Rickettsial Diseases

and friends....

MAJ Jason M. Blaylock, MD
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*Acknowledgements: LTC Paige Waterman, MD,
MAJ Leyi Lin, MD
Objectives

• Familiarization with:
  – Classification
  – Geographic distribution
  – Vector transmission
  – Clinical presentations
  – Disease specific features (risk factors, treatment)

• Clinical case exercises
Common Rickettsial Infections

**Rickettsiae**

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

• Obligate intracellular Gm-negative bacteria
• Transmitted by ectoparasites
  – Ticks, fleas, lice, mites (chiggers)
• Incubation: 1-2 weeks
• Some with bite eschar
• Rash not universal
• Non-specific symptoms
• Broad spectrum:mild flu-like to very ill
• ↓ platelets, ↓ WBCs, ↑ liver tests
• **Doxycycline is effective!**
Common things being common

<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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<td>Eastern Europe</td>
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<tr>
<td>North Africa</td>
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<tr>
<td>Sub-Saharan Africa</td>
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<td>Middle East</td>
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<tr>
<td>Northeast Asia</td>
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<td>1</td>
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<td>South central Asia</td>
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<td>1</td>
<td>1</td>
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<td>5</td>
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<tr>
<td>Southeast Asia</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>9</td>
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<tr>
<td>Australia/New Zealand</td>
<td>1</td>
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<td></td>
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<tr>
<td>Oceania</td>
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<tr>
<td>North America</td>
<td>1</td>
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<tr>
<td>Central America</td>
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<tr>
<td>Caribbean</td>
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<td>South America</td>
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<td></td>
</tr>
<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>
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</tbody>
</table>

*SFG, spotted fever group; TG, typhus 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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<tr>
<td><em>R. parkeri</em></td>
<td></td>
<td></td>
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</tbody>
</table>
R. africae (African tick bite fever)

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

- Incubation 5-7 days
- Acute, febrile, and influenza-like illness
  - severe headache, nausea, fatigue
  - Prominent myalgias (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

Lancet ID 2003;3:557-564
R. africae (African tick bite fever)
**R. africae (African tick bite fever)**

- Habitat: tall grasses/bush; shade; rainy season
- Typical victims: soldiers, safaris, campers, cattle farmers
  - Aggressive: single host attacked by several ticks, multiple times
- Diagnosis: difficult (clinical)
- Treatment: Doxycycline 100mg BID 7d
  - or until 48hrs 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)

Unlike African tick bite fever, eschars RARELY multiple in MSF

<table>
<thead>
<tr>
<th>Rickettsia</th>
<th>Vector</th>
<th>Symptoms present, % patients</th>
<th>Fatal forms? (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>R. conorii</em> conorii, isolates Malish, Moroccan, Kenyan</td>
<td>Rhipicephalus sanguineus, spotted Haemaphysalis leachi</td>
<td>Fever 91–100, Inoculation eschar 20–87, Rash 93–100</td>
<td>Yes (0–18.1)</td>
</tr>
<tr>
<td><em>R. conorii</em> israelensis</td>
<td><em>Rh. sanguineus</em></td>
<td>Fever 98–100, Inoculation eschar 94</td>
<td>Yes (0–3.5)</td>
</tr>
<tr>
<td><em>R. conorii</em> caspia</td>
<td><em>Rh. sanguineus</em></td>
<td>Fever 100, Inoculation eschar 23</td>
<td>No</td>
</tr>
<tr>
<td><em>R. conorii</em> indica</td>
<td><em>Boophilus microplus</em></td>
<td>Fever 100 (frequently purpuric)</td>
<td>No</td>
</tr>
</tbody>
</table>

EID. 2008;14(9):1360-1367
**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: Doxy 100mg BID 5-10 days
- Prevention: PPE
R. conorii – vector, eschar and rash
Rocky Mountain Spotted Fever

