Tick-borne agents of human disease of world-wide importance

<table>
<thead>
<tr>
<th>agent</th>
<th>disease</th>
<th>US cases 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>Lyme disease</td>
<td>14,536</td>
</tr>
<tr>
<td><em>Rickettsia rickettsii</em></td>
<td>Rocky Mountain spotted fever</td>
<td>1,550</td>
</tr>
<tr>
<td><em>Anaplasma phagocytophilum</em></td>
<td>human granulocytic anaplasmosis (HGA)</td>
<td>646</td>
</tr>
<tr>
<td><em>Ehrlichia chaffeensis</em></td>
<td>human monocytic ehrlichiosis (HME)</td>
<td>578</td>
</tr>
<tr>
<td>Babesia microti</td>
<td>human babesiosis</td>
<td>not reported*</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>tularemia</td>
<td>95</td>
</tr>
<tr>
<td><em>Borrelia spp.</em> (&gt;10 species)</td>
<td>relapsing fever</td>
<td>not reported**</td>
</tr>
<tr>
<td>Flavivirus/tick-borne encephalitis viruses</td>
<td>Powassan virus encephalitis (TBE, RSSE)</td>
<td>not reported***</td>
</tr>
</tbody>
</table>

---

* ≥ 147 cases in CT, NY, MA and RI, 1999
** ≥ 247 cases in AR, CA, CO, ID, MT, NV, NM, TX, UT, WA, WY, 1990-2000
*** 11,302 cases in Europe, 1999; rare in US

Tick-borne infections: a clinical dilemma?

<table>
<thead>
<tr>
<th>Tick-borne disease</th>
<th>Clinical presentations</th>
<th>Major lab diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>RMSF</em></td>
<td>Acute fever, headache (d0-5), rash (median d6)</td>
<td>IFA* serology, skin biopsy</td>
</tr>
<tr>
<td><em>HME and HGA</em></td>
<td>Acute fever, headache; infrequent rash</td>
<td>IFA serology, blood smear</td>
</tr>
<tr>
<td>Babesiosis</td>
<td>Fever, malaise, myalgia, arthralgia</td>
<td>blood smear</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>• early localized (erythema migrans)</td>
<td>ELISA and Western blot serology</td>
</tr>
<tr>
<td></td>
<td>• early disseminated (multiple EM, neuritis, carditis, arthritis, meningitis…)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Late (arthritis, acrodermatitis, encephalopathy)</td>
<td></td>
</tr>
</tbody>
</table>

* IFA – indirect fluorescent antibody
Ticks and tick-borne diseases in the Mid-Atlantic

<table>
<thead>
<tr>
<th>Disease</th>
<th>Tick vector</th>
<th>Common tick name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyme disease</td>
<td>Ixodes scapularis</td>
<td>Deer tick, black-legged tick</td>
</tr>
<tr>
<td>RMSF</td>
<td>Dermacentor variabilis</td>
<td>American dog tick</td>
</tr>
<tr>
<td>HGA</td>
<td>Ixodes scapularis</td>
<td>Deer tick, black-legged tick</td>
</tr>
<tr>
<td>HME</td>
<td>Amblyomma americanum</td>
<td>Lone star tick</td>
</tr>
</tbody>
</table>

Lyme disease — caused by members of the *Borrelia burgdorferi* sensu lato group

**general characteristics**
- spiral-shaped bacterium, 0.2 x 10 - 30 um in size
- typical cell wall with thin peptidoglycan layer
- flagella in periplasmic space > twisting motility
- obligate parasite found in association with mammals, birds, ticks
Lyme disease
_Borrelia burgdorferi_ sensu lato group

**ecological characteristics**
- maintained in a small mammal - _Ixodes_ species tick cycle
- eastern U.S. - _Peromyscus leucopus_ and _I. scapularis_
- western U.S.? reservoir, _I. pacificus_
- Europe and Asia - small mammals, _I. ricinus_ and _I. persulcatus_

Lyme disease - seasonality

- bimodal distribution
- most cases occur in May through July associated with emergence and activity of nymphal deer ticks
- secondary peak in late Fall associated with emergence and activity of adult deer ticks

Number of Cases of Lyme disease, by year
United States, 1983-2006
### Lyme disease in Maryland 2000-2006: cases and incidence (2000 census) by county or subdivision

