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Borrelia miyamotoi Infection in Nature and in Humans

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Abstract

Borrelia miyamotoi is a relapsing fever *Borrelia* group spirochete that is transmitted by the same hard-bodied (ixodid) tick species that transmit the agents of Lyme disease. It was discovered in 1994 in *Ixodes persulcatus* ticks in Japan. *B. miyamotoi* species phylogenetically cluster with the relapsing fever group spirochetes, which usually are transmitted by soft-bodied (argasid) ticks or lice. *B. miyamotoi* infects at least six *Ixodes* tick species in North America and Eurasia that transmit Lyme disease group spirochetes and may use small rodents and birds as reservoirs. Human cases of *B. miyamotoi* infection were first reported in 2011 in Russia and subsequently in the United States, Europe, and Japan. These reports document the public health importance of *B. miyamotoi*, as human *B. miyamotoi* infection appears to be comparable in frequency to babesiosis or human granulocytic anaplasmosis in some areas and may cause severe disease, including meningoencephalitis. The most common clinical manifestations of *B. miyamotoi* infection are fever, fatigue, headache, chills, myalgia, arthralgia, and nausea. Symptoms of *B. miyamotoi* infection generally resolve within a week of the start of antibiotic therapy. *B. miyamotoi* infection should be considered in patients with acute febrile illness who have been exposed to *Ixodes* ticks in a region where Lyme disease occurs. Because clinical manifestations are non-specific, etiologic diagnosis requires confirmation by blood smear examination, PCR, antibody assay, *in vitro* cultivation, and/or isolation by animal inoculation. Antibiotics that have been used effectively include doxycycline for uncomplicated *B. miyamotoi* infection in adults and ceftriaxone or penicillin G for meningoencephalitis.

Keywords

Borrelia miyamotoi; relapsing fever; Lyme disease; *Ixodes*; tick-borne disease; spirochete

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Introduction

Borrelia miyamotoi is a relapsing fever spirochete transmitted by the same hard-bodied (ixodid) ticks that are vectors of *Borrelia burgdorferi* and other Lyme disease agents [1–10]. As early as 1985, spirochetes that were likely *B. miyamotoi* were observed in ticks in the United States. They were mistakenly thought to be *B. burgdorferi* as a consequence of cross-reactive antibodies that were used in direct immunoassays. For example, two reports identified putative *B. burgdorferi* in *Ixodes scapularis* and *Ixodes pacificus* adult ovarial tissue, eggs and/or larvae [11–12]. This lead to the false conclusion that *B. burgdorferi* was transovarially transmitted by ticks. Recent experimental evidence has confirmed transovarial (vertical) transmission of *B. miyamotoi* but not *B. burgdorferi* in *I. scapularis* [13]. Misidentification not only led to false conclusions about the transovarial transmission of *B. burgdorferi* in *Ixodes* ticks but may have delayed recognition of *B. miyamotoi* as an etiologic agent.

It was not until 1994 that spirochetes identified as *B. miyamotoi* were isolated from field-collected *Ixodes persulcatus* ticks and the small Japanese field mouse *Apodemus argenteus* in Japan [1]. In 2000 a novel spirochete was serendipitously identified in laboratory-reared *I. scapularis* ticks that were expected to be free from *B. burgdorferi* infection. Sequencing of the 16S ribosomal gene and other loci revealed that this newly-discovered organism from the northeastern United States was closely related to *B. miyamotoi* isolates of Japan [2,4]. *B. miyamotoi* has subsequently been identified in all other tick species that are vectors of Lyme disease and probably occurs throughout much of the Holarctic Region [2–10, 13–30]. The discovery of *B. miyamotoi* expands the potential geographic range of relapsing fever group *Borrelia* species. Most other relapsing fever spirochetes are transmitted by soft-bodied ticks (Argasidae) and lice that have different ecologies and only occasionally are found in the same geographic locations as Lyme disease vectors [31].

Although the novelty and wide geographic distribution of *B. miyamotoi* have been recognized for several years now, this spirochete received comparatively little attention until human cases of a relapsing fever-like disease from *B. miyamotoi* infection were reported in 2011 in Russia, and subsequently in the United States, Europe, and Japan [10,32–38]. These reports have documented the public health importance of *B. miyamotoi*. Human *B. miyamotoi* infection appears to be comparable in frequency to babesiosis or human granulocytic anaplasmosis (HGA) in the northeastern U.S. and may cause severe disease, including meningoencephalitis in immunocompromised individuals, as well as coinfection with other *Ixodes*-borne pathogens [10,32–38]. Additionally, antigenic cross-reactivities in immunoassays between *Borrelia* species in North America may complicate diagnosis of both Lyme disease and relapsing fever [39].

