Title
Borrelia miyamotoi: The Newest Infection Brought to Us by Deer Ticks.

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***Borrelia miyamotoi*, the newest infection brought to us by deer ticks**

It's not just Lyme disease anymore. Residents and visitors in many parts of the northeastern, north-central and far-Western United States have more than one reason to avoid bites of hard bodied (ixodid) ticks. The latest addition to the list of infections transmitted to humans by the same ixodid ticks that are vectors of Lyme disease is *Borrelia miyamotoi*. While its genus is the same as that of *Borrelia burgdorferi*, *B. miyamotoi* is more closely related to species that cause relapsing fever than to Lyme disease agents [1]. Discovered in *Ixodes persulcatus* ticks in Japan in 1994 and subsequently documented in ticks and rodents in North America and Europe, *B. miyamotoi* was not recognized as a human pathogen until a report from Russia in 2011 [2]. It subsequently was reported in patients in the United States, Europe and Japan [3-8]. In this issue of the Annals, the first large case series in the United States is reported by Molloy et al. and provides important new information about the epidemiology and clinical presentation of human disease caused by this pathogen [8].

Whole blood samples from patients in the northeastern U.S. with suspected tick-borne illness during April to November in 2013 and 2014 were tested with PCR for four tick-borne pathogens. Amplifiable DNA of *B. miyamotoi*, *Anaplasma phagocytophilum*, *B. burgdorferi*, or *Babesia microti* was detected in approximately 1%, 1%, 2%, and 3%, respectively, of 11,515 samples from individual patients. The frequency of infection with *B. burgdorferi*, which is primarily a fixed tissue pathogen, should be greatly underestimated based on PCR of the blood alone. Furthermore, the relative frequencies of these four infections vary across regions in the Northeast, so different results might have been obtained with the samples from other locations. Nevertheless, based on Molloy et al.'s report and previous data [needs citation for "previous data"], the frequency of *B. miyamotoi* infection appears to be roughly the same as for *A. phagocytophilum* and *B. microti* [3].

Clinical information was provided for 51 *B. miyamotoi* patients. Interestingly, the peak incidence of positive assays for *B. miyamotoi* was in August with probable onsets of illness continuing into September, which is about a month after the peak incidence for Lyme disease. This temporal peak is similar to that observed in the naturally infected white-footed mice in Connecticut and

corresponds to the questing activity of *I. scapularis* larvae in the northeastern U.S [3]. Acquisition of *B. miyamotoi* infection from unfed larval ticks is possible because of transovarial transmission of *B. miyamotoi* from an infected female [9]. Bites from larval deer ticks have not been considered as a health threat but this needs to be re-evaluated. Larval transmission of *B. miyamotoi* has implications for checking for ticks and continuing tick precautions even after the risk of Lyme disease has abated. Human-to-human transmission by blood transfusion is possible [3], but a transfusion-associated case has not been reported to date.

The clinical manifestations of *B. miyamotoi* among the 51 American case-patients are very similar to those described for patients with undifferentiated acute febrile illness, including fever and headache as the most prominent findings [2-8]. Recurrence of fever was noted in 4 percent of patients in this case series and 10 percent in the original case series from Russia [2]. Higher relapse rates might have been observed if antibiotic therapy had been delayed or omitted. A rash was noted in 8 per cent of the American patients but none were described as an EM rash. Symptoms were often severe, resulting in hospital admission for about a quarter of the patients. None of the cases developed complications, however, presumably because of prompt antibiotic treatment. Meningoencephalitis due to *B. miyamotoi* has been described in two immunocompromised patients in separate reports from the United States and the Netherlands [4, 7]. Jarish-Herxheimer reactions, which consist of fever and chills with occasional hypotension following the first dose of an antibiotic, were not described in this case series, although such reactions were observed in a minority of previously reported *B. miyamotoi* patients [2-4]. Leucopenia, thrombocytopenia, and elevated liver enzyme concentrations were reported, as has been previously documented [2].

The diagnosis of *B. miyamotoi* in this case series was based upon PCR testing and subsequent sequencing of the product. *B. miyamotoi* antibody testing based on the GlpQ antigen was noted to be relatively insensitive in diagnosing acute illness but is a reasonable test to confirm the diagnosis if convalescent sera is available [5,6,8]. Antibodies to a *Borrelia* GlpQ protein are not observed in Lyme disease because *B. burgdorferi* does not make the protein, however, there may be cross-reactive antibodies with other forms of relapsing fever [10]. Both PCR and GlpQ

antibody assays for *B. miyamotoi* are available from some commercial and university laboratories, but to date there are no FDA approved *B. miyamotoi* tests. Although not examined in this report, a Wright- or Giemsa-stained blood smear is a routinely performed procedure that may reveal *B. miyamotoi* spirochetes in the blood during febrile episodes. Doxycycline, amoxicillin, or ceftriaxone appear to be effective in clearing symptoms and preventing complications [2-8]. Such therapy also would be effective against co-infection with *B. burgdorferi*. Doxycycline is preferred initial therapy in patients with suspected *B. miyamotoi* infection because it effectively treats Lyme disease and human granulocytic anaplasmosis, which may be the cause of illness or a coinfection with *B. miyamotoi*.

An official name for *B. miyamotoi* infection has not yet been adopted. The term "*Borrelia miyamotoi* disease", which is suggested by Molloy et al., is one option. As an alternative, we suggest "hard tick-borne relapsing fever", which accurately indicates the class of pathogens to which the agent belongs but also distinguishes it from the other types of vectors for this group of species, namely, soft tick-borne relapsing fever and louse-borne relapsing fever [2]. Regardless of the nomenclature, the report by Molloy et al. provides important new information about a bacterial zoonosis that may be as common as babesiosis or human granulocytic anaplasmosis in the northeastern United States and may lead to hospitalization for severe illness [refs].

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