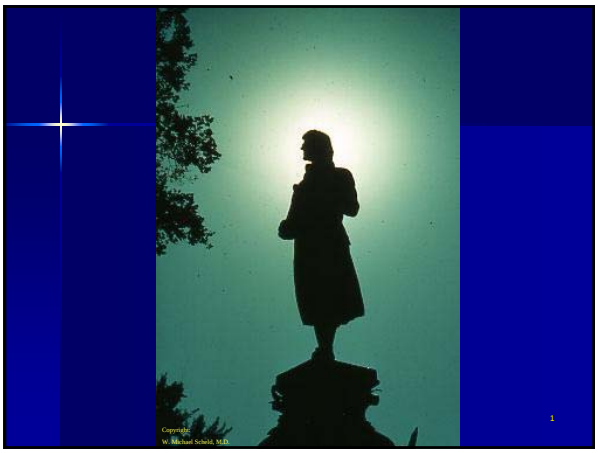


Emerging Tick-Borne Pathogens

W. Michael Scheld, M.D.
University of Virginia Health System
February 2010

2

Tick-borne Diseases of North America General Principles I

- Presentation non-specific: usually "flu-like illness" (e.g. fever, headache, myalgias)
- Diagnosis is clinical; i.e., treatment should be initiated prior to diagnostic testing results return
- May have characteristic rash
- Asymptomatic: symptomatic ratio is high

3

Tick-borne Diseases of North America General Principles II

- Seasonal; geographic distribution suggestive
- Abnormalities in CBC, LFT's frequent
- Doxycycline is preferred therapy for most common illnesses (e.g., Lyme, RMSF, ehrlichiosis…) even in children
- Prognosis in children generally good; most serious complications in adults, especially the elderly
- Convergence in tick vectors; co-infection underestimated

4

The Major Tick-borne Diseases Of North America

Lyme disease
Rocky Mountain spotted fever
Ehrlichiosis
Colorado tick fever
Tularemia
Relapsing fever
Babesiosis
Tick-borne encephalitis
Tick paralysis
R. parkeri
Southern tick associated rash illness (STARI)

5

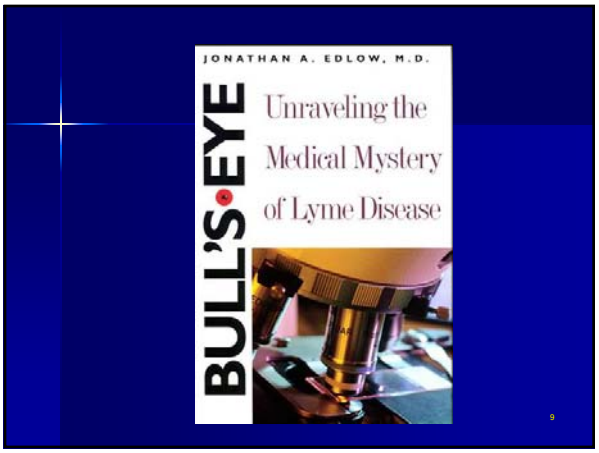
Ticks*

- By 1996: 869 species or subspecies
- Hematophagous arthropods, parasitize every class vertebrates ≅ entire world
- 2 major families: Ixodidae (hard ticks)
  Argasidae (soft ticks)
  Nuttilaellidae (one species)
- 3 basic life stages: larva, nymph, adult
- Second only to mosquitos as vectors of human disease

*e.g. Parola P, Raoult D. Clin Infect Dis 2001; 32:897-928

6


NORIEGA'S GOON SQUADS
Where Will Bush Draw the Line?
Newsweek
Lyme Disease
A tiny tick is spreading a mysterious illness in 43 states
How to protect yourself this summer


JONATHAN A. EDLOW, M.D.
BULL'S EYE
Unraveling the Medical Mystery of Lyme Disease

A 32 y.o. woman from western Massachusetts presents in July with a three day history of fever, malaise, myalgias, headache, and rash. Exam is unremarkable except for T38[3] and a 10 X 12 cm homogeneous erythematous plaque on the medial left thigh.

Which of the following is the most appropriate next step?

A. Order Lyme serologic testing

B. Order blood smear for babesiosis

C. Order HGE serologic testing

D. Begin doxycycline

E. Begin azithromycin

10

Lyme Disease - Epidemiology

- ≈ 64,382 reported cases in 2003-2005 (leading vector-borne disease in the U.S.) (up to 300/100,000 annually)
- Regional incidence varies > 100-fold; concentrated in NY, New England, upper Midwest (93% cases 10 states)
- Vectors: *Ixodes scapularis* and *I. pacificus*
- Incidence proportional to:
  - Tick density
  - Tick parasitism
    - *I. scapularis* - 15-60%
    - *I. pacificus* - 1-2%
- White tailed deer (adult)
- White-footed mouse (nymph) – reservoir

MMWR 2007; 56:573-6

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Figure. Lyme disease incidence in USA and Presidential election results, 2004. Upper=incidence (per 100000) of Lyme disease by county of residence, USA, 2002;[1] LOWER=US Presidential election results by state, 2004 (red=Bush, BLUE=Kerry).

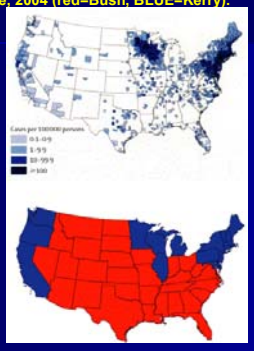

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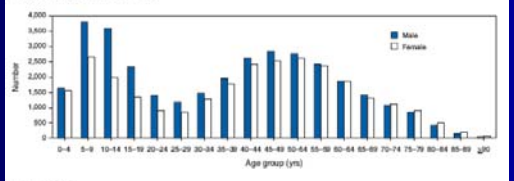
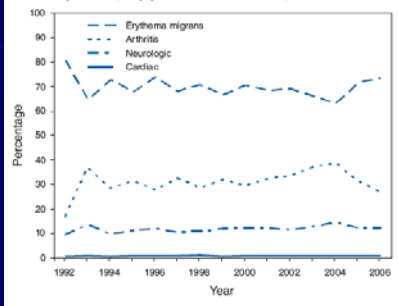
FIGURE 2. Number* of newly reported Lyme disease cases, by sex and age group — United States, 2003–2005



* N = 62,206.

13

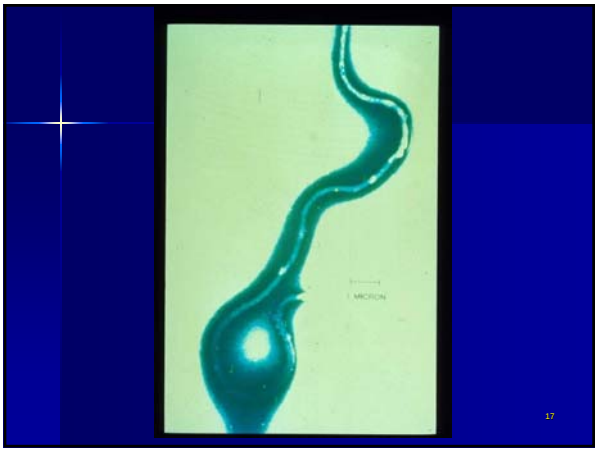
FIGURE 7. Percentage of symptoms reported among Lyme disease patients,* by year — United States, 1992–2006



* N = 150,829.

