Clinical Infectious Disease

SECOND EDITION

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165. Relapsing fever borreliosis

Sally Cutler

HISTORY

The relapsing fever spirochetes comprise a number of different species (Table 165.1) with many transmitted by specific tick species. *Borrelia recurrentis* is the notable exception in that it is transmitted by clothing lice.

CLINICAL PRESENTATION

The chief sign is that of fever, often accompanied by chills, headaches, arthralgia, myalgia, and tachycardia. Other signs may include jaundice, petecheal rash, conjunctivitis, nausea, hepatosplenomegaly, and epistaxis. Infection with *Borrelia*

Table 165.1 Characteristics of relapsing fever borrelliae

Organism name	Arthropod vector/reservoir	Vertebrate reservoirs	Clinical infection	Geographic region
B. recurrentis	*Pediculus humanus humanus*	Man	LBRF – human	Africa (formerly worldwide)
B. baltazardii	Unknown	Unknown	TBRF – human	Iran
B. crocidurae	*Ornithodoros sonrai*	Rodents	TBRF – human	West Africa
B. duttonii	*Ornithodoros moubata*	Man	TBRF – human	Africa (Central, Eastern)
B. hermsii	*Ornithodoros hermsi*	Rodents	TBRF – human; canine	Canada, Western USA
B. hispanica	*Ornithodoros marocanus; Ornithodoros occidentalis; Ornithodoros kairouanensis* (formerly *Ornithodoros erraticus*[a])	Rodents	TBRF – human	Algeria, Morocco, Portugal, Spain, Tunisia
B. latyschewii	*Ornithodoros tartakovskyi*	Rodents; reptiles	TBRF – human	Central Asia, Iran, Iraq
B. mazzottii	*Ornithodoros talaje*	Armadillos; rodents	TBRF – human	Southern USA, Mexico, Guatemala
B. merionesi	*Ornithodoros costalis* *Ornithodoros merionesi*	Rodents	Unknown	North Africa
B. microti	*Ornithodoros erraticus*[b]			Africa, Iran
B. parkeri	*Ornithodoros parkeri*	Rodents	TBRF – human	Western USA
B. persica	*Ornithodoros tholozani*	Rodents; bats	TBRF – human; cat	Asia, Middle East
B. turicatae	*Ornithodoros turicata*	Rodents	TBRF – human; canine; birds	USA, Mexico
B. venezuelensis	*Ornithodoros rudis*	Rodents	TBRF – human	Central and South America

[a] *Ornithodoros erraticus* represented a complex. Recent taxonomic molecular studies redressed the phylogeny suggesting that *O. erraticus sensu stricto* not an efficient vector for *Borrelia*.

[b] Molecular confirmation of *O. erraticus* identity unavailable at time of writing.

Abbreviations: LBRF = louse-borne relapsing fever; TBRF = tick-borne relapsing fever.

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Table 165.2 Treatment of relapsing fever borreliosis

Antibiotic	Dosage used	Duration	Comments
Penicillin	400 000–600 000 IU daily	7 to 14 d	Single dose can be curative for LBRF CNS involvement
Tetracycline	200–250 mg BID to 500 mg QID	7 to 14 d	Single dose can be curative for LBRF
Doxycycline	200-250mg 4mg/kg/d	7 to 14 d	Can be used as prophylaxis (200 mg d 1, then 100 mg daily 4 d post exposure)
Erythromycin	500 mg QID (50 mg/kg children)	7 to 14 d	During pregnancy or children
Chloramphenicol	500 mg QID (12.5 mg/kg children)	7 to 14 d	During pregnancy or children
Ceftriaxone	2 g daily	7 to 14 d	CNS involvement

Abbreviation: CNS = central nervous system.

duttonii has been associated with significant perinatal mortality in endemic regions such as Tanzania.

Although eventually eliminated by the adaptive immune response, repeat infections can occur in a previously infected individual.

TREATMENT (TABLE 165.2)

Cases are usually managed with penicillin, doxycycline, or tetracycline treatment. Some prefer penicillin as it is believed that this makes Jarisch–Herxheimer reactions (JHR) less likely. Less frequently, cephalosporins, erythromycin, and chloramphenicol have been used.

JHR

The JHR was first described by Adolf Jarisch in 1895 and later by Karl Herxheimer in 1902, in relation to another spirochetal infection, syphilis, but this also occurs in approximately 5% of relapsing fever patients upon treatment. Patients may show an exacerbation of symptoms or "therapeutic shock" during the initial 24 hours post commencing treatment. The JHR is mediated by a release of pyrogenic cytokines (including tumor necrosis factor-α [TNF-α], interleukin [IL]-6, and IL-8) and is treated symptomatically.

TRANSMISSION AND PATHOGENESIS

Transmission of tick-borne relapsing fever (TBRF) occurs during the feeding of *Ornithodoros* soft ticks (up to 20–30 minutes), generally whilst their host is sleeping. The spirochetes may be present within the tick salivary glands, coxal fluid, and feces, facilitating transmission to their vertebrate host. Transovarial transmission occurs for some TBRF borreliae.

