Rickettsial Infections

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UNCLASSIFIED
Take Home Points

• Rickettsial infections are:
  – More common than you think-increasing incidence
  – Potentially fatal
  – Have non-specific clinical presentations
  – Often require treatment prior to conclusive diagnosis
  – Respond to tetracyclines (Doxycycline)-even kids

No one dies of an infectious disease where a Rickettsia may be involved without Doxycycline!
Howard Ricketts

- 1906: Discovers vector for RMSF
- 1909: Funding cut, moves to Mexico
- Studies Epidemic Typhus - dies
Introduction

• Definitions
  – Rickettsiae: small obligate intracellular bacteria
  – Rickettsioses: diseases caused by rickettsia

• Rickettsia primarily found in arthropods
  • Ticks, mites, lice, fleas, beetles and homopterans

• Only blood-sucking arthropods may transmit disease

• Bacteria invade endothelial cells, cause vasculitis
  – Systemic illness, non-specific presentation

• Rickettsioses increasing in prevalence
  – Increased recognition and diagnostic capacity
  – Changing ecology beneficial to arthropods
  – Increased human/arthropod interface
Table 1. Current classification of rickettsioses and their estimated incidence among international travelers.

<table>
<thead>
<tr>
<th>Biogroup, disease</th>
<th>Species</th>
<th>Principal vectors</th>
<th>Geographic distribution</th>
<th>Incidence among travelers to areas of endemcity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidemic typhus</td>
<td><em>Rickettsia prowazekii</em></td>
<td>Body lice</td>
<td>Central Africa, South America</td>
<td>Very rare</td>
</tr>
<tr>
<td>Murine typhus</td>
<td><em>Rickettsia typhi</em></td>
<td>Rat fleas</td>
<td>Tropical and subtropical areas worldwide</td>
<td>Occasional</td>
</tr>
<tr>
<td>Spotted fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>Rickettsia rickettsii</em></td>
<td><em>Dermacentor</em> and <em>Amblyomma</em> ticks</td>
<td>North and South America</td>
<td>Very rare</td>
</tr>
<tr>
<td>Mediterranean spotted fever†</td>
<td><em>Rickettsia conorii</em></td>
<td><em>Rhipicephalus</em> and <em>Haemaphysalis</em> ticks</td>
<td>Mediterranean and Caspian littorals, Middle East, Indian subcontinent, Africa</td>
<td>Occasional</td>
</tr>
<tr>
<td>Siberian tick typhus</td>
<td><em>Rickettsia sibirica</em></td>
<td><em>Dermacentor</em> ticks</td>
<td>Northern Asia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Unnamed</td>
<td><em>Rickettsia sibirica</em></td>
<td><em>Hyalomma</em> ticks</td>
<td>China, France, sub-Saharan Africa</td>
<td>No data</td>
</tr>
<tr>
<td>Queensland tick typhus</td>
<td><em>Rickettsia australis</em></td>
<td><em>Ixodes</em> ticks</td>
<td>Eastern Australia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Flinders Island spotted fever</td>
<td><em>Rickettsia honei</em></td>
<td>Ticks of several genera</td>
<td>Australia, Southeast Asia, northwestern North America</td>
<td>No data</td>
</tr>
<tr>
<td>African tick bite fever</td>
<td><em>Rickettsia africae</em></td>
<td><em>Amblyomma</em> ticks</td>
<td>Sub-Saharan Africa, Caribbean</td>
<td>Common</td>
</tr>
<tr>
<td>Japanese spotted fever</td>
<td><em>Rickettsia japonica</em></td>
<td>Ticks of several genera</td>
<td>Japan</td>
<td>No data</td>
</tr>
<tr>
<td>Rickettsialpox</td>
<td><em>Rickettsia akari</em></td>
<td>Mouse mites</td>
<td>North and South America, Asia</td>
<td>No data</td>
</tr>
<tr>
<td>California flea rickettsiosis</td>
<td><em>Rickettsia felis</em></td>
<td>Cat fleas</td>
<td>Europe, North and South America, Africa, Asia</td>
<td>No data</td>
</tr>
<tr>
<td>Unnamed</td>
<td><em>Rickettsia helongjiangensis</em></td>
<td><em>Dermacentor</em> ticks</td>
<td>Eastern Asia</td>
<td>No data</td>
</tr>
<tr>
<td>Unnamed</td>
<td><em>Rickettsia slovaca</em></td>
<td><em>Ixodes</em> ticks</td>
<td>Southern and eastern Europe</td>
<td>No data</td>
</tr>
<tr>
<td>Unnamed</td>
<td><em>Rickettsia helvetica</em></td>
<td><em>Ixodes</em> ticks</td>
<td>Central and northern Europe, Asia</td>
<td>No data</td>
</tr>
<tr>
<td>Unnamed</td>
<td><em>Rickettsia aeschlimanni</em></td>
<td><em>Hyalomma</em> ticks</td>
<td>Mediterranean littoral, Morocco, South Africa</td>
<td>Very rare</td>
</tr>
<tr>
<td>Unnamed</td>
<td><em>Rickettsia parkeri</em></td>
<td><em>Amblyomma</em> ticks</td>
<td>United States</td>
<td>No data</td>
</tr>
<tr>
<td>Scrub typhus, scrub typhus</td>
<td><em>Orientia tsutsugamushi</em></td>
<td>Chigger mites</td>
<td>Southeast Asia, western Oceania</td>
<td>Occasional</td>
</tr>
</tbody>
</table>

