Rickettsial (and similar Diseases)

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted in an AAALACi accredited facility in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 2011 edition.
Objectives

• Familiarization with:
  – Classification
  – Geographic distribution
  – Vector transmission
  – Clinical presentations
  – Disease specific features

• Clinical case exercises
# Common Rickettsial Infections

<table>
<thead>
<tr>
<th>Rickettsiae</th>
<th>Tick-Borne</th>
<th>Flea-Borne</th>
<th>Louse-Borne</th>
<th>Mite-Borne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spotted Fever Group</td>
<td>R. rickettsii</td>
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<tr>
<td></td>
<td>R. conorii</td>
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<td></td>
<td>R. japonica</td>
<td>R. felis</td>
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<td>R. akari</td>
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<td></td>
<td>R. parkeri</td>
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<tr>
<td>Typhus Fever Group</td>
<td></td>
<td>R. typhi</td>
<td></td>
<td>R. prowazekii</td>
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<tr>
<td>Scrub Typhus</td>
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<tr>
<td>Anaplasma</td>
<td>A. phagocytophilum</td>
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<td>O. tsutsugamushi</td>
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<tr>
<td>Ehrlichia</td>
<td>E. chafeensis</td>
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<td></td>
<td>E. ewingii</td>
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<tr>
<td></td>
<td>E. canis</td>
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<tr>
<td>Q Fever</td>
<td>Coxiella burnetii</td>
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<tr>
<td>Lyme disease</td>
<td>Borrellia burgdorferi</td>
<td></td>
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</tr>
</tbody>
</table>
What’s in Common?

• Obligate intracellular Gram-negative bacteria
• Transmission
  – Ticks
  – Fleas
  – Lice
  – Mites (chiggers)
• Incubation: 1-2 weeks
• Non-specific symptoms
• Broad spectrum: mild flu-like to very ill
• ↓ platelets, ↓ WBCs, ↑ liver associated enzymes
• Doxycycline is effective
# GeoSentinel Surveillance

<table>
<thead>
<tr>
<th>Destination</th>
<th>SFG rickettsiosis</th>
<th>TG rickettsiosis</th>
<th>Indeterminate SFG/TG rickettsiosis</th>
<th>Scrub typhus</th>
<th>Anaplasmosis</th>
<th>Acute Q fever</th>
<th>Bartonellosis</th>
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<tbody>
<tr>
<td>Western Europe</td>
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<tr>
<td>Southeast Asia</td>
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<td>6</td>
<td>2</td>
<td>9</td>
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<tr>
<td>Australia/New Zealand</td>
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<td></td>
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<td></td>
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<tr>
<td>Oceania</td>
<td>1</td>
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<tr>
<td>North America</td>
<td>1</td>
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</tr>
<tr>
<td>Central America</td>
<td>3</td>
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<tr>
<td>Caribbean</td>
<td>1</td>
<td></td>
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<td></td>
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<td>3</td>
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<tr>
<td>South America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unknown</td>
<td>6</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>231</strong></td>
<td><strong>10</strong></td>
<td><strong>4</strong></td>
<td><strong>16</strong></td>
<td><strong>1</strong></td>
<td><strong>11</strong></td>
<td><strong>7</strong></td>
</tr>
</tbody>
</table>

*SFG, spotted fever group; TG, typhus group.*
## Spotted Fever Group

<table>
<thead>
<tr>
<th>Tick</th>
<th>Flea</th>
<th>Mite</th>
</tr>
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<tbody>
<tr>
<td><em>R. rickettsii</em></td>
<td><em>R. felis</em></td>
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<td><em>R. africae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>R. parkeri</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
R. africae (African tickbite fever)

Distribution map of the principal tick vectors of Rickettsia africae. Dotted line denotes approximate border between A. hebraeum (in southern Africa) and A. variegatum.

Lancet ID 2003:557-564
R. africae (African tick bite fever)

- Incubation 5-7 days
- Acute, febrile, and influenza-like illness
  - Severe headache, nausea, fatigue
  - Prominent myalgia (esp. neck)
- Inoculation eschar(s)
  - Black crusts surrounded by a red halo
- +/- vesicular rash/aphthous ulcers
- Regional lymphadenitis
- ~50% of patients have multiple eschars
- Rare complications; recovery is the rule
**R. Africae (African tick bite fever)**

- **Habitat:** tall grasses/bush; shade; rainy season
- **Risks:** soldiers, safaris, campers, farmers
  - Aggressive: single host attacked by several ticks, multiple times
- **Diagnosis:** difficult (clinical)
- **Treatment:** Doxycycline 100mg BID 7d or until 48 hrs post defervescence
- **Prevention:** PPE; skin exam, careful tick removal
R. conorii (Mediterranean spotted fever AKA Boutonneuse fever)

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.
R. conorii (Mediterranean spotted fever AKA Boutonneuse fever)

<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>R. conorii conorii, isolates Malish, Moroccan Kenyan</td>
<td>Rhipicephalus sp., Haemaphysalis leachii</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>R. conorii israelensis</td>
<td>Rh. sanguineus</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>R. conorii caspia</td>
<td>Rh. sanguineus, R. pumilio</td>
<td>Astrakhan region, Chad, Kosovo</td>
<td>Astrakhan spotted fever</td>
<td>100 23 94</td>
<td>No</td>
</tr>
<tr>
<td>R. conorii indica</td>
<td>Rh. sanguineus, Boophilus microplus, H. leachii</td>
<td>India, Pakistan</td>
<td>Indian tick typhus</td>
<td>100 Rare 100 (frequently purpuric)</td>
<td>No</td>
</tr>
</tbody>
</table>

