National Center for Emerging and Zoonotic Infectious Diseases

Tickborne Diseases of the United States

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ProMED yesterday

ANAPLASMOSIS, LYME DISEASE, BABESIOSIS - USA (MAINE): INCREASED CASES

A ProMED mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

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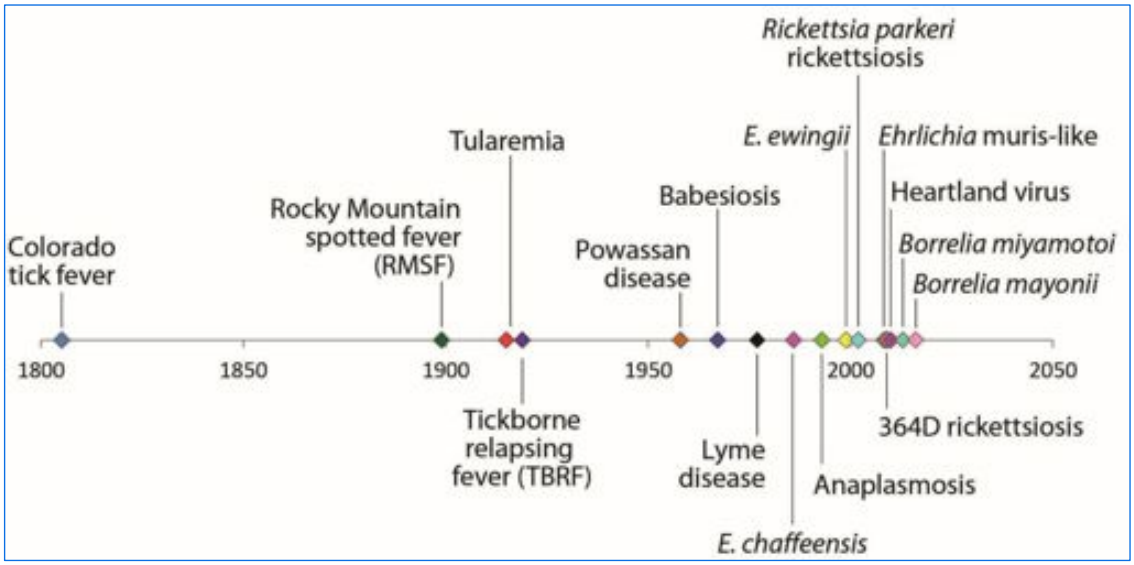
Source: Portland Press Herald [edited]
<http://www.pressherald.com/2017/11/13/anaplasmosis-cases-surging-in-maine/>

Reported cases of a tick-borne disease are swelling in Maine this year [2017], but it's not Lyme disease. Cases of anaplasmosis, an illness with flu-like symptoms that are similar to Lyme but typically more severe, have jumped from 52 a year in Maine 5 years ago to 433 this year, through [24 Oct 2017], according to the Maine Center for Disease Control and Prevention. Of this year's 433 cases, 113 were hospitalized, according to Maine CDC statistics.

Objectives

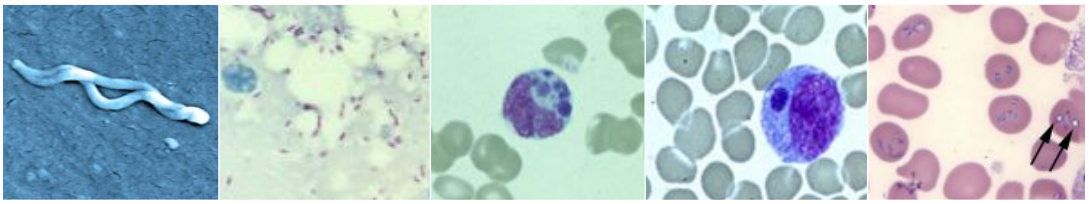
- Discuss the geographic distribution of Lyme disease, Southern tick-associated rash illness (STARI), Rocky Mountain spotted fever, Ehrlichiosis, Anaplasmosis, Babesiosis, and Powassan.
- Explain the signs and symptoms of tickborne diseases.
- Describe the appropriate use of serologic tests for confirming diagnoses of tickborne diseases.
- State the appropriate use of antibiotics in treatment of tickborne diseases.

