Rickettsia, Orientia, Ehrlichia, Anaplasma, Coxiella and Bartonella
History of Rickettsial Diseases

- Epidemic typhus - 16th century
- Associated with wars and famine
- WWI and WWII - 100,000 people affected
- Ricketts identifies causative agent of Rocky Mountain spotted fever - 20th century
- Arthropod vectors identified
- Arthropod control measures instituted
“Typhus is not dead. It will continue to break into the open whenever human stupidity and brutality give it a chance, as most likely they occasionally will. But its freedom of action is being restricted and more and more it will be confined, like other savage creatures, in the zoologic gardens of controlled diseases”

Hans Zinsser in *Rats, Lice and History*
Rickettsia, Orientia, Ehrlichia
Anaplasma and Coxiella Biology

• Small obligate intracellular parasites
• Once considered to be viruses
• Separate unrelated genera
• Gram-negative bacteria
  – Stain poorly with Gram stain (Giemsa)
• “Energy parasites”
  – Transport system for ATP
• Reservoirs - animals, insects and humans
• Arthropod vectors (except Coxiella)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Organism</th>
<th>Vector</th>
<th>Reservoir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>R. rickettsii</em></td>
<td>Tick</td>
<td>Ticks, rodents</td>
</tr>
<tr>
<td>Ehrlichiosis</td>
<td><em>E. chaffeensis</em></td>
<td>Tick</td>
<td>Deer</td>
</tr>
<tr>
<td></td>
<td><em>E. ewingii</em></td>
<td>Tick</td>
<td>Deer</td>
</tr>
<tr>
<td>Anaplasmosis</td>
<td><em>A. phagocytophlium</em></td>
<td>Tick</td>
<td>Small mammals</td>
</tr>
<tr>
<td>Rickettsialpox</td>
<td><em>R. akari</em></td>
<td>Mite</td>
<td>Mites, rodents</td>
</tr>
<tr>
<td>Scrub typhus</td>
<td><em>O. tsutsugamushi</em></td>
<td>Mite</td>
<td>Mites, rodents</td>
</tr>
<tr>
<td>Epidemic typhus</td>
<td><em>R. prowazekii</em></td>
<td>Louse</td>
<td>Humans, squirrel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fleas, flying squirrels</td>
</tr>
<tr>
<td>Murine typhus</td>
<td><em>R. thypi</em></td>
<td>Flea</td>
<td>Rodents</td>
</tr>
<tr>
<td>Q fever</td>
<td><em>C. burnetii</em></td>
<td>None</td>
<td>Cattle, sheep, goats, cats</td>
</tr>
</tbody>
</table>
Rickettsia and Orientia

_N.B. Orientia was formerly Rickettsia_
Replication of *Rickettsia and Orientia*

- Infect endothelial in small blood vessels - Induced phagocytosis
- Lysis of phagosome and entry into cytoplasm - Phospholipase
- Replication
- Release
Groups of Rickettsia Based on Antigenic Structure

Spotted fever group:

- **R. rickettsii**  Rocky Mountain spotted fever  Western hemisphere
- **R. akari**  Rickettsialpox  USA, former Soviet Union
- **R. conorii**  Boutonneuse fever  Mediterranean countries, Africa, India, Southwest Asia
  - **R. sibirica**  Siberian tick typhus  Siberia, Mongolia, northern China
- **R. australis**  Australian tick typhus  Australia
- **R. japonica**  Oriental spotted fever  Japan

Typhus group:

- **R. prowazekii**  Epidemic typhus  South America and Africa
  - Recrudescent typhus  Worldwide
  - Sporadic typhus  United States
- **R. typhi**  Murine typhus  Worldwide

Scrub typhus group:

- **O. tsutsugamushi**  Scrub typhus  Asia, northern Australia, Pacific Islands
Pathogenesis and Immunity

• No known toxins or immunopathology
• Destruction of cells
  – Leakage of blood into tissues (rash)
  – Organ and tissue damage
• Humoral and cell mediated immunity important for recovery
  – Antibody-opsonized bacteria are killed
  – CMI develops
Spotted Fever Group
Rickettsia rickettsii

