1

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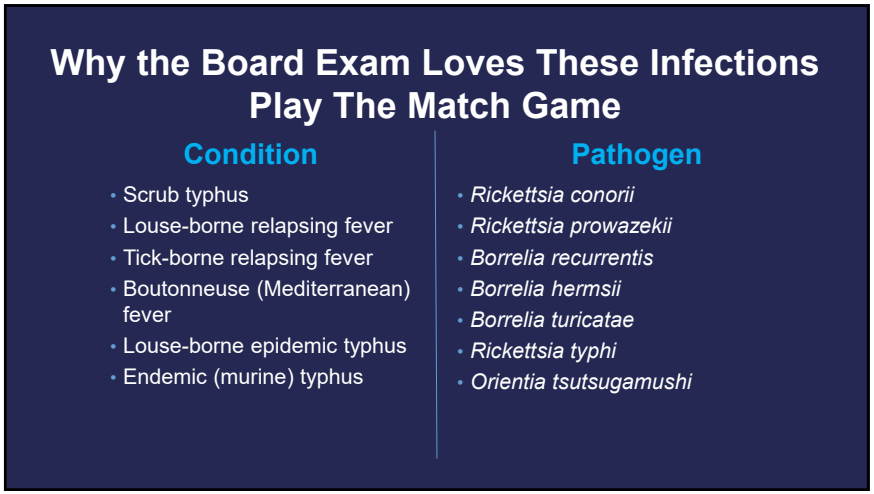

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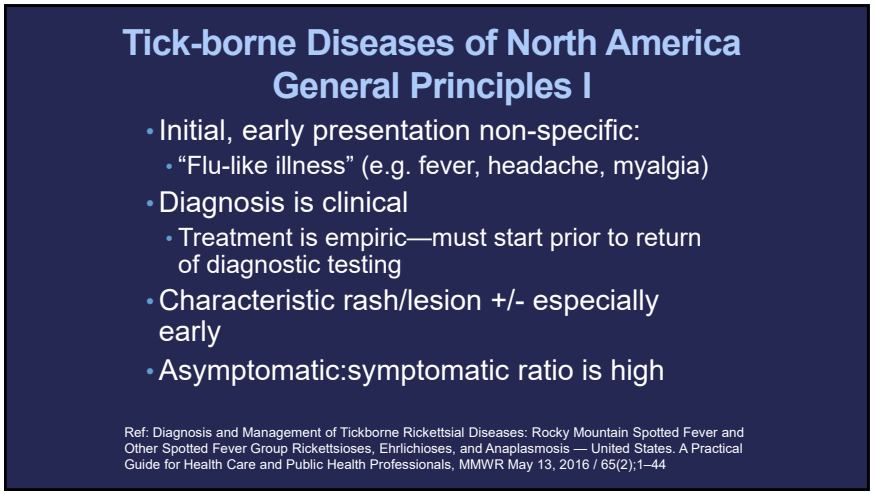


5

Tick-borne Diseases of North America General Principles II

- Seasonal but not always
- Geography informs etiology but often changes over time
- Lab tip-offs:
  - Thrombocytopenia
  - Leukocytosis or leukopenia
  - Elevated LFTs
- Doxycycline is preferred therapy for most
  (all ages including children, e.g., Lyme, RMSF, ehrlichiosis…)
- Prognosis is worse at age extremes < 10 and > 60 yrs
- Tick vectors
  - Ticks cause 95% of vector borne disease in the US
  - Co-infections in some patients

6

The Major Tick-borne Diseases of North America

- Lyme disease (separate talk)
- Rocky Mountain spotted fever (RMSF)
- Ehrlichioses
- Anaplasmosis
- Relapsing fever (*Borrelia* spp.)
- Babesia spp.

7

Other Tick-borne Diseases of North America

- Tick paralysis
- Southern tick associated rash illness (STARI)
- Viruses:
  - Powassan (Deer Tick Virus Lineage II, flavivirus)
  - Colorado tick fever (coltivirus)
  - Heartland virus (phlebovirus)
  - Bourbon virus (thogotovirus)
- Spotted Fever Group Rickettsia (partial)
  - R. parkeri
  - R. rickettsii subsp. californica
- Coxiella burnetti
- Tularemia
  - (< 10% tickborne)
- Other Borrelia
  - B. miyamotoi
  - B. mayonii

8

Ticks: Arachnids, Not Insects

- **Number of species**
  - **>900 species or subspecies worldwide**
    - **90 species in North America, handful cause most human infections**
- **Hematophagous arthropods**
  - **parasitize every class vertebrates ≅ entire world**
- **Two major families**
  - **Ixodidae, >700 species (hard ticks, attach & engorge)**
  - **Argasidae, >190 species (soft ticks, bite multiply & briefly)**
- **Four basic life stages**
  - **egg → larva → nymph → adult**
- **Vectors of human disease**
  - **#1 mosquitos**
  - **#2 ticks**

Parola, Raoult CID 2001; 32:897-928
Guglielmone, Zootaxa 2010;2528:1-28
Eisen, Ticks Tick Borne Dis 2022;12(6):102025

9

Top Ticks in North American That Transmit Human Pathogens (Ixodidae)

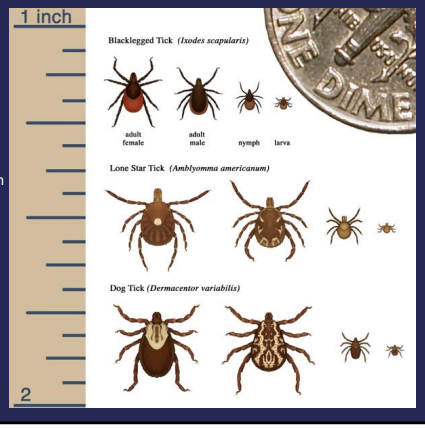
#1 Ixodes scapularis
Black-legged tick

#2 Amblyomma americanum
Lone star tick

#3 Dermacentor variabilis
Dog tick

#4 Ixodes pacificus
Western black-legged tick

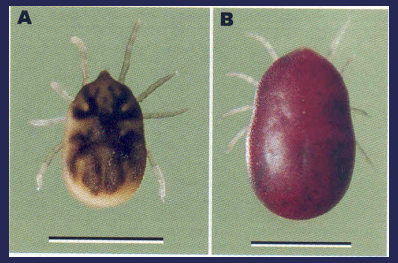
#5 Dermacentor andersoni
Rocky Mt wood tick



Eisen, Ticks Tick Borne Dis 2022;12(6):102025

10

Ornithodoros Hermsi nymphal Tick
Soft tick (Argasidae)



A: shows the nymph before its infective blood meal (from California)

