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Updates on *Borrelia burgdorferi* sensu lato complex with respect to public health

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Summary

Borrelia burgdorferi sensu lato (s.l.) complex is a diverse group of worldwide distributed bacteria that includes 18 named spirochete species and a still not named group proposed as genomospecies 2 (Postic et al., 2007). Descriptions of new species and variants continue to be recognized, so the current number of described species is probably not final. Most of known spirochete species are considered to have a limited distribution. Eleven species from the *B. burgdorferi* s.l. complex were identified in and strictly associated with Eurasia (*B. afzelii*, *B. bavariensis*, *B. garinii*, *B. japonica*, *B. lusitaniae*, *B. sinica*, *B. spielmanii*, *B. tanukii*, *B. turdi*, *B. valaisiana*, and *B. yangtze*), while another 5 (*B. americana*, *B. andersonii*, *B. californiensis*, *B. carolinensis*, and *B. kurtenbachii*) were previously believed to be restricted to the USA only (Rudenko et al., 2009b, 2009c; Margos et al., 2010). *B. burgdorferi* sensu stricto (s.s.), *B. bissettii*, and *B. carolinensis* share the distinction of being present in both the Old and the New World. Out of the 18 genomospecies, 3 commonly and 4 occasionally infect humans, causing Lyme borreliosis (LB) – a multisystem disease that is often referred to as the ‘great imitator’ due to diversity of its clinical manifestations. Among the genomospecies that commonly infect people, i.e. *B. burgdorferi* s.s., *B. afzelii*, and *B. garinii*, only *B. burgdorferi* s.s. causes LB both in the USA and in Europe, with a wide spectrum of clinical conditions ranging from minor cutaneous erythema migrans (EM) to severe arthritis or neurological manifestations. The epidemiological data from many European countries and the USA show a dramatic increase of the diagnosed cases of LB due to the development of new progressive diagnostic methods during the last decades (Hubálek, 2009). Recently, the definition of the disease has also changed. What was not considered Lyme borreliosis before might be now.

Keywords

Spirochetes; *Borrelia*; Genetic diversity; Lyme borreliosis; Distribution; New species

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Association of *Borrelia* species with human Lyme borreliosis

Lindgren and Jaenson stated that about 85,000 Lyme borreliosis (LB) cases were estimated in Europe alone, with additional 16,000–20,000 annual cases in the USA (Lindgren and Jaenson, 2006). Taking in consideration the significant number of underreported cases (Campbell et al., 1998), the total annual number of LB cases in the world might be as many as 255,000. *B. burgdorferi* s.s. is the primary pathogenic genospecies that causes LB worldwide. It was first isolated in the USA in 1981 by W. Burgdorfer (Burgdorfer et al., 1982) from the tick *Ixodes dammini* currently known as *I. scapularis* (Oliver et al., 1993). North American strains of *B. burgdorferi* s.s. are more heterogeneous than the European ones (Postic et al., 1998; Wang et al., 1999), and *B. burgdorferi* genotypes in the northeastern USA are associated with LB severity (Travinsky et al., 2010). Several subtypes of *B. burgdorferi* s.s. have been identified (Liveris et al., 1995, 1999), and associations between specific subtypes and invasiveness in patients (Seinost et al., 1999) and experimentally infected animals (Wang et al., 2001, 2002) have been reported. The heterogeneous clinical presentation of the disease has been linked to the genetic diversity of the *B. burgdorferi* s.l. complex in general and *B. burgdorferi* s.s. in particular. The wider molecular analysis of the local populations of *B. burgdorferi* species transmitted by hard ticks of the *I. ricinus* complex typically reveals discrete clusters of multilocus sequence types called ‘clonal complexes’. Members of the genus *Borrelia* largely possess clonal population structures (Dykhuizen et al., 1993) comprising several different strains or lineages (Bunikis et al., 2004; Girard et al., 2009). *Borrelia* intraspecific clonal complexes may differ in their host specificity and degree of human pathogenicity (Qiu et al., 2008). It still remains unknown how such factors as natural selection, low recombination rate, and genetic drift due to geographic structuring contribute to the formation and maintenance of these clonal complexes in natural bacterial populations (Qiu et al., 2008).