The organism

B. miyamotoi was not the first relapsing fever-group species shown to use a hard tick species as its primary vector. The association of the cattle pathogen *B. theileri* with *Boophilus* (now named *Rhipicephalus*) *microplus* hard ticks was noted by Arnold Theiler a century ago [40]. More recently, *B. lonestari* was discovered in *Amblyomma* species [41] and the reptile

pathogen *B. turcica* was shown to be transmitted by *Hyalomma* species hard ticks [42]. Nucleotide sequences of these organisms, including the complete chromosomes of isolates of *B. miyamotoi* from North America [43] and Japan (GenBank accession number CP004217) confirmed that *B. miyamotoi* and the other hard-tick associated species phylogenetically cluster with the relapsing fever *Borrelia* species [44]. These include both New World species *B. hermsii* and *B. turicatae* and the Old World species, such as *B. crocidurae*, that are transmitted by soft ticks (Figure 1). A real-time quantitative PCR based on the same primers but different probes for the 16S ribosomal RNA gene distinguishes between the relapsing fever group species (including *B. miyamotoi*) and the Lyme disease group species [45].

Differences exist between *B. miyamotoi* isolates according to tick vector and geographic region, but so far little genetic difference has been found between isolates within a given geographic area or with the same tick vector association [4,18,29]. The overall genetic difference between a North American *B. miyamotoi* isolate (LB-2001) and a Japanese *B. miyamotoi* isolate (FR64b) is about the same as between *B. turicatae* and *B. parkeri*, two North American relapsing fever species with different host and vector associations [31], but less than between the two major genomic groups of *B. hermsii* strains [46] (Figure 1). In our opinion, the designation “sensu lato” is provisionally applicable for the North American strains, with “sensu stricto” reserved for the original Japanese isolates until further genetic and phenotypic characterization is carried out [44].

Besides its overall genetic distance from *B. burgdorferi* and other Lyme disease species, *B. miyamotoi* shares with other relapsing fever group species the distinctive feature of carriage and expression of a GlpQ (glycerophosphodiester phosphodiesterase) biosynthetic gene [47]. An antibody response to *Borrelia* GlpQ antigen is a characteristic of relapsing fever that distinguishes it from the immune response to Lyme disease (see below) [47]. On the other hand, there are many antigenic similarities between *B. miyamotoi* and other relapsing fever group species and the Lyme disease species, which may account for cross-reactive antibody binding in diagnostic assays based on whole cell antigens [39]. These common antigens include 4 of the 10 antigens specified in standard Western blot criteria for Lyme disease testing [48].

Genetic differences correspond to biological differences between *B. miyamotoi* and the Lyme disease group of disease agents. As is the case for other relapsing fever group species, much higher densities of the spirochetes are observed in the blood of infected wild rodents and laboratory mice than are observed with Lyme disease species in either natural or experimental infections [49]. While *in vitro* cultivation of *B. miyamotoi* isolates from Japan was achieved shortly after discovery, the North American isolates appear to be more difficult to cultivate than *B. burgdorferi* (A.G.B., unpublished findings). There are reports of *in vitro* passage of a North American isolate in modified BSK medium that has been used for other *Borrelia* species but the yields of *in vitro* cultures have been low to date [50–52]. Transovarial transmission is another biological feature that distinguishes *B. miyamotoi* and several other relapsing fever species from *B. burgdorferi* [13].

Ecology

B. miyamotoi is transmitted to humans by ticks that had acquired the organism either horizontally from a vertebrate reservoir host or possibly by ticks infected transovarially from the female tick. *B. miyamotoi* has been found in several of the tick species known to be vectors of Lyme disease group *Borrelia* species. These include *I. scapularis* in the northeastern and north-central United States and adjoining areas of Canada; *Ixodes pacificus* in the far-western United States and British Columbia; *Ixodes ricinus* in Europe, and *Ixodes persulcatus* in Europe and Asia (Figure 2) [1–10,14–30]. *Ixodes ovatus* and *Ixodes pavlovskyi* in northern Asia are two other species that have been shown to carry *B. miyamotoi* [29]. *B. miyamotoi* infection rates in field collected nymphal *I. scapularis* populations range between 0% and 10% [2,5,7–8,17]. *I. pacificus* nymphal infection rates vary from 0% to 15% [18,20–21,28]. The ratios of *B. burgdorferi* to *B. miyamotoi* infection in *I. scapularis* nymphs in the northeastern United States range from 4:1 to 16:1. In California the prevalence of *B. burgdorferi* in *I. pacificus* is approximately 10-fold lower than that observed in the Northeast. Under these circumstances, *B. miyamotoi* infection prevalences in nymphal and adult *I. pacificus* approach and may exceed those of *B. burgdorferi* [20,28]. In Europe, the range of *B. miyamotoi* infection rates reported in *I. ricinus* nymphal ticks is 0–3.2% [3,9,15–16,18,22–26,30]. Infection rates in *I. scapularis* in Canada and *I. persulcatus* in Russia fall within the range of *B. miyamotoi* infection detected in *I. scapularis* ticks in the United States [10,19].

