Rickettsioses

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Rickettsial Diseases

General comments

• Rickettsias as a group have a worldwide distribution
• Many new rickettsial diseases were discovered in recent years, and the list is growing
• Rickettsias are associated with variety of different vectors and hosts
• Most types of rickettsiosis are geographic area-specific
**Rickettsia** and **Rickettsia-like Pathogens**

Phylogenetic trees based on molecular taxonomic methods show three major groups of rickettsias:

- *Rickettsia, Ehrlichia, Anaplasma*
- *Bartonella*
- *Coxiella*
Rickettsial Diseases
Epidemiology

- Most rickettsial diseases have arthropod vectors.
- Humans are incidental hosts, except for epidemic typhus (humans principal reservoir).
- Rickettsial life cycles typically involve arthropod and mammalian reservoirs, and animal-to-human or vector-to-human transmission occurs as a result of environmental or occupational exposure.
Rickettsial Diseases
General Characteristics 1

• Resemble bacteria/grow only in living cells (NOT viruses)
• Parasites of arthropods = lice, fleas, ticks, mites - infect humans via bite
• Similar in size and shape - nonmotile coccobacillary forms
• Most produce agglutinating antibody
Rickettsial Diseases

General Characteristics 2

• Rickettsial diseases are clinically non-specific with many overlapping signs and symptoms

• Rickettsiosis in humans may be: Subclinical, Mild, self-limited, Severe, life-threatening

• Confirmation of rickettsiosis cases requires consideration of clinical, and epidemiological, and laboratory data
Rickettsial Diseases
Pathogenesis

• Arthropod bite
• Invade endothelial cells/vascular
• Destroy endothelial cells
• Inflammatory cells accumulate/blood leakage: rash
• Released organisms reinfect
Rickettsial Diseases
Pathogenesis

- The disease is caused by the bite of an arthropod (flea, tick, mite, louse).
- As the insect bites it defecates on the skin surface; the irritated area causes the patient to rub the area, forcing the fecal organisms into the bite wound.
- Here they multiply in cells that line blood vessels = endothelial cells; this eventually causes the leakage of blood into tissue which is displayed as a rash.
Rickettsial Infections
Common Features

• Fever, rash, headache, myalgias, and RT symptoms
• Local primary eschars (spotted fever group)
• Systemic capillary and small vessel endothelial damage
• Can become life threatening rapidly
Signs of Infection

• Fever, chills
• Severe headache
• 4th-6th day later = skin rash = lasts throughout course of disease
• EXCEPTION: Q-fever = no rash
Genus *Rickettsia*

- Spotted fever group
- Typhus group
- Scrub typhus group

*R.tsutsugamushi* has been reclassified into a new genus, *Orientia*
Spotted Fever Group Rickettsias (SFG)

- About 30 different rickettsias in the group; Worldwide distribution
- At least 9 different rickettsias in USA.
- At least 3 of them cause human disease:
  - *R. rickettsii* cause of RMSF (tick vector)
  - *R. felis* cause of “Flea typhus” (flea vector)
  - *R. akari* cause of “Rickettsial pox” (house mouse mite vector); also associated with IV drug abuse
Spotted Fever Group

– *Rickettsia rickettsii* = spotted fever Rocky Mountain
  • Tick bite (*Ixodes* spp)
Rocky Mountains wood tick

Figure 7. Approximate distribution of the American dog tick

American dog tick (*Dermacentor variabilis*)

**Rocky Mountain wood tick** (*Dermacentor andersoni*) is found in the Rocky Mountain states and in southwestern Canada. The life cycle of this tick may require up to 2 to 3 years for completion. Adult ticks feed primarily on large mammals. Larvae and nymphs feed on small rodents.
Rocky Mountain spotted fever
Clinical Manifestations

- Fever, myalgia/severe headache
- Skin rash erythematous and macular and later maculopapular and often petechial= wrists and ankles to trunk/palms of hands, soles of feet
- Thrombocytopenia, leucopenia, anemia and hyponatremia
Rocky Mountain spotted fever Complications

Last as long as three weeks and can be severe with involvement of:

• Central nervous system
• Cardiac
• Pulmonary
• Gastrointestinal
• Renal tract

And develop DIC and shock leading to death
Other Rickettsial Spotted Fever Infections

