Rickettsia, Ehrlichia, and Borrelia

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Differential Diagnosis

- **Bacteria**
- **Viruses**
- **Fungi**
- **Parasites**
- **TB**
- **Non-TB mycobacteria**
- **Non-infectious**

ALWAYS THINK HIV and TB!!

EXPOSURE, EXPOSURE, EXPOSURE!!!

&

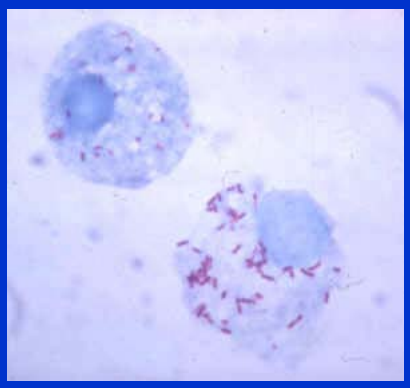
LOCATION, LOCATION, LOCATION!!!

Rickettsia Microbiology

- Gram negative bacteria

  - fastidious
  - obligate intracellular pathogens

Rickettsia Microbiology



Rickettsia Pathogenesis

- Vector (tick/louse/flea/mite) bites and feeds (at least 6 hours)
- Regurgitates bacteria into skin bite site
- Bacteria are carried via lymphatics/small blood vessels to general circulation where they invade endothelia cells (primary target)
- Spreads to contiguous endothelial cells, smooth muscle cells, and phagocytes
- Eventually spread via the microcirculation and invade virtually all organ systems
  - Angiitis resulting in local thrombus formation and end organ damage

Rickettsia Endemic Diseases

- Rocky Mountain Spotted Fever
  - *Rickettsia rickettsii*
  - Vector: tick
- Murine Typhus
  - *Rickettsia typhi*
  - Vector: flea (cat fleas important: TX and CA)

Rickettsia
Epidemic Diseases

- **Rickettsialpox**
  - ***Rickettsia akari***
  - **Vector: mite**
- **Epidemic Typhus**
  - ***Rickettsia prowazekii***
  - **Vector: louse**

Rickettsia
Rashes

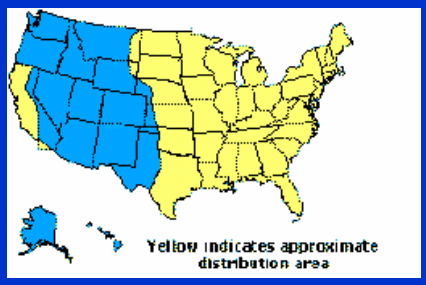
- **Rickettsial species cause a petechial rash in early disease that starts on the trunk and spreads outward (centrifugal)**
- **Two notable exceptions:**
  - ***R. akari***
  - **Rash not petechial but papulo-vesicular (looks like chicken pox)**
  - ***R. rickettsii***
  - **Centripetal rash (starts on wrists, ankles, soles, and palms and spreads proximally)**

Rocky Mountain Spotted Fever

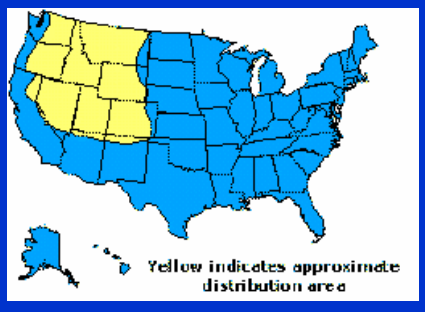
- **Causative agent: *Rickettsia rickettsii***
- **Vector: dog tick (Eastern) and wood tick (Western): *Dermacentor sp.***
- **Endemic regions: Southeastern, Mid-Atlantic, Midwest**
- **Peak incidence: May-Sept (when people are outside with potential tick exposure**