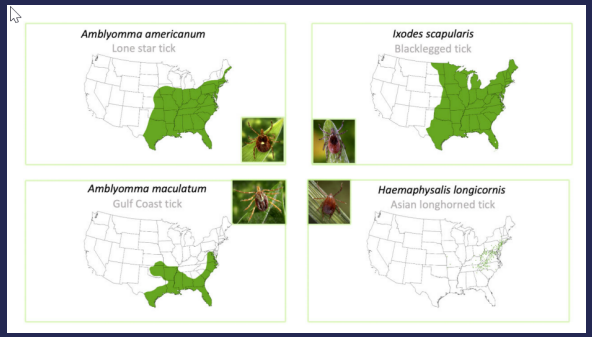
B: shows it after feeding

These are soft ticks that feed briefly at multiple spots—DO NOT remain attached

Scale bars = 2 mm

11

Expanding Range and Ticks New to the US



I. scapularis
-Ticks that carry B. burgdorferi and bite humans mostly northern tick populations

H. longicornis
May carry multiple pathogens, participation in transmitting to Humans occurs but uncertain to what degree

Molaei, JID 2022;226(3):370-373

12

Selected Tickborne Diseases in the US

Home | Data Summary | Cases by Year | Cases by Month

Tickborne Disease Surveillance Data Summary

Total Reported Cases by Tickborne Disease, 2019-2022

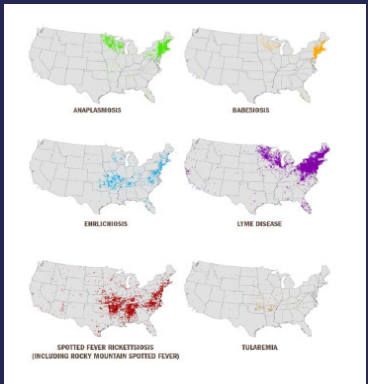
Disease	2019	2020	2021	2022
Lyme disease	34,945	18,010	24,611	62,551
Anaplasmosis	5,655	3,639	6,744	5,633
Spotted fever rickettsioses	5,207	1,175	1,278	1,271
Ehrlichia chaffeensis ehrlichiosis	2,093	1,180	1,347	1,557
Babesiosis	2,418	1,827	1,915	
Tularemia	274	150	162	167
Undetermined ehrlichiosis/anaplasmosis	185	50	77	95
Powassan virus disease	43	21	24	47
Ehrlichia ewingii ehrlichiosis	43	21	19	25
Total	**50,863**	**26,073**	**36,177**	**71,346**

New 2022 CDC Surveillance Definition for Lyme disease

CDC, https://www.cdc.gov/ticks/data-research/facts-stats/tickborne-disease-surveillance-data-summary.html#:~:text=During%202019%2D2022%2C%20state%20and,to%20CDC%20over%20the%20years. (accessed5/15/25)

13

New regions for Common Tickborne Infections



Range expanding for

- Lyme disease
  - Upper Midwest
  - South along Appalachians
- Babesiosis
  - Expanding w/i Lyme disease range
- Ehrlichioses
  - E. chaffeensis, northward

CDC. https://www.cdc.gov/ticks/tickbornediseases/overview.html
Accessed 1/16/23

14

Question #1

PREVIEW QUESTION

62-year-old M living in an exurb of Phoenix, Arizona presents in early September with a three-day history of fever, myalgia, headache and rash.

He works as an electrical lineman for a utility company. He lives with his family in an older adobe home with dogs. There is a faint maculopapular rash on extremities

Which of the following is the most likely diagnosis?

A. Human Monocytic Ehrlichiosis (HME)
B. Human Granulocytic Anaplasmosis (HGA)
C. Babesiosis
D. Rocky Mountain Spotted Fever (RMSF)
E. Tularemia

15

Rickettsial Species: Two Major Groups (Not a Comprehensive Rickettsial List)

Spotted Fever Group (SFG)

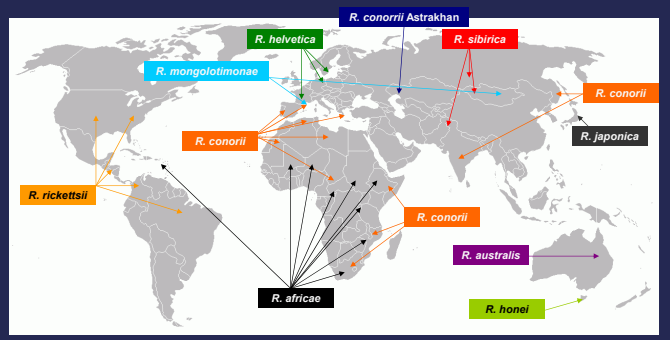
- RMSF (R. rickettsii)
  - R. rickettsia subsp californica (prev 364D)
- R. parkeri
- Rickettsia sp.
- Rickettsialpox (R. akari)
- R. conorii
- R. africae
- R. japonica
- R. australis
- …many more

Typhus Group

- Epidemic typhus
  - R. prowazekii
    - Body louse
    - Worldwide
- Murine/endemic typhus
  - R. typhi
    - Rat flea
    - Temperate--tropical, usually

16

Tick-borne Rickettsia Worldwide: Many Species

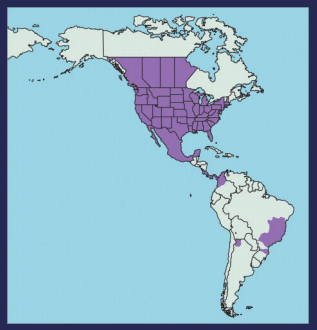


➢ 24 species causing human disease. List continues to grow.

Parola, Clin Microbiol Rev 2013;26(4):657-702

17

Approximate Geographic Distribution of R. rickettsii in the American Continents



See in all lower 48 states

Mexico

Parts of Canada

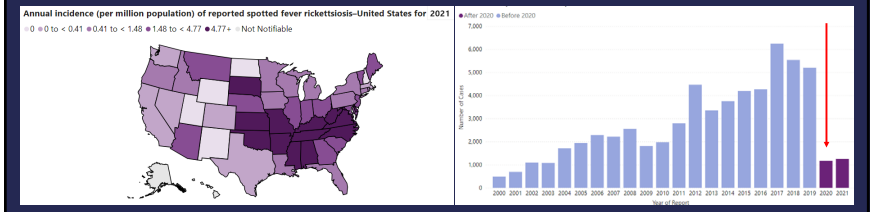
Central and South America

Ongoing epidemic in Northern Mexico (2015-present)

Alavarez-Hernandez, Lancet ID 2017;17(6):e189-196
Tinoco-Gracia, EID 2018;24(9):1723-25

18

CDC Changes:
--2010: RMSF to "spotted fever rickettsioses" 2010 due to lack of serologic specificity includes RMSF, *R. parkeri*, Pacific Coast tick fever, Rickettsialpox, and others
--2020: SFG criteria changes w/ IFA titer raise to ≥ 1:128 from 1:64 to raise specificity, elimination of IFA IgM ELISA

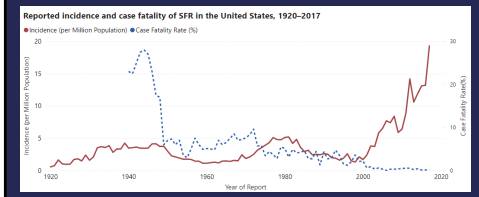


Source: CDC https://www.cdc.gov/rocky-mountain-spotted-fever/data-research/facts-stats/index.html