The reservoir hosts of *B. miyamotoi* throughout much of its distribution are poorly known or unknown. The white-footed mouse (*Peromyscus leucopus*) is a competent reservoir host of *B. miyamotoi* in the northeastern United States [2,7] but other species including birds [17], also may serve as reservoirs. In a study of 556 *P. leucopus* captured in eastern Connecticut, *B. miyamotoi* was identified in the blood of 7% of the mice and in skin tissue of 2% of mice; the corresponding prevalences for *B. burgdorferi* were 12% and 76% in blood and skin of this large sample [7]. While prevalence of *B. miyamotoi* was less than for *B. burgdorferi*, the densities of *B. miyamotoi* spirochetes in the blood were generally much higher than the density of *B. burgdorferi* spirochetes. Potential *B. miyamotoi* reservoir host species include species of field mice, voles, and birds in Europe, and field mice in Japan [25–26, 49]. Unlike Lyme disease *Borrelia* species, *B. miyamotoi* are carried by some unfed larvae, the consequence of transovarial acquistion. If larvae can transmit the infection to vertebrates, as a report from Japan indicates, there is the potential extension of the peak transmission season of certain species, such as *I. scapularis* into the later summer, when larval activity is at its highest [13,29,53].

Epidemiology

There is limited knowledge of the full geographic distribution of human *B. miyamotoi* infection but it is likely to be similar to that of Lyme disease. Human cases of *B. miyamotoi* have been reported in Russia, the United States, the Netherlands, and Japan. Two reports of *B. miyamotoi* seroprevalence have been published in healthy residents of southern New England. In the first study about 1% of 584 archived sera collected from 1990–2010 in healthy residents of Block Island, RI; Prudence Island, RI; and Brimfield, MA were

seropositive for *B. miyamotoi* compared with 3% of 277 suspected Lyme disease patients [33]. In the second study, of 639 sera obtained from healthy residents of southern New England between 1991 and 2012, 3.9% were *B. miyamotoi* seropositive and 9.4% were *B. burgdorferi* seropositive [34]. A similar *B. miyamotoi* seroprevalence rate of 2% was noted in healthy (blood donor) residents of the Netherlands, while higher rates were noted in forestry workers (10%), and patients experiencing HGA (14.6%) and Lyme disease (7.4%) [38].

The geographic range of *B. miyamotoi* infection in tick vectors is much broader than the countries where human infection has been reported. *B. miyamotoi* has been found in ticks from Asia (Japan and central Russia), North America (the United States and Canada), and Europe (Czech Republic, Denmark, England, Estonia, France, Germany, Netherlands, Poland, Sweden, and Switzerland). It likely coexists with *B. burgdorferi* or other Lyme disease *Borrelia* species throughout its distribution [1–10, 14–30].

B. miyamotoi infections might occur in residents living outside its known enzootic geographic range through blood transfusion. Recurrent high density spirochetemia is characteristic of relapsing fever and increases the risk of transfusion transmission. Transfusion-transmitted relapsing fever caused by *Borrelia recurrentis* and *Borrelia duttoni* have been reported [54–56]. A recent study showed that *B. miyamotoi* can be transmitted through blood transfusion in a mouse experimental model [57]. Motile spirochetes were observed microscopically in the blood of both immunocompromised and immunocompetent mouse recipients after transfusion of murine *B. miyamotoi*–infected blood that was either fresh or stored for 7 days under conditions used in human blood banks. Spirochetemia was observed in immunocompetent mice up to five days and in immunocompromised mice 28 days after transfusion with fresh or stored *B. miyamotoi*-infected blood. These data suggest that transfusion transmission of *B. miyamotoi* may occur in humans.

