Lyme disease despite treatment with antibiotics in humans:

Serum and CSF findings.

1. Serum

Yellow IDSA Authors
Green ILADS Authors

Authors	Text – Quotes
Duray PH, Steere AC. (1988) http://www.ncbi.nlm.nih.gov/pubmed/2847622	"All of these histologic derangements suggest immunologic damage in response to persistence of the spirochete, however few in number".
Dattwyler RJ, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG. (1988) http://www.ncbi.nlm.nih.gov/pubmed/2847622	„We conclude that the presence of chronic Lyme disease cannot be excluded by the absence of antibodies against B. burgdorferi and that a specific T-cell blastogenic response to B. burgdorferi is evidence of infection in seronegative patients with clinical indications of chronic Lyme disease".
Preac-Mursic V, Weber K, Pfister HW, Wilske B, Gross B, Baumann A, Prokop J. (1989) http://www.ncbi.nlm.nih.gov/pubmed/2613324	"Patients may have subclinical or clinical disease without diagnostic antibody titers to B. burgdorferi. We conclude that early stage of the disease as well as chronic Lyme disease with persistence of B. burgdorferi after antibiotic therapy cannot be excluded when the serum is negative for antibodies against B. burgdorferi".
Cimmino MA, Azzolini A, Tobia F, Pesce CM. (1989) http://www.ncbi.nlm.nih.gov/pubmed/2910019	"Borrelia-like spirochetes were identified histologically in the spleen; this finding was consistent with persistence of B. burgdorferi organisms in inner organs in chronic Lyme disease".
Logigian EL, Kaplan RF, Steere AC. (1990) http://www.ncbi.nlm.nih.gov/pubmed/2172819	"At the time of examination, chronic neurologic abnormalities had been present from 3 months to 14 years, usually with little progression".
MacDonald AB, Berger BW, Schwan TG (1990) http://www.ncbi.nlm.nih.gov/pubmed/1980573	"The latency and relapse phenomena suggest that the Lyme disease spirochete is capable of survival in the host for prolonged periods of time. Some patients with Lyme borreliosis may require more than the currently recommended two to three week course of antibiotic therapy to eradicate strains of the spirochete which grow slowly".
Banyas GT. (1992) http://www.ncbi.nlm.nih.gov/pubmed/1583267	"At present, seronegativity in persons strongly suspected of having Lyme disease does not necessarily exclude the diagnosis of Lyme disease. The clinician must recognize this in patients who may have Lyme disease or a recurrence of the disease".
Liegner KB, Shapiro JR, Ramsay D, Halperin JJ, Hogrefe W, Kong L. (1993) http://www.ncbi.nlm.nih.gov/pubmed/8436647	"The patient was seronegative by Lyme enzymelinked immunosorbent assay but showed suspicious bands on Western blot. Findings of a Warthin-Starry stain of a skin biopsy specimen of the eruption revealed a Borrelia-compatible structure".
Hulínská D, Krausová M, Janovská D, Rohácová H, Hancil J, Mailer H. (1993) http://www.ncbi.nlm.nih.gov/pubmed/8004045	"Results of studies using direct antigen detection suggest that seronegative Lyme borreliosis is not rare and support the hypothesis that Borrelia antigens can persist in humans".
Preac-Mursic V, Pfister HW, Spiegel H, Burk R, Wilske B, Reinhardt S, Böhmer R. (1993) http://www.ncbi.nlm.nih.gov/pubmed/8106639	**"**Persistence of B. burgdorferi cannot be excluded when the serum is negative for antibodies against it.**"**
Shadick NA, Phillips CB, Logigian EL, Steere AC, Kaplan RF, Berardi VP, Duray PH, Larson MG, Wright EA, Ginsburg KS, Katz JN, Liang MH (1994) http://www.ncbi.nlm.nih.gov/pubmed/8085687	"Persons with a history of Lyme disease have more musculoskeletal impairment and a higher prevalence of verbal memory impairment when compared with those without a history of Lyme disease. Our findings suggest that disseminated Lyme disease may be associated with longterm Morbidity".
Wahlberg P, Granlund H, Nyman D, Panelius J, Seppälä I. (1994) http://www.ncbi.nlm.nih.gov/pubmed/7884218	"Short periods of treatment were not generally effective." "To conclude, we have shown that long-term treatments beginning with intraveous ceftriaxone and continuing with amoxycillin plus probenecid or with cephadroxil were useful in the treatment of late Lyme borreliosis." (pp. 260-1)
Lawrence C, Lipton RB, Lowy FD, Coyle PK (1995) http://www.ncbi.nlm.nih.gov/pubmed/7796837	"Although the patient never had detectable free antibodies to B. burgdorferi in serum or spinal fluid, the CSF was positive on multiple occasions for complexed anti-B. burgdorferi antibodies, B. burgdorferi nucleic acids and free antigen". "We believe this to be an example of a patient with chronic relapsing Bb infection".
Waniek C, Prohovnik I, Kaufman MA, (1995) http://www.ncbi.nlm.nih.gov/pubmed/7580195	"LD must be considered even in cases with purely psychiatric presentation, and prolonged antibiotic therapy may be necessary".

