Babesia and Ehrlichia epidemiology: key points

1. Always test for babesia and ehrlichia if Lyme disease is suspected
2. "Endemic areas"—perhaps too broad a term; vector-borne infections are focally distributed
   - Agent may be enzootic but not zoonotic; there are known endemic "agents in search of an emerging disease"
   - Can we map relative magnitude of risk? Can we exclude risk? (Impact on pretest probability)
   - What is the utility of "infection rates"?
   - Risk distribution is dynamic
3. Seasonality of transmission—limited in nature to Epit weeks 15-40 but with annual variation
   - Ecological seasonality does not necessarily impact transfusion risk for babesiosis
   - HGE may be transmitted efficiently by adult ticks, therefore seen in cooler months

Holarctic distribution of Lyme disease
Ancient microbial guild transmitted by *Ixodes persulcatus* species complex:
*Borrelia burgdorferi sensu lato*; *Babesia microti*; *Babesia divergens*; *Anaplasma phagocytophilum*; *Ehrlichia muris*; tick borne encephalitis virus
The diagram illustrates the life cycle of ticks and their relationship with deer. Ticks go through three stages: larva, nymph, and adult. The lifecycle includes:

- **Larva**: During the summer, year 2, larva eggs hatch into larva ticks.
- **Nymph**: In the fall, year 1, larva ticks molt into nymphs.
- **Adult**: In the spring, year 3, nymph ticks molt into adult ticks.

The graph on the left shows the number of cases of Babesiosis and Lyme disease, with peaks in the summer and fall months.
How frequently do we expect coinfection?

On Nantucket, 7.5-14.5% of Lyme disease patients will be concurrently infected by *B. microti*; 3.4-8.8% with HGE; 13.0-21.4% with one or the other.
SEASONAL VARIATION OF TRANSMISSION RISK OF LYME DISEASE AND HUMAN BABESIOSIS

JOSEPH PIESMAN, THOMAS N. MATHER, GUSTAVE J. DAMMIN, SAM R. TELFORD, III, CATHERINE C. LASTAVICA, AND ANDREW SPIEGLMAN


The seasonal host-seeking pattern of nymphal *Ixodes dammini* infected with *Babesia microti* or *Borrelia burgdorferi* was determined on Nantucket Island, Massachusetts, during 1985. The peak period of host-seeking by infected nymphal *I. dammini* occurred in May and June. On a per person-hour basis, the number of infected ticks collected reached a maximum in May (*Babesia* = 17.3; *Borrelia* = 16.2). The number of infected ticks remained high in June, but decreased notably in July, August, and September. Transmission risk of the tick-borne etiologic agents of Lyme disease and human babesiosis in Massachusetts is greatest during the late spring-early summer months of May and June.

*Babesia; babesiosis; Borrelia; Lyme disease; seasons; ticks*

### Table 1

**Seasonal variation of transmission risk for Lyme disease (Borrelia burgdorferi) and babesiosis (Babesia microti) on Nantucket Island, 1985**

<table>
<thead>
<tr>
<th>Month</th>
<th>No. of nymphs per person-hour</th>
<th>% nymphs infected</th>
<th>No. of infected nymphs per person-hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>April</td>
<td>11.0</td>
<td>29.0</td>
<td>3.0</td>
</tr>
<tr>
<td>May</td>
<td>37.2</td>
<td>46.5</td>
<td>17.3</td>
</tr>
<tr>
<td>June</td>
<td>55.4</td>
<td>43.3</td>
<td>15.2</td>
</tr>
<tr>
<td>July</td>
<td>62.0</td>
<td>23.1</td>
<td>4.4</td>
</tr>
<tr>
<td>August</td>
<td>4.6</td>
<td>86.4</td>
<td>2.0</td>
</tr>
<tr>
<td>September</td>
<td>2.0</td>
<td>20.0</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*Table 1*: Seasonal variation of transmission risk for Lyme disease (Borrelia burgdorferi) and babesiosis (Babesia microti) on Nantucket Island, 1985.
“Infection rates”, sample vs. population, 95% confidence interval

If you assume that your sample is randomly selected from some population (that follows a Gaussian distribution), you can be 95% sure that the confidence interval includes the population mean. More precisely, if you generate many 95% CI from many data sets, you expect the CI to include the true population mean in 95% of the cases and not to include the true mean value in the other 5%. Since you usually don't know the population mean, you'll never know when this happens. (Motulsky, 2009, GraphPad)

