Tickborne infections in Connecticut

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CT CAFP October 2018

Key points:

Discussion of tick biology – ticks old and new
Discussion of pathogens – old and new
Duration of tick attachment
  Diagnostic pitfalls
  Seasonality of disease acquisition
Chronic symptoms – infection? Inflammatory?
Red meat allergy
Protection
Tick Management Handbook

An integrated guide for homeowners, pest control operators, and public health officials for the prevention of tick-associated disease

Revised Edition

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Excellent resource for tick management

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http://www.ct.gov/caes
Two major families of ticks: Hard vs Soft

Hard ticks – Ixodid family
Soft ticks – Argasid family

Table 1. Important ticks of the northeastern states and some other major ticks of medical importance in the United States.

<table>
<thead>
<tr>
<th>Tick</th>
<th>Common name</th>
<th>General Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hard Ticks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ixodes scapularis</em></td>
<td>Blacklegged tick</td>
<td>Northeastern, southeastern &amp; mid-western U.S.</td>
</tr>
<tr>
<td><em>Ixodes pacificus</em></td>
<td>Western blacklegged tick</td>
<td>Pacific coast &amp; parts Nevada, Arizona, Utah</td>
</tr>
<tr>
<td><em>Ixodes cookei</em></td>
<td>A woodchuck tick</td>
<td>Eastern United States &amp; northeast Canada</td>
</tr>
<tr>
<td><em>Ixodes dentatus</em></td>
<td>A rabbit tick</td>
<td>Eastern United States</td>
</tr>
<tr>
<td><em>Amblyomma americanum</em></td>
<td>Lone star tick</td>
<td>Southeastern U.S., Texas to S. New England</td>
</tr>
<tr>
<td><em>Dermacentor variabilis</em></td>
<td>American dog tick</td>
<td>Eastern U.S. &amp; parts of the west coast</td>
</tr>
<tr>
<td><em>Dermacentor andersoni</em></td>
<td>Rocky Mountain wood tick</td>
<td>Rocky Mountain states south to NM &amp; AZ</td>
</tr>
<tr>
<td><em>Dermacentor albipictus</em></td>
<td>Winter tick</td>
<td>Canada, United States south to Central America</td>
</tr>
<tr>
<td><em>Dermacentor occidentalis</em></td>
<td>Pacific coast tick</td>
<td>California, Oregon, northern Baja peninsula</td>
</tr>
<tr>
<td><em>Rhipicephalus sanguineus</em></td>
<td>Brown dog tick</td>
<td>All U.S. and worldwide</td>
</tr>
<tr>
<td><strong>Soft Ticks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ornithodoros species ticks</em></td>
<td>Relapsing fever ticks</td>
<td>Western United States</td>
</tr>
<tr>
<td><em>Carios kelleyi</em></td>
<td>A bat tick</td>
<td>A bat tick</td>
</tr>
</tbody>
</table>

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Deer tick or Dog tick?

Scutum “cape”

Ixodes – dark

Dermacentor - light

https://www.cdc.gov/ticks/tickborne_diseases/tickID.html
Ixodes (hard body) can enlarge dramatically with feeding

http://tickapp.tamu.edu/tickbiology.html
Ixodes Life Cycle

1. Egg, larva, nymph, adult

2. Larval ticks are uninfected with Lyme (B. burgdorferi) as adults do not transmit Lyme disease through eggs (transovarially), but may be infected with other pathogens. BUT B. miyamotoi is transmitted transovarially so larval ticks may be infected.

3. Nymphal ticks are the predominant vector for Lyme as they feed on infected mice which are the major reservoir.
Soft tick (Argasid) of importance in CT

**Soft tick** (note the head is not visible from above)

Bat tick (Carios kelleyi)

Ornithodoros hermsii – vector of tick-borne relapsing fever (Borrelia hermsii) – in Western US states
Basic Seasonal Guide to Major Ticks Affecting Humans in Connecticut (Also see seasonal graph for I. scapularis)

Fall (October-November)
Adult *Ixodes scapularis* active

Winter (December-February)
Adult *Ixodes scapularis* active during periods of warm weather (the ticks do not hibernate)

Early Spring (March-April)
Adult *Ixodes scapularis* (second peak of activity)
Adult *Dermacentor variabilis* appear late April
Adult *Amblyomma americanum* appear mid-April
(lone star ticks still are not common in CT)

Late Spring (May)
Adult *Ixodes scapularis* are disappearing
*Nymphal* *Ixodes scapularis* appear about mid-May
*Nymphal* *Amblyomma americanum* appear mid-May
(lone star ticks still are not common in CT)

Early Summer (June-July)
*Nymphal* *Ixodes scapularis* peak period activity
Adult *Dermacentor variabilis*
*Nymphs* *Amblyomma americanum*
(lone star ticks still are not common in CT)