<table>
<thead>
<tr>
<th>COUNTY</th>
<th>Population 2000</th>
<th>Cases 2000-2006</th>
<th>00-06 avg incid/10^5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Queen Anne's County</td>
<td>40,563</td>
<td>284</td>
<td>100.0</td>
</tr>
<tr>
<td>Kent County</td>
<td>19,197</td>
<td>113</td>
<td>84.1</td>
</tr>
<tr>
<td>Talbot County</td>
<td>20,967</td>
<td>115</td>
<td>100.5</td>
</tr>
<tr>
<td>Carroll County</td>
<td>150,897</td>
<td>628</td>
<td>59.5</td>
</tr>
<tr>
<td>Cecil County</td>
<td>85,951</td>
<td>351</td>
<td>58.3</td>
</tr>
<tr>
<td>Caroline County</td>
<td>29,772</td>
<td>115</td>
<td>55.5</td>
</tr>
<tr>
<td>Frederick County</td>
<td>192,277</td>
<td>501</td>
<td>30.6</td>
</tr>
<tr>
<td>Harford County</td>
<td>218,590</td>
<td>557</td>
<td>36.4</td>
</tr>
<tr>
<td>Howard County</td>
<td>247,842</td>
<td>570</td>
<td>32.9</td>
</tr>
<tr>
<td>Somerset County</td>
<td>24,747</td>
<td>52</td>
<td>30.0</td>
</tr>
<tr>
<td>Worcester County</td>
<td>46,543</td>
<td>73</td>
<td>22.4</td>
</tr>
<tr>
<td>Washington County</td>
<td>131,923</td>
<td>204</td>
<td>22.1</td>
</tr>
<tr>
<td>Prince George's County</td>
<td>120,546</td>
<td>192</td>
<td>16.2</td>
</tr>
<tr>
<td>Carroll County</td>
<td>485,646</td>
<td>532</td>
<td>19.0</td>
</tr>
<tr>
<td>St. Mary's County</td>
<td>84,644</td>
<td>146</td>
<td>11.2</td>
</tr>
<tr>
<td>Allegany County</td>
<td>29,846</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>Baltimore city</td>
<td>651,154</td>
<td>61</td>
<td>1.3</td>
</tr>
<tr>
<td>Maryland</td>
<td>5,296,486</td>
<td>5999</td>
<td>16.5</td>
</tr>
</tbody>
</table>

### Percentage of *I. scapularis* ticks infected with *B. burgdorferi* in regions of Baltimore County, 2001

![Percentage of ticks infected](chart.png)

**Baltimore County region**

- **Nymph**
- **Female**
- **Male**
- **Total**

*Courtesy Doug Norris, PhD, JHU Bloomberg School of Public Health*

### Lyme disease – early disseminated

- **Systemic manifestations**
  - **fever**
  - **multiple EMs**
  - **peripheral nervous system**
    - radiculopathy
    - cranial neuropathy
    - mononeuropathy multiplex
  - **central nervous system**
    - lymphocytic meningitis
    - rarely, encephalomyelitis (parenchymal inflammation of brain and/or spinal cord, with focal abnormalities)
  - **atrioventricular heart block ± clinical myopericarditis**
Lyme disease
clinical aspects
late infection
- Rheumatologic
  - mono- or oligoarticular arthritis
  - knees, large joints, TMJ
  - synovial fluid mean 24,250 WBC/mm$^3$
  - neutrophil predominance
  - antibiotic-refractory chronic arthritis
  - HLA-DR4
- Central nervous system
  - unifocal or multifocal encephalomyelitis
  - very rare in U.S.; CSF pleocytosis
  - peripheral neuropathy
  - "stocking glove" paresthesias; radicular pain
  - encephalopathy
  - mild memory and cognitive function abnormalities

Lyme disease
diagnosis
- culture
- PCR
- serology
  - enzyme immunoassay
  - western blot

Cultivation yield (%) of *Borrelia burgdorferi* from clinical samples

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Cultivation Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema migrans</td>
<td>&gt;50% (max 86%)</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>No data available</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>Anecdotal</td>
</tr>
<tr>
<td>Blood (plasma)</td>
<td>&gt;40% (&gt;9 mL)</td>
</tr>
</tbody>
</table>
Sensitivity and specificity meta-analyses of published assays for the Lyme disease diagnosis by PCR.

