

# What's Eating You? *Ixodes* Tick and Related Diseases, Part 2: Diagnosis and Treatment of Regional Tick-borne Diseases

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## PRACTICE POINTS

- Apart from the more familiar *Borrelia burgdorferi*, several less common pathogens associated with diseases transmitted by *Ixodes* ticks include *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia miyamotoi*, the Powassan virus, and the tick-borne encephalitis virus.
- Overlap in both the geographic distribution and the clinical presentations of these uncommon pathogens underscores the importance of being familiar with their capacity for causing illness and effective treatment.
- Intoxication with the saliva of some *Ixodes* species can cause an ascending flaccid tick paralysis.

The *Ixodes* tick is an important arthropod vector in the transmission of human disease. Although Lyme disease is the most prevalent zoonosis transmitted by *Ixodes* ticks, other less common diseases may be encountered, including human granulocytic anaplasmosis, babesiosis, Powassan virus infection, tick-borne encephalitis, *Borrelia miyamotoi* disease, and tick paralysis. In part 2 of this review, disease presentation, diagnosis, and treatment of these less commonly encountered tick-borne diseases are discussed.

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The *Ixodes* tick is prevalent in temperate climates worldwide. During a blood meal, pathogens may be transmitted from the tick to its host. *Borrelia burgdorferi*, a spirochete responsible for Lyme disease, is

the most prevalent pathogen transmitted by *Ixodes* ticks.<sup>1</sup> *Borrelia mayonii* recently was identified as an additional cause of Lyme disease in the United States.<sup>2</sup>

The *Ixodes* tick also is associated with several less common pathogens, including *Babesia microti* and the tick-borne encephalitis virus, which have been recognized as *Ixodes*-associated pathogens for many years.<sup>3,4</sup> Other pathogens have been identified, including *Anaplasma phagocytophilum*, recognized in the 1990s as the cause of human granulocytic anaplasmosis, as well as the Powassan virus and *Borrelia miyamotoi*.<sup>5-7</sup> Additionally, tick paralysis has been associated with toxins in the saliva of various species of several genera of ticks, including some *Ixodes* species.<sup>8</sup> Due to an overlap in geographic distribution (Figure) and disease presentations (eTable), it is important that physicians be familiar with these regional pathogens transmitted by *Ixodes* ticks.

## Human Granulocytic Anaplasmosis

Formerly known as human granulocytic ehrlichiosis, human granulocytic anaplasmosis is caused by *A phagocytophilum* and is transmitted by *Ixodes scapularis*, *Ixodes pacificus*, and *Ixodes persulcatus*. The incidence of human granulocytic anaplasmosis in the United States increased 12-fold from 2001 to 2011.<sup>9</sup>

Presenting symptoms generally are nonspecific, including fever, night sweats, headache, myalgias, and arthralgias, often resulting in misdiagnosis as a viral infection. Laboratory abnormalities include mild transaminitis, leukopenia, and thrombocytopenia.<sup>9,10</sup> Although most infections resolve spontaneously, 3% of patients develop serious complications. The mortality rate is 0.6%.<sup>11</sup>

