

It's a BEAR of a lecture: Borrelia, Ehrlichia, Anaplasma & Rickettsia
(but not in that order)

Lecture Objectives: To learn about the major clinical syndromes associated with various Rickettsia, Ehrlichia, Anaplasma, and Borrelia species. You will learn the epidemiology, causal agents (including vectors), clinical presentation, pathogenesis, diagnosis, and treatment of the syndromes associated with these species.

Rickettsia

Rickettsia are Gram negative coccobacilli or short bacilli that are obligate intracellular pathogens. They are usually spread by an insect vector (i.e. tick, louse, flea, mite) and have a mammalian reservoir. Except for louse-borne typhus, humans are incidental hosts. There are numerous Rickettsial species responsible for a variety of clinical syndromes. Select examples are illustrated here.

The Spotted Fever Group (*R. rickettsii* and *R. akari*)

Rocky Mountain Spotted Fever (RMSF) is caused by *R. rickettsii*, a small GN bacillus.

Epidemiology: RMSF occurs throughout the U.S., Mexico, Central and South America. In the U.S. it is most common in the S. Central and SE states, despite its namesake. In 2002, >1000 cases were reported in the U.S. RMSF is the only tick-borne disease endemic to NYC (24 cases reported in 2006). It is transmitted via tick salivary secretions (the American dog tick or the Rocky Mountain wood tick depending on the location). *R. rickettsii* is passed transovarially in the tick. Small mammals are reservoirs. Cases most frequently occur May-Sept

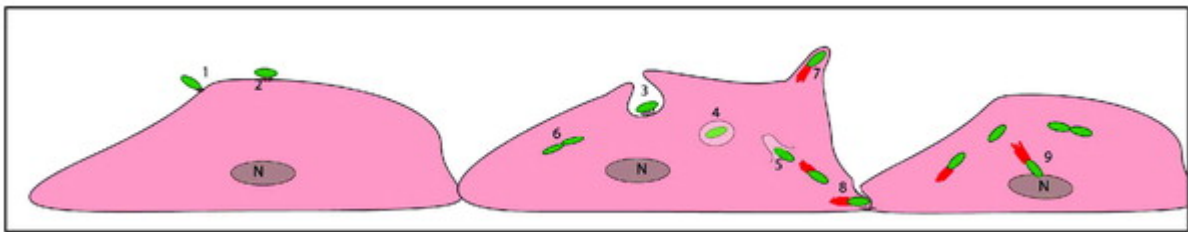
Clinical Presentation: After ~7 day incubation, there is the sudden onset of a flu-like illness including headache, myalgia, malaise, nausea, and fever. Subsequently a rash occurs that begins on the wrists/ankles and spreads to the trunk (centripetal). The rash can evolve from macules to papules, to petechiae (from hemorrhage). The palms/soles can become involved. This pathogen causes extensive injury to the microcirculation and, if left untreated, can result in multi-organ system damage (i.e. pulmonary, renal, hepatic, CNS, and cardiac injury) and death. Host factors associated with severe or fatal Rocky Mountain spotted fever include advanced age, male sex, African-American race, chronic alcohol abuse, and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Pathogenesis: After introduction of *R. rickettsii* at the tick bite site, it travels via lymphatics to the general circulation where it invades endothelial cells. The outer membrane proteins OmpA/OmpB mediate adhesion to the endothelial cells and the organism is engulfed. It escapes the phagosome, replicates in the cytosol, and uses host cell actin (activated by its surface protein RickA) to push it to the surface of the host cell. This causes the host cell membrane to invaginate into the adjacent cell (endothelial or smooth muscle cell) to which the Rickettsia spread. They may also enter the circulation and invade other organ systems (see Figure below). The major pathogenic

effect is increased vascular permeability which results from the disruption of junctions between endothelial cells. This leads to ischemia, edema, and hypovolemia.