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Meta-Analysis Sensitivity</th>
<th>Median Sensitivity</th>
<th>Range of sensitivity</th>
<th>Meta-Analysis Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema migrans</td>
<td>67%</td>
<td>71%</td>
<td>59-60%</td>
<td>100%</td>
</tr>
<tr>
<td>Plasma / serum</td>
<td>36%</td>
<td>28%</td>
<td>0-52%</td>
<td>100%</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>73%</td>
<td>65%</td>
<td>23-100%</td>
<td>90%</td>
</tr>
<tr>
<td>CSF</td>
<td>Overall 19%</td>
<td>24%</td>
<td>6-91%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Non-chronic 17%</td>
<td>21%</td>
<td>6-70%</td>
<td></td>
</tr>
</tbody>
</table>

Laboratory Diagnosis of Lyme disease

Serology

- Enzyme immunoassay (EIA) methods
  - very sensitive, limited specificity (false positives)
  - whole bacterial cell lysates or individual recombinant proteins
  - generally not immunoglobin class specific
- Western blot assays to aid specificity
  - supplemental method for EIA positives
  - requires presence of specific antigen bands on IgM or IgG immunoblots
- Pitfalls in serologic diagnosis
  - lack of early response
  - abrogation by early Rx
  - persistent antibody in absence of active disease
  - lack of standardization
  - no FDA-cleared test for detection of CSF antibodies

Serology in Lyme disease; % reactivity in patients with:

<table>
<thead>
<tr>
<th>Test</th>
<th>EM, acute phase</th>
<th>EM, convalescent phase</th>
<th>Neurological involvement</th>
<th>Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-cell ELISA</td>
<td>33-49</td>
<td>76-86</td>
<td>79 (IgG ELISA)</td>
<td>100 (IgG ELISA)</td>
</tr>
<tr>
<td>IgM IB</td>
<td>43-44</td>
<td>75-84</td>
<td>80</td>
<td>16</td>
</tr>
<tr>
<td>IgG III</td>
<td>0-13, 43.6</td>
<td>15-21, 80</td>
<td>64-72</td>
<td>96-100</td>
</tr>
<tr>
<td>Two-tier testing</td>
<td>29-40</td>
<td>29-78</td>
<td>87</td>
<td>97</td>
</tr>
</tbody>
</table>
**Recommendations for Two-Step Testing and Interpretation of Lyme borreliosis Serology**

- **Clinical diagnosis of Lyme disease**
  - ELISA test

- **Early sample**
  - Negative result
  - Can't exclude LD alone
  - Repeat in 2-4 weeks if strongly suspected

- **Later sample**
  - Negative result
  - No reliable evidence of infection
  - Can't exclude LD alone
  - Repeat in 2-4 weeks if LD strongly suspected

- **Positive result**
  - Serologic evidence of infection
  - May not be current infection
  - Supports clinical diagnosis

- **Supplemental test**
  - Immunoblot (Western blot)

---

**Appropriate use of ELISA test for Lyme disease diagnosis**

(Tugwell et al Ann Intern Med 1997)

- **Pretest probability**
  - Incidence of disease in community
  - Constellation of clinical findings

- **ELISA (and IFA) accurate if:**
  - Standardized
  - Appropriate cutoffs
  - Appropriate quality control

- **Only to be used if pretest probability exceeds 0.20 but is less than 0.80**

- **Arthralgia, myalgia, headache, fatigue, palpitations alone not sufficient to raise pretest probability to clinically useful range**

---

**Review of laboratory predictive value and likelihood ratios**

- **Sensitivity** = test + / true +
- **Specificity** = test - / true -
- **Positive predictive value** = true + / (true +) + (false +)

Therefore, a test with sensitivity and specificity of 95% used to test 1000 persons in which prevalence of disease is 1% would identify 60 positives, 10 true positives and 50 false positives.

