Rickettsia, Ehrlichia, Anaplasma, & Borrelia

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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
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.

Case 1

- Immunohistochemistry on a skin biopsy reveals *Rickettsia rickettsii*
Rocky Mountain Spotted Fever (RMSF)

- Caused by *R. rickettsii*, small GN bacillus
- The most severe rickettsial disease in 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

Tick Lifecycle

- Female
  - Eggs
  - Larva
  - Nymph
  - Male

Feeds on large and medium-sized mammals and humans

Feeds on small mammals

Feeds on small and medium-sized mammals
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

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

Also has wide Geographic distribution in the Western hemisphere
RMSF in NYC

<table>
<thead>
<tr>
<th>Borough/YR</th>
<th>2004</th>
<th>2005</th>
<th>2006</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>
<tr>
<td>Brooklyn</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Queens</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Staten Island</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>7</td>
<td>24</td>
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</tbody>
</table>

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)
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

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

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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.

• *R. rickettsii* in endothelial cells in a blood vessel wall:
Pathogenesis

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!

"Every Thursday I do her nails."
Rickettsialpox

- Etiology: *R. akari*
- Transmitted by a mite bite
- Reservoir: mice
- Most commonly recognized in NYC
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
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)
Case 3

- 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.

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
Morulae, Latin for ‘mulberry’

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
  - intraneutrophilic inclusions
- 1994--causative agent (*Anaplasma phagocytophilium*) was recognized as distinct from *E. chaffeensis*
Epidemiology: An emerging pathogen (most cases—occur April to September)
Average annual reported HGE rate (per 100,000) by age group, in NY and CT, 1995-1997

HME--Epidemiology

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

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 or sign</th>
<th>Patients, % (no. evaluated)</th>
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<tbody>
<tr>
<td>Fever</td>
<td>97 (633) 93 (521)</td>
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<tr>
<td>Myalgia</td>
<td>57 (250) 77 (516)</td>
</tr>
<tr>
<td>Headache</td>
<td>80 (240) 70 (285)</td>
</tr>
<tr>
<td>Malaise</td>
<td>82 (234) 94 (268)</td>
</tr>
<tr>
<td>Nausea</td>
<td>64 (143) 38 (258)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33 (199) 26 (269)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (197) 16 (99)</td>
</tr>
<tr>
<td>Cough</td>
<td>26 (156) 10 (260)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>41 (211) 46 (604)</td>
</tr>
<tr>
<td>Rash</td>
<td>31 (286) 6 (367)</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>3 (243) 21 (348)</td>
</tr>
<tr>
<td>Confusion</td>
<td>19 (279) 17 (211)</td>
</tr>
</tbody>
</table>
| Laboratory finding
| Leukopenia      | 62 (276) 49 (286)           |
| Thrombocytopenia| 71 (247) 71 (236)           |
| Elevated serum AST or ALT level | 83 (276) 71 (177) |

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

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
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—acutely, 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

- A 23 YO man camping in Lyme, CT gets a rash that looks like this:
Case 4

• Because he smokes a lot of marijuana, he forgets about the rash.
• After a few weeks, he looks like this:

Case 4

• His symptoms resolved on their own, but a few months later, his knee looked 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
**I. scapularis**

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

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**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
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

History Continued

• 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 Morray & 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>
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<tbody>
<tr>
<td>Preferred oral regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>500 mg 3 times per day&lt;sup&gt;3&lt;/sup&gt;</td>
<td>50 mg/kg per day in 3 divided doses (maximum, 500 mg per dose)&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg twice per day&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Not recommended for children aged &lt;8 years For children aged ≥8 years, 4 mg/kg per day in 2 divided doses (maximum, 100 mg per dose)</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>500 mg twice per day</td>
<td>30 mg/kg per day in 2 divided doses (maximum, 500 mg per dose)</td>
</tr>
<tr>
<td>Alternative oral regimens&lt;sup&gt;5&lt;/sup&gt;</td>
<td>For recommended dosing regimens, see footnote d in table 3</td>
<td>For recommended dosing regimens, see footnote in table 3</td>
</tr>
<tr>
<td>Preferred parenteral regimen</td>
<td></td>
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<tr>
<td>Ceftriaxone</td>
<td>2 g intravenously once per day</td>
<td>50–75 mg/kg intravenously per day in a single dose (maximum, 2 g)</td>
</tr>
<tr>
<td>Alternative parenteral regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>2 g intravenously every 8 h&lt;sup&gt;9&lt;/sup&gt;</td>
<td>150–200 mg/kg per day intravenously in 3–4 divided doses (maximum, 6 g per day)&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>18–24 million U per day intravenously, divided every 4 h&lt;sup&gt;11&lt;/sup&gt;</td>
<td>200,000–400,000 IU/kg per day divided every 4 h&lt;sup&gt;11&lt;/sup&gt; (not to exceed 18–24 million U per day)</td>
</tr>
</tbody>
</table>

<sup>3</sup> Although a higher dosage given twice per day might be equally as effective, in view of the absence of data on efficacy, twice-daily administration is not recommended.

<sup>5</sup> Tetracyclines are relatively contraindicated in pregnant or lactating women and in children <8 years of age.

<sup>6</sup> Because of their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins.

<sup>9</sup> Dosage should be reduced for patients with impaired renal function.
**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!
Prevention is the best medicine! Prevent exposure to the vector! Use bug repellent, protective clothing, and do tick checks!