- *Rickettsia africae* - (African tick bite fever)
- *Rickettsia conorii* - (Mediterranean spotted fever, Indian tick typhus, Marseilles fever, Israeli tick typhus, and Astrachan spotted fever)
- *Rickettsia sibirica* - (Siberian tick typhus)
- *Rickettsia australis* - (North Queensland tick typhus)
- *Rickettsia japonica* - (Japanese spotted fever)
- *Rickettsia honeyi* - (Thai tick typhus)
- *Rickettsia slovaca* - (Tick born lymphadenopathy)
- *Rickettsia felis* - (Cat flea rickettsiosis)
Other Rickettsial Spotted Fever Infections

• Each of these diseases has some clinical and pathologic features similar to those of Rocky Mountain spotted fever
• These diseases are of importance among people traveling to or returning from areas these agents are endemic
Typhus Group
Epidemic typhus

- Etiology
  - *Rickettsia prowazekii*
  - body louse = bite/feces
    - *Pediculus humanus sp corporis*
Epidemic typhus 
(*Rickettsia prowazekii*)

**Epidemiology**

- Humans are the usual reservoir
- Transmission from person to person by the human **body louse**
- Infected louse feces are rubbed into broken skin or mucous membranes or inhaled
- Direct person-to-person spread of the disease does not occur in the absence of louse vector
- Poverty, crowding, poor sanitary conditions, and poor personal hygiene contribute to spread of lice and hence the disease
- Occurred throughout the world most common during winter
Epidemic typhus
Clinical manifestations

• Abrupt onset of fever, chills, myalgias/severe headache and malaise
• Skin rash: macopurulent becomes petechial or hemorrhagic = trunk to extremities (face, palms and soles usually are not affected)
• Changes in mental status are common and delirium or coma can occur
Typhus Group
Endemic typhus
(Fleaborne Typhus or Murine Typhus)

• Etiology

*Rickettsia typhi*

(R.mooseri)
Endemic typhus  
(*Rickettsia typhi*)  
**Epidemiology**

- **Rats** are the natural reservoirs
- Opossums and domestic cats and dogs can also be infected and served as hosts
- Vector for transmission a *rat flea* (usually *Xenopsylla cheopis*)
- Infected flea feces are rubbed into broken skin or mucous membranes or inhaled
- In Mediterranean and Developing Countries occur more frequently in summer and autumn
Endemic typhus
Clinical manifestations

- Resembles epidemic typhus but usually has less abrupt onset with less severe symptoms:
  - fever
  - persistent headache
  - myalgias
  - rash (macular or maculopapular and no hemorrhagic)

- Illness seldom lasts longer than 2 weeks; visceral involvement is uncommon, but untreated severe diseases can be fatal
Scrub Typhus Group

Scrub typhus

— *Rickettsia tsutsugamushi*

• mite bite
• fever/severe headache
• skin rash = covers body/eschar

*R.tsutsugamushi* has been reclassified into a new genus, *Orientia*
Scrub Typhus Group

Scrub typhus

• Out of mites, fleas, ticks and lice, mites are the only arthropods that burrow beneath the skin, laying eggs that hatch to form more “baby” mites.

• Note skin rash that covers the body; an eschar or black spot is found at the mite bite site.
Diagnosis of Rickettsial Diseases

- Rise in serum antibody/often do not develop in early stages
Spotted Fever Group (SFG) Laboratory Diagnosis

- Isolation
- Immunohistochemistry
- PCR
- Serology
Isolation of *Rickettsia*

- Requires specialized techniques
- Requires BSL-3 Lab
- Limited to research labs, not used for routine diagnosis
- Organism may not be detected for a week or more after inoculation
Figure 5. Gimenez stain of tick hemolymph cells infected with *R. rickettsii*
Immunohistochemistry

• This test has been used to diagnose SFG in the acute stage especially if eschar was formed
• Limited to research and reference labs
• Sensitivity probably about 70%
• This test could be applied to autopsy specimen and has been used to confirm unexplained cause of death
• Very useful in *R. akari* caused eschar which could be misdiagnosed as cutaneous anthrax
PCR

- PCR can be used to detect rickettsial DNA in whole blood and tissue specimen (preferred)
- Positive PCR in acute case could be considered confirmatory from diagnostic point of view
- PCR methods can be rickettsia-specific, but are usually confirmed by DNA sequencing of the amplified gene fragments and referencing with existing sequence databases
- Varying degrees of sensitivity depending on timing of sample collection, treatment with *Doxycycline*
- Not widely available
SFG Serology

• *Weil-Felix* test is a classic test, widely available, but unacceptable for accurate diagnosis

• IFA is the “gold standard”

• ELISA, latex agglutination, hemagglutination, *Western blot* could be used as well for specific diagnostic purposes

• Patients presenting early into the illness may have antibody level below detection threshold of any test, including Western blot
IFA reaction of a positive human serum on *R. rickettsii* grown in chicken yolk sacs, CDC, 2005
IgM and IgG antibodies appear 3-10 days after disease onset, and peak after 3-4 weeks. Initial negative test should not be used to exclude diagnosis. The 2-d specimen should be tested 1-3 weeks later to establish diagnosis.

