CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES & HEALTH INFORMATION DESIGNS

Connecticut Medical Assistance Program Quarterly Newsletter

Vector-borne diseases are infections that are primarily transmitted by insects. Approximately 17% of worldwide infections are vector-borne.[1] The National Notifiable Disease Surveillance System (NNDSS), overseen by the Centers for Disease Control (CDC), tracks 16 vector-borne diseases transmitted by ticks, mosquitos, and fleas. Approximately 650,000 cases of vector-borne diseases were reported to the NNDSS from 2004 – 2016. More than 75% of these were tick-borne, predominantly reported from the eastern part of the country and the pacific coast.[2] NNDSS reports that tick-borne disease cases have more than doubled in the last 13 years.[2]

Ticks can carry and transmit multiple pathogens, such as bacteria, viruses, and protozoa. While there are approximately 900 species of ticks, only about 25 species are of medical or veterinary concern.[3] *Ixodes scapularis* (pictured below), also known as the black legged tick or deer tick, is the most common species of tick in the northeastern region of the United States and transmits the vast majority of tick-borne human pathogens.[4] *I. scapularis* historically presented in modest numbers in the northeastern region of the United States. However, this species of tick has spread to cover most of the Eastern U.S. and into southern Canada. An increase in reforestation and white-tailed deer population, coupled with warming climates, are thought to be contributing factors of the geographical spread of *I. scapularis*.[3]

I. scapularis feeds three times within its life cycle of approximately two years and goes through three stages of development; larvae, nymph, and adult. Each feeding, or blood meal, occurs once during each stage of life.[5] Egg laying typically begins in the spring with the larvae becoming predominant during the summer months. The larvae will feed on small mammals such as mice during the summer, although they can also feed on other animals such as birds and even lizards. White-footed mice are thought to serve as the primary reservoir for human pathogens transmitted by *I. scapularis*. Most pathogens infect the larval stage tick during their first blood meal. After their first blood meal, larvae go dormant during the winter and mold into the nymph stage during the following spring/summer. Nymphs will feed once on small or large mammals such as white-tailed deer or humans, potentially transmitting any pathogens acquired to their host. The nymph form of *I. scapularis* is responsible for the majority of pathogen transmission to humans.[6] Once the nymph takes its blood meal, it will mold into the adult stage. If the adult tick survives its second winter, it will seek out a final host for its third blood meal prior to laying eggs or completing its life cycle.[3,6,7] Adults will typically feed on large mammals such as white-tailed deer or humans, providing a second opportunity to transmit any pathogens acquired to its host.

While there are 7 human pathogens known to be transmitted by *I. scapularis*, five are transmitted to humans in the northeast region of the U.S.: *Borrelia burgdorferi* (*B. burgdorferi*), *Anaplasma phagocytophilum (A. phagocytophilum), Babesia microti (B.microti), Borrelia miyamotoi* (*B.miyamotoi*), and Powassan virus.[4]

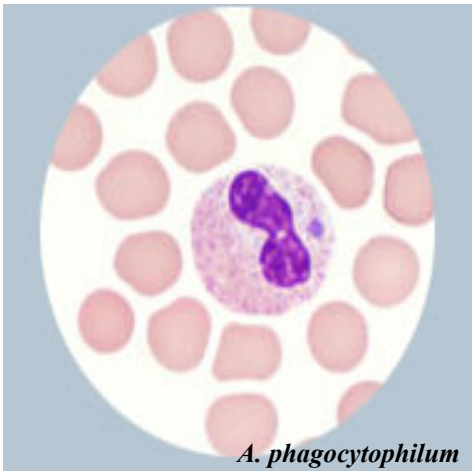
B. burgdorferi is a spirochete bacterium that causes Lyme Disease (LD), the most common tickborne disease in the U.S, and tracked by the NNDSS. According to the CDC, approximately 300,000 cases of LD occur each year, although this number is largely underreported.[8] During 2018, 3,692 Connecticut Medicaid patients were diagnosed with (LD). Most cases of LD occur in the summer, and ticks need to be attached to their host for a prolonged period of time (48-72 hours) to transmit the bacteria. There are 3 stages of LD: early localized disease; early disseminated disease; and late disseminated disease.[6,9]

