Arthropod borne diseases endemic to Missouri
MOAPA
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Outline
• What diseases do we have
• What diseases do we not have
• How to distinguish these diseases
• How to test for these diseases
• Treatments, follow-up
• Information for patients


MMWR Weekly / May 4, 2018 / 67(17):496-501

• In the United States, 16 vectorborne diseases are reportable to state and territorial health departments

MMWR May 13, 2016; vol 65:2-
• Download this document if you treat patients! (In the summer, in Missouri)
What’s New?

Since 2004

- 2 previously unknown, life-threatening tickborne RNA viruses, Heartland and Bourbon viruses—both in U.S. Midwest.
- A tickborne relapsing fever agent, Borrelia miyamotoi, first described in Japan, now in the US
- Bacterial spirochete, Borrelia mayonii in upper U.S. Midwest.
- Two tickborne spotted fever Rickettsiae, R. parkeri and Rickettsia species 364D
- Tickborne Ehrlichia (E. muris eauclairensis) discovered
- The mosquitoborne viruses chikungunya and Zika were introduced to Puerto Rico in 2014 and 2015.
What do we have?

- Ehrlichiosis
- RMSF
- Tularemia
- Babesia MO1
- Heartland virus
- Bourbon virus
- STARI
- West Nile
- STL
- Lacrosse
- EEE
- Typhus
- Dengue, Chickengunya and Zika (traveler)

Lyme Disease

- No Lyme Disease in MO
- Trust me or do you want to discuss?

Surveillance for and Discovery of *Borrelia* Species in US Patients Suspected of Tickborne Illness

- CID 2018:66 (15 June) • Kingry et al
- I am willing to soon change this dogmatic statement, but not yet
Vignette:

- 43 y/o female returns to Missouri from summer vacation in Martha’s Vineyard 6 days ago. She complains of fever, chills, myalgias, headache, and this rash.

Treatment?

- 1. Topical corticosteroids
- 2. Topical itraconazole
- 3. Doxycycline 100mg po bid for 21 days
- 4. Kellex 500mg po tid for 10 days
- 5. Doxycycline 100mg po bid for 10 days
- 6. Atov/Azithro
- 7. No treatment
- 8. None of the above
Follow-up

- She received 21 days of Doxycycline, could have received 10 days'.
- 5 days after completion of therapy she develops fevers, malaise, headache, N/V, and dark urine.
- Her Hgb is 7g/dL, serum bilirubin is 3.

What test could you order to definitively diagnose this patient? Or can you explain the diagnosis without a test?


Ixodes Scapularis

Black-Legged Tick

- Human Granulocytic Ehrlichiosis (Anaplasmosis)
- Lyme Disease
- Babesiosis
Objectives

- Tick Diseases in Missouri
  - HME
  - RMSF
  - Tularemia, Babesiosis, and a few more

- Tick Diseases not likely in Missouri
  - Lyme Disease
  - Relapsing Fever, Tick-borne Encephalitis, Tick Paralysis, HGA, Colorado Tick Fever, Rickettsia NOS

STARI

The major tick-borne diseases of North America

- Human Monocytic Ehrlichiosis
- Human Granulocytic Ehrlichiosis (Anaplasmosis)
- Lyme Disease
  - Borrelia lonsatori
- Rocky Mountain Spotted Fever
- Colorado Tick Fever
- Tularemia
- Relapsing Fever
- Babesiosis
- Tick-borne Encephalitis
- Tick Paralysis
- Brucellosis
- Powassan Encephalitis

Flea borne and some others

- Endemic Murine Typhus-R. typhi/febris-CA and So Texas-fleas, rats
- Epidemic Typhus-R. prowazekii-fever and rash, lice, crowds, flying squirrel in VA, severe dz
- Scrub Typhus-Orientia tsutsugamushi-Thailand, South America-eschar at bite, mites, fever and LAN
- Boutonneuse fever-R. conori
- Rickettsiaapox-R. akari-NYC

Point is not to memorize, just to take a history.
- Leptospirosis in rats in Baltimore
**Tick-Borne Diseases**

- Worldwide, ticks are second only to mosquitoes as vectors of disease.
- In North America, they are #1 disease vector.