Unlike African tick bite fever, eschars rarely multiple in MSF
R. conorii (Mediterranean spotted fever AKA Boutonneuse fever)

• Incubation 5-7 days
• Fever, HA, maculopapular rash; *tache noire*
• Ecology of exposure: peridomestic; buildings where dogs kept
• Diagnosis tough
  – Clinical +/- biopsy (eschar); serology (IFA), PCR, culture
• Treatment: Doxycycline 100mg BID 5-10 days
• Prevention: PPE
Rocky Mountain Spotted Fever

• *R. rickettsii*
• USA, southern Canada, C/S Americas
• Vector
  – *Dermacentor variabilis* (American dog tick)
  – *D. andersoni* (Rocky Mountain wood tick)
• Minimum attachment: 4-6 hrs
• Incubation: 2-14 days

[cdc.gov/rmsf/symptoms; cdc.gov/rmsf/stats]
RMSF Rash

cdc.gov/rmsf/symptoms
RMSF

RMSF Incidence, 2008

Cases per million

- 0
- 0.2-1.5
- 1.5-19
- 19-77

cdc.gov/rmsf/stats

American dog tick

Rocky Mountain Wood tick
R. akari (Rickettsialpox)

- Morphologically identical to *R. rickettsii*
- Vector: house mouse mite
- Reservoir: common house mouse
- “Urban zoonosis” since 1950s
  - NYC, Boston, West Hartford, Philadelphia, Pittsburgh, Cleveland
- Worldwide: Russia, Korea, South Africa

*J Am Acad Dermatol* Nov 2004
R. akari (Rickettsialpox)

- Incubation 7-10 days
- Painless bite
- Papulovesicle eschar within 1-2 days
- Fever, malaise 1 week later
- Diffuse papulovesicular rash 2-3 days after fevers
  - Trunk, extremities, oral mucosa
- Generalized lymphadenopathy
- Self-limited (7-10 days after symptom onset)
Rickettsialpox

J Am Acad Dermatol 2004;51:S137-42
healthfiles.net/disease/category/r
R. akari (Rickettsialpox)

- Labs: mild leukopenia; thrombocytopenia, mild proteinuria
- Definitive Dx: rise in serum R. akari Ab during convalescence (CF, IFA)
  - Cross-reactive with RMSF Ab
- Treatment: Doxycycline 100mg BID until clinically improved for 48 hrs (~ 5-7 days)
- Prevention: PPE
## “Pox” DDX

<table>
<thead>
<tr>
<th>Feature</th>
<th>Rickettsialpox</th>
<th>Chickenpox(^{24})</th>
<th>Smallpox (variola major)(^{25})</th>
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<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>
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<td>Prodrome</td>
<td>Usually mild, may be severe. Fever, malaise, and headache.</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. 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>
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<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>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>Pruritus/pain Distribution</td>
<td>Exanthem usually asymptomatic: occasional pruritus.</td>
<td>Commonly pruritic</td>
<td>Starts on trunk and face and spreads centrifugally. Palms, soles may be involved</td>
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<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</td>
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\(^{24}\) J Am Acad Derm. 2004;51(5)S137-S142
## “Pox” DDX

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J Am Acad Derm. 2004;51(5)S137-S142
# Typhus Group

<table>
<thead>
<tr>
<th>Flea</th>
<th>Louse</th>
<th>Chigger mite</th>
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<tbody>
<tr>
<td><em>R. typhi</em></td>
<td><em>R. prowazekii</em></td>
<td><em>O. tsutsugamushi</em></td>
</tr>
</tbody>
</table>
R. typhi (Murine/endemic typhus)

- Found sporadically worldwide
  - In US: Hawaii, California, Texas
- Hosts: Rats, cats, mice
- Vector: fleas

WHO, 1998
EID 1998;4(4):677-680
R. typhi (Murine/endemic typhus)

- R. typhi (Murine/endemic typhus) skin) or aerosolization
- Incubation 6-14 days
- Fever, headache, rash (triad in 50%)
- Leukocytosis or mild leukopenia
- Anemia (severe with G6PD deficiency)
- +/- ↓Na, hepatic/renal abnormalities

CID 2013; 46(6):913-918
R. typhi (Murine/endemic typhus)

- Ecology: Rat fleas; coastal areas
- Diagnosis (clinical): serology (IFA)
  - Cross-reactive with R. prowazekii and RMSF Abs
- Spontaneous recovery in 2 weeks
- Treatment: Doxycycline 100mg BID for 48-72 hrs after fever resolved
- Prevention: PPE

REPORT LICE AT ONCE
UIE LOUSE POWDER
R. Prowazekii (Louse borne/epidemic)

WHO, 1998
R. Prowazekii (Louse-borne/epidemic)