19

SFR in the United States

Incidence/Case Fatality 1920-2019



Risk Factors for Fatal RMSF ('99-'07)

- Native Americans
- Age extremes: 5-9, 70+
- Use of chloramphenicol (not doxycycline)
- Delay in diagnosis:
  - Treatment after 5 days illness
- Immunosuppression

https://www.cdc.gov/rocky-mountain-spotted-fever/data-research/facts-stats/index.html (accessed 6/22/24)

Am J Trop Med Hyg 2012;86:713-9

20

Rocky Mountain Spotted Fever Signs and Symptoms

Fever	99%
Headache	91%
Rash	88% (49% first 3 days)
Myalgia	83%
Nausea/vomiting	60%
Abdominal pain	52%
Conjunctivitis	30%
Stupor	26%
Edema	18%
Meningismus	18%
Coma	9%

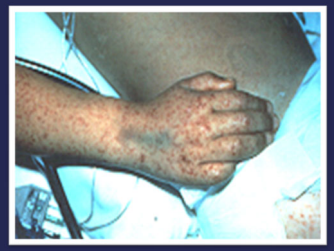
Adapted from Helnick CG et al. *J Infect Dis* 150:480, 1984

21

Rocky Mountain Spotted Fever

Early: rash absent or maculopapular
Starts on extremities

Later rash: petechial



22

Fulminant RMSF
Gangrenous Features
(usually seen with multi-organ failure)

23

RMSF Diagnosis and Treatment

- Start treatment upon suspicion: DON'T WAIT
  - Mortality 4% if doxycycline w/i 5d of symptom onset; 35% if > 5d.
- Labs: leukocytosis, thrombocytopenia, transaminitis
- Dx:
  - Preferred:
    - Skin bxp immunohistochemistry (DFA): timely diagnosis, ~70% sensitive.
    - PCR: *R. rickettsii*-specific
      - Skin bxp or swab (not routinely available, contact local health department → CDC)

Jay R. J Vector Borne Dis 2020;57(2):114-120

24

Outcome: RMSF According to the Day Doxycycline Started

	% mortality
Day 1-5	0
Day 6	33
Day 7-9	27-50

Most lethal of Rickettsial infections: "Black measles"

In US mortality with treatment ~2-5% (higher with delays)

Clin Infect Dis 2015; 60:1659-66

25

RMSF Diagnosis and Treatment

- Other diagnostics
  - Culture: cell culture-based (BSL3 agent)
  - Serology: obtain acute/convalescent samples
    - Not usually of timely clinical value.
    - IFA : gold standard; cross reacts w/ other SFG species.
      - May be helpful in confusing cases.
      - IgG is best to confirm
        - IgM with low specificity
- **DON'T USE AS FEVER SCREENING TEST**
- False positives (especially IgM) common
  - Georgia blood donor study 11.1% IgG > 1:64, but only 28% fit case definition for SFGR [Straily A, JID 2020;221:1371]
  - Single IgG titer insufficient for reliable diagnosis
- Background seroprevalence up to 20% in some regions, e.g., Carolinas
  - Asx infection likely common
- Both RMSF IgM & IGG can persist
  - May mislead diagnosis, cause necessary treatment

26

Pacific Coast Tick Fever

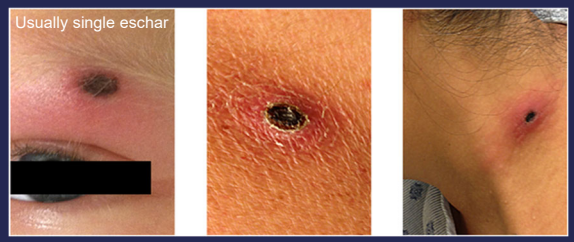
New Name:
Rickettsia rickettsii subsp *californica* (proposed)
(previously Rickettsia 364D/*R. philipii*)

Described in 1966

Transmitted by
Pacific Coast tick (*Dermacentor occidentalis*)

Northern Baja → Southern Oregon, Most cases

Common symptoms:
Eschar
Fever
Headache
Usually mild infection



Dermacentor occidentalis

Pladgett K PLOS Neg Trop Dis 2016
Paddock CF JID 2025:231(4):849-858

27

Question #2

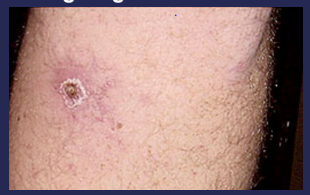
PREVIEW QUESTION

31-year-old M from Tidewater region of Virginia presents in June with three days of fever and rash.

Exam: unremarkable but T39.2°C, discrete black eschar on leg, scattered maculopapular rash elsewhere

Which of the following is the most likely etiologic agent?

A. Rickettsia rickettsii
B. Ehrlichia chaffeensis
C. Rickettsia parkeri
D. Anaplasma phagocytophilum
E. Rickettsia akari



28

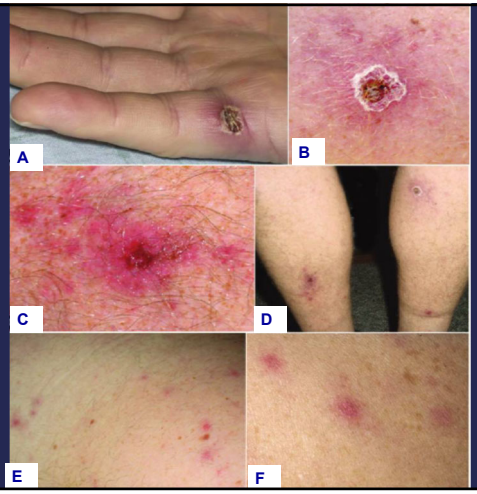
"American Boutonneuse Fever" Rickettsia parkeri

- Transmission: Lone Star or Gulf Coast ticks (*A. maculatum*)
  - Southeastern US, Gulf Coast
- AKA "Maculatum fever"
  - Also seen in Central and South America including Argentina, Uruguay, parts of Brazil
- Symptoms 2-10d post-bite
  - Headache, myalgia
  - Skin
    - Faint salmon-colored rash
    - Single or multiple eschars
- Diagnosis
  - Spotted fever group serology,
  - Immunohistochemistry
  - PCR or culture from skin bxp or swab of eschar

MMWR Morb Mortal Wkly Rep 2016; 65(28): 718-9
Kelman, Infection 2018;46(4):559-563
Scott, Trends in Micro 2022;30(5):511-512

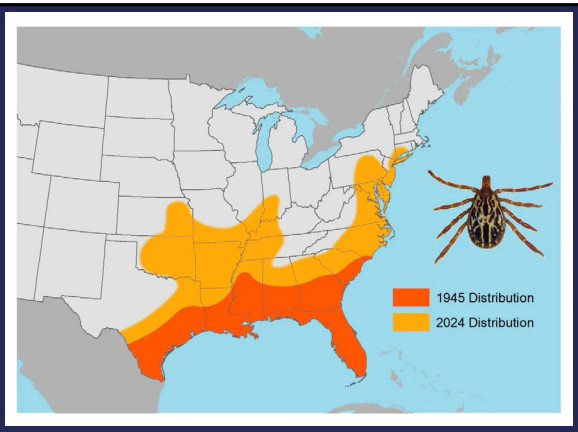
29

Examples of R. parkeri-associated Rashes



Source: CDC

30



A. maculatum (Gulf Coast Tick range); first human case of *R. parkeri* in CT (2024) (Connecticut Agricultural Experiment Research Station, 2024

31

Question #3

22-year-old M upstate NY July c/o HA and fever x 3d now confused. No known tick bite but an outdoorsman. Exam without meningism or rash. Labs normal.

