Vector-borne Infections: Rickettsia, Ehrlichia, Anaplasma, & Borrelia

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Case 1
• Immunohistochemistry on a skin biopsy reveals *Rickettsia rickettsii*

Vector-borne Infections

- **Vector**
  - An animal, most often an arthropod, which picks up a pathogen and transmits it to a susceptible individual.
- **Reservoir**
  - An ecological niche where a pathogen lives and multiples (can serve as a source of infection)
- **Host**
  - An organism that is infected with or is fed upon by a parasitic or pathogenic organism

Rocky Mountain Spotted Fever (RMSF)

- Caused by *R. rickettsii*, a small GN bacillus
- The most severe rickettsial disease in the U.S.
- Transmitted to humans via tick bite (60% recall a bite)
- Ixodid (hard ticks) are both the reservoir and vector for RMSF
  - American dog tick or RM wood tick, depending on location
- Hosts: various mammals—depends on tick and stage of development

Case 1
• It’s June in Oklahoma. A 12 YO boy develops fever and rash.
• He was bitten by a tick 10 days ago.
• Five days later he developed the sudden onset of fever, chills, severe headache, and muscle pain.
• He then developed a rash that started on his wrists and ankles and subsequently spread inward to cover his whole body.
• He presents in multi-organ system failure and dies in the emergency room before antibiotics can be administered.

Tick Lifecycle

- Female and male ticks feed on large and medium-sized mammals and humans.
- Nymphs feed on small mammals and humans.
**History**

- 1896 - Recognized in Snake River Valley, Idaho
- “Black measles” killed 100s
- Howard T. Ricketts discovered the causative agent
- Ricketts died of typhus (another Rickettsial disease) in Mexico in 1910

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**“Rocky Mountain” is a Misnomer: most common in SE/S.Central states**

> Also has wide Geographic distribution in the Western hemisphere

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**RMSF Epidemiology**

- 90% of cases occur May—September
- Children are at the greatest risk (2/3 cases <15 YO)
- Exposure to dogs and residence in a wooded/high grass area may increase risk (↑exposure to vector)

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**Clinical Presentation**

- After ~1 week incubation: acute onset of flu-like symptoms (i.e. fever, myalgias, severe headache, malaise, nausea/vomiting)
- 2-5 days later a macular rash appears on the wrists/ankles (rash in 90-95%)
- Rash spreads centripetally (proximally) and can become maculopapular (from edema) → petechial (from hemorrhage) w/o treatment

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**RMSF in NYC**

<table>
<thead>
<tr>
<th>Borough</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manhattan</td>
<td>9</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Bronx</td>
<td>3</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

Total: 23, 7, 24

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**Late/Severe Disease**

- Full body petechial rash with palm/sole involvement
- Abdominal and joint pain
- Edema, ischemia, hypovolemia, and multi-organ system failure (from microvascular injury)
- Labs: hyponatremia, thrombocytopenia, & elevated liver enzyme levels
- Severe/fatal cases associated with: advanced age, male sex, African-American, chronic alcohol abuse, and glucose-6-phosphate dehydrogenase (G6PD) deficiency
**Pathogenesis**

- Introduction of *R. rickettsii* at the bite site
- Travels via lymphatics to the circulation where it invades endothelial cells
  - OmpA/B mediate adherence
- The organism is engulfed, but escapes the phagosome
  - Phospholipase D and tlyC lyse the membrane
- Replication in the cytosol by binary fission

**Pathogenesis**

- RickA activates host cell actin, which pushes it to the cell surface or nucleus
  - Extracellular release (to other organ systems) or
  - Cell to cell spread*
- The major pathogenic effect is increased vascular permeability resulting from the disruption of junctions between endothelial cells.