- Incubation 6-14 days
- Fever, headache (abrupt), tachypnea, myalgia
- Rash (macular-papular/petechial) on days 4-7
  - Spreads peripherally (unlike RMSF)
- CNS disease: confusion, drowsiness, coma
- Shock: multifocal/multi-organ vasculitis
  - Mortality 60% w/o abx; 4% w/ abx
- Recrudescence (Brill-Zinsser disease)
  - Mild illness, elderly, years after initial episode
Figure 4: (A) Skin rash and (B) toe gangrene in a patient infected with epidemic typhus during Burundi outbreak 1997.
R. Prowazekii (Louse borne/epidemic)

- Vector: body louse (*Pediculosis humanus*)
- Reservoir: humans, flying squirrels
- Ecology: crowded, war/disasters, famine, poverty
- Diagnosis: serology (IFA), biopsy, PCR
- Treatment: Doxycycline (as endemic)
- Prevention: delousing (permethrin>lindane, malathion)
  - Boiling clothes, bedding
  - Long-acting insecticides
  - Prophylaxis (doxycycline)
O. tsutsugamushi (Scrub typhus)

- Painless bite
- Eschar - painless papule, central necrosis
- Fever, chills, HA, conjunctival suffusion
  - All prior to centrifugal rash
- Cough, tachypnea, pulmonary infiltrates
  - Most common
- Gastrointestinal symptoms
- Regional lymphadenopathy
- Acute hearing loss in 1/3 cases
- CFR 10% if untreated
**O. tsutsugamushi** (Scrub typhus)

- **ECOLOGY:** ACTIVE RICE FIELDS, AGRICULTURAL AREAS, WARM HUMID TROPICS
- **RATS KEY TO POPULATION DENSITIES**
- **DIAGNOSIS:** CLINICAL; IFA GOLD STANDARD; PCR, ISOLATION IN BLOOD
- **ESCHAR IN SE ASIA PATHOGENOMONIC**
- **TREATMENT:** DOXYCYCLINE (RESISTANCE POSSIBLE)
  - AZITHROMYCIN, RIFAMPIN
- **PREVENTION:** TOPICAL REPELLENTS TO CLOTHING, WEEKLY DOXYCYCLINE
Tick-Borne Rickettsiae in Africa

- R. africae
- R. conorii conorii
- R. conorii caspia
- R. conorii israelensis
- R. sibirica mongolitimonae
- R. aeschlimannii
- R. massiliae
- R. rhipicephali
Tick-Borne Rickettsiae in Asia/ Australia
Tick-Borne Rickettsiae in the Americas
Tick-Borne Rickettsiae in Europe

- R. conorii conorii
- R. conorii israelensis
- R. conorii caspia
- R. sibirica mongolitimonae
- R. aëschlimannii
- R. slovaca
- R. helvetica
- R. massiliae
- « R. monacensis » and related rickettsias
- R. rhipicephali
- Rickettsia sp. RpA4
Agents of Ehrlichiosis

• *E. chaffeensis*
  -Infects peripheral monocytes/ macrophages
  -Major cause of Ehrlichiosis in USA

• *E. Ewingii*
  -Infects neutrophils; immunocompromised

• *E. canis*
  -Asymptomatic
## 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>E. chaffeensis</td>
<td>A. Phagocytophilum</td>
<td>E. ewingii</td>
</tr>
<tr>
<td>Monocyte macrophage</td>
<td>Granulocyte</td>
<td>Granulocyte</td>
</tr>
<tr>
<td>&gt;1600 cases/yr</td>
<td>&gt;2100 cases/yr</td>
<td>~20 (immuno-compromised)</td>
</tr>
<tr>
<td>SC, SE, mid-Atl</td>
<td>NE, MW, Pac coast</td>
<td>SC</td>
</tr>
</tbody>
</table>

Dumler JS, Walker DH. *Ehrlichiosis and Anaplasmosis* in *Tropical Infectious Diseases* 2006.
HME Distribution

- Vector: lone star tick
  • *Amblyomma americanum*
- Reservoir: White-tailed deer
- Only occurs in USA

Clin Lab Med March 2010
HGA Distribution

- International distribution
- Vector: *Ixodes* ticks
  - *I. scapularis* (EUS)
  - *I. pacificus* (WUS)
  - *I. ricinus* (Europe)
  - *I. persulcatus* (Asia)
- Reservoir: white-footed mouse
Anaplasma Life Cycle

Increasing Incidence of *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum* in the United States, 2000–2007

F. Scott Dahlgren, Eric J. Mandel, John W. Krebs, Robert F. Massung, and Jennifer H. McQuiston*

Division of Vectorborne Infectious Diseases, National Center for Enteric, Zoonotic, and Infectious Disease, Centers for Disease Control and Prevention, Atlanta, Georgia
## 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>
Ehrlichiosis

- Incubation 5-14 days
- Rash rare; *no* vasculitis
- Ecology:
  - grassy areas, forest edge, un-mowed areas
  - May-Sept in USA
- Diagnosis: paired serology; peripheral blood smears (morulae=cytoplasmic inclusions); PCR
- Treatment: Doxycycline 100mg BID ~ 3d after afebrile (~5-7 days)
- Prevention: PPE
Ehrlichiosis and Anaplasmosis

<table>
<thead>
<tr>
<th>Symptom, sign, or finding</th>
<th>HME</th>
<th>HGA</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory finding</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<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; 45 (Suppl 1)
# Ehrlichiosis and Anaplasmosis

<table>
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<tr>
<th>Symptom, sign, or finding</th>
<th>Patients, % (no. evaluated)</th>
</tr>
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<tbody>
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<td></td>
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Lyme disease (Borrelia sp.)

