Zoonoses: Emerging Rickettsial Diseases

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Learning Objectives

- Review the major groups of rickettsioses and their clinical manifestations
- Identify risk factors for rickettsial infection
- Understand the considerations for rickettsial diagnostics and treatments
Rickettsioses and Their Clinical Manifestations
What Are Rickettsia?

- Members of the *Alphaproteobacteria* order *Rickettsiales*
- Obligate endosymbionts of eukaryotic cells
- Gram negative bacilli
- Primarily transmitted by arthropod vectors
  - Laboratory acquired infections associated with aerosols, accidental parenteral inoculation
  - One report of nosocomial *A. phagocytophilum* transmission from China (Zhang et al. *JAMA*. 2008;300(19):2263-2270)
  - Anaplasmosis and ehrlichiosis have been contracted though contaminated blood transfusion products or solid organ transplant

### Spotted Fever Group
- *Rickettsia rickettsia* (Rocky Mountain Spotted Fever, RMSF)
- *R. parkeri* (*R. parkeri* rickettsiosis)
- *R. conorii* (Mediterranean spotted fever)
- *R. africae* (African tick bite fever)

### Typhus Group
- *R. prowazekii* (epidemic typhus)
- *R. typhi* (murine typhus)

### Transitional Group
- *R. akari* (rickettsialpox)
- *R. felis* (flea-borne spotted fever)

### Scrub Typhus Group
- *Orientia tsutsugamushi*
- *Candidatus Orientia chuto*
- *Candidatus Orientia chiloensis*

### Anaplasma Group
- *Anaplasma phagocytophilum* (Anaplasmosis, formerly human granulocytic ehrlichiosis (HGE))

### Ehrlichia Group
- *Ehrlichia chaffeensis*
- *E. ewingii*
- *E. muris eauclairensis*
Transmission Vectors

Spotted Fever Group, Anaplasmas, Ehrlichias
- Hard body (ixodid) tick bites

Typhus Group
- *R. prowazekii*: bites from infected body lice (*Pediculous humanus humanus*) or ectoparasites from infected flying squirrels; inhalation or accidental mucosal or parenteral inoculation of body louse feces
- *R. typhi*: accidental mucosal or parenteral inoculation of rat flea (*Xenopsylla cheopis*)

Transitional Group
- *R. akari*: accidental mucosal or parenteral inoculation of mouse mite (*Liponyssoides sanguineus*) feces
- *R. felis*: bites from cat fleas (*Ctenocephalides felis*)

Scrub Typhus Group
- Trombiculid mite larvae (chigger) bites
U.S. Geographical Distribution

Reported incidence rate per 1,000,000 persons per year, by county, 2000-2013

- Spotted fever rickettsiosis, including Rocky Mountain Spotted Fever
- *Ehrlichia chafeensis* ehrlichiosis
- Anaplasmosis

Vector (And Pathogen) Distribution Is Changing

- Gulf Coast tick (*Ambylomma maculatum*) reported in Illinois for the first time during surveys in 2013 and 2019–8 of 14 screened specimens were positive for *R. parkeri* (Phillips et al. J Parasitol. 2020;106(1):9-13)

- Asian longhorned tick (*Haemaphysalis longicornis*) first confirmed in the U.S. in 2017, with archived samples suggesting introduction in 2010 or earlier; confirmed in 14 states as of August 2020.
  - Shown to carry at least 30 human pathogens naturally, including seven spotted fever group rickettsiae, three species of *Ehrlichia*, and seven species of *Anaplasma* (Zhao et al. Lancet Planet Health. 2020;4(8):e320-e329)
  - Shown experimentally to support *R. rickettsia* infection (Stanley et al. J Med Entomol. 2020;57(5):1635-1639)

- Murine typhus is re-emerging in areas of Texas where it was previously eradicated (Ruiz et al. Emerg Infect Dis. 2020;26(5):1044-1046)

