Diseases caused by *Rickettsia* and related organisms: Zoonoses

**Rickettsia, Ehrlichia, and related bacteria**

I. **Rickettsiaceae**

II. **Anaplastaceae**

III. **Coxiellaceae**

Diagnosis:
- Symptoms
- Epidemiology
- Serology

Terms in red: "Trigger words"

**Rickettsia, Ehrlichia, and related bacteria**

I. **Rickettsiaceae**

   - Spotted Fever group
     - *R. rickettsii* (RMSF)
   - Typhus group
     - *R. prowazekii* (epidemic typhus)
   - *R. typhi* (endemic (murine) typhus)

   - *Orientia*
     - D. tsutsugamushi (scrub typhus)

   - *O. tsutsugamushi* (scrub typhus)

   - *R. akari* (rickettsialpox)
Typical Characteristics of Rickettsiaceae

<table>
<thead>
<tr>
<th><strong>Morphology and structure</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Small rods</td>
</tr>
<tr>
<td>Gram negative (Giemsa)</td>
</tr>
<tr>
<td>Typical morphology of a gram-negative pathogen</td>
</tr>
<tr>
<td><em>Orientia</em> lacks LPS, peptidoglycan</td>
</tr>
<tr>
<td>No flagella</td>
</tr>
</tbody>
</table>

**Growth and metabolism**
- Division occurs through binary fission
- Growth is slow 9-12 h
- Obligate intracellular pathogens
- Use host ATP, coenzyme A, nicotinamide adenine dinucleotide and available amino acids

Typical Characteristics of Rickettsiaceae

**Pathogenesis**
- Bacteria enter by phagocytosis
- Bind host receptors
- Bacteria initially in membrane-bound vesicle
- Escape using Phospholipase A
- Bacteria replicate freely in host cytoplasm

**Pathogenesis**
- Spotted Fever Group and *Orientia*:
  - Move using host cytoskeletal components
  - Permits cell-to-cell spread
  - "Budding"
  - Facilitates exiting
  - Exit depends on lysis
  - Movement between cells facilitates avoidance of the immune system
  - Once released, pathogens are unstable and die rapidly

- Typhus Group:
  - Does not move
**Epidemiology**

**Spread by arthropod vectors**

- Ticks
- Mites
- Lice
- Flea

See Table 34-2

**Animal reservoirs**

- Rodents
  - RMSF
  - Rickettsialpox
  - Murine typhus
- Dogs
- Flying squirrels

Exception: *R. prowazekii*: humans are the primary reservoir

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**Rickettsia, Ehrlichia, and related bacteria**

1. *Rickettsiaeaceae*
   - *Rickettsia*
     - Spotted Fever group
     - Typhus group
   - *Orientia*
     - *O. tsutsugamushi*
     - Scrub typhus

**R. rickettsii**

- (RMSF)
- *R. akari* (rickettsialpox)
- *R. prowazekii* (epidemic typhus)
- *R. typhi* (endemic (murine) typhus)

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**Rickettsia rickettsii**

- **Disease**: Rocky Mountain Spotted Fever (RMSF)
- **Symptoms**:
  - High fever
  - Severe headache
  - Rash within 3 days*
  - "Macular rash"
    - Initially involving the extremities
    - May spread to trunk
    - May evolve to a petechial rash
      - Maculo: flat discoloration
      - Petechial: minute reddish or purplish
  - Associated symptoms: malaise, myalgias, nausea, vomiting, abdominal pain, diarrhea
  - Incubation period: 2 to 7 days, but may be upwards of two weeks

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*Macular rash*

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Oster and associates (N Engl J Med 297:859–863, 1977) described a series of patients who acquired Rocky Mountain spotted fever after working with *Rickettsia rickettsii* in the laboratory. One patient, a 21-year-old veterinary technician, presented to a clinic with complaints of myalgia and a nonproductive cough. He was treated with penicillin and discharged. Over the next few days, he developed chills and a headache. When he returned to the hospital, he had a temperature of 40.0°C and a macular rash on his extremities and trunk. Intramuscular tetracycline was started, but he remained febrile, and the rash evolved to petechiae on his trunk, his extremities, and the soles of his feet. Bilateral pleural effusions developed, and intravenous tetracycline was begun. Over the next 2 weeks, the effusions resolved and the patient made a slow but uneventful recovery.