Admitted, doxycycline, CTX, vancomycin started. Head CT: normal

LP: WBC 130 60%P, 40%L, glucose: nl, protein 65 mg/dL (elevated).

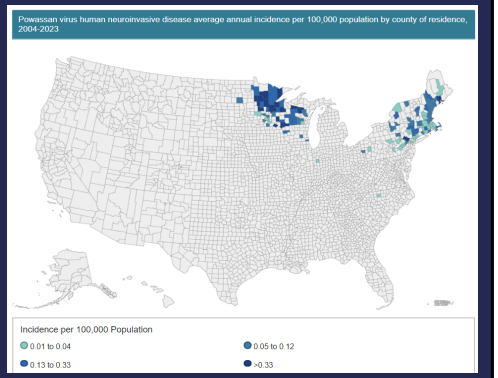
Which of the following is the most likely etiologic agent?

A. Anaplasma phagocytophilum
B. Ehrlichia chaffeensis
C. Heartland virus
D. Powassan virus
E. Borrelia miyamotoi

32

POWV: >Report cases mostly neuroinvasive >Tick-borne flavivirus infection

- Mostly present in Spring-Summer
  - But can be year round
  - Related to nymphal *Ixodes scapularis*
- All ages, median 62 years, 72% male
- Clinical Syndromes
  - Neuroinvasive (90%)
    - Encephalitis (72%)
    - Meningitis (16%)
    - Other neurologic (2%)
  - Non-Neuroinvasive (10%)
- Hospitalized (90%)
- Death (11%, most > 50 years)



Krow-Lucal ER. Vect Borne Zoo Dis 2018; 18(6):286-290
https://www.cdc.gov/powassan/data-maps/historic-data.html

33

Powassan virus Diagnosis & Care

- Antibody testing best sensitivity
  - CT or MRI may be normal; severe cases often with cerebellar changes (70%)
  - CSF: IgM POWV
    - Commercial, State Public Health labs & CDC
    - Needs confirmation by plaque-reduction neutralizing test to r/o cross-reactivity with other flaviviruses
- Other:
  - Viral RNA serum, CSF, tissue
    - Performs best early in illness
  - Immunohistochemistry, fixed tissue
- Treatment: supportive care
- Prognosis: mortality ~ 10%, neurologic sequelae 50%

Piantadosi A. Inf Dis Clin N Am 2022;36(3):671-688

34

Question #4

28-year-old F presents 8d after from a safari in Tanzania

Fever, mild headache, fatigue x 5d

Prior to travel, immunized against yellow fever

Took malaria prophylaxis: atovaquone/proguanil

Temperature is 38.6º, P76, R14, BP 116/70

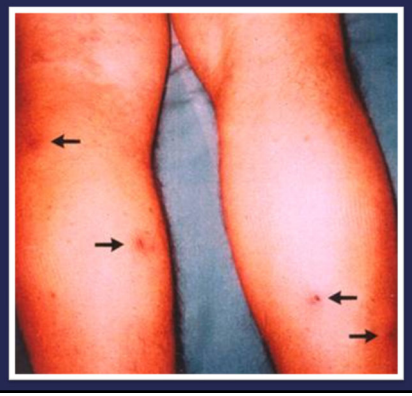
Exam is unremarkable except for four punctuate eschars on the legs and bilateral inguinal lymph node enlargement

Lab: Thick and thin blood smears (x 2) negative

35

Question #4

Four Inoculation Eschars (Arrows)



36

Question #4

Which of the following is the most likely etiologic agent?

A. Rickettsia conorii
B. Rickettsia africae
C. Rickettsia rickettsii
D. Anaplasma phagocytophilum
E. Ehrlichia chaffeensis

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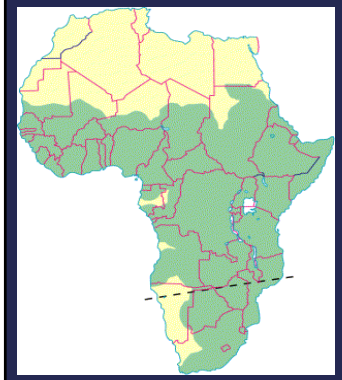
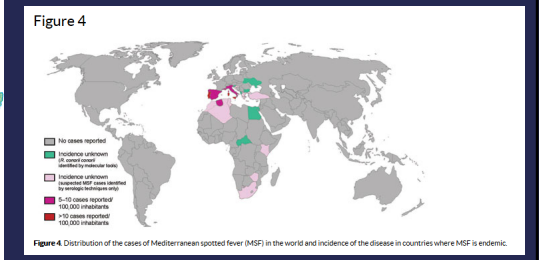
Range of R. africae
African Tick Bite Fever (green)



Range of R. conorii
Mediterranean Spotted Fever



Rovery, EID 2008;14(9)

38

Clinical Characteristics of R. africae Infection

	%
Fever ≥ 38.5º	88
Neck muscle myalgia	81
Inoculation eschars	95
Multiple eschars	54
Lymphadenopathy	43
Rash (vesicular)	46(45)
Death	0

Raoult D, et al. N Engl J Med 2001; 344:1504-10

39

African Tick Bite Fever

- Seroprevalence:
  - High in residents, R. africae, 30-56%
- Amblyomma ticks (cattle, ungulates)
  - Clusters of cases, multiple eschars
- Incubation period 6-7d
- Dx:
  - Biopsy or swab: PCR or MIFA
  - Serology
- Rx: doxycycline
- Complications unusual

40

Rickettsioses and The Returning Traveler Common Cause of Fever After Malaria, Typhoid

Most common: 280 travelers (1996-2008)
- Spotted fever group (83.5%)
  - 87.5% acquired in sub-Saharan Africa

Others
- Scrub typhus (5.7%)
- Q fever (3.6%)
- Typhus group (2.5%)
- Human granulocytic ehrlichiosis (0.4%)

Jensenius M, EID 2009;15(11)

41

Question #5

48-year-old M presents in October with fever and rash

Supervisor for apartment bldg in Queens, NY. Lives in cellar apt.