Late Summer (August-September)
*Larval* *Ixodes scapularis* peak
A few nymphs of *Ixodes scapularis* & adults of *Dermacentor variabilis* may still be present

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Geographic distribution of *Ixodes* tick vectors

The Most Common Vector-Borne Disease in the Northern Hemisphere

Geographic Distribution of *Borrelia Burgdorferi Sensu Lato*

*B. burgdorferi ss*

Different RST types vary in virulence

*Borrelia mayonii* is a newly identified species that causes Lyme disease in the upper Midwest

Cases of Lyme Disease

18 named genospecies
Human diseases transmitted by *Ixodes* ticks

<table>
<thead>
<tr>
<th>Infection</th>
<th>Microorganism</th>
<th>First human case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babesiosis</td>
<td>Protozoa (Piroplasm)</td>
<td>1957</td>
</tr>
<tr>
<td>Tick borne encephalitis</td>
<td>Virus (Flavivirus)</td>
<td>1958  1937 TBE</td>
</tr>
<tr>
<td>(Powassan in US, TBE/FSME in Europe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Bacteria (Borrelia)</td>
<td>1975  (1909)</td>
</tr>
<tr>
<td>Anaplasmosis  (Formerly “Ehrlichiosis”)</td>
<td>Bacteria (rickettsia)</td>
<td>1994</td>
</tr>
<tr>
<td><em>Ehrlichia muris</em>-like infection</td>
<td>Bacteria (rickettsia)</td>
<td>2009</td>
</tr>
<tr>
<td><em>Borrelia Miyamotoi</em> infection</td>
<td>Bacteria (Borrelia)</td>
<td>2011</td>
</tr>
<tr>
<td><em>Borrelia mayonii</em> infection</td>
<td>Bacteria (Borrelia)</td>
<td>2012  (published 2016)</td>
</tr>
</tbody>
</table>
Distribution of the tick species associated with human granulocytic anaplasmosis (HGA), *I. scapularis*, *I. pacificus*; and human monocytotropic ehrlichiosis (HME), *A. americanum* (CDC).
1 dot = 1 confirmed case
95% of confirmed Lyme disease cases were reported from 14 states

- Connecticut
- Delaware
- Maine
- Maryland
- Massachusetts
- Minnesota
- New Hampshire
- New Jersey
- New York
- Pennsylvania
- Rhode Island
- Vermont
- Virginia
- Wisconsin

Confirmed cases: N=28,453
Probable cases: N=9,616

CDC estimates true annual incidence
~300,000
Lyme disease emergence in the United States
**Case Incidence of Other Ixodes Tick-Borne Diseases is Rising**

- **Babesiosis**
  - Risk: young and elderly people without a spleen, compromised immune systems, liver or kidney disease
  - Most common transfusion-transmitted pathogen
  - Congenital transmission
  - Case fatality approaches 25%
  - N=1762 in 2013

- **Anaplasmosis**
  - Risk: males, age>40 compromised immune systems
  - Transfusion transmitted
  - 0.7% case fatality

- **Lyme disease**
  - Risk: endemic area with activities
  - Peak ages 5-10 and 40-50
  - Not transfusion transmitted
Milestones in Lyme Disease 1975 - 2002

- **1975**: Discovery of Lyme arthritis
  - Rx: ATBs, steroids
  - Multisystem disease
  - Evidence for tick vector
  - Spirochetal etiology
  - ATBs prevent arthritis
  - Bb cultured; 1st serologic assay
  - 1st ICLB Mtg

- **1980**: PCN effective for established arthritis; 10% have ATB-refractory LA

- **1985**: 1st Nat’l conf on serologic testing

- **1990**: ATBs prevent arthritis
  - Mouse model
  - OspA vaccine protects mice

- **1995**: CDC recommends 2-tier serologic tests for LD
  - Molecular mimicry between OspA and human LFA-1
  - 1st Nat’l conf on serologic testing

- **2000**: LYMERRix licensed by SKB
  - Class action lawsuit against SKB
  - OspA vaccine protects mice

- **2002**: LYMERRix withdrawn

- **2005**: IDSA Rx Guidelines
Global Changes in Borrelia Gene Expression

OspC required for mammalian infection

Unfed tick
OspA+ OspC-

Feeding tick
OspA+/-, OspC+

OspC = variable major protein

VlsE required for infection persistence

VlsE = variable major protein-like sequence E

C6 Peptide ELISA
VlsE1, PepC10 ELISA
LYMErix: Significant Prevention of Definite Lyme Disease

3 doses – 78% protection

- **2 Doses**
  - Vaccine: N=5166, n=20
  - Placebo: N=5148, n=40
  - 50% protection

- **3 Doses**
  - Vaccine: N=4765, n=13
  - Placebo: N=4784, n=61
  - 78% protection
LYMErix: Significant Prevention of Asymptomatic Infection