- **Positive likelihood ratio (LHR)** = true + rate / false + rate
  (used in calculation of post test odds or post test probability)
- **Pretest odds x LHR = post test odds**
<table>
<thead>
<tr>
<th>Recombinant antigen or peptide</th>
<th>Range % positive in the indicated LB disease stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EM IgM IgG Ig IgM IgG Ig IgM IgG Ig</td>
</tr>
<tr>
<td>FlagA</td>
<td>41-73 38-43</td>
</tr>
<tr>
<td>FlagC10</td>
<td>40-53 53 9</td>
</tr>
<tr>
<td>Flag internal fragment</td>
<td>42-53 35-52</td>
</tr>
<tr>
<td>VlsE</td>
<td>10-40 44-63 63 75 100 100 97 87</td>
</tr>
<tr>
<td>Invariable region-6 (IR-6, C6 peptide)</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>45-74 60-95 94-100</td>
</tr>
<tr>
<td>Convalescent</td>
<td>70-90 64 82-98</td>
</tr>
<tr>
<td>FlagA (37-4Da)</td>
<td>45-68 15</td>
</tr>
</tbody>
</table>

CSF serology in Lyme disease

- ELISA indicated only with prior positive serum ELISA
- No FDA-approved test or cutoff criteria
- Need to implicate intrathecal antibody synthesis (IgG index)
PCR on CSF for B. burgdorferi

Predictive value of B. burgdorferi PCR on plasma

- overall NPV
- overall PPV

[Graph showing relationship between pretest probability (prevalence) and probability of a true test]
Other tests for Lyme disease
Detection of B. burgdorferi antigen in urine

### Alternative lab testing at "Lyme literate" facilities

<table>
<thead>
<tr>
<th>Patients with Lyme Disease Like Symptoms (n=55)</th>
<th>General Population (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA only Positive: 4 (TP)</td>
<td>LDA Positive: 1 (FP)</td>
</tr>
<tr>
<td>LDA and PCR Positive: 4 (TP)</td>
<td>PCR Positive: 0</td>
</tr>
<tr>
<td>LDA and RWB Positive: 2 (TP)</td>
<td>RWB Positive: 0</td>
</tr>
<tr>
<td>LDA, PCR, and RWB Positive: 4 (TP)</td>
<td>LDA, PCR, and RWB Negative: 94 (TN)</td>
</tr>
<tr>
<td>PCR only Positive: 6 (TP)</td>
<td></td>
</tr>
<tr>
<td>LDA, PCR, and RWB Negative: 35 (TN)</td>
<td></td>
</tr>
</tbody>
</table>

TP = true Positive; TN = true Negative; FP = false Positive; FN = false Negative

9. Symptoms of Lyme disease


- Fatigue
- Low grade fevers, ‘hot flashes’ or chills
- Night sweats
- Sore throat
- Swollen glands
- Stiff neck
- Migrating arthralgias, stiffness and, less commonly, frank arthritis
- Myalgia
- Chest pain and palpitations
- Abdominal pain, nausea
- Diarrhea
- Sleep disturbance
- Poor concentration and memory loss

- Irritability and mood swings
- Depression
- Back pain
- Blurred vision and eye pain
- Jaw pain
- Testicular/pelvic pain
- Tinnitus
- Vertigo
- Cranial nerve disturbance (facial numbness, pain, tingling, palsy or optic neuritis)
- Headaches
- ‘Lightheadedness’
- ‘Dizziness’
“Lyme literate” lab 1

**Specificity**
Any sample positive by LDA, and confirmed by either PCR or RWB or both, was considered a true positive. Any sample that was negative by all methods was considered a “true negative.” Of the 162 individuals samples, 148 were considered true negatives.

141 individuals were negative by LDA. 4 patients suspected of Lyme Disease and 1 normal control were positive by LDA, but negative by either PCR or RWB. Therefore, these were considered false positives. Based on this data, the specificity of LDA is >96%.

Note that LDA and other unproven lab tests are part of the definition of “true positive” and “true negative”

**Sensitivity**
Of the 16 true positives, 10 samples were positive by LDA. Based on the limited data, the sensitivity of the LDA is approximately 60%.

The number of “true positives” increased from 10 to 16 (88%) when PCR was performed.