Emerging Tickborne Diseases

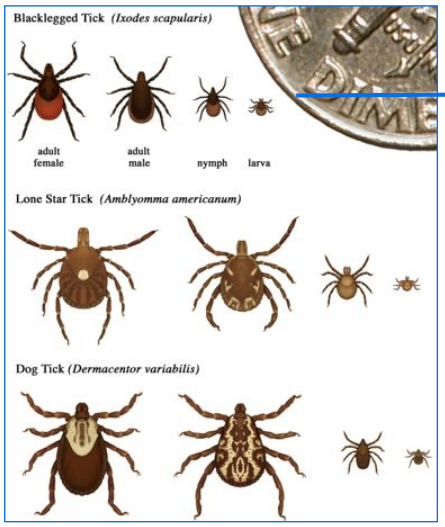


Leading Tickborne Diseases in US

- Lyme disease (*Borrelia burgdorferi*)
- Rocky Mountain spotted fever (*Rickettsia rickettsii*)
- Ehrlichiosis (*Ehrlichia chaffeensis,* others)
- Anaplasmosis (*Anaplasma phagocytophilum*)
- Babesiosis (*Babesia microti*)



Selected Tick Vectors



Transmit pathogens that cause the following diseases:

Lyme disease
Anaplasmosis
Babesiosis
Powassan virus disease
Borrelia miyamotoi disease

Ehrlichiosis
STARI
Tularemia

Rocky Mtn. Spotted Fever
Tularemia

Blacklegged tick (*Ixodes scapularis*)

- Lyme
- Anaplasmosis
- Babesiosis
- Powassan

Lone star tick (*Amblyomma americanum*)

- Ehrlichiosis
- Heartland
- STARI

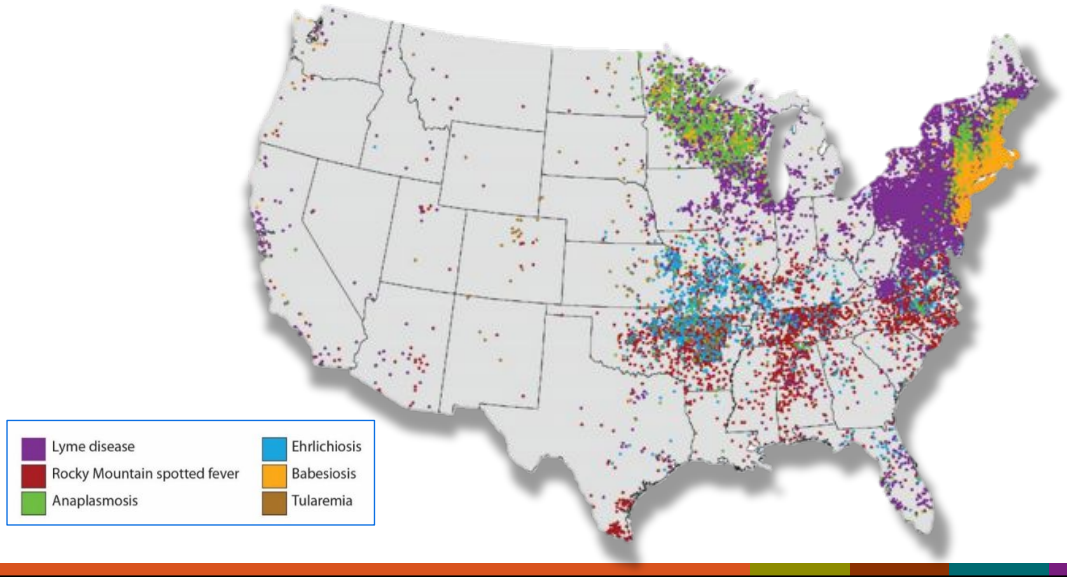
American dog tick (*Dermacentor variabilis*)

- Tularemia
- Rocky Mountain spotted fever

Brown dog tick (Rhipicephalus sanguineus)

- Rocky Mountain spotted fever

Distribution of Key Tickborne Diseases

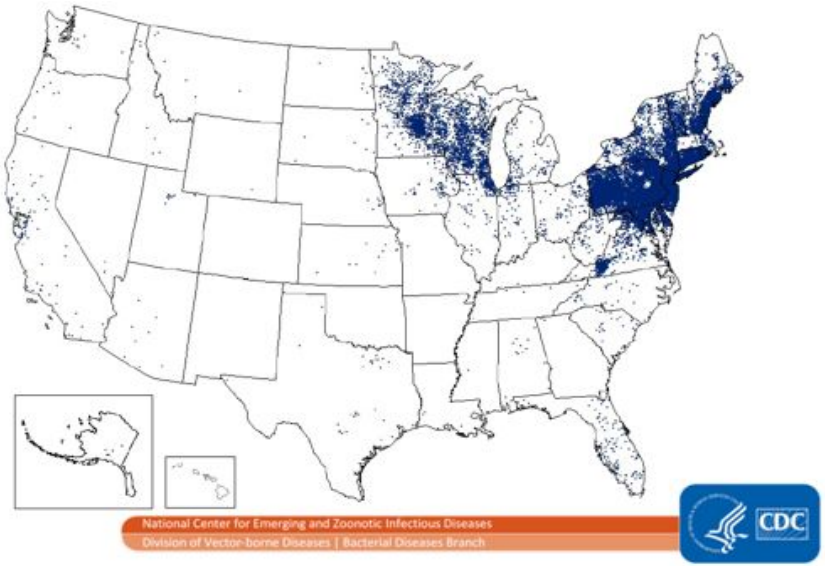


Lyme Disease

Lyme Disease

- Caused by spirochete *Borrelia burgdorferi* (and newly discovered *Borrelia mayonii*)
- Occurs in areas of North America, Europe, and Asia
- ~30,000 cases reported annually in US
- Transmitted in US by blacklegged ticks

Reported Lyme Disease Cases, 2016



Diseases reported to CDC by county of residence.