<table>
<thead>
<tr>
<th>Month</th>
<th>%</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>April</td>
<td>20.0</td>
<td>7.8-40</td>
</tr>
<tr>
<td>May</td>
<td>46.5</td>
<td>35.2-57.5</td>
</tr>
<tr>
<td>June</td>
<td>43.3</td>
<td>32.0-54.7</td>
</tr>
<tr>
<td>July</td>
<td>23.1</td>
<td>8.9-53.2</td>
</tr>
<tr>
<td>August</td>
<td>36.4</td>
<td>13.4-69.1</td>
</tr>
<tr>
<td>Sept</td>
<td>20.0</td>
<td>0.51-71.6</td>
</tr>
</tbody>
</table>
Distribution and prevalence is dynamic, varying over time

- Intensification and coalescence of small foci
- Dependence on local factors (weather, rodent population dynamics, tick demography)

Figure 1. Human babesiosis incidence per census tract, Rhode Island, USA, 1998–2004. Data from Rhode Island Department of Health.
Is there anything that we can measure that predicts human risk?

Mouse density indices (captures/trapnight) for July-August each year

Babesiosis case data from Nantucket Cottage Hospital Clinical lab suggests that there is no linear relationship between mice and case numbers


Confirmatory testing laboratory changed at least twice

HGE only recognised in 1995

Retrospective chart review would be very expensive

<table>
<thead>
<tr>
<th>regressor</th>
<th>Rank correlation</th>
<th>slope</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tick/mouse</td>
<td>-0.332</td>
<td>-1.70</td>
<td>2.6</td>
</tr>
<tr>
<td>Mouse density</td>
<td>-0.078</td>
<td>-0.05</td>
<td>0.2</td>
</tr>
<tr>
<td>Infected ticks</td>
<td>-0.120</td>
<td>-20.90</td>
<td>0.4</td>
</tr>
<tr>
<td>Prev x ticks/mouse</td>
<td>-0.085</td>
<td>-6.20</td>
<td>1.6</td>
</tr>
<tr>
<td>Questing ticks</td>
<td>0.603</td>
<td>0.20</td>
<td>11.8</td>
</tr>
</tbody>
</table>
Subadult deer tick phenology varies by year

Graphs by timesort
Babesiosis in the NY Times
Thursday, June 23, 2011

It's official, Babesiosis is on the rise. Approximately 25% of people who live on Block Island (near Martha's Vineyard) test positive for it. In places where Lyme disease is endemic, experts believe that Babesiosis is becoming very common...places like coastal Rhode Island, Massachusetts, Connecticut and Long Island.

It's in the Times. Babesiosis (the disease one gets from the protozoan Babesia) is now something that is common enough for people to look out for. It's carried by ticks. And unlike Lyme disease, which sometimes causes a rash, there is no outward indicator that a person is infected. So if you didn't notice the tick, you might be sick for mysterious reasons.

Herwaldt et al 2011
**DIVERSITY OF BABESIA INFECTING DEER TICKS (LYODES DAMMINI)**

PHILIP M. ARMSTRONG, PAULA KATAVOLOS, DIANE A. CAPORALE, ROBERT P. SMITH, ANDREW SPIELMAN, AND SAM R. TELFORD III

*Department of Tropical Public Health, Harvard School of Public Health, Boston, Massachusetts; Research Department, Maine Medical Center, Portland, Maine*

**Sera (n=771) from coastal New England residents**

-- 0% reactive to *B. odocoilei*

-- 4.5% (3.2-6.3) reactive to *B. microti*
Eastern cottontail rabbits

- Introduced to New England from Missouri and Kansas in the 1920s
- Peridomestic, can reach great densities (15/hectare)
- Previously demonstrated to maintain parallel cycle of transmission of *Borrelia burgdorferi* s.l. with *Ixodes dentatus* (Telford and Spielman 1988)
- Also good reservoirs for *Anaplasma (Cytoecetes) phagocytophilum* (Goethert and Telford 2003) as well as *A. bovis* (Goethert and Telford 2004)
- Known to maintain Kemerovo group orbiviruses, with *Haemaphysalis leporispalustris* as vector
Rabbits and *B. divergens*?

- *Babesia microti* infects rabbits (about 5%)
- Another *Babesia* sp found by sequencing 18S rDNA amplicons
- Morphology suggested *B. divergens* (paired pyriforms, accole forms)
- Identical by 18S sequencing to Kentucky human infection due to “MO-1”
- 99.8% similar to Purnell strain *B. divergens* for 18S rDNA
- Serologically reactive more to Purnell strain (IFAT GMT 1:325) compared to endemic *B. odocoilei* (1:180)
Is the rabbit *Babesia B. divergens*?

