s_cid=rr6502a1_w
Human Babesiosis

- Infection caused by an intraerythrocytic protozoan
- First described in US in 1969
- Vector is the deer tick
Babesiosis, a tickborne parasitic infection, became nationally notifiable in 2011. Approximately 97% of cases were reported from the Northeast and Upper Midwest.
Clinical Presentation of Babesiosis

- Symptoms develop from ~1 week to 5 weeks following a tick bite
- Symptoms can include:
  - cyclic fever
  - chills
  - myalgia
  - fatigue
  - enlargement of liver and/or spleen
- Most cases asymptomatic

- Frequent findings on lab testing include:
  - Hemolytic anemia
  - Thrombocytopenia

- Additional findings
  - Proteinuria
  - Hemoglobinuria
  - Elevated levels of liver enzymes, BUN and Cr
Risk Factors for Severe Babesiosis

• Age >50 years
• Splenectomy
• Underlying malignancy
• Immunosuppression due to
  – disease (eg, HIV/AIDS)
  – therapies of cancer
  – associated with transplantation, blockade of TNF-alpha activity (etanercept, infliximab) and depletion of B cells (rituximab)
Diagnosis of Babesiosis

• **Definitive diagnosis**
  – microscopic examination of **thin** blood smears
  – thick smears not recommended
  – may require multiple smears over several days if parasitized red blood cells are rare

• **Do not use PCR or serology**
Who should be treated for Babesiosis

- Most asymptomatic persons do not require treatment
- Treat symptomatic patients with babesial parasites on blood smear
Treatment Regimens for Babesiosis

• The two major antimicrobial regimens
  – Atovaquone plus azithromycin OR quinine plus clindamycin
  – Atovaquone plus azithromycin is preferred
    • better tolerated

• Regimens are administered orally for 7 to 10 days
Tick Bite Prevention

- Ticks do not jump, fly or drop from trees
- Grasp passing hosts from tips of grass or bushes
- Most ticks picked up on the lower legs and then crawl up the body seeking a place to feed
- Use personal protection to prevent acquisition of ticks
Prevention – Talk About It!

• Avoid tick habitat
• Use DEET and wear permethrin-treated clothing
• After being outdoors:
  – Tumble clothes in the dryer on high heat for 5-10 min
  – Shower within 2 hrs – washes away unseen nymphs
• Daily tick checks – remove attached ticks ASAP
• Treat pets appropriately for ticks year-round

Nelson et al. The heat is on: Killing blacklegged ticks in residential washers and dryers to prevent tick-borne diseases. Ticks Tick Borne Dis. 2016 Apr 28.
Personal Protection

• Light-colored clothing with long pants tucked into socks

• May use DEET to repel ticks
  – 30% for adults and children >2 years of age
    – apply sparingly to small children
  – not recommended for children <2 months of age

• Permethrin-based mosquito and tick repellents on clothing
Tick Checks

• Carefully inspect the entire body and remove any attached ticks
  – Ticks may feed anywhere on the body
  – Tick bites are usually painless - most people will be unaware that a tick is attached and feeding
Tick Removal

• Use thin-tipped tweezers or forceps
• Pull the tick straight upward with steady even pressure
• Thoroughly clean the bite area and your hands with
  • rubbing alcohol OR
  • an iodine scrub OR
  • soap and water
• Do not use other methods of tick removal such as
  • "painting" the tick with nail polish or petroleum jelly
  • using heat to make the tick detach from the skin
Antibiotic prophylaxis for patients with a tick bite

• Single dose of doxycycline for prevention of Lyme disease:
  – Highly endemic area
  – Attached tick identified as an adult or nymphal *I. scapularis*
  – Tick attached for >36 hours based on engorgement or history
  – Prophylaxis can be started within 72 hrs. of tick removal

• Dose
  – 200 mg for adults or
  – 4 mg/kg (up to 200 mg) for children of any age

• The value of prophylaxis for other tick-borne diseases is not known

• Testing the tick for tick-borne infections has poor predictive value and is not recommended
Take Home Points

• Clustered in the Northeast, Middle Atlantic and Upper Midwest
• Nonspecific early clinical signs make diagnosis difficult – exception is Lyme rash
• Serologic tests used to diagnose all tick-borne diseases except Babesia
• Doxycycline used for all except Babesia
• Prevention is key
Thank you for your attention!

Questions??
Which patient has Lyme Disease?
Question 1

- All of the following may be affected in Lyme disease, EXCEPT:
  - A. Skin
  - B. CNS
  - C. Liver
  - D. Cardiac muscle
Question 2

• A 5-year-old presents with flulike symptoms and a red expanding target lesion on his back where his parents thought he got a spider bite. You think it may be Lyme disease and want to start treatment. Which is the best treatment for this patient?

A. Oral amoxicillin
B. Oral azithromycin
C. Oral cefuroxime
D. Oral doxycycline
E. Intravenous ceftriaxone
Question 3

• A 6-year-old with a previous episode of anaphylaxis to amoxicillin and clavulanic acid given for otitis media is suspected of having Lyme disease. Which of the following antibiotics should she be treated with?
  A. Azithromycin
  B. Ceftriaxone
  C. Cefuroxime
  D. Doxycycline
Question 4

Rocky Mountain spotted fever is transmitted by:

A. Deer or blacklegged tick
B. Dog tick
C. Lone star tick
A 7-year-old presents to the ED in New England with a history of high fevers, chills, sweating, weakness, and headache 10 days after a tick bite. On exam he has no rashes. The laboratory reports leukopenia with neutropenia, thrombocytopenia and elevated hepatic transaminases. Which of the following is your working diagnosis?

A. Anaplasmosis
B. Babesiosis
C. Lyme Disease
D. Rocky Mountain spotted fever