Sensitivity and specificity of LDA based on alternate gold standards

- **True positive = clinical diagnosis only**
  - Sensitivity 25% (14/55)
  - Specificity 99% (106/107)
- **True positive = clinical diagnosis + PCR**
  - Sensitivity 50% (6/12)
  - Specificity 95% (143/150)
- **True positive = clinical diagnosis + RWB**
  - Sensitivity 100% (6/6)
  - Specificity 95% (148/156)

Other tests for Lyme disease

T-cell proliferative assay

- Suggested for partially-treated or seronegative persons
- LT positive in 75% of normal, healthy subjects
- Assay not amenable to clinical laboratory
Prophylaxis after tick bites in Lyme disease

- Nadelman et al. (NEJM 2001):
  - prophylaxis with single 200 mg dose doxycycline prevents Lyme disease after *Ixodes scapularis* bites in 87%
  - adverse reactions occur 3X more often than placebos

Lyme disease

- antibiotic therapy
  - localized infection: po amoxicillin, doxycycline
  - disseminated infection without neurologic or cardiac involvement: po amoxicillin, doxycycline, cefuroxime
  - disseminated neurologic or cardiac infection: IV ceftriaxone

- vaccine (adults 85% effective)
  - Withdrawn from market by SKB

- chronic Lyme disease
  - misdiagnoses
  - true persistence of infection

Health-related quality of life is not affected by prolonged antibiotic treatment in patients with persistent manifestations of Lyme disease

antibiotic: IV ceftriaxone 2 g daily x 30 days, and PO doxycycline, 200 mg daily for 60 days;
placebo: matching intravenous and oral placebos

Cases and incidence of TBRD in the U.S., 1920-2006
2006 data extrapolated from MMWR August 5, 2006

Comparison of reported life-threatening domestic infectious diseases in the U.S., 2005
(MMWR 2006; 54:1320)

RMSF  HME  HGA  ehrlichiosis nos   total TBRD

Comparison of reported life-threatening domestic infectious diseases in the U.S., 2005
(MMWR 2006; 54:1320)

Comparison of reported life-threatening domestic infectious diseases in the U.S., 2005
(MMWR 2006; 54:1320)

ROCKY MOUNTAIN SPOTTED FEVER. Number of reported cases — United States and U.S. territories, 2004
Rocky Mountain spotted fever (RMSF)

Tick vectors of *R. rickettsii*

- **Known tick vectors**
  - *Dermacentor variabilis* - American dog tick (eastern U.S.)
  - *Dermacentor andersoni* - Wood tick (western U.S.)
- **Possible tick vectors**
  - *Rhipicephalus sanguineus* - brown dog tick
  - *Amblyomma cajennense* (Central and South America)

Pathogenesis of Rickettsial infections

- Rickettsia endothelial cells
- Ehrlichia and Anaplasma - phagosome escape
- Macrophages and neutrophils - phagolysosome fusion inhibition

Clinical manifestations of RMSF

- Fever, headache, myalgias, rash
- Rash - macular, maculopapular, petechial
- Shock and multi-organ failure
- Gastrointestinal system
- Renal system - acute tubular necrosis 2nd to hypotension
- Cardiopulmonary system - non-cardiogenic pulmonary edema
- Central nervous system - meningoencephalitis
  - Cerebral edema, herniation
  - Ecchymosis
  - Macular
  - Maculopapular
  - Petechial
  - Erythema
Rocky Mountain spotted fever diagnosis and risk

- risk of death 5 x in patients after day 5 of illness
- most patients are initially examined before day 5, but not treated until after day 5
- major factors for ineffective diagnosis and delayed therapy:
  - absence of typical rash
  - presentation during non-peak tick activity season
  - presentation during first 3 days of illness

<table>
<thead>
<tr>
<th>Laboratory abnormality in TBRD</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count ≤ 10,000/mL</td>
<td>20</td>
</tr>
<tr>
<td>White blood cell count &gt; 10,000/mL</td>
<td>80</td>
</tr>
<tr>
<td>Platelet count ≤ 100,000</td>
<td>32</td>
</tr>
<tr>
<td>Serum sodium ≤ 132 mEq/L</td>
<td>56</td>
</tr>
<tr>
<td>ALT or AST ≥ 2x normal</td>
<td>62</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td></td>
</tr>
<tr>
<td>Pleocytosis</td>
<td>49</td>
</tr>
<tr>
<td>Mononuclear cell predominance</td>
<td>40</td>
</tr>
<tr>
<td>Neutrophil predominance</td>
<td>30</td>
</tr>
<tr>
<td>Glucose &lt; 50 mg/dL</td>
<td>9</td>
</tr>
<tr>
<td>Protein &lt; 50 mg/dL</td>
<td>35</td>
</tr>
<tr>
<td>Opening pressure &gt; 290 mm H2O</td>
<td>14</td>
</tr>
</tbody>
</table>
### Sensitivity and specificity of serological tests for confirmation of RMSF

