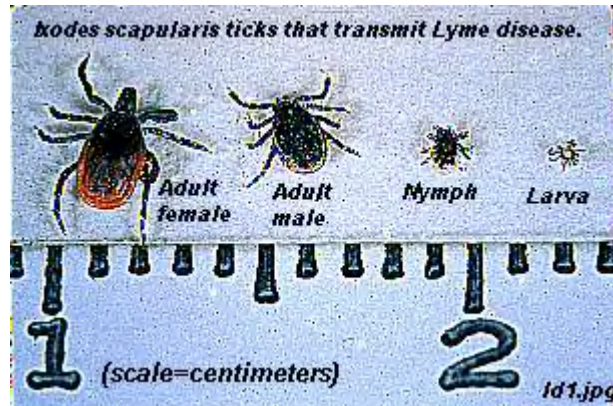


Lyme Disease

Symptoms Supplement

Additional topics in peer-reviewed literature reports.



Borrelia burgdorferi.

Burgdorfer W. Keynote Address - The Complexity of Vector-borne Spirochetes.
12th International Conference on Lyme Disease and Other Spirochetal
and Tick-Borne Disorders. 1999.

“Disease variability among patients probably is the result of multiple factors, including bacterial strain differences in virulence and organotropism, inoculum size, host immunity, and simultaneous co-infection with other tick-borne organisms.”

Halperin JJ. Neuroborreliosis: central nervous system involvement. *Semin Neurol*, 17(1):19-24. 1997.

“...in vectorborne diseases, multiple infections can occur in the same patient.”

Javed MZ; Srivastava M; et al. Concurrent babesiosis and ehrlichiosis in an elderly host.
Mayo Clinic Proceedings, 76(5):563-5. 2001.

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Ticks & Tick Bites

Majority of Patients Do Not Recall Tick Bite

- “...only 14-32 % of patients recall such a bite. This is probably the result of several factors. Nymphal *Ixodes scapularis* ticks, which account for the overwhelming majority of Lyme disease cases in the northeastern and midwestern United States, are tiny (approximately the size of poppy seeds) and may easily be overlooked...”
Nadelman RB; Wormser GP. Erythema migrans and early Lyme disease. American Journal of Medicine, 98(4A):15S-23S; discussion 23S-24S. 1995.
- “Unlike spider or insect bites, nymphal tick bites rarely cause significant tenderness or pruritus that would draw attention to the attached arthropod. ...Patients often recall the exact moment when a spider or insect bite occurred, in contrast to the frequently asymptomatic tick bite.”
Nadelman RB; Wormser GP. Erythema migrans and early Lyme disease. American Journal of Medicine, 98(4A):15S-23S; discussion 23S-24S. 1995.

Tick Bite May Be Confused With Brown Recluse Spider Bite

- “We report a case of Lyme disease with clinical features resembling those described from brown recluse spider bites. The most striking manifestation was a necrotic skin wound. Brown recluse spider bites may be overdiagnosed in some geographic regions. Tick bite and infection with *Borrelia burgdorferi* should be considered in the differential diagnosis of necrotic arachnidism in regions endemic for Lyme disease.”
Osterhoudt KC; Zaoutis T; Zorc JJ. Lyme disease masquerading as brown recluse spider bite. Annals of Emergency Medicine, 39(5):558-561. 2002.