- Lone Start tick (*A. americanum*), a key vector for *Ehrlichia* species, has markedly increased its range in the last 70 years (Monzón et al. Genome Biol Evol. 2016:8(5):1351-1360).
### Clinical Manifestations - Tick-borne Rickettsioses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incubation period</th>
<th>Common initial signs and symptoms</th>
<th>Cutaneous signs</th>
<th>Common laboratory findings</th>
<th>Severe disease</th>
<th>Estimated case-fatality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocky Mountain spotted fever</td>
<td>3–12 days</td>
<td>Fever, headache, chills, malaise, myalgia, nausea, vomiting, abdominal pain, photophobia, anorexia</td>
<td>Maculopapular rash approximately 2–4 days after fever onset in most, might become petechial and involve palms and soles</td>
<td>Thrombocytopenia, slightly increased hepatic transaminase levels, normal or slightly increased white blood cell count with increased immature neutrophils, hyponatremia</td>
<td>Meningoencephalitis, acute renal failure, ARDS, cutaneous necrosis, shock, arrhythmia, seizure, focal neurologic deficits, fulminating vasculitis, sudden transient hearing loss</td>
<td>5%–10% (treated), 25% (untreated)</td>
</tr>
<tr>
<td>Rickettsia parkeri rickettsiosis</td>
<td>2–10 days</td>
<td>Fever, myalgia, headache</td>
<td>Eschar, sparse maculopapular or vesiculopapular rash that might involve palms and soles</td>
<td>Mild thrombocytopenia, mild leukopenia, increased hepatic transaminase levels</td>
<td>Vasculitis</td>
<td>—*</td>
</tr>
<tr>
<td>Ehrlichia chaffeensis ehrlichiosis (human monocytic ehrlichiosis)</td>
<td>5–14 days</td>
<td>Fever, malaise, myalgia, nausea, diarrhea, vomiting</td>
<td>Rash in approximately 30% of adults and 60% of children, variable rash pattern that might involve palms and soles, appears a median of 5 days after illness onset</td>
<td>Leukopenia, thrombocytopenia, increased hepatic transaminase levels, hyponatremia, anemia</td>
<td>Anemia, ARDS, DIC-like coagulopathies, central nervous system involvement, renal failure</td>
<td>1% (treated), 3% (untreated)</td>
</tr>
<tr>
<td>Ehrlichia ewingii ehrlichiosis</td>
<td>—†</td>
<td>Fever, malaise, myalgia</td>
<td>Rash rare</td>
<td>Leukopenia, thrombocytopenia, increased hepatic transaminase levels</td>
<td>—*</td>
<td>—*</td>
</tr>
<tr>
<td>Ehrlichia muris-like agent ehrlichiosis</td>
<td>—†</td>
<td>Fever, malaise, myalgia</td>
<td>Rash in approximately 12%</td>
<td>Thrombocytopenia, lymphopenia, leukopenia, increased hepatic transaminase levels, anemia</td>
<td>—*</td>
<td>—*</td>
</tr>
<tr>
<td>Human anaplasmosis (human granulocytic anaplasmosis)</td>
<td>5–14 days</td>
<td>Fever, malaise, myalgia, chills</td>
<td>Rash rare, in &lt;10%</td>
<td>Thrombocytopenia, leukopenia, ARDS, peripheral neuropathies, DIC-like coagulopathies, hemorrhagic manifestations, rhabdomyolysis, pancreatitis, acute renal failure, secondary opportunistic infections</td>
<td>&lt;1% (treated), 1% (untreated)</td>
<td>—*</td>
</tr>
</tbody>
</table>

*No known deaths. †Not documented.*

## Clinical Manifestations - Other Rickettsioses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incubation period</th>
<th>Common initial signs and symptoms</th>
<th>Cutaneous signs</th>
<th>Common laboratory findings</th>
<th>Severe disease</th>
<th>Estimated case-fatality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murine typhus</td>
<td>7-14 days</td>
<td>Fever, headache, arthralgia</td>
<td>Rash in 20-80%</td>
<td>Thrombocytopenia, hyponatremia, increased hepatic transaminase levels, dissociated cholestasis, haematuria</td>
<td>Cough, anorexia, nausea, vomiting, myalgia, encephalitic signs, acute kidney injury</td>
<td>1-4%</td>
</tr>
<tr>
<td>Epidemic typhus</td>
<td>10-14 days</td>
<td>Fever, headache, tachypnoea, chills, myalgia</td>
<td>Erythematous rash progressing to petechial and purpuric lesions</td>
<td>Thrombocytopenia, increased hepatic transaminase levels, increased blood urea</td>
<td>ARDS, splenomegaly, hypotension, vascular collapse, renal insufficiency, encephalitic signs, ecchymosis with gangrene, pneumonia, multiple organ failure</td>
<td>&lt;5% (treated), 60% (untreated)</td>
</tr>
<tr>
<td>Rickettsialpox</td>
<td>7-10 days</td>
<td>Fever, chills, sore throat, rigor and profuse sweating, myalgia, anorexia</td>
<td>Eschar, papulovesicular rash developing 2-3 days after symptom onset that might involve palms and soles, occasional oropharyngeal enanthem</td>
<td>Leukopenia with relative lymphocytosis and mild proteinuria, thrombocytopenia</td>
<td>—†</td>
<td>—*</td>
</tr>
<tr>
<td>Flea-borne spotted fever</td>
<td>—†</td>
<td>Fever, fatigue, headache, myalgia</td>
<td>Eschar in 13%, maculopapular rash in 75%</td>
<td>Increased aspartate and alanine aminotransferase levels</td>
<td>Acute meningoencephalitis</td>
<td>—*</td>
</tr>
</tbody>
</table>