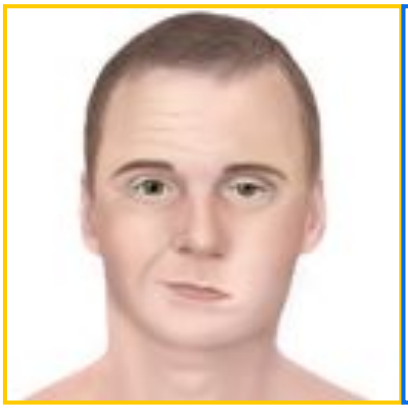
Erythema Migrans (EM)

- 70-80% of cases
- ~7-14 days after tick bite
- Expands over days
- Rarely painful
- Distinguish from allergic reaction

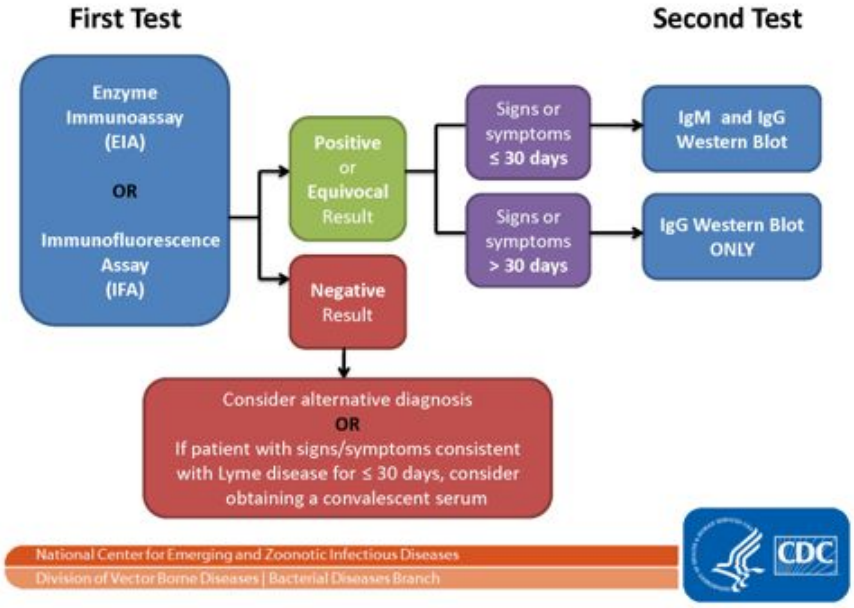
Atypical EM Presentations

Disseminated and Late Lyme Disease

- Facial palsy
  - Summer months
  - May be bilateral
- Meningitis
- Arthritis
  - Intermittent
  - Oligoarticular
- Late-stage neurologic
  - Peripheral neuropathy



Two-Tiered Testing for Lyme Disease



Sensitivity of Two-Tiered Serologic Testing

Lyme Disease Stage	Sensitivity (%)
EM rash (acute)	38
EM rash (convalescent)	67
Early neurologic	87
Late neurologic	100
Arthritis	97

Bottom line:

- Good in later stages of disease
- Testing of patients with EM and exposure in an endemic area is not generally necessary

Treatment

AGE CATEGORY	DRUG	DOSAGE	MAXIMUM	DURATION, DAYS (RANGE)
Adults	Doxycycline	100 mg, twice per day orally	N/A	14 (14–21)
	Cefuroxime axetil	500 mg, twice per day orally	N/A	14 (14–21)
	Amoxicillin	500 mg, three times per day orally	N/A	14 (14–21)
Children	Amoxicillin	50 mg/kg per day orally, divided into 3 doses	500 mg per dose	14 (14–21)
	Doxycycline	4 mg/kg per day orally, divided into 2 doses	100 mg per dose	14 (14–21)
	Cefuroxime axetil	30 mg/kg per day orally, divided into 2 doses	500 mg per dose	14 (14–21)

