



## SELECTED REFERENCES ON LYME DISEASE

January 2017

### Pathogenesis, Microbiology

Weis, Janis and Bockenstedt, Linda. **Borrelia: Molecular Biology, Host Interaction and Pathogenesis: Chapter 15: Host Response.** (Edited by Justin D. Radolf, D. Scott Samuels.) Mar 1, 2010. [https://books.google.com/books\(abbreviated\)](https://books.google.com/books(abbreviated)) *This chapter describes the dynamics of host responses to Borrelia burgdorferi, particularly in the mouse model, starting with tick feeding.*

Brisson D, Drecktrah D, Eggers CH, Samuels DS. **Genetics of Borrelia burgdorferi.** *Annu Rev Genet.* 2012;46:515-36. <https://www.ncbi.nlm.nih.gov/pubmed/22974303> *This review describes the genomic structure of Borrelia burgdorferi sensu lato genospecies, several antibiotic-resistant mutants, the outer membrane lipoprotein OspC, and vls recombination.*

Samuels DS. **Gene regulation in Borrelia burgdorferi.** *Annu Rev Microbiol.* 2011;65:479-99. <https://www.ncbi.nlm.nih.gov/pubmed/21801026> *This review describes the molecular mechanisms utilized to effect the enzootic cycle, including the RpoN-RpoS pathway.*

Rosa PA, Tilly K, Stewart PE. **The burgeoning molecular genetics of the Lyme disease spirochaete.** *Nat Rev Microbiol.* 2005 Feb;3(2):129-43. <https://www.ncbi.nlm.nih.gov/pubmed/15685224> *This review describes the phylum Spirochaetes, the infectious cycle, the Borrelia burgdorferi genome, genetic tools, constructed mutants, and genetic analysis of key bacterial components in both the tick vector and the mammalian host.*

Radolf JD, Caimano MJ, Stevenson B, Hu LT. **Of ticks, mice and men: understanding the dual-host lifestyle of Lyme disease spirochaetes.** *Nat Rev Microbiol.* 2012 Jan 9;10(2):87-99. <https://www.ncbi.nlm.nih.gov/pubmed/22230951> *This review discusses the molecular and cellular events that occur as Lyme disease spirochaetes transit between their arthropod and vertebrate hosts during the enzootic cycle.*

de Silva AM, Tyson KR, Pal U. **Molecular characterization of the tick-Borrelia interface.** *Front Biosci (Landmark Ed).* 2009 Jan 1;14:3051-63. <https://www.ncbi.nlm.nih.gov/pubmed/19273256>

Tilly K, Rosa PA, Stewart PE. **Biology of infection with Borrelia burgdorferi.** *Infect Dis Clin North Am.* 2008 Jun;22(2):217-34, v. <https://www.ncbi.nlm.nih.gov/pubmed/18452798>



## **PATHOGENESIS AND HOST RESPONSE MECHANISMS**

### **Mouse Model and Host Response**

Barthold SW, Persing DH, Armstrong AL, Peeples RA. **Kinetics of *Borrelia burgdorferi* dissemination and evolution of disease after intradermal inoculation of mice.** *Am J Pathol.* 1991 Aug;139(2):263-73. <https://www.ncbi.nlm.nih.gov/pubmed/1867318>

Hastey CJ, Elsner RA, Barthold SW, Baumgarth N. **Delays and diversions mark the development of B cell responses to *Borrelia burgdorferi* infection.** *J Immunol.* 2012 Jun 1;188(11):5612-22. <https://www.ncbi.nlm.nih.gov/pubmed/22547698>

Kelesidis T. **The Cross-Talk between Spirochetal Lipoproteins and Immunity.** *Front Immunol.* 2014 Jun 30;5:310. <https://www.ncbi.nlm.nih.gov/pubmed/25071771>

Bramwell KK, Teuscher C, Weis JJ. **Forward genetic approaches for elucidation of novel regulators of Lyme arthritis severity.** *Front Cell Infect Microbiol.* 2014 Jun 5;4:76. <https://www.ncbi.nlm.nih.gov/pubmed/24926442>