Sala-Lizarraga JA. Salcede-Vivo J, Ferris J, Lopez-Andreu JA (1995) http://www.lymeinfo.net/medical/LDPersist.pdf	"We add, however, in accord with the advice of others that antibiotics should be continued in the long term, until we achieve cure or delay the progression of the disease."
Nanagara R, Duray PH, Schumacher HR Jr. (1996) http://www.ncbi.nlm.nih.gov/pubmed/8892586	"Electron microscopy […] adds further evidence for persistence of spirochetal antigens in the joint in chronic Lyme disease. Spirochaetes may elude host immune response and antibiotic treatment. High-dose parenteral antibiotics, or combination therapies with long duration may be needed to kill the living spirochetes." (p.1032)
Preac Mursic V, Marget W, Busch U, Pleterski Rigler D, Hagl S. (1996) http://www.ncbi.nlm.nih.gov/pubmed/8852456	"Furthermore, the persistence of B. burgdorferi s.l. and clinical recurrences in patients despite seemingly adequate antibiotic treatment is described. The patients had clinical disease with or without diagnostic antibody titers to B. burgdorferi".
Petrovic M, Vogelaers D, Van Renterghem L, Carton D, De Reuck J, Afschrift M (1998) http://www.ncbi.nlm.nih.gov/pubmed/9701852	"Difficulties in diagnosis of late stages of Lyme disease include low sensitivity of serological testing and late inclusion of Lyme disease in the differential diagnosis. Longer treatment modalities may have to be considered in order to improve clinical outcome of late disease stages. Several aspects of late borreliosis: false negative serology due to narrow antigen composition of the used ELISA format, the need for prolonged antibiotic treatment in chronic or recurrent forms".
Mikkilä H, Karma A, Viljanen M, Seppälä I. (1999) http://www.ncbi.nlm.nih.gov/pubmed/10090586	"For efficient diagnosis of ocular Lyme borreliosis, immunoblot analysis and PCR should be used in addition to ELISA. A positive PCR seems to be associated with a negative immunoblot".
Oksi J, Marjamäki M, Nikoskelainen J, Viljanen MK (1999) http://www.ncbi.nlm.nih.gov/pubmed/10442678	"The response to retreatment was considered good in nine patients. We conclude that the treatment of Lyme borreliosis with appropriate antibiotics for even more than 3 months may not always eradicate the spirochete".
Phillips SE, Mattman LH, Hulínská D, Moayad H. (1998) http://www.ncbi.nlm.nih.gov/pubmed/9861561	"This new method for culturing B. burgdorferi from patients with chronic Lyme disease certainly defines the nature of the illness and establishes that it is of chronic infectious etiology".
Logigian EL et al. (1999) http://www.ncbi.nlm.nih.gov/pubmed/10395852	"We conclude that Lyme encephalopathy can be treated successfully with ceftriaxone". Commentary: http://www.praxis-berghoff.de/dokumente/Behandlungsparameter_der_Neuroborreliose.pdf
Breier F, Khanakah G, Stanek G, Kunz G, Aberer E, Schmidt B, Tappeiner G (2001) http://www.ncbi.nlm.nih.gov/pubmed/11251580	"Despite treatment with four courses of ceftriaxone with or without methylprednisone for up to 20 days, progression of LSA was only stopped for a maximum of 1 year. Spirochaetes were isolated from skin cultures obtained from enlarging LSA lesions. These spirochaetes were identified as Borrelia afzelii by sodium dodecyl sulphate--polyacrylamide gel electrophoresis and polymerase chain reaction (PCR) analyses. However, serology for B. burgdorferi sensu lato was repeatedly negative. These findings suggest a pathogenetic role for B. afzelii in the development of LSA and a beneficial effect of appropriate antibiotic treatment".
Klempner MS, Hu LT, Evans J, et al. (2001) http://www.ncbi.nlm.nih.gov/pubmed/11450676	Commentary: http://www.praxis-berghoff.de/dokumente/Behandlungsparameter_der_Neuroborreliose.pdf
Honegr K (2001) http://www.ncbi.nlm.nih.gov/pubmed/11233667	"In 18 patients with Lyme borreliosis the authors proved the persistence of Borrelia burgdorferi sensu lato by detection of the causal agent by immune electron microscopy or of its DNA by PCR in plasma or cerebrospinal fluid after an interval of 4-68 months. Clinical manifestations common in Lyme borreliosis were present in only half the patients, in the remainder non-specific symptoms were found. In nine subjects with confirmed Borrelia burgdorferi sensu lato in the cerebrospinal fluid the cytological and biochemical finding was normal. Examination of antibodies by the ELISA method was negative in 7 of 18 patients during the first examination and in 12 of 18 during the second examination".
Grignolo MC, Buffrini L, Monteforte P, Rovetta G. (2001) http://www.ncbi.nlm.nih.gov/pubmed/11317136	"..true positives at clinical examination but negatives at serologic tests. The obtained results suggested a good reliability of positive results obtained with the PCR technique used in this study".
Tylewska-Wierzbanowska S, Chmielewski T.	"Lyme borreliosis patients who have live spirochetes in body fluids have