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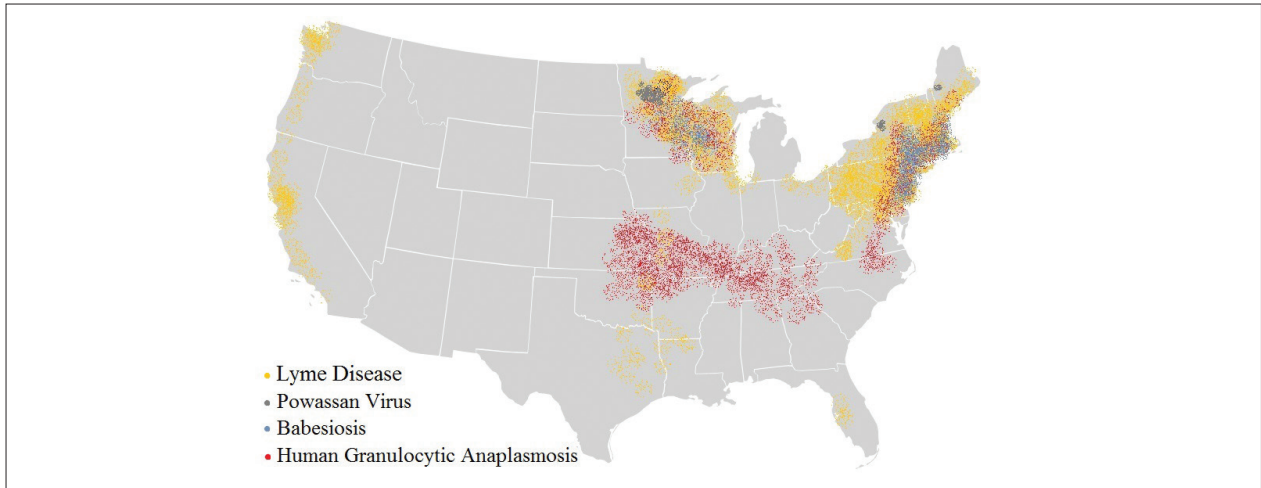
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The eTable is available in the Appendix online at [www.mdedge.com/cutis](http://www.mdedge.com/cutis).

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Approximation of the geographic distribution of reportable tick-borne diseases transmitted by *Ixodes* species in the United States, including Lyme disease, Powassan virus, babesiosis, and human granulocytic anaplasmosis.

A diagnosis of human granulocytic anaplasmosis should be suspected in patients with a viral-like illness and exposure to ticks in an endemic area. The diagnosis can be confirmed by polymerase chain reaction (PCR), acute- and convalescent-phase serologic testing, or direct fluorescent antibody screening. Characteristic morulae may be present in granulocytes.<sup>12</sup> Treatment typically includes doxycycline, which also covers *B burgdorferi* coinfection. When a diagnosis of human granulocytic anaplasmosis is suspected, treatment should never be delayed to await laboratory confirmation. If no clinical improvement is seen within 48 hours, alternate diagnoses or coinfection with *B microti* should be considered.<sup>10</sup>

### Babesiosis

The protozoan *B microti* causes babesiosis in the United States, with *Babesia divergens* being more common in Europe.<sup>13</sup> Reported cases of babesiosis in New York increased as much as 20-fold from 2001 to 2008.<sup>14</sup> Transmission primarily is from the *Ixodes* tick but rarely can occur from blood transfusion.<sup>15</sup> Tick attachment for at least 36 hours is required for transmission.<sup>13</sup>

The clinical presentation of babesiosis ranges from asymptomatic to fatal. Symptoms generally are nonspecific, resembling a viral infection and including headache, nausea, diarrhea, arthralgia, and myalgia. Laboratory evaluation may reveal hemolytic anemia, thrombocytopenia, transaminitis, and elevated blood urea nitrogen and creatinine levels.<sup>16</sup> Rash is not typical. Resolution of symptoms generally occurs within 2 weeks of presentation, although anemia may persist for months.<sup>13</sup> Severe disease is more common among elderly and immunocompromised patients. Complications include respiratory failure, renal failure, congestive heart failure, and disseminated intravascular coagulation. The mortality rate in the United States is approximately 10%.<sup>10,16</sup>

A diagnosis of babesiosis is made based on the presence of flulike symptoms, laboratory results, and history of recent travel to an endemic area. A thin blood smear allows identification of the organism in erythrocytes as ring forms or tetrads (a “Maltese cross” appearance).<sup>17</sup> Polymerase chain reaction is more sensitive than a blood smear, especially in early disease.<sup>18</sup> Indirect fluorescent antibody testing is species-specific but cannot verify active infection.<sup>10</sup>