3 doses – 100% protection

2 Doses
V: N=5166
P: N=5148

3 Doses
V: N=4765
P: N=4784

Placebo
Vaccine

No. of LD cases

0 2 4 6 8 10 12 14

83%
100%
Reported Clinical Findings Among US Lyme Disease Cases, 2001 - 2015

- Cardiac: 1%
- Meningitis/Encephalitis: 2%
- Radiculoneuropathy: 4%
- Bell’s palsy: 9%
- Arthritis: 30%
- Erythema migrans: 71%

N = 236,327

Adapted from CDC website
The Stages and Most Common Clinical Features of Lyme Borreliosis

**Early localized infection**

- **Erythema migrans**
  - Often accompanied by flu-like symptoms in the United States

**Disseminated infection, systemic symptoms**

- **Lyme neuroborreliosis**
  - Acute neurological involvement, often lymphocytic meningitis, cranial neuritis or radiculoneuritis

**Localized infection, usually without systemic symptoms**

- **Lyme arthritis**
  - Arthritis in one or a few joints, most commonly the knee, with minimal, if any, systemic symptoms

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**Stage 1**

- **Days–weeks**
  - **Borrelial lymphocytoma**
    - Dense polyclonal lymphocytic infiltration, often on the nipple in adults or the earlobe in children

**Stage 2**

- **Weeks–months**
  - **Carditis**
    - First-to-third-degree atroventricular block

**Stage 3**

- **Months–years**
  - **Acrodermatitis chronica atrophicans**
    - Oedema (purplish in colour), atrophy of the skin and local peripheral sensory neuritis, usually without systemic symptoms

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Nature Reviews | Disease Primers

Steere, A. C. et al. (2016) Lyme borreliosis

*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.90
Erythema Migrans

• Present in ~70% of cases
• Solitary lesion in 20%
• Lesion may have tingling, burning quality, occasionally mildly pruritic
• Typically expands 2-3 cm/day; not always a bull’s eye rash

Lyme EM can be vesicular or necrotic and mimic cellulitis or the infamous “spider bite”
Some tickborne infections show up in odd places.
Rash and fever in Costa Rica

• 10 year-old girl developed a fever of 101F and a localized, annular erythematous lesion on the forehead

• Email from her dad in Costa Rica: Symptoms developed about 3-4 days after arrival in Costa Rica (La Selva biological station – tropical rain forest)

• Could this be a tropical disease?
Costa Rica - rash and fever
Babesiosi in Colorado (NOT)

61 yo old healthy man – UCONN Professor
Exposure – walks his dogs in the woods every day – exposed to many ticks but no clear h/o tick bite

June 16 Headaches then improved
June 18 Left CT for Idaho, Washington, Colorado
June 19 Chills/sweats
June 25 Admitted to hospital with fever, chills, rigors, respiratory distress - ?malaria or brucella
Parasitemia 10%, transfused x4, platelets 40K, bilirubin 5.5. AST 350, respiratory failure – intubated on ventilator for 1 wk
Treated with clindamycin, quinine, doxycycline
Eventually made a full recovery
STARI: Southern Tick Associated Rash Illness

- **Ixodes scapularis**
- **Amblyomma americanum**

**Distribution of Amblyomma americanum**

- STARI: EM-like rash with fever, headache, myalgias
- Not linked to arthritis, neurologic disease or chronic symptoms
- Responds to Doxycycline

www.cdc.gov
STARI vs Lyme - summary

- 2005 study STARI (Missouri) vs Lyme (NY):
  - Patients with STARI were more likely to recall a tick bite than were patients with Lyme disease.
  - The time period from tick bite to onset of the skin lesion was shorter among patients with STARI (6 days, on average).
  - STARI patients with an erythema migrans rash were less likely to have other symptoms than were Lyme disease patients with erythema migrans rash.
  - STARI patients were less likely to have multiple skin lesions, had lesions that were smaller in size than Lyme disease patients (6-10 cm for STARI vs. 6-28 cm for Lyme disease), and had lesions that were more circular in shape and with more central clearing.
  - After antibiotic treatment, STARI patients recovered more rapidly than did Lyme disease patients.

https://www.cdc.gov/stari/disease/index.html
Two-Tiered Serologic Testing

- **First Tier:**
  - Lyme ELISA (IgM, IgG)
    - Allows cut-off for reactivity to be set 2-standard deviations above normal human serum
- **Second Tier:**
  - Immunoblot *only* for equivocal or positive ELISA
    - IgM: 2 of 3 bands (23, 39, 41)
    - IgG: 5 of 10 bands (18, 21, 28, 30, 39, 41, 45, 58, 66, 93)
  - IgM valid during first month of symptoms only; use IgG for symptoms >1-2 months duration.
  - **Be cautious about non-FDA approved or experimental tests for Lyme.**

Lane 1: Location of indicated Bb proteins
Lane 2: Reactivity of IgG from sera of a patient with Lyme disease

www.cdc.gov
Clinical Response of Lyme Disease to Antibiotics

• ~25% of patients with early Lyme disease have musculoskeletal symptoms when assessed 3 months after therapy.