Early localized disease typically occurs 7-10 days after the tick bite and 70-80% of patients will develop an erythema

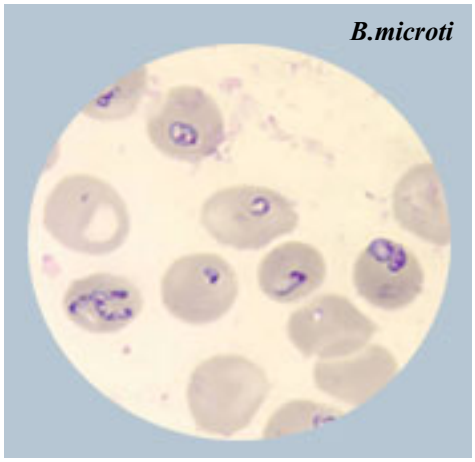
June 2019
Published Quarterly by Health Information Designs, LLC
Heather L. Kissinger, PharmD

migrans rash, or bullseye rash, at the site of the bite.[10] Patients can experience flu-like symptoms and lymphadenopathy during the early localized disease stage. [6,9] Early disseminated disease can include signs and symptoms from the localized stage, but patients may also experience cardiac manifestations such as atrioventricular heart block, or myocarditis and neurologic manifestations such as peripheral nerve palsy, meningitis, or encephalitis. Late disseminated disease presents with rheumatologic manifestations including Lyme arthritis, or baker's cysts as well as neurologic manifestations.[6,9] During early localized disease, patients should be diagnosed clinically as serological tests are not always sensitive during the first stage of infection, although titers may be helpful at this time in making a diagnosis. For patients with suspected LD for over a one-month period, a two-tier diagnosis approach should be made using serum testing and confirmed by western blot.[9] Coinfection with B.microti and/or A. phagocytophilum should be considered and tested for in patients who present with more severe symptoms such as patients with high grade fever for > 48 hours despite antibiotics, or patients who have unexplained anemia, leukopenia, or thrombocytopenia.[9] Treatment recommendations for LD can be found in Table 1.

A. phagocytophilum is an intraleukocytic bacterium that causes anaplasmosis.[9,11] Formerly known as Human Granulocytic Ehrlichiosis (HGE) and now known as Human Granulocytic Anaplasmosis (HGA), this is a bacterial infection affecting leukocytes. Added to the NNDSS list of notifiable diseases in 2000, reported cases increased from 351 in 2000 to 4,151 in 2016.[12] During 2018, 141 Connecticut Medicaid patients were diagnosed with ehrlichiosis (other/unspecified). A search of the ICD -10 database did not return results for anaplasmosis, leading to the conclusion that anaplasmosis diagnoses in Connecticut may be classified under the formerly known ehrlichiosis. Disease presentation tends to be less severe than other Ehrlichiosis infections, such as Rocky Mountain Spotted Fever (RMSF), and presents with fever, chills, and myalgias. Lab abnormalities can include leukopenia, thrombocytopenia, and increased liver function tests (LFTs).[9,11] Risk factors for more severe infection include: immunosuppression, advanced age, comorbid disease states, and delay in diagnosis and treatment.[9,11] Case fatality rate is <1% for patients who seek medical help.[9,11] Coinfection with other *I.scapularis* pathogens may present as a more severe case of anaplasmosis. Using a blood smear to detect morulae in the cytoplasm of granulocytes is highly suggestive of anaplasmosis (image below[9]) but


A. phagocytophilum

must be confirmed by an additional test such as a polymerase chain reaction (PCR) test, serum test, or immunohistochemical staining from tissue samples.[9] Treatment recommendations for anaplasmosis can be found in Table 1, and it should be noted that the American Academy of Pediatrics (AAP) recommends doxycycline as first line treatment for all children with tick-borne anaplasmosis, regardless of age. No evidence has been shown to cause staining of permanent teeth, even when multiple courses are given before the age of eight. [9]