IgM and IgG could be still detectable after 1 and 4 years, respectively.

Treatment within 2 days of disease onset may abrogate antibody production. Following prompt treatment, IgG titers decline below detectable levels within 8-11 months.
SFG Serology (cont’d)

**False-positive**

Cross-reaction with *Ehrlichia* (little), *Bartonella*, *Legionella*, *Proteus*, other rickettsias, also rheumatoid factor, *CMV*, *EBV*

*Western blot assay is especially useful in differentiating true-positive from false-positive tests*

**False-negative**

if tested early into the illness

*IgG antibodies are more specific and reliable than IgM antibody titers*
Western blot of pooled mouse antisera to *R.africae*
– human isolate (lane 1),
*R.africae* – tick isolate (lanes 2–4),
*R.conorii* – Kenyan strain (lane 5),
*R.conorii* – Moroccan strain (lane 6) and
Israeli SFG rickettsia (lane 7).

Molecular masses (in thousands) are shown.
Routine Laboratory Tests

- Neutropenia in the acute phase, leukocytosis in the later stages (not always); thrombocytopenia
- Hypoproteinemia, hypoalbuminemia, and decreased sodium, potassium, chloride during the first 10 days
- Elevated ALT, AST, and alkaline phosphatase
- CPK and LDH often elevated in acute infection
Typhus Group Rickettsias

- **R. typhi** – agent of endemic or murine typhus (rat flea vector)
- **R. prowazekii** – agent of epidemic typhus (body lice vector)
- Considerable cross-reactivity between two; may also cross-react with SFG antigens
- Interpretation of serology similar to SFG
- Combination of IFA and Western blot can help differentiate epidemic and endemic typhus
Summary of Rickettsial Tests

- No widely available sensitive tests exist to make early diagnosis of rickettsiosis
- Most existing assays generally provide only retrospective confirmation
- Most Labs report IFA reactivity to the group-specific rickettsia
- Do not compare group-specific antibodies with agent-specific antibodies when available
Ehrlichiosis

- Human *Ehrlichiae* encountered in USA:
  1. *E. chaffeensis* – human monocytic ehrlichiosis (HME)
  2. *E. phagocytophilia* (Anaplasma) – human granulocytic ehrlichiosis (HGE)
  3. *E. ewingii* – HME-like illness in MO, OK, and TN
- Most cases of HME in SE and South-central USA
- Most cases of HGE in Upper Midwest and “Lyme-areas”
- Incidence of Ehrlichiosis likely 5-6 times that of RMSF
- Significant numbers of human cases of Ehrlichiosis could be asymptomatic
Areas where human ehrlichiosis may occur based on approximate distribution of vector tick species. CDC, 2000
Ehrlichia
Pathogenesis:

- Tick bite (deer or dog)
- Invasion of white cells: lymphocytes, neutrophils, monocytes
- 20% of patients show rash
- Lymph nodes up, high fever, headache, malaise, myalgia
- Treat with doxycycline
Ehrlichiosis

Laboratory Tests

• Culture-based
• Molecular (PCR)
• Serologic (IFA)

*Routine tests indicative of possible ehrlichiosis include leukopenia, lymphopenia, thrombocytopenia, elevated liver enzymes. The organisms can be occasionally seen in blood smears by staining*
Multiple morulas of *Ehrlichia canis* in culture DH82 cells
Ehrlichioses

Polymerase Chain Reaction (PCR)

- PCR tests remain unstandardized; diagnostic sensitivity (50-80% acute phase) and specificity vary
- Positive results indicate presence of specific DNA from *E.chaffeensis*, *E.phagocytophilia*, *or* *E.ewingii*; species-specific PCR tests are available; further testing, e.g. sequencing, needed for final identification
- A negative result doesn’t indicate absence of disease
- PCR detected organisms 3-5 weeks into the illness in HGE, and up to 7 weeks in HME
Ehrlichiosis
Serology