Prognosis

- Most patients treated with antibiotics recover completely
- In patients with persistent or recurrent joint swelling, re-treatment with a second 4-week course may be needed
- Some patients – particularly those diagnosed with later stages of disease – may have persistent symptoms of fatigue, muscle aches, reduced concentration
  - Preferred term for this is Post-treatment Lyme Disease Syndrome (PTLDS)
  - Placebo-controlled trials have not shown a sustained benefit of extended antibiotic treatment

Antibiotic prophylaxis for patients with a tick bite

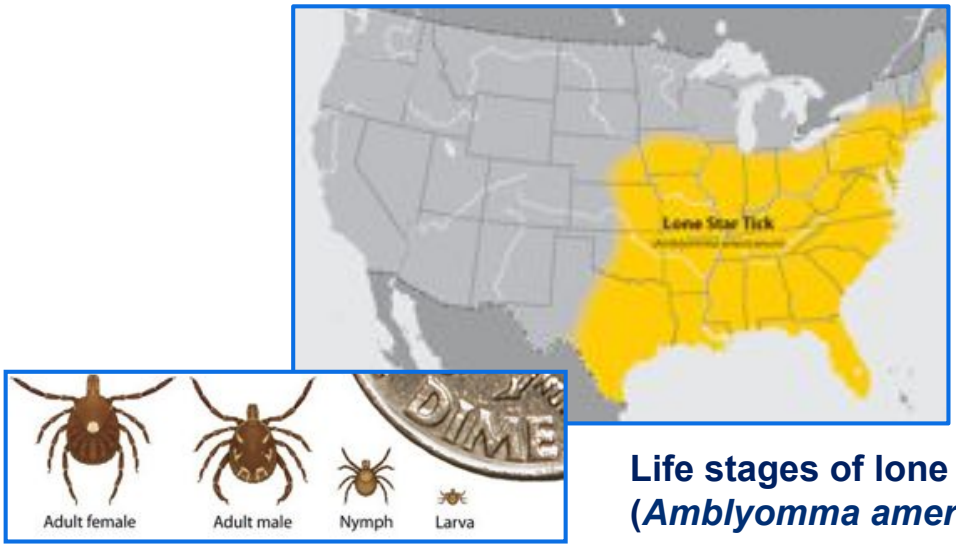
- Single dose of doxycycline for prevention of Lyme disease when all of the following conditions are met:
  - Highly endemic area
  - Attached tick identified as an adult or nymphal *I. scapularis*
  - Tick attached for > 36 hours based on engorgement or history
  - Prophylaxis can be started within 72 hrs. of tick removal
  - Doxycycline treatment is not contraindicated
- Dose = 200 mg po x 1 for adults

From: The Clinical Assessment, Treatment and Prevention of Lyme disease, human granulocytic anaplasmosis and babesiosis: Clinical practice guidelines from the Infectious Diseases Society of America; CID; 2006

STARI or Lyme Disease?

- Southern tick-associated rash illness (STARI)
  - Rash indistinguishable from Lyme disease EM
  - May be accompanied by fatigue, fever, headache, muscle and joint pains
  - Follows bite of lone star tick, *Amblyomma americanum*
- Also known as Master's disease
- Cause of STARI is not known

Southern Tick-associated Rash Illness (STARI)



Life stages of lone star tick (*Amblyomma americanum*)

Treatment of STARI

- It is not known whether antibiotic treatment is necessary or beneficial for patients with STARI
- STARI has not been linked to arthritis, neurologic disease, or chronic symptoms
- Nevertheless, because STARI resembles early Lyme disease, physicians will often treat patients with oral antibiotics

Rickettsial Diseases

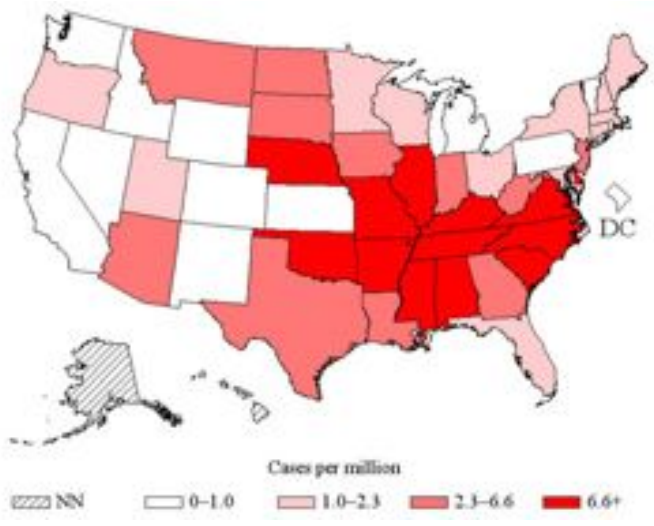
Tickborne Rickettsial Diseases

- Some are rapidly progressing and may be fatal
- Nonspecific early clinical signs make them difficult to diagnose
- Increasing incidence