B.microti

B.microti is a protozoan intraerythrocytic parasite that causes Babesiosis. Added to the NNDSS list of notifiable diseases in 2011, approximately 2,000 cases of babesiosis occur each year in the U.S., up from approximately 1,000 cases reported in 2011.[12,13] During 2018, 161 Connecticut Medicaid patients were diagnosed with babesiosis. There are a few *Babesia* species that can infect humans, however, *B.microti* is the primary species.[14] Babesiosis is emerging in areas endemic for LD and presentation can range from subclinical to severe.[15] Babesiosis can often be asymptomatic in healthy patients, however, certain risk factors can increase a patient's risk for symptomatic and more severe presentation of the illness. Patients who are asplenic, immunocompromised, and of older age have a higher risk of severe disease.[16] Symptomatic infection presents similarly to malaria with patients experiencing fever and fatigue, chills, sweats, arthralgias, and myalgias. Lab findings tend to be consistent with hemolytic anemia, as this bacterium attacks a patients red blood cells. Patients can also experience thrombocytopenia, elevated LFTs and abnormal kidney function tests.[17] Severe cases can present with disseminated intravascular coagulation, hemodynamic instability, acute respiratory distress, renal failure, hepatic failure, and death. Mortality rates of 6-21% have been reported, and end-stage organ complications can develop in

57% of immunocompromised patients.[18,19] Diagnosis of babesiosis can be made by identification of intraerythrocytic *Babesia* parasites in a blood smear sample (image on page 2[9]), positive PCR, or isolation of the parasite from a whole blood sample.[9] Treatment recommendations for babesiosis can be found in Table 1.

B.miyamotoi is another spirochete bacterium transmitted by *I. scapularis* that causes relapsing fever.[9,20] The bacterium was first discovered in Japan in 1994 and then subsequently in Connecticut during 2000. During 2018, 10 Connecticut Medicaid patients were diagnosed with tick-borne relapsing fever. *B.miyamotoi* is one of two *I. scapularis* pathogens that can be transmitted both horizontally and vertically (from mother to egg) and can be transmitted to humans by larval ticks. Most other pathogens are only transmittable during the nymph or adult stage, after the tick becomes infected with a pathogen during a blood meal. Human transmission commonly occurs during the summer months, and while *B. miyamotoi* has not been added to the NNDSS list of notifiable diseases, recent reports suggest infection rates are comparable in frequency to babesiosis or anaplasmosis in areas endemic for LD.[15] In 2014, a study reported that 4% of healthy southern New Englanders had seroprevalence of *B.miyamotoi*, indicating prior infection.[21] *B.miyamotoi* relapsing fever presents with fatigue, headache, chills, myalgia, arthralgia, nausea, and relapsing fever. Risk factors for severe disease are similar to other *I. scapularis* pathogens and severe disease can present as meningoencephalitis. If *B.miyamotoi* is suspected, especially in an area known for LD, blood smear, PCR and/or antibody-based tests should be performed for diagnosis. Treatment recommendations for *B.miyamotoi* relapsing fever can be found in Table 1. Symptoms will resolve within a week of starting treatment; however, it has been reported that an adverse reaction, the Jarisch-Herxheimer reaction, can occur in patients receiving the first or second dose of antibiotics. Jarisch-Herxheimer reaction presents as returning fever, chills, rigor, diaphoresis, hypotension and even shock. This has been reported in up to half of people treated with antibiotics for relapsing fever and in 15% of patients in Russia treated for *B.miyamotoi.*[22,23] Supportive measures are recommended if this occurs.

Powassan Virus (POWV), also known as the deer tick virus (DTV), is caused by a tick-borne flavivirus that can be transmitted by larval ticks, due to vertical transmission, as well as nymph and adult ticks. Transmission to humans occurs quickly, within 15 minutes after initial tick attachment (much faster than *B. burgdorferi*). [24,25] Due to the increasing incidence, POWV was added to the NNDSS list of notifiable diseases in 2002, and approximately 100 cases have been reported to the CDC in the last decade.[26] During 2018, 10 Connecticut Medicaid patients were diagnosed with tick-borne viral encephalitis. Symptomatic POWV presents with sore throat, drowsiness, headache, and disorientation. POWV can cause severe neuroinvasive illness such as encephalitis, meningoencephalitis, and aseptic meningitis which presents with vomiting, respiratory distress, loss of coordination, difficulty speaking, and seizures.[27] Approximately 10% of all POWV encephalitis cases are fatal, and severe neurological symptoms can remain in over 50% of survivors.[28] Serologic testing is the primary method for diagnosis, using POWV-specific IgG and IgM antibodies to detect the virus in patients' blood or plasma.[29] Testing is available through the CDC and certain state health departments, however, there is limited commercial testing available.[9] Currently, there are no available vaccines for prevention of POWV. If a patient does become infected and requires hospitalization, supportive care is the best form of treatment (IV fluids, respiratory support, and reducing cerebral edema).