- Most commonly used; IFA is a principal tool
- There is no agreement on what constitutes a positive test among different laboratories; consult individual lab for their threshold levels
- In some PCR-confirmed cases IFA has been negative possibly due to insufficient sensitivity
- Seroprevalence of HGE ehrlichiosis in endemic areas is about 11-15%
Ehrlichioses
Serology (cont’d)

• Most patients have increased IgM and IgG by the 2-d or 3-d week;
• Antibody levels decline significantly in 1 year, but in some cases may persist up to 2.5 years
• Antibodies can be cross-reactive (10-30% sera) among different *Ehrlichia* species. For example, *E. ewingii* antibodies cross-react with *E. chaffeensis*
• *E. ewingii* accounted for 7% of all ehrlichia-positive specimens at Washington University Lab
Trench fever (Bartonellosis)

- Trench Fever Group – *Bartonella*
  transferred to *Rochalimaea quintana* -
  - body louse bite/feces
  - fever/headache/mild symptoms
  - skin rash - global
Bartonellosis

- *B. quintana* and *B. henselae* are the most important pathogens in this group of Gram-negative rods
- *B. quintana* - agent of trench fever and endocarditis, *B. henselae* - agent of cat-scratch disease (CSD), peliosis hepatitis, and endocarditis; Both can cause bacillary angiomatosis;
- Both can be important pathogens in AIDS and transplant patients
Bartonellosis
Laboratory Diagnosis

- Primary isolation from blood is complicated and may require a month or more
- PCR used for the tissue specimen or blood; may differentiate *B. quintana* and *B. henselae*. Negative test indicates absence of detectable DNA, but does not rule out recent disease
- Serology using IFA and ELISA. Little cross-reactivity with other rickettsias, but may cross-react with *Coxiella* and *Chlamydia spp.*
Q-Fever Group

– *Coxiella burnetii* - Q fever
  • inhale contaminated aerosol; resist dessication = up to 3 years outside host
  • intermittent fever/pneumonia
  • **NO** skin rash
Q Fever
Epidemiology

• Infections occur worldwide, except for New Zealand
• The causative agent, Coxiella burnetii, is a Gram-negative intracellular coccobacillus
• C. burnetii survives extreme environmental conditions for years; very low infectious dose; transmitted by inhalation of infectious aerosol
• Up to 60% of all cases are asymptomatic.
• Infection may also occur by ingestion of infected milk or meat. Most such infections result in seroconversion without disease symptoms.
Q-Fever
Acute Disease

Clinical Manifestations

• Abrupt onset of fever, chills, weakness, headache, anorexia and other non specific systematic symptoms.
• Weight loss weakness can be pronounce
• Cough and chest pain can accompany pneumonia (20%-50%)
• Hepatitis (40%-60%)
• The illness typically lasts 1-4 weeks
• Rare complications meningoencephalitis and myocarditis
Q-Fever
Chronic disease

- Occurs in approximately 1% of acutely ill

Clinical manifestations

Endocarditis
Hepatitis

Mortality

- Fatal if untreated
- Endocarditis despite treatment: 10%
Q Fever
Laboratory Diagnosis

• **Isolation** from body fluids in acute disease; only specially equipped laboratory should do that
• **PCR** assay for different human specimens
• **Serology** using IFA, ELISA, complement fixation. During the course of infection, the outer membrane of the agent undergoes changes called phase variation. Differences in Phase I and Phase II antigen presentation help in distinguishing acute and chronic infection
• **All specimens of suspected Q fever cases should be handled with extreme care!**
Q Fever
Serology (cont’d)

- **IgM** antibody appear early, reaching maximal phase II titers by week 3 and declining by week 14; phase I IgM titers follow same pattern at much lower level
- In some cases IgM may persist for nearly 2 years
- **IgG** antibody is seen early, peak by week 8, and persist for longer than 1 year
- It is possible to see IgG titers to both phases simultaneously
- **IgA** antibody to phase I → chronic infection likely
KINETICS OF ANTIBODY RESPONSES TO PHASE VARIANTS OF COXIELLA BURNETII

![Graph showing kinetics of antibody responses to phase variants of Coxiella burnetii.](image)

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Conclusion

• Serological tests are most commonly used for the diagnosis of rickettsial diseases
• Serology may not allow early diagnosis
• Follow-up testing required for reliable diagnosis
• Good epidemiologic history is helpful for laboratory data interpretation
• When in doubt, call testing Lab!
Rickettsiosis
Treatment, Prevention, and Control

- tetracycline/chloramphenicol or a fluoroquinolone
- vaccines under study
  - Q fever
- Control = insecticidies/cleanliness
Questions?