Tickborne Diseases

CMED/EPI-526
Spring 2009
Ben Weigler, DVM, MPH, Ph.D

“Reports of tick-borne disease in Washington state are relatively few in comparison to some areas of the United States. Though tick-borne disease may not be common, the severity of these diseases generates public concern and questions.”

Washington State Dept. of Health
Tick Vector Ecology:

I. Deer ticks ("Ixodes ricinus-like") occur in all temperate biomes circumglobally.

II. Glacial terminal moraines = The maximum advance of a glacier during previous ice ages…. Ecologic refugia for deer tick survival and evolution.

III. Changing composition of lands across North America in past 2 centuries.

IV. Increasing associations of humans with wildlife.
White-tailed Deer

Odocoileus virginianus

The most abundant large game species in North America
Prior to European settlers: 23 to 34 Million deer in USA
Early 1900’s: 300,000 to 500,000 deer
Today: ~27 Million deer

- 1.5 Million deer/vehicle collisions annually
- → 130-200 human deaths
White-Footed Mouse

*Peromyscus leucopus*

- Principal lyme disease mammalian reservoir in North America
- First *B. burgdorferi* isolation in 1894 (museum specimens)
- Also reservoir host for Babesiosis and Ehrlichiosis
**Tick-borne Disease Ecology Terms:**

**Repletion** = full of blood (e.g., engorged female)

**Transovarial transmission** = e.g., *B. burgdorferi* in *I. Scapularis*, transmission to succeeding generations within the tick.

**Transstadial transmission** = among stages in life cycle, e.g., from nymph to adult

**Reservoir competence** = the capacity of a vertebrate animal species to maintain a pathogen as a continued source of infection for invertebrates.

**Vector competence** = capacity of an arthropod species to act as a biologically important source for infection of vertebrate animals, e.g., through replication of the agent within the vector.
Tick Phylogeny, based upon 18S RNA Sequence

~ 900 recognized species of ticks in the world
Some Tick Species Found in WA

- **Dermacentor spp.** – Throughout the State
  Prefer woodland areas, medium height grasses and shrubs between wetlands and woods, and sunny or open areas around woods. Immature ticks feed primarily on small mammals, particularly rodents, while the adults feed on deer, livestock, dogs, and humans.

- **Ixodes spp.** – West of the Cascades
  Live in heavily-forested or dense brushy areas, but not open areas. Preferred hosts for immature ticks are birds and small mammals, primarily rodents but humans and dogs serve as good substitutes. For adults, common hosts include livestock, dogs, and humans.

- **Ornithodoros spp.** – Mostly East of the Cascades
  Prefer burrows and nests. Usually feeds on rodents such as squirrels and chipmunks. Humans can be incidental hosts when sleeping in cabins or dwellings inhabited with tick-infested squirrels, chipmunks or other rodents.

1. Lyme Disease → 8 cases, perhaps 1/3 of which are imported.
2. Relapsing Fever (*Borrelia recurrentis*) → 2 cases. *Ornithodoros* spp.
3. Babesiosis “WA1” (3 cases in 1990’s, 1 case in 2002) → vector not identified
6. Tularemia → 1 case; tick is one of the several routes of possible exposure.
7. Tick paralysis (34 cases reported from 1946-2000) → esp. *Dermacentor andersoni* toxin. All cases occur in March through June.
Tickborne Diseases of WA State

- Lyme Disease: *I. pacificus*, but Eastern WA?
- Babesiosis: *Ixodes* spp., blood transfusions?
- RMSF: *Dermacentor* spp.
- Tularemia: *Dermacentor* spp.
- Relapsing Fever: *Ornithodoros* (soft ticks)
- Tick Paralysis: *Dermacentor* spp. In USA
Notifiable Tick-borne Diseases in Washington