† Including Astrakhan fever, Israeli tick typhus, and Indian tick typhus.
Commonalities of Rickettsioses

• Fever, headache, +/- myalgias, +/- rash ("Viral-like illness")
• Low WBC, low PLTS, elevated AST/ALT
• Diagnose by serology, immunofluorescence assays, PCR, culture (lab risk)
  – Clinical diagnose is most often required to properly manage the patient. You must make a decision to treat without a definitive diagnosis.
• Tetracyclines are the drugs of first choice for treatment
  – Doxycycline 100 mg po bid x 5 days –or- until 48 hours after defervescence (EVEN for children)
  – Pregnant women, chloramphenicol, josamycin, or a combination of rifampin and erythromycin
## Rash Characteristics

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rash Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>Peticheal/Macular (50-90%) --&gt; Hemorrhage/Gangrene (4-5%)</td>
</tr>
<tr>
<td>Spotted Fever</td>
<td>Petechial/Papular (90-100%) --&gt; Rare Hemorrhage</td>
</tr>
<tr>
<td>Rickettsial Pox</td>
<td>2-10 mm Macules (90-100%) --&gt; Vesicular --&gt; Crusting</td>
</tr>
<tr>
<td>Typhus</td>
<td>Macular --&gt; Maculopapular (spares face/palms/soles) --&gt; Petechial (20-30%)</td>
</tr>
<tr>
<td>Murine Typhus</td>
<td>Macular --&gt; Maculopapular (40-50%) --&gt; Petechial (&lt;10%)</td>
</tr>
<tr>
<td>Scrub Typhus</td>
<td>Macular/Maculopapular (Often mild and evanescent)</td>
</tr>
<tr>
<td>Ehrlichia spp</td>
<td>Not</td>
</tr>
<tr>
<td>Coxiella</td>
<td>Not</td>
</tr>
</tbody>
</table>

**PLAMS / SOLES**
Eschar

• Yes
  – African Tick bite fever
  – Mediterranean spotted fever
  – Rickettsial pox
  – Scrub typhus

• No
  – RMSF (may be very faint)
  – Epidemic typhus
  – Murine typhus (may be faint)
  – Ehrlichiosis
  – Q Fever
  – Trench Fever
Eschar
Global Distribution of Rickettsiae, Anaplasma, and Ehrlichia

Update on Rickettsial Infections • CID 2007:45 (Suppl 1) • S41
Global Distribution of Rickettsiae
(colored shapes = known pathogens)
Global Distribution of Rickettsiae
(colored shapes = known pathogens)

- R. africae
- R. conorii conorii
- R. conorii caspia
- R. conorii israelensis
- R. sibirica mongolitimonae
- R. aeschlimannii
- R. massiliae
- R. rhipicephali
- R. slovaca
- R. conorii indica
- R. conorii conorii
- R. conorii israelensis
- R. conorii caspia
- R. sibirica sibirica
- R. sibirica mongolitimonae
- R. japonica
- R. honei
- R. helongjiangensis
- R. australis
- "R. marmionii"
- Strain S
- Strain AT1
- R. hulinensis
- R. helvetica
- Unnamed rickettsias (RpaA4, DNS28, DNS14)
- Unnamed rickettsias (RDla420, RDla440, ATT, HOT1)
- Unnamed rickettsia
Case #1

- Service Members (SMs) are presenting to your clinic with similar illnesses following recent redeployment from Southern Africa (unit #1).
- Illnesses vary in severity and include symptoms of fever, neck pain, and headache. Exam findings include mouth blisters, vesicular rash, and multiple lesions on the lower extremities (picture). There are enlarged inguinal lymph nodes.
- Some soldiers recall “bug” exposure and many have already recovered from their illness without treatment.
Case #1

Ankle

Lancet ID 2003;3:557-564
African Tick Bite Fever

• Rickettsia: *R. africae* - >80% of acquired SF in travelers.
• Ticks
  – *Amblyomma hebraeum*: Southern Africa
  – *A. variegatum*: Caribbean
• Epidemiology
  – Men, exposure activities, case clusters
• Illness:
  – Incubation 5-7 days, may be up to 10 days
  – Febrile illness, headache, neck myalgia
  – Rash (50%) (may be vesicular – 50% or rashes)
  – Mouth blisters, regional lymphadenitis
  – ~50% of patients have multiple eschars
Case #2

• Retired male SM with chronic alcohol dependency presents with high fever, not feeling well, vomiting, a generalized maculopapular rash sparing the face, and an eschar.