- Rocky Mountain spotted fever

Fluorescent Ab staining
Vector - Tick

From: G. Wistreich, Microbiology Perspectives, Prentice Hall
Epidemiology - *R. rickettsii*
Rocky Mountain Spotted Fever

- Most common rickettsial infection in USA
  - 400 - 700 cases annually
  - South Central USA
Epidemiology - *R. rickettsii*
Rocky Mountain Spotted Fever

- Most common *rickettsial* infection in USA
  - 400 - 700 cases annually
  - South Central USA
- Most common from April - September
- Vector - Ixodid (hard) tick via saliva
  - Prolonged exposure to tick is necessary
- Reservoirs - ticks (transovarian passage) and rodents
  - Humans are accidentally infected
Epidemiology - *R. rickettsii*
Rocky Mountain Spotted Fever

<table>
<thead>
<tr>
<th>Year</th>
<th>USA</th>
<th>SC</th>
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<tbody>
<tr>
<td>2006</td>
<td>2,288</td>
<td>43</td>
</tr>
<tr>
<td>2007</td>
<td>2,106</td>
<td>63</td>
</tr>
<tr>
<td>200 (through 9/15)</td>
<td>1,456</td>
<td>29</td>
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</tbody>
</table>
Clinical Syndrome - Rocky Mountain Spotted Fever

- Incubation period - 2 to 12 days
- Abrupt onset fever, chills, headache and myalgia
- Rash appears 2 -3 days later in most (90%) patients
  - Begins on hands and feet and spreads to trunk (centripetal spread)
  - Palms and soles common
  - Maculopapular but can become petechial or hemorrhagic
Rash of Rocky Mountain Spotted Fever
Clinical Syndrome - Rocky Mountain Spotted Fever

- Incubation period - 2 to 12 days
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  - Palms and soles common
  - Maculopapular but can become petechial or hemorrhagic
- Complications from widespread vasculitis
  - Gastrointestinal, respiratory, seizures, coma, renal failure
  - Most common when rash does not appear
- Mortality in untreated cases - 20%
Laboratory Diagnosis - *R. rickettsii*

- Initial diagnosis - clinical grounds
- Fluorescent Ab test for Ag in punch biopsy
  - reference labs
- PCR based tests - reference labs
- Weil-Felix test - no longer recommended
- Serology
  - Indirect fluorescent Ab test for Ab
  - Latex agglutination test for Ab
Treatment, Prevention and Control

*R. rickettsii*

- Tetracycline and chloramphenicol
  - Prompt treatment reduces morbidity and mortality
- No vaccine
- Prevention of tick bites (protective clothing, insect repellents)
- Prompt removal of ticks
- Can’t control the reservoir
Consequences of Delayed Diagnosis of RMSF

• In Oklahoma on July 7 a 6 year-old presented with 1-day history of fever, headache, myalgia, and a macular rash on the arms, legs, palms, and soles
• On July 1 a tick had been removed from the patients neck
• Diagnosis: Viral illness; patient given oral cephalosporin
• On July 11 the patient was hospitalized with dehydration, irritability, confusion and throbocytopenia
• On July 12-13 patient developed disseminated intravascular coagulation and iv doxycycline was administered.
• The patient subsequently developed gangrene, requiring limb amputation and removal of the upper stomach and distal esophagus
• August 19 the patient died.
• Serum samples from July 12 and August 3 tested positive for antibodies to *R. rickettsii*
Rickettsia akari

• Rickettsialpox
Epidemiology - *R. akari*

Rickettsialpox

- Sporadic infection in USA
- Vector - house mite
- Reservoir - mites (transovarian transmission) and mice
- Humans accidentally infected
Clinical Syndrome - Rickettsialpox

- Phase I (1 week incubation period)
  - papule at bite site
  - Eschar formation

- Phase II (1 -3 week later)
  - Sudden onset of fever, chills headache and myaglia
  - Generalized rash - papulovessicular, crusts

- Mild disease; fatalities are rare
Laboratory Diagnosis - *R. akari*

- Not available except in reference laboratories
Treatment, Prevention and Control

*R. akari*

- Tetracycline and chloramphenicol
- Control of mouse population
Typhus Group
**Rickettsia prowazekii**