Agent: *B. afzelii*, *B. garinii*

Vectors: *I. ricinus* – Europe

*I. persulcatus* – E. Europe, Russia

Agent: *B. burgdorferi*

Vectors: *I. scapularis* – EUS

*I. pacificus* - WUS

Lancet 2003; CDC.gov
Stages of Infection

*Early Infection*
- Rash (erythema migrans) in ~ 70-80%
  - At site of tick bite after 3-30 days
  - Gradually expands over several days
  - Central clearing (Bull's-eye 50% of time); warm but not painful
  - Occasional additional EM lesions days later
- +/- fatigue, chills, fever, headache, swollen lymph nodes

*Late Infection*
- Encephalomyelitis
- Carditis
- Arthritis in 60% untreated
  - Large and small joints, intermittent
  - Can develop chronic arthritis

Steere AC. *Borrelia burgdorferi (Lyme Disease, Lyme Borreliosis)* in PPID.2005.
Lyme Disease Manifestations

• Neuroborreliosis (5%)
  – Can occur at any time
  – Early: aseptic meningitis; cranial nerve palsies; peripheral neuritis/paresis
  – *Borrelia* DNA (PCR) in CSF

• Carditis
  – Conduction disturbances (AV block – complete block)
  – Check ECG if patient reports palpitations or syncope

• Arthritis
  – Intermittent attacks of inflammation
  – Synovial fluid positive for *Borrelia* DNA (PCR)
  – US > Europe

Steere AC. *Borrelia burgdorferi* (Lyme Disease, Lyme Borreliosis) in PPID.2005.
Central clearing is not always present; look for unusual patterns or locations of cellulitis in summer months.
Lyme Disease Manifestations

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  - Can occur at any time
  - Early: aseptic meningitis; cranial nerve palsies; peripheral neuritis/paresis
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Steere AC. *Borrelia burgdorferi (Lyme Disease, Lyme Borreliosis)* in PPID.2005.
<table>
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<tr>
<th>Indication</th>
<th>Treatment</th>
<th>Duration, days (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tick bite in the United States</td>
<td>Doxycycline, 200 mg in a single dose&lt;sup&gt;a,b&lt;/sup&gt;; (4 mg/kg in children ≥8 years of age) and/or observation</td>
<td>...</td>
</tr>
<tr>
<td>Erythema migrans</td>
<td>Oral regimen&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>14 (14–21)&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Early neurologic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis or radiculopathy</td>
<td>Parenteral regimen&lt;sup&gt;c,f&lt;/sup&gt;</td>
<td>14 (10–28)</td>
</tr>
<tr>
<td>Cranial nerve palsy&lt;sup&gt;a,g&lt;/sup&gt;</td>
<td>Oral regimen&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Oral regimen&lt;sup&gt;a,c,h&lt;/sup&gt; or parenteral regimen&lt;sup&gt;a,c,h&lt;/sup&gt;</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td>Borrelial lymphocytoma</td>
<td>Oral regimen&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>14 (14–21)</td>
</tr>
<tr>
<td>Late disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis without neurologic disease</td>
<td>Oral regimen&lt;sup&gt;c&lt;/sup&gt;</td>
<td>28</td>
</tr>
<tr>
<td>Recurrent arthritis after oral regimen</td>
<td>Oral regimen&lt;sup&gt;a,c&lt;/sup&gt; or parenteral regimen&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>14 (14–28)</td>
</tr>
<tr>
<td>Antibiotic-refractory arthritis&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Symptomatic therapy&lt;sup&gt;j&lt;/sup&gt;</td>
<td>...</td>
</tr>
<tr>
<td>Central or peripheral nervous system disease</td>
<td>Parenteral regimen&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14 (14–28)</td>
</tr>
<tr>
<td>Acrodermatitis chronica atrophicans</td>
<td>Oral regimen&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21 (14–28)</td>
</tr>
<tr>
<td>Post-Lyme disease syndrome</td>
<td>Consider and evaluate other potential causes of symptoms; if none is found, then administer symptomatic therapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>...</td>
</tr>
</tbody>
</table>

Annals of Internal Medicine

Borrelia miyamotoi: The Newest Infection Brought to Us by Deer Ticks

It's not just Lyme disease anymore. Residents and visitors in many parts of the northeastern, north-central, and far western United States have more than one reason to avoid bites from hard-bodied (ixodid) ticks. The latest addition to the list of infections transmitted to humans by the same ixodid ticks that are vectors of Lyme disease is Borrelia miyamotoi. Although B. miyamotoi is in the same genus as B. burgdorferi, it is more closely related to species that cause relapsing fever than to Lyme disease agents (1). Discovered in Ixodes persulcatus ticks in Japan in 1994 and subsequently documented in ticks and rodents in North America and Europe, B. miyamotoi was not recognized as a human pathogen until a report from Russia in 2011 (2). It has since been reported in patients in the United States, Europe, and Japan (3-8). In this issue, Molloy and colleagues report the first large case series in the United States and provide important new information about the epidemiology and clinical presentation of human disease caused by this pathogen (8).