<table>
<thead>
<tr>
<th>Disease</th>
<th>Serological assay</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>IFA IgG</td>
<td>89 – 100%</td>
<td>99 – 100%</td>
</tr>
<tr>
<td></td>
<td>IFA IgM</td>
<td>83 – 85%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>LA</td>
<td>79 – 94%</td>
<td>94 – 100%</td>
</tr>
</tbody>
</table>

* IFA = indirect fluorescent antibody; LA = latex agglutination

---

### Laboratory diagnosis in TBRD

<table>
<thead>
<tr>
<th>Phase of Illness</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>BSC</td>
</tr>
<tr>
<td></td>
<td>Culture</td>
<td>PCR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab test availability</th>
<th>≥14 days</th>
<th>&lt;14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>+++</td>
<td>±±</td>
</tr>
<tr>
<td>HME</td>
<td>+++±±±±</td>
<td>±±±±±±</td>
</tr>
<tr>
<td>HGA</td>
<td>+++±±±±±±</td>
<td>±±±±±±±±</td>
</tr>
</tbody>
</table>

---
<table>
<thead>
<tr>
<th>Phase of Illness</th>
<th>Serology &lt; 14 days</th>
<th>Blood smear</th>
<th>PCR</th>
<th>HIC</th>
<th>Culture</th>
<th>Serology ≥ 14 days</th>
<th>Blood smear</th>
<th>PCR</th>
<th>HIC</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab test availability</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>RMSF</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HME</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HGA</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
<td>++ ++ ++ ++</td>
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</tbody>
</table>

Laboratory diagnosis in TBRD
Rocky Mountain spotted fever treatment

- adults: doxycycline, tetracycline
- children: doxycycline, tetracycline, chloramphenicol, rifampin?
- chloramphenicol associated with excess mortality as compared with doxycycline or tetracycline when controlled for all other factors

Human *Anaplasmataceae* infections (human ehrlichiosis)

- human monocytic ehrlichiosis (HME) - *Ehrlichia chaffeensis*
- Human granulocytic anaplasmosis (HGA) - *Anaplasma phagocytophilum*
- ehrlichiosis "Ewingii" - caused by *E. ewingii*, genetically like *E. chaffeensis*, phenotypically like human anaplasmosis
- HME and human anaplasmosis are undifferentiated febrile illnesses with typical laboratory findings.

Cases of ehrlichiosis and anaplasmosis in the U.S. reported to the CDC, 1986 - 2006
**HME – Ehrlichia chaffeensis**

- Epidemiology and ecology
  - Risk for disease increased with age, male sex
  - South central and southeastern US, World-wide?
  - Transmitted by *A. americanum*
  - Active in summer months
  - Reservoir white-tailed deer

**HGA – Anaplasma phagocytophilum**

- Epidemiology and ecology
  - Risk for disease increased with age, male sex
  - Upper Midwest and northeast US, northern California, Europe
  - Transmitted by *Ixodes* spp. nymphs and adults
  - Reservoir white-footed mice (*Peromyscus leucopus*), deer

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<table>
<thead>
<tr>
<th>Laboratory finding</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td></td>
</tr>
<tr>
<td>10,000–15,000/μL</td>
<td>29</td>
</tr>
<tr>
<td>&gt;15,000/μL</td>
<td>86</td>
</tr>
<tr>
<td>10% bands</td>
<td>93</td>
</tr>
<tr>
<td>Platelet count/μL</td>
<td>52</td>
</tr>
<tr>
<td>&lt;150,000</td>
<td>72</td>
</tr>
<tr>
<td>Serum sodium (mg/dL)</td>
<td>50</td>
</tr>
<tr>
<td>ALT or AST (twice normal value)</td>
<td>50</td>
</tr>
<tr>
<td>Opening pressure (mm HgO)</td>
<td>50</td>
</tr>
</tbody>
</table>

**Laboratory abnormalities in TBRD (%)**

- Pleocytosis
  - Mononuclear cell predominance: 10–20%
  - Neutrophil predominance: 50–60%
- Glucose: ≤ 50 mg/dL
- Protein: ≤ 50 mg/dL
- Cerebrospinal fluid

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**HME and HGA clinical and epidemiologic features**