**Diagnosis**

- Clinical Suspicion
- Immunohistochemistry on a skin biopsy
- Serologic tests (IFA) and PCR available
  - results take time
- Culture and staining difficult and not recommended

**RMSF Treatment**

- Doxycycline (a tetracycline)
- Use even in children
- DO NOT DELAY TREATMENT while awaiting laboratory confirmation
- Or else…

**Case 2**

- A Columbia medical student trying to save money finds an extra-cheap rental in the neighborhood
- She develops a little bite on her upper arm
- 10 days later she gets terrible flu-like symptoms
- A diffuse macular rash develops that becomes papulovesicular
- She thinks it’s odd that she has the chickenpox again
The bite site reveals an eschar:

Her home reveals: mice!

Rickettsialpox
- Clinical presentation as per case
- Regional lymphadenopathy
- Diagnosis is clinical, but immunohistochemistry on a skin biopsy may be used
- Disease is self-limited w/o treatment
- Doxycycline may be used

Epidemic Typhus
- *R. prowazekii*
- Vector: human body louse
- Reservoir: Humans
- Humans infected after scratching infected louse species into the bite
- Outbreaks occur in crowded, unsanitary conditions

Rickettsialpox
- Etiology: *R. akari*
- Transmitted by a mite bite
- Reservoir: mice
- Most commonly recognized in NYC
Epidemic Typhus

- Serious illness, ~1 week incubation
- Fever, myalgia, severe HA, cough
- Cetrifugal rash (spreads outward), but spares the face, palms, soles
- Multiorgan system failure, fatal 5-40%
- Brill-Zinsser disease: reactivation (less severe)

Ehrlichioses

- Tickborne infections caused by members of the Anaplasmataceae family
- *Ehrlichia chaffeensis* causes Human Monocytic Ehrlichiosis (HME)
- *Anaplasma phagocytophilum* causes Human Granulocytic Anaplasmosis (HGA)
- These are very small, obligate intracellular, Gram negative bacteria that generally have a coccoid appearance
- They target either monocytes or granulocytes and are named accordingly

Epidemic Typhus

- A 65 YO avid gardener and golfer who lives in Westchester, NY presents in June with fever, myalgias, arthralgias, headache, malaise, and nausea.
- Lab tests: leukopenia, thrombocytopenia, and elevated liver enzymes
- Doxycycline is prescribed
- PCR is positive for *Anaplasma phagocytophilum* and there is a 4-fold increase in convalescent antibody titers.

Morulae, Latin for 'mulberry'

- 1994--causative agent (*Anaplasma phagocytophilum*) was recognized as distinct from *E. chaffeensis*

A little history

- Ehrlichioses first described by vets
- Human ehrlichiosis due to *Ehrlichia chaffeensis* was first described in 1987
- HGA: first recognized 1990
  - Wisconsin patient
  - intranuetoophilic inclusions
Epidemiology: An emerging pathogen
(most cases—occur April to September)

Number of Ehrlichiosis cases (caused by Ehrlichia chaffeensis) reported to CDC by state health departments, 1999-2006.

HME--Epidemiology
• S. Central, SE, mid-Atlantic states
• Vector: Ixodes ticks (hard ticks)
  – Lone Star tick (Amblyomma americanum)
• Reservoir: white-tailed deer

Number of Anaplasmosis cases reported to CDC by state health departments, 1999-2006.

Average annual reported HGE rate (per 100,000) by age group, in NY and CT, 1995-1997.
HGA--Epidemiology

- NE, mid-Atlantic, Upper Midwest, Pacific NW states + internationally
- Vector: Ixodes ticks (hard ticks) – *I. scapularis* (aka blacklegged tick or deer tick) or Western Blacklegged tick
- Reservoir: small mammals (esp. white-footed mice)

Pathogenesis

- Still being elucidated*
- Introduced via tick bite and binds to the cell membrane of target WBC
- Internalized and form clusters inside cytoplasmic vacuoles—morulae
- Key to survival is preventing fusion of the phagosome with the lysosome