• 10% of patients with Lyme arthritis develop chronic synovitis that does not respond to antibiotics (“post-antibiotic Lyme arthritis”)

• A minority of patients develop a post-Lyme disease syndrome with subjective symptoms that do not respond to antibiotics.
Sources of Controversy

• Performance of serologic tests

• Efficacy of antibiotics

• Existence of “chronic Lyme disease”
Sources of Controversy

• Performance of serologic tests
  – Two-tier method is effective if performed and interpreted as recommended

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• Performance of serologic tests
  – Two-tier method is effective if performed and interpreted as recommended

• Efficacy of antibiotics
  – Antibiotics eliminate viable spirochetes, but clearance of inflammatory products may take time
  – Persistent objective signs may be due to residual damage or underlying genetic susceptibilities associated with immune dysregulation

• Existence of “chronic Lyme disease”
Sources of Controversy

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• Efficacy of antibiotics
  — Antibiotics eliminate viable spirochetes, but clearance of inflammatory products may take time
  — Persistent objective signs may be due to residual damage or underlying genetic susceptibilities associated with immune dysregulation

• Existence of “chronic Lyme disease”
  — Term previously described untreated late disease
  — No evidence yet that active infection with *Borrelia burgdorferi* can persist in people after IDSA recommended therapies for Lyme disease
  — New episodes of EM after treatment for LD are due to reinfection rather than recrudescence of a partially treated infection
PLEASE Trial
Persistent Lyme Empiric Antibiotic Study Europe

- 280 subjects with h/o Lyme disease based on objective evidence of disease (96, 34%) or nonspecific symptoms attributed to Lyme disease based on positive IgM and/or IgG immunoblot assays.

- All participants received 2 weeks IV ceftriaxone before 12-week randomized treatment phase: doxycycline or clarithromycin + hydroxychloroquine

  - No differences between antibiotic treatment groups and those receiving placebo

  - 68.6% had at least 1 adverse reaction that was thought to be drug related

- Conclusion: long-term antibiotics provide no additional benefit to short-term treatment for Lyme disease

PEARL #1

No Lyme serology can be used to follow-up on response to therapy

No Lyme serology can be used to prove eradication of Borrelia organisms after treatment
Treatment-resistant Lyme Disease

Fatigue, memory problems, myalgias, arthralgias

1. ? Chronic infection
2. ? Persistent inflammatory response
3. ? Autoimmune response (reaction to living or dead spirochetes)
NIH research

Xenodiagnosis

Experimental technique using a known vector (larval tick) to acquire infection (Borrelia) from a suspect host (human or animal with or without persistent symptoms following Lyme disease)
Xenodiagnosis
Xenodiagnosis

Purpose:
Answer this question, “do Borrelia persist in humans after treatment?”
Attempt to isolate Borrelia from patients with persistent symptoms after treatment
Ticks may be the most efficient way to isolate Borrelia
**Borrelia persists in dogs after antibiotic treatment**

Dogs were treated with either doxycycline or amoxicillin for 30 days, then tested by punch biopsy

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Culture pos (2 months post-Rx)</th>
<th>PCR pos (6 months post-Rx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>1 / 6</td>
<td>3 / 4</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1 / 6</td>
<td>2 / 4</td>
</tr>
</tbody>
</table>

Staubinger et al, J Clin Micro, 1997
Fig 1. Feeding of Ixodes larvae under a Nitex mesh. *Ixodes* ticks were placed on the forearm of the subject using tweezers and covered with a Nitex mesh sealed with tape on all sides (A). The mesh was removed 24 hours later to reveal the attached ticks (B).

**Xenodiagnosis research**
- Based on animal research in dogs, mice, monkeys
- 30 larval ticks free of disease
- Applied under a dressing
- Removed after 4-5 days
- Ticks are examined for Borrelia by a variety of laboratory methods including culture, feeding on mice, mass spectroscopy, PCR
- Results so far – evidence of Borrelia infection but no cultured spirochetes
Human Relapsing Fever Infection History

1868 Spirochetes discovered in blood of patients with relapsing fever (Obermeir et al.)

1903 **Soft bodied ticks** identified as vectors for relapsing fever in Africa (Dutton and Todd)

1907 Human body louse identified as a vector for relapsing fever in India (Mackie et al.)

1995 **Hard-bodied ticks** identified as a vector for a new relapsing fever *Borrelia* in Japan and named *Borrelia miyamotoi* after Kenji Miyamoto (Fukunaga et al.)

2001 *B. miyamotoi* found in *Ixodes scapularis* in the US (Scoles/Fish et al.)