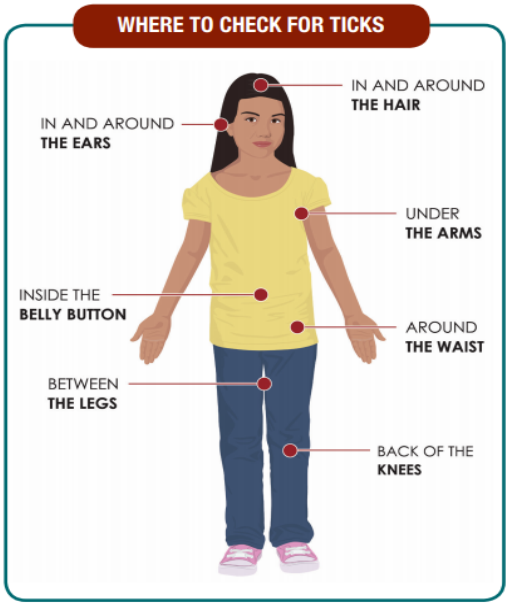
During the 1970's, *I. scapularis* was not known to transmit pathogens to animals or humans. Now, more than 40 years later, *I. scapularis* is the most prominent vector in the United States[4,30] known to transmit 5 pathogens to humans in the northeast; *B. burgdorferi*, *A. phagocytophilum, B.microti, B.miyamotoi* and Powassan virus. With an increase in the geographical spread of *I. scapularis*, the number of human pathogens it can transmit, and the incidence of infections, tick-borne diseases are an important public health concern. Measures can be taken to prevent tick bites such as avoiding tall grass, wooded areas with leaf covered grounds, and avoiding plants such as the Japanese Barberry, which trap humidity and create an attractive breeding ground for *I. scapularis*.[31] Wearing permethrin treated clothing and using insect repellent can decrease tick attachment as well. After being outdoors, it is important to check clothing and pets, shower within two hours of coming indoors, and perform whole body tick checks. Tumble drying clothes in a dryer at high temperatures for 10 minutes can kill any ticks attached to clothing. Early detection and appropriate treatment of any tick-borne infections are key. If an infection is

Table 1. *I.scapularis Pathogen Treatment*[9]

Pathogen	Treatment (Adults)	Treatment (Pediatrics)
B. burgdorferi (LD)	Doxycycline 100 mg PO BID for 10-21 days*	Amoxicillin 50 mg/kg/day PO, divided into 3 doses for 14-21 days
	Cefuroxime 500 mg PO BID for 14-21 days	Doxycycline 4 mg/kg/day PO, divided into 2 doses for 10-21 days*
	Amoxicillin 500 mg PO TID for 14-21 days	Cefuroxime 30 mg/kg/day PO, divided into 2 doses for 14-21 days
B.microti (babesiosis)	Atovaquone 750 mg PO BID for 7-10 days plus Azithromycin 500-1000 mg PO QD day 1, 250-1000 mg** PO QD 6-9 days	Anecdotal cases of babesiosis in children, including infants (> 5 kg), have been safely treated with azithromycin plus atovaquone.[38]
	Clindamycin*** 300-600 mg IV Q6h or 600 mg PO Q8h plus Quinine*** 650 mg PO Q6-8h for 7-10 days	
A. phagocytophilum (anaplasmosis)	Doxycycline 100 mg BID (PO or IV) for 10-14 days	Doxycycline 2.2 mg/kg per dose BID (PO or IV) for 10-14 days
B.miyamotoi (relapsing fever)	Recommended treatment with antibiotics and doses used for LD	Recommended treatment with antibiotics and doses used for LD
Powassan Virus (POWV)	Supportive care	Supportive care