**How Do Ticks Get On You?**

- Highly responsive to host stimuli.
  - Chemicals (CO₂, NH₃, phenols, humidity, aromatics).
  - Airborne vibrations.
  - Body temperature.

- Ticks do not jump, fall, or fly!
- Found within three to four feet of the ground (deer, bison height).
How Do Ticks Get On You?

- Some species use an ambush or questing strategy.
  - The tick is brushed by a moving animal or person, lets go of the vegetation, and grasps the host.

Hunting Strategy

“Hunter Ticks” – Some species actively crawl or run towards their hosts; may crawl across distances of many yards to attack and feed on animals resting nearby.

How Do Ticks Get Into A Person?

- Superficial Feeder
  - American Dog Tick
- Deep Feeder
  - Lone Star Tick

“Made” to go deep into the skin.
Pathogen Transmission

The longer an infected tick is attached, the greater the risk of transmission.

Reported Cases of Tick-borne Disease, Confirmed and Probable, Missouri, 2013 – 2017*

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>0</td>
</tr>
<tr>
<td>2014</td>
<td>175</td>
</tr>
<tr>
<td>2015</td>
<td>350</td>
</tr>
<tr>
<td>2016</td>
<td>525</td>
</tr>
<tr>
<td>2017*</td>
<td>700</td>
</tr>
</tbody>
</table>

Source: Missouri Department of Health and Senior Services (DHSS), Bureau of Reportable Disease Informatics, Missouri Health Surveillance Information System (WebSurv).

*2017 data are preliminary and subject to change as case investigations are completed.

What's Causing This Increase?

Medical technology
- Better recognition by medical providers.
- Diagnostic tests more available.
  - More people tested.
  - More cases reported to public health.

Lone star tick
*Amblyomma americanum*
What's Causing This Increase?

The age structure of our population is changing

- Age-associated declines in immune-system health.
- Increases in immunosuppressive therapies (chemo, organ transplants).

Bacterial Tick-Borne Diseases

The Spectrum of a Typical Tick-Borne Infection

- Infected - No Illness
- Infected - Mild Illness
- Infected - Serious Illness
- Infected - Serious Complications or Death
The Spectrum of a Typical Tick-Borne Infection (continued)

- Even a healthy person can develop serious illness as a result of a tick bite.
- Persons with other health problems are even more likely to develop serious illness from a tick bite.
  - This is true for most infectious diseases, not just those that are transmitted by ticks.

Tick-Borne Diseases in Missouri

- RMSF, Ehrlichiosis
- Other Bacterial Diseases
  - Tularemia
  - Lyme disease
  - Southern Tick-Associated Rash Illness
- Tick-Borne Viruses

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Tick-Borne Diseases in Missouri

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  - Southern Tick-Associated Rash Illness
- Tick-Borne Viruses
  - Lone Star Tick
  - Brown Dog Tick
  - Black Legged or Deer Tick
  - American Dog Tick

What is our main vector borne disease in MO?

Human Monocytic Ehrlichiosis

- *E. chaffeensis*
- Lone Star Tick (*A. americanum*)
- White tailed deer (host of tick and reservoir of *E. chaffeensis*)
- Reportable
- Bulk of cases reported are from: MO, OK, TN, & AR
Ehrlichiosis

- **Agent:** Ehrlichia chaffeensis, E. ewingii in Missouri.
- **Primary Vector:** Lone star tick (LST), Amblyomma americanum.
- **Reservoir:** The white-tailed deer is major host to all stages of LST and thought to be important natural reservoir of *E. chaffeensis*; LST found in woodland habitats with deer.

Lone Star Tick (Amblyoma americanum)

- E. chaffeensis causing HME

Human Monocytic Ehrlichiosis

**Epidemiology**

- 138 cases/100,000 in SE MO
- Ehrlichiosis and Anaplasmosis = parasitism of phagocytes
- Multiply in vacuoles = morulae
- *E. chaffeensis* infects monocytes
- *A. phagocytophilum* and *E. ewingii* infect granulocytes.
- Buffy coat with Wright or Giemsa stained. Occurs in HGA >> HME (seen in 1-20% of early cases)

1. Olano EID 2003;9:1579-86
Morulae=intra-phagosomal microcolonies-apparent after several days-turn into large mature inclusions that can be seen here as morulae.