• He reports recently returning from a vacation in southern Italy where he stayed at a friend’s home and took care of his dogs while the friend was traveling.

• Your examination reveals he is intravascularly deplete and lab values demonstrate multi-organ involvement.
Mediterranean Spotted Fever
(Boutonneuse Fever)

• Rickettsia: *R. conorii*
• Ticks (dog ticks)
  – Rhipicephalus and Haemaphysalis genera
• Epidemiology
  – Mediterranean basin, Middle East, India, expanding
• Illness:
  – Incubation of ~6 days then abrupt onset of symptoms
  – High fever (39°C), flu-like symptoms
  – Single black eschar
  – 1-7 days after fever there is a generalized MP rash
    • Palms and soles but spares the face
  – Recover within 10 days without any sequelae
  – Mortality ~2.5%
Global Distribution of MSF

Figure 4. Distribution of the cases of Mediterranean spotted fever (MSF) in the world and incidence of the disease in countries where MSF is endemic.
### Mediterranean spotted fever

**Table 2. Distribution, vector, and main clinical features of the different subspecies of *Rickettsia conorii* complex**

<table>
<thead>
<tr>
<th>Rickettsia</th>
<th>Vector tick</th>
<th>Geographic repartition</th>
<th>Human disease name</th>
<th>Symptoms present, % patients</th>
<th>Fatal forms? (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>R. conorii conorii</em>, isolates Malish, Moroccan, Kenyan</td>
<td><em>Rhipicephalus</em> sp., <em>Haemaphysalis leachii</em></td>
<td>Mediterranean area (southern Europe, northern Africa), Croatia, Slovenia, Kenya, Somalia, South Africa, and surrounding the Black Sea (Turkey, Bulgaria, Ukraine, Romania)</td>
<td>Mediterranean spotted fever</td>
<td>91–100 20–87 93–100</td>
<td>Yes (0–18.1)</td>
</tr>
<tr>
<td><em>R. conorii israelensis</em></td>
<td><em>Rh. sanguineus</em></td>
<td>Israel, Portugal, Sicily</td>
<td>Israeli spotted fever</td>
<td>100 0–46 98–100</td>
<td>Yes (0–3.5)</td>
</tr>
<tr>
<td><em>R. conorii caspia</em></td>
<td><em>Rh. sanguineus</em>, <em>R. pumilio</em></td>
<td>Astrakhan region, Chad, Kosovo</td>
<td>Astrakhan spotted fever</td>
<td>100 23 94</td>
<td>No</td>
</tr>
<tr>
<td><em>R. conorii indica</em></td>
<td><em>Rh. sanguineus</em>, <em>Boophilus microplus</em>, <em>H. leachii</em></td>
<td>India, Pakistan</td>
<td>Indian tick typhus</td>
<td>100 Rare 100 (frequently purpuric)</td>
<td>No</td>
</tr>
</tbody>
</table>
Figure 1. *Rickettsia conorii conorii* in Vero cells (red rods; magnification ×1,000).

Figure 6. *Rhipicephalus sanguineus* adult tick, the suspected vector for *Rickettsia conorii conorii*. 
Case #3

- SM develops a fever and rash 3 days into deployment. Additional symptoms include headache, malaise, sweats, and nausea. The rash looks like chicken-pox and there is associated lymph node enlargement. The SM claims to have had chicken-pox as a child. The SM was on leave in NYC prior to deployment.
Rickettsialpox

- Rickettsia: *R. akari*
- Mite (mouse)
  - *Liponyssoides sanguineus*
- Epidemiology
  - NYC, eastern Europe, Korea, and South Africa
- Illness:
  - Incubation 9-14 days
  - Triad of the disease = fever, rash, and eschar
  - Varied constitutional symptoms
  - Papule to vesicle to a brown or dark eschar
  - Rash on day 3 or 4 (papular to vesicular)
  - Self-limited illness (14-21 days)
**Fig 2.** Case 2: Eschar on left cheek.

**Fig 3.** House mouse mite, *Liponyssoides sanguineus*, brought in by case 2. (Whole mount; original magnification: ×40.)