*Recent publications suggest the efficacy of shorter courses of treatment for early Lyme disease
**Upper end of dose used for immunocompromised patients
*** The standard of care for patients with severe babesiosis (e.g., with parasitemia levels ≥10% and/or organ-system dysfunction) is quinine plus clindamycin; typically, the clindamycin is administered intravenously. Such patients also might require or benefit from exchange transfusions, vasopressor therapy, mechanical ventilation, or dialysis.
PO=by mouth, QD=once a day, BID=twice a day, TID=three times a day, IV=intravenous

suspected, health care professionals should consider testing patients for all tick-borne pathogens, especially if there is uncertainty as to what it is causing the patients symptoms, symptoms appear severe, or the patient is non-responsive to traditional therapy. Testing for all pathogens might help to increase awareness of the overall prevalence of underreported diseases and decrease the severity of pathogen coinfection cases.



1. Huntington MK, Allison J. Emerging vector-borne diseases. *Am Fam Physician*. 2016;94(7):551-557.
2. Rosenberg R, Lindsey NP, Fischer M, et al. Vital signs: trends in reported vectorborne disease cases – United States and territories, 2004-2016. *MMWR* 2018;67(16):496-501.
3. Sonenshine DE. Range expansion of tick disease vectors in North America: implications for spread of tick-borne disease. *Int J Environ Res Public Health* 2018;15(478).
4. Nelder MP, Ruddell CB, Sheehan NJ, et al. Human pathogens associated with the blacklegged tick *Ixodes scapularis*: a systematic review. *Parasites & Vectors* 2016; 9:265-278.
5. McClure M, Diuk-Wasser MA. Climate impacts on black legged tick host-seeking behavior. *Int J Parasitol* 2019; 49:37-47.
6. Dumic I, Severnini E. "Ticking bomb": the impact of climate change on the incidence of lyme disease. *Can J Infec Dis Med Microb* 2018.
7. Eisen RJ, Kugeler KJ, Eisen L, et al. Tick-borne zoonoses in the United States: persistent and emerging threats to human health. *ILAR J* 2017; 58(3): 319-335.
8. Kuehn, B. M. CDC estimates 300,000 US cases of Lyme disease annually. *JAMA* 2013; 310 (1110).
9. Centers for Disease Control and Prevention. Tickborne diseases of the United States, a reference manual for health care providers, 5th edition 2018. https://www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf
10. Steere, A. C. Lyme disease. *N Engl J Med* 2001; 345:115–125.
11. Centers for Disease Control and Prevention. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States: a practical guide for health care and public health professionals. *MMWR* 2016;65.
12. National Notifiable Diseases Surveillance System (NNDSS). CDC. Available from: www.cdc.gov/nndss
13. Djokic V, Primus S, Akoolo L, et al. Age-related differential stimulation of immune response by Babesia microti and Borrelia burgdorferi during acute phase of infection affects disease severity. *Front* Immunol 2018; 2891.
14. Westblade LF, Simon MS, Mathison BA, et al. Babesia microti: from mice to ticks to an increasing number of highly susceptible humans. *J Clin Microb* 2017; 55(10): 2903-2912.
15. Diuk-Wasser MA, et al. Coinfection by *Ixodes* tick-borne pathogens: ecological, epidemiological, and clinical consequences. *Trends Parasitol* 2016;32:30–42.
16. White DJ, Talarico J, Chang HG, Birkhead GS, Heimberger T, Morse DL. Human babesiosis in New York State: review of 139 hospitalized cases and analysis of prognostic factors. *Arch Intern Med* 1998; 158: 2149–54.
17. Nathavitharana RR, Mitty JA. Diseases from North America: focus on tick-borne infections. *Clin Med* 2015; 15(1):74-7.
