Tick-borne relapsing fever in Arizona

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Case presentation

- serology and again his symptoms resolved.

 A 72 year-old man developed shaking chills and fever in June 2017 while staying at his cabin near Greer, AZ for the previous 3 weeks.

 He was evaluated in the local ED and amoxicillin for presumed sinusitis was prescribed. Several hours after the first dose, he developed severe rigors and was admitted to the hospital. WBC 1800/µL; platelets 44,000/µL; total bilirubin 2.3 mg/dL; AST 78 IU; peripheral smear: toxic granulations only. He improved with observation and was discharged.

 One week later, he developed recurrent rigors and fatigue. He was evaluated in the MCA ED in Phoenix and lymphopenia was again noted. Fluconazole was started based on positive EIA coccidioidal





Case presentation

- tachycardia. He stopped the doxycycline.
- during the previous admission was reported as indeterminate. and completed a 2-week course with resolution of symptoms.
- performed at the CDC.

• Two weeks later, the fevers with rigors recurred. He represented to the MCA ED and was prescribed oral doxycycline 100 mg BID. Within hours of the first dose, he developed severe rigors, dizziness and

• Subsequently, a whole blood PCR for Borrelia miyamotoi obtained Because of this, doxycycline was restarted The patient tolerated this

 Subsequent immunofluorescent serology for Borrelia hermsii revealed an IgG titer of 1:128 with positive IgM and IgG serology that was



Tick-Borne Relapsing Fever in the White Mountains, Arizona, USA, 2013–2018

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Case series

- Six patients were identified diagnosed with relapsing fever were identified from practitioners in Phoenix and Tucson between 2013 and 2018
- All visited cabins in the White Mountains of Arizona from late spring to early fall
- In five patients, the first complaint was recurrent fever \bullet
- All were diagnosed in either Phoenix or Tucson •
- Most had laboratory abnormalities \bullet
 - leukopenia
 - thrombocytopenia -
 - elevated aminotransaminases
- All responded to doxycyline •

Two had Jarisch-Herxheimer reactions associated with antibiotic treatment



Wright stain of peripheral blood demonstrating extracellular spirochetes (arrows) confirming tick-borne relapsing fever in a 64-year-old woman, Tucson, Arizona, USA, October 2016 (courtesy Brentin Roller).

History of relapsing fever in Arizona

- TBRF first described in Arizona in 1930 in a patient living near Greer.
- Several major outbreaks around the Grand Canyon (Coconino County) in recent years
 - · 1977
 - 27 employees and 35 over-night guests residing at "rustic" cabins on North Rim
 - rodent nests found in walls and attics
 - O. hermsii ticks isolated
 - 1990
 - 15 cases
 - over-night stay in cabins not rodent-proofed
 - ·2014
 - 6 cases among high-school students
 - all slept in the camp-site's only cabin
 - it had been rodent-proofed but no acaricides had been applied



Exposure location for historic (1973–2014) tick-borne relapsing fever outbreaks in Coconino County and 6 (2013–2018) cases in the White Mountains region, Arizona, USA (courtesy Hayley Yaglom).







Soft Tick Relapsing Fever — United States, 2012–2021

O White dot = one case

MMWR 2023; 72 (29):777

Borrelia associated with relapsing fever

- Spirochetes with a small genome
 - of blood smears
- Four forms:
 - Louse-borne (LBRF): *B. recurrentis*
 - Tick-borne (TBRF):
 - Ornithodoros (soft-bodied): multiple species, **B. hermsii** most frequent
 - Ixodes (hard-bodied): **B. miyamotoi** (geography similar to Lyme disease)
 - Amblyomma americanum (lone-star tick): **B. lonestari** recent case in Alabama (Emerg Infect Dis 2023; 29:441)

- Not visualized on Gram stain but can be visible on Giemsa or Wright staining

Common Borrelia species associated with Ornithodoros relapsing fever in the United States

Organism	Arthropod vector	Geographic distribution	Tick habitat	Reservoir
Borrelia hermsii	Ornithodoros hermsii	Western United States and Canada; higher elevations (1500-8000')	Intermittently occupied cabins	Ground squirrels, tre squirrels, and chipmur

 Borrelia turicata	Ornithodoros turicata	Western and southwestern United	Caves	Prairie dogs, ground squirrels, rodents, catt
		States; lower elevations		and snakes
Borrelia parkeri	Ornithodoros parkeri	rare cases in Western	Burrows, rodent nests,	Ground squirrel

Don cha parken	Ominodoros parken	rare cases in Western	Burrows, rodent nests,	Ground squirrel
		United States; only	and caves	
		confirmed case in		
		Colorado		

adapted from Dworkin et al, Infect Dis Clinics North Am 2008; 22:449

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Symptoms of TBRF

TABLE 2. Documented signs and symptoms in patients with soft tick relapsing fever (n = 207) — United States, 2012–2021

Sign or symptom	No. (%)* of patients		
Fever (at least one episode)	201 (97)		
Headache	130 (63)		
Myalgias	123 (59)		
Chills	112 (54)		
Nausea/Vomiting	94 (45)		
Sweats	65 (31)		
Fatigue/Malaise	65 (31)		
Anorexia	63 (30)		
Arthralgias	43 (21)		
Cough	28 (13)		
Altered mental status	24 (12)		
Thrombocytopenia	21 (10)		
Rash	20 (10)		
Photophobia	14 (7)		
Neurologic or ocular symptoms [†]	10 (5)		
Abdominal pain	9 (4)		

- or symptoms.
- vision, eye pain, and eye swelling.