Rocky Mountain Spotted Fever

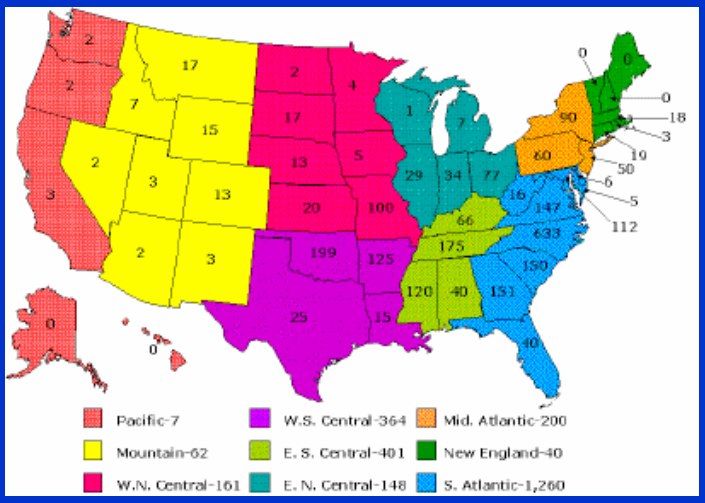
Dog Tick (*Dermacentor variabilis*)



Rocky Mountain Wood Tick (*Dermacentor andersoni*)



Distribution of Cases



Rocky Mountain Spotted Fever

- After tick bite, 7-14 day asymptomatic incubation period
- Sudden onset of fever, headache, malaise, myalgia
- Rash, menigismus, photophobia, renal failure, diffuse pulmonary infiltrates, encephalopathy
- Gastrointestinal disturbances, hepatomegaly, and jaundice can occur in the later stages
- Thrombocytopenia, anemia, coagulopathy (DIC), hyponatremia

Rocky Mountain Spotted Fever Rash

Only small fraction patients have rash first day

- **49% during first three days**
- **Usually 3-5 days**

Three stages:

- **Erythematous macule: blanches on pressure**
- **Macular-papular: results from fluid leakage from infected blood vessels**
- **Hemorrhage: into center with frank petechiae**

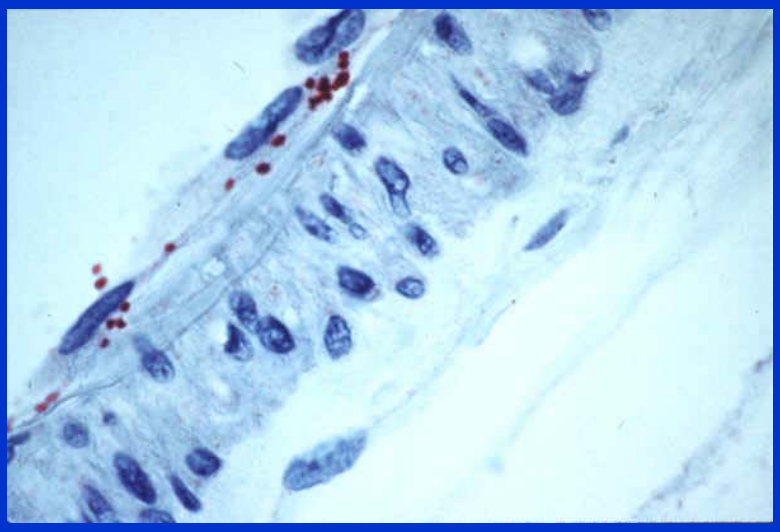
Rocky Mountain Spotted Fever Early Rash

Rocky Mountain Spotted Fever
Late Stage Petechial Rash

Rocky Mountain Spotted Fever
Diagnosis

- ***R. rickettsii***
  - **Fastidious organism (difficult to culture)**
  - **Skin biopsy with immunohistochemical staining of organism (PCR)**
  - **Serologies (Indirect immunofluorescence, EIA, latex agglutination--not Weil-Felix)**
    - **Acute and convalescent**