• Lyme disease (within 3 work days)
• Q fever (within 3 work days)
• Relapsing fever (immediately)
• Tularemia (within 3 days)
<table>
<thead>
<tr>
<th>Tick Species</th>
<th>Distribution</th>
<th>Feeding Hosts</th>
<th>Affinity for Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ixodes scapularis</em></td>
<td>East/SE USA and Canada</td>
<td>Small mammals, reptiles, birds. Large mammals for adults</td>
<td>High</td>
</tr>
<tr>
<td>(Black legged tick)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ixodes pacificus</em></td>
<td>Canadian Pacific Coast</td>
<td>Small mammals, reptiles, birds. Large mammals for adults</td>
<td>Yes</td>
</tr>
<tr>
<td>(Westrn Black Legged tick)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Rhipicephalus sanguineus</em></td>
<td>USA, Africa, Middle East, India</td>
<td>Dogs principally (Brn dog tick)</td>
<td>Low</td>
</tr>
<tr>
<td><em>Dermacentor variabilis</em></td>
<td>USA, Canada, Mexico</td>
<td>Small mammals, Mice, Voles, Dogs</td>
<td>High</td>
</tr>
<tr>
<td>(Am. Dog Tick)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ixodes scapularis ticks, life stages
Ixodes scapularis ticks demonstrating changes in blood engorgement after various durations of attachment.

- **Nymphal Stage**
- **Adult Stage**
~180,000 human tick bites per year in Westchester County, NY
~15% of those persons experience a second bite within 6 weeks

Westchester County Census = 850,000 residents
Scanning EM of Ixodid mouthparts

Ixodid tick hypostome inserted into skin
Ixodes tick life cycle

- Engorged female mates with male
- Gravid female lays thousands of eggs on the grass (4-6 weeks)
- Eggs hatch into larvae (4-6 weeks)
- Engorged larvae shelter in grass and moult into nymphs (4-6 weeks)
- Engorged nymphs shelter in grass and moult into adults (10-20 weeks)
- Small mammals, birds
- Small mammals (rodents)
Deer tick on vegetation – “questing behavior”
Tick removal methods
Engorged on human skin

*Ixodes scapularis* and its distribution

(Black legged tick)
*Ixodes pacificus* and its distribution

(Western black legged tick)
Lone Star Tick and its distribution

(*Amblyomma americanum*)
Rhipicephalus sanguineus (Brown dog tick)
American Dog Tick

(Dermacentor variabilis)
Dragging for Ticks, woodland habitat
CDC Notifiable Disease Report: USA Year 2002

- Ehrlichiosis – 511
- Anaplasmosis – 216
- Lyme Disease – 23,763 (tripled since 1991)
  (11,873 Mid Atlantic, 7,807 New England)
- Q Fever – 61
- RMSF – 1,104
- Tularemia - 90

Steere AC, Malawista SE, Snydman DR, Shope RE, Andiman WA, Ross MR, Steele FM

“An epidemic form of arthritis has been occurring in eastern Connecticut at least since 1972, with the peak incidence of new cases in the summer and early fall. Its identification has been possible because of tight geographic clustering in some areas, and because of a characteristic preceding skin lesion in some patients.....”
Reported cases of Lyme disease—United States, 2005

1 dot placed randomly within county of residence for each reported case
• Bimodal distribution by age; highest in 5-9 year olds & 50-59 year olds.
• More likely in males (53.6% male) over all age groups.
Average Annual Incidence of Reported Cases of Lyme Disease by Age Group and Sex, United States, 1992-2004.
Reported Cases of Lyme Disease by Month of Illness Onset United States, 1992-2004
Reported Clinical Findings Among Lyme Disease Patients, 1992-2004

- Erythema migrans (rash): 68%
- Arthritis: 33%
- Facial palsy: 8%
- Radiculopathy: 4%
- Meningitis or encephalitis: 1%
- Heart block: 1%
Established* and reported** distribution of the Lyme disease vectors Ixodes scapularis (I. dammini) and Ixodes pacificus, by county, United States, 1907-1996

*at least 6 ticks or 2 life stages (larvae, nymphs, adults) identified.
**at least 1 tick identified.
Borrelia burgdorferi spirochetes
ECM Lesions
In endemic areas, \( p(\text{Lyme}|\text{Tick Bite}) = 0.012 \) to 0.05.
WASHINGTON - With tick season approaching, the maker of the nation's only vaccine against Lyme disease pulled it off the market, citing poor sales.

Lymerix had caused controversy in recent years, as patients said they were sickened by the vaccine and asked the government to restrict sales. Some filed lawsuits against maker GlaxoSmithKline.