Clinical manifestations

The most commonly reported clinical presentation of *B. miyamotoi* infection is a febrile illness consisting of fever that may exceed 40°C, fatigue, headache, chills, myalgia, arthralgia, and nausea (Table 1). In the first reported case series of *B. miyamotoi* infection, patients were enrolled who had a history of recent tick bite [10]. Five of the 46 (11%) *B. miyamotoi* cases experienced two to three episodes of fever, each lasting 2 to 5 days with a mean interval of 9 days between episodes (range 2 days to 2 weeks). The frequency of cases with a relapse of illness might have been higher if most patients had not been given empiric antibiotic therapy during their first episode of fever. The fever associated with *B. miyamotoi* infection generally lasts less than a week without antibiotic therapy while other symptoms such as fatigue may persist for as long as several weeks following antibiotic therapy [32–37]. The course of relapsing fever transmitted by soft-bodied ticks is similar. It generally consists of two or more episodes of fever lasting 1 to 5 days each with intervals of well being lasting at least 2 days and no more than 7 days between febrile episodes in untreated patients [58]. Patients infected with relapsing fever spirochetes have experienced as many as six episodes of recurrent fever [58]; the maximum noted with *B. miyamotoi* thus far is three episodes [10].

In contrast to the clinical course of the majority of reported *B. miyamotoi* cases, two patients with well-documented *B. miyamotoi* infections of the central nervous system experienced symptoms and signs of meningoencephalitis. They each had a progressive decline in cognition and unsteady gait over several months but no fever [32,35]. One was an 80 year old woman from the United States and the other a 70 year old man from the Netherlands. Both had a lymphoproliferative disorder (non-Hodgkin's and diffuse large B-cell lymphoma, respectively) and had received chemotherapy that was discontinued 6 months or more prior to the onset of symptoms. The diagnosis of *B. miyamotoi* infection was confirmed in both cases by cerebrospinal fluid analysis, which showed spirochetes on Giemsa staining of a cytospin of CSF sediment or direct darkfield examination of CSF, increased white blood cell count and protein, and amplification and sequencing of *B. miyamotoi* DNA. The patient in the United States was given one dose of ceftriaxone and four weeks of intravenous penicillin. The patient from the Netherlands was given two weeks of ceftriaxone. Both patients had a full recovery, including neurologic function, a month after the start of antibiotic therapy.

B. miyamotoi and *B. burgdorferi* coinfection has been documented in reports from the United States and Japan [34,37]. In the Russian *B. miyamotoi* case series, 9 of the 46 cases had an erythema migrans rash. Although there was no confirmation, *B. burgdorferi* coinfection was the most likely cause because erythema migrans rash has not been associated with soft tick transmitted relapsing fever [10, 58]. Previous studies have shown that coinfections of *B. burgdorferi* with either *Babesia microti* or with *Anaplasma phagocytophilum* are associated with more severe disease compared with that *B. burgdorferi* infection alone [59–61]. Further studies with a large sample size will be needed to determine whether *B. miyamotoi* and *B. burgdorferi* coinfection influences the outcome of disease in humans.

Diagnosis

Diagnosis of *B. miyamotoi* infection should be considered in any patient who resides in or has recently traveled to a region where Lyme disease is endemc in the North American or Eurasian continents during tick disease transmitting season and develops fever. Unlike Lyme disease, babesiosis, and HGA, it is conceivable that *B. miyamotoi* infection can be acquired by humans from the bite of a larval tick, because of transovarial transmission [29]. Consistent clinical findings such as fever, fatigue, and headache provide support for the diagnosis but similar symptoms may occur with other *Ixodes* transmitted diseases (such as Lyme disease, babesiosis, human granulocytic anaplasmosis, tick-borne encephalitis in Eurasia and deer tick virus encephalitis in North America) and acute viral infections. Diagnosis therefore requires confirmation using specific laboratory tests that include blood smear, polymerase chain reaction (PCR), and/or antibody determination [10,32–38]. At least one commercial laboratory is offering an antibody and a PCR test for *B. miyamotoi* and these tests are likely to be available in the near future from other commercial companies. *B. miyamotoi* can be isolated following *in vitro* culture or inoculation into immunodeficient laboratory mice but these methods are confined to a limited number of research laboratories.