MMWR 2008; 57 (SS-10)1-9

15



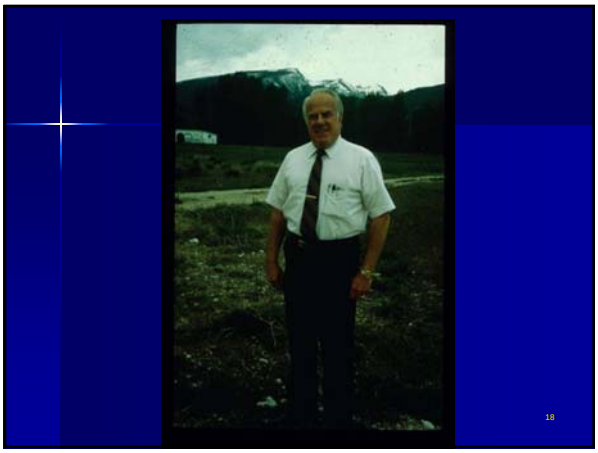


Table 6. Hierarchical analysis of invasive *Borrelia burgdorferi* infection among patients from suburban New York City with erythema migrans.

ospC genotype	RST genotype	Patients with proven dissemination,[a] %
K	2	31.4
A	1	26.5
B	1	13.7
I	3	10.8

NOTE. Findings were calculated from the data shown in table 4. RST, ribosomal spacer type.

[a] Proven on the basis of positive blood culture and/or multiple erythema migrans skin lesions.

JID 2008; 198:1362-64

20

Lyme Disease - Clinical Manifestations (Stage I)

Systemic manifestations	% patients
malaise, fatigue	80
headache	64
fever and chills	59
stiff neck	48
arthralgias	48
myalgias	43
back pain	26
anorexia	23
sore throat	17
nausea	17
dysesthesia	11
vomiting	10

21

Erythema Migrans In Microbiologically Confirmed Lyme Disease*

- 1995 vaccine trial (10, 936 participants)
- 118 culture or PCR (+)
- 59% homogeneous lesions, 32% dense central erythema, 9% central clearing, 7% multiple lesions (not influenced by vaccine)
- With low grade fever, HA, myalgias, arthralgias, neck, stiffness, fatigue
- 96% resolution sx <30 days after Rx

*Smith RP, et al. Annals Intern Med 2002; 136:421-8.

22

23

Early Lyme Disease: Systemic Sx Without EM?*

- 1995 vaccine trial; 1917/10,936 evaluated for suspected Lyme disease; 269 met criteria (42 [16%] without EM)
- 28/42 definite V1sE peptide seroconversion or PCR

*Steere AC, et al. Am J Med 2003; 114:58-62.

24

Early Lyme Disease: Systemic Sx Without EM?*

- Arthralgias/myalgias/occipital HA/paresthesias (no resp/GI sx)
- 14% with Ehrlichia or Babesia
- Resolution of sx within days of Rx
- No long-term sequelae

*Steere AC, et al. Am J Med 2003; 114:58-62.

25

Frequency Of Presenting Manifestations Of Lyme Disease*

Presenting Disease Manifestation	
Erythema migrans (EM)	142 (71)
Systemic symptoms, without EM	35 (17)
Cranial neuropathy	2 (1)
Carditis	0 (0)
Arthritis	4 (2)
Asymptomatic IgG seroconversion	18 (9)

* *NEJM*, 2003;384:2472-3.

26

Lyme Disease - Cardiac Manifestations

Occur in ≈ 8% patients, @ - 5 weeks, lasts days to weeks

Fluctuating degrees of A-V block	90%
Myopericarditis	56%
LV dysfunction	42%
Valvular involvement	0%

27

Lyme Disease - Neurologic Manifestations

Stage 1: clinically suggests meningitis, CSF normal

Stage 2: 15% @ 2-11 weeks

- bilateral Bell's palsy
- other cranial nerves VII>III, IV, VI >VIII
- radiculopathy, often dermatome of tick bite
- meningitis/encephalitis (CSF pleocytosis)
- papilledema, A-R pupil, optic atrophy, etc.

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Acute Disseminated Lyme Disease

Facial Palsy

29

Acute Disseminated Lyme Disease

"Lymphocytic" Meningitis And Facial Palsy

30

Lyme Disease - Natural History Of Untreated ECM

No progression	- 20%
Arthralgia	- 20%
Intermittent episodes arthritis	- 50%
Chronic erosive arthritis	- 10%

31

Lyme Disease - Relative Frequency Of Joint Movement

knee	90%
shoulder	50%
ankle	43%
elbow	39%
temporomandibular	39%
wrist	32%
back	29%
hip	25%
neck	21%

32

Reinfection In Patients With Lyme Disease

Figure 1 *Top,* First episode of erythema migrans (note the punctum). *Bottom,* Second episode of erythema migrans in the same patient at a different location 13 months after the first episode.

34

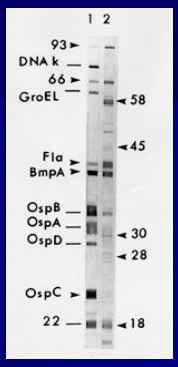
Table 2. Clues to differentiating reinfection from relapse of Lyme disease.

Variable	Reinfection	Relapse
Previous treatment	Recommended antimicrobial regimen for *Borrelia burgdorferi*	Antimicrobial agents not active against *B. burgdorferi* (e.g., cephalexin)
Recent tick bite	Within 3–30 days of erythema migrans lesion at site of lesion	None
Season	Spring or summer	Seasonality less likely but has not been studied
Time of recurrence of infection	>1 year after the initial episode	Within a few weeks to months after the initial episode
Site of erythema migrans	Different from prior episode	Same as prior episode
Presence of punctum	Yes	No

Table 2 Clues to differentiating reinfection from relapse of Lyme disease.

35

36



Western blot for *B. burgdorferi* antibodies

37

W. B. Interpretive Criteria

- IgM Western Blot
  - 23 kD
  - 39
  - 41
- Requires 2 of 3

- IgG Western Blot
  - KD 18 23
  - 28 30 39
  - 41 45 58 66
  - 93
- Requires 5 of 10

38

Table 1. Comparison of the sensitivity of C6 testing and 2-tier testing among patients according to the ribosomal spacer type (RST) of the strain of *Borrelia* isolated from the patients (excludes mixed infections).

RST	No. of patients	No. (%) of patients with a positive test result		*P*
		C6 test	2-tier test	
RST1	46	32 (69.6)	25 (54.3)	.20
RST2	81	54 (66.7)	30 (37.0)	<.001
RST3	40	30 (75.0)	10 (25.0)	<.001
All	167	116 (69.5)	65 (38.9)	<.001

CID 2008; 47:910-14

IDSA GUIDELINES

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

Gary P. Wormser,[1] Raymond J. Dattwyler,[2] Eugene D. Shapiro,[5,6] John J. Halperin,[3,4] Allen C. Steere,[9] Mark S. Klempner,[10] Peter J. Krause,[8] Johan S. Bakken,[11] Franc Strle,[13] Gerold Stanek,[14] Linda Bockenstedt,[7] Durland Fish,[5] J. Stephen Dumler,[12] and Robert B. Nadelman[1]
Divisions of [1]Infectious Diseases and [2]Allergy, Immunology, and Rheumatology, Department of Medicine, New York Medical College, Valhalla, and [3]New York University School of Medicine, New York, New York; [4]Atlantic Neuroscience Institute, Summit, New Jersey; Departments of [5]Pediatrics and [6]Epidemiology and Public Health and [7]Section of Rheumatology, Department of Medicine, Yale University School of Medicine, New Haven, and [8]Department of Pediatrics, University of Connecticut School of Medicine and Connecticut Children's Medical Center, Hartford; [9]Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, and [10]Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts; [11]Section of Infectious Diseases, St. Luke's Hospital, Duluth, Minnesota; [12]Division of Medical Microbiology, Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland; [13]Department of Infectious Diseases, University Medical Center, Ljubljana, Slovenia; and [14]Medical University of Vienna, Vienna, Austria

40

Lyme Disease - Treatment

- Stage 1: oral antibiotic regimen
- Stage 2: carditis - IV antibiotic regimen
  - Oral antibiotic regimen only for mild involvement (first degree AV block with PR less 0.3 seconds)
    - meningitis - IV antibiotic regimen
  - Oral regimens unproven but potentially an alternative
    - radiculoneuritis - IV antibiotic regimen
    - facial nerve paralysis - Oral antibiotic regimen may be sufficient if isolated finding

41

Duration Of Antibiotic Therapy For Early Lyme Disease (N=180 With EM)

complete response @ 30 mos (%)	
doxycycline x10d	90.3
doxycycline x 20d	83.9
ceftriaxone + doxy	86.5

Wormser GP, et al. Annals Intern Med 2003; 138:697-704

42

Lyme Disease - Treatment (Cont.)