**Fig 4.** Case 3: Early-stage eschar on right ankle.
<table>
<thead>
<tr>
<th>Feature</th>
<th>Rickettsialpox</th>
<th>Chickenpox$^{24}$</th>
<th>Smallpox (variola major)$^{25}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eschar</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Incubation period</td>
<td>9-14 days</td>
<td>14 days (range 10-23)</td>
<td>12 days (range 10-14)</td>
</tr>
<tr>
<td>Prodrome</td>
<td>Usually mild, may be severe.</td>
<td>Absent or mild and brief (less than one day)</td>
<td>Usually severe with high fever, headache, backache. Vomiting and severe abdominal pain may be present. Lasts 2 to 4 days.</td>
</tr>
<tr>
<td>Timing and evolution of lesions</td>
<td>Lesion develops at the site of the bite within 24 to 48 hrs and evolves into eschar. Rash begins 2 to 3 days after prodrome. Papules may eventuate in papulovesicles.</td>
<td>Lesions occur in “crops” over 2 to 4 days. Different stages characteristic: macules, papules, vesicles, pustules, crusts</td>
<td>Emerge over 1-2 days and then progress at same rate. The lesions progress over several days from macules (day 1), to papules (day 2), to vesicles (days 3-5), to pustules (days 7-14), to scabs (day 14-20).</td>
</tr>
<tr>
<td>Pruritus/ pain Distribution</td>
<td>Exanthem usually asymptomatic: occasional pruritus.</td>
<td>Commonly pruritic</td>
<td>Pruritic during healing, otherwise may be painful. Begins on the oral mucosa, face, and extremities and spreads centripetally. Palms, soles commonly involved.</td>
</tr>
<tr>
<td>Enanthem Scarring</td>
<td>Minority of cases. Eschar leaves depressed scar, papulovesicles do not.</td>
<td>Common, especially palate. If bacterial superinfection occurs</td>
<td>Starts in mouth Yes</td>
</tr>
</tbody>
</table>
Case #4

• SM serving in Central America on a humanitarian mission presents after 3 days of an evolving illness to include fever, headache, fatigue, and abdominal discomfort.

• He has no medical or surgical history. He smokes and uses alcohol infrequently. He lives in a private room and has no sick contacts. All water, to include ice and brushing teeth, is from bottles. He occasionally eats on the economy but has not done so for 3 weeks. During the past 4 weeks he has been conducting missions in rural villages. He recalls no insect exposure. He declines to provide a sexual activity history.

• On exam he is febrile (38°C) and appears ill. You notice a few macules on his palms.
Rocky Mountain Spotted Fever

- **Rickettsia**: *R. rickettsii*
- **Tick (dog)**
  - Dermatocenter, Rhipicephalus
- **Epidemiology**
  - US, Southern Canada, Mexico, C. and S. America
- **Illness**:
  - Does not generally elicit an eschar
  - High fever, headache, malaise, myalgias, nausea, vomiting, anorexia, abdominal pain, and diarrhea
  - RMSF rash is usually not apparent until the third day
    - Small, irregular, pink macules, peripheral → central
    - Classic spotted rash (50%) not until day 5 = severe
  - MOST SEVERE Rickettsioses (fatal in 5% or greater)
Fig. 2  Acral petechial rash of Rocky Mountain spotted fever (reprinted with permission from Brooke Army Medical Center Teaching File).
Case #5

- SM presents with headache and fever following leave in Mexico. Review of systems indicates associated nausea, vomiting, and new onset cough. You appreciate hepatomegaly and confusion on examination.
- A travel history indicates he was in Mexico for 1 week with a group of friends. He stayed at economy hotels and hostels. He stated the rooms were clean but the neighborhoods were in some disrepair with garbage on the street; he noticed numerous rodents. There were no sexual exposures and no use of drugs. He had no animal exposures. Food and water were on the economy.
Murine Typhus (endemic)

- **Rickettsia: R. typhi**
- **Flea (rat)**
  - Xenopspylla cheopis
- **Epidemiology**
  - United States, Mexico, Europe, Africa, SE Asia, Australia
- **Illness:**
  - 6-14 day incubation period
  - Fever and headache, rash less often
  - Nausea, vomiting, abdominal pain, diarrhea, jaundice, cough, confusion, and seizures have been reported
  - Typically a self-limited illness
R. typhi Global Distribution
Case #6

- SM on mission in Africa (Burundi) presents with fever, headache, and confusion. His duties while on mission included working at a refugee camp for displaced persons. The SM had very close contact with refugees in his day to day duties of supporting sustainment operations. He states other people were also sick and some had died before they could access care.
Epidemic Typhus

- Rickettsia: *R. prowazekii*
- Flea (body lice): *Pediculus humanus humanus*, infected louse fecal material.