Large-scale systematic surveys conducted in the northeastern, north-central, mid-Atlantic, and, recently, in the far-western USA reveal striking differences among *B. burgdorferi* genotypes found in different parts of the country. These differences might be due to differences in the enzootiology of those genotypes, based on existing or predominant vector–reservoir cycles that are discrete or overlapping in different geographic regions. The genetic differences in the regional populations might also be related to limited migration of the strains between the regions due to barriers (Margos et al., 2008). This is corroborated by the distinct distributional ranges of *I. scapularis* and *I. pacificus*, the principal vectors of LB in eastern North America and the Pacific region of North America, respectively (Piesman and Gern, 2004). *B. burgdorferi* exhibits considerable heterogeneity, and some isolates differ remarkably from those recovered in other regions (Brown et al., 1992, 2006; Girard et al., 2009; Travinsky et al., 2010).

Data generated during the last decade demand reevaluation of the previously held concepts about LB around the world. Although *B. burgdorferi* s.l. is endemic in many foci over large geographical areas, sometimes just a few human cases are reported from those regions. The lower prevalence of LB has been attributed to (i) a parallel cycle in nature involving nonhuman-biting maintenance vectors (Brown et al., 1992); (ii) the borreliacidal effects of the alternative complement pathway in the blood of certain hosts (Lane and Quistad, 1998); or to (iii) different subsets of *B. burgdorferi* lineages that are present in different regions (Girard et al., 2009; Travinsky et al., 2010).

From the time of *B. burgdorferi* discovery a large number of *Borrelia* isolates has been obtained from various vertebrate species, including humans. Except for *B. burgdorferi* s.s. (North America and Europe), *B. afzelii* and *B. garinii* (Europe and Asia) were considered to be the only causative agents of disease around the world for a rather long time.

Involvements of other species from the *B. burgdorferi* s.l. complex were recognized recently. *Borrelia* spirochetes are transmitted to hosts (including humans) by all 3 developmental stages of ixodid ticks, but the nymphal stage appears to be the most important (Anderson et al., 1990; Kurtenbach et al., 1995, 1998; Danielová et al., 2010; Scott et al., 2010). Considering the human sensitivity to *B. burgdorferi* s.l. and results of the newest publications, the complex of 18 *Borrelia* species (Table 1) can be divided into 2 major groups:

1. 9 species that have not yet been reported in or isolated from humans. This group includes *B. americana*, *B. andersonii*, *B. californiensis*, *B. carolinensis*, *B. japonica*, *B. tanukii*, *B. turdi*, *B. sinica*, and *B. yangtze*.
2. 9 species with pathogenic potential. This group includes *B. afzelii*, *B. bavariensis*, *B. bissettii*, *B. burgdorferi* s.s., *B. garinii*, *B. kurtenbachii*, *B. lusitaniae*, *B. spielmanii*, and *B. valaisiana* (Picken et al., 1996; Rijpkema et al., 1997; Strle et al., 1997; Wang et al., 1999; Ryffel et al., 1999; Collares-Pereira et al., 2004; Rudenko et al., 2008, 2009a; Girard et al., 2010).

It was suggested that different *Borrelia* species possess different organotropisms and may preferentially cause distinct clinical manifestations of the disease. Lyme arthritis is the most common musculoskeletal symptom resulting from *B. burgdorferi* s.s. infection. About 60% of untreated patients with EM experience brief or sustained attacks of arthritis in North America (Steere, 1989). In contrast, only 3–15% of LB patients suffer from arthritis in Europe (Oschmann et al., 1998), where *B. garinii* and *B. afzelii* are more frequently recovered than *B. burgdorferi* s.s. Serotyping studies of isolates from Europe reveal a striking correlation between neuroborreliosis and infection with *B. garinii*. But *B. burgdorferi* s.s. and *B. afzelii* can also be associated with neurological manifestation, however not at such a high rate (Ornstein et al., 2001, 2002; Ružić-Sabljić et al., 2002). *B. afzelii* in humans seems to have an organotropism for skin since it preferentially causes EM, lymphadenitis benigna cutis (Grange et al., 2002), and acrodermatitis chronica atrophicans (ACA). Molecular studies of isolates from patients in several European countries confirm the association of ACA with *B. afzelii* infection (van Dam et al., 1993). *B. afzelii* is the predominant, but not the exclusive etiologic agent of ACA; *B. garinii* has also been detected there (Picken et al., 1998; Ružić-Sabljić et al., 2002). Although ACA rarely has been reported in the USA, it may be seen in approximately 10% of European cases of LB (Smetanick et al., 2010). It is interesting to note that ACA has never been observed in Americans who have never left the USA confirming that endemic *B. burgdorferi* s.s. rarely, if ever, induces this form of disease.