Immunohistochemical Stain Endothelial Cells



Rocky Mountain Spotted Fever

- **Treatment: Doxycycline and supportive care**
- **If treated within first 4-5 days of disease, fever subsides 24-72 h**
- **Outcome:**
  - **Prognosis largely related to timeliness of initiation of therapy**
  - **Untreated, death occurs 8-15 days**

Rickettsialpox

- Causative agent: *Rickettsia akari*
- Vector: mouse mite
- Endemic regions: Urban areas (NYC), South Africa, Korea, Russia

Rickettsialpox

- Eschar forms at site of mite bite
- Incubation 9 to 14 days
- Papular-vesicular rash (2-3 days after onset) with fever, headache, lymphadenopathy, chills, myalgia
- Diagnosis: Clinical; Serologies (but X-reaction)
- Treatment: self-limited or doxycycline
- Outcome:Excellent, relapse uncommon

Rickettsialpox

Rickettsialpox

Epidemic Typhus

- Causative agent: *R. prowazekii*
- Vector: Human body louse
- USA reservoir: Southern flying squirrel
- Risk Factors: Crowding and poor sanitation (wartime)

Epidemic Typhus

Epidemic Typhus

- Incubation: Approximately one week
- Abrupt onset intense headache, chills, fever and myalgia
- Can have CNS involvement with decreased mental status
- No eschar
- Rash starts fifth day of illness in the axillary folds and upper trunk
  - Spreads centrifugally
  - Spares face, palms, and soles

Epidemic Typhus: Petechial Rash Day 7

Epidemic Typhus

- Diagnosis: Clinical; Serologies X-react (Weil-Felix)
- Treatment: Doxycycline
- Outcome: under adverse conditions, untreated mortality as high as 40%

Brill-Zinsser Disease

- Recrudescence of Epidemic Typhus in elderly (waning of immune function)
- Seen most often in immigrants who had the disease during WWII
- Pathogenesis unknown

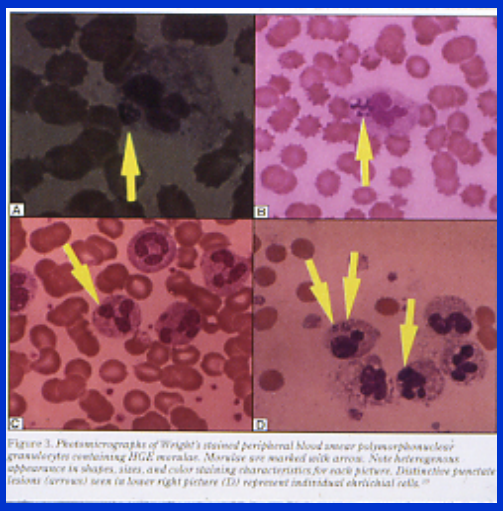
Ehrlichia

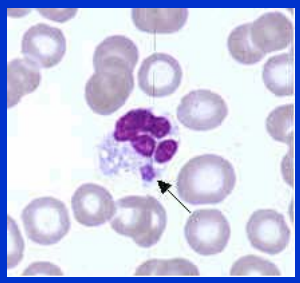
- Small, obligate intracellular gram negative bacteria
- Cause flu-like illness (fever, headache, chills, myalgia, malaise)
- Symptoms of ehrlichiosis are similar to those of rickettsial diseases
  - Dubbed "Spotless" Fever
  - Beware! 20-30% of HME can have rash
- Lab abnormalities: thrombocytopenia, leukopenia, and elevated LFTs

Ehrlichia Pathogenesis

- Bacteria introduced via tick bite
  - Except *Ehrlichia sennetsu*: acquired by eating raw fish (Asia)
- Spreads via lymphatics to blood
- Multiple species that infect either granulocytes or monocytes
- Clustered inclusion-like appearance in the host cell vacuoles:
  - Morula (Latin for "mulberry")
  - Pathognomonic, but only seen in approximately 20% cases