Significant Percentage of Ticks in Endemic Areas Carry Lyme Disease

- *Ixodes scapularis* ticks in Pennsylvania:
Northwestern PA: **61.6%** positive for Lyme disease; **1.9%** positive for Ehrlichiosis
Southeastern PA: **13.1%** positive for Lyme disease; **39.8%** positive for Ehrlichiosis
Findings reported in: Courtney JW; Dryden RL; Montgomery J; et al. Molecular characterization of Anaplasma phagocytophilum and Borrelia burgdorferi in Ixodes scapularis ticks from Pennsylvania. Journal of Clinical Microbiology, 41(4):1569-1573. 2003.
- *Ixodes scapularis* ticks in New Jersey:
“Using polymerase chain reaction, we analyzed 529 *Ixodes scapularis* Say adults collected from 16 of New Jersey's 21 counties for the presence of *Borrelia burgdorferi*, the etiological agent of Lyme disease. Overall, 261 (**49.3%**) were positive.”
Schulze TL; Jordan RA; Hung RW; Puelle RS; Markowski D; Chomsky MS. Prevalence of Borrelia burgdorferi in Ixodes scapularis adults in New Jersey, 2000-2001. J Med Entomol.40(4):555-8. 2003.
- *Ixodes scapularis* ticks in Connecticut:
Woodbridge, CT: **32.9%** of nymphal ticks / **52.6%** of adult ticks positive for Lyme disease
Bridgeport, CT: **32.7%** of nymphal ticks / **55.0%** of adult ticks positive for Lyme disease
Findings reported in: Levin ML; des Vignes F; Fish D. Disparity in the natural cycles of Borrelia burgdorferi and the agent of Human Granulocytic Ehrlichiosis. Emerg Infect Dis 1999; Vol 5(2):204-8. URL: www.cdc.gov/ncidod/eid/vol5no2/levin.htm.

Alternate Vectors

- “...tick bites very often go unrecognized... We have shown earlier that deer flies can transmit *B. burgdorferi* to the human skin. Thus, lack of recollection of a tick bite cannot be used as an exclusion criterion of EM and Lyme borreliosis.”
Early dissemination of Borrelia burgdorferi without generalized symptoms in patients with erythema migrans. Oksi J; Marttila H; Soini H; Aho H; Uksila J; Viljanen MK. APMIS,109(9):581-8. 2001.
- “Viable spirochetes were recovered from RBCs inoculated with 10(6) organisms per mL, after refrigeration for as long as 6 weeks. It is concluded that *B. burgdorferi* may survive storage under blood banking conditions and that transfusion-related Lyme disease is theoretically possible.”
Survival of Borrelia burgdorferi in human blood stored under blood banking conditions. Nadelman RB; Sherer C; Mack L; Pavia CS; Wormser GP Transfusion, 30(4):298-301. 1990.

Transmission of Multiple Pathogens / Mixed Infections

Ticks May Transmit Multiple Pathogens

- “In medicine, general emphasis has been to explain most of the manifestations with a single diagnosis; however, in vectorborne diseases, multiple infections can occur in the same patient.”
Javed MZ; Srivastava M; Zhang S; Kandathil M. Concurrent babesiosis and ehrlichiosis in an elderly host. Mayo Clinic Proceedings, 76(5):563-5. 2001.

Babesiosis & Ehrlichiosis Co-Infections: Increased Disease Severity

- “Because these infections [Lyme disease, human babesiosis, and human granulocytic ehrlichiosis (HGE)] share the same rodent reservoir and tick vector hosts, they can be cotransmitted to human hosts. Indeed, human coinfections involving various combinations of these pathogens are common, and some tend to be particularly severe.”
Thompson C; Spielman A; Krause PJ. Coinfecting deer-associated zoonoses: lyme disease, babesiosis, and ehrlichiosis. Clinical Infectious Diseases, 33(5):676-85. 2001.
- “Of 96 patients with Lyme disease, 9.4% were seropositive for *B. microti* or the agent of HGE (or both). Of note, symptoms and duration of illness in patients with concurrent infections can be greater than in those with either infection alone.”
*Sweeney CJ; Ghassemi M; Agger WA; Persing DH. Coinfection with *Babesia microti* and *Borrelia burgdorferi* in a western Wisconsin resident. Mayo Clinic Proceedings, 73(4):338-341. 1998.*
- “Coinfection resulted in increased levels of both pathogens and more severe Lyme arthritis compared with those in mice infected with *B. burgdorferi* alone. ...These results suggest that coinfection of mice with *B. burgdorferi* and the HGE agent modulates host immune responses, resulting in increased bacterial burden, Lyme arthritis, and pathogen transmission to the vector.”
*Thomas V; Anguita J; Barthold SW; Fikrig E. Coinfection with *Borrelia burgdorferi* and the agent of Human Granulocytic Ehrlichiosis alters murine immune responses, pathogen burden, and severity of Lyme arthritis. Infection and Immunity, 69:3359-33. 2001.*