Morulae in a neutrophil-
A. phagocytophilum and E. equi

Human Monocytic Ehrlichiosis
Pathophysiology

- Infects peripheral blood monocytes and RE tissues.
- What are monocytes?
- Proinflammatory stimulation causes RE activation and erythrophagocytosis.
- This accounts for the characteristic CBC
- Infected monocytes cross BBB and release TNF, etc.
Human Monocytic Ehrlichiosis

Signs and Symptoms

- 75% of symptomatic patients need to be hospitalized.
- M>>F
- Elderly and IC patients dev. severe disease
- S&S-abrupt onset 7-14 days after tick bite
- Is there a rash with HME?

Reported Cases of Ehrlichiosis, Confirmed and Probable, 2013 – 2017

*2017 data are preliminary and subject to change as case investigations are completed.

Source: Missouri Department of Health and Senior Services (DHSS), Bureau of Reportable Disease Informatics, Missouri Health Surveillance Information System (Missouri Center for Disease Control and Prevention).

Human Monocytic Ehrlichiosis

Signs and Symptoms

- All have fever
- All adults have HA
- Kids may have a rash
- Anorexia and myalgias
- Septic/toxic shock-like illness in minority
- Rash in 1/3 of adults and up to 2/3 of children-diffuse erythema, petechial, or MP
Human Monocytic Ehrlichiosis

Signs and Symptoms

- Thorough history.
- No tick exposure does not r/o TBRD.
- High grass, low brush, April-Sept within 2 weeks of presentation.
- A large % of patients won't recall an attached tick (68% of ehrlichiosis and 60% of RMSF cases) MMWR 2004 55

Human Monocytic Ehrlichiosis

Signs and Symptoms

- Round One of labs:
- Question: Name 5 typical lab derangements

- Round One of labs:
  - Leukopenia
  - Lymphopenia
  - Left shift with Meta/Myelocytes and Band forms
  - Thrombocytopenia in over 50% of patients
  - Hyponatremia
  - Mild elevations in transaminases
  - May have atypical lymphocytosis after 3 weeks
Human Monocytic Ehrlichiosis

Diagnostics

1. Buffy Coat - approx. 1-20% have morulae and only a minority will have morulae seen on peripheral smear

2. PCR-for 16s rRNA for HME - very specific, rapid, and sensitive in the early stages. Will diagnose up to 80% of infections. **Best Test**
   Use specific E. chaffeensis primers
   Send-out test, but not for long hopefully

3. Serology-IFA - need a 4X increase between acute and convalescent titers and a minimum of 1:64 titer (probable diagnosis) at any time
   - No IgM!
   - Any titer ≥256 with clinical syndrome = confirmed case
   - Morulae + 1:64 titer = confirmed case

4. Clinically-nonspecific viral illness in an endemic area with spring with tick exposure**Bingo!**
   This sounds good, but you need to firm up the diagnosis with PCR and serologies in the event there are late sequelae or alternate diagnosis.

Treatment

- Treat immediately if you suspect
- Doxycycline is cidal
- Clinical response in 48h
- Oral therapy unless GI absorption is unpredictable
- Treat for 3d after defervescence
- Usually at least 7 days
- In contrast to HGA for which you have to treat at least 14d to cover incubating Lyme disease
Human Monocytic Ehrlichiosis

Treatment

- Pregnant woman?
- Hope you don’t see this patient
- Life-threatening: Tetracyclines
- Non-life-threatening: chloramphenicol?? Grey baby synd
- Rifampin for HGA
- Sulfur can lead to increased severity of TBRD
- No post-exposure prophylaxis!!! (in contrast to Lyme endemic areas)

Oh By the way!

- E. ewingii
- MO geography and MO Lone Star Ticks
- Same epi as E. chaffeensis

Case Records of the Massachusetts General Hospital

Case 16-2018: A 45-Year-Old Man with Fever, Thrombocytopenia, and Elevated Aminotransferase Levels

Kimiyoishi J. Kobayashi, M.D., Ana A. Weil, M.D., M.P.H., and John A. Branda, M.D.
Summary
A 45-year-old man from New England presented with fever, thrombocytopenia, and elevated aminotransferase levels several months after he had visited Mexico.
A circular skin lesion with a central scab was noted below the left lateral malleolus.
Diagnostic tests were performed.