Stage 3 - arthritis - Oral antibiotic regimen (if using amoxicillin, add probenecid)

IV antibiotic regimen if oral fails

- CNS - IV antibiotic regimen

43

Lyme Disease - Oral Antibiotic Regimens

- **Adults:**
  Doxycycline 100 mg po bid for 14-21 days or
  Amoxicillin 500 mg po tid with probenecid 500 mg po tid for 14-21 days
- **Children (<8):**
  Amoxicillin 250 mg po tid or 20 mg/kg/day in divided doses for 14-21 days
- **Penicillin allergic:**
  Azithromycin 500 mg po QD for 7-21 days
- **Pregnancy:**
  Amoxicillin 500 mg po tid for 14-21 days

44

Lyme Disease - Intravenous Antibiotic Regimens

- **Ceftriaxone 2 gm iv QD for 14-28 days or Penicillin G, 20 million units QD in divided doses for 14-28 days (in most studies, the response to penicillin has been inferior to ceftriaxone)**
- **Pregnant women with stage 2 or 3 disease: IV Penicillin G regimen**

45

Lyme Arthritis: Therapy Of Recurrences*

First:

repeat oral regimen for 28d or ceftriaxone 2 gm i.v. qd for 14-28 d

Two or more:

NSAIDS, intraarticular steriods and/or arthroscopic synovectomy

***Wormser GP et al. Clin Infect Dis 2001**

46

National Guideline Clearinghouse

www.guideline.gov

Brief Summary

GUIDELINE TITLE
Evidence-based guidelines for the management of Lyme disease.

BIBLIOGRAPHIC SOURCE(S)
Evidence-based guidelines for the management of Lyme disease. Expert Rev Antiinfect Ther 2004;2(1 Suppl):S1-13. [66 references]

47

International Lyme and Associated Diseases Society

Post-lyme Disease Syndromes

"There is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease. Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (≥ 6 months) subjective symptoms after recommended treatment regimens for Lyme disease. (E-I)"

Wormser GP, et al. Clin Infect Dis 2006;43:1089-1134.

48

Uproar! Outrage!

Lyme disease divide
Hartford Courant 9/18/06
Chronic Lyme sufferers, others react to article
Hartford Courant 9/22/06
New Lyme disease guidelines prompt patient protests
New Jersey Starledger 11/3/06
New Lyme disease guidelines sparks showdown
HealthDay.com 11/10/06
Lyme guidelines outrage sufferers
Cape Cod Times 11/20/06
Lyme disease activists to protest
NewsTimes.com 11/28/06
Lyme advocate takes issue with new diagnosis and treatment
The Stanford Times 1/11/07

49

And More Rhetoric

"The national non-profit Lyme Disease Association, representing more Lyme Disease patients than any organization in the United States, objects strenuously and with great alarm to the restrictive new Clinical Practice Guidelines published this October by the Infectious Diseases Society of America…the reckless new IDSA guidelines state (without offering evidence or any supporting citations)…arbitrarily dismissing all studies documenting persistent infection…are so draconian…"

Ukiah Daily Journal 11/2/06

50

Alternative Therapy For Lyme Disease Results In Death

FDA investigation; MD in Kansas treated two patients with i.v. bismacine-renal failure, cardiac arrest

American Biologies Corp.; Bradford Research Institute; "antibacterial" contains bismuth

Lancet Infect Dis 2006; 6:546

51

"An Appraisal Of Chronic Lyme Disease"

"The media frequently disregard complex scientific data in favor of testimonials…All these factors have contributed to a great deal of public confusion with little appreciation of the serious harm caused to many patients who have received a misdiagnosis and have been inappropriately treated"

NEJM 2007; 357:1422-30

52

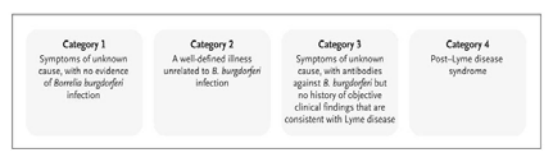


Figure 1. The Four Predominant Categories of Disease Associated with Chronic Lyme Disease. Only patients with category 4 disease have post–Lyme disease symptoms.

53

Table 3. Evidence against Active Infection in Patients with Subjective Symptoms Persisting for More Than 6 Months after Antibiotic Treatment for Lyme Disease.

Signs and symptoms

Absence of concomitant objective clinical signs of either disease or inflammation and no progression to objective signs or development of inflammation[29,32]

Similar symptoms common in persons who have never had Lyme disease[29,31,40,41,48]

Laboratory tests

Persistence of symptoms independently of persistent seropositivity[29,39,41,47]

Absence of either positive cultures or positive polymerase-chain-reaction results from clinical specimens[34,40]

Treatment

No substantive response to antibiotic therapy in controlled treatment trials[32,34]

No documented resistance of *Borrelia burgdorferi* to recommended antibiotics[2]

Absence of recognized risks for failure of antibiotic therapy; these include host immunodeficiency or an infection in which there is local ischemia, a foreign body (biofilm), a sequestrum, or an abscess[2]

Other evidence

Certain studies in animals[2]

Lack of precedent for the use of long-term antibiotic treatment in other spirochetal infections[33,49]

Table 3. Evidence against Active Infection in Patients with Subjective Symptoms Persisting for More Than 6 Months after Antibiotic Treatment for Lyme Disease.

54

Single dose (200mg) doxycycline after *I. scapularis* tick bite

Consider if all are met:

1. adult or nymphal, attached ≥ 36h
2. can start ≤ 72h after tick removal
3. *B. burgdorferi* infection ticks ≥ 20%
4. no contraindication

Wormser GP, et al. Clin Infect Dis 2006; 43:1089-1134. (regardless of prior Lyme disease vaccine or illness)

55

A 62 y.o. man from North Carolina presents in early September with a three day history of fever, myalqias, headache, and rash. He works as a electrical lineman for Duke Power. Exam is notable only for T 39^0 and a faint petechial rash on the wrists and ankles.

Which of the following is the most likely diagnosis?

A. RMSF

B. HME

C. HGE

D. Babesiosis

E. Tularemia

56

RMSF, USA, 1993-1996*

- 2,313 cases reported to CDC (72% confirmed)
- Cases from 42 states and DC
- Incidence rising; $2.2/10^6$; highest children
- 52% South Atlantic
- 9% death over age 70

*Treadwell TA, et al. Am J Trop Med Hyg 2000; 63:21-6

57

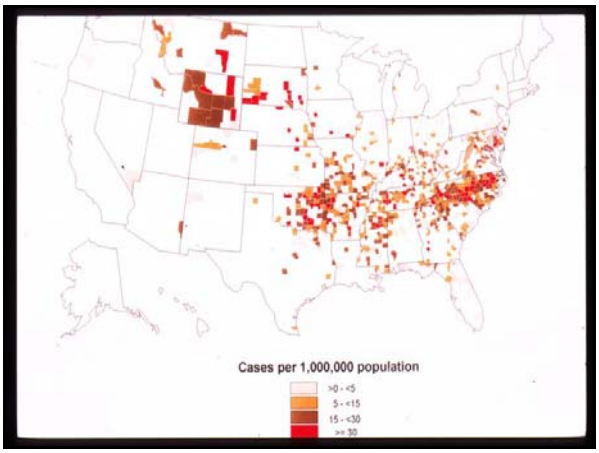


Figure 4. Approximate geographical distribution of RMSF in the American continent

59

Rocky Mountain Spotted Fever Signs And Symptoms

Fever	99%
Headache	91%
Rash	88%
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

60

RMSF

61

RSMF

62

Figure 6. Typical rash on the right hand and wrist of a child with RMSF

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Figure 7. Typical rash on the right arm of a child with RMSF

64

Risk Factors For Fatal RMSF*

1981-1998; 6338 cases, 213 deaths (3.3%)

4.9% in 1982, 1.1% in 1996

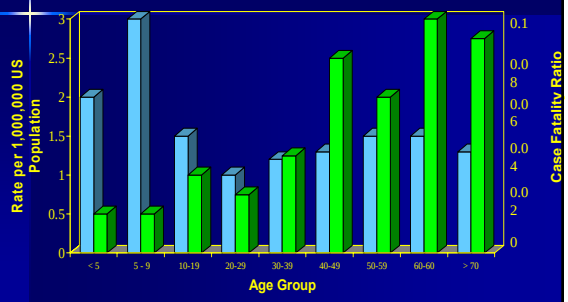
Risk factors: age >60, use of chloramphenicol,

non-tetracycline use, treatment after 5 days illness, black race (?)