Frequency of Ehrlichiosis Infection in Lyme Disease Patients

- “Our data on IgM titers suggest that, in a region of New England in which Lyme disease is endemic, at least one of every five persons with seropositive early *B. burgdorferi* infection also has evidence of recent exposure to the agent of human granulocytic ehrlichiosis. Therefore, the diagnosis of human granulocytic ehrlichiosis should be considered in persons in the northeastern United States who are being evaluated for Lyme disease.”
*De Martino SJ; Carlyon JA; Fikrig E. Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis. New England Journal of Medicine, 345(2):150-1. 2001.*

I. Scapularis Ticks May Transmit Ehrlichiosis Within 24 Hours

- “Infected *I. scapularis* nymphs transmitted *E. phagocytophila* within 24 h in 2 of 3 attempts, which indicates that daily tick removal may not be adequate to prevent human infection with this agent.”
*des Vignes F; Piesman J; Heffernan R; Schulze TL; Stafford KC 3rd; Fish D. Effect of tick removal on transmission of *Borrelia burgdorferi* and *Ehrlichia phagocytophila* by *Ixodes scapularis* nymphs. J Infect Dis, 183(5):773-8. 2001.*

Ehrlichiosis Not Responsive to Antibiotic Used For Children With Lyme Disease

- “Early recognition of concurrent Lyme disease and HGE is important because amoxicillin, an antibiotic of choice for young children with early Lyme disease, is ineffective for HGE.”
*Moss WJ; Dumler JS. Simultaneous infection with *Borrelia burgdorferi* and human granulocytic ehrlichiosis. Pediatric Infectious Disease Journal, 22(1):91-2. 2003.*

Recommendations to Test for Ehrlichiosis & Babesiosis

- “In tick-dominated areas, patients should always be tested for coinfection with Ehrlichia, Babesia, and Borrelia burgdorferi.”
Javed MZ; Srivastava M; Zhang S; Kandathil M. Concurrent babesiosis and ehrlichiosis in an elderly host. Mayo Clinic Proceedings, 76(5):563-5. 2001.
- “Physicians should consider use of tests designed to diagnose babesiosis and HGE [human granulocytic ehrlichiosis] in patients with Lyme disease who experience a prolonged flulike illness that fails to respond to appropriate antiborrelial therapy.”
Krause PJ; McKay K; Thompson CA; Sikand VK; Lentz R; Lepore T; Closter L; Christianson D; Telford SR; Persing D; et al. Disease-specific diagnosis of coinfecting tickborne zoonoses: babesiosis, human granulocytic ehrlichiosis, and Lyme disease. Clinical Infectious Diseases, 34(9):1184-91. 2002.

Bartonella Co-Infection

- “To investigate the role of B. henselae in patients with symptoms suggesting neuroborreliosis, serum and cerebrospinal fluid samples were tested with serological and PCR methods. Among 17 examined patients, in 12 cases Borrelia burgdorferi infections were detected, in 1 case Bartonella henselae infection was ascertained, and in two patients mixed B. burgdorferi and B. henselae infections were found. These results indicate that mixed infections should be taken into consideration in establishing diagnosis of neurological disorders.”
Bartonella henselae and Borrelia burgdorferi infections of the central nervous system. Podsiadly E; Chmielewski T; Tylewska-Wierzbanowska S. Ann NY Acad Sci, 990:404-6. 2003.
- “Our data implicate B henselae as a potential human tick-borne pathogen. Patients with a history of neuroborreliosis who have incomplete resolution of symptoms should be evaluated for B henselae infection.”
Eskow E; Rao RV; Mordechai E. Concurrent infection of the central nervous system by Borrelia burgdorferi and Bartonella henselae: evidence for a novel tick-borne disease complex. Archives of Neurology, 58(9):1357-1363. 2001.