- RMSF, \textit{R. rickettsii}
- USA, southern Canada, C/S Americas
- Vector: \textit{Dermacentor variabilis} (American dog tick), \textit{D. andersoni} (Rocky Mountain wood tick)
- Minimum attachment: 4-6hrs; Incubation: 2-14 days
- Fever, HA, nausea/vomiting
- abdominal pain, conjunctival injection
- Rash:
  - Occurs in 90%
  - Red to purple, spotted (petechial) rash in 35-60%
    - Usually not seen until after 6\textsuperscript{th} day
- Can be fatal early if untreated (doxycycline)
RMSF Rash
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
**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
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 48hrs (~ 5-7 days)
- Prevention: PPE
### “Pox” DDX

<table>
<thead>
<tr>
<th>Feature</th>
<th>Rickettsialpox</th>
<th>Chickenpox&lt;sup&gt;24&lt;/sup&gt;</th>
<th>Smallpox (variola major)&lt;sup&gt;25&lt;/sup&gt;</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. 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.</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.</td>
</tr>
<tr>
<td>Enanthem</td>
<td>Anywhere. Palms, soles not usually involved.</td>
<td>Starts on trunk and face and spreads centrifugally. Palms, soles may be involved</td>
<td>Begins on the oral mucosa, face, and extremities and spreads centripetally. Palms, soles commonly involved.</td>
</tr>
<tr>
<td>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>
# Typhus group

<table>
<thead>
<tr>
<th>Flea</th>
<th>Louse</th>
<th>Chigger mite</th>
</tr>
</thead>
<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
**R. typhi (murine/endemic typhus)**

- Flea bites (infected feces contaminate skin) or aerosolization
- Incubation 6-14 days
- Fever, headache, rash (triad in 50%)
- Leukocytosis or mild leukopenia
- Anemia (severe with G6PD def)
- +/- ↓Na, hepatic/renal abnormalities

**R. typhi (murine/endemic typhus)**

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

R. prowazekii (louse-borne/epidemic)
**R. prowazekii (louse-borne/epidemic)**

- Incubation 6-14 days
- Fever, headache (abrupt), tachypnea, myalgias
- Rash (mac-pap/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 outbreak, 1997

Figure 1: Scratching lesion on the upper arm of a homeless man
**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)

- Chigger-borne zoonosis
- Vector: larval mites
  - “mite islands”
- “Tsutsugamushi Triangle”
  - Tropical Asia
  - west Pacific islands
  - UAE

EID. 1997;3(2):105-111
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 pathognomonic
- Treatment: Doxycycline (resistance possible)
  - Azithromycin, rifampin
- Prevention: topical repellents to clothing, weekly doxycycline
Tick-Borne Rickettsiae in Africa

- R. africæ
- R. conorii conorii
- R. conorii caspia
- R. conorii israelensis
- R. sibirica mongolitimonæ
- R. æschlimannii
- R. massiliae
- R. rhipicephali
Tick-Borne Rickettsiae in Asia/Australia
Tick-Borne Rickettsiae in the Americas

- R. bellii
- R. amblyommii
- R. texiana
- R. montanensis
- R. canadensis
- R. rhipicephali
- strain COOPERI
- R. peacockii
- "R. andeanae"
- "R. midichlorii"
- unnamed rickettsias
- strain "Tillamook"
- R. rickettsii
- R. parkeri
- R. africae
- R. honei
## “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><em>A. 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 cases/yr</td>
<td>&gt;2100 cases/yr</td>
<td>~20 (immunocompromised)</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
• International distribution

• Vector: *Ixodes* ticks
  • *I. scapularis* (East US)
  • *I. pacificus* (West US)
  • *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
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
# Ehrlichioses and Anaplasmosis

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

Agent: *B. afzelii*, *B. garinii*
Vectors: *I. ricinus* – Europe

*I. persulcatus* – E. Europe, Russia

Agent: *B. burgdorferi*
Vectors: *I. scapularis* – East

*I. pacificus* - West

Reported Cases of Lyme Disease -- United States, 2010

Lancet 2003; CDC.gov
Common presenting symptoms

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); 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 (*B. borgdorferi*)
### Treatment:

- **Primary EM:** Doxycycline 100mg PO BID (10-14 days)
- **Meningitis or radiculopathy:** Ceftriaxone x 14 days (range 10-28 days)
- **CN palsy:** Doxy x 14 days (range 14-21 days) or treat as CNS disease
- **Cardiac disease:** oral or 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)