Federal health officials said Tuesday they had found no evidence that the vaccine was dangerous. They urged people in Lyme-plagued states to take precautions against the pin-sized ticks that spread the disease.

Lymerix had $40 million in sales its first year on the market, and hundreds of thousands were vaccinated. But GlaxoSmithKline projected that fewer than 10,000 people would seek vaccination this year, and ended sales because "there's just no demand for it," said company spokeswoman Ramona Dubose.
FIGURE 1. Cost-effectiveness of Lyme disease vaccination

Note: This graph documents the effect of variations in cost of vaccination, vaccine effectiveness, and the probability of contracting Lyme disease on the cost-effectiveness of vaccination. The left-hand y-axis measures cost per case of Lyme disease averted. The right-hand y-axis measures the cost per long-term sequela (e.g., cardiac, neurologic, and musculoskeletal sequelae) averted. Underlying assumptions are as follows: probability of identifying and treating early Lyme disease, 85%; cost of treating cardiac sequelae, $6,845; cost of treating neurologic sequelae, $61,193; cost of arthritis $34,304; cost of treating early Lyme disease without sequelae $161).
Lyme Disease Vaccine Is Taken Off Market
Associated Press
Wednesday, February 27, 2002

The maker of the nation's only Lyme disease vaccine pulled it off the market yesterday, citing poor sales.

Lymerix had caused controversy in recent years, as patients who argued they were sickened by the vaccine asked the government to restrict sales and filed numerous lawsuits against maker GlaxoSmithKline.

But after a year of investigation, the Food and Drug Administration had found no proof that the vaccine was dangerous and thus did not tell the manufacturer to end sales, an agency spokeswoman said yesterday.

Lymerix had $40 million in sales its first year on the market, and hundreds of thousands were vaccinated. But GlaxoSmithKline projected that fewer than 10,000 people would seek vaccination this year, and decided it didn't make financial sense to keep selling the vaccine.
• Vaccine Development Timeline: 7-12 years
• Stages: Discovery, Early Development, Advanced Development, Preparation of FDA Application

• Then: On to Phase 1, Phase 2, and Phase 3 Trial (FDA)

• Total Cost to Licensure: $110 Million to $802 Million
The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

Gary P. Wormser,1 Raymond J. Dattwyler,2 Eugene D. Shapiro,5,6 John J. Halperin,3,4 Allen C. Steere,9 Mark S. Klempner,10 Peter J. Krause,4 Johan S. Bakken,11 Franc Sirle,12 Gerold Stanek,14 Linda Bockenstedt,1 Durland Fish,4 J. Stephen Dumler,12 and Robert B. Nadelman1

Clinical Infectious Diseases 2006;43:1089-1134
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1058-4838/2006/4309-0001$15.00
Table 2. Recommended antimicrobial regimens for treatment of patients with Lyme disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage for adults</th>
<th>Dosage for children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred oral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500 mg 3 times per day&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50 mg/kg per day in 3 divided doses (maximum, 500 mg per dose)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg twice per day&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not recommended for children aged &lt;8 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For children aged ≥8 years, 4 mg/kg per day in 2 divided doses (maximum, 100 mg per dose)</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>500 mg twice per day</td>
<td>30 mg/kg per day in 2 divided doses (maximum, 500 mg per dose)</td>
</tr>
<tr>
<td><strong>Alternative oral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected macrolides&lt;sup&gt;c&lt;/sup&gt;</td>
<td>For recommended dosing regimens, see footnote &lt;sup&gt;d&lt;/sup&gt; in table 3</td>
<td>For recommended dosing regimens, see footnote in table 3</td>
</tr>
<tr>
<td><strong>Preferred parenteral regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g intravenously once per day</td>
<td>50–75 mg/kg intravenously per day in a single dose (maximum, 2 g)</td>
</tr>
<tr>
<td><strong>Alternative parenteral regimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g intravenously every 8 h&lt;sup&gt;d&lt;/sup&gt;</td>
<td>150–200 mg/kg per day intravenously in 3–4 divided doses (maximum, 6 g per day)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>18–24 million U per day intravenously, divided every 4 h&lt;sup&gt;d&lt;/sup&gt;</td>
<td>200,000–400,000 U/kg per day divided every 4 h&lt;sup&gt;d&lt;/sup&gt; (not to exceed 18–24 million U per day)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Although a higher dosage given twice per day might be equally as effective, in view of the absence of data on efficacy, twice-daily administration is not recommended.