But…

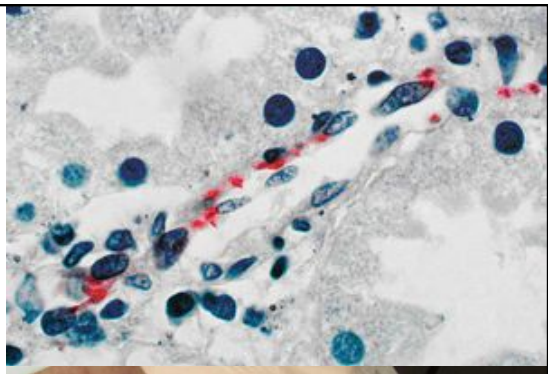
- Are all treated with doxycycline
- Use similar laboratory methods for diagnostic confirmation

Incidence for Spotted Fever Rickettsiosis in the United States for 2014



Rocky Mountain spotted fever

- Causative organism is *Rickettsia rickettsii*
  - Gram negative intracellular bacterium
  - Primarily infects vascular endothelial cells



Three Tick Vectors

Brown Dog Tick

Rocky Mountain Wood Tick

American Dog Tick

Early Illness (Days 1-4)

- **Signs and Symptoms**
  - Non-specific
    - Abrupt onset of high fever
    - Headache, myalgia, and malaise

- **Laboratory Indicators**
  - Often within normal limits
    - White blood cell (WBC) count
    - Hepatic transaminases
    - Platelets
    - Electrolytes

Early Rash

Never wait for the rash to begin treatment

Doxycycline is the recommended treatment of choice for all age groups and is most effective at preventing severe illness and death if administered within the first 5 days of symptoms

Illness onset days 5-7

- **Signs and Symptoms**
  - High fever
  - Worsening abdominal pain
    - Can mimic appendicitis or cholecystitis
  - Worsening respiratory status
  - Rash becomes petechial and more widespread
  - CNS manifestations (coma)

- **Laboratory Indicators**
  - ↑ Transaminases
  - ↓ Platelets
  - ↓ Sodium

Progression of Rash

Illness onset days 7-9

- **Signs and Symptoms**
  - Septic shock
  - Cerebral edema
  - Pulmonary edema (ARDS)
  - Myocarditis and cardiac arrhythmias
  - Coalescent rash forming purpura
  - Necrosis of digits and peripheral gangrene

- **Laboratory Indicators**
  - ↑ WBC
  - ↓ Platelets
  - ↑ Creatinine, CK, Lactic acid

20-25% of untreated cases of RMSF will be fatal with most deaths occurring within the 7th to 9th day of illness

Sequelae

- Necrosis necessitating amputation
- Profound neurologic deficits (especially in children)
- Permanent organ damage

Doxycycline in Pediatric Patients

- In 1970, FDA placed a warning label on all tetracycline-related medications, including doxycycline
  - Believed to be associated with enamel hypoplasia and tooth discoloration
  - Mortality rate in children < 10 years of age is 5 times higher than adults

Doxycycline and Tooth Staining, Arizona

- 2013 Study examined the erupted teeth of 58 children who received doxycycline before 8 years old
  - NO staining or hypoplasia, even with multiple courses
  - NO significant difference in objective tooth shade between exposed and unexposed children
- CDC and the American Academy of Pediatrics (AAP) recommend doxycycline as first line treatment for suspected RMSF in children

Treat Early!

- Delay in treatment is the single most important predictor of fatal outcome
  - Doxycycline within the first 5 days of illness reduces mortality

Doxycycline: Dosing

- Dosing:
  - Adult or Child ≥ 45 kg: 100 mg twice daily
  - Child < 45 kg: 2.2 mg/kg/day twice daily
  - Pregnant adult or tetracycline allergy: consult infectious diseases specialist, in severe cases doxycycline may be warranted
- Duration of treatment: 5-7 days (or 3 days past defervescence)

Key Take Home Points

- **Treat early (day 5 or earlier)**
- **Do not wait for rash**
- **Early clinical signs and symptoms can be non-specific**
- **Doxycycline is the treatment of choice in all age groups**

Other Pathogenic Tickborne Spotted Fever Rickettsioses

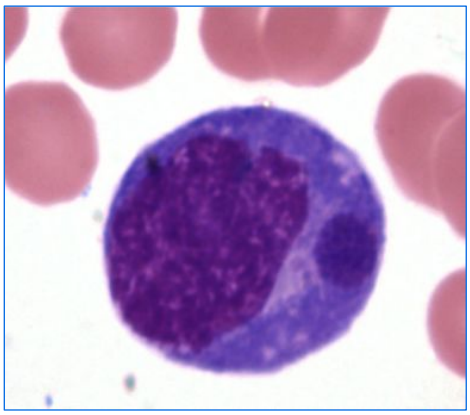
- ***Rickettsia parkeri* rickettsiosis:**
  - Transmitted by *A. maculatum*
  - Southeastern United States
  - Eschar-associated, febrile illness, no fatal cases