*How might this case of RMSF be diagnosed?*

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**Rickettsia rickettsii**

**Epidemiology**

- ~2000 cases annually in U.S.
- Most U.S. cases: Southeast Atlantic and South Central states
- Majority: North Carolina, Oklahoma, Arkansas, Tennessee, Missouri

**Transmitted by hard tick vectors**

- *Dermacentor andersoni*, *Dermacentor variabilis*: Western US
- *American Dog tick*: Southeastern U.S., West coast
- *Brown Dog tick*: Arizona
- Other tick vectors in Central, South America
  - Associated with exposure to wooded areas where ticks exist
  - Incidence higher in summer months
**Rickettsia rickettsii**

**Transmission**
Transovarian transmission of *R. rickettsii*

Reservoirs for *R. rickettsii*:
- Small rodents and dogs

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**Pathology**

- Outer membrane protein OmpA permits adherence to endothelial cells
- Bacteria multiply in cells lining small blood vessels
- Symptoms result from replication of bacteria and resulting cell damage
- Rupture results in rash
- Primary lesion: vasculitis in many organs
  - Prominent in the skin (rash)
- Hypovolemia and hypoproteinemia caused by loss of plasma into tissues: organ failure

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**Diagnosis**

- Clinical symptoms, epidemiology
- Microimmunofluorescence assay (MIF): detects outer membrane proteins (species specific) and LPS antigen (shared among Rickettsial species)
- (PCR with gene targets such as ompA)
- (Microscopy)

**Treatment**

- Doxycycline; start before diagnosis is confirmed
- Chloramphenicol: higher relapse
- Delayed treatment: increased likelihood of death
- 10-25% mortality if untreated

**Prevention**

- No vaccine
- Avoidance or reduction of tick contact
- Control is virtually impossible
  - Non-feeding ticks survive as long as 4 years
I. Rickettsiaceae

Rickettsia

- Spotted Fever group
  - R. rickettsii (RMSF)
  - R. akari (rickettsialpox)

- Typhus group
  - R. prowazekii
  - R. typhi
    - Epidemic typhus
    - Endemic (murine) typhus

Orientia

- O. tsutsugamushi
  - Scrub typhus

Rickettsia, Ehrlichia, and related bacteria


Mild disease with vesicular rash

Phase 2: 9-14 days: high fever, severe headache, chills/sweats, myalgias, photophobia, papulovesicular rash develops

Develops into vesicle, then a black eschar

Bacteria spread

Self-limiting after 1 week; no deaths have been reported


Rickettsialpox Disease

Symptoms/Disease progression

Mild disease with vesicular rash

Phase 1: Firm red papule at the site of the bite
Develops into vesicle, then a black eschar
Bacteria spread

Phase 2: 9-14 days: high fever, severe headache, chills/sweats, myalgias, photophobia, papulovesicular rash develops

Self-limiting after 1 week; no deaths have been reported

Epidemiology/Transmission

USA (NYC), Ukraine, Croatia, Korea
Vector: bloodsucking mites, found on mice; Transovarian transmission

Prevention

Eliminate rodents

Clinical Case 2

18 patients presented to Columbia Presbyterian Medical Center in New York City during a 20-month period after the anthrax bioterrorism attack in the fall of 2001. The patients also had fever, headache, and a papulovesicular rash. Many patients also complained of myalgias, sore throat, arthralgias, and gastrointestinal symptoms.

What is the diagnosis?

Which information was most informative for diagnosis?