18. Krause PJ, Gewurz BE, Hill D, et al. Persistent and relapsing babesiosis in immunocompromised patients. *Clin Infect Dis* 2008; 46:370.
19. White DJ, Talarico J, Chang HG, et al. Human babesiosis in New York State: review of 139 hospitalized cases and analysis of prognostic factors. *Arch Intern Med* 1998;158:2149–2154.
20. Krause PJ, Fish D, Narasimhan S, et al. *Borrelia miyamotoi* infection in nature and in humans. Clin Microbiol Infect 2015;21(7):631-639.
21. Krause PJ, Narasimhan S, Wormser GP et al. *Borrelia miyamotoi* sensu lato seroreactivity and seroprevalence in the northeastern United States. *Emerg Infect Dis* 2014;20:1183-1190.
22. Platonov AE, Karan LS, Kolysanikova NM, et al. Humans infected with relapsing fever spirochete *Borrelia miyamotoi*, Russia. *Emerg Infect Dis* 2011:17:1816-1823.
23. Dworkin MS, Anderson DE Jr, Schwan RG, et al. Tick-borne relapsing fever in the northwestern United States and southwestern Canada. *Clin Infect Dis* 1998;26:122-131.
24. Ebel GD, Kramer LD. Short report: Duration of tick attachment required for transmission of Powassan virus by deer ticks. Am J Trop Med Hyg 2004; 71:268–271.
25. Tutolo JW, Staples E, Sosa L, et al. Powassan virus disease in an infant – Connecticut, 2016. *MMWR* 2017; 66(15):408.
26. Powassan Virus Statistics and Maps in 2018. CDC. Available from:https://www.cdc.gov/powassan/statistics.html
27. Hermance ME, Thangamani S. Powassan virus: an emerging arbovirus of public health concern. Vector Borne Zoonotic Dis 2017; 17(7):453-462.
28. Ebel GD. Update on Powassan virus: Emergence of a North American tick-borne flavivirus. *Annu Rev Entomol* 2010; 55: 95–110.
29. Thomm AM, Schotthoefer AM, Dupuis AP, et al. Development and validation of a serologic test panel for detection of Powassan virus infection in U.S. patients residing in regions where Lyme disease is endemic. mSphere 3:e00467-17.
30. Strickland R, Gerriah RR, Hourrigan JL, Schubert, GO. Ticks of veterinary importance. Washington, DC: Animal and Plant Health Inspection Service, US Department of Agriculture, Agriculture Handbook No. 485; 1976.
31. Williams SC, Linske MA, Ward, JS. Long-term effect of *Berberis thunbergii* (ranunculales: berberidaceae) management on *Ixodes scapularis* (acari: Ixodidae) abundance and *Borrelia burgdorferi* (spirochaetales: spirochaetaceae) prevalence in Connecticut, USA. *Environmental Entomology*, 2017;46(6):1329–1338.
32. Krause PJ, McKay K, Thompson CA, et al. Disease-specific diagnosis of coinfecting tickborne zoonoses: babesiosis, human granulocytic ehrlichiosis, and Lyme disease. *Clin Infect Dis* 2002; 34:1184-91.
33. Centers for Disease Control and Prevention. Arboviral Disease Case Definition. 2015. Available at https://wwwn.cdc.gov/nndss/conditions/powassan-virus-disease/case-definition/2015
34. Rosenberg R, Lindsey NP, Fischer M, et al. Vital signs: trends in reported vectorborne disease cases — United States and Territories, 2004–2016. *MMWR Morb Mortal Wkly Rep* 2018;67(17):496–501.
35. Record number of tickborne diseases reported in U.S. in 2017. CDC online newsroom. CDC. Available from: https://www.cdc.gov/media/releases/2018/s1114-record-number-tickborne-diseases.html.
36. Swanson SJ, Neitzel D, Reed KD, et al. Coinfections acquired from ixodes ticks. *Clin Microbiol Rev* 2006;19:708–727.
37. Eisen RJ, Eisen L. The blacklegged tick, Ixodes scapularis: an increasing public health concern. *Trends Parasitol* 2018 34(4):295-309.
38. Resources for Health Professionals in 2018. CDC. Available from:https://www.cdc.gov/parasites/babesiosis/health_professionals/index.html

June 2019
Published Quarterly by Health Information Designs, LLC
Heather L. Kissinger, PharmD