2003 *B. miyamotoi* found in *Ixodes ricinus* in central Europe (Richter et al.)

2011 Discovery of first cases of human *B. miyamotoi* infection (Platonov et al.)

2013 First human cases of *B. miyamotoi* infection in US (Gugliotta et al. and Krause et al.)

2013 The *B. miyamotoi* genome sequenced (Hue/Barbour et al.)
Soft bodied tick relapsing fever

Fig. 1. Reported cases of tick-borne relapsing fever by county, United States, 1990 to 2002 (From Centers for Disease Control and Prevention. Tick borne relapsing fever trends. Available at: http://www.cdc.gov/ncidod/dvbid/RelapsingFever/TBRF_DiseaseTrends.html. Accessed December 12, 2007.)
Hard tick-borne relapsing fever epidemiology

- Should be found wherever Lyme disease is endemic
- Cases described thus far from Connecticut, Massachusetts, Rhode Island, New Jersey, New York, Japan, Netherlands, Russia
- Frequency of infection appears to be less than that of Lyme disease but similar to that of anaplasmosis and babesiosis, based on seroprevalence and PCR studies
- One study suggests peak in cases occurs in August, one month later than Lyme disease peak; Possibly due to larval transmission (larval questing peak in August in Northeast)
- **Prevalence** 1% PCR, 3-10% seropositive in those suspected of tickborne disease
Seasonal distribution of acute *Borrelia miyamotoi* incident infection

Prevalence of *B. miyamotoi*-infected ticks: <4%

**Mendocino County: 1.4%**

**Statewide:**
- Adults 0.5%
- Nymphs 1.4%

**Midwest (MN, WI, MI, IL, IN): 2.2%**
- MN: 0.6%-2.6%
- WI: 1%

**NE Urban Forest: 0.8% nymphs**
- NE national parks: <1-4%
- DE: 0.8% nymphs
- TE:

Blue dots = cases of Lyme disease, 2016
Phylogenetic Analysis of *Borrelia miyamotoi*

Relapsing fever—hard ticks

Relapsing fever—soft ticks

Duration of Tick Attachment and *B. miyamotoi* Transmission

Table 2

Transmission outcomes for mice fed upon for different durations of time by a single *B. miyamotoi*-infected *I. scapularis* nymph.

<table>
<thead>
<tr>
<th>Duration of nymphal feeding</th>
<th>Evidence of <em>B. miyamotoi</em> DNA in mouse blood&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. mice examined</td>
</tr>
<tr>
<td>24 h</td>
<td>30</td>
</tr>
<tr>
<td>48 h</td>
<td>35</td>
</tr>
<tr>
<td>72 h</td>
<td>35</td>
</tr>
<tr>
<td>Complete feed (&lt; 72–96 h)</td>
<td>30</td>
</tr>
</tbody>
</table>

<sup>a</sup> Blood collected 9–11 days after the nymphal tick started to feed.

Breuner NE, *et al.* *Ticks Tick-borne Dis* 8 (2017):677
### Borrelia miyamotoi Disease: Summary

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset after known tick-bite</td>
<td>Usually within 2 weeks</td>
</tr>
<tr>
<td>Signs/symptoms</td>
<td>Fever, headache, fatigue, arthralgia, myalgia, nausea/anorexia</td>
</tr>
<tr>
<td>Laboratory testing</td>
<td>May have leukopenia or leukocytosis, thrombocytopenia, AST/ALT elevation</td>
</tr>
<tr>
<td>Concomitant erythema migrans</td>
<td>Coinfection with <em>B. burgdorferi sl</em></td>
</tr>
<tr>
<td>Risk factors for more severe disease or unusual presentations</td>
<td>Advanced age, known immunodeficiency (splenectomy, lymphoma), use of immunosuppressive medications (CHOP, rituximab)</td>
</tr>
</tbody>
</table>
Summary of Published Studies

- *B. miyamotoi* has limited diversity that correlates with *Ixodes* vector
- Prevalence varies but generally <4% of ticks are infected
- Transmitted by larvae; vertebrate reservoir(s) unknown
- Transmitted by nymphs within 24 hours attachment
- Surveillance studies with PCR-based assays vs serologic assays show evidence of human exposure and illness
- Most common clinical symptoms: fever, fatigue, headache, myalgia, arthralgia
- Immunocompromised or aged hosts may develop meningoencephalitis
- Clinical disease resolves without therapy in people without known immune deficiencies; possible self-limited infection
- Doxycycline or Ceftriaxone administered for 2-4 weeks are effective therapies, even with long-standing infection
- No apparent long-term sequelae
- Diagnosis? – may test neg for “Lyme” – use GlpQ assay or PCR
The Emergence of *Borrelia mayonii*