Clinical Presentation

- Can be a mild illness/asymptomatic to a severe, fatal infection (up to 3%)
- Immunocompromise (HIV, asplenic, on steroids/chemotherapy) puts at risk for more severe disease

Clinical Presentation: similar to rickettsial diseases, but less likely to get a rash

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Presence/Non-Presence</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
<td>99/90%</td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
<td>97/77%</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>95/70%</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>90/64%</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>90/64%</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>79/50%</td>
</tr>
<tr>
<td>Blood smear</td>
<td></td>
<td>79/50%</td>
</tr>
<tr>
<td>Laboratory finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td>50/27%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>75/47%</td>
</tr>
<tr>
<td><em>Bacterial culture or IGM test</em></td>
<td></td>
<td>69/49%</td>
</tr>
</tbody>
</table>

*NOTE: Data are from [1], [2], [3], [4], and [5].* 

Some specifics-- Pathogenesis HGA

- Msp-2 binds to PSGL-1 (CD162), a receptor on neutrophils/granulocytes
- Bacteria stay in early endosome and acquire nutrients for replication (type 4 secretion apparatus)
- Secretes one protein, AnkA, which binds to nuclear proteins (role unclear)
- Neutrophil function disrupted—including endothelial cell adhesion and transmigration, motility, degranulation, respiratory burst, and phagocytosis.

Diagnosis and Treatment

- Clinical suspicion (fever/flu symptoms) in endemic region during tick season
- PCR—aclutely, diagnostic tool of choice
- Serologic—look for 4x rise in antibodies – Most sensitive test
- Examination of peripheral blood for morulae (very low yield)
- Treatment: Doxycycline
HME Outbreak

• 1993 Outbreak in a “Golf-oriented Retirement Community” in TN
• Wildlife reserve next door
• 11 cases
• Increased risk: tick bites, exposure to wildlife, no insect repellent, golfing, and among golfers, retrieving lost golf balls from the rough

  * NEJM Volume 333:420-425; August 17, 1995

Case 4

• His symptoms resolved on their own, but a few months later, his knee looked like this:

Case 4

• A 23 YO man camping in Lyme, CT gets a rash that looks like this:

Lyme Disease

• Etiology: *Borrelia burgdorferi*, a Gram negative spirochete
• The most common vector-borne disease in the U.S.
• Predominant in the NE
• Vector: *Ixodes* tick—usually the nymph (must feed 24+ hrs)
• Reservoir: white-footed mouse for nymphal/larval ticks and white-tailed deer for adult ticks
• Peak transmission: June, July, August

Case 4

• Because he smokes a lot of marijuana, he forgets about the rash.
• After a few weeks, he looks like this:
In 2007, 27,444 cases of Lyme disease were reported yielding a national average of 9.1 cases per 100,000 persons. In the ten states where Lyme disease is most common, the average was 24.7 cases per 100,000 persons.

**Removing the Tick per the CDC:**

- Remove a tick from your skin as soon as you notice it. Use fine-tipped tweezers to firmly grasp the tick very close to your skin. With a steady motion, pull the ticks body away from your skin. Then clean your skin with soap and warm water. Throw the dead tick away with your household trash.
- Avoid crushing the ticks body. Do not be alarmed if the ticks mouthparts remain in the skin. Once the mouthparts are removed from the rest of the tick, it can no longer transmit the Lyme disease bacteria. If you accidentally crush the tick, clean your skin with soap and warm water or alcohol.
- Don’t use petroleum jelly, a hot match, nail polish, or other products to remove a tick.