Treatment of babesiosis is indicated for symptomatic patients with active infection. Positive serology alone is not an indication for treatment. Asymptomatic patients with positive serology should have diagnostic testing repeated in 3 months with subsequent treatment if parasitemia persists. Mild disease is treated with atovaquone plus azithromycin or clindamycin plus quinine. Severe babesiosis is treated with quinine and intravenous clindamycin and may require exchange transfusion.<sup>10</sup> Coinfection with *B burgdorferi* should be considered in patients with flulike symptoms and erythema migrans or treatment failure. Coinfection is diagnosed by Lyme serology plus PCR for *B microti*. This is an important consideration because treatment of babesiosis does not eradicate *B burgdorferi* infection.<sup>19</sup>

### Powassan Virus

Powassan virus is a flavivirus that causes encephalitis. It is transmitted by *Ixodes cookei* (Powassan virus, lineage I) in the Great Lakes region and by *I scapularis* (Powassan virus, lineage II, or deer tick virus) in the northeastern United States. Transmission can occur within 15 minutes of tick attachment.<sup>6,20,21</sup>

Patients typically present with fever, headache, altered mental status, seizures, and focal neurologic deficits. Gastrointestinal symptoms and rash also have been reported.<sup>21</sup> The diagnosis is made based on clinical

presentation and laboratory testing with PCR or enzyme-linked immunosorbent assay (ELISA). Cross-reactivity on ELISA exists, necessitating confirmation with a neutralizing antibody or PCR. Treatment is supportive. Corticosteroids and intravenous immunoglobulin have been proposed as treatment modalities, but evidence of their efficacy is limited.<sup>22</sup>

### Tick-borne Encephalitis

Tick-borne encephalitis is caused by the flavivirus tick-borne encephalitis virus in Europe and Asia. The tick-borne encephalitis virus is transmitted by *Ixodes ricinus* in Europe and by *Ixodes persulcatus* in eastern Russia, China, and Japan. It also has been associated with consumption of unpasteurized milk.<sup>23,24</sup>

Tick-borne encephalitis presents in a biphasic pattern. The initial viremic phase can persist for as long as 8 days with headache, nausea, myalgia, and fever. One-third of patients then enter an asymptomatic phase, followed by virus penetration into the central nervous system. The neurologic phase produces continued headache and fever with photophobia, focal neurologic deficits, seizures, respiratory depression, or coma. Neurologic sequelae persist in 10% to 20% of patients.<sup>25,26</sup>

In the viremic stage, diagnosis is made with PCR or culture. During the latent phase or neurologic phase, serologic testing for tick-borne encephalitis virus antibodies is indicated. Neutralizing antibody evaluation may be necessary due to cross-reactivity among flaviviruses.<sup>27</sup> Treatment is supportive. An inactivated vaccine is available for high-risk populations.<sup>28</sup>

### *Borrelia miyamotoi* Disease

*Borrelia miyamotoi* is a symbiont of the *Ixodes* tick formerly believed to have no pathogenic significance; however, *B miyamotoi* was isolated in febrile patients in Russia in 2011<sup>7</sup> and was identified as a pathogen in both North America<sup>29</sup> and Europe in 2013.<sup>30</sup> Disease presentation includes nonspecific symptoms of fever, fatigue, headache, arthralgia, myalgia, and nausea. Rash is uncommon. Laboratory abnormalities include leukopenia, thrombocytopenia, and transaminitis.<sup>31,32</sup> Meningoencephalitis may occur in immunocompromised patients.<sup>29,30</sup>

The diagnosis of *B miyamotoi* disease is confirmed by PCR or serology. An ELISA that is positive for *B burgdorferi* IgM but negative with confirmatory immunoblot suggests *B miyamotoi* disease. Seroconversion using a glpQ protein ELISA also can be assessed.<sup>31</sup> If ELISA is positive, Lyme disease can be excluded because *B burgdorferi* does not possess glpQ. Treatment is with doxycycline.<sup>32</sup>