If the density of spirochetes in the blood is ≥10^4 per milliliter, *B. miyamotoi* might be identified by examining several high-power fields of a thin blood smear or spun sample of cerebrospinal fluid (for those suspected of meningitis or menigoencephalitis) stained with Giemsa or Wright stain. The blood smear used for a manual white blood cell differential will serve. A thick smear, such as prepared for a malaria screen, that has been de-hemoglobinized and then stained with acridine orange may reveal spirochetes present at lower densities in the blood. Motile spirochetes may be detected by dark-field or phase contrast of a wet mount of anticoagulated blood mixed with an equal volume of physiologic saline (Figure 3).

Several PCR assays have been described for the detection of *B. miyamotoi* in whole blood, plasma, CSF, and tissues using primers specific for 16S ribosomal RNA and for the *flaB* and *glpQ* genes [3,7,32,35]. One of these discriminates between the Lyme disease and relapsing fever groups of *Borrelia* species, is quantitative, and has been shown to amplify *B. miyamotoi* DNA in ticks and in animal blood and tissues [7]. *In vitro* cultivation of *B. miyamotoi* isolates from Japan and North America have been achieved in specialized media but the reported yields of cultures for a North American isolate were lower than that expected for *B. burgdorferi* and several other *Borrelia* species [50–52].

Serologic testing can help confirm *B. miyamotoi* diagnosis. A 2-tiered antibody assay based on recombinant *B. miyamotoi* GlpQ protein has been developed that detects GlpQ-specific antibodies during the acute and convalescent stages of infection [33–34,47]. *B. miyamotoi* GlpQ protein is no more than 50% identical to the GlpQ proteins of some other bacterial pathogens, such as *Klebsiella pneumoniae* and *Salmonella enterica*. On the basis of this distance, *B. miyamotoi* GlpQ is not expected to cross-react with anti-GlpQ antibodies elicited by other disease agents, but this has not been established as yet. More clinically relevant is the presumption that sera from Lyme disease patients will not cross-react in a GlpQ assay because Lyme disease *Borrelia* species (as well as *Anaplasma*, *Babesia* and *Erhlichia* species) lack the gene for GlpQ [47]. In contrast, the sera of 10% of *B. miyamotoi* infected patients met the criteria for seropositivity in a standard 2-tier *B. burgdorferi* antibody assay [34]. Possible causes included a prior *B. burgdorferi* infection, acute co-infection with *B. burgdorferi*, a false-positive test reaction, and/or cross-reactivity of antibodies elicited by the *B. miyamotoi* infection against one or more *B. burgdorferi* antigens. The results of whole cell *B. burgdorferi* EIA tests were positive in some patients who apparently had *B. miyamotoi* alone, possibly due to cross-reactivity of *B. miyamotoi*-elicited antibodies with some *B. burgdorferi* proteins [10,34]. *B. miyamotoi* genes encode the homologues of many *B. burgdorferi* proteins, including the flagellin FlaB protein, GroEL heat shock proteins, P66 outer membrane protein, and the BmpA (P39)-type basic membrane protein. *B. miyamotoi* antibody probably cross reacts with the GlpQ proteins of other relapsing fever *Borrelia* species, as well as *B. lonestari*. These organisms are not transmitted by *Ixodes* ticks and generally have different areas of distribution than *B. miyamotoi* in North America and Eurasia, although there are some areas in California where both *B. miaymotoi* and *B. hermsii* are enzootic [34,47,58, new ref].

The development of a method to grow cultures of *B. miyamotoi* strains *in vitro* provides an opportunity to identify additional antigenic *B. miyamotoi* proteins that would not be

expected to cross-react with Lyme disease *Borrelia* antigens or other clinically relevant etiologic agents [43, 50–52]. The database of the deduced proteins from the genome sequences provides a basis for identifying informative antigens that are expressed *in vivo* but not *in vitro*, as was carried with a genome-wide protein array for *B. burgdorferi* [62]. If the immunodominant antigens during *B. miyamotoi* infection include the variable membrane proteins, which are the basis for antigenic variation during relapsing fever from other species [62], then there may need to be several variant antigens in a microarray-based or bead-based assay to detect the spectrum of antibody responses in infected patients.

Treatment and prevention

Treatment recommendations for *B. miyamotoi* infection are based on the few case reports and series that have been published thus far and supplemented here by the recommendations for treatment of other relapsing fever *Borrelia* infections [32–37,58]. There have been no therapeutic trials nor any experimental data published on the antibiotic susceptibility either *in vitro* or *in vivo* of *B. miyamotoi*. Therefore, optimal antibiotics of choice, their dosages, and treatment duration have yet to be determined.

