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 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)
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
Late Stage Petechial Rash

- *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
**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

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
Epidemic Typhus

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

- Can be asymptomatic to fatal
- ARDS with septic shock-like presentation, rhabdomyolysis
- Neurological sequelae include demyelinating 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
**Ehrlichiosis**

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

- **Treatment:** Doxycycline

**RMSF vs. Ehrlichiosis**

<table>
<thead>
<tr>
<th>Rash</th>
<th>RMSF: 90% patients, petechial in 50%</th>
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<tr>
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<td>HME: rash 30% and maculopapular</td>
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<td>HGE: rare</td>
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<tr>
<th>WBC</th>
<th>Leukocytosis rare in either RMSF or Ehrlichiosis</th>
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<td>Leukopenia seen in Ehrlichiosis but rare RMSF</td>
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| Vasculitis            | Hallmark of RMSF; not seen Ehrlichiosis        |
Borrelia

- Treponemes
- Microaerophilic with complex nutritional requirements

Lyne Disease: *Borrelia burgdorferi*

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

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!)

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**Relapsing Fever**

- **Incubation:** One to three weeks
- **Onset:** High fever with rigors, severe 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!