Whole blood samples from patients in the northeastern United States with suspected tickborne illness during April to November in 2013 and 2014 were tested with polymerase chain reaction (PCR) for 4 tickborne pathogens. Amplifiable DNA of B. miyamotoi, Anaplasma phagocytophilum, B. burgdorferi, or Babesia microti was detected in approximately 1%, 1%, 2%, and 3%, respectively, of 11,515 samples from individual patients. The frequency of infection with B. burgdorferi, which is primarily a fixed-tissue pathogen, should be greatly underestimated on the basis of PCR of the blood alone. Furthermore, the relative frequencies of these 4 infections vary across different regions of the northeastern United States, so different results might have been obtained with samples from other locations. Nevertheless, on the basis of the current report and previous data, the frequency of B. miyamotoi infection seems to be similar to that of A. phagocytophilum and B. microti (3, 6, 8).

The researchers provide clinical information for 51 patients infected with B. miyamotoi. Of note, the peak incidence of positive assay results for B. miyamotoi was in August, with probable onsets of illness continuing into September, which is about a month after the peak incidence of Lyme disease. This temporal peak is similar to that observed in naturally infected white-footed mice in Connecticut and corresponds to the questing activity of Ixodes scapularis larvae in the northeastern United States (3). Acquisition of B. miyamotoi infection from unfed larval ticks is possible because of transovarial transmission of the pathogen from an infected female (9). Bites from larval deer ticks have not been considered as a health threat, but this needs to be reevaluated. Larval transmission of B. miyamotoi has implications for checking for ticks and continuing tick precautions even after the risk for Lyme disease has abated. Human-to-human transmission by blood transfusion is theoretically possible (3), but a transfusion-associated case has not been reported to date.

The clinical manifestations of B. miyamotoi among the 51 infected American patients are similar to those described for patients with undifferentiated acute febrile illness, including fever and headache as the most prominent findings (2-8). Recurrence of fever was noted in 4% of patients in this case series and 10% in the original case series from Russia (2). Higher relapse rates might have been observed if antibiotic therapy had been delayed or omitted. A rash was noted in 8% of the American patients, but none was described as an erythema migrans rash. Symptoms were often severe, resulting in hospitalization for about one quarter of the patients. None of the patients developed complications, however, presumably because of prompt antibiotic treatment. Meningoencephalitis due to B. miyamotoi has been described in 2 immunocompromised patients in separate reports from the United States and the Netherlands (4, 7). Jarisch-Herxheimer reactions, which consist of fever and chills with occasional hypotension after the first dose of an antibiotic, were not described in this case series, although such reactions were observed in a minority of previously reported patients with B. miyamotoi (2-4). Leukopenia, thrombocytopenia, and elevated liver enzyme concentrations were reported, as has been documented previously (2).

The diagnosis of B. miyamotoi in this case series was based on PCR testing and subsequent sequencing of the product. Borrelia miyamotoi antibody testing using the glycerophosphodiester phosphodiesterase (GlpQ) antigen was noted to be relatively insensitive in diagnosing acute illness, but it is a reasonable test to confirm the diagnosis if convalescent sera are available (5, 6, 8). Antibodies to a Borrelia GlpQ protein are not observed in Lyme disease because B. burgdorferi does not make the protein; however, there may be cross-reactive antibodies with other forms of relapsing fever (10). Both PCR and GlpQ antibody assays for B. miyamotoi are available from commercial and university laboratories, but to date no B. miyamotoi tests have been approved by the U.S. Food and Drug Administration. Although not examined in this report, a Wright- or Giemsa-stained blood smear is a routinely performed procedure that may reveal B. miyamotoi spirochetes in the blood during febrile episodes. Doxycycline, amoxicillin, and ceftriaxone seem to be effective in alleviating symptoms and preventing complications (2-8). Such therapy would also be effective against co-infection with B. burgdorferi. Doxycycline is the preferred initial therapy in patients with suspected B. miyamotoi infection because it effectively treats Lyme disease and human granulocytic anaplasmosis, which may be the cause of illness or co-infection with B. miyamotoi.
Borrelia miyamotoi

- Relapsing fever spirochete that has only recently been identified as a human pathogen
- Like *Borrelia burgdorferi*, is transmitted by Ixodes ticks
- Genetically and ecologically distinct from *Borrelia burgdorferi*
- Although infection can cause Lyme-like symptoms, acute Lyme disease often presents with rash, while infection with *B. miyamotoi* does not. Moreover, patients infected with *B. miyamotoi* tend to have more severe symptoms (next slide).
Borrelia miyamotoi

- Presenting symptoms typically include fever, myalgia, influenza-like illness, headache, or rash and patients are often found to have leukopenia, thrombocytopenia, and elevated aminotransferase levels, mimicking human anaplasmosis infection.
- Patients are commonly described as appearing 'toxic'; in one study, more than 50% were suspected of having sepsis, and 24% required hospitalization.
- The headaches were most commonly described as severe, resulting in head computed tomography scans and spinal taps in 5 patients.
Borrelia miyamotoi

• Blood tests for Lyme disease are not helpful in the diagnosis of B. miyamotoi infections. Currently, confirmation of a diagnosis relies on 1) PCR or 2) antibody-based tests. Both types of tests are under development and not widely commercially available but can be ordered from a limited number of CLIA-approved laboratories.