What features of the illness are most similar to RMSF, and how would you differentiate these illnesses?
**Rickettsia, Ehrlichia, and related bacteria**

I. Rickettsiaceae

- **Spotted Fever group**
  - *R. rickettsii* (RMSF)
  - *R. akari* (rickettsialpox)

- **Typhus group**
  - *R. prowazekii* Epidemic typhus
  - *R. typhi* Endemic (murine) typhus

- **Orientia**
  - *O. tsutsugamushi* Scrub typhus

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**Rickettsia prowazekii**

**Disease** Epidemic typhus or Louse-borne Typhus Fever

**Symptoms**
- Non-specific symptoms, ~8 days after exposure
- Then, within 1-3 days, high fever, severe headache and myalgias
- Petechial or macular rash in many; may be difficult to detect
- First on the trunk and then spreads to the extremities
- Other symptoms: pneumonia, arthralgia, neurologic
- Fatality from 20% to 30% if untreated
- More fatal in patients with poor help or medical care

**Epidemiology**
- Disease associated with unsanitary conditions
- Peaks in winter
- Transmission by human body louse
- Organisms are present in feces of infected lice

**Reservoirs** include humans and flying squirrels
- Lice die after 2-3 weeks: no transovarian transmission

**Diagnosis**
- Symptoms, Epidemiology, MIF

**Treatment**
- Doxycycline

**Prevention**
- Louse control
- Vaccine available

**High risk population**

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Relapse of louse-borne typhus can occur
Appears 10-40 years after the primary attack
Called Brill-Zinsser (Recrudescent Typhus or Brill's disease)

Brill-Zinsser is milder and less often fatal
Partial immunity may still be present

Rickettsia persist for many years in the lymph nodes
Humans themselves are thus the reservoir

**Rickettsia prowazekii**

- Incubation period 1-2 weeks
- Doxycycline; No vaccines
- Found in warm, humid places worldwide
- Africa, Asia, Australia, Europe, S. America
- 50-100 cases annually in U.S.: Gulf states (esp. Texas) and California, warm months
- Rat flea, cat flea (U.S.) vectors
- Rodents are reservoirs

**Murine Typhus (Endemic Typhus)**

- Disease: Murine Typhus (Endemic Typhus)
- Symptoms: Involuntary shivering, fever, headache, myalgia, confusion, nausea
- Incubation period: 1-2 weeks
- Rash: 50% of cases—late—maculopapular on trunk
- Maculopapular: flat, red area, with small confluent bumps
- Low mortality

**Clinical features:** IFA

**Diagnosis:** Clinical features; IFA

**Treatment/Prevention:** Doxycycline; No vaccines
**Rickettsia, Ehrlichia, and related bacteria**

I. Rickettsiaceae

Rickettsia

- Spotted Fever group
  - *R. rickettsii* (RMSF)
  - *R. akari* (rickettsialpox)

- Typhus group
  - *R. prowazekii* Epidemic typhus
  - *R. typhi* Endemic (murine) typhus

Orientia

- *O. tsutsugamushi* Scrub typhus

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**Orientia tsutsugamushi**

**Disease:** Scrub Typhus

**Symptoms:**
- Severe headache, fever, myalgias
- <50%: Maculopapular rash on trunk, spreads to extremities
- 50 to 80% develop initial lesion: necrotic eschar at site of bite
- Generalized lymphadenopathy, splenomegaly, CNS complications, heart failure can occur

**Epidemiology:**
- Mites (Chiggers) are the vectors and reservoir.
- Transovarian transmission
- Found in the Far East: Southwest Pacific, Eastern Asia, Japan, Australia

**Treatment:**
- Fever responds to doxycycline; untreated: resolves within 2-3 weeks

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**Rickettsia, Ehrlichia, and related bacteria**

I. Rickettsiaceae

Rickettsia

- Spotted Fever group
  - *R. rickettsii* (RMSF)
  - *R. akari* (rickettsialpox)

- Typhus group
  - *R. prowazekii* Epidemic typhus
  - *R. typhi* Endemic (murine) typhus