Involvement of *Borrelia* species previously considered non-pathogenic to human

Although *B. valaisiana* has been considered to be non-pathogenic to humans, lately it was suspected among patients with EM (Rijpkema et al., 1997). Association of *B. valaisiana* with chronic clinical symptoms is also known (Ryffel et al., 1999). Moreover, molecular analysis of a *B. lusitaniae* isolate from a Portuguese patient suggests a clinical pattern for *B. lusitaniae* different from the other *Borrelia* spp. examined so far (Collares-Pereira et al., 2004). Also, the role of *B. spielmanii* as a causative agent of LB was confirmed by reported cases of patients with EM in the Netherlands, Germany, Hungary, and Slovenia (Maraspin et al., 2006). For a long time, the conclusion about the lack of pathogenicity of *B. bissettii* was based on the analysis of strain 25015. This strain was isolated from a fully fed *I. scapularis* larva removed from a white-footed mouse captured in Millbrook (New York, USA). Infectivity, but not pathogenicity of strain 25015 was confirmed years ago (Anderson et al., 1990) and persisted until seemingly incongruous reports linked European isolates of *B.*

bissettii with human LB. More than a decade ago, Strle presented clinical findings about some patients from Slovenia who had LB that was caused by *Borrelia* species with genotypic and phenotypic similarity to the North American strain 25015 (Strle et al., 1997). Strain 25015 was assigned to the DN127 genomic group of *B. bissettii*, although differences in 5S-23S intergenic spacer region between 25015 and DN127 were noticed (Postic et al., 1998). Studies with a murine model indicated that this strain was mildly arthritogenic (Fikrig et al., 1992). Recent reinvestigation of the phylogenetic relatedness of several strains from California, Colorado, New York, and Illinois previously included into the genospecies *B. bissettii* showed that 25015 and a few other strains from Illinois represent a distinct group, separate from *B. bissettii*. This group includes as well one sample that was not a cultured isolate but DNA-extracted from a nymphal *I. scapularis* collected in Nova Scotia (Canada) from a human. They all constitute a novel *Borrelia* genospecies proposed as *B. kurtenbachii* sp. nov. (Margos et al., 2010). MLSA used by Margos and colleagues split the genospecies *B. bissettii* into 2 separate species, both with pathogenic potential to humans. The growing recognition of *B. bissettii* as a causative agent of LB in Europe is supported by multiple detection of spirochetes similar to strain 25015 (Strle et al., 1997) and DN127 (Rudenko et al., 2008, 2009a) in European patients for more than a decade. Also, the first case of a description of *B. bissettii*-like strains in samples of human origin in North America was published just recently (Girard et al., 2010). Analyzing the genetic diversity of LB spirochetes in north-coastal Californian residents, Girard and colleagues detected spirochetes closely related to *B. bissettii* in 3 out of 27 PCR-positive sera (11%). Using the pair-wise distance matrix analysis, they confirmed that a 195-bp region of the 5S-23S IGS amplified from Californian patients sera were 97–100% similar to *B. bissettii* strains 25015 (now known as *B. kurtenbachii*) and DN127. Earlier, Schneider employing a mouse model reported the potential pathogenesis of *B. bissettii* to cause human LB. Two Colorado isolates of *B. bissettii* (CO-Bb) induced lesions of the bladder, heart, and femorotibial joint 8 weeks after inoculation into mice (Schneider et al., 2008). It was also shown that rodent-originated strains of *B. bissettii* were capable of inducing disease, whereas tick-originated strains did not disseminate or induce pathology to the above tissues. Perhaps tick-originated strains exhibit different tissue tropisms and that is why they were not found in tissues traditionally infected by spirochetes, or may be these strains cannot successfully colonize mammal hosts and are rapidly cleared by the immune system (Schneider et al., 2008). Studies employing the natural spirochete hosts and vectors are valuable and may provide an answer to the above-noted disparity between vector- and host-originated groups of *Borrelia* strains. Detection of *B. kurtenbachii* (previously considered a member of the *B. bissettii* group) in patients in Slovenia (Picken et al., 1996; Strle et al., 1997; Strle, 1999), detection of *B. bissettii* in cardiac valve tissue and in serum samples of patients in the Czech Republic (Rudenko et al., 2008, 2009a), followed by detection of spirochetes similar to both species in sera of north-coastal Californian patients (Girard et al., 2010) raise questions of whether the issue of pathogenic potential of a former *B. bissettii* group was adequately addressed. The fact that *B. bissettii* shares with *B. burgdorferi* s.s. the distinction of being present in both Old and New Worlds might mean the involvement of this species in LB worldwide.