### **OspA vaccine**

Fikrig E, Barthold SW, Kantor FS, Flavell RA. **Long-term protection of mice from Lyme disease by vaccination with OspA.** *Infect Immun.* 1992 Mar;60(3):773-7. <https://www.ncbi.nlm.nih.gov/pubmed/1541551>

de Silva AM, Telford SR 3rd, Brunet LR, Barthold SW, Fikrig E. ***Borrelia burgdorferi* OspA is an arthropod-specific transmission-blocking Lyme disease vaccine.** *J Exp Med.* 1996 Jan 1;183(1):271-5. <https://www.ncbi.nlm.nih.gov/pubmed/8551231>

Fikrig E, Telford SR 3rd, Barthold SW, Kantor FS, Spielman A, Flavell RA. **Elimination of *Borrelia burgdorferi* from vector ticks feeding on OspA-immunized mice.** *Proc Natl Acad Sci USA.* 1992 Jun 15;89(12):5418-21. <https://www.ncbi.nlm.nih.gov/pubmed/1608951>

### **OspA, OspC Gene Regulation**

Carroll JA, Garon CF, Schwan TG. **Effects of environmental pH on membrane proteins in *Borrelia burgdorferi*.** *Infect Immun.* 1999 Jul;67(7):3181-7. <https://www.ncbi.nlm.nih.gov/pubmed/10377088>



Srivastava SY, de Silva AM. **Reciprocal expression of ospA and ospC in single cells of Borrelia burgdorferi.** *J Bacteriol.* 2008 May;190(10):3429-33.

<https://www.ncbi.nlm.nih.gov/pubmed/18359818>

Pal U, de Silva AM, Montgomery RR, Fish D, Anguita J, Anderson JF, Lobet Y, Fikrig E. **Attachment of Borrelia burgdorferi within Ixodes scapularis mediated by outer surface protein A.** *J Clin Invest.* 2000 Aug;106(4):561-9.

<https://www.ncbi.nlm.nih.gov/pubmed/10953031>

Schwan TG, Piesman J, Golde WT, Dolan MC, Rosa PA. **Induction of an outer surface protein on Borrelia burgdorferi during tick feeding.** *Proc Natl Acad Sci USA.* 1995 Mar 28;92(7):2909-13.

<https://www.ncbi.nlm.nih.gov/pubmed/7708747>

Ohnishi J, Piesman J, de Silva AM. **Antigenic and genetic heterogeneity of Borrelia burgdorferi populations transmitted by ticks.** *Proc Natl Acad Sci USA.* 2001 Jan 16;98(2):670-5.

<https://www.ncbi.nlm.nih.gov/pubmed/11209063>

Grimm D, Tilly K, Byram R, Stewart PE, Krum JG, Bueschel DM, Schwan TG, Policastro PF, Elias AF, Rosa PA. **Outer-surface protein C of the Lyme disease spirochete: a protein induced in ticks for infection of mammals.** *Proc Natl Acad Sci USA.* 2004 Mar 2;101(9):3142-7.

<https://www.ncbi.nlm.nih.gov/pubmed/14970347>

Schwan TG, Piesman J. **Temporal changes in outer surface proteins A and C of the Lyme disease-associated spirochete, Borrelia burgdorferi, during the chain of infection in ticks and mice.** *J Clin Microbiol.* 2000 Jan;38(1):382-8. <https://www.ncbi.nlm.nih.gov/pubmed/10618120>

## **Lyme Borreliosis and Systemic Associations**

### **Arthritis**

Arvikar SL, Steere AC. **Diagnosis and Treatment of Lyme Arthritis.** *Infect Dis Clin North Am.* 2015 Jun;29(2):269-80. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4443866/>

Bockenstedt LK, Wormser GP. **Review: unraveling Lyme disease.** *Arthritis Rheumatol.* 2014 Sep;66(9):2313-23. <https://www.ncbi.nlm.nih.gov/pubmed/24965960>

Bockenstedt LK, Gonzalez DG, Haberman AM, Belperron AA. **Spirochete antigens persist near cartilage after murine Lyme borreliosis therapy.** *J Clin Invest.* 2012 Jul;122(7):2652-60.