**Epidemiology**
- Africa (Ethiopia, Nigeria, Burundi), Mexico, Central America, South America, Eastern
- War, refugees, prison, close quarters, bad hygiene

**Illness:**
- Incubation 10-14 days
- Malaise, F, headache, myalgia, N, V, coughing, rash
- Confusion, stupor, coma, diarrhea, pulmonary involvement, myocarditis, splenomegaly
- Case fatality rate: 4% Untreated up to 10-60%

**Brill-Zinsser disease:** Recrudescence months to years
Epidemic Typhus

TYPHUS IS SPREAD BY LICE

REPORT LICE AT ONCE USE LOUSE POWDER
Military Importance

• Napoleonic’s March: 20% died from Epidemic typhus
• WWI: 25 million Russians infected w/ 3 million deaths
• WWII: Impacted both sides in N. Africa campaign, present in Naples
• Vaccination, education, and DDT lead to reduction in US troops (only 104 cases)
• 1997: 100,000 infected in Burundi civil war
Epidemic Typhus

- Only typhus group with humans as usual host
- Flying squirrels also a host
- Crowded, war/disasters, lacking water; body lice

Fig. 4  Eruption in a patient with epidemic typhus imported from Algeria to France (from Ref. [39]).
Case #7

• Young female presented with fever, lymphadenopathy and a faint rash after a 2 week trek in the Northern territory of Thailand. She was treated with Doxycycline for 5 days, 200mg po qd. Her symptoms continued and worsened, she now has N, V, abdominal pain and a new cough.
Scrub typhus

- Rickettsia: Orientia tsutsugamushi
- Larval trombiculid mites: chiggers
- Epidemiology
  - Asia-Pacific, Korea to Papua New Guinea, Australia and from Japan to India and Afghanistan
  - Rural exposures, agriculture
- Illness:
  - Incubation 7 - 10 days
  - Papule at the bite site, ulcerates, forms eschar
  - Fever, lymphadenopathy, M or MP rash, headache, myalgia. GI and respiratory symptoms are frequent.
  - Asymptomatic infection to fatal (30%) (strain)
  - DOXY MAY BE RESISTANT IN THAILAND
    - Azithromycin or rifampin
Scrub typhus Distribution

Darker color is higher incidence of disease.
Figure 4. Typical area of scrub typhus endemicity in Thailand.
# Prevalence of Signs and Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Phongmany(^{[5a]})</th>
<th>Tattersall(^{[4]})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td>2006</td>
<td>1945</td>
</tr>
<tr>
<td><strong>Number of cases</strong></td>
<td>31</td>
<td>500</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Laos</td>
<td>India, Burma</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Local residents</td>
<td>Soldiers and local residents</td>
</tr>
</tbody>
</table>

## Signs and Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Phongmany(^{[5a]})</th>
<th>Tattersall(^{[4]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Mental changes</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td>Cough</td>
<td>38%</td>
<td>68%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>Adenopathy</td>
<td>59%</td>
<td>92%</td>
</tr>
<tr>
<td>Eschar</td>
<td>52%</td>
<td>11%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>59%</td>
<td>47%</td>
</tr>
<tr>
<td>Rash</td>
<td>27%</td>
<td>64%</td>
</tr>
<tr>
<td>Case-fatality rate</td>
<td>1.5%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Scrub typhus

Fig. 6 Macular eruption in a patient with scrub typhus (from Ref. [44]).
(urban) Trench Fever

- **Bartonella quintana**
  - originally *Rickettsia quintana*
- Napoleon’s Grand Army, WWI, WWII
- Human body louse - *Pediculus humanus*
  - Infected feces or crushed louse into broken skin
  - Aerosol to mucous membranes
- Densely populated, poverty-stricken areas of Africa, Latin America, Eastern Europe
- Bacteremia, bacillary angiomatosis, parenchymal peliosis
  - More severe in immunocompromised
  - Can also cause endocarditis
  - Doxycycline and Azithromycin are effective, Gentamicin for endocarditis
Q fever (*Coxiella burnetii*)

- **Q = Query**
- **Worldwide distribution (↓ USA, ↓↓ New Zealand)**
- **Infectious particles inhaled or ingested**
- **1 organism can cause clinical infection**
- **Incubation 2-3 weeks**
- **Unpasteurized milk or fresh cheese; localizes to mammary glands and uterus of infected animals**
- **Farmers, vets, abattoir and lab workers**
Q fever (Coxiella burnetii)