Immune Response to *Borrelia burgdorferi*

Chronic Infection: *Borrelia burgdorferi* May Survive in Body for Years

- “Lyme borreliosis is a chronic infectious disease caused by the spirochete *Borrelia burgdorferi*.”
Dattwyler RJ; Volkman DJ; Luft BJ. Immunologic Aspects of Lyme Borreliosis. Reviews of Infectious Diseases, 11(6)S6; S1494-8. 1989.
- “The pathogenesis of this disease appears to be centered around the long-term persistence of the organisms in tissues.”
Garcia-Monco JC; Benach JL. The pathogenesis of Lyme disease. [Review] Rheumatic Diseases Clinics of North America, 15(4):711-26. 1989.
- “[Our] findings imply that the Lyme spirochete may survive for years in affected synovium and may be directly responsible for the microvascular injury.”
Johnston YE; Duray PH; Steere AC; Kashgarian M; Buza J; Malawista SE; Askenase PW. Lyme arthritis. Spirochetes found in synovial microangiopathic lesions. American Journal of Pathology, 118(1):26-34. 1985.
- “Infection with Lyme disease spirochetes can be chronic. This suggests that the spirochetes are capable of immune evasion.”
McDowell JV; Sung SY; Price G; Marconi RT. Demonstration of the genetic stability and temporal expression of select members of the Lyme disease spirochete OspF protein family during infection in mice. Infect Immun, 69(8):4831-4838. 2001.

Borrelia burgdorferi Persists Despite Immune Response

- “Despite the development of humoral and cellular immunity that results in the resolution of the early localized lesions, both *B. burgdorferi* and *T. pallidum* persist in the host to cause chronic infection.”
Lukehart SA; Marra C. A comparison of syphilis and Lyme disease: central nervous system involvement. In: Lyme Disease: Molecular and Immunologic Approaches. Ed. Steven E. Schutzer. Cold Spring Harbor Laboratory Press, 1992.
- “*Borrelia burgdorferi*, the Lyme disease spirochete, persistently infects mammalian hosts despite the development of strong humoral responses directed against the pathogen.”
Liang FT; Jacobs MB; Bowers LC; Philipp MT. An immune evasion mechanism for spirochetal persistence in Lyme borreliosis. Journal of Experimental Medicine, 195(4):415-22. 2002.
- “...they [*Borrelia burgdorferi* spirochetes] have been demonstrated in tissues obtained from individuals with high levels of antiborrelial antibodies, a finding that indicates the presence of immunity alone does not guarantee eradication of this organism.”
Dattwyler RJ; Volkman DJ; Luft BJ. Immunologic aspects of Lyme borreliosis. Reviews of Infectious Diseases, 11(6)S6; S1494-8. 1989.
- “Persistence of the Lyme disease spirochete, *Borrelia burgdorferi*, in the presence of an active immune response has been well documented. Evidence from the past year indicates that modulation of surface antigens by the spirochete may be a major mechanism for evading the immune response.”
Seiler KP, Weis JJ. Immunity to Lyme disease: protection, pathology and persistence. Current Opinion in Immunology, 8(4):503-9. 1996.
- “It is still unknown how this pathogen manages to persist in the host in the presence of competent immune cells. It was recently reported that *Borrelia* suppresses the host's immune response, thus perhaps preventing the elimination of the pathogen...”
Diterich I; Rauter C; Kirschning CJ; Hartung T. Borrelia burgdorferi-induced tolerance as a model of persistence via immunosuppression. Infect Immun, 71(7):3979-87. 2003.
- “Even if the immune response is not capable of eliminating the organism, it is nonetheless important in determining the extent and severity of illness and in containing the organism. Immune-suppressed animals develop more severe illness...”
Louis Reik, Jr., M.D. Lyme Disease and the Nervous System. New York: Thieme Medical Publishers, Inc. 1991.