- ***Rickettsia* species 364D rickettsiosis:**
  - Transmitted by *D. occidentalis*
  - All cases have been reported out of California
  - Eschar-associated, febrile illness, no fatal cases
  - Rash not reported in few described cases

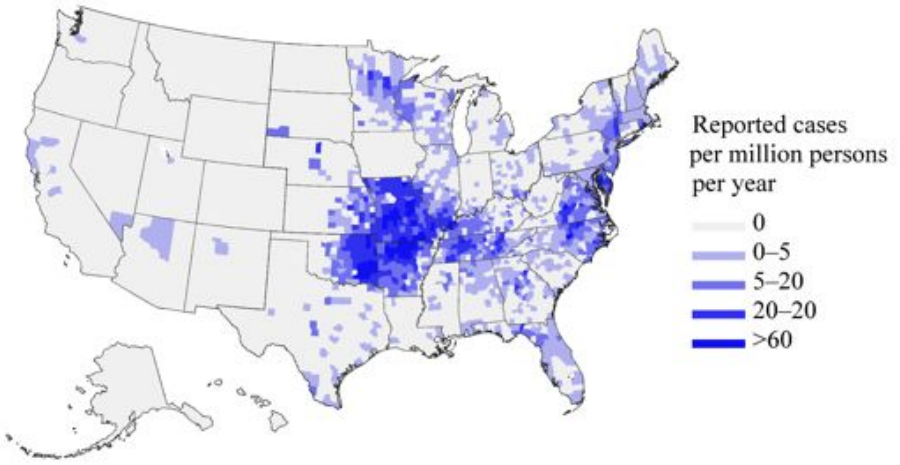
Ehrlichiosis

Ehrlichiosis

- Most commonly caused by *Ehrlichia chaffeensis* in United States
- Obligate intracellular bacteria which infect the peripheral blood leukocytes



Incidence of *Ehrlichia chaffeensis*, 2000-2013



NOTE: Incidence based on national surveillance data, 2000-2013

Symptoms—Ehrlichiosis

- Fever / chills
- Headache / malaise
- Muscle pain
- Nausea / vomiting / diarrhea
- Confusion
- Rash
  - In up to 60% of children, less than 30% of adults
- Thrombocytopenia, leukopenia and elevated liver enzymes

Severe clinical presentation may include multiple organ failure, septic shock, or respiratory failure.

Other Ehrlichial Species

- *Ehrlichia ewingii*
  - Primarily reported out of Missouri, Arkansas Indiana
  - Transmitted by *A. americanum*
- *Ehrlichia muris eauclairensis*
  - First case confirmed in 2011
  - Suspected transmission by *I. scapularis*
  - Wisconsin and Minnesota

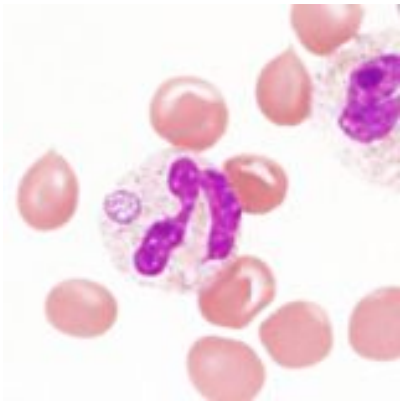
Treatment: Ehrlichiosis

AGE CATEGORY	DRUG	DOSAGE	MAXIMUM	DURATION (DAYS)
Adults	Doxycycline	100 mg twice per day, orally or IV	100 mg/dose	Patients should be treated for at least 3 days after the fever subsides and until there is evidence of clinical improvement. Minimum course of treatment is 5–7 days.
Children weighing <100 lbs. (45.4 kg)	Doxycycline	2.2 mg/kg per dose twice per day, orally or IV	100 mg/dose	

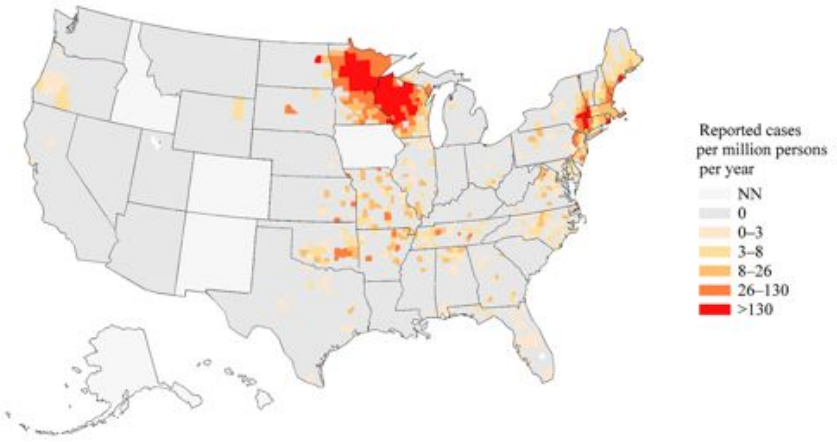
Anaplasmosis

Human Granulocytic Anaplasmosis (HGA)