- Epidemic typhus
- Brill-Zinsser disease

Fluorescent-Ab staining  Vector - Louse

From: G. Wistreich, Microbiology Perspectives, Prentice Hall
Epidemiology - *R. prowazekii*

**Epidemic typhus**

- Associated with unsanitary conditions
  - War, famine, etc.
- Vector - human body louse
  - Bacteria found in feces
- Reservoir
  - Primarily humans (epidemic form)
  - No transovarian transmission in the louse
- Sporadic disease in Southeastern USA
  - Reservoir - flying squirrels
  - Vector - squirrel fleas
Clinical Syndrome - Epidemic typhus

- Incubation period approximately 1 week
- Sudden onset of fever, chills, headache and myalgia
- After 1 week rash
  - Maculopapular progressing to petechial or hemorrhagic
  - First on trunk and spreads to extremities (centrifugal spread)
- Complications
  - Myocarditis, stupor, delirium (Greek “typhos” = smoke)
- Recovery may take months
- Mortality rate can be high (60-70%)
Clinical Syndrome - Brill-Zinsser Disease

• Recrudescent epidemic typhus
  – Commonly seen in those exposed during WWII
• Disease is similar to epidemic typhus but milder
• Rash is rare
• High index of suspicion need for diagnosis
Laboratory Diagnosis - *R. prowazekii*

- Weil-Felix antibodies - not recommended
- Isolation possible but dangerous
- Serology
  - Indirect fluorescent Ab and latex agglutination tests
  - Epidemic typhus - IgM followed by IgG Abs
  - Brill-Zinsser - IgG anamnestic response
Treatment, prevention and Control

*R. prowazekii*

- Tetracycline and chloramphenicol
- Louse control measures
- Vaccine available for high risk populations
Rickettsia typhi

• Murine or endemic typhus
Epidemiology - *R. typhi*
Murine or endemic typhus

- Occurs worldwide
- Vector - rat flea
  - Bacteria in feces
- Reservoir - rats
  - No transovarian transmission
  - Normal cycle - rat to flea to rat
- Humans accidentally infected
Clinical Syndrome- Murine Typhus

• Incubation period 1 - 2 weeks
• Sudden onset of fever, chills, headache and myalgia
• Rash in most cases
  – Begins on trunk and spreads to extremities (centrifugal spread)
• Mild disease - resolves even if untreated
Laboratory Diagnosis - *R. typhi*

- Serology
  - Indirect fluorescent antibody test
Treatment, Prevention and Control

*R. typhi*

- Tetracycline and chloramphenicol
- Control rodent reservoir
Scrub Typhus Group
Oriensia (Rickettsia) tsutsugamushi

- Scrub typhus
- Japanese “tsutsuga” = small and dangerous and “mushi” = creature
- “Scrub” - associated with terrain with scrub vegetation
Epidemiology - *O. tsutstugamushi*

Scrub Typhus

- **Vector** - chiggers (mite larva)
- **Reservoir** - chiggers and rats
  - Transovarian transmission
  - Normal cycle - rat to mite to rat
- **Humans are accidentally infected**
Clinical Syndrome - Scrub Typhus

- Incubation period - 1 to 3 weeks
- Sudden onset of fever, chills, headache and myalgia
- Maculopapular rash
  - Begins on trunk and spreads to extremities (centrifugal spread)
- Mortality rates variable
Laboratory Diagnosis - *O. tsutsugamushi*

- Serology
Treatment, Prevention and Control

*O. tsutsugamushi*

- Tetracycline and chloramphenicol
- Measures to avoid exposure to chiggers
Ehrlichia and Anaplasma
Replication of *Ehrlichia* and *Anaplasma*

- Infection of leukocytes - Phagocytosis
- Inhibition of phagosome-lysosome fusion
- Growth within phagosome - Morula
- Lysis of cell
## Epidemiology - *Ehrlichia*