Ehrlichia Morula

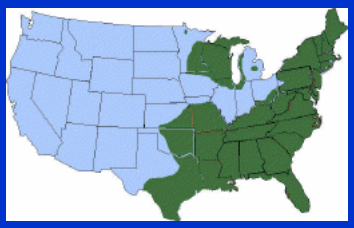


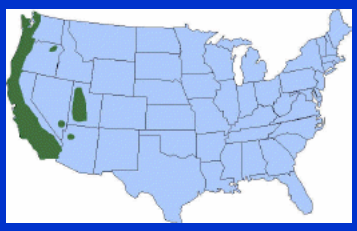


Human Granulocytic Ehrlichiosis (HGE)

- **Causative agent: *Anaplasma phagocytophilum***
- **Vectors: Ixodes ticks**
- **Reservoirs: White-footed mouse, chipmunks, and voles**
- **Distribution: Northeast**
- **Incidence: Year round with one peak in July and second in November**

Human Granulocytic Ehrlichiosis (HGE)





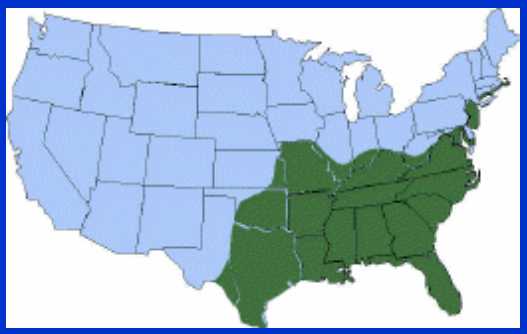
Human Granulocytic Ehrlichiosis (HGE)

- **Can be asymptomatic to fatal**
- **ARDS with septic shock-like presentation, rhabdomyolysis**
- **Neurological sequalae include demylinating polyneuropathy and brachial plexopathy**

Human Monocytic Ehrlichiosis (HME)

- Causative agent: *Ehrlichia chaffeensis*
- Vectors: Lone star tick (*Amblyomma americanum*)
- Reservoirs: Dog
- Distribution: Southeastern and South Central USA
- Incidence: May-July

Human Monocytic Ehrlichiosis (HME)



Ehrlichiosis

- **Diagnosis:**
  - **Clinical**
  - **Extremely difficult to culture**
  - **Light microscopy (limited)**
  - **PCR**
  - **Serologies**
- **Treatment: Doxycycline**

RMSF vs. Ehrlichiosis

Rash	**RMSF: 90% patients, petechial in 50%**
	HME: rash 30% and maculopapular
	HGE: rare
WBC	**Leukocytosis rare in either RMSF or Ehrlichiosis**
	Leukopenia seen in Ehrlichiosis but rare RMSF
Vasculitis	**Hallmark of RMSF; not seen Ehrlichiosis**

Borrelia

- Treponemes
- Microaerophillic with complex nutritional requirements

  Lyme Disease: ***Borrelia burgdorferi***

  Relapsing Fevers: ***B. recurrentis, B. hermsii***

Borrelia

Lyme Disease

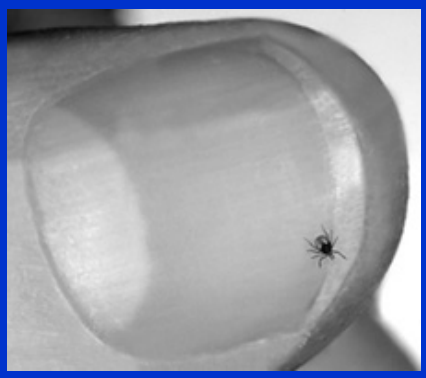
- Causative Agent: *Borrelia burgdorferi*
- Accounts for 90% of all vector born illnesses in USA
- Vector: Ixodes ticks (deer tick, stage: nymphs)