Early Treatment May Abrogate Development of Antibodies

- “However, as in syphilis, prompt antimicrobial therapy aborts the development of a mature humoral response. Thus, patients treated before they develop a mature response often lack diagnostic levels of *Borrelia*-specific antibodies.”

Dattwyler RJ; Volkman DJ; Luft BJ. Immunologic aspects of Lyme borreliosis. Reviews of Infectious Diseases, 11(6)S6; S1494-8. 1989.

- [Syphilis:] “Even in immunocompetent persons, partial therapy may increase risk of progression to symptomatic neurosyphilis. Musher and co-workers (1990) have suggested that the use of benzathine penicillin, with clearance of peripheral organisms, may serve to abort the developing immune response while leaving the CNS infected and therefore susceptible to neuro-relapse; a similar phenomenon of neurorelapse was noted following therapy with the partially efficacious arsenical preparations used prior to the discovery of penicillin.”

Lukehart SA; Marra C. A comparison of syphilis and Lyme disease: central nervous system involvement. In: Lyme Disease: Molecular and Immunologic Approaches. Ed. Steven E. Schutzer. Cold Spring Harbor Laboratory Press, 1992.

Seronegativity

- “Three separate groups of investigators have reported individuals who lacked diagnostic levels of specific antibody in their serum, yet had neurologic involvement and diagnostic levels of antibody in their CSF. We have confirmed this finding in our laboratory.”

Dattwyler RJ; Volkman DJ; Luft BJ. Immunologic Aspects of Lyme Borreliosis. Reviews of Infectious Diseases, 11(6)S6; S1494-8. 1989.

- “*B. burgdorferi* antigen can be detected in CSF that is otherwise normal by conventional methodology, and can be present without positive CSF antibody. Since CSF antigen implies intrathecal seeding of the infection, the diagnosis of neurologic infection by *B. burgdorferi* should not be excluded solely on the basis of normal routine CSF or negative CSF antibody analyses.”

*Coyle PK; Schutzer SE; Deng Z; Krupp LB; Belman MD; Benach JL; Luft BJ. Detection of *Borrelia burgdorferi*-specific antigen in antibody negative cerebrospinal fluid in neurologic Lyme disease. Neurology, (45):2010-2014. 1995.*

- “Although *ospA*, *ospB*, *ospC*, and flagellin were present at the time of inoculation, only flagellin was expressed by spirochetes in tissues 4 months later.”

*Cadavid D; O'Neill T; Schaefer H; Pachner AR. Localization of *Borrelia burgdorferi* in the nervous system and other organs in a nonhuman primate model of Lyme disease. Laboratory Investigation, 80(7):1043-52. 2000.*

Presence Of *Borrelia Burgdorferi* In CNS Without Inflammation

- “Despite substantial presence of *Borrelia burgdorferi*, the causative agent of Lyme borreliosis, in the central nervous system, only minor inflammation was present there, though skeletal and cardiac muscle, which contained similar levels of spirochete, were highly inflamed. Anti-*Borrelia burgdorferi* antibody was present in the cerebrospinal fluid but was not selectively concentrated. All infected animals developed anti-*Borrelia burgdorferi* antibody in the serum, but increased amplitude of antibody was not predictive of higher levels of infection. These data demonstrate that Lyme neuroborreliosis is a persistent infection, that spirochetal presence is a necessary but not sufficient condition for inflammation, and that antibody measured in serum may not predict the severity of infection.”