From CID 2007:45(Suppl 1) Walker:

Spotted fever group rickettsia–endothelial cell interaction. 1, Attachment of rickettsia via adhesins (e.g., outer membrane protein B) to host cell receptors (e.g., Ku70); 2, recruitment of more Ku70 receptors and their ubiquitination by ubiquitin ligase; 3, signal transduction leading to actin rearrangement and engulfment; 4, rickettsia in cytoplasmic endosome; 5, rickettsial enzymes (phospholipase D and tlyC) lyse vacuolar membrane, allowing rickettsial escape into the cytosol; 6, replication by binary fission fueled by host cell building blocks; 7, rickettsial RickA activation of Arp 2/3 leads to host actin-based mobility, with entry into a filopodium and extracellular release; and 8, cell-to-cell spread, or invagination into the endothelial cell nucleus (N) followed by entry into the nucleoplasm. Illustrated by Aaron Medina-Sanchez.



Diagnosis: Acutely: immunohistochemistry of a skin biopsy. Serologic tests (indirect immunofluorescence assay [IFA]/PCR) may be performed, but are not useful in the acute setting. Culture and staining are difficult to perform for Rickettsia and are not useful diagnostic tools. *Key point: if you suspect RMSF, do not wait for diagnostic tests—start treatment!*

Differential Diagnosis (includes, but not limited to): influenza, enterovirus, mononucleosis, viral hepatitis, leptospirosis, typhoid fever, sepsis (GN, GP bacteria), ehrlichiosis, anaplasmosis, murine typhus, rickettsialpox.

Treatment: doxycycline (a tetracycline)

Rickettsialpox: Rickettsial pox is caused by *R. akari* and was first described in NYC.

Epidemiology: Most commonly recognized in NYC, but has been seen in other states, European countries, and the Ukraine. It is transmitted by mice (reservoir) and their mites (vector).

Clinical Presentation: At the site of the mite bite: papule→vesicle→eschar with surrounding erythema (this can be confused with cutaneous anthrax). About 10+ days later flu-like symptoms (HA, fever, chills, malaise) occur and a papulo-vesicular rash develops (looks like chicken pox). Without treatment, this disease is self-limited and is not fatal.

Diagnosis and Treatment: Diagnosis is clinical although IFA and immunohistochemistry on a skin biopsy may be performed. Treatment: doxycycline

Typhus Group Rickettsioses: (*R. typhi* and *R. prowazekii*)

R. typhi causes endemic murine typhus (flea borne) and *R. prowazekii* causes epidemic typhus (louse borne).

Endemic murine typhus

Epidemiology: This disease is found globally with ~100 cases/yr in the U.S. Classically, the vector is a flea and the reservoir is a rat, but several other mammals (such as the cat) can be reservoirs. Most often, humans are infected when infected flea feces are inoculated into the skin by scratching the flea bites. People generally don't remember getting bitten by fleas, but do remember contact with an animal. In the U.S., most cases occur in Southern California or Texas. Cases peak April-June in Southern Texas and peak in warm summer/fall months in other locations.

Clinical Presentation: After a few days of a viral prodrome, there is the abrupt onset of fever/chills, nausea/vomiting (incubation period ~11 days). Rash is usually not present when patients first present for medical attention, but develops in 50% of patients a few days later (50% never get a rash). The maculopapular rash mainly involves the trunk and it may spread outward (centrifugally); however, the face, palms, and soles are *rarely* involved. Pulmonary symptoms are frequently prominent (cough, pulmonary infiltrates). CNS, hepatic/GI signs & symptoms may be present. Lab tests may reveal leukopenia followed by leukocytosis, anemia, hyponatremia (low Na), thrombocytopenia (low platelets), and mildly elevated liver enzymes. Complications include respiratory failure, hemolysis, GI/CNS hemorrhage among others. This disease can be fairly benign although ~10% require ICU admission and 1% die.

Diagnosis: IFA (antibody titers), immunohistochemistry on skin biopsy, PCR, others

Treatment: doxycycline

Epidemic Typhus

Epidemiology: The vector is the human body louse and humans are the reservoir. The louse becomes infected by feeding on an infected human. The *R. prowazekii* replicate in the louse gut and are expelled in the feces. Humans become infected after scratching the infected louse feces into the bite. Epidemic typhus occurs in crowded conditions with poor hygiene and often emerges during war and disaster situations. It is also common in jails where it's known as jail fever. An outbreak occurred in a Burundi refugee camp in >100,000 individuals in 1997.

