Relapsing Fever Borreliae
A Global Review

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KEYWORDS

• *Borrelia* • Tick-borne relapsing fever • Louse-borne relapsing fever
• Argasid (soft) ticks • *Pediculus humanus* • Clothing lice • Epidemic relapsing fever
• Endemic relapsing fever

KEY POINTS

- Most relapsing fever borreliae are transmitted by soft ticks belonging to the *Argasidae* genera; these are rapid-feeding ticks, and their bites may go unnoticed.
- The epidemic member of this group, *Borrelia recurrentis*, is transmitted by the human clothing louse, *Pediculus humanus*.
- Most relapsing fever *Borrelia* are zoonotic, with the exception of *Borrelia duttonii* and *B recurrentis*.
- Relapsing fever borreliosis should be considered among individuals with a relapsing febrile illness and travel history to an endemic region, particularly when malaria is in the differential diagnosis.
- Most infections are successfully managed with penicillin, tetracycline, or doxycycline. The Jarisch-Herxheimer (JHR) reaction can complicate treatment.

HISTORICAL BACKGROUND

The term relapsing fever was first coined after an outbreak of relapsing febrile illness in Edinburgh, United Kingdom. Although Otto Obermeier revealed the infectious etiology of relapsing fever in 1868, fulfillment of Koch's postulates proved challenging because of the predilection of this spirochete for its human host.[1] This limitation prevented publication of his findings until 1873, when sufficient additional evidence was generated to substantiate a causative role for the spirochete. Mackie subsequently disclosed the role of the human clothing louse, *P humanus*, as the vector responsible for transmission of this infection in 1907.[2] During these times, epidemic louse-borne relapsing fever (LBRF) resulted in substantial mortality, particularly during situations of overcrowding and poverty that favored rapid spread of the organism, facilitated

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primarily by the clothing louse vector. Massive outbreaks resulted in millions of cases throughout Africa and globally during World Wars I and II.[3]

Livingstone described another variant of relapsing fever in 1857, this time associated with soft tick vectors.[4] Both Ross and Milne and also Dutton and Todd independently established the role of ticks in transmitting this form of relapsing fever in 1904, with Dutton and Todd both becoming accidentally infected themselves while undertaking their research.[5,6] Dutton kept a temperature chart of his relapsing fever until he succumbed to the illness, with the infectious agent being named after him to reflect his contribution to the understanding of this infection. These researchers drew the parallel between this agent and its louse-borne variant, and their observations were recently substantiated by full genomic sequencing of both infectious organisms.

Subsequently, other *Ornithodoros* soft ticks have been identified as vectors for different species of relapsing fever borreliae. Most of these species seem to have adapted to a particular tick species, and consequently, many are named after their tick vectors (**Table 1**).

CLASSIFICATION

Classification of members within the borreliae was initially based on the type of tick species that serves as their vectors, with the *Borrelia burgdorferi* sensu lato complex transmitted by *Ixodes* species ticks (hard ticks) and the relapsing fever borreliae transmitted by ticks belonging to the *Argasidae* genera (soft ticks; **Fig. 1**). This rather simplistic division has been challenged with the finding that *Borrelia miyamotoi* and *Borrelia lonestari* cluster phylogenetically among the relapsing fever *Borrelia*, yet are transmitted by hard ticks. There are now 23 validated relapsing fever *Borrelia* species, although others are awaiting sufficient data to achieve such status, and many of these agents show a distinct preference for transmission by a specific tick vector species. *Borrelia recurrentis* is the notable exception being transmitted by clothing lice (*P humanus*). **Table 1** lists most of the currently accepted species, although several novel species have recently been described, including *Borrelia mvumii* in ticks from Tanzania,[7] *Borrelia microti* and other species from Iran,[8,9] *Borrelia turicatae*-like *Borrelia* in bat ticks from the United States,[10] and as of yet unnamed species from penguins in South Africa,[11] although the species status and potential virulence of this agent for humans remains to be established.

The taxonomic position of relapsing fever spirochetes is a matter of controversy. Application of discriminatory typing tools (see section on diagnosis and typing) has revealed clades within species such as *Borrelia hermsii*. Others have reported different subpopulations within *B duttonii*, with all of the cultivable isolates grouped into just 1 of 4 subtypes.[12] Conversely, 16S rRNA gene sequencing has underscored the similarity between some species.[13] These similarities have been corroborated by whole genomic sequencing, which suggests that the LBRF, *B recurrentis*, actually represents a degraded subset of *B duttonii*.[14] Sequencing of the closely related zoonotic *Borrelia crocidurae* that predominates in West Africa has further highlighted how conserved these 3 African species are, despite their profound differences in host preferences, severity, and arthropod vectors.[15] Based on their conserved genomic makeup, yet diverse ecology, the above-mentioned 3 relapsing fever *Borrelia* spp may best be considered as ecotypes of a single species.

MICROBIOLOGY

Members of this group have a characteristic Gram-negative helical structure with 3 to 10 coils and a length of 10 to 30 μm and a width of 0.2 to 0.5 μm.[16] Typical of this