Doxycycline (100 mg orally every 12 hours) given for 7 to 14 days is the most commonly prescribed antibiotic for patients experiencing uncomplicated *B. miyamotoi* infection to date [10,32–37]. This tetracycline appears to have been effective based on fever defervescence within 5 days of initiation and absence of further fever episodes. Intravenous ceftriaxone (2 grams once a day) given for two weeks or penicillin G (24 million U per day) given for four weeks were used successfully in the two patients with meningoencephalitis.

Amoxicillin or cefuroxime given orally are suitable alternatives to doxycycline or other tetracycline, which are generally contraindicated for children less than 9 years of age and for pregnant and nursing women. These antibiotics are commonly used for treatment of Lyme disease and would be expected to be effective against *B. miyamotoi* infection based on susceptibilities of other relapsing fever *Borrelia* species. Penicillin G or cefotaxime are alternatives to ceftriaxone for parenteral therapy of documented or suspected CNS involvement or other severe infection. Azithromycin would also probably clear infection but macrolides are generally less effective than tetracyclines and most beta-lactam antibiotics for *Borrelia* infections. Some first generation cephalosporins like cephalexin are likely not as effective against *B. miyamotoi* as other beta-lactam antibiotics. On the basis of other *Borrelia* species, *B. miyamotoi* is likely to be relatively resistant to fluroquinolones and aminoglycosides. If human granulocytic anaplasmosis is suspected, then doxycycline, but not beta-lactam antibiotics or macrolides, would probably be effective for both infections.

The Jarisch-Herxheimer reaction is a commonly encountered, mild to serious adverse effect of the first dose or two of antibiotic therapy for relapsing fever [58,63]. The fever returns or increases to ≥40°C. There are accompanying chills and rigors followed by diaphoresis. Hypotension and a shock-like state may occur suddenly and be life-threatening. It has been reported in up to half of people given antibiotics for tick-borne relapsing fever and 15% of people treated for *B. miyamotoi* infection in Russia [10,58]. A patient from the United States experiencing meningoencephalitis developed manifestations of a Jarisch-Herxheimer

reaction, including hypotension, within nine hours after her initial dose of ceftriaxone [32]. Effective management of this problem includes anticipation of the reaction with the initiation of antibiotics and the provision of monitoring and supportive measures, such as volume expansion and antipyretics.

Effective preventive measures for *B. miyamotoi* infection are expected to be the same as for other *Ixodes* tick-borne diseases, such as Lyme disease. They include personal protective measures to avoid tick bite, landscape modification, and environmental measures to reduce tick abundance. No vaccine has been developed and approved for *B. miyamotoi* or any other relapsing fever *Borrelia* species.

Summary

B. miyamotoi is a recently discovered human pathogen belonging to the relapsing fever group of species in the spirochete genus of *Borrelia*. It is transmitted by the same hard-bodied tick species that are the vectors of Lyme disease and is likely to be found wherever Lyme disease occurs. Human infection has been shown to be prevalent in the northeastern United States. Disease severity is variable but patients most commonly present with fever and non-localizing symptoms. Meningoencephalitis requiring hospital admission has been reported. There is limited availability of laboratory testing for infection at this time. Laboratory procedures that can be widely implemented but are of uncertain sensitivity include examination of a stained blood smear for spirochetes and amplification of *B. miyamotoi* DNA using PCR. Assays of acute and convalescent sera for antibodies to the GlpQ protein of *B. miyamotoi* may provide confirmation of a diagnosis; other immunoassays are in development. Procedures with very limited availability for direct detection are *in vitro* cultivation and animal inoculation. The most common antimicrobial agents that have been used to achieve cure are doxycycline and ceftriaxone, but other antibiotics that are used to treat tick-borne relapsing fever and Lyme disease are likely to be as effective as well.