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**Table 3. Recommended therapy for patients with Lyme disease.**

<table>
<thead>
<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;e&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>Borreliotic 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>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>

Q fever (*Coxiella burnetii*)

- Worldwide distribution
  - ↓ USA, ↑ Netherlands, OIF
- Zoonosis: wildlife, ticks are main reservoir
- Transmitted from cattle, sheep, goats
  - Urine, feces, milk, birth products
  - Localizes to uterus/mammary glands
  - Via inhalation or ingestion
- Highly infectious
  - 1 organism can cause clinical infection
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 (*Coxiella burnetii*)

- Ecology: farmers, vets, abattoir/lab workers
- Diagnosis: paired serology (Ph II, Ph I)
  - Culture (USAMRIID, CDC)
- Treatment:
  - Acute: fluoroquinolone or Doxy x 21 days
  - Chronic/endocarditis: FQ + rifampin or doxy + hydroxychloroquine x 18 mo.
- Prevention: educate (livestock, dairy)
  - disposal of birth products (animals)
  - quarantine/restriction of infected animals
  - caution high risk patients (valve disease)
Size comparison

Blacklegged Tick (*Ixodes scapularis*)
- Adult female
- Adult male
- Nymph
- Larva

Lone Star Tick (*Amblyomma americanum*)

Dog Tick (*Dermacentor variabilis*)

Lyme
Anaplasma
Ehrlichia
Rocky Mountain Spotted Fever
Leptospirosis

- Obligate spirochete bacteria
- Wide array of animal reservoirs
  - Rodents, cattle, swine, dogs, sheep, goats, horses
- Infection via abrasions, conjunctiva, mucous membranes
- Exposure to: animal urine, contaminated water/soil, infected animal tissues (placenta, etc.)
  - Rarely ingestion, aerosolization
- US outbreaks: Hawaii, Puerto Rico
- Isolated cases worldwide
Leptospirosis: Clinical Presentation

- Incubation 2-26 days
- Broad spectrum of symptoms
  - Biphasic
  - Mild to life-threatening
  - Abrupt onset fever, rigors, myalgias, HA (75-100%)
- Weil’s Disease (severe)
  - 5-10%
  - Jaundice, renal failure, hemorrhage, cardiac arrhythmias, pneumonitis, hemodynamic collapse.
  - 5-15% mortality
Leptospirosis
Diagnosis

- Clinical – always consider in the differential!
  - Fevers, myalgias, jaundice, HA
- Labs: ↓Plt, ↓Na, ↓K, sterile pyuria, AKI, mild ↑LFTs, ↑bilirubin, ↑CK
- Serology: microscopic agglutination test (MAT), ELISA
- Molecular tests: PCR
- Culture: blood, urine, CSF (takes weeks)
Treatment / Prophylaxis

• Start early in severe disease
• IV Penicillin: DOC for severe disease
  – Jarish-Herxheimer reactions
    • Acute response to clearance of organism
    • fever, rigors, hypotension
• Doxycycline (oral) 100 mg twice daily x 7 days
  – Toxicity in children and pregnant women
• Alt: ceftriaxone, azithromycin
• Antibiotic prophylaxis
  – At risk individuals: 200 mg PO WEEKLY, start 2 days before entry
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 \((R. \text{rickettsii})\)
B. Q fever \((C. \text{burnetii})\)
C. Scrub typhus \((O. \text{tsutsugamushi})\)
D. Murine typhus \((R. \text{typhi})\)
E. Louse-borne Typhus \((R. \text{prowazekii})\)
Case #1

- 35yo USMC medic in Iraq x 7 months
- En route CONUS – fever 104°F
- Now 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

• 23yo 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 (500yds 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)
- Alkphos-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
- Alkphos-137
- AST-173
- ALT-131
- Tbili-2.8
- WBC-4.8
- Plt-45
Case #1

- Differential?
- Malaria smears (-)
- Blood, stool, urine cultures (and CSF #1) (-)
- Acute HIV, RPR (-)
- Viral, Dengue, Hepatitis A/B/C (-)
- Leptospirosis 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
• Married, 2 children – all healthy
• Vegetarian; makes yogurt
• Water – well or river (wife gathers)
• No TOB, ETOH, drugs, meds, allergies
• Childhood vaccines (WHO) completed
Blacklegged Tick (*Ixodes scapularis*)

Courtesy: N. Aronson, MD
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

• 2^{nd} wk (if untreated):
  – Splenomegaly
  – Pneumonia
  – Myocarditis
  – Delirium
  – Death

• Diagnosis?