<sup>b</sup> Tetracyclines are relatively contraindicated in pregnant or lactating women and in children <8 years of age.

<sup>c</sup> Because of their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins.

<sup>d</sup> Dosage should be reduced for patients with impaired renal function.
Human Ehrlichiosis

- Family *Anaplasmataceae*
- Acute febrile multisystemic illnesses
  
  Main vector = *Amblyomma americanum*


  Main vector = *Ixodes scapularis, I. pacificus*


  Main vector = *Amblyomma americanum*
Human infection with *Ehrlichia canis*, a leukocytic rickettsia.

Maeda K, Markowitz N, Hawley RC, Ristic M, Cox D, McDade JE. Henry Ford Hospital, Detroit, MI.

- First identification of *E. chaffeensis*
- Resembled RMSF, but no rash.
Phylogram tree of the Family *Anaplasmataceae* based on 16S rRNA sequence similarity.
*Ehrlichia chaffeensis*

Within monocyte
Ehrlichia within bone marrow cells
Diff-Quick Stain for Ehrlichia
Ehrlichia chaffeensis (A and C; Wright stain) and Anaplasma phagocytophilum (B and D; Hema3 stain) morulae (arrows) in peripheral blood monocytes (A), peripheral blood neutrophils (B), DH82 canine histiocytic cell culture (C), and human HL-60 promyelocytic cell culture (D). Original magnification, ×260. (Panel A courtesy of A. Marty.)
Anaplasma phagocytophilum
Laboratory Detection

Ehrlichial infections pose difficult diagnostic challenges to both clinicians and laboratorians, and the availability of confirmatory assays is limited. Therefore, treatment decisions should be based on epidemiologic and clinical clues, and should never be delayed while waiting for confirmation. Similarly, test results should be interpreted in the context of the patient’s illness and the epidemiologic setting. **Problems arise from overuse of specialized tests for patients with a low probability of the disease and in areas with a low prevalence of disease.** Fundamental understanding of the signs, symptoms, and epidemiology of the disease is crucial in guiding requests for tests for ehrlichiosis and interpretation of testing results. **Routine clinical laboratory tests indicative of ehrlichiosis include low white blood cell count, low platelet count, and elevated liver enzymes.** The organisms can be demonstrated in blood smears by staining with Diff-Quik or Giemsa stains.
Cases of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) reported in the United States since 1986. The data reflect information available until January 2006; data for the year 1998 were unavailable.
Table 1. Meta-analysis of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) symptoms, signs, and laboratory findings.

<table>
<thead>
<tr>
<th>Symptom, sign, or finding</th>
<th>Patients, % (no. evaluated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HME</td>
</tr>
<tr>
<td>Symptom or sign</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>97 (633)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>57 (250)</td>
</tr>
<tr>
<td>Headache</td>
<td>80 (240)</td>
</tr>
<tr>
<td>Malaise</td>
<td>82 (234)</td>
</tr>
<tr>
<td>Nausea</td>
<td>64 (143)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33 (192)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (197)</td>
</tr>
<tr>
<td>Cough</td>
<td>26 (155)</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>41 (211)</td>
</tr>
<tr>
<td>Rash</td>
<td>31 (286)</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>3 (240)</td>
</tr>
<tr>
<td>Confusion</td>
<td>19 (279)</td>
</tr>
<tr>
<td>Laboratory finding</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>62 (276)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>71 (247)</td>
</tr>
<tr>
<td>Elevated serum AST or ALT level</td>
<td>83 (276)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from [1]. ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Table 3. Diagnostic tests for human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), by time interval after onset of clinical illness.