- Etiologic agent = *Anaplasma phagocytophilum*
- Small, gram-negative, intracellular bacterium
- Infects granulocytes
- Organisms multiply to form microcolonies known as morulae



A. phagocytophilum Anaplasmosis Incidence — United States, 2008–2012



Dahlgren, F. S., Heitman, K. N., Drexler, N. A., Massung, R. F., & Behravesh, C. B. (2015). Human Granulocytic Anaplasmosis in the United States from 2008 to 2012: A Summary of National Surveillance Data. The American Journal of Tropical Medicine and Hygiene, 93(1), 66–72. http://doi.org/10.4269/ajtmh.15-0122

Vectors for *A. phagocytophilum*

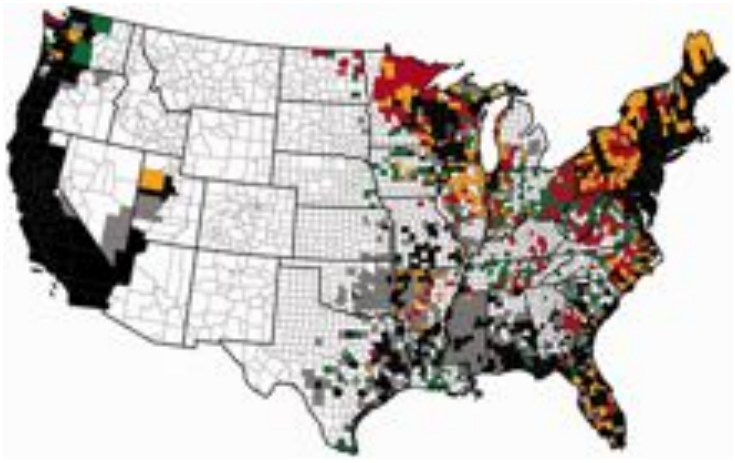
- *Ixodes scapularis* main vector in the Northeast and Midwest

- *Ixodes pacificus* main vector along the West Coast

Expansion of *Ixodes scapularis* and *I. pacificus*

- Dennis et al. (1998) documented *I. scapularis* and *I. pacificus* in 1,058 counties in 41 states.
- Eisen et al. (2016) updated previous study
  - Now recorded in 1,531 counties in 43 states
  - 44.7% increase in number of established counties
  - First recorded presence in Nebraska and North Dakota
  - *I. scapularis* now established in Kentucky, North Dakota, Ohio

Expansion of *Ixodes scapularis* and *I. pacificus*



What's driving this expansion?

- Second growth woodland with dense underbrush
  - Favorable temperature and humidity conditions for ticks
  - Also favorable for white-tailed deer
- Extensive deforestation and deer hunting during 18th and 19th centuries followed by reforestation and increases in white-tailed deer populations
  - Ticks → white-tailed deer

Slide courtesy of Anne Straily

Coinfections

- *Ixodes scapularis* and *Ixodes pacificus* also primary vectors
  - *Borrelia burgdorferi* (Lyme Disease)
  - *Babesia microti* (babesiosis)
- Simultaneous infection of *A. phagocytophilum* and *B. burgdorferi* or *B. microti* have occurred
  - <10% of Lyme disease patients have confirmed anaplasmosis infection

Treatment: Anaplasmosis

AGE CATEGORY	DRUG	DOSAGE	MAXIMUM	DURATION (DAYS)
Adults	Doxycycline	100 mg twice per day, orally or IV	100 mg/dose	Patients with suspected anaplasmosis infection should be treated with doxycycline for 10-14 days to provide appropriate length of therapy for possible incubating co-infection with Lyme disease
Children weighing <100 lbs. (45.4 kg)	Doxycycline	2.2 mg/kg per dose twice per day, orally or IV	100 mg/dose	

Diagnosis: Rickettsial Diseases

- Molecular diagnostics (whole blood, biopsy)
  - Highest yield: 3-4 days
  - Sensitivity can be low
    - New assays with improved detection
- Serology (serum)
  - Demonstration of a four-fold change in IgG-specific antibody titer by indirect immunofluorescence antibody (IFA) assay in paired serum samples
    - Acute: first week
    - Convalescent: 2 to 4 weeks later
- Immunohistochemical (IHC) staining of organism from skin or tissue biopsy specimen