*Minnesota, Wisconsin, North Dakota*

- 2012-2014: Detected in 6 subjects found to have atypical melting point for Borrelia DNA target (oppA1 gene) on clinical samples (5 blood, 1 synovial fluid)
- Findings that distinguish *B. mayonii*
  - Nausea/vomiting
  - Atypical rash (diffuse macular face, arms, trunk, extremities)
  - Hospital admission in 2 of 6 patients
  - Lymphopenia, mild thrombocytopenia, high hepatic transaminases
  - Visible bacteremia (by PCR 180 X level seen with *B. burgdorferi*)
  - Potential for heightened Jarisch Herxheimer reactions
Human Granulocytic Anaplasmosis (HGA) – not "Ehrlichiosis"

- **Ehrlichiosis** is Human Monocytic Ehrlichiosis caused by *Ehrlichia chaffeensis*, vector is *Amblyomma americanum* (lone star tick); named for Fort Chaffee, Arkansas
- HGA is caused by the bacterium *Anaplasma phagocytophilum*.
- Symptoms typically begin within 1-2 weeks after the bite of an infected tick.
  - Fever
  - Headache
  - Muscle pain
  - Malaise
  - Chills
  - Nausea / Abdominal pain
  - Cough
  - Confusion
  - Rash (rare with anaplasmosis)
- Anaplasmosis can be a serious illness that can be fatal if not treated correctly, even in previously healthy people.
- Severe clinical presentations may include difficulty breathing, hemorrhage, renal or hepatic failure, neurological problems.
- Estimated case fatality rate is less than 1%.
- Patients who are treated early may recover quickly on outpatient medication, while those who experience a more severe course may require intravenous antibiotics, prolonged hospitalization or intensive care.
- Treatment – doxycycline, 3 days after fever subsides
Anaplasmosis
Epidemiology

Percent of anaplasmosis cases reported in each month:
This figure shows the percent of cases reported from 1994 through 2010 by month of onset to give the seasonality of cases. There are cases reported in each month of the year, however most are reported in June and July, with more than 25% of cases are reported in June.

https://www.cdc.gov/anaplasmosis/stats/index.html
Tick-Transmitted Flavivirus: Emergence of Powassan Virus (POWV/Deer Tick Virus)

Risk: Young and elderly
Rapid transmission (15 min)
Presents 1-4 weeks after tick bite with fever, generalized weakness, lethargy, ± seizures/confusion
Brain MRI nonspecific
Dx: direct detection of virus by PCR in blood, CSF, brain tissue
Fatality rates: 10-36%

Note: CT first human case, infant 2016; probably transmitted from his father’s hunting clothing. POWV has been found in ticks in CT since 1978.
Human babesiosis

• Causative pathogens: protozoan parasites in phylum Apicomplexa
• Target tissue: erythrocytes
• Transmission:
  • *Ixodes* ticks
  • Blood transfusion
  • Transplacental
• Diagnosis: epidemiology, symptoms, microscopy, PCR, antibody
• Treatment: atovaquone/azithromycin or clindamycin/quinine
### Table A

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Plasmodium vivax</em></td>
<td>Human Malaria</td>
</tr>
<tr>
<td><em>Plasmodium knowlesi</em></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium malariae</em></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium ovale</em></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td></td>
</tr>
<tr>
<td><em>Babesia microti</em></td>
<td>Babesiosis</td>
</tr>
<tr>
<td><em>True Babesia</em></td>
<td>Babesiosis</td>
</tr>
<tr>
<td><em>Cyclospora cayetanensis</em></td>
<td>Cyclosporiasis</td>
</tr>
<tr>
<td><em>Isospora belli</em></td>
<td>Isosporiasis</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Toxoplamosis</td>
</tr>
<tr>
<td><em>Cryptosporidium parvum</em></td>
<td>Cryptosporidiosis</td>
</tr>
</tbody>
</table>

*B. divergens, B. duncani, B. venatorum*

### Diagram B

- **A.**
  - *B. microti* in human RBCs
  - *P. falciparum* in human RBCs

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From: Case report of the patient source of the *Babesia microti* R1 reference strain and implications for travelers

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Babesia epidemiology summary

World wide distribution
Emerging infectious disease
Geographic dispersion follows Lyme disease (not malaria)
When Lyme disease and babesiosis are endemic for a long time in an area, they may have a similar frequency
From: Case report of the patient source of the Babesia microti R1 reference strain and implications for travelers
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Babesiosis clinical manifestations

- Asymptomatic infection
- Viral-like illness
  - Fever, chills, sweats, headache, fatigue/malaise
- Severe illness and death (3-20%)
  - >50, asplenia, HIV-AIDS, malignancy, blood transfusion recipients
- Persistent, relapsing illness despite standard therapy
  - Malignancy/asplenia/immunosuppressive drugs/HIV-AIDS
  - May require treatment for 6wks after neg. smear
Reported cases of babesiosis
United States 1986-2014
Babesiosis is spreading in a similar pattern, although at a slower rate than Lyme disease.