• ACUTE
  – Prolonged fever (>10 days)
  – Normal leukocyte count (25% elevated)
  – Low platelets
  – Increased liver enzymes
  – Children with Q fever generally have a milder acute illness than adults.
  – Children are more likely to have a rash than adults. Rash has been reported in up to 50% of children with acute Q fever.
  – Women infected with Q fever during pregnancy are at increased risk for miscarriage and preterm delivery

• CHRONIC
  – 5% post acute infection
  – May occur in asymptomatic acute infection
  – Those with valvular heart disease (endocarditis), chronic lung infections, osteomyelitis
Q fever (*Coxiella burnetii*)

• Diagnosis:
  - Clinical Algorithm
  - Paired serology (Phase II - acute, Phase I - chronic)
• Treatment: 100mg Doxy BID 14-21 days
• PPE: educate (livestock, dairy)
  - disposal birth products (animals)
  - quarantine/restriction of infected animals
cautions
  - high risk folks (valve disease)
**Acute**

If a patient has clinical evidence of acute Q fever infection (e.g., fever, headache, rigors, weight loss, myalgia, arthralgia, pneumonia, or hepatitis), and acute Q fever is suspected, perform diagnostic testing and initiate empiric treatment with doxycycline. Do not wait for laboratory results to begin treatment and do not stop treatment based on negative acute serology results.

Patient has any one of the following laboratory findings that indicate acute Q fever infection:
- Fourfold increase in phase II IgG or IgM antibody titer by IFA test in paired serum samples
- Convalescent phase II IgG antibody titer by IFA of ≥ 1:128
- Detection of DNA in a clinical specimen by PCR assay
- IHC staining of organism in a clinical specimen
- Isolation of Coxiella burnetii from a clinical specimen by culture

- No
  - Consider alternative diagnoses.
- Yes
  - Acute Q fever case
    - Perform clinical evaluation to determine whether patient is at high risk for chronic disease (e.g., heart valve or vascular defect).*
      - No risk
        - Repeat clinical assessment and serology in approximately 6 months.
      - Risk identified
        - Repeat clinical assessment and serology at 3, 6, 12, 18, and 24 months.
    - To chronic algorithm

**Chronic**

Patient has clinical evidence of chronic Q fever infection with organ involvement

Patient has laboratory evidence of chronic Q fever infection:
- Demonstration of phase I IgG antibody titer by IFA ≥ 1:1024; or
- Detection of DNA in a clinical specimen (e.g., heart valve or serum) by PCR assay; or
- IHC staining of organism in a clinical specimen (e.g., heart valve); or
- Isolation of Coxiella burnetii from a clinical specimen by culture

- No
  - Not a case unless clinical and laboratory evidence are present (see Pregnancy section for exception). Continue serologic and clinical monitoring. If nonspecific clinical findings are present with laboratory evidence, perform a thorough search for foci of infection (e.g., echocardiogram and PET/CT scan).
- Yes
  - Chronic Q fever case
    - Treat appropriately (minimum 18 months [native valves] and 24 months [prosthetic valves] for endocarditis); monitor clinically and serologically throughout treatment.
    - Continue antimicrobial treatment and serologic monitoring. Consult a Q fever expert.
      - No
        - Serologic monitoring demonstrates fourfold decrease in phase I IgG with complete disappearance of phase II IgM and clinical recovery.
          - Yes
            - Discontinue antibiotic treatment and continue twice yearly serologic monitoring for potential relapse (minimum 5 years).
## Q Fever in U.S. Military

### Table. Postdeployment serum antibody titers to phase II antigen for Q fever in 8 US military personnel who served in Iraq, March 1–August 20, 2003*

<table>
<thead>
<tr>
<th>Patient</th>
<th>IgG</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1,024</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>1:128</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>&gt;1:1,024</td>
<td>1:512</td>
</tr>
<tr>
<td>4</td>
<td>1:256</td>
<td>1:256</td>
</tr>
<tr>
<td>5</td>
<td>1:512</td>
<td>&gt;1:1,024</td>
</tr>
<tr>
<td>6</td>
<td>1:512</td>
<td>1:512</td>
</tr>
<tr>
<td>7</td>
<td>1:64</td>
<td>1:64</td>
</tr>
<tr>
<td>8</td>
<td>&gt;1:1,024</td>
<td>&gt;1:1,024</td>
</tr>
</tbody>
</table>

*All predeployment titers were negative for immunoglobulin (Ig) G and IgM.
# Ehrlichiosis