  Needs at least 24 hours to feed for transmission of treponem
- Reservoirs: White-footed mouse, white tailed deer, cattle, horses, dogs
- Throughout USA, but highest incidence Northeast

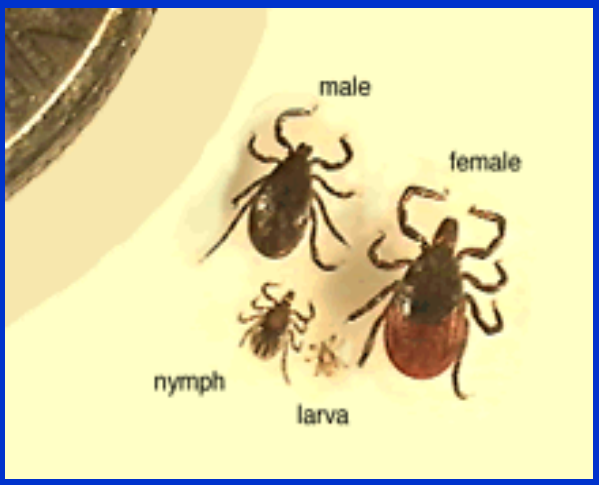
Lyme Disease

Lyme Disease

Lyme Disease



Lyme Disease



Lyme Disease

Three stages of infection:

- **Local (acute)**
- **Early Disseminated**
- **Late Disseminated (Persistent)**

Local

- **Rash: Erythema migrans (few days to one month after bite)**
  - **Migrates outward and exhibits central clearing**
  - **May occur at site of tick bite, but rash does not always correlate (hematogenous spread)**
  - **Treponemes can be isolated from rash**

Erythema Migrans

Erythema Migrans

Early Disseminated

- **Few weeks after bite, EM may still be present**
- **Cardiac**
  Heart block, myocarditis, myopericarditis
- **Musculoskeletal**
  Arthralgias and arthritis (knee common, aspirate with *Borrelia*)
- **Neurological**
  Meningitis, Bell's palsy, peripheral neuropathy, encephalitis (rare)

Early Disseminated

Facial Nerve Paralysis - Bell's Palsy

Early Disseminated Arthritis

Swollen knee of a youth with Lyme arthritis.

Late Disseminated (Persistent)

- Months to years after bite
- Chronic destructive arthritis of large joints
- End-stage cardiomyopathy
- Stroke, meningoencephalitis, dementia, neuropathies
- Acrodermatitis chronica atrophicans

Acrodermatitis chronica atrophicans

Progressive, fibrosing skin process

Extremities: usually extensor surfaces

Starts as a bluish-red discoloration

More common with European *B. afzelii*

Diagnosis

- CLINICAL!!!
- Demonstration of organism: PCR, staining
- Antibody detection (most practical)

  ELISA followed by Western Blot
  False positives
  False negatives

Treatment

- Based on stage of disease
- Local (EM), early arthritis, CNS (isolated Bell's Palsy)

  Oral therapy with doxycycline
- Disseminated (heart, CNS, chronic arthritis)

  Intravenous therapy with ceftriaxone
- Treatment of seropositive asymptomatic patients is not indicated

Tick Bite Prophylaxis

- Based on geographic location and tick characteristics
- Prophylaxis with single dose oral doxycycline indicated if:
  - Deer tick, engorged nymph
  - Endemic area
- Prophylaxis reduces incidence of EM from 3% to 0.4%

Relapsing Fever

- Two causative agents:
  - Tick-Borne Relapsing Fever
    - *Borrelia hermsii*
  - Louse-Borne Relapsing Fever
    - *Borrelia recurrentis*