• Treatment includes 2-4 weeks of doxycycline (alternatively, amoxicillin and ceftriaxone).
Q fever (Coxiella burnetii)

- Bacterial disease of humans and livestock endemic almost world-wide
  - 50 cases/year in U.S.
  - ↓ USA, ↑ Netherlands, OIF
- Zoonosis: wildlife, ticks are main reservoir
- Transmitted through aerosol contact with infected animals or animal remains (cattle, sheep, goats)
  - Urine, feces, milk, birth products/ localizes to uterus/mammary glands
  - Via inhalation or ingestion
  - By eating or drinking raw milk and cheese
- Highly infectious
  - 1 organism can cause clinical infection
Q fever (Coxiella burnetii)

From Lancet 1984: 12 people were playing poker in the same room as a parturient cat. All 12 handled either the cat or litter and all 12 were diagnosed with acute Q fever (placentas carry $10^9$ organisms).
Q fever (Coxiella burnetii)

- 3 clinical presentations (major)
  - Febrile illness: self-limited; most common
  - Pneumonia (with fever): severe HA, retro-orbital pain
  - Hepatitis (with fever): “doughnut” granulomas
  - * 60% asymptomatic

Complications:
- Endocarditis
  - Culture negative; chronic
- Optic neuritis
- Encephalitis
Q Fever: Acute Signs & Symptoms
Nonspecific, febrile syndrome

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>99%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>82%</td>
</tr>
<tr>
<td>Headache</td>
<td>68%</td>
</tr>
<tr>
<td>Shortness of Breath</td>
<td>64%</td>
</tr>
<tr>
<td>Myalgias</td>
<td>54%</td>
</tr>
<tr>
<td>Cough</td>
<td>51%</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>45%</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>27%</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>23%</td>
</tr>
</tbody>
</table>
Q Fever: Diagnosis

- Serologic testing: Main method of laboratory diagnosis
  - Ab to phase II antigen: high in acute
  - Ab to phase I antigen: high in chronic; indicates continued exposure to agent
  - Indirect immunofluorescent antibody/assay (IFA)
    - Fourfold/greater change in IgG antibody titer to phase II antigen between paired acute- and convalescent-phase serum samples (3-6 weeks apart)
- Confirmed via other methods
  - Single positive IFA IgG titer of ≥ 1:128 to phase II antigen (with clinical correlation) defines a probable case
  - Serologic evidence of elevated phase II IgG or IgM antibody reactive with *C. burnetii* antigen by enzyme-linked immunosorbent assay (ELISA), dot-ELISA, or latex agglutination.
  - PCR available in specialized labs
  - Immunohistochemical staining of biopsy material
  - Culture from biopsy material less sensitive than serology
    - Cell (not blood) cx is possible
  - *A significant laboratory hazard* -> Done in BSL-3 labs only
Q Fever: Treatment

• 98% self-limited, but always treat if found

• Acute:
  – Doxy 100 mg po bid for ≥ 14 days, or
  – TCN 500 mg po qid for ≥ 14 days, or
  – Fluoroquinolones (14-21 days), or
  – TMP-SMX (14-21 days)
  – Pregnancy: TMP-SMX 160 mg/800mg po bid
  – Children <8 yrs: TMP-SMX or Macrolides

• Chronic endocarditis:
  – Doxy 100 mg BID plus Hydroxychloroquine 200 mg tid for > 18 mos until IgG & IgA levels drop to < 1:200 OR
  – Ofloxacin 200 mg tid for > 3 years
  – Cipro 750 BID + rifampin 300 BID
  – Possible valve replacement
Diagnosis and Management of Q Fever — United States, 2013

Recommendations from CDC and the Q Fever Working Group

Acute

If the patient has clinical evidence of acute Q fever infection (e.g., fever, headache, rigors, weight loss, myalgia, arthralgia, pneumonia, or hepatits), and acute Q fever is suspected, perform diagnostic testing and initiate empirical 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 FA of 1:128
- Detection of ONA in a clinical specimen by PCR assay
- IHC staining or organism in a clinical specimen
- Isolation of Coxiella burnetii from a clinical specimen by culture

No

Consider alternative diagnoses.

Acute Q fever case

Perform clinical evaluation to determine whether patient is at high risk for chronic disease (e.g., heart disease).

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 laboratory evidence of chronic Q fever infection:
- Demonstration of phase II IgG antibody titer by IFA 1:1024, or
- Detection of ONA 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

Consider alternative diagnoses.

Acute Q fever case

Serologic monitoring demonstrates fourfold decrease in phase II IgG with complete disappearance of phase II IgM and clinical recovery.

No

Discontinue antibiotic treatment and continue twice yearly serologic monitoring for potential relapse (minimum 5 years).

Yes

Continue antimicrobial treatment and serologic monitoring.