<table>
<thead>
<tr>
<th>HME</th>
<th>HGA</th>
<th>E. ewingii</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>1994</td>
<td>1999</td>
</tr>
<tr>
<td><em>E. chaffeensis</em></td>
<td>A. <em>Phagocytophilum</em></td>
<td><em>E. ewingii</em></td>
</tr>
<tr>
<td>Monocyte macrophage</td>
<td>Granulocyte</td>
<td>Granulocyte</td>
</tr>
<tr>
<td>&gt;1600</td>
<td>&gt;2100</td>
<td>~20</td>
</tr>
<tr>
<td>SC, SE, mid-Atl</td>
<td>NE, MW, Pac coast</td>
<td>SC (S. central)</td>
</tr>
</tbody>
</table>
## Military importance (Ehrlichiosis)

<table>
<thead>
<tr>
<th>Group, disease</th>
<th>Causative agent</th>
<th>Mode</th>
<th>Geographic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canine</td>
<td><em>E. canis</em></td>
<td>Tick bite</td>
<td>SE Asia, SW US, Venezuela</td>
</tr>
<tr>
<td>HME</td>
<td><em>E. chaffeensis</em></td>
<td>Tick bite</td>
<td>Americas, Europe, Thailand</td>
</tr>
<tr>
<td>HGA</td>
<td><em>A. phagocytophilum</em></td>
<td>Tick bite</td>
<td>USA, Europe, Asia</td>
</tr>
<tr>
<td>Sennetsu fever</td>
<td><em>Neorickettsia sennetsu</em></td>
<td>unknown</td>
<td>Japan, Malaysia</td>
</tr>
</tbody>
</table>
HME / HGA

• Incubation 5-14 days
• Rash rare; NO vasculitis
• Ecology of exposure:
  – HME: grassy areas, forest edge, un-mowed areas
  – Anaplasma: similar (May-Sept in USA)
• Diagnosis: paired serology
• Morulae = cytoplasmic inclusions
• Treatment:
  – doxycycline 100mg BID
  – 3d after afebrile (~5-7 days)
• Prevention: PPE
Ehrlichia – disease symptoms

<table>
<thead>
<tr>
<th>Symptom, sign, or finding</th>
<th>HME (no. evaluated)</th>
<th>HGA (no. evaluated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>97 (633)</td>
<td>93 (521)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>57 (250)</td>
<td>77 (516)</td>
</tr>
<tr>
<td>Headache</td>
<td>80 (240)</td>
<td>76 (385)</td>
</tr>
<tr>
<td>Malaise</td>
<td>82 (234)</td>
<td>94 (288)</td>
</tr>
<tr>
<td>Nausea</td>
<td>64 (143)</td>
<td>38 (258)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33 (192)</td>
<td>26 (90)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (197)</td>
<td>16 (95)</td>
</tr>
<tr>
<td>Cough</td>
<td>26 (155)</td>
<td>19 (260)</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>41 (211)</td>
<td>46 (504)</td>
</tr>
<tr>
<td>Rash</td>
<td>31 (286)</td>
<td>6 (357)</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>3 (240)</td>
<td>21 (24)</td>
</tr>
<tr>
<td>Confusion</td>
<td>19 (279)</td>
<td>17 (211)</td>
</tr>
<tr>
<td>Laboratory finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>62 (276)</td>
<td>49 (336)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>71 (247)</td>
<td>71 (336)</td>
</tr>
<tr>
<td>Elevated serum AST or ALT level</td>
<td>83 (276)</td>
<td>71 (177)</td>
</tr>
</tbody>
</table>

CID, 2007
Ehrlichiosis

- Incubation 5-14 days
- Rash rare; NO vasculitis
- Ecology of exposure:
  - HME: grassy areas, forest edge, un-mowed areas
  - Anaplasma: similar (May-Sept in USA)
- Diagnosis: paired serology; morulae=cytoplasmic inclusions
- Treatment: doxycycline 100mg BID ~ 3d after afebrile (~5-7 days)
- Prevention: PPE
Case #8

• 24 y/o male presents to clinic with Hx of swollen, painful right knee for past 5 days.
• Able to bear weight, but c/o discomfort with running or standing for long periods.
• Denies known trauma to knees.
• No fever or chills with either episode.
• Current medications: Motrin
Lyme disease (B. borgdorferi)
Ixodid tick range
Pathogenesis

- The agent of Lyme disease includes three pathogenic species (*B. burgdorferi*, *B. afzelii*, and *B. garinii*), only *B. burgdorferi* strains are found in the United States.
Lyme labs

- **LYME AB TOTAL**: >4.50
- **Western Blot**
  - 18KD: PRESENT
  - 23KD: PRESENT
  - 28KD: PRESENT
  - 30KD: PRESENT
  - 39KD: PRESENT
  - 41KD: PRESENT
  - 45KD: NOT PRESENT
  - 58KD: PRESENT
  - 66KD: PRESENT
  - 93KD: PRESENT
  - 23KD IGM: PRESENT
  - 39KD IGM: PRESENT
  - 41KD IGM: PRESENT
Common presenting symptoms

• Rash ~ 70-80% of infected persons
  – Begins at the site of a tick bite after a delay of 3-30 days
  – Gradually expands over a period of several days, reaching up to 12 inches (30 cm) across
  – Center of the rash may clear as it enlarges (Bull's-eye). It may be warm but not usually painful. Some patients develop additional EM lesions in other areas of the body after several days.

