Tickborne Rickettsial Diseases

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Objectives

- Describe the epidemiologic characteristics of tickborne rickettsial diseases
- Review the clinical symptoms, diagnosis, and treatment of tickborne rickettsial diseases
- Explain how the case definitions are used to classify reported cases of tickborne rickettsial diseases
Tickborne Rickettsial Diseases (TBRD)

- Group of clinically similar but epidemiologically and etiologically distinct illnesses
  - Rocky Mountatin Spotted Fever
    - *Rickettsia rickettsii*
  - Ehrlichiosis
    - *Ehrlichia chaffeensis* and *E. ewingii*
  - Anaplasmosis
    - *Anaplasma phagocytophilum*
- Incidence of these diseases increasing in US
Epidemiology of TBRD

- Maintained in natural cycles involving wild mammals and ixodid ticks

- 90%–93% of cases are reported during April–September

- Males appear at higher risk for all TBRD

- Age incidence varies among diseases
Rocky Mountain Spotted Fever

• Disease in the spotted fever rickettsiosis group
• Most severe tickborne illness in US
• Transmitted by several tick species in US
  – American dog tick (*Dermacentor variabilis*)
  – Rocky Mountain wood tick (*D. andersoni*)
  – Brown dog tick (*Rhipicephalus sanguineus*)
• Affects dogs
  – Can develop disease with other human household members
RMSF Epidemiology

• 1997–2002
  – Estimated US average annual incidence was 2.2 cases per million
  – 56% of cases from five states
    • TN, NC, SC, OK, AR
• Highest incidence among persons <15 years
  – Peak age 5–9 years
• Household clusters of disease reported
RMSF Annual Incidence – US, 2002
Ehrlichiosis

- *Ehrlichia chaffeensis* most common
  - Human monocytotropic ehrlichiosis (HME)
- *E. ewingii* has also been identified
- Transmitted by lone star tick (*Amblyomma americanum*)
- White-tailed deer major host for tick species and natural reservoir for bacteria
- Infections in coyotes, dogs, and goats have been documented
Ehrlichiosis Epidemiology

- **2001–2002**
  - HME Average US annual incidence was 0.7 cases per million population
  - Incidence varied by state
    - Most commonly reported from MO, OK, TN, AR, MD
- Highest incidence among persons >60 years
- HME clusters have been reported
Anaplasmosis

• Human granulocytotropic anaplasmosis (HGA)
• Transmitted by blacklegged tick (*Ixodes scapularis*) and western blacklegged tick (*I. pacificus*)
  – Same vectors as Lyme disease
  – Coinfections have been reported
• Deer, elk, and wild rodents are reservoirs
Anaplasmosis Epidemiology

- 2001–2002
  - Average US annual incidence was 1.6 cases per million population
  - Highest incidence in RI, MN, CT, NY, MD, possibly WI
- Highest incidence among persons >60 years
Geographic Distribution of Tick Species for HME and HGA
Summary of TBRD Epidemiology

- RMSF and HME most commonly reported in southeastern and south central US
- HGA most commonly reported in New England, north central states, and focal areas of West Coast
- RMSF has highest incidence among children <15 years
- HME and HGA have highest incidence among adults >60 years
TBRD Clinical Signs and Symptoms

• Early signs of TBRD may be non-specific
• Overlap in initial clinical presentation of TBRD
  – Sudden onset of fever
  – Chills
  – Headache
  – Malaise
  – Myalgia
  – Nausea, vomiting, anorexia
RMSF Clinical Information

- Onset occurs about 5–10 days after tick bite
- Infects endothelial cells
- Small vessel vasculitis
  - Maculopapular or petechial rash
  - Vasculitis in organs can be life-threatening
- Rash typically appears 2–4 days after onset of fever
RMSF Rash Appearance

- Occurs earlier in children than adults
- ~90% of children will get rash
- Small, blanching, pink macules on ankles, wrists, or forearms
- Evolves to maculopapules or petechiae
- Can include palms and soles
- Limited presentation on face
Photo/G.S. Marshall, University of Louisville School of Medicine, Louisville, KY
Ehrlichiosis Clinical Information

- Onset occurs 5–10 days after tick bite
- Infects leukocytes
  - *E. chaffeensis* prefers monocytes
  - *E. ewingii* prefers granulocytes
  - Morulae can be identified
- Rash observed ~33% of patients with HME
  - Vary from petechial or maculopapular to diffuse erythema
  - Occurs later in disease
- Rash rarely seen with *E. ewingii* infections
Anaplasmosis Clinical Information

• Onset occurs about 3 weeks after tick bite
• Infects leukocytes
  – Prefers granulocytes
  – Morulae can be identified
• Rash rarely seen
TBRD Treatment

• All agents of TBRD susceptible to tetracycline-class antibiotics
  – Doxycycline is drug of choice for children and adults

• RMSF and HME
  – Treat for 3 days after fever subsides
  – Standard duration of 5–10 days

• HGA
  – Treat for 10–14 days
TBRD Diagnosis

• Clinical symptoms
• History of tick bite or tick exposure
  – Recreational or occupational exposures
  – Recent travel
• Similar illness in family members, coworkers, pet dogs
• Laboratory tests
  – CBC, metabolic panel
• Diagnostic tests
Laboratory Findings

• Common to all TBRD
  – Thrombocytopenia
  – Elevated hepatic transaminases

• RMSF
  – Hyponatremia

• Ehrlichiosis and Anaplasmosis
  – Leukopenia
Diagnostic Tests — General

• Rapid confirmatory tests not commonly available
• Laboratory confirmation
  – Retrospectively validates clinical diagnosis
  – Important to understanding epidemiology and public health impact
• Treatment should not be delayed
Diagnostic Tests