Orientia

- *O. tsutsugamushi* Scrub typhus
Disease | Average Incubation (Days) | Clinical Presentation | Mortality without Treatment (%) |
--- | --- | --- | --- |
Rocky Mountain spotted fever | 7 | Abrupt onset; fever, headache, myalgias, nausea, vomiting, abdominal pain | >90%; macular; centripetal spread |
Rickettsialpox | 9 | Abrupt onset; fever, headache, chills, myalgias, photophobia | 100%; papulovesicular; generalized |
Epidemic typhus | 7 | Abrupt onset; fever, headache, myalgias, cough | 20%‐80%; macular; centrifugal spread |
Endemic typhus | 7−14 | Gradual onset; fever, headache, myalgias, cough | 50%; maculopapular rash on trunk |
Scrub typhus | 10−12 | Abrupt onset; fever, headache, myalgias | <50%; maculopapular rash; centrifugal |

Table 34-3 Diseases (modified to contain only Rickettsia and Orientia)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
<th>Reservoir</th>
<th>Vector</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rickettsia rickettsii</td>
<td>Rocky Mountain spotted fever</td>
<td>Ticks, wild rodents</td>
<td>Hard ticks (dog tick, wood tick)</td>
<td>Western Canada, continental US, Mexico, Panama, Argentina, Brazil, Bolivia, Colombia, Costa Rica</td>
</tr>
<tr>
<td>R. akari</td>
<td>Rickettsialpox</td>
<td>Mites (chiggers), wild rodents</td>
<td>Mites</td>
<td>North America (particularly urban areas of Northeastern US), Mexico, Europe (e.g., Croatia, Ukraine, Turkey), Asia (e.g., Korea), Africa</td>
</tr>
<tr>
<td>R. prowazekii</td>
<td>Epidemic (louse‐borne) typhus</td>
<td>Humans</td>
<td>Human body louse</td>
<td>Mountainous regions of Central and Eastern Africa (Burundi, Rwanda, Ethiopia), Central and South America, Asia</td>
</tr>
<tr>
<td>R. typhi</td>
<td>Recrudescent typhus</td>
<td>Humans</td>
<td>Human body louse</td>
<td>Worldwide</td>
</tr>
<tr>
<td>R. conorii</td>
<td>Mediterranean spotted fever</td>
<td>Cats, opossums, raccoons, deer, wild rodents</td>
<td>Cat fleas, dog fleas</td>
<td>Mediterranean region of North and Southern Africa (Morocco, Algeria, Tunisia, Iraq, Iran, Syria), Asia, Europe, South America</td>
</tr>
</tbody>
</table>

Table 34-2 Epidemiology (modified to contain only Rickettsia and Orientia)

Case study 3

A 24-year-old man living in North Carolina came to the local emergency department because of fever, arthralgias (joint pain), myalgias, and malaise. He was well until 4 days before admission, when he developed a fever reaching 40°C, chills, severe headache, and muscle aches. Physical examination revealed a critically ill man with a temperature of 39.7°C, pulse of 110 beats/min, respiratory rate of 28 breaths/min, blood pressure of 100/60 mm Hg, and a rash over his extremities, including his palms and soles. The patient recalled having had numerous tick bites 10 days before the onset of symptoms.

What is the diagnosis?

Which information was most informative for diagnosis?
### Rickettsia, Ehrlichia, and related bacteria

<table>
<thead>
<tr>
<th>I. Rickettsiaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. Anaplasmataceae</td>
</tr>
<tr>
<td>III. Coxiiellaceae</td>
</tr>
</tbody>
</table>

#### Diagnosis:
- Symptoms
- Epidemiology
- Serology

### II. Anaplasmataceae
- Human anaplasmosis (HA)
- Human monocyte ehrlichiosis (HME)
- Anaplasma phagocytophilum
- Ehrlichia ewingii
- Ehrlichia chaffeensis