*No known deaths.  
†Not documented.
Risk Factors for Rickettsial Infection
Risk Factors for Severe Rickettsiosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RMSF</th>
<th>Epidemic typhus</th>
<th>Murine typhus</th>
<th>Anaplasmosis</th>
<th>Ehrlichiosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt; 10)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (≥ 40)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Age (≥ 60)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Race (Black)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Glucose 6-phosphate dehydrogenase deficiency</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Immunosuppression</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Diabetes</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Hepatic and/or renal dysfunction</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Lung infiltrates on admission</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Leukocytosis on admission</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Treatment with sulfa antibiotics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Delayed treatment (onset-to-treatment ≥ 5 days)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood product transfusion</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Solid organ transplantation</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Alcoholism</td>
<td>X</td>
<td></td>
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<td>X</td>
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</tbody>
</table>
Environmental And Behavioral Risk Factors For Exposure

- Occupational or recreational exposure to brushy or wooded areas with tall grasses or shrubs
- Lack of use of appropriate tick repellents
- Lack of appropriate clothing worn in high-risk areas
- Exposure to animals and birds (wild, livestock, and/or peridomestic)
- International travel
- Exposure to individuals living with poor sanitation and hygiene availability

Examples of at-risk populations:

- Hunters
- Outdoor enthusiasts
- Utility workers
- Veterinarians / animal control
- International travelers
- Those working or living in refugee / detention camps
- Forestry / park workers
- Surveyors
- Pet / livestock owners
- Agricultural workers
- Scientists / students involved in fieldwork
- Unhomed individuals
- Those working with or near unhomed populations
- Military personnel
Considerations for Diagnostics and Treatment
Diagnostic Challenges

• Poor awareness of vector exposure
• Poor public awareness of their risks of vector-transmitted diseases
  • Review of responses to the 2009, 2011, and 2012 HealthStyles surveys found 13.9% of respondents from New England and 20.8% from the Mid-Atlantic reported that no tickborne diseases were present in their area (Hook et al. 2015. Ticks Tick Borne Dis;6(4)-483-488).
• Initial symptoms nonspecific
• Characteristic rashes often develop after initial clinical visit
• Characteristic rashes under-identified in patients with darker skin
• For epidemic typhus, late relapse can occur months or years after the initial infection, with a similar but milder clinical presentation (Brill-Zinsser disease)


## Diagnostic Recommendations

<table>
<thead>
<tr>
<th>Assay</th>
<th>Pathogen</th>
<th>Specimen</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Culture</strong></td>
<td>Spotted fever group, Typhus group, Anaplasmas, Ehrlichias</td>
<td>Whole blood; punch biopsy of eschar or rash; autopsy specimens</td>
<td><strong>Microbiological reference standard</strong></td>
<td>Requires biosafety level 3 facility; may require ≥ 10 days; effectiveness decreases after first week of illness, commencement of therapy</td>
</tr>
<tr>
<td><strong>Nucleic acid detection (polymerase chain reaction (PCR))</strong></td>
<td>Spotted fever group, Anaplasmas, Ehrlichias</td>
<td>Whole blood; serum; eschar swab; punch biopsy; autopsy specimens</td>
<td>Increasingly common; easier differentiation between pathogens; short turnaround time; no specialized facilities required</td>
<td>Most sensitive when performed on eschar biopsy; most sensitive within first week of illness and before/within 48 hours of commencing therapy</td>
</tr>
<tr>
<td><strong>Blood smear</strong></td>
<td>Anaplasmas, Ehrlichias</td>
<td>Whole blood</td>
<td>Rapid</td>
<td>Low sensitivity; requires specialized stains; requires experienced microscopist to read</td>
</tr>
<tr>
<td><strong>Indirect immunofluorescent assay (IFA)</strong></td>
<td>Spotted fever group, Typhus group, Anaplasmas, Ehrlichias</td>
<td>Serum</td>
<td><strong>Current reference standard; short turnaround time; effective independent of commencement of therapy</strong></td>
<td>Antibodies generally absent during first week of illness; confirmation requires fourfold or greater increase in titer between acute and convalescent serum specimens; antibodies usually specific to genus rather than species</td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td>Spotted fever group, Typhus group, Anaplasmas, Ehrlichias</td>
<td>Punch biopsy (spotted fever group); autopsy specimens; formalin-fixed tissue</td>
<td>Effective with spotted fever eschars and rash lesions; effective post-mortem</td>
<td>Availability restricted to reference centers or research laboratories</td>
</tr>
</tbody>
</table>
Treatment Challenges