• Blood Smear Microscopy
  – Identify morulae in circulating cells
  – Not useful for RMSF

• Nucleic acid detection or PCR
  – Skin biopsy or autopsy tissue

• Immunohistochemical (IHC) staining
  – Skin biopsy or autopsy tissue

• Cell culture
  – RMSF is Biosafety Level-3 (BSL-3) agent
Serologic Testing

• Principle diagnostic tool for TBRD
• Paired serum samples 2–3 weeks apart is most appropriate approach for TBRD confirmation
• Indirect immunofluorescence (IFA) assay
  – Gold standard of serologic testing
  – Sensitivity depends on timing of specimen collection
• ELISA also used but cannot monitor changes in antibody titer
RMSF Testing

• Serologic testing with IFA available at CAMC for free
  – Providers should call DIDE for approval
  – Clinically appropriate specimens
    • Have clinical evidence of infection
  – Paired serum samples needed to confirm diagnosis
CAMC Testing Criteria

- Specimens taken <7 days from illness onset will be held for 45 days
  - Will not be tested if convalescent specimen not received within 45 days

- Specimens taken ≥7 days will be tested immediately
  - Strongly recommend convalescent specimen sent for testing
TBRD Surveillance

• All TBRD are nationally notifiable diseases
  – RMSF – 1989
  – Ehrlichiosis and Anaplasmosis – 1998
• West Virginia surveillance
  – All TBRD are reportable to LHD in 1 week
• TBRD case definitions
  – Clinical evidence
  – Laboratory criteria
RMSF Case Definition — Clinical Evidence

• Any reported fever and one or more of the following:
  – Eschar
  – Rash
  – Headache
  – Myalgia
  – Anemia
  – Thrombocytopenia
  – Hepatic transaminase elevation
RMSF Case Definition — Laboratory Criteria

• Confirmed
  – Serological evidence of fourfold change in IgG by IFA among paired serum specimens
  – *R. rickettsii* DNA detected by PCR assay
  – *R. rickettsii* antigen by IHC in biopsy or autopsy specimen
  – Isolation of *R. rickettsii* in cell culture

• Supportive
  – Increased serum IgG or IgM by IFA, ELISA, or latex agglutination
RMSF Case Definition

• Confirmed
  – Clinical evidence and confirmatory laboratory results

• Probable
  – Clinical evidence and supportive laboratory results

• Suspect
  – Laboratory results but no clinical information
Four Sub-Categories of Erhlichiosis/Anaplasmosis

- *Ehrlichia chaffeensis* infection (HME)
- *Ehrlichia ewingii* infection
- *Anaplasma phagocytophilum* infection (HGA)
- Ehrlichiosis/Anaplasmosis, human, undetermined
Ehrlichioses Case Definition — Clinical Evidence

• Any reported fever and one or more of the following
  – Headache
  – Myalgia
  – Anemia
  – Leukopenia
  – Thrombocytopenia
  – Any hepatic transaminase elevation
**E. Chaffeensis** Laboratory Criteria

- **Confirmed**
  - Fourfold change in IgG by IFA in paired serum samples
  - Detection of DNA by PCR
  - Demonstration of antigen by IHC in biopsy or autopsy sample
  - Isolation of bacteria by cell culture
- **Supportive**
  - Elevated IgG or IgM by IFA, ELISA, dot-ELISA or other formats
  - Morulae identification by blood smear microscopic examination
**E. chaffeensis** Case Definition

- **Confirmed**
  - Clinical evidence and confirmatory laboratory results
- **Probable**
  - Clinical evidence and supportive laboratory results
- **Suspected**
  - Laboratory evidence but no clinical information available
E. ewingii Laboratory Criteria

- **Confirmed**
  - Only diagnosed by molecular detection methods
  - *E. ewingii* DNA detected by PCR

- **Supportive**
  - Not applicable
E. ewingii Case Definition

• Confirmed
  – Clinical evidence and confirmatory laboratory results

• Probable
  – Not applicable

• Suspected
  – Not applicable
Anaplasmosis Case Definition — Clinical Evidence

• Any reported fever and one or more of the following
  – Headache
  – Myalgia
  – Anemia
  – Leukopenia
  – Thrombocytopenia
  – Any hepatic transaminase elevation
Anaplasmosis Case Definition — Laboratory Criteria

• Confirmed
  – Fourfold change in IgG by IFA in paired serum samples
  – Detection of DNA by PCR
  – Demonstration of antigen by IHC in biopsy or autopsy sample
  – Isolation of bacteria by cell culture

• Supportive
  – Elevated IgG or IgM by IFA, ELISA, dot-ELISA or other formats
  – Morulae identification by blood smear microscopic examination
Anaplasmosis Case Definition

• Confirmed
  – Clinical evidence and confirmatory laboratory results

• Probable
  – Clinical evidence and supportive laboratory results

• Suspected
  – Laboratory evidence but no clinical information available
Ehrlichiosis/Anaplasmosis, Undetermined

• Cases can only be reported as probable
  – Weakly supported by laboratory results
• Cases have clinical evidence with laboratory evidence of Ehrlichia/Anaplasmosis
  – Cannot be definitively placed in one of the previously described categories
Summary of TBRD

• Numerous tick species that transmit TBRD
• Some differences among TBRD in incidence, geographic distribution, and clinical appearance
• Treatment is similar for TBRD
• Diagnosis can be difficult
  – Patient history important
• Serologic testing is most appropriate method to diagnose TBRD
• TBRD reportable nationally and in WV