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
<th>Vector</th>
<th>Reservoir</th>
<th>Distribution</th>
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</thead>
<tbody>
<tr>
<td><em>E. chaffeensis</em></td>
<td>Human monocytic ehrlichiosis</td>
<td>Lone star tick</td>
<td>White-tailed deer</td>
<td>Southeastern, Mid-Atlantic and South Central United States</td>
</tr>
<tr>
<td><em>E. ewingii</em></td>
<td>Human granulocytic ehrlichiosis</td>
<td>Deer and dog ticks</td>
<td>White-tailed deer</td>
<td>Southeastern, Mid-Atlantic and South Central United States</td>
</tr>
<tr>
<td><em>A. phagocytophilium</em></td>
<td>Human granulocytic anaplasmosis</td>
<td>Deer and dog ticks</td>
<td>Small mammals</td>
<td>Wisconsin, Minnesota and Connecticut</td>
</tr>
</tbody>
</table>
## Epidemiology - Ehrlichia

<table>
<thead>
<tr>
<th>Year</th>
<th>USA</th>
<th>SC</th>
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</thead>
<tbody>
<tr>
<td>2006</td>
<td>1,455</td>
<td>?</td>
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<tr>
<td>2007</td>
<td>1,345</td>
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</tr>
<tr>
<td>2008 (through 9/15)</td>
<td>1,999</td>
<td>?</td>
</tr>
</tbody>
</table>
Ehrlichia chaffeensis

- Human monocytic ehrlichiosis

Vector - Tick

From: Koneman et al. Color Atlas and Textbook of Diagnostic Microbiology, Lippincott
Clinical Syndrome - Human
Monocytic Ehrlichiosis

E. chaffeensis

- Sudden onset of fever, chills, headache and myalgia
- No rash in most (80%) patients
- Leukopenia, thrombocytopenia and elevated serum transaminases
- Mortality rates low (<5%)
Laboratory Diagnosis - *E. chaffeensis*

- Microscopic observation of morula in blood smears is rare
- Culture is possible but rarely done
- Serology is most common
- DNA probes are available

From: Koneman *et al.* Color Atlas and Textbook of Diagnostic Microbiology, Lippincott
Treatment, Prevention and Control

E. chaffeensis

- Doxycycline
- Avoidance of ticks
Ehrlichia ewingii and Anaplasma phagocytophilium

- Human granulocytic ehrlichiosi and anaplasmosis

Vector - Tick

From: Koneman et al. Color Atlas and Textbook of Diagnostic Microbiology, Lippincott
Clinical Syndrome - Human Granulocytic Ehrlichiosis or Anaplasmosis

*E. ewingii* or *Anaplasma phgocytophilium*

- Sudden onset of fever, chills, headache and myalgia
- No rash in most (80%) patients
- Leukopenia, thrombocytopenia and elevated serum transaminases
- Mortality rates low (<5%)
Laboratory Diagnosis - *E. ewingii* and *A. phagocytophilum*

- Microscopic observation of morula in blood smears is rare
- Culture is possible but rarely done
- Serology is most common
- DNA probes are available

From: Koneman *et al.* Color Atlas and Textbook of Diagnostic Microbiology, Lippincott
Treatment, Prevention and Control

*E. ewingii* and *A. phagocytophilum*

- Doxycycline
- Avoidance of ticks
Coxiella
Coxiella burnetii

- Q fever (Q for query)

Fluorescent-Ab Stain

From: G. Wistreich, Microbiology Perspectives, Prentice Hall
Replication of *Coxiella burnetii*

- Infection of macrophages
- Survival in phagolysosome
- Replication
- Lysis of cell
Pathogenesis and Immunity - *C. burnetii*

- Inhalation of airborne particles (ticks are the primary vector in animals)
- Multiplication in lungs and dissemination to other organs
- Pneumonia and granulomatous hepatitis in severe cases
- In chronic disease immune complexes may play a role in pathogenesis
- Cellular immunity is important in recovery
Pathogenesis and Immunity - *C. burnetii*

- Phase variation in LPS
  - Acute disease - Antibodies to phase II antigen
  - Chronic disease - Antibodies to both phase I and phase II antigens
Epidemiology - *C. burnetii*

Q fever

- Stable “spore like”
- Infects many animals including sheep, goats, cattle, and cats
- High titers in placentas of infected animals
- Persists in soil
- Found in milk of infected animals
- No arthropod vector (ticks in animals)
- Disease of ranchers, veterinarians, and abattoir workers
Epidemiology – *C. burnetii*