Central and peripheral nervous system infection, immunity, and inflammation in the NHP model of Lyme borreliosis. Pachner AR; Cadavid D; Shu G; Dail D; Pachner S; Hodzic E; Barthold SW. Annals of Neurology, 50(3):330-8. 2001.

Early Dissemination & Early CNS Invasion

Early Dissemination

- “Our study shows that *B. burgdorferi* infection can already disseminate in the EM phase from the skin to the blood...the majority of patients with confirmed dissemination did not report generalized symptoms. Thus, the dissemination of *B. burgdorferi* cannot be diagnosed on clinical grounds.”
Early dissemination of Borrelia burgdorferi without generalized symptoms in patients with erythema migrans.
Oksi J; Marttila H; Soini H; Aho H; Uksila J; Viljanen MK. *APMIS*, 109(9):581-8. 2001.
- “The bacteria spread early in the progression of infection (25), such that all organs and tissues may be infected.”
Susceptibility of motile and cystic forms of Borrelia burgdorferi to ranitidine bismuth citrate.
Brorson O; Brorson SH. *Int Microbiol*, 4(4):209-15. 2001.

Early Central Nervous System (CNS) Invasion

- “Seeding of the central nervous system is a common feature of spirochetal diseases. There is increasing evidence that in Lyme disease such seeding may occur very early in the infection.”
Neurologic presentations in Lyme disease. Coyle PK; Schutzer SE.
Hospital Practice, Nov 15;26(11):55-66; discussion 66, 69-70. 1991.
- “...Neither the clinical presentation nor routine laboratory tests accurately predicted which patients had *B. burgdorferi* DNA in their CSF. ...Our findings demonstrate that *B. burgdorferi* can disseminate to the CNS very early on in the course of the infection with little or no clinical evidence of CNS involvement. Acute primary and secondary infections due to *Treponema pallidum* are also associated with a high rate of early dissemination to the CNS. Although the full range of the late CNS manifestations of Lyme borreliosis remains controversial and ill defined, as in syphilis, the presence of CNS infection could have serious long-term consequences.”
Invasion of the central nervous system by Borrelia burgdorferi in acute disseminated infection.
Luft BJ; Dattwyler RJ. *JAMA*, 267:1364-67. 1992.

Jarish-Herxheimer Reaction to Antibiotics

- “Jarisch-Herxheimer reactions, uncommon in other microbiologic illnesses, commonly occur in these same four diseases [Lyme disease, syphilis, leptospirosis, relapsing fever].”
Schmid GP. Epidemiology and clinical similarities of human spirochetal diseases.
Reviews of Infectious Diseases, 11(Suppl. 6):S1460-S1469. 1989.
- “A 31-year-old woman diagnosed with Lyme disease was treated with amoxicillin. One hour after the first antibiotic dose, the patient became acutely ill. She developed hypertension, fever, and rigors. Shortly afterward, she became hypotensive and required fluid resuscitation. This systemic illness, the Jarisch-Herxheimer reaction, was first noted in association with antibiotic therapy for neurosyphilis. Thus, the institution of antibiotic therapy may be complicated by the Jarisch-Herxheimer reaction.”
Maloy AL; Black RD; Segurolo RJ Jr. Lyme disease complicated by the Jarisch-Herxheimer reaction.
Emergency Medicine, 16(3):437-8. 1998.

Lyme Disease Risk Factors

Risk Factors Associated With Lyme Disease Infection

- “Analysis of age-matched case-control data showed that rural residence; clearing periresidential brush during spring and summer months; and the presence of rock walls, woods, deer, or a bird feeder on residential property were associated with incident Lyme disease.”
Orloski KA; Campbell GL; Genese CA; Beckley JW; Schriefer ME; Spitalny KC; Dennis DT.
Emergence of Lyme disease in Hunterdon County, New Jersey, 1993: a case-control study of risk factors and evaluation of reporting patterns. *American Journal of Epidemiology*, 147(4):391-7. 1998.