- Treatment is less effective at preventing severe complications and death when started $\geq 5$ days after the onset of symptoms
  - Case fatality rate for untreated RMSF is 20-25%, with most deaths within 7-9 days of symptom onset
  - Case fatality rate for untreated epidemic typhus can be up to 60%

- Diagnostic tests are not typically helpful for making a timely diagnosis of rickettsial disease
  - Laboratory findings often remain within normal ranges until disease is severe
  - Microbiological reference standard test (organism culture) can take 10 or more days to complete
  - IFA requires at least 2 weeks (need paired acute and convalescent sera, 2-4 weeks apart)
  - Sensitivity of PCR assays vary by species, specimen type, time since onset of symptoms, and whether treatment has been started
Current Treatment Recommendations

TREATMENT SHOULD BE INITIATED IMMEDIATELY IN PERSONS WITH SIGNS AND SYMPTOMS OF RICKETTIAL DISEASE!

<table>
<thead>
<tr>
<th>Age category</th>
<th>Drug</th>
<th>Dosage</th>
<th>Maximum</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults*</td>
<td>Doxycycline</td>
<td>100 mg twice per day, orally or IV</td>
<td>100 mg per dose</td>
<td>At least 3 days after fever subsides and until evidence of clinical improvement is noted; minimum treatment course of 5–7 days†</td>
</tr>
<tr>
<td>Children weighing &lt;100 lbs (45 kg)</td>
<td>Doxycycline</td>
<td>2.2 mg/kg of body weight per dose twice per day, orally or IV</td>
<td>100 mg per dose</td>
<td></td>
</tr>
</tbody>
</table>

† Treatment for patients with anaplasmosis should be extended to 10 days if concurrent Lyme disease is suspected, or alternatively, another antimicrobial with efficacy against *Borrelia burgdorferi* should be included. From CDC. Tickborne diseases of the United States: A reference manual for healthcare providers, 5th ed. Fort Collins, CO: US Department of Health and Human Services, CDC; 2018.

- Rifampin has been reported to be effective in a small number of pregnant women and young children treated for anaplasmosis, but no clinical trials have been performed. Rifampin is not recommended for treatment of RMSF.
National Reporting Requirements

• Spotted fever group rickettsioses (including RMSF), ehrlichioses, and anaplasmosis are nationally notifiable in the U.S.
  • State or local health departments should be notified of potential cases of tickborne disease
  • Health department should be able to help obtain confirmatory laboratory testing
  • Health department staff may contact the healthcare provider and patient for information to determine the surveillance case definition.

• Typhus group rickettsioses are no longer nationally notifiable, although murine typhus is reportable in at least 14 states, including DE, MA, NH, OH, and PA. However…

• *R. prowazekii* is listed as a Health and Human Services Select Agent under 42 CFR Part 73. Clinical or diagnostic specimens used for diagnosis are considered exempt from the requirements within the regulation provided:
  • The specimens are secured against theft, loss, or release during the period of time between the identification of *R. prowazekii* and the transfer or destruction of the specimens; and
  • Any theft, loss, or release of the specimens is reported; and
  • Unless otherwise directed by the HHS Secretary, the specimens collected from the positive patient are transferred to a registered entity or destroyed on-site by a recognized sterilization or inactivation process within 7 calendar days of the conclusion of patient care; and
  • The laboratory notifies the specimen provider, CDC, and other appropriate authorities of the identification of *R. prowazekii* by telephone, fax, or email, and must submit an APHIS/CDC Form 4 to CDC within 7 calendar days of identification.
Select References


THANK YOU

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