<table>
<thead>
<tr>
<th>Year</th>
<th>USA</th>
<th>SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>169</td>
<td>?</td>
</tr>
<tr>
<td>2007</td>
<td>169</td>
<td>?</td>
</tr>
<tr>
<td>2008 (through 9/15)</td>
<td>78</td>
<td>?</td>
</tr>
</tbody>
</table>

Notifiable in <40 states
Clinical Syndrome - Q Fever

- Acute Q fever
  - Can be mild or asymptomatic
  - fever, chills, headache and myalgia
  - Respiratory symptoms usually mild (atypical pneumonia)
  - Hepatomegaly and splenomegaly can be observed
  - Granulomas in the liver are observed histologically

- Chronic Q fever
  - Typically presents as endocarditis on a damaged heart valve
  - Prognosis is poor
Laboratory Diagnosis - *C. burnetii*

• Serology
  – Acute disease - Ab to phase II antigen
  – Chronic disease - Ab to both phase I and phase II antigens
Treatment, Prevention and Control

*C. burnetii*

- Acute Q fever - tetracycline
- Chronic Q fever - combination of antibiotics
- Vaccine is available but it is not approved for use in the USA
Case Study – *Coxiella burnetii*

- A 56 year-old woman presented with a high fever (104°F), hepatomegaly and elevated liver enzymes
- Diagnosis: Acute cholecystitis; cholecystectomy performed
- Patient’s symptoms persisted
- Chest CT scan performed 4 weeks later revealed nonspecific interstitial lung disease.
- Serum samples obtained at the time of the CT scan and 6 weeks later revealed antibodies to *C. burnetii* phase II antigens
- Her husband also developed a febrile illness 3 days after her illness started and his serum samples revealed the presence of antibodies to *C. burnetii* phase II antigens
- The patients were both treated with doxycycline and their symptoms resolved
- They did not own livestock but drove on an unpaved road past a neighbor who raised goats.
- The goats tested positive for antibodies to *C. burnetii*
Bartonella
Microbiology - *Bartonella*

- Small Gram-negative aerobic bacilli
- Difficult to culture
- Infect animals but do not cause disease in animals
- Insects are thought to be the vectors in human disease
- Some species infect erythrocytes other attach to cells
# Bartonella

<table>
<thead>
<tr>
<th>Organism</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. quintana</em> (formerly <em>Rochalimaea quintana</em>)</td>
<td>Trench fever (shin-bone fever, 5 day fever), bacillary angiomatosis, bacillary peliosis endocarditis</td>
</tr>
<tr>
<td><em>B. henselae</em></td>
<td>Cat-scratch disease, bacillary angiomatosis, bacillary peliosis endocarditis</td>
</tr>
<tr>
<td><em>B. bacilliformis</em></td>
<td>Oroya fever (bartonellosis, Carrion’s disease)</td>
</tr>
<tr>
<td><em>B. elizabethae</em></td>
<td>Endocarditis (rare)</td>
</tr>
</tbody>
</table>
Bartonella quintana

- Trench fever
  - Shin-bone fever
  - 5 day fever
Epidemiology - *B. quintana*

**Trench Fever**

- Associated with war and famine
- **Vector** - human body louse
  - Organism found in feces
- **Reservoir** - humans
  - No transovarian transmission
  - Cycle - human to louse to human
Clinical Syndrome - Trench Fever

- Infection may be asymptomatic or severe
- Sudden onset of fever, chills, headache and myalgia
- Severe pain in the tibia (shin-bone fever)
- Symptoms may appear at 5 day intervals (5 day fever)
- Maculopapular rash may or may not develop on the trunk
- Mortality rates very low.
Laboratory Diagnosis - *B. quintana*

- Serology - reference laboratories
- PCR - reference laboratories
Treatment, Prevention and Control

*B. quintana*

- Various antibiotics
- Control of body louse
Bartonella henselae

- Cat-scratch disease
Epidemiology - *B. henselae*
Cat-scratch Disease

- Acquired from cat bite or scratch and possibly from cat fleas
Clinical Syndrome
Cat-scratch Disease

• Benign disease
• Chronic regional lymphadenopathy
Laboratory Diagnosis - *B. henselae*

- Serology
Treatment - *B. henselae*

- Does not respond to antimicrobial therapy