Unlike TBRF, in louse-borne relapsing fever (LBRF) the borreliae within the louse vector penetrate the louse's gut epithelium where they can multiply in the louse hemolymph and are also able to be excreted in louse feces, but do not undergo transovarial transmission. Human transmission occurs through crushing lice or their feces into skin abrasions often through scratching.

Once the human is infected, spirochetes multiply in the blood, sometimes to levels of up to 100 000/mm^3. This spirochetemia evokes the typical febrile response after which this infection is named. The induced antibody response clears the bloodborne infection; however, the spirochtes soon re-emerge having undergone antigenic variation. A new wave of infection follows that again is eventually controlled through the host's antibody response. Clinically, up to 4 to 5 febrile episodes can occur in LBRF, whilst up to 13 relapses have been recorded for TBRF. Persistence within the human host is a result of a complex interplay of antigenic variation, complement evasion strategies, erythrocyte rosetting, and potentially other mechanisms.

The spirochetes show varying neurotropic potential. This can promote cerebral hemorrhage, for example with *B. recurrentis*. They cross the placenta with associated foetal loss through abortion or congenital infection, particularly *B. duttonii*. Myocarditis and hepatic failure may complicate infection with some of the more virulent members of the relapsing fever borreliae (*B. recurrentis/B. duttonii*), where mortality can reach 10% in untreated cases.

LABORATORY DIAGNOSIS

Microscopy has been the primary diagnostic approach, with demonstration of the spirochetes in blood with Wright's or Giemsa stains, silver staining, or the use of dark-field microscopy for observing motile spirochetes (Figure 165.1). Whilst these methods can detect the causative species, sensitivity is poor, particularly for some species such as *Borrelia crocidurae* where the blood burden is lower than for example *B. recurrentis*. This is further complicated by the need to collect blood during febrile episodes. It is not possible to differentiate species using microscopy.

Animal inoculation can recover and identify cultivable strains. Cultivation can also be achieved from clinical samples into specialized media (such as BSKII) but this is technically demanding. This has been largely superseded by molecular identification approaches, and molecular diagnostics are currently the mainstay for both detection and typing of relapsing fever borreliae.

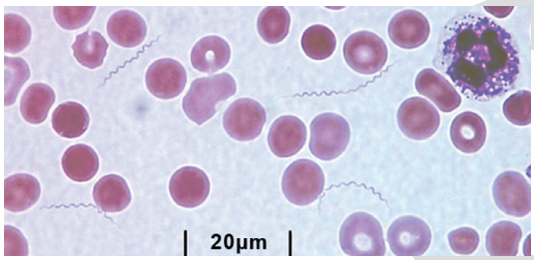

Figure 165.1. Motile spirochetes.

CURRENT EPIDEMIOLOGY

The relapsing fever spirochetes have been divided into those in the Old World and New; however, with improving phylogenetic tools, this division now appears artificial. The prevalence of tick-borne strains correlates with specific regions, particularly African TBRF, probably resulting from climatic conditions conducive for its tick vector. This has not been the case for louse-borne *B. recurrentis*, which was formerly worldwide, but now is restricted to areas where clothing lice persist.

Figure 165.2 depicts the global location of relapsing fever.

It is increasingly apparent that the burden of relapsing fever infections in endemic regions is underdiagnosed. Recent reports from Senegal have suggested that this is the cause of some 13% of fevers presenting at local dispensaries, representing an alarming 11 to 25 cases per 100 person-years. Studies of febrile patients in Morocco have suggested that 20.5% were TBRF cases. Although not at these levels, cases are more frequently being detected in the USA.