New face of human Lyme borreliosis

Involvement of new or unknown *Borrelia* species in LB changes drastically the understanding and recognition of the clinical manifestation of the disease. It has long been suspected that Lyme borreliosis is mimicking a wider spectrum of diseases that were never proven to have a spirochete etiology, such as: central nervous system lymphoma (Bahrain et al., 2007); lupus-like syndrome (Molin et al., 2010); distal axonal polyneuropathy and chronic encephalopathy (Créange 2007); pontine tumour (Latsch et al., 2006); intracranial lymphoma (Louis et al., 2005); prostate carcinoma with a painless paraparesis (Ruitenberget al., 2005); multiple sclerosis associated with primary effusion lymphoma (Batinac et al.,

2007); carditis and psychiatric disorders (Legatowicz-Koprowska et al., 2008); hypersomnia (Dalal et al., 2010); necrotizing granulomatous hepatitis (Zanchi et al., 2007); cerebral sinuvenous thrombosis (Adamaszek et al., 2010); paralytic strabismus (Sauer et al., 2009); Horner syndrome (Morrison et al., 2009), and others. More definitive evidence of spirochete etiology in the above-cited diseases is needed before general acceptance of the link between any of them and spirochetes can be made.

***Borrelia*–vector–host association**

In Europe, LB endemic areas are maintained through complex interactions among different tick species, a variety of *B. burgdorferi* s.l. strains, and a large number of mammalian, avian, and reptilian species upon which ticks feed. *I. scapularis*, *I. pacificus*, *I. ricinus*, and *I. persulcatus* are responsible for the majority of *Ixodes*-vectored human disease and are known as ‘bridge’ vectors. They not only feed on species that are competent reservoirs for multiple tick-borne pathogens but also readily bite humans (Oliver, 1996). There are other tick species of the *I. ricinus* complex as well as those not included in the *I. ricinus* complex and non-*Ixodes* tick species known to be naturally infected and to transmit *B. burgdorferi* among wildlife. The short list of them include: *I. minor*, *I. affinis*, *I. dentatus*, *I. spinipalpis*, *Dermacentor variabilis*, *D. albipictus*, *Amblyomma americanum* (USA), *I. hexagonus*, *I. trianguliceps*, *I. uriae* (Europe), *I. turdus*, *I. tanukii*, *I. ovatus*, *I. columnae*, *I. nipponensis*, *I. granulatus*, *I. monospinosus*, *I. moschiferi*, *Haemaphysalis longicornis*, *H. concinna*, *H. bispinosa* (Asia) (for references see Oliver, 1996). The majority of them usually does not bite humans; however, they serve as maintenance vectors and in some areas appear to be more important in the enzootic cycle of *B. burgdorferi* s.l. than the ‘bridge’ vectors that feed on the same hosts and bite humans (Oliver, 1996).