### Physiology and Structure
- Intracellular pathogens
- Cell wall similar to gram-negative bacteria
  - Except: lack peptidoglycan and LPS
- Ehrlichiae infect circulating leukocytes: granulocytes, monocytes, erythrocytes, platelets
- Replicate inside phagosome—Protective
  - Killed if lysosomes fuse with phagosome
  - Prevent lysosomal fusion
- Two morphologic forms:
  - Elementary bodies: small (0.2 to 0.4 μm)
  - Reticulate bodies: larger (0.8 to 1.5 μm)
- Elementary bodies assemble: morulae
- Detection of morulae is diagnostic, but few infected cells
- Growth of bacteria leads to lysis
Anaplasma and Ehrlichia

**HA:** granulocytes primarily infected (neutrophils, eosinophils, basrophils)

**HME:** monocytes, mononuclear phagocytes

**Symptoms**
- Flu-like illness, with high fever, headache, malaise, myalgias
- Onset ~1-2 weeks after tick bite
- Typically no rash, except: HME Late-onset rash in 30-40%
- Leukopenia, thrombocytopenia, and elevated serum transaminases develop in majority of patients
- Mortality low but >50% require hospitalization
- Symptoms disproportionate to # infected cells; prob due to immune system disregulation

**Epidemiology**

- **Tick Vector:** Lone Star (Lone Star Ixodes)
- **Reservoir:** White-tailed deer, Small mammals (Mice, chipmunks)
- **Geographic distribution:**
  - Midwest (MO, AR, OK) (30%)
  - Coastal Atlantic (MD, VA, NY, NJ)
  - Upper Midwest (MN, WI)
  - Northeast Atlantic (RI, CN, NY, NJ)
  - These 6 states account for 90% cases

*No transovarian transmission*

**This tick also transmits Lyme disease, and co-infections have been reported**

Most common in the summer

**Diagnosis**
- Symptoms and history of tick exposure
- (Morulae—detected in less than 10%, but diagnostic)
- PCR (NAA—nucleic acid amplification)
- IFA—confirmatory

**Treatment/Prevention**
- Doxycycline
- Vaccines not available

*https://www.cdc.gov/anaplasmosis/stats/index.htm*
Case study 4

A 73-year-old man presented to the hospital with fever, weakness, and leg myalgias. Six days before his admission, he had traveled to South Carolina, and 3 days later, he developed intense leg pains, a high fever, and generalized weakness. Upon admission, he was febrile, tachycardic, hypertensive; the liver and spleen could not be palpated; and no cutaneous rash was noted. The patient did not remember a tick bite during his trip. Cultures for bacteria, fungi, and viruses were negative. A peripheral blood smear showed rare intracytoplasmic inclusion in the granulocytes suggestive of morulae. PCR was used to confirm the diagnosis.

What is the diagnosis?
Which information was most informative for diagnosis?
Which information might make you question your diagnosis?
What features of the illness permit you to distinguish this form of Ehrlichiosis from another form?

Rickettsia, Ehrlichia, and related bacteria

I. Rickettsiaceae

II. Anaplasmataceae

III. Coxiellaceae  Coxiella burnetii

Coxiella burnetii

Disease  Q-Fever

Symptoms
Most human infections are NOT apparent: No rash
A mild, dry, hacking cough and pneumonia sometimes present.
9 to 20 days: abrupt onset of fever, chills, and headache—flu-like
Chronic Q fever: subacute endocarditis
Fatalities are rare

Epidemiology
Transmission from animals to humans by inhalation of dust
World-wide distribution
Carried by mammals such as cattle, sheep, and goats
**Coxiella burnetii**

**Pathogenesis**
- Gram negative (weakly staining), intracellular, pathogen multiplies in CCV
- Phagosome fuses with endosomes, acidifies
- Requires low pH for growth
- Delayed lysosome fusion
- **Resistant to drying:** viable for years outside the host

