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Mini Review

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

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ABSTRACT

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. 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. *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 genospecies, 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 genospecies 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.

Introduction

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 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 over-

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lapping 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 and Lane, 1992; Brown et al., 2006; Girard et al., 2009; Travinsky et al., 2010).

Association of Borrelia species with human Lyme borreliosis

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 and Lane, 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., 1990a; 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, lymphadenosis 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

Table 1
Currently known spirochete species from the *Borrelia burgdorferi* sensu lato complex.

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