Clinical Presentation: This is a severe illness. After ~1 week incubation, there is the abrupt onset of high fever, severe headache, and prostration. Cough is very common and myalgias can be intense. After 5 days, a rash begins on the trunk and spreads centrifugally, but spares the face, palms, and soles. The rash evolves from macular, to maculopapular to hemorrhagic/confluent without treatment (a rash may not occur/be detected on dark-skinned individuals). Photophobia/conjunctival injection is common. If severe/untreated, multiorgan system failure can result (often with prominent neurologic findings). Fatal 7-40% cases.

Brill-Zinsser disease occurs when *R. prowazekii* reactivates (causing a milder illness) in older or immunocompromised individuals years after the initial infection.

Treatment: Doxycycline

Ehrlichia/Anaplasma

Human ehrlichioses are tickborne infections caused by members of the Anaplasmataceae family. **Human monocytic ehrlichiosis (HME)** is caused by *Ehrlichia chaffeensis* and **Human granulocytic anaplasmosis (HGA)** is caused by *Anaplasma phagocytophilum*. These species are small, obligate intracellular Gram negative bacteria that infect either monocytes (HME) or granulocytes (HGA), respectively. Ehrlichia differ from other Gram negatives in that they don't have a significant amount of peptidoglycan in their cell wall.

Epidemiology: Ehrlichiosis is an emerging infectious disease with an increasing incidence. HME occurs across the south-central, SE, and mid-Atlantic states where its major reservoir (white-tailed deer) and its vector (lone star tick) coexist. HGA occurs in the U.S. in the NE, mid-Atlantic, Upper Midwest, and Pacific NW states, but also occurs internationally (Europe and Asia). Ixodes ticks are the vector while small mammals (especially mice) are likely reservoirs. Infections occur most frequently April through September.

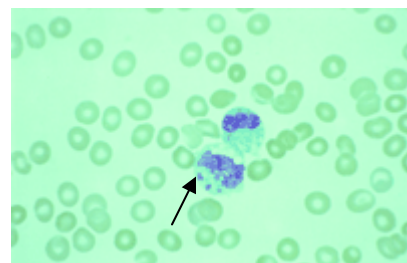
Clinical Presentation: The clinical presentation for ehrlichiosis is similar to that of the rickettsial diseases (e.g. RMSF); however, patients are very unlikely to have a rash with HGA and only 30% likely to have a rash with HME. A summary of clinical/lab findings is listed here (from Dumler *et al.* CID 2007:45 Suppl 1). Note that thrombocytopenia, elevated transaminases, and leukopenia are common and are clues to the diagnosis. Life-threatening complications (7-17%) and death (up to 3%) can occur—generally HME has a greater risk of serious complications compared to HGA.

Pathogenesis: The pathogenesis of these infections is still being elucidated. Ehrlichia/Anaplasma bind to the cell membrane (of monocytes and granulocytes, respectively) and are internalized. They multiply and form clusters in cytoplasmic vacuoles (called 'morulae', Latin for 'mulberry')—see figure. Key to their survival is

Table 1. Meta-analysis of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) symptoms, signs, and laboratory findings.

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

NOTE. Data are from [1]. ALT, alanine aminotransferase; AST, aspartate aminotransferase.



the prevention of fusion of the phagosome with the lysosome.

Diagnosis: Think of the diagnosis when someone presents with fever, thrombocytopenia, elevated transaminases, and leukopenia, in an endemic region during tick activity (April-September).

Acutely, the most rapid test is examination of a blood smear for morulae; however, this has a very low sensitivity because <10% with HME have visible morulae at presentation. 25-75% of patients with HGA have morulae. Acutely, PCR is the diagnostic tool of choice with sensitivity 60-85% for HME and 67-90% for HGA. Cultures are difficult to perform and require several weeks. The most sensitive test is the detection of a 4-fold rise in antibody titers during the convalescent phase--sensitivity is $\geq 90-95\%$.