*Holman RC, et al. J Infect Dis 2001; 184:1437-44

65

RMSF: Case-Fatality Ratio by Age



Dalton MJ et al. *Am J Trop Med Hyg* 52(5):405-413, 1995

67

Figure 1. Digital gangrene in a patient (case 2) with *Rickettsia australis* infection.

68

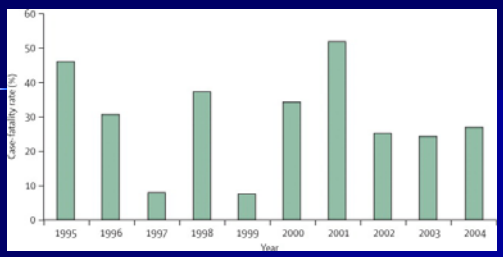


Figure 5. Case fatality of RMSF in Brazil (as reported by the Brazilian Ministry of Health)

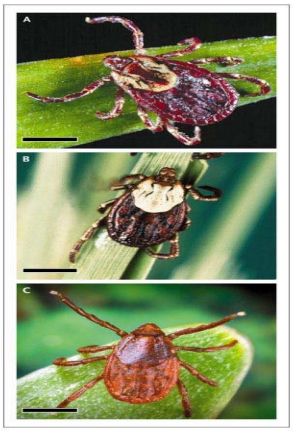
69

RMSF, Arizona, 2002-2004

n=16, 81% < 12 years old
94% hospitalized (38% in ICU)
12% died
New vector: Rhipicephalus sanguineous

Derma LJ, et al. N Engl J Med 2005; 353: 587-94.

70



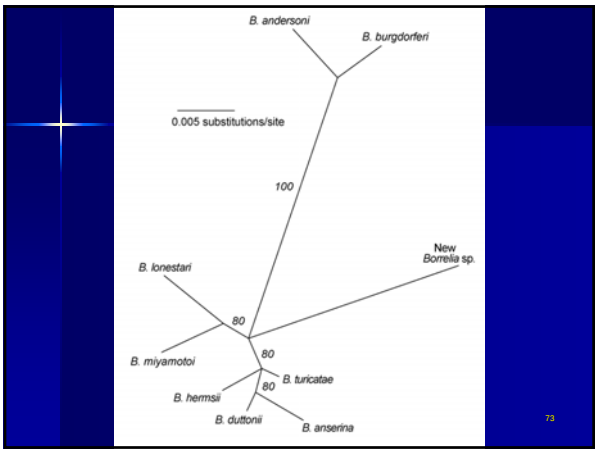
71

A 56 y.o man from southern Missouri presents in July with fever malaise, and rash of two days duration. Exam is only notable for T 38^0 and an annular "bulls-eye" 6 X 8 cm lesion on the lower back with a central engorged tick (≈7 mm long engorged).

Which of the following is the most likely diagnosis?

A. Lyme disease
B. HME
C. HGE
D. Southern tick-associated rash illness
E. B. lonestari infection

72



Borrelia lonestari

- ≅ 2% *A. americanum* ticks from SE, SC U.S. contain spirochetes (genus-specific antisera)
- Cannot cultivate in BSK medium
- Oligonucleotides for flagellin and 16s rRNA genes
- Distinct from *B. burgdorferi*
- Now confirmed in human tissues (James AM, et al. J Infect Dis 2001; 183:1810-4)

74

EM in Missouri

- 30 patients (31 skin biopsies)
- *B. lonestari* PCR (-) in all
- *B. burgdorferi* culture (-) (vs 63% NY state)
- Serology (-) (vs 75% NY state)
- Suggest: Southern tick-associated rash illness (STARI)

Wormser GP, et al. Clin Infect Dis 2005; 40: 423-8.

76

Clinical Characteristics Of Patients With EM: Two Locales

	Missouri (21)	New York (97)
time of year	earlier	
Hx tick bite	86%	20%
tick → lesion	6.1d	10.4d
other Sx	19%	76%
multiple skin lesions	5%	27%
size	8.3 cm	16.4 cm
Rx → recovery	more rapid	

Wormser GP, et al. Clin Infect Dis 2005; 41: 958-65.

77

78

A 31 y.o. man from tidewater Virginia presents in June with three days of fever and rash. Exam is unremarkable except for T 39² and four discrete black eschars on the lower extremities.

Which of the following is the most likely etiologic agent?

A. R. rickettsia

B. E. chafeensis

C. R. parkeri

D. A. phagocytophilum

E. R. akari

79

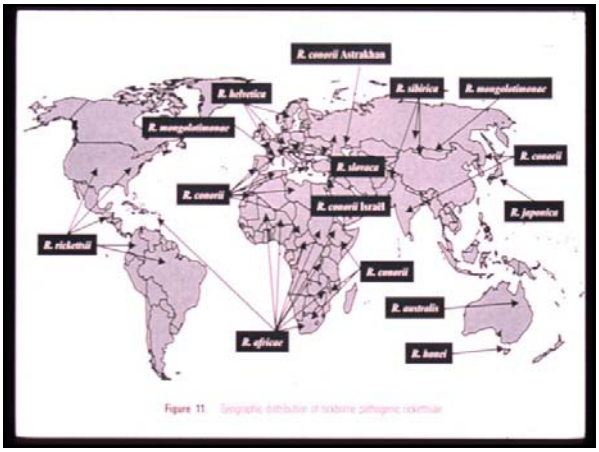
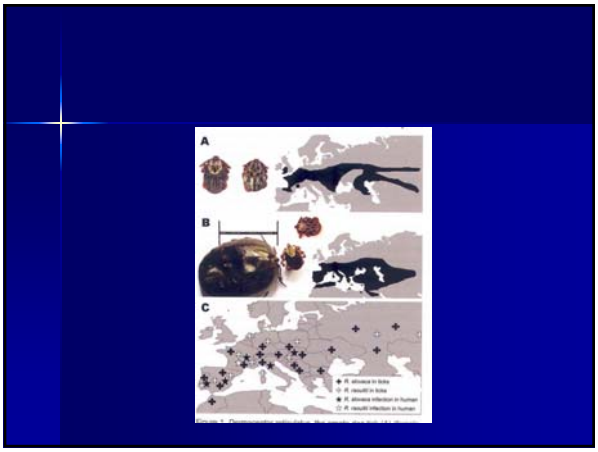


Figure 11.

R. Slovaca Infection; D. Marginatus Ticks (1-17%)

- Europe; < 10 years; cold months
- Scalp lesions with lymphadenopathy
- Fever and rash unusual
- Alopecia and persistent asthenia > 50%
- Dx: IF, WB, PCR

81



Lone Star Tick and Its Geographic Distribution16

Stone, J. H. et al. JAMA 2004;292:2263-2270.

Figure 3. Lone Star Tick and Its Geographic Distribution16
Approximate geographic distribution of *Amblyomma americanum* in the United States.