<https://www.ncbi.nlm.nih.gov/pubmed/22728937>

### **Carditis**



Krause PJ, Bockenstedt LK. **Lyme Disease and the Heart.** *Circulation.* 2013;127:e451-e454. <http://circ.ahajournals.org/content/127/7/e451.full>

### **Chronic Lyme, PTLSD and other controversies**

Hodzic E, Imai D, Feng S, Barthold SW. **Resurgence of persisting non-cultivable Borrelia burgdorferi following antibiotic treatment in mice.** *PLoS One.* 2014 Jan 23;9(1):e86907. <https://www.ncbi.nlm.nih.gov/pubmed/24466286>

Lantos PM. **Chronic Lyme disease.** *Infect Dis Clin North Am.* 2015 Jun;29(2):325-40. <https://www.ncbi.nlm.nih.gov/pubmed/25999227>

Fallon BA, Pavlicova M, Coffino SW, Brenner C. **A comparison of Lyme disease serologic test results from 4 laboratories in patients with persistent symptoms after antibiotic treatment.** *Clin Infect Dis.* 2014 Dec 15;59(12):1705-10. <https://www.ncbi.nlm.nih.gov/pubmed/25182244>

Embers ME, Barthold SW, Borda JT, Bowers L, Doyle L, Hodzic E, Jacobs MB, Hasenkampf NR, Martin DS, Narasimhan S, Phillippi-Falkenstein KM, Purcell JE, Ratterree MS, Philipp MT. **Persistence of Borrelia burgdorferi in rhesus macaques following antibiotic treatment of disseminated infection.** *PLoS One.* 2012;7(1):e29914. <https://www.ncbi.nlm.nih.gov/pubmed/22253822>

Hodzic E, Imai D, Feng S, Barthold SW. **Resurgence of persisting non-cultivable Borrelia burgdorferi following antibiotic treatment in mice.** *PLoS One.* 2014 Jan 23;9(1):e86907. <https://www.ncbi.nlm.nih.gov/pubmed/24466286>

Klempner MS, Baker PJ, Shapiro ED, Marques A, Dattwyler RJ, Halperin JJ, Wormser GP. **Treatment trials for post-Lyme disease symptoms revisited.** *Am J Med.* 2013 Aug;126(8):665-9. <https://www.ncbi.nlm.nih.gov/pubmed/23764268>

Lantos PM, Shapiro ED, Auwaerter PG, Baker PJ, Halperin JJ, McSweeney E, Wormser GP. **Unorthodox alternative therapies marketed to treat Lyme disease.** *Clin Infect Dis.* 2015 Jun 15;60(12):1776-82. <https://www.ncbi.nlm.nih.gov/pubmed/25852124>

Halperin JJ, Baker P, Wormser GP. **Common misconceptions about Lyme disease.** *Am J Med.* 2013 Mar;126(3):264.e1-7. <https://www.ncbi.nlm.nih.gov/pubmed/23321431>

Shapiro ED. **Repeat or persistent Lyme disease: persistence, recrudescence or reinfection with Borrelia Burgdorferi?** *F1000Prime Rep.* 2015 Jan 5;7:11. <https://www.ncbi.nlm.nih.gov/pubmed/25705394>



### Clinical diagnosis/testing

Claudia R. Molins, Christopher Sexton, John W. Young, Laura V. Ashton, Ryan Pappert, Charles B. Beard, Martin E. Schriefer. **Collection and Characterization of Samples for Establishment of a Serum Repository for Lyme Disease Diagnostic Test Development and Evaluation.** *J Clin Microbiol.* 2014 Oct;52(10):3755-62. <https://www.ncbi.nlm.nih.gov/pubmed/25122862>  
*The CDC used two-tiered testing on sera from Lyme patients, healthy donors, and patients with “look-alike” diseases. Results corroborate the need for improved diagnostics, particularly for earlier stages of infection.*