**HME**

- Interval to medical attention – 4 days
- Incubation period: 10.6 d (mean: 9.5 d median)
- Tick exposure – 80%
- Severity
  - 40 to 62% hospitalized
  - Median length of illness – 23 days
  - Case fatality rate – 2.7%

**HGA**

- Interval to medical attention – 4 to 8 days
- Incubation period – median 6 to 10 d (range 1 to 60 d)
- Tick exposure – 75 to 85%
- Severity
  - 55% hospitalized
  - 7% require ICU admission
  - Median hospitalization – 6 days
  - Case fatality rate – 0.5 to 1%
HME and HGA - diagnosis

- blood smear (acute phase only)
  - HME - 2% sensitive
  - HGA - 25 to 75% sensitive
- PCR on blood (acute phase only)
  - Sensitivity ~50-60% during acute phase
  - no chronic phase in humans, brief persistence of DNA after therapy
- Serology (paired acute and convalescent)
  - IFA - preferred
  - Western blot - rarely used
  - Recombinant protein EIA - no proven benefit

Ehrlichioses and Anaplasmosis: Complications

<table>
<thead>
<tr>
<th>Clinical complication</th>
<th>HME</th>
<th>HGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>pneumonia/ARDS</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>meningencephalitis</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>peripheral neuropathies</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Toxic or septic shock-like syndrome</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>fulminant infections in immunocompromised</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>increased severity with pre-existing disease</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>opportunistic infections</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>myocarditis or heart failure</td>
<td>*</td>
<td>+</td>
</tr>
<tr>
<td>death</td>
<td>3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Results of diagnostic laboratory testing for HGA and outcome of tests of 144 patients with HGA in the upper Midwest and from lower New York State

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Upper Midwest</th>
<th>New York</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive blood culture result</td>
<td>11/12 (91.7)</td>
<td>18/19 (94.7)</td>
</tr>
<tr>
<td>Arv: A phago: IFA titer &gt;800</td>
<td>18/19 (100.0)</td>
<td>20/21 (95.2)</td>
</tr>
<tr>
<td>Arv: A phago: EIA titer &gt;1:100</td>
<td>9/10 (90.0)</td>
<td>21/21 (100.0)</td>
</tr>
</tbody>
</table>

**NOTE:** Data are n/N (w) of patients. IFA, indirect immunofluorescent antibody
*$^*$ Only a single serum sample was available.
**$^** For acute and convalescent phase samples.
Effect of therapy and kinetics of serologic reactions in HGA

Sensitivity and specificity of serological tests for confirmation of HME and HGA.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Serological Assay</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HME</td>
<td>IFA IgG</td>
<td>88%</td>
<td>Not determined</td>
</tr>
<tr>
<td></td>
<td>IFA IgM</td>
<td>86%</td>
<td>Not determined</td>
</tr>
<tr>
<td>HGA</td>
<td>IFA IgG</td>
<td>82-100%</td>
<td>82-100%</td>
</tr>
<tr>
<td></td>
<td>IFA IgM</td>
<td>27-37%</td>
<td>83-100%</td>
</tr>
</tbody>
</table>

HME and HGA - therapy

- **Doxycycline**
  - 200 mg po twice daily for 3-5 days after afebrile
  - empirical clinical efficacy
  - good in vitro activity
- **Rifampin for pregnancy and children?**
  - scant empirical efficacy data
  - good in vitro activity
  - Potentially useful in children, pregnancy
- **Fluoroquinolones?**
  - Potentially active against *A. phagocytophilum* (HGA), but apparently non bactericidal
  - Not active against *E. chaffeensis* (HME)
    - gyrA QRDR serine 83 (susceptible) → alanine (resistant)
Prevention of Lyme disease, RMSF, HME, and HGA in humans

- Prompt tick removal
- Transmission of A. phagocytophilum may require as little as 4h

No vaccine currently available for humans

Prophylaxis for HME and HGA after tick bite not investigated

Human monocytic and granulocytic ehrlichiosis when and what to test...

- Fever, headache, history of tick-bite or exposure during at-risk season
- Leukopenia, thrombocytopenia, elevated LFTs
- Acute phase EDTA- or citrate-anticoagulated blood
- Obtain blood prior to or at the time of first therapy
- Do not withhold therapy until laboratory-confirmed

Thanks for listening. Questions?