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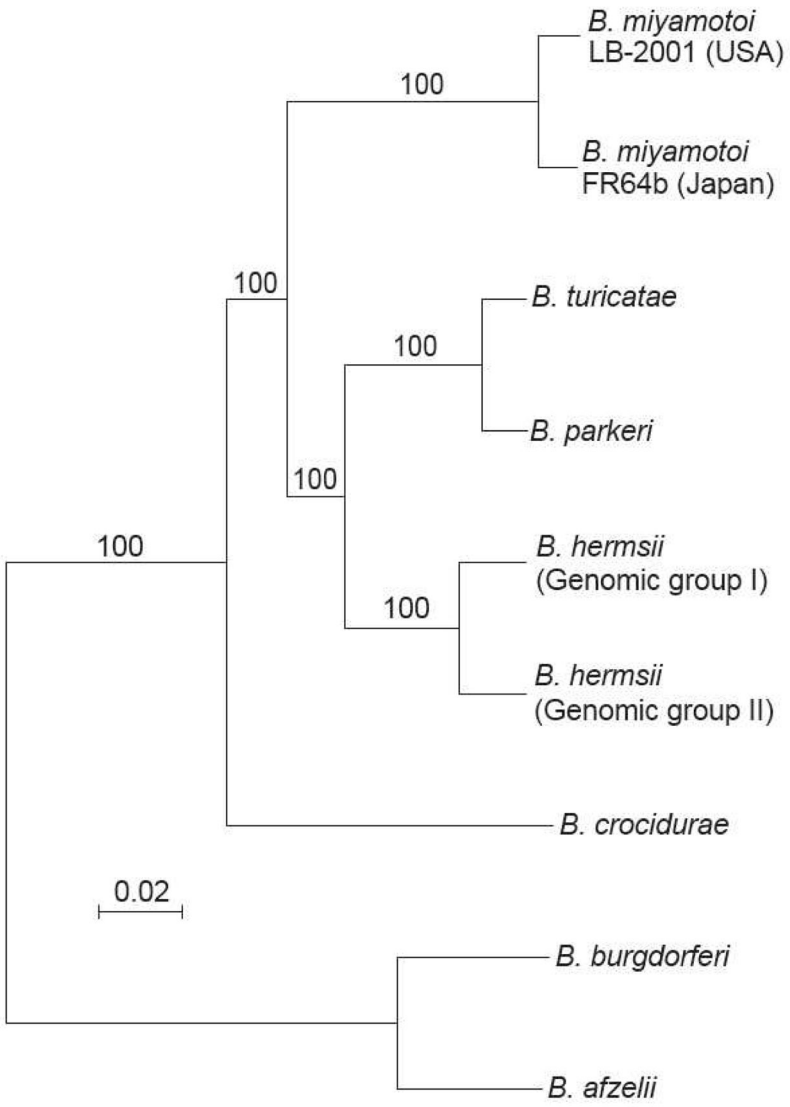

Figure 1.

Phylograms of aligned syntenic chromosome sequences of nine selected relapsing fever group and Lyme disease group *Borrelia* species by BioNJ neighbor-joining protocol for observed differences at 850,377 ungapped sites by a procedure described in reference 44. Nodes with bootstrap values of ≥70% support after 100 replicates are shown. The bar represents nucleotide substitutions per site. The organisms (with GenBank accession numbers) were *B. miyamotoi* strain LB-2001 from Connecticut, USA (CP006647); *B. miyamotoi* strain FR64b from Japan (CP004217); North American tickborne relapsing fever species *B. turicatae* strain 91E135 (CP000049), *B. parkeri* strain HR1 (CP007022), *B. hermsii* strain DAH of genomic group I (CP000048), *B. hermsii* strain YOR of genomic group II (CP004146); the Old World tickborne relapsing fever species *B. crocidurae* strain DOU (CP004267); and two Lyme disease species, *B. burgdorferi* strain B31 (AE000783) and *B. afzelii* strain PKo (CP002933).

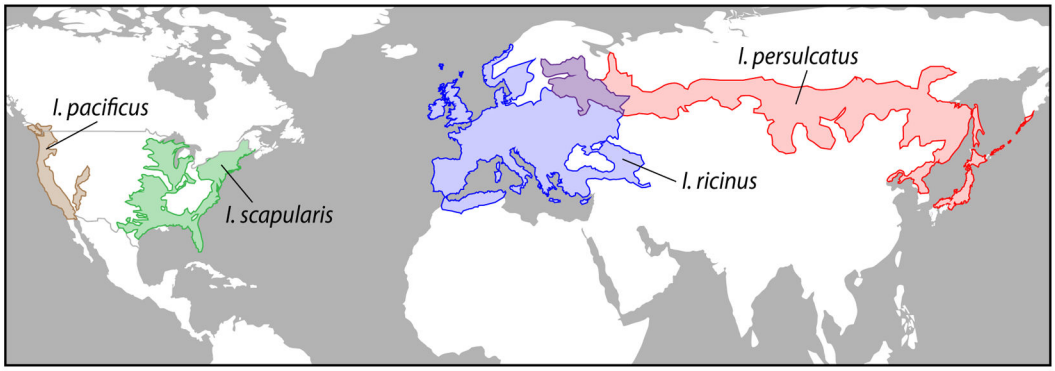

Figure 2.