Marques AR. **Laboratory diagnosis of Lyme disease: advances and challenges.** *Infect Dis Clin North Am.* 2015 Jun;29(2):295-307. <https://www.ncbi.nlm.nih.gov/pubmed/25999225>  
*This review describes the laboratory diagnostics for Lyme disease (with a focus on the U.S.) and discusses current recommendations and new developments in the field.*

Steere AC, McHugh G, Damle N, Sikand VK. **Prospective study of serologic tests for Lyme disease.** *Int J of Antimicrob Ag.* 2014; 44(1):16-25.  
<https://www.ncbi.nlm.nih.gov/pubmed/18532885> *This research compared two-tier tests and the C6 peptide ELISA method prospectively in patients with Lyme, other illnesses, and in healthy subjects.*

CDC Lyme Panel. **Supplemental Table S1. Repository inclusion and exclusion criteria for Lyme disease patients. Supplemental Table S2. Repository inclusion and exclusion criteria for negative control healthy donors Supplemental Table S3. Repository inclusion and exclusion criteria for negative control disease patients.**  
<http://jcm.asm.org/content/suppl/2014/09/15/JCM.01409-14.DCSupplemental/zim999093774so1.pdf> *Tables showing inclusion and exclusion criteria for Lyme disease patients, healthy donors, and negative control disease patients.*

Johnson, Barbara. **Lyme Disease: An Evidence-Based Approach: Chapter 4: Laboratory Diagnostic Testing for Borrelia burgdorferi Infection.** CAB International 2011. (Ed. J.J. Halperin).  
[https://www.cdc.gov/lyme/resources/halperin\\_2012\\_chap4\\_johnsonb.pdf](https://www.cdc.gov/lyme/resources/halperin_2012_chap4_johnsonb.pdf) *This chapter reviews two-tiered serology, ELISAs vs immunoblots, exclusion of OspA and OspB, IgM, newer serological tests, and direct assays.*

Branda JA, Linskey K, Kim YA, Steere AC, Ferraro MJ. **Two-tiered antibody testing for Lyme disease with use of 2 enzyme immunoassays, a whole-cell sonicate enzyme immunoassay followed by a VlsE C6 peptide enzyme immunoassay.** *Clin Infect Dis.* 2011 Sep;53(6):541-7.  
<https://www.ncbi.nlm.nih.gov/pubmed/21865190>



Moore A, Nelson C, Molins C, Mead P, Schriefer M. **Current Guidelines, Common Clinical Pitfalls, and Future Directions for Laboratory Diagnosis of Lyme Disease, United States.** *Emerg Infect Dis.* 2016 Jul;22(7). <https://www.ncbi.nlm.nih.gov/pubmed/27314832>

Golightly MG. **Laboratory considerations in the diagnosis and management of Lyme borreliosis.** *Am J Clin Pathol.* 1993 Feb;99(2):168-74. <https://www.ncbi.nlm.nih.gov/pubmed/8438790>

Schwan TG, Schrupf ME, Hinnebusch BJ, Anderson DE Jr, Konkel ME. **GlpQ: an antigen for serological discrimination between relapsing fever and Lyme borreliosis.** *J Clin Microbiol.* 1996 Oct;34(10):2483-92. <https://www.ncbi.nlm.nih.gov/pubmed/8880505>

Kuehn BM. **CDC estimates 300,000 US cases of Lyme disease annually.** *JAMA.* 2013 Sep 18;310(11):1110. <https://www.ncbi.nlm.nih.gov/pubmed/24045727>

Yang L, Ma Y, Schoenfeld R, Griffiths M, Eichwald E, Araneo B, Weis JJ. **Evidence for B-lymphocyte mitogen activity in Borrelia burgdorferi-infected mice.** *Infect Immun.* 1992 Aug;60(8):3033-41. <https://www.ncbi.nlm.nih.gov/pubmed/1639470>

Agüero-Rosenfeld ME, Wang G, Schwartz I, Wormser GP. **Diagnosis of Lyme Borreliosis.** *Clin Microbiology Reviews.* 2005 July;484–509. <http://cmr.asm.org/content/18/3/484>