At least 237 animal species are implicated as hosts for ticks in the maintenance of *I. ricinus* tick populations and thus are available to serve as potential reservoir hosts for *Borrelia* (Gern, 2008). Nevertheless, compared to the large number of known tick hosts, little information is available on the real significance of most animal hosts as sources for infecting *I. ricinus* with *B. burgdorferi* s.l. Today, the reservoir role of various bird species is widely recognized, especially concerning ground-nesting and ground-foraging birds, like thrushes, blackbirds, robins, wrens, nightingales, blue throats, and pheasants (Kurtenbach et al., 1998; Spitalská et al., 2006; Brinkerhoff et al., 2009; Scott et al., 2010). Migratory birds have also been shown to participate in the enzootic maintenance of *B. burgdorferi* s.l., and their role in the distribution of infected ticks is now also well documented (Comstedt et al., 2006; Olsén et al., 1995; Poupon et al., 2006). *B. burgdorferi* s.l. spirochetes differ significantly in their host association pattern. Recently, analysis of *B. garinii* strains revealed interesting results in their population structure (Margos et al., 2008) and evolution. It is known that the OspA proteins of *B. garinii* are antigenically diverse and are divided into 5 distinct OspA serotypes (serotypes 3–7). *B. garinii* OspA serotypes 3, 5, 6, and 7 are maintained by birds (Kurtenbach et al., 1998, 2002; Hanincova et al., 2003). *B. garinii* OspA serotype 4 strains are highly pathogenic to humans and were frequently cultivated from cerebrospinal fluid of European patients with neuroborreliosis. Their geographic distribution is highly focal (Wilske et al., 1996), and *Apodemus* mice are the first identified reservoir hosts for *B. garinii* OspA serotype 4 strains (Hu et al., 2001; Huegli et al., 2002). MLSA that involved 8 housekeeping genes, *OspA*, *OspC*, and 5S-23S IGS, confirmed that *B. garinii* as it was known earlier represents at least 2 ecotypes, bird- and rodent-associated. The rodent-associated OspA serotype 4 strains formed a distinct subclade in phylogenetic trees, distant from the bird-associated *B. garinii* strains. The rodent-associated subclade was basal to the rest of strains analyzed suggesting that specialization of strains to rodents is more ancient. Genetic distance between bird- and rodent-associated strains was much greater than the distance between bird-associated *B. garinii* among themselves (Margos et al., 2008). A new

species, proposed as *B. bavariensis* (former *B. garinii* OspA serotype 4 strains), was recognized as separate from *B. garinii* based on genetic distance and ecological differences. All known *B. bavariensis* strains were isolated from samples of human origin (Margos et al., 2008). It seems that genetic elements that allowed *B. garinii* strains to adapt to birds as reservoir hosts were acquired more recently. Adaptation of *Borrelia* species to birds may explain their wide distribution today. The birds' impact in the appearance of new *B. burgdorferi* s.l. loci in nature and in spreading of Lyme borreliosis worldwide cannot be underestimated.

Conclusions

In recent years, the taxonomy of *B. burgdorferi* s.l. spirochetes has become more interesting and complicated. Among 18 named *Borrelia* species identified to date, 8 are confirmed to circulate in endemic areas in Europe: *B. afzelii*, *B. bavariensis*, *B. bissettii*, *B. burgdorferi* s.s., *B. garinii*, *B. spielmanii*, *B. lusitaniae*, and *B. valaisiana* (Hanincova et al., 2003; Rauter and Hartung, 2005; Rudenko et al., 2005, 2008, 2009a; Richter et al., 2006; Margos et al., 2009). Separation of the recently described *B. kurtenbachii* (type strain 25015) from the North American *B. bissettii* strains (Margos et al., 2010) with respect to their earlier identification in Slovenian patients (Picken et al., 1996; Strle et al., 1997) adds one more spirochete species pathogenic to human to this list, but does not close it. One more North American species (*B. carolinensis*) that was recognized from South Carolina (USA) was recently detected in questing *I. ricinus* in the west of France (Cotte et al., 2010), however, its pathogenicity to humans is unknown. Out of 10 *Borrelia* species detected in Europe so far, 3 were considered to be the North American species (*B. bissettii*, *B. carolinensis*, and *B. kurtenbachii*). Naturally, the question is raised: How strict is the geographical association of different species of *B. burgdorferi* s.l. complex and what defines the limitations in spirochete worldwide distribution? The answer to this question might resolve the case of the yet not named genomospecies 2, represented by 2 far-western US isolates with no 'relatives' so far anywhere in the world.