Exam: T 39^0C

brown-black 8mm eschar on RLE

~30 papulovesicular lesions on trunk

42

Question #5

Which of the following Is the most likely etiologic agent?

A. R. rickettsii
B. R. parkeri
C. R. akari
D. R. conorii
E. Borrelia recurrentis

43

Rickettsialpox

Organism
- R. akari

Reservoir
- House mouse

Vector
- Mouse mites

Clinical
- Single eschar
- Rash: papulovesicular (20-40) or maculopapular
- Diagnosis
  - PCR swab eschar/vesicle
- Treatment: doxycycline

Maculopapular rash due to R. akari (CDC)

44

Partial DDx of Vesicular Rash

HSV
VZV
Pox viruses
  mpox
Rickettsialpox
African tick bite fever
Queensland tick typhus

45

Scrub Typhus

"Scrub typhus is probably the single most prevalent, under-recognized, neglected, and severe but easily treatable disease in the world"

Paris DH et al. Am J Trop Med Hyg 2013;89:301-7

46

Scrub Typhus

Organism
- O. tsutsugamushi (> 70 strains)

Vector
- Trombiculid mite (chiggers)

Geography
- Triangle from Japan to Eastern Australia to Southern Russia (rural)
  - Southern China an endemic focus (Yunnan province)

Clinical
- ~1 million cases/yr
- Severe (~ 35%) high fever
- Eschar, painful/draining lymph nodes, rash, delirium
  - Meningitis and meningoencephalitis with progressive infection
  - Development of multiorgan system failure
  - Case fatality rates up to 70%

47

Eschar is often associated with regional lymphadenitis

48

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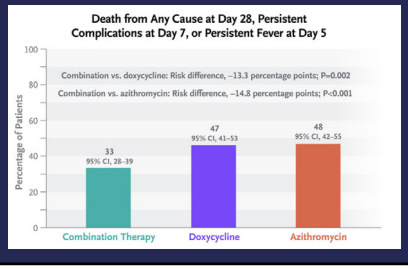
Scrub Typhus Treatment

Treatment

- Doxycycline x 7 days, relapses common
  - Alt: azithromycin (AAC 2014;58:1488-93)
- Combination: appears superior, and safe
  - Doxycycline 200 mg twice daily day 1, then 100 mg twice daily x 6d PLUS Azithromycin 500 mg PO twice daily d1, then 500 mg daily x 6d [Varghese, NEJM 2022]



50

Question #6

31M presents in January with 3d fever, HA, malaise, and myalgia.

Works as counselor at wilderness camp in Pennsylvania.

Flying squirrels common at camp, including residing in the walls of his cabin.

Exam is notable only for fever (39.6^0; no rash), tachycardia (P110)

For which of the following is a diagnostic test most likely to be positive?

A. Murine typhus
B. Epidemic typhus
C. RMSF
D. Tularemia
E. Relapsing fever

51

If You Read a Question with a "Flying Squirrel" You Say "Epidemic typhus" or "R. prowazekii"

MMWR 2003; 9 (10); Lancet Infec Dis 2008;8(7):417

Rare infection in US (1976-2001, 39 cases)
Generally East Coast
None with louse exposure (the classic vector) in N America, so not "epidemic" but sporadic
Most with flying squirrel exposure (Glaucomys volans)

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Body louse: infestation = pediculosis
Pediculus humanus humanus

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Typhus: Two Forms

	Epidemic	Endemic
Organism	***R. prowazekii***	***R. typhi***
Vector	Louse (body, head)	Flea (rat, cat)
Who	War refugees, crowded conditions/poor hygiene	Worldwide (U.S. Southern California, Texas, Hawaii)
Severity	Lethal	Usually milder, some fatalities
Treatment	Tetracycline Doxycycline Chloramphenicol	Tetracycline Doxycycline Chloramphenicol
Prevention	Boil clothes, delouse (lindane, malathion, permethrin, DDT)	Flea prevention (cats, domestic animals) Reduce rodent population
Recrudesce	Brill-Zinsser Disease (years-decades)	None known

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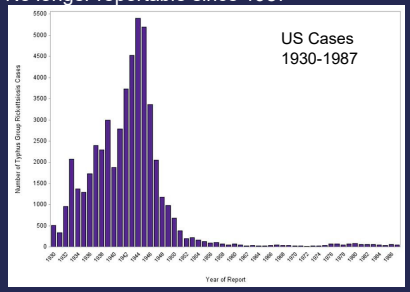
Murine (or Endemic) Typhus

- In US, mostly seen in California, Hawaii, and Texas
- Agent: *Rickettsia typhi*
- Infected cat/rat flea feces → skin
- Most don't recall fleabite
- Usually non-specific febrile infection
  - Underdiagnosed
  - ~50% with rash
  - Occasional severe disease:
    - Meningoencephalitis
    - Pneumonitis
    - Shock

Historically, decline w/ better sanitation
No longer reportable since 1987



Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53

CDC, accessed 7/6/2023 https://www.cdc.gov/typhus/murine/history.html

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CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Search

Morbidity and Mortality Weekly Report (*MMWR*)

Fleaborne Typhus–Associated Deaths — Los Angeles County, California, 2022

Weekly / August 4, 2023 / 72(31);838–843

Incidence:
2010: 1
2022: 171
Deaths 3 (autopsies)
-HLH
-Myocarditis
-Septic shock
>late or no doxycycline

Case fatality usually < 1.0%
LA Series: 1.8%

Suspect: exposure to rodents, cats
Homeless

→Doxycycline

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Murine (or Endemic) Typhus

- Consider especially febrile illness: CA, TX, Gulf coast
- Dx:
  - Serology *R. typhi* (IFA)
    - Acute/convalescent, 4x rise
    - Cross-reacts with R. prowazekii and SFG rickettsia
  - PCR
    - Blood, often negative
- Treatment: No RCTs
  - Doxycycline (preferred)
    - Azithromycin: recent open label trial found azithromycin inferior to doxy
  - Alternatives: limited data
    - Chloramphenicol
    - Levofloxacin
    - Ciprofloxacin

Dittrich, Lancet Global Health 2015;3:e104; Blanton Am J Trop Med 2017;96(1):53

Newton, CID 2019;68(1 March):739

57

Flea-borne Typhus (*R. felis*)

- Found globally; underdiagnosed
- Discovered 1990
  - Cat fleas
- Often lumped in with murine typhus
- Usually mild illness but can be severe
  - Fever, headache
  - Rash variable (macular)
  - Eschar in 12%
- Dx:
  - RMSF serology is often reactive
    - Acute/convalescent R. typhi serology
  - PCR (tissue)
- Treatment: doxycycline

Martinez MAC, Resp Rep Trop Med 2021;12:1-15

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Other Location-specific Tick-borne Rickettsioses: Partial

- Queensland tick typhus, *R. australis*
  - Australia-Queensland, New South Wales, Tasmania, coastal areas of eastern Victoria
- North Asian tick fever, *R. sibeirica*
  - North China; Mongolia; Asiatic areas of Russia
- Tick-borne lymphadenopathy (TIBOLA) or *Dermacentor*-borne necrosis erythema and lymphadenopathy (DEBONEL), ascribed to *R. slovaca* or *R. raoulti:*
  - Europe and Asia.
- Far-Eastern tick-borne rickettsiosis, *R. beilongjiangensis:*
  - Far East Russia and northern China.
- Oriental spotted fever, *R. japonica:*
  - Japan.
- Thai tick typhus, *R. bonei:*
  - Thailand, Australia, Tasmania, Flinders Island
- Australian spotted fever:
  - *R. marmionii*, Australia.