Hinckley AF, Connally NP, Meek JI, Johnson BJ, Kemperman MM, Feldman KA, White JL, Mead PS. **Lyme disease testing by large commercial laboratories in the United States.** *Clin Infect Dis.* 2014 Sep 1;59(5):676-81. <https://www.ncbi.nlm.nih.gov/pubmed/24879782>

Weiner ZP, Crew RM, Brandt KS, Ullmann AJ, Schriefer ME, Molins CR, Gilmore RD. **Evaluation of Selected Borrelia burgdorferi lp54 Plasmid-Encoded Gene Products Expressed during Mammalian Infection as Antigens To Improve Serodiagnostic Testing for Early Lyme Disease.** *Clin Vaccine Immunol.* 2015 Nov;22(11):1176-86. <https://www.ncbi.nlm.nih.gov/pubmed/26376927>

Simpson WJ, Burgdorfer W, Schrupf ME, Karstens RH, Schwan TG. **Antibody to a 39-kilodalton Borrelia burgdorferi antigen (P39) as a marker for infection in experimentally and naturally inoculated animals.** *J Clin Microbiol.* 1991 Feb;29(2):236-43. <https://www.ncbi.nlm.nih.gov/pubmed/2007630>

Mogilyansky E, Loa CC, Adelson ME, Mordechai E, Tilton RC. **Comparison of Western immunoblotting and the C6 Lyme antibody test for laboratory detection of Lyme disease.** *Clin Diagn Lab Immunol.* 2004 Sep;11(5):924-9. <https://www.ncbi.nlm.nih.gov/pubmed/15358654>





Lipsett SC, Branda JA, McAdam AJ, Vernacchio L, Gordon CD, Gordon CR, Nigrovic LE. **Evaluation of the C6 Lyme Enzyme Immunoassay for the Diagnosis of Lyme Disease in Children and Adolescents.** *Clin Infect Dis.* 2016 Oct 1;63(7):922-8. <https://www.ncbi.nlm.nih.gov/pubmed/27358358>

### **Treatment**

Bhate C, Schwartz RA. **Lyme disease: Part I. Advances and perspectives.** *J Am Acad Dermatol.* 2011 Apr;64(4):619-36. <https://www.ncbi.nlm.nih.gov/pubmed/21414493> **A review of Lyme disease epidemiology, pathophysiology, and management, it also covers the three clinical stages of Lyme disease that parallel those of the spirochetal disease syphilis.**

Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, Krause PJ, Bakken JS, Strle F, Stanek G, Bockenstedt L, Fish D, Dumler JS, Nadelman RB. **The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America.** *Clin Infect Dis.* 2006 Nov 1;43(9):1089-134. <https://www.ncbi.nlm.nih.gov/pubmed/17029130> **Guidelines for health care providers for the management of patients with Lyme disease, human granulocytic anaplasmosis, and babesiosis, including recommended doses and durations of antimicrobial therapy for treatment and prevention of Lyme disease.**

Stanek G, Wormser GP, Gray J, Strle F. **Lyme borreliosis.** *Lancet.* 2012 Feb 4;379(9814):461-73. <https://www.ncbi.nlm.nih.gov/pubmed/21903253> **This review covers clinical manifestations of Lyme disease and, depending on those clinical signs, primary and supporting diagnostic testing methods, and treatment regimens.**

Engstrom SM, Shoop E, Johnson RC. **Immunoblot interpretation criteria for serodiagnosis of early Lyme disease.** *Clin Microbiol.* 1995 Feb;33(2):419-27. <https://www.ncbi.nlm.nih.gov/pubmed/7714202> **In this study, patients with early Lyme disease and erythema migrans were monitored for antibody responses until one year after antibiotic therapy. A relational database management system was used to analyze the results and provide criteria for early disease immunoblot interpretation.**

### **Additional**

Barbour AG. **Isolation and cultivation of Lyme disease spirochetes.** *Yale J Biol Med.* 1984 Jul-Aug;57(4):521-5. <https://www.ncbi.nlm.nih.gov/pubmed/6393604>