Consult a Q fever expert

Chronic Q fever case

Treat appropriately (minimum 18 months [native valves] and 24 months [prosthetic valves] for endocarditis); monitor clinically and serologically throughout treatment.
• Follow-up of Q fever is complicated
• ID should be consulted to manage follow-up of Q fever patients
Q Fever Summary

- Ecology: farmers, vets, abattoir/lab workers
- Diagnosis: paired serology
- Treatment:
  - Acute: Doxycycline x 14 days
  - Chronic/endocarditis: doxycycline + hydroxychloroquine x 18 mos.
- Prevention: education (livestock, dairy)
  - Disposal of birth products (animals)
  - Quarantine/restriction of infected animals
  - Caution high risk patients (valve disease)
Matching

1. Rat-infested grain stores
2. Close living quarters, poverty
3. Sheep or cattle exposure
4. Transitional vegetation
5. Land navigation exercises

A. Spotted fever (R. rickettsii)
B. Q fever (C. burnetii)
C. Scrub typhus (O. tsutsugamushi)
D. Murine typhus (R. typhi)
E. Louse-borne Typhus (R. prowazekii)
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B. Q fever (C. burnetii)
C. Scrub typhus (O. tsutsugamushi)
D. Murine typhus (R. typhi)
E. Louse-borne Typhus (R. prowazekii)
Case #1

- 35 yo USN corpsman in Iraq x 7 months
- En route CONUS develops fever 104°F
- Then daily fever/chills + retro-orbital HA, lower back and bilateral calf pain
- ROS: sore throat, watery diarrhea x 6 days
- Exposures: insect bites, slept in revamped Iraqi chicken factory, goats roaming, walked in brackish water, ate local Iraqi-prepared food
Case #1

• **PE:**
  - T-103°F, HR-90, BP-110/60, O$_2$ Sat-99% (RA)
  - Unremarkable

• **CXR, abdominal CT both normal**
Case #1 Part B

- 23 YO USMC – BECOMES ILL 3 DAYS AFTER #1
- SIMILAR FEVER, CHILLS, SORE THROAT, DIARRHEA
- ROS: BLISTERS ON FEET (WADED THROUGH SEWAGE); ONLY ATE MRES, DID NOT SLEEP IN CHICKEN FACTORY (500 YDS AWAY)
- PE: T-106°F, HR-104, BP-120/70, O₂ SAT -98%
  -MILD JAUNDICE O/W NORMAL
Lab Data

Patient 1
- Na-130 (137-145)
- K-3.0 (3.6-5.0)
- Alk phos-310 (36-126)
- AST-125 (17-49)
- ALT-130 (7-56)
- Tbili 1.8 (0.2-1.3)
- WBC 4.5 (4.0-11.0) 74N/E2
- Plt-120 (150-450)

Patient 2
- Na-130
- K-2.9
- Alk phos-137
- AST-173
- ALT-131
- Tbili-2.8
- WBC-4.8
- Plt-45
Case #1

• Malaria smears (-)
• Blood, stool, urine cultures (and CSF #1) (-)
• Acute HIV, RPR (-)
• Viral, Dengue, Hepatitis A/B/C (-)
• Leptospirosis Ab (-)
Case #1

- Malaria smears (-)
- Blood, stool, urine cultures (and CSF #1) (-)
- Acute HIV, RPR (-)
- Viral, Dengue, Hepatitis A/B/C (-)
- Leptospiroosis Ab (-)

Q Fever
Current Recommendations of the Tri-Service Infectious Diseases Q Fever Working Group

Clinical syndrome potentially consistent with acute Q fever

Include doxycycline 100 mg po BID for 21 days in therapeutic regimen.

Send acute (now) and convalescent (in 2 weeks) serum to USAFSAM for Q fever IFA testing

If negative testing no further action required.

Confirmed Q fever

Obtain Infectious Diseases consult and transthoracic echo (TTE) upon redeployment to CONUS.

Repeat serologies at USAFSAM every 3 months for 1 year then every 6 months for 1 year

Anti-phase I IgG > four-fold higher than previous test and anti-phase II IgG the same or decreasing?

Other clinical evidence of inflammatory disease?

Yes

No

TEE + Coxiella PCR on whole blood (CDC)

Repeat serology in 3 months

If either abnormal then treat with minimum of 18 months doxycycline + hydroxychloroquine

Fevers, sweats, weight loss, chest pain, elevated erythrocyte sedimentation rate, C reactive protein, liver-associated enzymes, white blood cell count, rheumatoid factor
Case #2

- 44YO INDIAN SUBSISTENCE FARMER WITH FEVER X 7 DAYS
- FEVER UNREMITTING, INITIALLY ABRUPT ONSET
- PREVIOUSLY WELL
- ONE DAY SEVERE FRONTAL HA, N/V, PHOTOPHOBIA, DOE AND NOW TENDER SWELLING IN LEFT GROIN
• NO TRAVEL
• CHICKENS ON FARM
• MARRIES, 2 CHILDREN - ALL HEALTHY
• VEGETARIAN; MAKES YOGURT
• WATER- WELL OR RIVE (WIFE GATHERS)
• NO TOB, ETOH, DRUGS, MEDS, ALLERGIES
• CHILDHOOD VACCINES (WHO) COMPLETED
More clinical information

• Following incubation (6-21 d), sxs appear
• After initial sxs (F, HA, chills, fever, hearing, conjunctivitis/suffusion, LAD), ulcer seen then centrifugal rash within 1 wk
• 2nd week (if untreated):
  – Splenomegaly
  – Pneumonia
  – Myocarditis
  – Delirium
  – Death
• Diagnosis?
More clinical information

• Following incubation (6-21 d), sx appear
• After initial sx (F, HA, chills, fever, hearing, conjunctivitis/suffusion, LAD), ulcer seen then centrifugal rash within 1 wk
• 2nd week (if untreated):
  – Splenomegaly
  – Pneumonia
  – Myocarditis
  – Delirium
  – Death
• Diagnosis?