85

JAMA

"American Boutonneuse Fever"

- Virginia; August; 40 y.o. male with fever (39.2º), HA, myalgias, faint salmon-colored rash, multiple eschars,
- SFG by serology, immunohistochemistry
- Culture from skin bx (Vero cells) = R. parkeri (known in Gulf coast and Lone Star ticks)

*Paddock CD, et. al., Clin Infect Dis-2004

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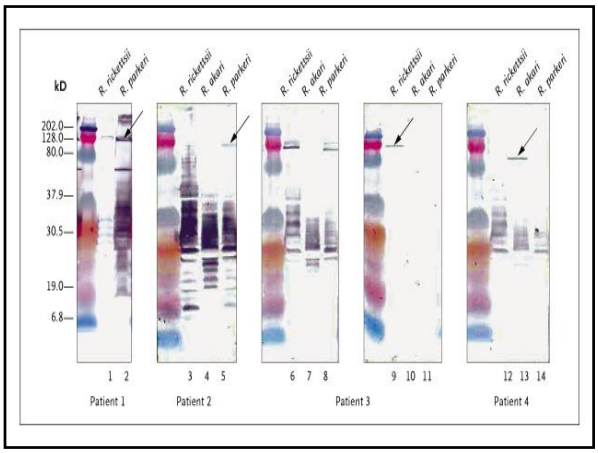

Figure. Adult *Amblyomma maculatum* (the Gulf Coast tick). A) Female; B) Male. Photographs courtesy of James Gathany, Centers for Disease Control and Prevention.

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Figure 1. *A*, Life stages of the Gulf Coast tick *(Amblyomma maculatum)*. From left: larva, nymph, adult male, and adult female. Each stage can feed on human hosts and can be infected with *Rickettsia parkeri*. The head of a pin is included for scale. *B*, Classic range *(dark blue)* of *A. maculatum* in the United States, based on historical and contemporary records [3, 4]; a hypothetical range *(pale blue)*, based on published incidental tick collection data (Pete Teel, Texas A&M University, personal communication); and the locations of confirmed *(shaded circles)* and probable *(unshaded circles)* cases of *R. parkeri* rickettsiosis discussed in this report.
CID 2008; 47:1188-96

Table 2. Comparison of selected clinical features of *Rickettsia parkeri* rickettsiosis with those of Rocky Mountain spotted fever (RMSF) and rickettsialpox, as reported in well-characterized case series.

Clinical characteristic	*R. parkeri* rickettsiosis[a] (*n* = 12)	RMSF[b] (*n* = 206)	Rickettsialpox[c] (*n* = 197)
Fever	100 (100)	100 (100)	99 (100)
Inoculation eschar(s)			
Any	92 (100)	ND	92 (70)
Multiple eschars	17 (100)	ND	14 (18)
Rash			
Any type	83 (100)	92 (100)	100 (100)
Macules or papules	83 (100)	83 (37)	100 (100)
Petechiae	17 (100)	47 (80)	ND
Vesicles or pustules	42 (100)	ND	100 (82)
On palms or soles	45 (92)	82 (70)	2 (91)
Myalgia	92 (100)	59 (98)	39 (9)
Headache	83 (100)	72 (100)	92 (100)
Lymphadenopathy	25 (100)	20 (29)	17 (9)
Nausea or vomiting	8 (100)	60 (94)	7 (82)
Diarrhea	0 (92)	20 (94)	ND
Coma, delirium, or seizure	0 (100)	27 (86)	0 (100)
Hospitalization	33 (100)	78 (100)	18 (100)
Death	0 (100)	7 (100)	0 (100)

NOTE. Data are percentages of patients with characteristic (% of patients for whom frequency of the characteristic was specifically assessed). ND, feature not documented in the series evaluated.

[a] From references 6–8 and data herein.
[b] From references 14–17.
[c] From references 18–20.

CID 2008; 47:1188-96

Figure 2. Cutaneous lesions from patients with confirmed *Rickettsia parkeri* rickettsiosis. Inoculation eschars, representing the site of primary infection following a bite from an *R. parkeri*–infected tick, are present on the lateral aspect of the palm of patient 5 (*A*) and on the lower extremities of patient 4 (*B–D*). These lesions are 0.5–1.5 cm wide, with a central area of ulcerated or scabbed skin surrounded by a halo of erythema (*A* and *B*) or petechiae (*C*). Panel D shows multiple eschars on patient 4. The rash of *R. parkeri* rickettsiosis, as seen on patients 4 (*E*) and 5 (*F*), is a maculopapular or papulovesicular eruption on the trunk and extremities, occasionally involving the palms and soles.

CID 2008; 47:1188-96

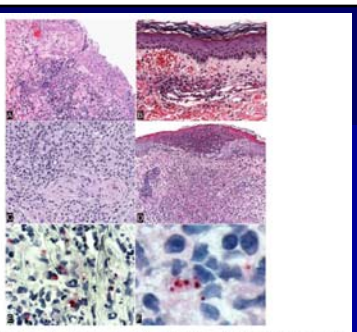

Figure 3. Histopathological and immunohistochemical characteristics of eschars (*A–C* and *F*) and rash lesions (*D* and *E*) of patients with *Rickettsia parkeri* rickettsiosis. *A*, Denuded epidermis with dermal necrosis and mixed inflammatory cell infiltrates (patient 7). *B*, Lymphocytic vasculitis in a small vessel in the superficial dermis associated with partially occlusive fibrin thrombi and extravasated erythrocytes (patient 1). *C*, Dense perivascular lymphohistiocytic infiltrates in the deep dermis (patient 5). *D*, Intraepidermal pustule and extensive neutrophilic and mononuclear inflammatory cell infiltrates associated with necrosis in the middermis. *E*, Immunohistochemical localization of intact *R. parkeri* and rickettsial antigens in the cytoplasm of mononuclear cells (patient 6). *F*, Coccobacillary forms of *R. parkeri* in mononuclear inflammatory cells in an eschar (patient 7). Hematoxylin and eosin stain (*A–D*) and alkaline phosphatase with polyclonal anti–*R. rickettsii* antibody (1:500) and naphthol-fast red, with hematoxylin counterstain (*E* and *F*). Original magnifications, ×25 (*A* and *D*), ×50 (*B*), ×100 (*C* and *E*), and ×156 (*F*).

CID 2008; 47:1188-96

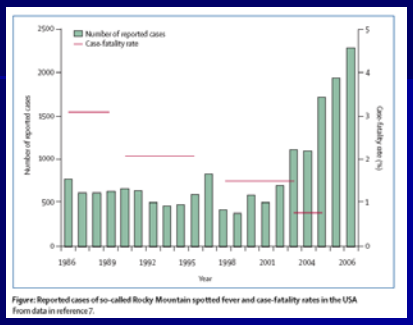

Figure: Reported cases of so-called Rocky Mountain spotted fever and case-fatality rates in the USA from data in reference 7.

Lancet ID 2008; 8:587-89

A 28 year old woman comes to the travel medicine clinic eight days after returning from a safari in Tanzania and Swaziland. She has had fever, mild headache, and fatigue for five days. Prior to travel, she was immunized against yellow fever. She has not taken mefloquine as prescribed because it made her "feel weird".

95

Temperature is 38.1º, P76, R14, BP 116/70. Exam is unremarkable except for four punctuate eschars on the legs and bilateral inguinal lymph node enlargement. Thick and thin blood smears (x2) for malaria are negative.

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Which Of The Following Is The Most Likely Etiologic Agent?

A. Rickettsia conorii
B. Rickettsia africae
C. Borrelia duttonii
D. Leishmania donovani
E. Yersinia pestis

97

African Tick Bite Fever

- Seroprevalence, *R. africae*, 30-56%
- *Amblyomma* ticks (cattle, ungulates) not host specific
- Clusters of cases, multiple eschars
- Incubation period 6-7d
- Dx: PCR, MIFA, WB, culture
- Complications unusual
- Rx: doxycycline (? single day)

98

99

Clinical Characteristics Of *R. Africae* Infection

	%
fever ≥ 38.5º	88
neck muscle myalgias	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

100

Figure 2. Four Inoculation Eschars (Arrows) on the Legs of a Patient Who Presented with African Tick-Bite Fever after Returning from a Safari in South Africa.

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Rickettsiosis And The Returning Traveler *

- *R. africae* > murine typhus > mediterranean spotted fever > scrub typus
- Others: RMSF, epidemic typhus, N. Asian or Queensland tick typhus
- ? 3rd after malaria, typhoid

* Jensenius M, et al. Clin Infect Dis 2004; 39: 1493-9, and Inter J Infect Dis 2004; 8: 139-46.