*Anaplasma phagocytophilum* infection.

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Babesiosis and HGA

**Common diseases elsewhere**

- Upper NE, islands.
- Babesiosis: few cases in MO
- Severe in immunosuppressed, splenectomized and elderly
- RBC parasite
- TX=quinine/+clinda or azithro+atov
Rocky Mountain Spotted Fever
Epidemiology:

- *Rickettsia rickettsii*
- *Dermacentor variabilis* and several other tick species
- 1/2 of US cases are from NC, SC, TN, OK, AR
- Look for simultaneously sick dogs (pets)

Common dog tick (*Dermacentor variabilis*)
- can be vector for either HME or HGA

*FIGURE 5: Average reported annual incidence* of Rocky Mountain spotted fever by state — United States, 1997–2002

* Per 1,000,000 persons per year.
Rocky Mountain Spotted Fever

Clinical:
- Parasitizes endothelium, this explains the pathophysiology
- Purpura fulminans in G6PD def
- Constitutional symptoms with rash at 2-4 days after fever: small blanching macules starting on wrists and forearms, centripetal spread. Petechial rash at 5-6th day if disease progresses.
- PCR only for tissue, serologic diagnosis using paired sera.
- Immunostaining of skin lesions is the best.

Tick-borne Spotted Fevers

- Agent: Most common spotted fever is Rocky Mountain spotted fever; agent is Rickettsia rickettsii.
- Primary Vector: American dog tick (ADT), Dermacentor variabilis.
- Reservoir: Principal hosts of ADT are deer, dogs, and livestock, which are likely reservoir. ADTs found in wooded, shrubby, grassy areas (along walkways/trails) and in residential areas/city parks.

Reported Cases of Tick-Borne Spotted Fevers, Confirmed and Probable, 2013 – 2017*

<table>
<thead>
<tr>
<th>Year</th>
<th>MO, OK, NC, TN and AR</th>
<th>Missouri</th>
<th>US</th>
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</thead>
<tbody>
<tr>
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<td>3359</td>
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<td>2014</td>
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</tr>
<tr>
<td>2017</td>
<td>5370</td>
<td>634</td>
<td>5370</td>
</tr>
</tbody>
</table>

Missouri Deaths

| Year | 1 | 2 | 1 | 1 | 0 |

*2017 data are preliminary and subject to change as case investigations are completed.
Source: Missouri Department of Health and Senior Services (DHSS), Bureau of Reportable Disease Informatics, Missouri Health Surveillance Information System (WebSurv).
Rates of Tick-Borne Spotted Fevers, Confirmed and Probable, 2013 – 2017

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate per 100,000</th>
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<tbody>
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<td>2013</td>
<td>1.1</td>
</tr>
<tr>
<td>2014</td>
<td>1.1</td>
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<tr>
<td>2015</td>
<td>1.2</td>
</tr>
<tr>
<td>2016</td>
<td>1.4</td>
</tr>
<tr>
<td>2017</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*2017 data are preliminary and subject to change as case investigations are completed.

Source: Missouri Department of Health and Senior Services (DHSS), Bureau of Reproductive Disease Informatics, Missouri Health Surveillance Informatics.

Rocky Mountain Spotted Fever

Clinical:
- Treatment = doxycycline 100mg bid for 3-5 days after defervescence.
- No clear alternative treatment
- Rare sequelae if treated early, but possible severe complications if not identified early: vasculitis, pulmonary, cardiac, CNS, renal complications
- No chronic infection!

Rickettsia and spotted fevers

- *R. africae*: African tick fever
- *R. parkeri*: Emerging TBD with eschar, SE coastal areas
- *R. conori*: Boutonneuse fever (Mediterranean)
- *R. rickettsii*: RMSF
- *R. typhi*: Endemic murine typhus-old world (Scrub typhus)
- *R. felis*: Endemic murine typhus-CA and south TX
- *R. prowazekii*: Epidemic typhus, flying squirrel in VA
- *R. slovaca*:
African tick borne fever-common febrile illness in Safari/Big game hunter. Multiple eschars.

American Boutonneuse Fever: HA, fever, rash, multiple eschars, in VA, R. parkeri.