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Question #7

- 43F visited southern Missouri on vacation, returns 7d later with fever, headache and diffuse myalgia x 3d
- Physical examination: no findings
- Laboratory evaluation :
  - WBC: 2.1/mm³ (80% PMNs, 10% lymphocytes, 8% monocytes
  - Hemoglobin: 7.0 g/dL, hematocrit: 24%
  - Platelets: 105,000/mm³
  - AST: 364 U/L, ALT: 289 U/L
  - renal function: normal

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Question #7

Which of the following is the most likely etiologic agent?

A. Anaplasma phagocytophilum
B. Ehrlichia chaffeensis
C. Borrelia hermsii
D. Babesia divergens
E. Borrelia burgdorferi

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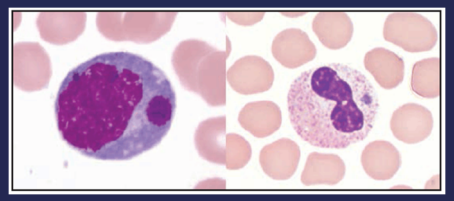
Morulae

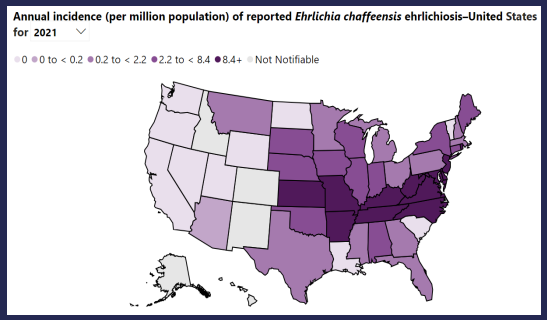


HME HGA

62

Human Monocytic Ehrlichiosis (HME)

- E. chaffeensis
- Vector: Lone star tick
- Rash: ~30%
  - Maculopapular or petechial
- Labs: LFTs ↑, leukopenia, thrombocytopenia
- Mortality 2.7%
- Diagnosis
  - PCR
  - Morulae (2-38%)
  - Serology: acute/convalescent
  - Treatment: doxycycline



Source: CDC https://www.cdc.gov/ehrlichiosis/data-research/facts-stats/index.html (accessed 6/22/24)

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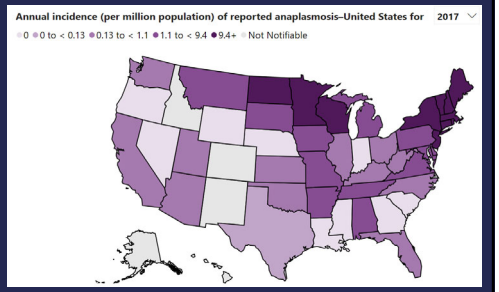
Human Granulocytic Anaplasmosis

- Anaplasma phagocytophilum
- Vector: Ixodes scapularis
- Rash rare
- Labs: LFTs, leukopenia, thrombocytopenia
- Mortality 0.3-0.7% (immunosuppressed ↑ 16 x)
- Diagnosis: same as HME (but morulae seen > 25%)



Geography: cross reactivity with HME accounts
For most Southern state representation

Source: CDC https://www.cdc.gov/anaplasmosis/hcp/statistics/index.html (accessed 6/22/24)

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Borrelia miyamotoi (AKA Hard Tick Relapsing Fever HTRF)

- Unusual vector: Ixodes ticks
- Epidemiology = Lyme disease, but late summer/fall
- Appears similar to HGA (rash infrequent)
  - Severe infection may be sepsis-like
  - Meningoencephalitis in immunocompromised
  - ↓ wbc, ↓ plt, ↑ LFTs
- Diagnosis: blood smear (observing spirochetes), PCR, serology
- Treatment: similar to Lyme disease

Telford, Clin Microbiol Infect 2015
https://www.cdc.gov/relapsing-fever/about/about-htrf.html (accessed 5/15/25)

65

Other Ehrlichia (Less Common)

Organism	Vector	Geography	Risk	Mortality
E. ewingii (aka canine Ehrlichia)	Lone star	Most cases in Southcentral US	Immune compromised	Low
E. muris	*Ixodes persulcatus* *H. flava*	Europe, Russia, Japan, West Coast US	Older patients	Low
Ehrlichia muris eauclairensis (former Ehrlichia muris-like [EML] agent)	Deer tick	Wisconsin, Minnesota	Elderly, immune compromised	Low

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Question #8

- 48F c/o headache and fatigue worsening over 2 months since May tick bite
  - PMH: negative
  - SH: Married, works from home, has a dog, resides in suburban eastern PA
  - Treated with doxycycline for Lyme disease, no benefit
- Physical examination: afebrile, normal vital signs, no findings

- Laboratory evaluation :
  - WBC: 7.0 cells/mm³ (70% PMNs, 18% lymphocytes, 12% monocytes
  - Hemoglobin: 11.8 g/dL, hematocrit: 35%
  - Platelets: 145,000/mm³
  - ALT: 22 U/L
  - Babesia IgG 1:128 (positive ≥ 1:64)
  - Blood smear: no parasites

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Question #8

What is the best recommended next step?

A. Check Babesia duncani serology
B. Check Babesia PCR
C. Repeat blood smear
D. Azithromycin + atovaquone for 7-10 days
E. None of the above

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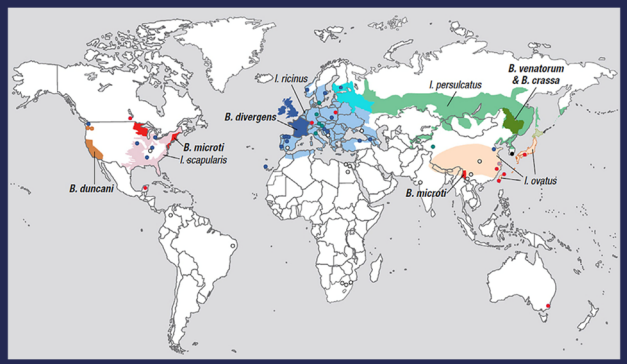
Babesia spp: Global



Vannier et al, NEJM 2012 366;2397

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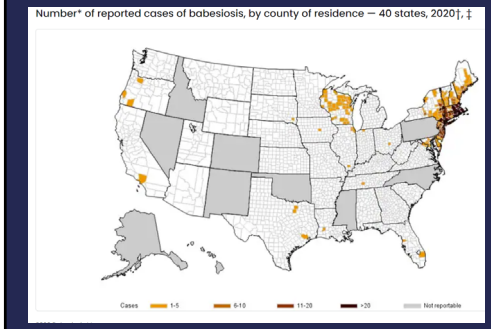
Babesia in the US