<table>
<thead>
<tr>
<th>Weeks after onset, diagnostic test</th>
<th>Sensitivity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HME</td>
</tr>
<tr>
<td>≤1</td>
<td></td>
</tr>
<tr>
<td>Blood smear evaluation</td>
<td>2–38</td>
</tr>
<tr>
<td>PCR</td>
<td>60–85</td>
</tr>
<tr>
<td>Culture</td>
<td>Highly variable&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serologic testing</td>
<td>22–55 (IgM, ≤44)</td>
</tr>
<tr>
<td>1–2</td>
<td></td>
</tr>
<tr>
<td>Blood smear evaluation</td>
<td>Unknown</td>
</tr>
<tr>
<td>PCR</td>
<td>Unknown</td>
</tr>
<tr>
<td>Culture</td>
<td>Unknown</td>
</tr>
<tr>
<td>Serologic testing</td>
<td>68</td>
</tr>
<tr>
<td>≥3</td>
<td></td>
</tr>
<tr>
<td>Serologic testing</td>
<td>≥90</td>
</tr>
</tbody>
</table>

<sup>a</sup> May require weeks of incubation.

<sup>b</sup> May require weeks of incubation; results are often positive within 2 weeks.
Table 4. Currently recommended therapeutic regimens for human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA).

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Treatment duration&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline hyclate</td>
<td>100 mg iv or po every 12 h</td>
<td>2.2 mg/kg po every 12 h</td>
</tr>
<tr>
<td>Tetracycline hydrochloride</td>
<td>500 mg po every 6 h</td>
<td>25–50 mg/kg/day po in 4 divided doses</td>
</tr>
<tr>
<td>Rifampin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>300 mg po every 12 h</td>
<td>10 mg/kg po every 12 h</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from [8]. Antibiotic treatment is not recommended for seropositive patients who are asymptomatic or who lack the typical manifestations of HME or HGA. iv, intravenously; po, by mouth.

<sup>a</sup> Antibiotic therapy should be continued for 3–5 days after fever subsides.

<sup>b</sup> Rifampin is recommended only for patients with contraindications to doxycycline or tetracycline therapy (e.g., allergy and pregnancy).
Human Anaplasmosis: Spatial Analysis, Lyme, Connecticut

→ Cases are not distributed randomly!
Rocky Mountain Spotted Fever

RMSF – *Rickettsia rickettsii*

American dog tick
(*Dermacentor variabilis*)

Rocky Mountain wood tick
(*Dermacentor andersoni*)
Number of reported cases of Rocky Mountain spotted fever by state and region, 1994-1998

2002: 16 patients, 2 deaths. Endemic.
Figure 7. Spatial distributions of isolates from the A.I. and A.II. subpopulations of Francisella tularensis subsp. tularensis relative to A) distribution of tularemia vectors Dermacentor variabilis, D. andersoni, Amblyomma americanum, and Chrysops discalis; and B) distribution of tularemia hosts Sylvilagus nuttallii and S. floridanus.
Dispatch

Transfusion-Associated Babesiosis after Heart Transplant

Joseph Z. Lux,* Don Weiss,† Jeanne V. Linden,‡ Debra Kessler,§ Barbara L. Herwaldt,¶ Susan J. Wong,‡ Jan Keithly,‡ Phyllis Della-Latta,# and Brian E. Scully*

We describe a 54-year-old spleen-intact man with transfusion-associated Babesia microti infection after a heart transplant. Adult respiratory distress syndrome developed in the patient, and he required mechanical ventilation. Our experiences with this patient suggest that babesiosis should be considered in the differential diagnosis of transplant patients who have fever and hemolytic anemia.
Babesia Life Cycle
Babesia microti in human blood smears
Tick Exposure Prevention

DEET!

Frequent Checks!

Remove Promptly!


“Numerous prevention strategies are available, and although they vary in cost, acceptability and effectiveness, uptake has been universally poor. Research in areas where Lyme disease is endemic has demonstrated that despite adequate knowledge about its symptoms & transmission, many people do not perform behaviors to reduce their risk of infection.”
Therapeutic Options

Lyme Disease: Doxycycline (100 mg twice daily)
Amoxicillin (500 mg 3-4 times daily)
If neuro involvement, ceftriaxone IV

Ehrlichiosis: Doxycycline (but maybe more monitoring)
Rifampin for young kids?

RMSF: Doxycycline

Babesiosis: Clindamycin (600 mg qid) & Quinine (650 mg tid)
Better - Azithromycin and Atovaquone