Update and Commentary on Four Emerging Tick-Borne Infections

Ehrlichia muris–like Agent, *Borrelia miyamotoi*, Deer Tick Virus, Heartland Virus, and Whether Ticks Play a Role in Transmission of *Bartonella henselae*

Gary P. Wormser, MD[a,*], Bobbi Pritt, MD, MSc, DTM&H[b]

KEYWORDS

• Tick-transmitted infections • *Ehrlichia* • *Borrelia* • Deer tick virus • Powassan virus • Heartland virus • *Bartonella*

KEY POINTS

- Emerging tick-transmitted infections in the United States include infections due to *Ehrlichia muris*–like agent, *Borrelia miyamotoi* sensu lato, deer tick virus, and Heartland virus.
- Too few cases have been reported to characterize accurately or completely the range of possible clinical and laboratory manifestations of these infections.
- There is a need for the development of sensitive and specific serologic and molecular assays for these infections that are easily accessible to clinicians.

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[a] Division of Infectious Diseases, New York Medical College, 40 Sunshine Cottage Road, Skyline Office #2N-C20, Valhalla, NY 10595, USA; [b] Division of Clinical Microbiology, Department of Pathology and Laboratory Medicine, Mayo Clinic, 200 1st Street, SW, Rochester, MN 55905, USA
* Corresponding author.
E-mail address: gwormser@nymc.edu

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INTRODUCTION

Besides Lyme disease, there are 5 other known *Ixodes scapularis* transmitted infections in the United States: babesiosis, human granulocytic anaplasmosis, deer tick virus infection, *Ehrlichia muris*–like agent infection (also referred to as *Ehrlichia* sp Wisconsin), and *Borrelia miyamotoi* sensu lato infection. This review provides current information on the epidemiology, clinical and laboratory features, and treatment of the newest, least common, and least well-understood members of this group of infections: infection due to *E muris*–like agent, deer tick virus infection, and *B miyamotoi* sensu lato infection (**Table 1**). Heartland virus infections (for which a vector has not been definitely established) is also discussed and the evidence that *Bartonella henselae* is a tick-borne pathogen is critically reviewed.

EHRLICHIA MURIS–LIKE AGENT

Ehrlichiae are obligate intracellular gram-negative bacteria that infect leukocytes and cause a febrile illness in humans. Ehrlichiosis in the United States is due primarily to *Ehrlichia chaffeensis*, and less commonly, to *Ehrlichia ewingii*, which are both transmitted by *Amblyomma americanum*, the Lone Star tick. In 2009, a third cause of human ehrlichiosis was identified in patients from the upper Midwest, with the first cases reported in the medical literature in 2011.[1] The formal taxonomic disposition of this agent is currently unclear, but studies have demonstrated a 95% to 98% sequence homology between this organism and *E muris* when examining multiple genes (*gro*EL, 16S, *glt*A, *fbp*A, *nad*A, and *dsb*),[2] and the organism is commonly referred to as the *E muris*-like (EML) agent. *E muris* is currently recognized to exist in Eastern Europe and parts of Asia, where it is found in ticks of the *Ixodes persulcatus* complex and in rodents and deer.[3–5]

The first published report of clinical illness associated with this infection described 4 patients from Wisconsin and Minnesota.[1] In total from 2009 to 2013, 67 patients have been identified by testing EDTA whole-blood samples using a polymerase chain reaction (PCR) assay targeting the *groEL* gene.[6] All of the patients were from the upper Midwestern United States and reported probable tick exposure in Wisconsin or Minnesota. The 67 patients included 42 men and 25 women. All of the patients were adults or adolescents whose ages ranged from 15 to 94 years (mean age, 61 years). Patients presented commonly with fever (89%), fatigue (81%), headache (69%), and myalgia (63%), while laboratory findings included lymphopenia (66%) and thrombocytopenia (58%). Elevated liver enzyme levels have been noted but the frequency is uncertain from the available data. Twelve (50%) of the 24 patients whose immune status was known were immunocompromised because of receipt of immunosuppressive therapies. Thirteen patients were hospitalized for a median duration of 7 days.[6] Nevertheless, all patients recovered, with 66 of the 67 receiving doxycycline. Patients seemed to respond to doxycycline as would be expected from experience with the treatment of human monocytic ehrlichiosis and human granulocytic anaplasmosis.

The diagnosis has been most conclusively established by PCR detection of pathogen DNA in blood samples, although seroreactivity with *E chaffeensis*, but not with *Anaplasma phagocytophilum*, has been noted.[1] The cell type that is infected by this microorganism in humans is unknown, and intracellular inclusions (morulae) have not yet been identified in peripheral blood smears of patients with this infection.

As of 2012, the EML agent has been detected by PCR targeting the *groEL* gene in at least 34 (2.5%) of 1384 *I scapularis* ticks from Wisconsin or Minnesota collected from 2007 to 2010 but has not been found in ticks outside of this geographic area, including 1547 *I scapularis* and 6563 *A americanum* ticks that were tested.[1,7] Indeed,