102

Question

A 43 year old is visiting southern Missouri on vacation and returns to your office 7 days later with fever, headache, and diffuse myalgias. Your physical examination does not localize any specific findings.

Your laboratory evaluation shows: CBC- WBC: 2.1/mm^3 (80% PMNs, 10% lymphocytes, 8% monocytes), hemoglobin: 7.0/hematocrit: 24, platelets: 105,000/mm^3; electrolytes: normal, AST: 364/ALT: 289, renal function: normal

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Response

The most appropriate cause of this systemic presentation is:

A. *Histoplasma capsulatum*
B. *Ehrlichia chaffeensis*
C. *Staphylococcus aureus*
D. *Hepatitis B virus*
E. *Borrelia burgdorferi*

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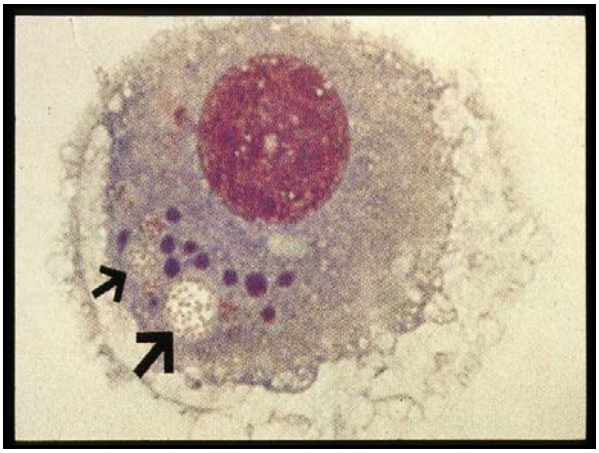
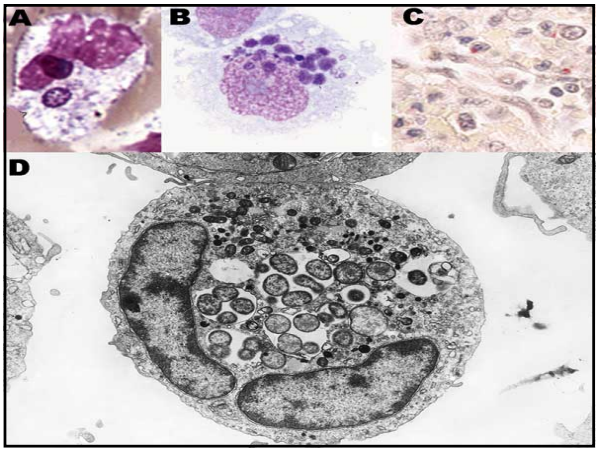


HME

E. chaffeensis, lone star tick
SE, SC, MA USA
80-90% tick exposure; 67% male
≥ 1500 cases
Mortality 2.7%
Dx acute: PCR, morulae (2-3%)
convalescent: serology

106



HGE (Anaplasmosis)

A. phagocytophilum; deer ticks
NE, upper MW, W, Europe
45-85% tick exposure; 56% male
> 2200 cases
Mortality 0.5-1.0%
Dx: same as HME (morulae > 20%)

108

Table 2. Risk Factors for Acquisition of Human Granulocytic Anaplasmosis Among 39 Contacts Exposed to Index Patient While at the Regional Hospital

Exposure to Index Patient	No./Total (%)		Relative Risk (95% Confidence Interval)[a]	*P* Value[b]
	Attack Rate With Exposure Factor	Attack Rate Without Exposure Factor		
≤50 cm to nose and mouth	9/28 (32.1)	0/11 (0)		.04
>2 h	9/20 (45.0)	0/19 (0)		.001
During or after intubation	9/30 (30.0)	0/9 (0)		.09
During massive hemorrhage period	4/9 (44.4)	5/30 (16.7)	2.7 (0.9-7.9)	.17
Any direct blood contact	9/22 (40.9)	0/17 (0)		.002
Direct respiratory or tracheal secretion contact	7/13 (53.8)	2/26 (7.7)	7.0 (1.7-29.1)	.003

[a] Infinite or not able to be calculated.
[b] Fisher exact test (2 tailed).

JAMA 2008; 300:2263-70

Ehrlichiosis "ewingii"

- *E. ewingii*; lone star ticks
- SE, SC, MA USA
- 90% tick exposure; 100% male
- ≈ 20 cases (most immunocompromised)
- Mortality: none to date
- Dx: same as HME

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Ehrlichiosis/Anaplasmosis

- Spring-summer illness; geography
- Fever, HA, ,malaise, myalgias, arthralgias, anorexia, +/- rash, +/- tick bite (occ. serious)
- Leukopenia, thrombocytopenia, ↑ LFTs
- PCR, morulae, serology
- Doxycycline (? rifampin)

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Ehrlichia sp./HIV co-infection*

21 patients (20 male); median age=43
E. chaffeensis (13), *E. ewingii* (4), either (4)
Median CD4 = 137; $^{11}/_{21}$ on HAART
Presenting sx similar but *E. chaffeensis* more severe (ARDS, ARF, DIC etc.)

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Ehrlichia sp./HIV co-infection*

Nadir cytopenias << non-HIV
Dx: PCR ($^{16}/_{18}$), ≥4-fold Ab ($^{12}/_{14}$), morulae ($^{7}/_{11}$), immunohistochemistry ($^{3}/_{3}$), culture ($^{6}/_{7}$)
6 deaths (≅50% CD4<100), all *E. chaffeensis*

*Paddock CD, et al. Clin Infect Dis 2001; 33:1586-94

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Antibiotic activity vs. *Anaplasma phagocytophila* strains*

	MIC_{90} (μg/ml)
β lactams	≥ 128
aminoglycosides	≥ 64
chloramphenicol	≥ 8
macrolides	≥ 16
doxycycline	≤ 0.03
rifampin	≤ 0.03
Levofloxacin/moxi	0.06 – 0.5/0.03

*Maurin M, et al. Antimicrob Agents Chemother 2003; 47:413-5.
Brauger S et al. Antimicrob Agents Chemother 2004; 48: 4822-8.

114

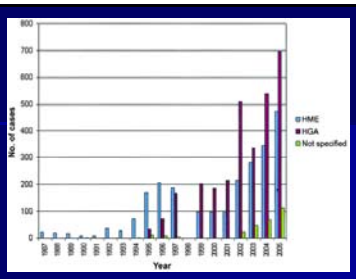

Figure 1 Cases of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) reported in the United States since 1986. The data reflect information available until January 2006; data for the year 1998 were unavailable.

115

Table 1. Meta-analysis of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) symptoms, signs, and laboratory findings.

Symptom, sign, or finding	Patients, % (no. evaluated) HME	HGA
Symptom or sign		
Fever	97 (633)	93 (521)
Myalgia	57 (250)	77 (516)
Headache	80 (240)	76 (365)
Malaise	82 (234)	94 (288)
Nausea	64 (143)	38 (258)
Vomiting	33 (192)	26 (90)
Diarrhea	23 (197)	16 (95)
Cough	26 (155)	19 (260)
Arthralgias	41 (211)	46 (504)
Rash	31 (286)	6 (357)
Stiff neck	3 (240)	21 (24)
Confusion	19 (279)	17 (211)
Laboratory finding		
Leukopenia	62 (276)	49 (336)
Thrombocytopenia	71 (247)	71 (336)
Elevated serum AST or ALT level	83 (276)	71 (177)

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

Table 1 Meta-analysis of human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) symptoms, signs, and laboratory findings.