- Morphology: paired pyriforms, accoile forms
- 18S rDNA sequence difference (0.2%) well within what might be expected from allopatric populations
- Seroreactivity: greater reactivity to *B. divergens* Purnell than to sympatric *B. odocoilei* (IFAT GMT 325 vs 180 respectively)
- Association of PCR positivity with larval *I. dentatus* abundance, suggesting transovarial transmission (main mode of perpetuation for *B. divergens*)
- Failed to infect jirds.
- Unusual host (although *B. divergens* may infect humans and jirds)
- No evidence of cattle exposure ever in the U.S.
- Found on different continent

**FIGURE 1.** Hematocrit (A) and rectal temperature (B) postinoculation. Individual values for the splenectomized (x) and spleen-intact (□) control calves inoculated with *Babesia divergens* and means for two splenectomized (△) and three spleen-intact (○) principal calves inoculated with the Nanucket *Babesia* isolate are shown.
Sera (n=771) from coastal New England residents -- 1.6% (95% CI 0.8-2.7) IgG reactive to *B. divergens* Purnell by IFAT

-- 0% reactive to *B. odocoilei*

-- 4.5% (3.2-6.3) reactive to *B. microti*
Ehrlichiosis

- First described in the 1930s as a canine infection (E. canis)
- Tickborne fever of sheep due to Cytoecetes/Ehrlichia phagocytophila
- Ehrlichia equi described in late 1960s, causing self-limited infection of horses
- Human monocytic ehrlichiosis due to E. chaffeensis described in mid 1980s
- Human granulocytic ehrlichiosis agent now called Anaplasma phagocytophilum
- Agent of canine granulocytic ehrlichiosis (E. ewingii) zoonotic in southcentral U.S.
Ehrlichiosis (includes disease caused by *Ehrlichia chaffeensis*, *E. ewingii*, *E. muris*, *Anaplasma phagocytophilum*

Clinical presentation: A tick-borne illness characterized by acute onset of fever and one or more of the following symptoms or signs: headache, myalgia, malaise, anemia, leukopenia, thrombocytopenia, or elevated hepatic transaminases. Nausea, vomiting, or rash may be present in some cases.

Clinical evidence: Any reported fever and one or more of the following: headache, myalgia, anemia, leukopenia, thrombocytopenia, or any hepatic transaminase elevation.

CSTE Position Statement Number: 09-ID-15
Human granulocytic ehrlichiosis (HGE), a.k.a. human anaplasmosis

3.1-5.6% of adult *I. dammini* (n>1000) from coastal New England are infected by *A. phagocytophilum*

•If deer “genotypes” do not cause human disease, what use is measuring prevalence of infection in host seeking ticks or animals?
Lone Star ticks

- **Amblyomma americanum**
- All 3 stages aggressively bite humans; notorious pest tick in the South
- Vector for Masters Disease/STARI (Lyme disease mimic, etiology unknown); human ehrlichiosis (*E. chaffeensis, E. ewingii*); RMSF; tularemia
- Deer are the main hosts for all developmental stages
- Very microhabitat dependent, seems associated with kudzu or bittersweet invasion
- Stable infestations only on Cuttyhunk, Nashawena, and Prudence Islands; sporadic specimens from other New England sites do NOT imply persistent infestation
LETTER
Prevalence of *Ehrlichia muris* in Wisconsin Deer Ticks Collected During the Mid 1990s
Sara R. Telford III*, Heidi K. Goethert and Jenny A. Cunningham
Tufts University, Cummings School of Veterinary Medicine, 200 Westboro Road, North Grafton, MA 01536, USA

**Fig. (1).** Phylogenetic analysis of *Ehrlichia* sp. DNA amplified from archived adult deer ticks collected in Spooner, Wisconsin during 1992-1997. DNA sequences of other *Ehrlichia* spp. were downloaded from NCBI Genbank, aligned using ClustalW, and then adjusted by eye using GeneDoc. MEGA was used to generate neighbor-joining trees for citrate synthase (left panel) and groEL (right panel) sequences using the Kimura 2-parameter model. 500 bootstrap replicates were done to assess the stability of the resulting branch nodes.
Acknowledgments

We are supported by grants from the NIH (past – AI 19693, AI 39002; current RO1 AI064218).

We thank local physicians and pathologists who send us interesting specimens, particularly Dr. Tim Lepore, Nantucket Cottage Hospital.