**Physiology and disease progression:**
- Phase I: intact LPS
- Phase II: missing outermost O-antigen of LPS

**Diagnosis**
- Serology—acute, phase II antigens; chronic, high levels of both phase I and II present
- PCR

**Treatment/prevention**
- Doxycycline or combination for chronic infections
- Vaccines have been developed—for unexposed

---

**Case study 5**

A 31-year-old man from Wester Virginia was admitted to the hospital with an 11-month history of fevers, night sweats, paroxysmal coughing, fatigue, and weight loss. He had received various antibiotic treatments for bronchitis, with no relief. His past medical history was significant for congenital heart disease, with placement of a shunt as an infant. He lived on a farm and participated in birthing his calves. His cardiac examination upon admission revealed a murmur, no hepatosplenomegaly or peripheral stigmata of endocarditis was noted, and his liver enzymes were elevated. All bacterial and fungal blood cultures were negative.

What aspects of the symptoms and epidemiological findings would prompt a presumptive diagnosis of *Coxiella burnetii* endocarditis?

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**Rickettsia, Ehrlichia, and related bacteria**

I. Rickettsiaceae

II. Anaplasmataceae

III. Coxiellaceae

**Diagnosis:**
- Symptoms
- Epidemiology
- Serology
Folklore Remedies Don't Work!

Folklore remedies, such as the use of petroleum jelly or hot matches, do little to encourage a tick to detach from skin. In fact, they may make matters worse by irritating the tick and stimulating it to release additional saliva or regurgitate gut contents, increasing the chances of transmitting the pathogen.

A number of tick removal devices have been marketed, but none are better than a plain set of fine tipped tweezers.

Tick removal: http://www.cdc.gov/ncidod/dvrd/rmsf/Prevention.htm

To remove attached ticks:

1. Use fine-tipped tweezers
   When possible, avoid removing ticks with bare hands.
2. Grasp the tick as close to the skin surface as possible and pull upward with steady, even pressure. Do not twist or jerk the tick; this may cause the mouthparts to break off and remain in the skin.
3. Do not squeeze, crush, or puncture the tick body because its fluids may contain infectious organisms.
4. After removing the tick, thoroughly disinfect the bite site and wash your hands with soap and water.
5. Save the tick for identification in case you become ill. This may help your doctor make an accurate diagnosis.
**Causes:** Rocky Mountain Spotted Fever

Intracellular, replicates in cytoplasm and spreads via actin polymerization

Most common rickettsial pathogen in US

**Symptoms:** Vasculitis, macular rash on extremities, high fever, headache, mental confusion, myalgia

**Epidemiology:**

Hard ticks (dog, wood) are vectors

Transovarial transmission

Transmission requires prolonged contact

Disease most common in summer

Most common in Southeast Atlantic, South central states

**Diagnosis:** Symptoms, epidemiology, Microimmunofluorescence test

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**Summary**

**Disease:** Epidemic or Louse-borne typhus

Intracellular, replicates in cytoplasm, no actin polymerization

**Symptoms:** Vasculitis: Rash on trunk, fever, headache

**Epidemiology:**

Infection world-wide, most in Central and South America and Africa

Lice are vectors; humans reservoir

Disease most common under crowded conditions

**Misc:**

Brill-Zinsser: Recrudescence disease can develop years later

Vaccine available for high risk populations

**Diagnosis:** Symptoms, epidemiology, Microimmunofluorescence test

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**Anaplasma and Ehrlichia**

**Summary**

**Symptoms:** Fever, headache, but generally no rash; leukopenia, thrombocytopenia, and elevated serum transaminases develop in majority of patients

**Causes:**

Human monocyte ehrlichiosis: *E. chaffeensis*

Human anaplasmosis: *A. phagocytophilum, E. ewingii*

Intracellular, infects white blood cells (monocytic and granulocytic disease)

replicates in phagosome (prevents fusion with lysosome; morulae

**Epidemiology:**

In US, most common in Atlantic states, northern, central and southern Midwest states, northern California

Disease transmitted by ticks (summer, tick exposure)

various reservoirs, including deer and mice