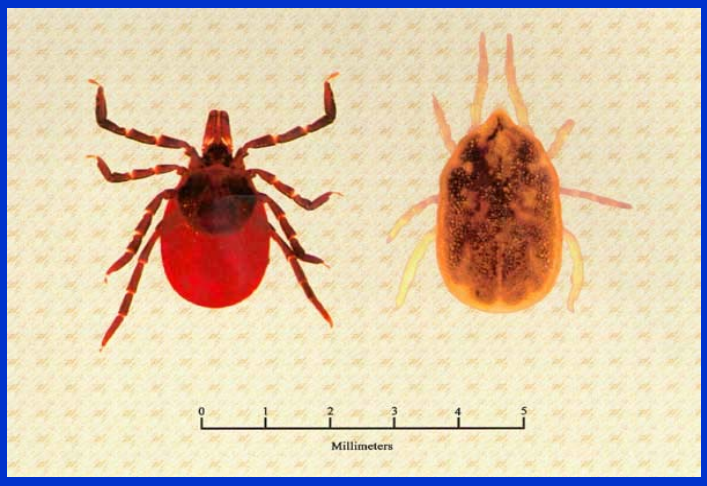
Borrelia hermsii

- **Vector: Soft ticks (*Ornithodoros)***

  High altitudes (caves, decaying wood)
  Night feeder (short feeding time: 5 minutes)
  World-wide distribution (including Western USA)

- **Reservoirs: chipmunk, squirrel, rabbit, rat, rodents**

Ixodes scapularis and *Ornithodoros hermsi* (Hard vs. Soft ticks)



Borrelia recurrentis

- **Vector: Human louse (*Pediculus humanus*)**

  Epidemic during wars and natural disasters

  South American Andes and Central and East Africa (not in USA!)

Relapsing Fever

- **Incubation: One to three weeks**
- **Onset of high fever with rigors, sever headache, myalgias, arthralgias, lethargy, and photophobia**
- **Truncal rash 1-2 duration at the end of first febrile episode (more common in tick-borne disease)**
- **Multiple relapses with tick-borne disease (louse-borne only one)**

Relapsing Fever

- Abrupt termination of primary febrile episode after 3 to 6 days
- Onset of afebrile period associated with hypotension and shock
- Relapse of fever: Tick-borne (7 days); Louse-borne (9 days)
- Relapses last 2-3 days
- Mortality of untreated disease:

  Tick-borne: 5%
  Louse-borne: up to 40%

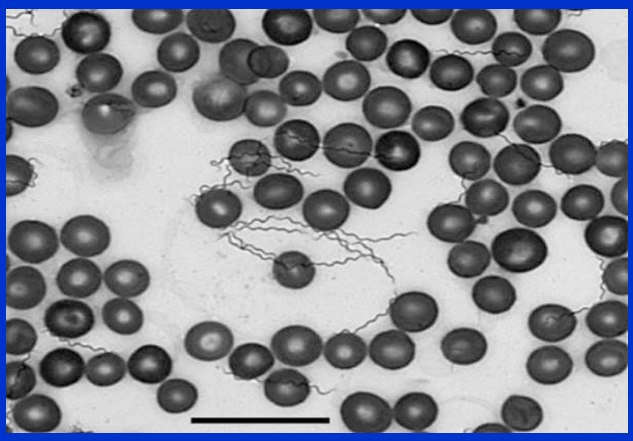
Relapsing Fever

- Diagnosis: Demonstration of spirochete on blood smear (80%)
  Need special media to culture
- Treatment:

  Tick-borne: Doxycycline 5 to 10 days
  Louse-borne: Single dose

  Monitor for Jarisch-Herxheimer reaction

Relapsing Fever



Prevention of Vector Borne Illnesses

- **AVOID EXPOSURE!**
  - **Long sleeved clothing, tuck pant legs into socks**
  - **DEET reduces risk of tick attachment**
  - **Examine for ticks and remove**
    - **Use forceps and grab tick by head and pull straight up**

Take Home Message

- **Fever, severe headache, and potential exposure**

  Do NOT wait for diagnostic tests!
  Do NOT wait for rash!

  TREAT with doxycycline!