### Tick Paralysis

Tick paralysis is an intoxication with holocyclotoxin from the saliva of gravid hard ticks. In the United States, intoxication is associated with ticks of various species of *Amblyomma*, *Dermacentor*, and *Ixodes* in the Northwest, Southeast, and Northeast. In Australia, intoxication is

associated with *Ixodes*.<sup>33</sup> Patients present with weakness and fatigue, progressing to ascending flaccid paralysis with sensory sparing. The treatment is tick removal.<sup>8,33</sup>

### Conclusion

Arthropods carry many regional pathogens. Physicians outside of those regions should seek a travel history and be alert for imported disease.

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## APPENDIX

**eTABLE. Regional Tick-borne Diseases Associated with *Ixodes* Tick Transmission**

Disease (Pathogen)	Geographic Distribution	Peak Season	Clinical Presentation	Laboratory Abnormalities	Method of Diagnosis	Treatment
Human granulocytic anaplasmosis ( <i>Anaplasma phagocytophilum</i> )	Northeastern and midwestern United States	May–October	Flulike symptoms <sup>a</sup>	Transaminitis, leukopenia, thrombocytopenia	PCR, serology, blood smear: morulae in granulocytes	Doxycycline 100 mg twice daily for 10–14 d
Babesiosis ( <i>Babesia microti</i> , <i>Babesia divergens</i> )	Northeastern and midwestern United States ( <i>B. microti</i> ); Europe, South America, Africa, Asia ( <i>B. divergens</i> )	June–August	Flulike symptoms <sup>a</sup>	Hemolytic anemia, thrombocytopenia, transaminitis, elevated blood urea nitrogen and creatinine levels	PCR; blood smear: organism has “Maltese cross” appearance in red blood cells; recent history of travel to an endemic area	Mild to moderate: (1) atovaquone 750 mg 3 times daily plus azithromycin 500–1000 mg, both for 1 d, then continue azithromycin 250 mg once daily for 7–10 d; (2) clindamycin 600 mg and quinine 650 mg, both 3 times daily for 7 to 10 d; Severe: IV clindamycin 600 mg 3 times daily plus oral quinine 650 mg 3 times daily for 7 to 10 d; +/- exchange transfusion
Powassan virus (Powassan virus, lineage I; Powassan virus, lineage II [deer tick virus])	Midwestern United States; northeastern United States, Europe, Canada	June–September	Flulike symptoms, <sup>a</sup> encephalitis, seizures, altered mental status, focal neurologic deficits	None	PCR, IgM serology, 4-fold increase in IgG antibody titer (ELISA)	Supportive care
Tick-borne encephalitis (TBEV)	Europe, eastern Russia, China, Japan	May–November	Viremic phase: flulike symptoms <sup>a</sup> ; neurologic phase: flulike symptoms, <sup>a</sup> photophobia, seizures, focal neurologic deficits	None	PCR, IgM serology, 4-fold increase in IgG antibody titer, serologic testing for TBEV antibodies	Supportive care
<i>Borrelia miyamotoi</i> disease ( <i>B. miyamotoi</i> )	North America, Europe, Russia	May–August	Flulike symptoms <sup>a</sup>	Leukopenia, thrombocytopenia, transaminitis	PCR, serology; ELISA for gIpQ protein	Doxycycline 100 mg twice daily for 14 d
Tick paralysis (holocyclotoxin)	Australia	April–September	Ascending flaccid paralysis with sensory sparing, weakness and fatigue	None	Tick parts observed on physical examination	Tick removal

Abbreviations: PCR, polymerase chain reaction; IV, intravenous; ELISA, enzyme-linked immunosorbent assay; TBEV, tick-borne encephalitis virus.

<sup>a</sup>Fever, fatigue, headache, myalgia, arthralgia, and nausea.