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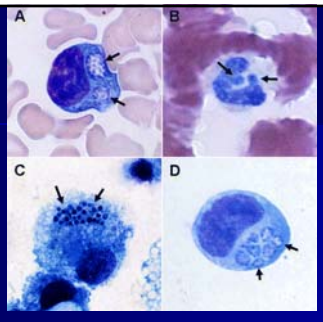

Figure 2 *Ehrlichia chaffeensis* (*A* and *C*; Wright stain) and *Anaplasma phagocytophilum* (*B* and *D*; Hema-3 stain) morulae *(arrows)* in peripheral blood monocytes *(A)*, peripheral blood neutrophils *(B)*, DH82 canine histiocytic cell culture *(C)*, and human HL-60 promyelocytic cell culture *(D)*. Original magnification, ×260. (Panel A courtesy of A. Marty.)

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Table 3. Diagnostic tests for human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), by time interval after onset of clinical illness.

Weeks after onset, diagnostic test	Sensitivity, %	
	HME	HGA
≤1		
Blood smear evaluation	2–38	25–75
PCR	60–85	67–90
Culture	Highly variable[a]	≥55[b]
Serologic testing	22–55 (IgM, ≤44)	24–44 (IgM, 33)
1–2		
Blood smear evaluation	Unknown	63
PCR	Unknown	68
Culture	Unknown	33
Serologic testing	68	91
≥3		
Serologic testing	≥90	≥95

[a] May require weeks of incubation.
[b] May require weeks of incubation; results are often positive within 2 weeks.

Table 3 Diagnostic tests for human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), by time interval after onset of clinical illness.

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Babesia microti

- Nantucket, Martha's Vineyard, Long Island, Eastern Seaboard
- > 300 cases; "flu-like" to fatal
- White-footed mouse; *I. scapularis*
- Severe disease: asplenic, HIV, chemotherapy, age >55, transplant
- Transmission: tickbite, blood transfusion, transplacental

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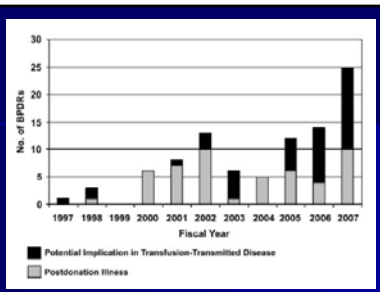
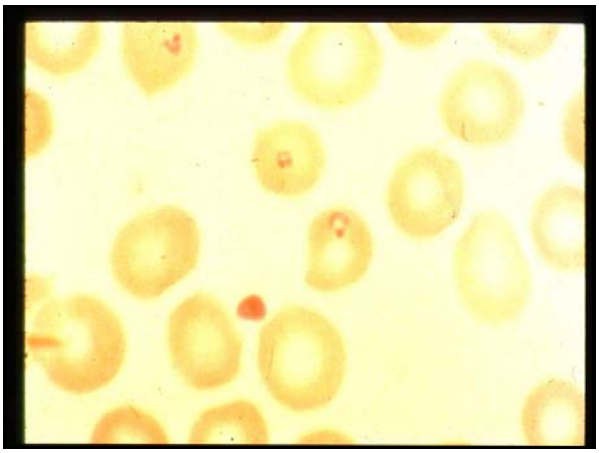
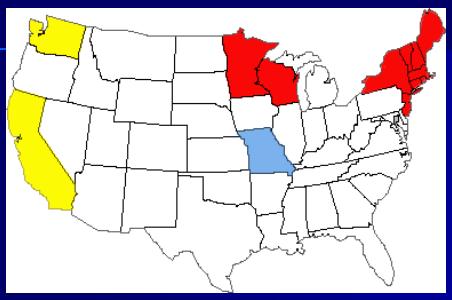


Figure 1. Summary of babesiosis-related Biological Product Deviation Reports (BPDRs) received by the US Food and Drug Administration (FDA)during fiscal years 1997–2007 (the FDA fiscal year is from 1 October through 31 September). These data do not include reports of infected donors identified prospectively through antibody assay research trials. BPDRs may include 11 recipient, unit, or donation. Potential implication in transfusion-transmitted disease refers to reports that indicate the safety of a blood component unit that may have been affected (e.g., instances when a blood transfusion recipient received a diagnosis of babesiosis, but the donor could not be contacted for confirmation). Postdonation illness refers to illness in donors who notified the blood collection establishment after donation that they had received a diagnosis of babesiosis. Whether these donors were infected at the time of donation was unknown; all units (not yet transfused) from these donors were withdrawn, and the donors were indefinitely deferred. CID 2009; 48:25-30



Babesiosis: USA



WA-1 MO-1 *B. microti*

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Risk Factors For Severe Babesiosis*

- n=34 over 13 years on Long Island (2)
- 41% ARDS, DIC, CHF, ARF (3 deaths)
- Risk factors: age >60, splenectomy, immunosuppression (inc. HIV), increased LTFs, thrombocytopenia, anenia (Hb<10), parasitemia (>10%)

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

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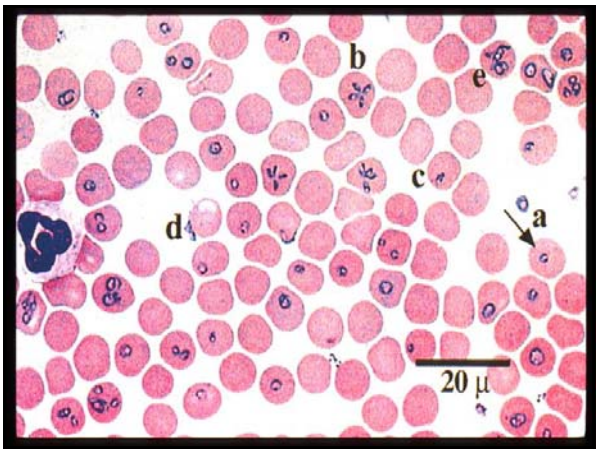

Diagnosis Of Babesiosis

- Wright-Giemsa stained thin blood smears (1-3µ intraerythrocytic merozoites, no hemozoin deposition, parasitemia 1- >80%)
- IFAT: dx of choice for Ab (88-96% sensitivity, 92-100% specificity)
- ELISA (cattle screening)
- Inoculation of animals
- PCR: 18s r RNA gene (supportive but promising)

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Treatment Of Babesiosis

- Standard: Guinine 650mg p.o. tid plus clindamycin 1200mg p.o. bid x7d
- Blood exchange transfusion (all *B. divergens* and severe cases)
- HIV: consider addition of doxycycline 200mg qd, azithromycin 2000mg qd, atovaquone (?)
- Heparin (?)

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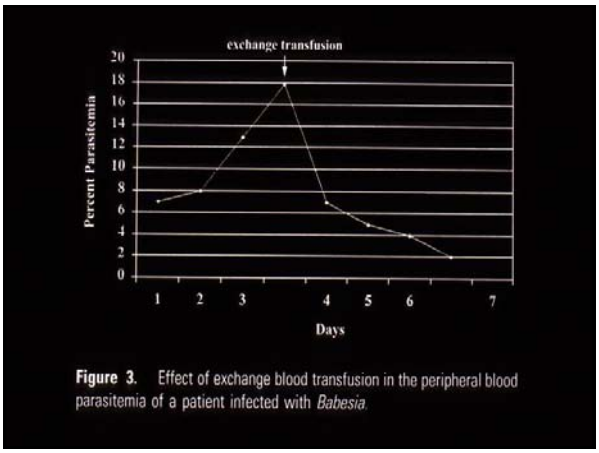

Figure 3. Effect of exchange blood transfusion in the peripheral blood parasitemia of a patient infected with *Babesia*.

Tick Paralysis, Washington State; 1946-1996*

- 33 cases; 76% female; 82% < 8 years old
- Most acquired east of cascade mountains
- 54% hospitalized; April to June
- All *Dermacentor andersoni*
- 2 deaths

*Adapted fromDworkin MS et al. Clin Infect Dis 1999; 29:1435-9

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Cluster Of Tick Paralysis Cases, Colorado

- May 26-31, 2006; 4 cases within 20 miles of each other; ages 6, 58, 78, 86 years
- Ticks on neck or back
- Ascending motor paralysis without sensory loss

MMWR 2006; 55: 933-5.