The description of the various *Borrelia* species in ticks has opened an entire new field of research in the ecology of LB. It seems prudent to review the importance of the different types of associations between *Borrelia* species, tick vectors, and vertebrate hosts in various geographic areas. Clearly, additional field studies are needed of *Borrelia* host specificities, keeping in mind particularly the newly described *Borrelia* species and the great subtype diversity hidden in most *Borrelia* species, as well as the geographic diversity of local ecosystems. Future studies in LB ecology seeking to identify the *Borrelia* species in both ticks and reservoir hosts in various endemic areas are strongly encouraged. Those studies are extremely important for the determination of the complete spectrum of *Borrelia* species involved in human Lyme borreliosis worldwide with its unknown, rare, and unusual clinical manifestation.

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Table 1

Currently known spirochete species from the *Borrelia burgdorferi* sensu lato complex.

<i>Borrelia</i> species	Vector	Hosts/reservoirs	Geographical distribution	Reference
<i>B. afzelii</i>	<i>I. ricinus</i> , <i>I. persulcatus</i>	Rodents	Asia, Europe	Canica et al. (1993)
<i>B. americana</i>	<i>I. pacificus</i> , <i>I. minor</i>	Birds	United States	Rudenko et al. (2009c)
<i>B. andersonii</i>	<i>I. dentatus</i>	Cotton tail rabbit	United States	Marconi et al. (1995)
<i>B. bavariensis</i>	<i>I. ricinus</i>	Rodents	Europe	Margos et al. (2009)
<i>B. bissettii</i>	<i>I. ricinus</i> , <i>I. scapularis</i> , <i>I. pacificus</i> , <i>I. minor</i>	Rodents	Europe, United States	Postic et al. (1998)
<i>B. burgdorferi</i> sensu stricto	<i>I. ricinus</i> , <i>I. scapularis</i> , <i>I. pacificus</i>	Rodents, birds, lizards, big mammals	Europe, United States	Baranton et al. (1992)
<i>B. californiensis</i>	<i>I. pacificus</i> , <i>I. jellisonii</i> , <i>I. spinipalpis</i>	Kangaroo rat, mule deer	United States	Postic et al. (2007)
<i>B. carolinensis</i>	<i>I. minor</i>	Rodents, birds	United States	Rudenko et al. (2009b)
<i>B. garinii</i>	<i>I. ricinus</i> , <i>I. persulcatus</i> , <i>I. hexagonus</i> , <i>I. nipponensis</i>	Birds, lizards, rodents	Asia, Europe	Baranton et al. (1992)
<i>B. japonica</i>	<i>I. ovatus</i>	Rodents	Japan	Kawabata et al. (1993)
<i>B. kurtenbachii</i>	<i>I. scapularis</i>	Rodents	Europe, United States	Margos et al. (2010)
<i>B. lusitaniae</i>	<i>I. ricinus</i>	Rodents, lizards	Europe, North Africa	LeFleche et al. (1997)
<i>B. sinica</i>	<i>I. ovatus</i>	Rodents	China	Masuzawa et al. (2001)
<i>B. tanukii</i>	<i>I. tanuki</i>	Unknown (possibly dogs and cats)	Japan	Fukunaga et al. (1996)
<i>B. turdi</i>	<i>I. turdus</i>	Birds	Japan	Fukunaga et al. (1996)
<i>B. spielmanii</i>	<i>I. ricinus</i>	Rodents	Europe	Richter et al. (2006)
<i>B. valaisiana</i>	<i>I. ricinus</i> , <i>I. granulatus</i>	Birds, lizards	Asia, Europe	Wang et al. (1997)
<i>B. yangtze</i>	<i>Haemaphysalis longicornis</i> , <i>I. granulatus</i>	Rodents	China	Chu et al. (2008)
Genomospecies 2	<i>I. pacificus</i>	Unknown	United States	Postic et al. (2007)