Scrub Typhus
African tick bite fever

- *R. africae*
- *Amblyomma* tick
- ↑ tourists (~5%)
- HA, myalgia, eschar(s)
- Vesicular rash, mouth blisters 30%
- Reactive arthritis (5%)
- Self-limited

CID 2004
Scrub typhus

- *Orientia tsutsugamushi*
- Mites
- Loggers, rice farmers, military
- Fever, LAD (70%), eschar (50%)
- PNA, CNS, DIC, renal failure
- Independent predictor mortality: metabolic acidosis (↑ ast, wbc, ↓ plt)

CID 2004
Case #3

40 yo male Thai subsistence farmer is brought to clinic with report of headache, chills, hearing loss, and cough. You note an eschar on his leg and elicit confusing responses to simple questions. What would be your drug of choice for treatment?

A. Doxycycline
B. Atovaquone
C. Azithromycin
D. Gentamicin
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Case #4

A 44-year-old male traveler returning from Tanzania presents 7 days after return with fever and respiratory symptoms. Among rickettsial diseases to be considered, which of the following is most likely to be the cause of his illness?

A. Ehrlichiosis
B. Spotted fever group rickettsiosis
C. Bartonellosis
D. Typhus group rickettsiosis
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A. Ehrlichiosis
B. Spotted fever group rickettsiosis
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Which of the following is the most commonly used treatment for rickettsial disease among returning international travelers?

A. Tetracycline
B. Minocycline
C. Tmp/Smx (Septra)
D. Doxycycline
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A. Tetracycline
B. Minocycline
C. Tmp/Smx (Septra)
D. Doxycycline
During war with many displaced people, which organism would you be most concerned about because of high associated mortality rates, complications, and epidemic potential?

A. *Orientia tsutsugamushi*
B. *Rickettsia rickettsii*
C. *Rickettsia prowazekii*
D. *Rickettsia typhi*
During war with many displaced people, which organism would you be most concerned about because of high associated mortality rates, complications, and epidemic potential?

A. *Orientia tsutsugamushi*
B. *Rickettsia rickettsii*
C. *Rickettsia prowazekii*
D. *Rickettsia typhi*
Location, location, location...

<table>
<thead>
<tr>
<th>Rickettsial disease</th>
<th>Geographic locations where most prevalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSF</td>
<td>• Primarily in the continental United States and rarely elsewhere</td>
</tr>
<tr>
<td>Rickettsialpox</td>
<td>• Large cities in Russia, South Africa, and Korea</td>
</tr>
<tr>
<td>Boutonneuse fever</td>
<td>• Mediterranean countries, such as Spain, Italy, and Israel</td>
</tr>
<tr>
<td>Louse-borne typhus (Epidemic)</td>
<td>• Europe, Asia and Africa</td>
</tr>
<tr>
<td>Brill-Zinsser disease</td>
<td>• In the last 2 decades African countries, especially Ethiopia and Nigeria, have reported most cases</td>
</tr>
<tr>
<td>Murine</td>
<td>• Large cities around the world with high rate infestations</td>
</tr>
<tr>
<td>Tsutsugamushi disease</td>
<td>• Japan, Solomon Islands and Pakistan</td>
</tr>
<tr>
<td>Q fever</td>
<td>• Australia, Canada and other parts of the world where humans come into contact with infected animals</td>
</tr>
<tr>
<td>Disease</td>
<td>Causative rickettsia</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Rocky Mountain Spotted Fever (RMSF)</td>
<td><em>R. rickettsii</em></td>
</tr>
<tr>
<td>Rickettsialpox</td>
<td><em>R. akari</em></td>
</tr>
<tr>
<td>Boutonneuse fever</td>
<td><em>R. conorii</em></td>
</tr>
<tr>
<td>Louse-borne typhus</td>
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<tr>
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<td><em>R. prowazekii</em></td>
</tr>
<tr>
<td>Murine</td>
<td><em>R. typhi</em> and <em>R. felis</em></td>
</tr>
<tr>
<td>Tsutsugamushi disease</td>
<td><em>O. tsutsugamushi</em></td>
</tr>
<tr>
<td>Q fever</td>
<td><em>C. burnetii</em></td>
</tr>
</tbody>
</table>
## Differential diagnosis of an eschar

### Infectious
- **Bacterial**: ecthyma caused by *Staphylococcus* or *Streptococcus*, ecthyma gangrenosum, necrotizing fasciitis, anthrax, glanders, plague, phagedenic ulcer, rat bite fever, tularemia
- **Viral**: orf/milker's nodule, herpes simplex virus
- **Rickettsial**: scrub typhus, the spotted fever group including *Rickettsia* pios, South African tick bite fever, Siberian tick typhus, Queensland tick typhus, and boutonneuse fever
- **Fungal**: aspergillosis, fusariosis, mucormycosis

### Inflammatory
- **Brown recluse spider bite**
- **Thrombotic disease**: antiphospholipid syndrome ulcers, coumadin and heparin necrosis, calciphylaxis
SUMMARY

• Rickettsial diseases have nonspecific symptoms
  – Fever, headache, abnormal LFTs, thrombocytopenia
• Thorough skin exam: look for eschars
• Rashes are not always present
• Get a thorough travel history
• Know what is endemic
• Mortality is high for some conditions
• Treat with doxycycline when in doubt

No one should die without empiric doxycycline.