- Not reportable in all states
- Occurs within Lyme disease geography, but is more limited
- Vector:
  - *B. microti* → *Ixodes scapularis*
  - *B. duncani* → *Dermacentor albipictus* (likely, west coast only)
- 1500-2500 cases/ yr

https://www.cdc.gov/babesiosis/maps-graphs (accessed 5/18/25)

70

Babesia Species

- Malaria-like parasite, resides in RBCs
- Geography: Babesia microti (most cases in U.S.)
  - Nantucket, Martha's Vineyard, Long Island, Mid-Atlantic/New England, upper Midwest (similar to Lyme disease)
- Range of illness: Asx to "flu-like" to fatal

Was a common cause of blood transfusion-related infection in US

- Though decreasing through screening
  - But question may still appear on the boards

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Severe Babesiosis

- n=34, Long Island NY
- Clinical manifestations
  - 41% Multi-organ failure
    - ARDS, DIC, CHF, ARF
- Risk factors:
  - age >60
  - splenectomy,
  - immunosuppression (e.g., HIV, rituximab)
- Labs
  - increased LTFs,
  - thrombocytopenia
  - anemia (Hb<10),
  - parasitemia (>10%)

Immunocompromised mortality

- > 20%

Hatcher JC, et al. Clin Infect Dis 2001; 32:1117-25

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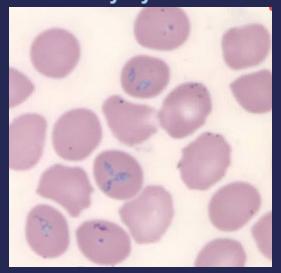
Babesiosis: Smear Diagnosis

Maltese Cross Tetrads

Species level identification only by PCR



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Diagnosis of Babesiosis

- May observe hemolysis
- Wright-Giemsa stained thin blood smears
  - 1-3µ intraerythrocytic merozoites
    - Parasitemia range: 0-80% (may be confused with malaria)
    - Maltese cross: diagnostic (not seen w/ malaria)
    - Quick, if technical expertise available
- PCR: now widely available
  - Highly specific, but often send-out test = delay
- Serology (IFA)
  - High titer or acute/convalescent c/w active or recent infection
    - Low titer, negative smear: don't treat!

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Treatment of Babesiosis

- Severe (2020 IDSA guidelines)
  - Atovaquone 750 mg PO q12h +Azithromycin 500 mg IV q24h
    - Previous: quinine + clindamycin (now an alternative)
  - Duration: 7-10d (may require longer for persistent parasitemia or immunosuppressed)
- Blood exchange transfusion: severe only
  - B. divergens, many require
  - B. microti, some cases
  - Limited evidence for benefit
    - Severe hemolytic anemia or multi-organ failure
- Mild-moderate severity
  - Azithromycin PO plus atovaquone PO

Krause, et al CID 2021; 72 (2) e49-65

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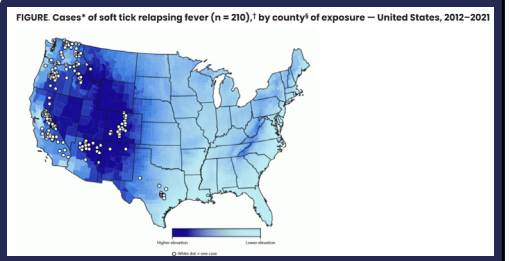
Tickborne Relapsing Fever US

Borrelia spp. (mainly B. hermsii)
- Ornithodorus soft ticks (brief, painless)

Epidemiology
- Western states; 14-45 cases/yr
- Rustic housing and rodents
- Elevation 1500-8000 feet

Clinical Manifestations
- Fever (relapsing), HA, myalgia, N/V
  - Can be severe : ARDS
- Laboratory
  - AKI, ↓ platelets,
  - Dx: blood microscopic exam, PCR
- **Rx: PCN, doxycycline**
  - Jarisch Herxheimer reaction in 54%



Beeson AM MMWR 2023;72(23):777-781

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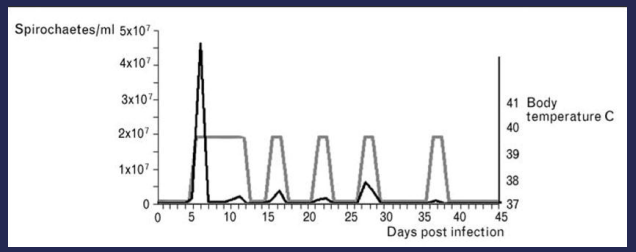

Relapsing Fever: recurrent bacteremia (black line) correlates with sudden fever (grey).

After initial bacteremia, relapses are lower and fever duration somewhat shorter.

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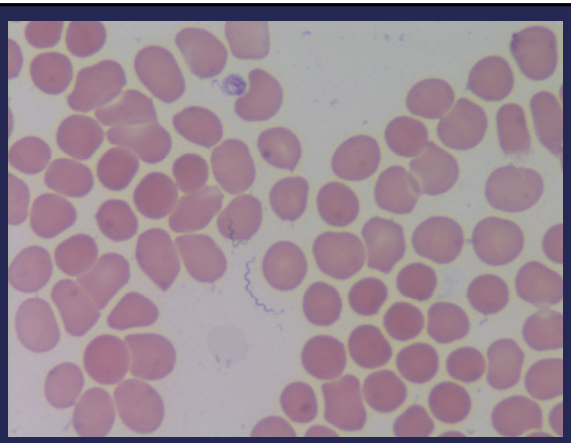

Diagnosis: observation of spirochetes in blood film

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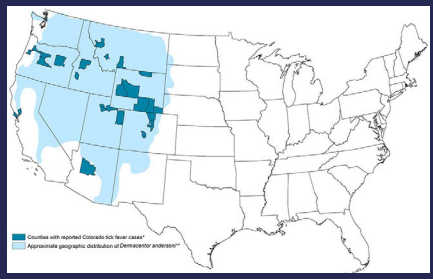
Colorado Tick Fever

- Transmission D. andersoni
  - 4,000-10,000 feet
- Agent: Coltivirus
- Sx range from
  - Mild febrile flu-like illness
    - May include rash: maculopapular or petechial
  - Rare: severe illness multi-system, neuroinvasive disease
- Labs:
  - ↓ WBC, atypical lymphocytes
  - ↓ plt
- Dx: samples to state lab, some commercial lab testing
  - Not a reportable illness



Diagnostic Testing

Preliminary diagnosis of Colorado tick fever (CTF) is based on signs and symptoms, places and dates of travel, activities, and history of potential tick exposure. Acute samples should be tested by reverse-transcriptase polymerase chain reaction (RT-PCR) to detect viral RNA as antibody production is delayed until 14–21 days after onset of symptoms.