* Among persons with available clinical data; patients could have multiple signs

[†] Reported neurologic or ocular symptoms included uveitis, Bell's palsy, blurred

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Laboratory abnormalities of TBRF

Abnormality

Thrombocytopenia

Leukocytosis, leukopenia

Anemia

Liver abnormalities

ESR

Coagulation abnormalities

Comment

Most frequent finding, generally moderate, <150,000/µL; occasionally <50,000µL

May be moderately elevated (>10,000/µL) or modestly suppressed

(<4,000/µL) Mild-to-moderate (Hb<12 gm/dL) and normocytic

↑aminotransaminases; ↑bilirubin

Elevated, sometimes >100 mm/hr; CRP and procalcitonin also occasionally elevated

↑PT and PTT

Diagnosis of TBRF

Method	Advantage	Disadvantage	Use
Microscopy	Fast; widely available	Variable sensitivity and requires 10 ⁴ -10 ⁵ spirochetes/mL; does not allow species differentiation	Diagnostic gold standard
Serology	Allows retrospective evaluation of infection based on 4-fold rise; can be species specific	Not useful as acute diagnostic method; not commercially available; cross-reactivity with other non-RF <i>Borrelia</i>	Available at few laboratories
PCR	Species specific ; high sensitivity allows to differentiate TBRF- from LBRF- <i>Borrelia</i> and among TBRF- <i>Borrelia</i>	Currently no standardized protocol available	Largely restricted to research institutions
Culture	Isolation and growth of <i>Borrelia</i> spp.	Time and resource demanding; overall challenging	Largely restricted to research institutions
Animal inoculation	Enhanced sensitivity in cases with negative microscopy; allows differentation between TBRF and LBRF	Time and resource demanding	Historical research method

adapted from Jakab et al; PLoS Neglected Tropical Diseases 2022; doi: 10.1371/journal.pntd.0010212

Diagnosis and treatment of TBRF

Diagnosis

- Wright or Giemsa stain of peripheral blood smear
 - sensitivity 70% during febrile episode
- Acute and convalescent serology (IFA, EIA)
 - need to request AZDHS to send to CDC
 - cross-reactivity
 - Lyme disease serology
 - VDRL
- PCR or special culture rarely
- Treatment
 - Doxycycline: 100 mg BID for 10 days
 - For CNS disease
 - Penicillin G: 3 million U q4 hr IV 10-14 days
 - Ceftriaxone: 2 gm q12 hr IV 10-14 days

Antigenic variation and relapsing fever

- Borrelia have genes for serospecific outer membrane surface lipoproteins on extrachromosomal linear plasmids
 - these genes are normally transcriptionally silent
 - if the gene recombines at another site on the plasmid, it may become active if it is located down-stream from a promoter gene
 - Borrelia hermsii has 30 variant genes that may recombine
- Results in waves of antigenically distinct organisms as immune response occurs to each new antigenic variant
- Clinical result is recurrent fevers with bacteremia until antigenic repertoire is exhausted



Dai Q, et al. Mol Microbiol 2006; 60: 1329







Ornithodoros ticks and relapsing fever

- "Soft-bodied" ticks
- <u>Nidicolous</u> or nesting: inhabit rodent burrows, decaying wood, "rustic cabins;" caves; live in close proximity to their small mammal hosts
- Obligate blood feeders on squirrels, mice, rats, owls, and lizards
- Feed at night for ~20 minutes and the bite is minimally symptomatic
- Persistence

 - Individual ticks can survive without a blood meal for 5 years and can live as long as 20 years - Borrelia within the ticks concentrate in salivary glands for life
 - Transovarian transmission occurs
- Therefore, in addition to rodent-proofing of cabins, acaracides (anti-tick, anti-mite pesticides) must be applied for prevention



Ornithodoros hermsii



Jarisch-Herxheimer reaction (JHR)

- Transient reaction usually within 1-12 hr of treating a spirochete infection and resolving within 24 hr
 - Syphilis (particularly secondary form)
 - Leptospirosis
 - Lyme disease
 - Relapsing fever

Common manifestations

- Fever and chills
- Tachycardia
- Hypotension
- Worsening rash (if present)
- Mechanism of action
- Not fully delineated
- response

- Presumed to be due release of endogeneous pyrogens from spirochete resulting in acute inflammatory

Questions or comments?