Babesiosis

Babesiosis by county of residence, 2014

Babesiosis

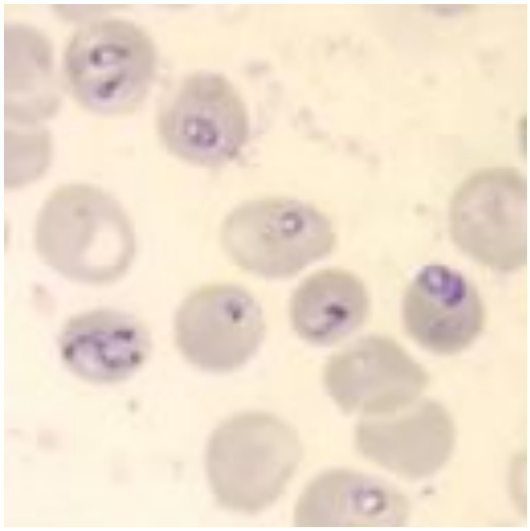
- Caused by *Babesia microti* parasite
  - Infect and destroy red blood cells → hemolytic anemia
- Many people are asymptomatic, others develop flu-like symptoms

High-risk populations

- Asplenic
- Immunocompromised
- Other serious health conditions (liver or kidney disease)
- Elderly

Diagnosis

- Peripheral blood smear
- Reference serology or molecular can also be performed

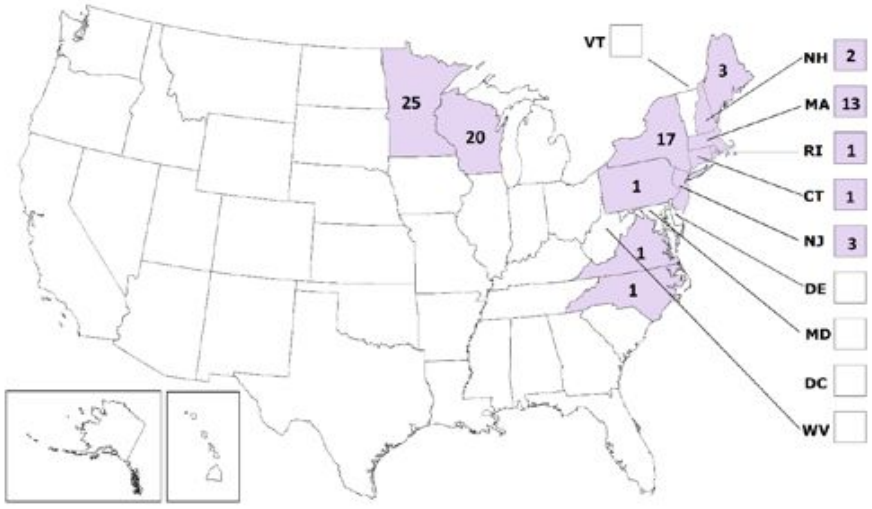


Treatment

- Asymptomatic patients do not require treatment
- Ill patients:
  - Atovaquone 750 mg PO BID
  - PLUS Azithromycin (500-1000 mg Day 1, 250-1000mg Days 2+)

Powassan

Powassan Virus Neuroinvasive Disease, 2007–2016



Clinical

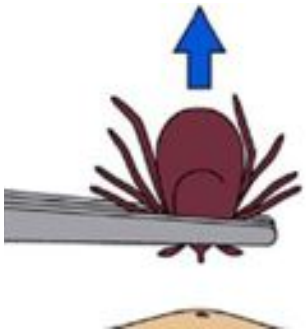
- Incubation period: 1 week to 1 month
- Encephalitis and meningitis
- Symptoms include: fever, headache, vomiting, weakness, confusion, loss of coordination, speech difficulties, and seizures
- Approximately half of survivors have permanent neurological symptoms, such as recurrent headaches, muscle wasting and memory problems
- Approximately 10% of POW virus encephalitis cases are fatal

Treatment

- Supportive care

Prevention – Talk About It!

- Avoid tick habitat
- Use DEET and wear permethrin-treated clothing
- After being outdoors:
  - **Tumble clothes in the dryer on high heat for 5-10 min**
  - Shower within 2 hrs – washes away unseen nymphs
- Daily tick checks – remove attached ticks ASAP
- Treat pets appropriately for ticks year-round



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Additional Tests: Questionable Utility

- Single-tier Western blot tests without a previous EIA
- In-house criteria for interpretation of Western blots
- Capture assays for antigens in urine
- Tests for "cystic forms" of *B. burgdorferi*
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- Novel culture techniques

More info on www.cdc.gov/Lyme