Timing of specimen collection	Specimens	Preferred Test
<14 days after symptom onset	Serum (CSF if suspected CNS involvement)	RT-PCR for viral RNA
≥14 days after symptom onset	Serum (CSF if suspected CNS involvement)	Antibody testing*; consider RT-PCR for samples from days 14-21

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Louse-borne Relapsing Fever (LBRF)

Organism:	Borrelia recurrentis
Vector:	Human body louse
Geography:	Worldwide, but now seen in Sudan, Ethiopia, Somalia, Bolivia…
	(Refugee camps, famine, natural disasters)
Clinical Illness	More severe than TBRF,
	(incl. jaundice)
Therapy	Doxycycline

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Cluster of Tick Paralysis Cases

- Four cases within 20 miles of each other
  - Ages 6, 58, 78, 86 years
- Ticks on neck or back
  - Usually dog ticks or Rocky Mt wood ticks
- Ascending motor paralysis without sensory loss
- Treatment: remove tick = cure
- Pathogenesis: neurotoxin in tick saliva

MMWR 2006; 55: 933-5

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Question #9

A 59-year-old man from Missouri presents with fever (39^0), headache, myalgia, anorexia, nausea, one week after removing an engorged tick from his groin. No travel.

Exam: unremarkable except ill appearing, no rash.

Lab: wbc 2300 plt 42,000 ALT 111

Suspect ehrlichiosis (but no morulae on blood smear)

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Question #9

After sending appropriate diagnostic tests the patient has not improved after three days of doxycycline.

Which of the following is the most likely etiologic agent?

A. R. rickettsii
B. B. burgdorferi
C. R. parkeri
D. Heartland virus
E. Severe fever with thrombocytopenia syndrome virus

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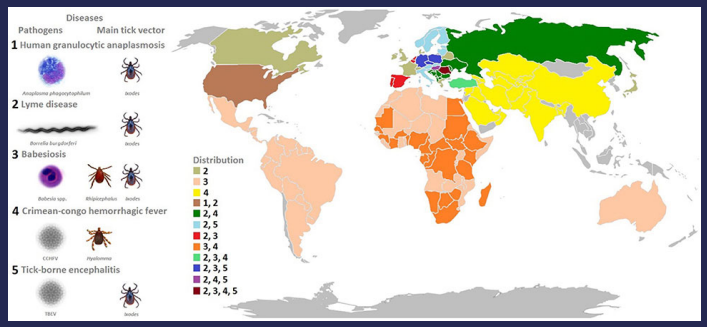
But Wait: There's More (#4) and More (#5)



Front Cell Infect Microbiol, 2017;7:114

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Tick-borne Infections: Some Testable Points

- Rash: RMSF rash appears after several days of fever and viral-like prodrome
  - Meningococcal rash is earlier
  - No bite site (tache noire)
  - Give doxycycline, even for kids
- Blood smear maybe helpful
  - Morulae: PMN = Anaplasma, Monocyte = Ehrlichia
  - Spirochete: relapsing fever Borrelia or B. miyamotoi
  - Erythrocyte inclusions: Babesia

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Tick-borne Infections: Some Testable Points

- Babesia:
  - Cause of blood transfusion infection in US
  - Splenectomy or immunocompromise = risk severe infection risk
- Co-infections in the US: may complicate some infections especially after black-legged tick (*I. scapularis)* bite
  - Lyme disease + Babesia OR Lyme disease + HGA mostly
- Flying squirrels: epidemic typhus
- Rodent infested urban house: Rickettsialpox
  - Mouse mites.
  - Tache noire first → > dozen papules/vesicles

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Key features of select tick, louse, and mite-borne diseases

Disease	Usual Organism	Geography	Eschar	Rash	High fever	Comment
TICK-BORNE						
RMSF	R. rickettsii	N,C,S ,America	No	Yes	Yes	Serious
STARI	Unknown	S, SC, MA	No	Yes (EM)	No	Mild
R. parkeri	R. parkeri	Gulf, South, Atlantic	Yes (>1)	Yes	No	
African tick bite fever	R. africae	Sub-Saharan Africa	Yes (>1)	Yes	No	Mild
HME	E. chaffeensis	S, SC, MA	No	Yes (+/-)	Yes	Cytopenias Transaminitis
HGA	A. phagocytophilum	NE, NY, MA, MW	No	Yes (+/-)	Yes	Cytopenias Transaminitis
Babesiosis	B. microti	NE, NY, MA, MW	No	Yes (+/-)	Yes	
TBRF	B hermsii	W Mountains	No	No	Yes	Spirochetes in blood smear
LOUSE-BORNE						
Epidemic typhus	R. prowazekii	Worldwide	No	Yes	Yes	War, refugee camps serious
MITE-BORNE						
Rickettsialpox	R. akari	Worldwide	Yes (1)	Yes (V)	No	Mouse exposure
Scrub typhus	O. tsutsugamushi	India, Asia, N. Australia	Yes	Yes	Yes	Serious

C	Central	NY	New York
EM	Erythema Migrans	RMSF	Rocky Mountain Spotted Fever
HGA	Human Granulocytic Anaplasmosis	S	South
HME	Human Monocytic Ehrlichiosis	SC	South Central
MA	MidAtlantic	SE	Southeast
MW	Mid-West	STARI	Southern Tick Associated Rash Illness
N	North	TBRF	Tick-borne Relapsing Fever
NE	New England	V	Vesicular
		W	West

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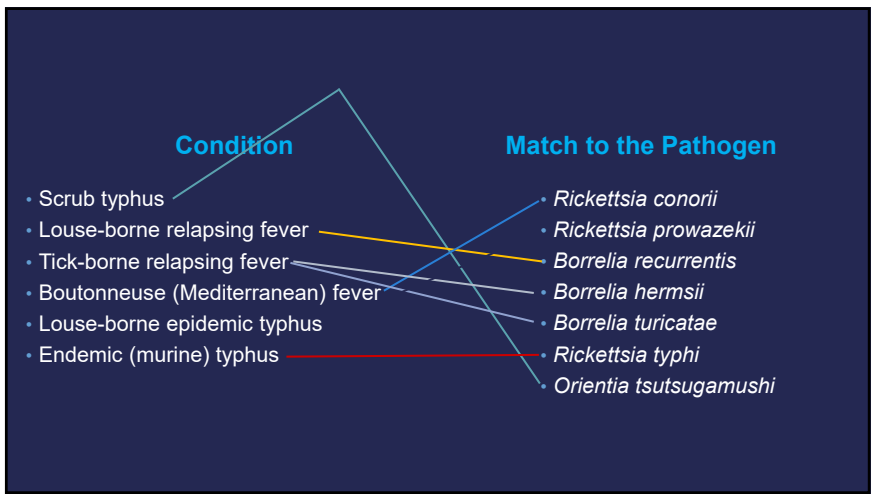

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Thank You! and The End.

B. mayonii Spirochete in Culture

Pritt, Clin Micro and Inf 2022

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