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Question

A 35 year old man from Arkansas presents to your office with eye pain, fever, and a pre-auricular lymphadenitis. He has been camping this spring and has multiple outdoor exposures. The physical examination reveals conjunctivitis with small, yellow scleral nodules. The lymph node is 2.0 X 1.5 cm with tenderness but no fluctuance. The remainder of his physical examination does not reveal a focus of infection.

His laboratory shows a WBC of 18.5 cells/mm³ (85% polymorphonuclear leukocytes), a normal hemoglobin and hematocrit with a platelet count of 312,000/mm³. You initiate topical gatifloxacin and oral cephalexin. He returns in 48 hours with fever and worsening symptoms

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Response

A. The most likely etiology of this presentation is:

B. Ocular methicillin-resistant *Staphylococcus aureus*

C. Pseudomonas conjunctivitis secondary to contaminated contact lens solution

D. Oculoglandular tularemia

E. Parinaud's complex due to *Bartonella henselae*

F. Adenovirus conjuncitivitis

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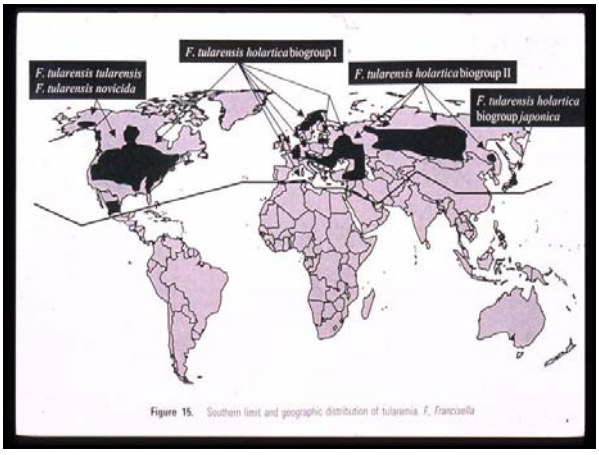
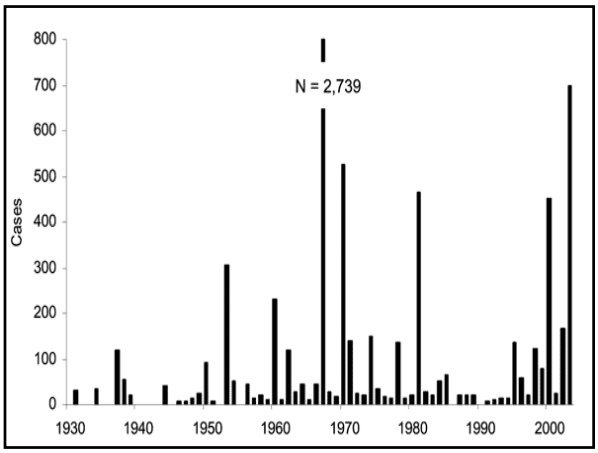
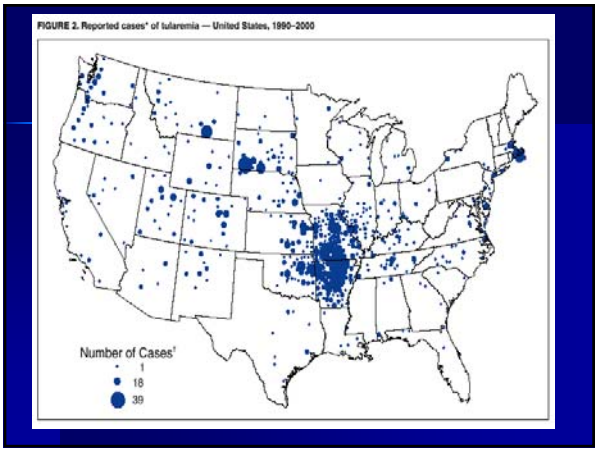


Figure 15. Southern limit and geographic distribution of tularemia. F. Francisella





Tularemia: Signs and Symptoms

	Children	Adult
Lymphadenopathy*	96%	65%
Fever (> 38.3° C)	87%	21%
Ulcer/papule	45%	51%
Myalgia/Arthralgia	39%	2%
Hepatosplenomegaly	35%	
Headache	9%	5%

*Children - cervical, adults - inguinal

Adapted from Jacobs RF et al. *Pediatrics* 76:818, 1985

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Tularemia

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Treatment Of Tularemia, Spain, December 1997-february 1998 (N=142)*

	% success
streptomycin	76.6
ciprofloxacin	95.5
tetracycline	57.1
other	50.0

*Pérez-Castrillón JL, et al. Clin Infect Dis 2001; 33:57

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Tickborne Relapsing Fever US

- *Borrelia sp.* (mainly *B. hermsii*)
- Ornithodorus ticks (brief, painless)
- Fever (relapsing), HA, myalgias,; N/V
- Can be severe; ARF, ↓ platelets, ↑
- AST/bilirbin, ARDS (5-6%), JHR
- 11 Westeren states; ≈ 25 cases/yr (CDC)

MMWR 2007; 56:1073-6.

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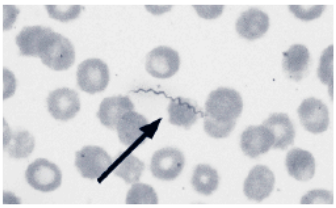
FIGURE. Spirochete (noted by arrow) on peripheral blood smear obtained from California patient (Giemsa stain)



Photo/CDC

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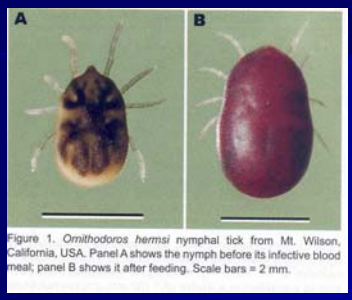

Figure 1. *Ornithodoros hermsi* nymphal tick from Mt. Wilson, California, USA. Panel A shows the nymph before its infective blood meal; panel B shows it after feeding. Scale bars = 2 mm.

Borrelia – Relapsing Fever In Africa

- B. crocidurae: West Africa
- B. duttonii, unnamed species: Tanzania
- Ornithodoros sp. ticks (60% (+))
  ≈ children, pregnant women (384/1000!)
- Up to 11% fever by PCR, blood smear

*Kisinza WN, et. al. Lancet 2003; 362:1283-4

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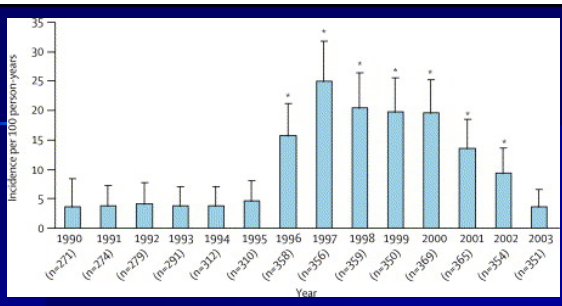

Figure 2. Incidence (95% CI) of TBRF, 1990–2003
*Significantly more cases of TBRF than in 1990 ($p<0.05$ with GEE model). Number of persons under survey ranged from minimum 271 in 1990 to maximum 369 in 2000.

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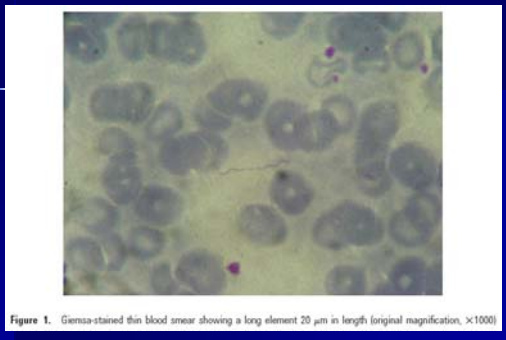

Figure 1. Giemsa-stained thin blood smear showing a long element 20 μm in length (original magnification, ×1000)

CID 2008; 47:1442

Postexposure doxycycline for prevention of tick borne relapsing fever

- Israel; n=93; doxy 200 mg day 1, 100 mg qd x 4d mean 2 days after tick bite
- 47 on doxy, 46 placebo; all 10 cases TBRF in placebo

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Thank You! and The End.

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