Approximate current geographic distributions of the main tick vectors of *Borrelia miyamotoi: I. scapularis* (green) and *I. pacificus* (brown) in North America and *I. ricinus* (blue) and *I. persulcatus* (red) in Eurasia. *I. ovatus and I. pavlovskyi* are two other species that have been shown to carry *B. miyamotoi*.

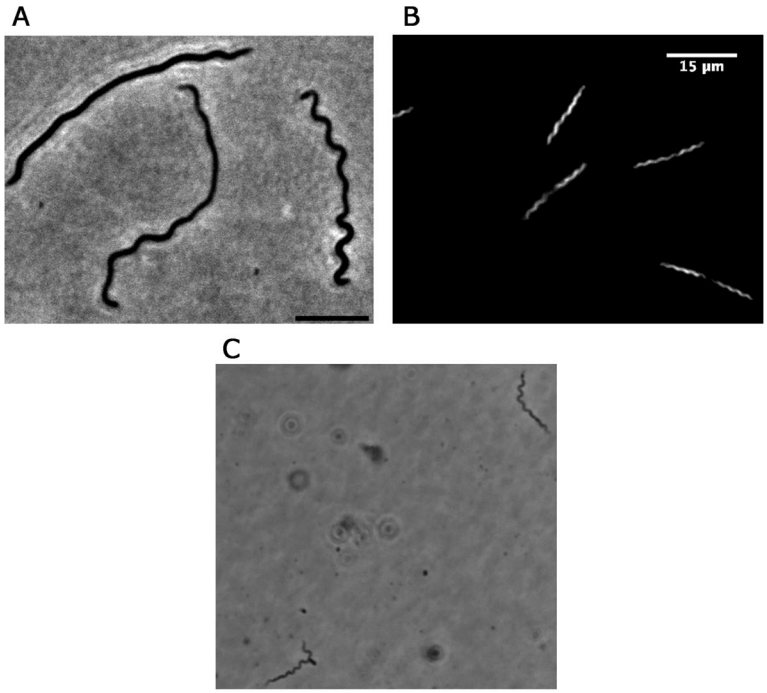

Figure 3.

A. *B. miyamotoi* grown *In vitro* (phase contrast, 100x [bar 5 um]), B. *B. miyamotoi* grown *In vitro* (dark-field, 40x [bar 15 um]), C. *B. miyamotoi* in infected mouse blood (phase contrast of wet mount of plasma [400x]).

Table 1

Clinical manifestations in patients with *Borrelia* spp. infection, Yekaterinburg City, Russia, 2009, and northeastern United States, 1991–2008. Adapted from Platonov AE, Karan LS, Kolyasnikova NM, Makhneva NA, Toporkova MG, Maleev VV, Fish D, Krause PJ. Humans infected with relapsing fever spirochete *Borrelia miyamotoi*, Russia. *Emerg Infect Dis* 2011;17:1816–23 [10].

	% Patients			p value		
Manifestation	***B. miyamotoi*, n=46**	***B. garinii*, n = 21**	***B. burgdorferi*, n = 92**	***B. miyamotoi* vs. *B. garinii***	***B. miyamotoi* vs. *B. burgdorferi***	***B. garinii* vs. *B. burgdorferi***
Individual						
EM	9	91	89	<0.001	<0.001	>0.999
Multiple EM	0	14	7	0.03	0.18	0. 36
Fever[†]	98	67	32	0.001	<0.001	0.005
Fatigue	98	86	74	0.09	<0.001	0.4
Headache	89	57	63	0.007	0.001	0.63
Chills	35	10	43	0.04	0.36	0.005
Myalgia	59	52	63	0.8	0.71	0.46
Arthralgia	28	29	62	>0.999	<0.001	0.007
Nausea	30	10	24	0.07	0.420	0.24
Vomiting	7	5	7	>0.999	>0.999	>0.999
Neck stiffness	2	0	38	>0.999	<0.001	<0.001
Overall						
No. symptoms, mean ± SD	4.5 ± 1.4	4.2 ± 2.0	5.0 ±2.3	0.43	0.13	0.13
No. symptoms (excluding EM and multiple EM), mean ± SD	4.5 ± 1.4	3.1 ± 1.9	4.1 ± 2.3	0.007	0.46	0.09

[*] EM, erythema migrans.

[†] Maximum axillary temperature >37.2°C for patients in Russia and maximum oral temperature >37.7°C for patients in the United States.