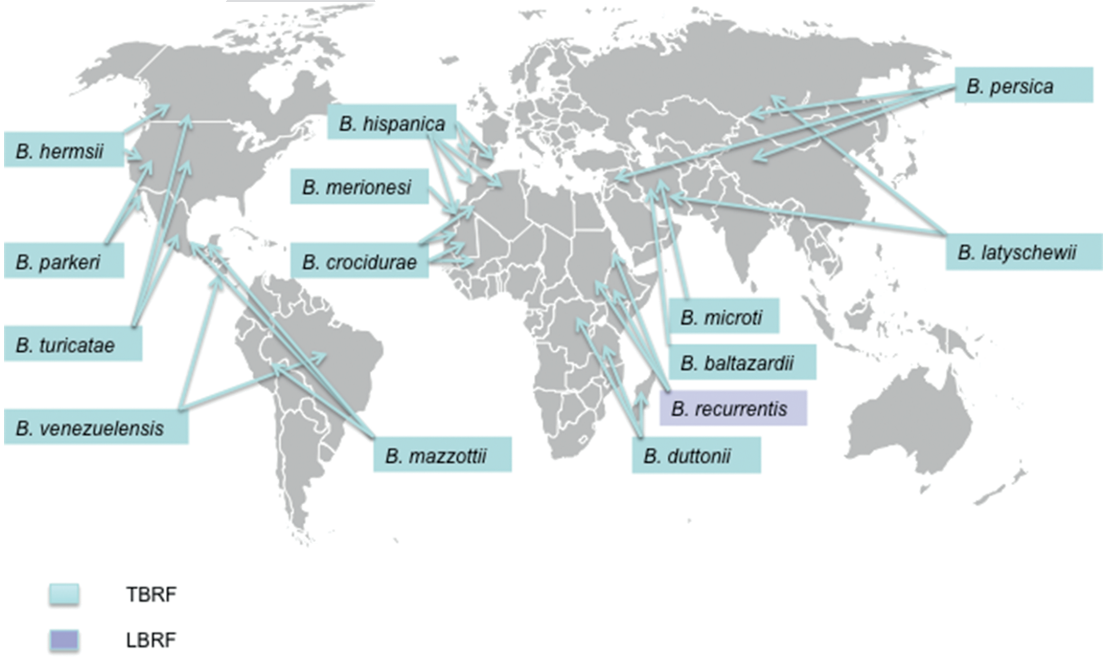

Figure 165.2. Global location of relapsing fever.

Epidemiology of LBRF has changed drastically with the reduced level of infestation with clothing lice. The infection remains in areas of extreme poverty such as Ethiopia, sometimes spilling into adjacent regions, such as an outbreak in the Darfur region of Sudan. During this outbreak between 1999 and 2000 some 20 000 cases occurred with a 10% mortality rate.

RESERVOIRS OF INFECTION

The majority of relapsing fever spirochetes are zoonoses with vertebrate reservoir species (Table 165.1). In the majority of cases, these reservoir species are rodents; however, bats, birds, and reptiles may also have a reservoir role. The notable exceptions are *B. recurrentis* and *B. duttonii*, both of which have an exclusive human reservoir. Many also consider the tick vector a reservoir of infection for TBRF, facilitated by the impressive longevity of these ticks that can survive for many years with their infecting spirochetes.

RISK GROUPS

Both LBRF and TBRF have their greatest burden among those living in extreme poverty.

Occupational contact with tick-infested environments has resulted in clusters of infection, particularly among military personnel who have used caves during training activities, with a resulting clinical burden of up to 6.4 cases/100 000 in Israel. Similarly, conservation workers are at risk. Imported cases have been encountered through migration and tourism, typically in rural regions where intermittently used holiday accommodation has provided refuge for reservoir hosts and their associated tick vectors.

CONTROL AND PREVENTION

Relapsing fever spirochetes remain susceptible to penicillin, tetracycline/doxycycline, chloramphenicol, ceftriaxone, and erythromycin (Table 165.2). Wide use of antimicrobials coupled with improvements in living conditions has reduced the incidence of infection. This is not so apparent for the tick-borne forms of disease that persist in their longer-lived tick vector/reservoirs and through zoonotic vertebrate reservoir species. The burden of TBRF among subsistence agro-pastoralist communities in developing nations remains substantial. Use of acaracides has met with some success, but costs are prohibitive. If contact is unavoidable, doxycycline prophylaxis has been used for short-term prevention.

SUGGESTED READING

Assous MV, Wilamowski A. Relapsing fever borreliosis in Eurasia – forgotten, but certainly not gone! *Clin Microbiol Infect*. 2009;15:407–414.

Cutler SJ. Possibilities for relapsing fever reemergence. *Emerg Infect Dis*. 2006;12:369–374.

Cutler SJ. Relapsing fever – a forgotten disease revealed. *J Appl Microbiol*. 2010;108:1115–1122.

Dai Q, Restrepo B, Porcella S, *et al*. Antigenic variation by *Borrelia hermsii* occurs through recombination between extragenic repetitive elements on linear plasmids. *Mol Microbiol*. 2006;60:1329–1343.

Elbir H, Gimenez G, Sokhna C, *et al*. Multispacer sequence typing relapsing fever borreliae in Africa. *PLoS Negl Trop Dis*. 2012;6:e1652. doi: 10.1371/journal.pntd.0001652.

Guerrier G, Doherty T. Comparison of antibiotic regimens for treating louse-borne relapsing fever: a meta-analysis. *Trans R Soc Trop Med Hyg*. 2011;105:483–490.

Lescot M, Audic S, Robert C, *et al*. The genome of *Borrelia recurrentis*, the agent of deadly louse-borne relapsing fever, is a degraded subset of tick-borne *Borrelia duttonii*. *PLoS Genet*. 2008;4:e1000185.

Lopez J, Schrumpf M, Nagarajan V, *et al*. A novel surface antigen of relapsing fever spirochetes can discriminate between relapsing fever and Lyme borreliosis. *Clin Vaccine Immunol*. 2010;17:564–571.

Porcella SF, Raffel SJ, Schrumpf ME, *et al*. Serodiagnosis of louse-borne relapsing fever with glycerophosphodiester phosphodiesterase (GlpQ) from *Borrelia recurrentis*. *J Clin Microbiol*. 2000;38:3561–3571.

Trape J-F, Diatta G, Arnathau C, *et al*. The epidemiology and geographic distribution of relapsing fever borreliosis and its vector ticks in West and North Africa, with a review of the *Ornithodoros erraticus* complex (Acari: Ixodida). *PLoS One*. 2013;6(8):e1810.