

209 Relapsing Fever

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Relapsing fever is caused by infection with any of several species of *Borrelia* spirochetes. Physicians in ancient Greece distinguished relapsing fever from other febrile disorders by its characteristic clinical presentation: two or more fever episodes separated by varying periods of well-being. In the nineteenth century, relapsing fever was one of the first diseases to be associated with a specific microbe by virtue of its characteristic laboratory finding: the presence of large numbers of spirochetes of the genus *Borrelia* in the blood.

The host responds with systemic inflammation that results in an illness ranging from a flulike syndrome to sepsis. Other manifestations are the consequences of central nervous system (CNS) involvement and coagulopathy. Antigenic variation of the spirochetes' surface proteins accounts for the infection's relapsing course. Acquired immunity follows the serial development of antibodies to each of the several variants appearing during an infection. Treatment with antibiotics results in rapid cure but at the risk of a moderate to severe Jarisch-Herxheimer reaction.



Louse-borne relapsing fever caused large epidemics well into the twentieth century and currently occurs in northeastern Africa. At present, however, most cases of relapsing fever are tick-borne in origin. Sporadic cases and small outbreaks are focally distributed on most continents, with Africa most affected. In North America, the majority of reports of relapsing fever have been from the western United States and Canada. Nevertheless, the recent discovery that another species in the relapsing fever group causes human disease in the same geographic distribution as Lyme disease (Chap. 210) confounds epidemiologic distinctions between the two major types of *Borrelia* infection.

ETIOLOGIC AGENT

Coiled, thin microscopic filaments that swim in one direction and then coil up before heading in another were first observed in the blood of patients with relapsing fever in the 1880s (www.youtube.com/watch?v=VxDPV2lBd9U). These microbes were categorized as spirochetes and grouped as several species in the genus *Borrelia*. It was not until the 1960s that the organisms were isolated in pure culture. The breakthrough cultivation medium and its derivatives are rich in their ingredients, ranging from simple (e.g., amino acids and *N*-acetylglucosamine) to more complex (e.g., serum and protein hydrolysates). The limited biosynthetic capacity of *Borrelia* cells is accounted for by a genome content one-quarter that of *Escherichia coli*.

Like other spirochetes, the helix-shaped *Borrelia* cells have two membranes, the outer of which is more loosely secured than in other double-membrane bacteria, such as *E. coli*. As a consequence, fixed organisms with damaged membranes can assume a variety of morphologies in smears and histologic preparations. The flagella of spirochetes run between the two membranes and are not on the cell surface. Although technically gram-negative in their staining properties, the

10- to 20- μ m-long *Borrelia* cells, with a diameter of 0.1–0.2 μ m, are too narrow to be seen by bright-field microscopy of Gram-stained specimens.

EPIDEMIOLOGY



The several species of *Borrelia* that cause relapsing fever have restricted geographic distributions (Table 209-1). The exception is *Borrelia recurrentis*, which is also the only species transmitted by the louse. Louse-borne relapsing fever (LBRF) is usually acquired from a body louse (*Pediculus humanus corporis*), with humans serving as the reservoir. Acquisition occurs not from the bite itself but from either rubbing the insect's feces into the bite site with the fingers in response to irritation or inoculation of feces into the conjunctivae or an open wound. Although LBRF transmission is currently limited to Ethiopia and adjacent countries, the disease has had a global distribution in the past, and that potential remains. Epidemics with thousands of cases of LBRF can occur under circumstances of famine, natural disaster, refugee migration, and war.

All other known species of relapsing fever agents are tick-borne—in most cases, by soft ticks of the genus *Ornithodoros* (Fig. 209-1). Tick-borne relapsing fever (TBRF) is found on most continents but is absent or rare in tropical, low-desert, arctic, or alpine environments. For most species, the reservoirs of infection are small to medium-sized mammals, usually rodents but sometimes pigs and other domestic animals living in or around human habitats. However, one species, *Borrelia duttonii* in sub-Saharan Africa, is largely maintained by tick transmission between human hosts. In North America, TBRF occurs as single cases or small case clusters through transient exposure of persons to infested buildings or caves in less populated areas where the rodent reservoirs have nests. The two main *Borrelia* species involved in North America are *Borrelia hermsii* (in the mountainous west) and *Borrelia turicatae* (in the southwestern and south-central regions). The soft tick vectors typically feed for no more than 30 min, usually without being noticed, while the victim is sleeping. Transovarial transmission from one generation of ticks to the next means that infection risk may persist in an area long after incriminated mammalian reservoirs have been eradicated.

A newly recognized pathogen, *Borrelia miyamotoi*, belongs to the clade of relapsing fever species but is transmitted to humans from other mammals by hard ticks (e.g., *Ixodes scapularis* in the eastern United States) that also transmit Lyme disease, babesiosis, anaplasmosis, ehrlichiosis, and arboviral encephalitis. *B. miyamotoi* is acquired through outdoor activities and through contact with ticks in forested and shrubby areas during recreation, work, or activities around the home. In residents of areas where *B. miyamotoi* and *Borrelia burgdorferi* coexist, the prevalence of antibodies to the former is about one-third of that to the latter.

PATHOGENESIS AND IMMUNITY

Unlike LBRF spirochetes, TBRF spirochetes enter the body in the tick's saliva with the onset of feeding. From an inoculum of a few cells, the spirochetes proliferate in the blood, doubling every 6 h to numbers of 10^6 – 10^7 /mL or more. *Borrelia* species are extracellular pathogens; their

TABLE 209-1 RELAPSING FEVER BORRELIA SPECIES, BY GEOGRAPHIC REGION, VECTOR, AND PRIMARY RESERVOIR

Species	Region(s)	Arthropod Vector(s)	Primary Reservoir
<i>B. crocidurae</i>	Africa	<i>Ornithodoros erraticus</i> , <i>O. sonrai</i> (soft ticks)	Mammals
<i>B. duttonii</i>	Africa	<i>O. moubata</i>	Humans
<i>B. hermsii</i>	North America	<i>O. hermsii</i>	Mammals
<i>B. hispanica</i>	Europe, North Africa	<i>O. erraticus</i> complex	Mammals
<i>B. miyamotoi</i>	Eurasia, North America	<i>Ixodes</i> species (hard ticks)	Mammals
<i>B. persica</i>	Eurasia	<i>O. tholozani</i>	Mammals
<i>B. recurrentis</i>	Africa, global ^a	<i>Pediculus humanus corporis</i> (human body louse)	Humans
<i>B. turicatae</i>	North America	<i>O. turicata</i>	Mammals
<i>B. venezuelensis</i>	Central and South America	<i>O. rudis</i>	Mammals

^aAlthough transmission is currently limited to Ethiopia and adjacent countries, *B. recurrentis* infection has had a global distribution in the past, and that potential remains.