*Town defined as ‘endemic’ the 1st year when cases are reported in two consecutive years*

Finch et al. Plos One, 2014
# Tick-borne disease coinfection

<table>
<thead>
<tr>
<th>Study</th>
<th>Diseases</th>
<th>% LD coinfected (number LD cases)</th>
<th>Acute symptoms of LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krause et al. 1996</td>
<td>Lyme disease/babesiosis</td>
<td>11% (240)</td>
<td>Mean no. 4 vs 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration Increased</td>
</tr>
<tr>
<td>Mitchell et al. 1996</td>
<td>Lyme disease/babesiosis</td>
<td>4% (96)</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Lyme disease/anaplasmosis</td>
<td>7% (96)</td>
<td>ND</td>
</tr>
<tr>
<td>Bologna et al. 1999</td>
<td>Lyme disease/anaplasmosis</td>
<td>13% (94)</td>
<td>ND</td>
</tr>
<tr>
<td>Krause et al. 2002</td>
<td>Lyme disease/babesiosis</td>
<td>22% (76)</td>
<td>Mean no. 5 vs 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration Increased</td>
</tr>
<tr>
<td></td>
<td>Lyme disease/anaplasmosis</td>
<td>4% (76)</td>
<td>Mean no. 5 vs 9</td>
</tr>
<tr>
<td>Steere et al. 2003</td>
<td>Lyme disease/babesiosis</td>
<td>2% (97)</td>
<td>Mean no. 4 vs 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration Increased</td>
</tr>
<tr>
<td></td>
<td>Lyme disease/anaplasmosis</td>
<td>2% (97)</td>
<td>Mean no. 4 vs 9</td>
</tr>
<tr>
<td>Horowitz et al. 2012</td>
<td>Lyme disease/anaplasmosis</td>
<td>2%-5%-8%-11% (311)</td>
<td>Mean no. 6 vs 6-8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration ND</td>
</tr>
</tbody>
</table>
Transfusion-transmitted babesiosi

• 1.4% of blood donors sero-positive, half of those were PCR positive
• *B. microti* is the most commonly reported transfused pathogen in the US
• More than 200 cases described and the incidence is increasing
• Cases reported in endemic and non-endemic areas
• Cases occur during and beyond “season”
• Risk of transfusion transmitted babesiosis= ~1:600 to 1:1 million units blood
• Symptoms similar to those of tick-transmitted disease but often more severe because blood recipients often are immunocompromised
• Mortality rate is ~20%
• Rhode Island Blood Center instituted the first *B. microti* laboratory-based screening of the blood supply in July 2010 and results were promising
• Letter from the Red Cross – what to do? *(Check a smear)*
Babesiosis treatment

Don’t treat based ONLY on positive serology – your patient may have self-cured an asymptomatic infection.

Mild to moderate disease
Atovaquone and azithromycin for 7 to 10 days

Severe disease
Clindamycin and quinine for 7 to 10 days
Exchange transfusion

Severe disease in severely immunosuppressed
Continue antibiotics for at least 6 weeks after smear-negative
Monitor for at least a month after antibiotics discontinued
Tick bite – red meat allergy

- Symptoms vary (mild itch, hives, GI, respiratory, or severe life-threatening anaphylaxis)
- Delayed reaction (3-6 hrs) to Galactose alpha 1-3 galactose (“alpha gal”)
- Alpha gal is a carbohydrate (sugar) found in red meat (beef, pork, lamb, venison, bison) – NOT in poultry or fish
- Also found in tick saliva (Amblyomma americanum – Lonestar tick)
- Also found in the chemotherapy drug cetuximab
PEARL #2
Fever, Flu-like Symptoms April-October
Mansfield Family Practice Approach

• Assume that all patients presenting with these symptoms in this time period COULD have a tickborne infection
• EM rash is definite Lyme – but don’t ignore co-infection
• Tick bite history is mostly irrelevant
• Lab: CBC, blood smear for babesia, Lyme ELISA (reflex to WB)
• Leukopenia and thrombocytopenia – highly suggestive of Lyme or anaplasma
• Optional serology for Anaplasma, Babesia
• Start empiric Rx with doxycycline 100mg BID (doxy monohydrate may be better tolerated than doxy hyclate)
• Dramatic response in 48 hrs is highly suggestive
• Treat babesia only if positive smear (serology may not help) – continue treatment until smear negative.
• Complex cases – use Imugen Lab in Norwood Mass for B.miyamotii serology, PCR
PEARL #3
I’ve been bitten by a tick...