**Clinical Presentation**

- **Local:** erythema migrans
  - Early: may also have fever, flu-symptoms
- **Early neurologic disease:**
  - Meningitis or radiculopathy
  - Cranial nerve palsy
- **Cardiac disease:**
  - Heart block, myopericarditis
- **Late Disease:**
  - Arthritis, CNS or PNS disease

**Reported Clinical Findings Among Lyme Disease Patients, 1992-2004**

- 66% erythema migrans
- 22% arthritis
- 9% facial palsy
- 4% radiculopathy
- 1% meningitis
- 1% heart block
- 1% others

**I. scapularis**

- The *I. scapularis* nymphal ticks that spread *B. burgdorferi* are very small!
Pathogenesis

- *B. burgdorferi* inoculated into the skin at the bite site, multiples, and spreads outward causing the characteristic rash
- OspC variant helps determine dissemination
- Facilitating hematogenous spread:
  - OspA binds plasminogen
  - Surface proteins binding platelet-specific integrin
- DbpA & DbpB mediate binding to decorin, a peptidoglycan on the surface of collagen
  - Binding to collagen matrix in ECM of joints, heart, C/PNS
- Other surface proteins bind:
  - Heparan & dermatan sulfate (endo/epithelial cells)
  - Fibronectin (an extracellular matrix protein)
- Host Immune Response

Diagnosis

- If there is erythema migrans, diagnosis can be clinical
- Acute/convalescent antibodies
- CSF examination may be indicated
  - Lymphocytosis, elevated protein, normal glucose
- Co-infection with HGA and babesia may occur (same vector!)

History

- 1883- Skin manifestations identified by Buchwald in Breslau, Germany
- 1909- Arvid Afzelius, a Swedish dermatologist, coined the term 'erythema migrans'
- 1920s- Neuro symptoms identified
- 1930s- Connection made between EM and neuro symptoms
- 1940s- Illness associated with spirochetes
- 1949- First treated with penicillin
- 1970- First case of EM in the US
- 1975- Outbreak of what first appeared to be juvenile rheumatoid arthritis in 3 SE CT towns including Lyme and Old Lyme
  - Health Dept first contacted by 2 mothers -- Polly Murray & Judith Mensch
- 1982- Spirochete cultured from Shelter Island ticks

Treatment Essentials

- Doxycycline (or alternative) for erythema migrans
- Oral regimen may also be used for isolated Bell's palsy, mild cardiac disease, arthritis
- IV Ceftriaxone (3rd gen cephalosporin) for heart block, symptomatic cardiac disease, other PNS/CNS disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage for adults</th>
<th>Dosage for children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>100, 150, 200, 300 mg q.d.</td>
<td>100, 150, 200, 300 mg q.d.</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1 g once daily concomitant with doxycycline</td>
<td>10 mg/kg bid for 7 days</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1 g IV q.24h</td>
<td>Not recommended for children under 4 years</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>500 mg bid</td>
<td>Not recommended for children under 4 years</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg bid</td>
<td>Not recommended for children under 4 years</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg q.d.</td>
<td>2.5 mg/kg q.d. for 10 days</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>500 mg q.d.</td>
<td>Not recommended for children under 10 years</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500 mg q.d.</td>
<td>Not recommended for children under 12 years</td>
</tr>
</tbody>
</table>

\( ^{a} \) Although a higher dosage given twice per day might be equally effective, in view of the absence of data on efficacy, once daily administration is recommended.

\( ^{b} \) Tetracyclines are relatively contraindicated in pregnancy or lactating women and in children under 8 years of age.

\( ^{c} \) Because of their lower efficacy, macrolides are reserved for patients allergic to penicillins or those with severe symptoms (e.g., meningitis, endocarditis, and abscesses).
Case #5

- **Time:** May 2009
- **Place:** Sag Harbor, Long Island
- **Who:** Lilly, my 2-year old
- **What happened:** My husband found a tick on her, but it was not attached
- **What I did:** Nothing

- **Until 5 days later…**

Amoxicillin was prescribed

Common Themes in this Lecture

- Exposure to vector-reservoir
  - Time of year
  - Geographic location
  - Possible history of bite
- Clinical presentation often involves a flu-like illness and possibly a rash
- Doxycycline is often the treatment of choice!