• +/- fatigue, chills, fever, headache, and muscle and joint aches, and swollen lymph nodes

• In context of outdoor exposure
Lyme disease (*B. borgdorferi*)

‘Classic’ Rash

CDC.gov
<table>
<thead>
<tr>
<th>System</th>
<th>Stage 1 (Early) Localized</th>
<th>Stage 2 (Early) Disseminated</th>
<th>Stage 3 (Late) Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Erythema migrans</td>
<td>Secondary annular lesions</td>
<td>Prolonged arthritis attacks, chronic arthritis</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Myalgia, arthralgia</td>
<td>Migratory pain in joints; brief arthritis attacks</td>
<td>Encephalopathy, polyneuropathy, leukoencephalitis</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache</td>
<td>Meningitis, Bell palsy, cranial neuritis, radiculoneuritis</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td>Atrioventricular block, myopericarditis, pancarditis</td>
<td></td>
</tr>
<tr>
<td>Constitutional</td>
<td>Flulike symptoms</td>
<td>Malaise, fatigue</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>Regional lymphadenopathy</td>
<td>Regional or generalized lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Clinical feature</td>
<td>American LNB</td>
<td>European LNB</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Causative <em>Borrelia</em> subspecies</td>
<td><em>B. burgdorferi</em> sensu stricto</td>
<td>Mostly <em>B. garinii</em>, occasionally <em>B. afzelii</em></td>
<td></td>
</tr>
<tr>
<td>LNB as a percentage of all Lyme cases</td>
<td>&lt;10%</td>
<td>&gt;35%</td>
<td></td>
</tr>
<tr>
<td>Multiple erythema migrans lesions</td>
<td>Common</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Painful radiculitis</td>
<td>Rare (&lt;10%)</td>
<td>Common (&gt;50%)</td>
<td></td>
</tr>
<tr>
<td>“Aseptic” meningitis presentation</td>
<td>Majority</td>
<td>Minority</td>
<td></td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>VII, very rarely others</td>
<td>Usually VII, but can include others</td>
<td></td>
</tr>
<tr>
<td>Associated chronic skin manifestation (lymphooytoma or ACA)</td>
<td>Never</td>
<td>Not rare</td>
<td></td>
</tr>
<tr>
<td>Associated with Lyme arthritis</td>
<td>Common</td>
<td>Almost never</td>
<td></td>
</tr>
<tr>
<td>Chronic encephalomyeloradiculitis</td>
<td>Very rare (&lt;0.1% of LNB)</td>
<td>More frequent, but unusual (&lt;3% of LNB)</td>
<td></td>
</tr>
<tr>
<td>Intrathecal antibody production</td>
<td>Minority of cases</td>
<td>Common (&gt;50%)</td>
<td></td>
</tr>
</tbody>
</table>

ACA = acrodermatitis chronica atrophicans.

Table: Differences between European and American LNB
Lyme disease (*B. borgdorferi*])

**Treatment:**
- Erythema migrans: doxycycline 100mg PO BID (10-14 days) *(Amox for children)*
- Meningitis or radiculopathy: ceftriaxone x 14 days (range 10-28 days)
- Cranial nerve palsy: doxy x 14 days (range 14-21 days), some use parenteral regimen especially if abnl CSF seen
- Cardiac disease: parenteral regimen 14 days (range 14-21 days)
- Arthritis (late lyme disease): oral regimen 28 days
- Recurrent arthritis after oral regimen: repeat oral 28 days course or parenteral regimen 14-28 days
- CNS or peripheral nervous system disease: parenteral regimen 14 days (range 14-28 days)
- Acrodermatitis chronica atrophicans(seen mostly in Europe): oral regimen 21 days (14-28 days)

**Prevention:**
- PPE (tick checks, permethrin, DEET); doxy 200mg x1 within 72hrs *(not for children)*
Take Home Points

• Rickettsial infections are:
  
  – More common than you think
  
  – Potentially fatal
  
  – Have non-specific clinical presentations
  
  – Often require treatment prior to conclusive diagnosis
  
  – Respond to tetracyclines (Doxycycline)-even kids

No one dies of an infectious disease where a Rickettsia may be involved without Doxycycline!
Questions?

Consequences of Budget Cuts