Scrub Typhus
African tick bite fever

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

Scrub typhus

- *Orientia tsutsugamushi*
- Mites
- Loggers, rice farmers, military
- F, LAD (70%), eschar (50%)
- PNA, CNS, DIC, renal failure
- Indep. predictor mort: met. acidosis (↑ ast, wbc, ↓ plt)
Case #3

40yo 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
40yo 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
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
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
#5
Which of the following is the most commonly used treatment for rickettsial disease among returning international travelers?

A. Tetracycline
B. Minocycline
C. Septra
D. Doxycycline
Which of the following is the most commonly used treatment for rickettsial disease among returning international travelers?

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

A. *Orientia tsutsugamushi*
B. *Rickettsia rickettsii*
C. *Rickettsia prowazekii*
D. *Rickettsia typhi*
#6
During war with many displaced people, which organism would you be most concerned about because of its high mortality rates, complications, and epidemic potential?

A. *Orientia tsutsugamushi*
B. *Rickettsia rickettsia*
C. *Rickettsia prowakzeii*
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>
</tbody>
</table>
| Louse-borne typhus (Epidemic) Brill-Zinsser disease | • Europe, Asia and Africa  
• In the last 2 decades African countries, especially Ethiopia and Nigeria, have reported most cases |
<p>| Murine                                  | • Large cities around the world with high rate infestations                                              |
| Tsutsugamushi disease                   | • Japan, Solomon Islands and Pakistan                                                                    |
| Q fever                                 | • Australia, Canada and other parts of the world where humans come into contact with infected animals  |</p>
<table>
<thead>
<tr>
<th>Disease</th>
<th>Causative rickettsia</th>
<th>Transmitting vector/carrier</th>
</tr>
</thead>
</table>
| Rocky Mountain Spotted Fever (RMSF) | *R rickettsii*       | Vector: wood tick, dog tick, and Lone Star tick  
Humans become incidental host after being bitten by infected adult tick                                      |
| Rickettsialpox        | *R akari*            | Vector: house mouse is the natural host of the mouse mite transmitting rickettsialpox  
Distribution: Russia, South Africa, Korea                                                                                                    |
| Boutonneuse fever      | *R conorii*          | Vector: various ticks including dog ticks                                                                                                                 |
| Louse-borne typhus     | *R prowazekii*       | Vector: Human lice                                                                                                                                          |
| Brill-Zinsser disease  | *R prowazekii*       | Vector: lice  
Reactivation of the organism from a latent state up to decades after primary infection                                                                |
| Murine                  | *R typhi* and *R felis* | Transmitted between rats by a rat flea  
Humans accidentally infected by the faeces of infected fleas                                                                                          |
| Tsutsugamushi disease  | *O tsutsugamushi*    | Vector: larval trombiculid mites in soil and scrub                                                                                                         |
| Q fever                 | *C burnetii*         | Vector: Airborne droplets from infected cattle, sheep goats, rodents and cats  
Slaughterhouse and animal research workers at risk  
Ticks transmit disease to rodents and domestic animals but are seldom the cause of human infection  
Organism remains latent in infected host until stressor such as birth activates it. Then multiplies and contaminates animals’ surrounding, persisting as potential source of infection for months |
Summary

• Rickettsial diseases have nonspecific symptoms
• Thorough skin exam: look for eschars
• Rashes are not always present
• Know what is endemic where you are
• Mortality is high for some conditions
• Treat with doxycycline when in doubt

NO ONE DIES WITHOUT DOXYCYCLINE ON BOARD!!
QUESTIONS?