• STAT dose 200mg doxycycline for adults >18yo (reduces the risk of Lyme 87%)*
• Within 3 days of the tick bite
• Does NOT protect against babesia, anaplasma
• Placebo group only 3% developed Lyme
• Don’t bother testing the tick
  – Wastes time
  – May not test for all pathogens
  – Even if the tick is negative symptoms demand DX

*Nadelman et al, NEJM 2001
“To avoid infections from biting insects, quit biting them.”
Integrated Tick Management Tools

- Personal protection measures
- Tick bite prophylaxis
- Landscape modifications
- Chemical control
  - Synthetic insecticides
  - Botanicals, “natural” compounds
- **Host-targeted acaricides**
  - Human, deer, mouse
- Host reduction or exclusion
- Host-targeted vaccines
- Education and behavior change

Dr. Kirby Stafford, CT Agricultural Experiment Station
Personal Protection

• Long-sleeve shirts, long pants
• Repellent with polymer-DEET or picaridin on the skin
• 0.5% Permethrin on clothing, netting, tents
  • Combination DEET/permethrin reduces mosquito bites by 99.9%
ON, not OFF

Use the correct product following the correct instructions

“Wait a minute! McCallister, you fool! This isn’t what I said to bring!”
Avoiding bites....

Will the real Family(ies) please stand up?

All contain DEET – which is best?
Avoiding bites....

My vote is Sawyer Family – sustained release, lasts the longest, lowest absorption.
Avoiding bites....

How safe is DEET?
Since 1957 – 10 Billion uses
1961-2000 - 42 published cases
  • Cutaneous 12 (irritant bullous)
  • Allergic 5 (urticaria)
  • Ingestion 7 (3 deaths)
  • Encephalopathy < 8yrs, 14 cases, 3 deaths, 11 resolved
    27-41 yrs, 4 cases, all resolved
EPA re-registered DEET in 1980 – estimate risk of 1/100 million (max), not oncogenic or teratogenic, not uniquely toxic to children
Picaridin (KBR-3023)
Avoiding bites….

Comparison in the field (Black saltmarsh mosquitos in the Everglades)

Mean complete protection times:
DEET (5.6)
Picaridin, KBR3023-Bayrepel (5.4)
PMD – eucalyptus (3.8)
IR3535-Skin-so-Soft BugGuard Plus (3.0)
Ethanol controls provided 0 percent repellency.
Interaction between DEET and sunscreen
Probably does not matter much but current advice is: Apply the sunscreen first, let it dry, then OK to apply the DEET
• BUT 1/3 decrease in SPF when DEET is applied after SPF – even 90 min later; need to re-apply SPF
• No decrease in DEET effectiveness when used with SPF
• No testing of picaridin or other repellents
• Many products, formulations, concentrations – can’t generalize
• Avoid combination products – may need more sunscreen than DEET, more often

Table 4. Acaricides with products labeled for the control of ticks in the residential landscape.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Some brand or common names*</th>
<th>Chemical type and usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bifenthrin</td>
<td>Talstar® Ortho® product</td>
<td>Pyrethroid insecticide. Available as liquid and granular formulations. Products available for homeowner use and commercial applicators.</td>
</tr>
<tr>
<td>Carbaryl</td>
<td>Sevin®</td>
<td>Carbamate insecticide. A common garden insecticide for homeowner use, some products are for commercial use only.</td>
</tr>
<tr>
<td>Cyfluthrin</td>
<td>Tempo® Powerforce™</td>
<td>Pyrethroid insecticide. Available for commercial and homeowner use with concentrates and ready to spray (RTS) products.</td>
</tr>
<tr>
<td>Deltamethrin</td>
<td>Suspend® DeltaGard® G</td>
<td>A pyrethroid insecticide for commercial applicators.</td>
</tr>
<tr>
<td>lambda-cyhalothrin</td>
<td>Scimitar® Demand®</td>
<td>A pyrethroid insecticide for commercial applicators.</td>
</tr>
<tr>
<td>Permethrin</td>
<td>Astro® Ortho® products Bonide® products Tengard® SFR Others</td>
<td>Pyrethroid insecticide. There are concentrates and ready to spray (RTS) products. Most are for homeowner use, a few are for commercial use.</td>
</tr>
<tr>
<td>Pyrethrin</td>
<td>Pyrenone® Kicker® Organic Solutions All Crop Commercial &amp; Agricultural Multipurpose Insecticide®</td>
<td>Natural pyrethrins with the synergist piperonyl butoxide (PBO) or insecticidal soap provide limited tick control. A combination of pyrethrin and PBO with either insecticidal soap or silicon dioxide (from diatomaceous earth) was found effective against ticks in one trial.</td>
</tr>
</tbody>
</table>

*Active ingredients and brand names frequently change as new products are registered and others discontinued. New formulations for homeowner use may become available. Mention of a product is for information purposes only and does not constitute an endorsement by the Connecticut Agricultural Experiment Station.
YOU ARE HERE

YOUR BAGGAGE IS HERE