Newly discovered disease

**Lyme Disease**

**Question:**

- Is there Lyme disease in Missouri?
- Answer: Probably not.
- Campbell JID 1995;172(2):470-80 23 pts from MO underwent cx of EM lesions and no B. borgdorferi were cultured
- This has been duplicated, now the disease is called STARI.

**Introduction:**

- *Borellia borgdorferi* transmitted by *Ixodes scapularis* and *Ixodes pacificus*
- Tiny nymph tick
- Erythema migrans
- Diagnose with ELISA then WB (either pos or neg)
**Lyme Disease**

**Clinical:**

- Yes/No
  - Post Treatment Chronic Lyme Disease has been proven to be due to chronic infection with *Borellia* spirochetes?

- Yes/No
  - Are there any data proving that parenteral antibiotics are not efficacious in treating PTCLD?
Lyme Disease

Clinical:

- Post Treatment Chronic Lyme Disease: Misonomer and is not susceptible to prolonged course of IV abx.

- The large joint synovitis is not due to chronic infection, but may be assoc with HLA-DR4. Molecular mimicry between self and cell surface antigens. Steer NEJM 1990;323:219-23

- Current DBRCT, 37 pts with objective cognitive impairment following treatment of documented Lyme Disease were randomized to 10weeks of ceftriaxone vs placebo.
- No improvement and 19% of study subjects experienced AEs related to IV abx. (abstract form: Fallon BA 2005)

- Isolated 7th nerve palsy is incidental and transient and does not mandate a change in therapy.

- 3 RCTs have proven that a prolonged course of therapy for initial treatment does not improve the rate of resolution of symptoms.
  
  CID 2006;43:1089-134
Lyme Disease
Clinical:

- Post Treatment Chronic Lyme Disease: Misonomer and not susceptible to to prolonged course of IV abx
- The prevalence of chronic pain and fatigue in the US is 20-30%. (2003 NHIS) and this is lower than the PTCLD attributable rate.
- Same goes for baseline prevalence of fibromyalgia in the general US population. (2%)

- No consistent definition of PTCLD and when you study this heterogenous group, you rarely find objective evidence of past Lyme Disease and over half of these patients have an alternative, treatable diagnosis.
- Therefore, serologies in areas of low endemicity have very low pos pred values.

- Steer NEJM 1990;323:219-23
  None of these 129 pts with a past hx of Lyme Diasease had a microbiologic diagnosis of Borellia infection!!
  Data safety monitoring board stopped the trial early.
**Lyme Disease Question:**

- Name 3 spirochete diseases.
- Knowing the pathophysiology explains the natural history of Lyme disease.

**Lyme Disease Question:**

- Syphilis-latent infection?
- Leptospirosis-latent infection?
- Borellia recurrentis-latent infection?
- Lyme Disease-latent infection?

- No latent infection if these are treated.
- None of these are intracellular pathogens and Jarisch-Herxheimer Reaction is possible with all of the above.

**EM in Missouri?**

- If not due to *B. burgdorferi*, then what?
- Southern tick-associated rash illness (STARI), Master’s Disease
- Typically due to Lone Star Tick, vs in NY-Ixodes
- Compared to EM in NY: earlier in year, usually a known tick exposure, rarely other symptoms, smaller EM lesion, and recover rapidly without sequelae

**STARI**

- EM illness in MO
- Etiology is very controversial
- Eubacterial PCR: no evidence of an infectious cause.
- For now, treat with 10 days of Doxycycline and look for another cause and reassess.
- Dennis DT Clin Inf Dis 2005;41:966-7

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**Summary**

1. Think. Please. Describe the syndrome.
2. Our TBD are HME, RMSF, STARI, E. ewengii, and possibly tularemia, and babesiosis. Bourbon and Heartland viruses
3. Lots of viruses transmitted by mosquitoes
4. Treat TBD and then diagnose with PCR and paired sera.
5. No Lyme Disease in MO (EM=STARI), and PTCLD is not an infectious disease amenable to parenteral antibiotics.

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**Summary**

- Do not send “tick panel”, “tick titer”, or any test with the name “tick”. We do not test for ticks. Send the right test, they are in the slide set.
- Treat and test at same time.
- These diseases are all cured, there are no chronic sequelae.
- Talk to your patients, inform them. They are misinformed

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