Treatment: Doxycycline (a tetracycline) should be started as soon as the diagnosis is suspected.

Borrelia

Borrelia are spirochetal (helical) Gram negative bacteria. The important species for you to know are *B. burgdorferi* (Lyme Disease), *B. recurrentis* (louse borne relapsing fever), and *B. hermsii* and *B. turicatae* (tick borne relapsing fever in the U.S.). Note that several other Borrelia species exist.

Lyme Disease: *Borrelia burgdorferi*

Epidemiology: Lyme Disease is the most common vector-borne disease in the U.S. and is predominant in the NE. It is caused by *B. burgdorferi*, a spirochete, and is transmitted via the bite of Ixodes ticks (hard ticks). A tick must feed for ≥ 24 hours in order to transmit the spirochete. The white-footed mouse is the preferred host for immature/larval and nymphal ticks while the white-tailed deer is the preferred host for the adult tick. The nymphal ticks are primarily responsible for transmission, which occurs most frequently in June, July, and August. 20,000 to 25,000 cases are reported in the U.S. each year. Incidence is ~ 7.6 cases per 100,000 per year.

History: Signs and symptoms of Lyme disease were recorded as early as 1883 in Europe and in 1970, the first case of erythema migrans (the classic rash associated with this disease) was identified in the US. In 1975, there was an outbreak of what initially appeared to be juvenile rheumatoid arthritis in 3 towns in SE Connecticut, including the towns of Lyme and Old Lyme. The full syndrome of this tick-associated illness was coined 'Lyme Disease' after these two towns.

Clinical Presentation: Localized, stage 1 infection: 3 to 30 days after an infected tick bite, 70-80% of people develop an expanding rash called erythema migrans. Usually the tick bite goes unnoticed because the tick is so small. As the rash expands there may be an area of central clearing, giving it a bull's eye appearance (see figure). In stage 2, disseminated infection, flu-like symptoms such as fever, headache, and myalgias frequently occur and may be the only symptoms. If untreated, the borrelia can cause disease in different organ systems:

- 1) cardiac (heart block, myopericarditis)—8% of untreated individuals



- 2) neurologic (Bell's palsy (CN VII), meningitis, radiculopathy)—15% of untreated
- 3) musculoskeletal pain

If left untreated, Stage 3 or 'late' disease may occur: 60% develop arthritis, usually of the knee or other large joint. This arthritis can last for weeks to months even with antibiotic therapy. Late neurologic Lyme disease can also occur which manifests as an encephalomyelitis, peripheral neuropathy, or encephalopathy. There is another 'entity' termed 'Post-Lyme disease syndrome' which is when a patient remains symptomatic months to years after appropriate antibiotic therapy. This is a controversial issue, but the latest guidelines (endorsed by the IDSA) clearly state, "there is no compelling evidence that prolonged treatment with antibiotics has any beneficial effect in post-Lyme syndrome (Level A)." NEUROLOGY 2007;69:1-1 Chronic antibiotic therapy is *not* recommended for these patients who often have another treatable diagnosis such as depression, rheumatoid arthritis, or myasthenia gravis.

Pathogenesis: *B. burgdorferi* is introduced into the skin at the tick bite site. It multiplies at the site and spreads outward, causing the characteristic rash. OspC (outer surface protein C) is upregulated in the tick salivary gland and in the mammalian host. Whether or not the organism disseminates to other organs may depend on the variant of the OspC protein as only a few variants are associated with disseminated disease. Surface proteins that bind to platelet-specific integrin are expressed and OspA mediates binding to plasminogen—both may facilitate hematogenous spread. In addition, *B. burgdorferi* expresses surface proteins that bind to 1) heparan sulfate and dermatan sulfate, which are present on the surface of epithelial/endothelial cells and 2) fibronectin, an extracellular matrix protein. The organism also expresses decorin binding proteins A & B (DbpA and DbpB) which mediate binding to decorin, a proteoglycan on the surface of collagen. This may partly explain *B. burgdorferi*'s propensity to affect collagen fibrils within the extracellular matrix of joints, heart, and nervous system. *B. burgdorferi* has not been identified intracellularly in the *in vivo* setting. Likely, the host's immune response to the organism plays a role in its pathogenesis, which is incompletely understood.

Diagnosis: Observing erythema migrans is sufficient to make the initial diagnosis. In situations where the diagnosis is less certain, acute and convalescent antibodies can be obtained. In cases of CNS involvement, a lumbar puncture may be indicated (CSF usually reveals a lymphocytosis, elevated protein, and normal glucose). An important concept is that HGA and Babesia are transmitted via the same Ixodes tick vector and that co-infection may occur.

Treatment: The treatment for Lyme disease is fairly complex. Erythema migrans is preferentially treated with doxycycline in adults, although amoxicillin and cefuroxime (a second generation cephalosporin) are alternatives for children, pregnant women, and those intolerant to doxycycline. Isolated Bell's palsy, arthritis, and mild cardiac disease can be treated with the same oral regimen. When there is meningitis or radiculopathy or hospitalization is required for heart block or symptomatic cardiac disease, treatment with IV ceftriaxone, a third generation cephalosporin, is recommended. Prophylaxis with doxycycline is not routinely offered for a tick bite without erythema migrans. Generally, observation alone is recommended unless several conditions are met (see Wormser et al. CID 2006;43 Nov 1) for more information on treatment recommendations.

Relapsing Fevers

There are two forms of relapsing fever: louse borne relapsing fever (LBRF) or epidemic relapsing fever and tick-borne relapsing fever (TBRF) or endemic relapsing fever.

Epidemiology: LBRF is caused by *B. recurrentis*. Human body lice become infected with *B. recurrentis* by feeding on infected humans, the only reservoirs for this infection. *B. recurrentis* is transmitted to humans when the louse is crushed (e.g. via scratching) and their infected body fluids are introduced via mucous membranes or broken skin. It is *not* transmitted via a louse bite. People in war-torn and other disaster areas are prone to body louse infestations and relapsing fever. Currently, it is an issue in NE Africa—particularly in Ethiopia in the setting of homeless men living in crowded, unhygienic situations.

TBRF is caused by numerous species, including *B. hermsii* and *B. turicatae* in the U.S. TBRF is spread via soft ticks (their saliva/excreta) when they feed on humans. Rodents and rabbits/hares are the most common reservoirs. TBRF is uncommon in the U.S., but is most common west of the Mississippi, particularly in inhabitants of rustic mountain cabins (e.g. outbreaks among tourists staying in cabins around the Grand Canyon). *B. turicatae* has occurred among individuals exposed in tick-infested caves in the Southwest.

Clinical Presentation: LBRF and TBRF have similar clinical presentations, though LBRF may have up to 20% mortality, while death due to TBRF is rare. There is sudden onset of fever, chills, headache, myalgias, and arthralgias. Nausea/vomiting are common and several other signs/symptoms such as abdominal pain, confusion, hemorrhage, and rash may occur. The first fever ends with a 15-30 minutes crisis characterized by a further increase in temperature, blood pressure, and pulse rate. Crisis is followed by profuse diaphoresis and hypotension. Death is most common during the crisis and immediately thereafter. After the first febrile episode the patient is afebrile for 4-14 days. Subsequent febrile episodes (there must be at least one) are usually less severe than the initial one.

Pathogenesis: After inoculation through broken skin/mucous membranes, the *Borrelia* multiply in the bloodstream and spread throughout the body, including the liver, spleen, bone marrow, and CNS. Febrile episodes are associated with higher spirochetemia compared to periods of remission.

Diagnosis: detection of spirochetes (usually in the blood), best seen with dark-field microscopy. Antibody testing can be done, but is not particularly reliable. Other laboratory findings are generally non-specific.

Differential Diagnosis: typhus, typhoid fever, nontyphoid salmonella, malaria, dengue, TB, leptospirosis, and viral hemorrhagic fevers

Treatment: options include doxycycline (a tetracycline), erythromycin (a macrolide), and chloramphenicol (not routinely used in the U.S.)