(2002) http://www.ncbi.nlm.nih.gov/pubmed/12422608	low or negative levels of borrelial antibodies in their sera. This indicates that an efficient **diagnosis of Lyme borreliosis has to be based** on a combination of various techniques such as serology, PCR and culture, **not solely on serology**".
Kaplan R et al. (2003) http://www.ncbi.nlm.nih.gov/pubmed/12821733	Commentary: http://www.praxis-berghoff.de/dokumente/Behandlungsparameter_der_Neuroborreliose.pdf
Krupp LB, Hyman LG, Grimson R, et al. (2003) http://www.ncbi.nlm.nih.gov/pubmed/12821734	Commentary: http://www.praxis-berghoff.de/dokumente/Behandlungsparameter_der_Neuroborreliose.pdf
Diterich I, Rauter C, Kirschning CJ, Hartung T. (2003) http://www.ncbi.nlm.nih.gov/pubmed/12819085	„It was recently reported that Borrelia suppresses the host's immune response, thus perhaps preventing the elimination of the pathogen (I. Diterich, L. Härter, D. Hassleret al, Infect. Immun. 69:687-694, 2001)"
Fallon BA (2008) http://www.ncbi.nlm.nih.gov/pubmed/17928580	"IV ceftriaxone therapy results in short-term cognitive improvement for patients with posttreatment Lyme encephalopathy, but relapse in cognition occurs after the antibiotic is discontinued".
DeLong AK, Blossom B, Maloney E, Phillips SE. (2012) http://www.ncbi.nlm.nih.gov/pubmed/22922244	"This biostatistical review reveals that retreatment can be beneficial. Primary outcomes originally reported as statistically insignificant were likely underpowered. The positive treatment effects of ceftriaxone are encouraging and consistent with continued infection, a hypothesis deserving additional study. Additional studies of persistent infection and antibiotic treatment are warranted".

2. CSF (Commentary: http://www.praxis-berghoff.de/dokumente/Liquordiagnostik_bei_LNB.pdf)

Authors	**Text – Quotes**
Pfister HW (1989) http://www.ncbi.nlm.nih.gov/pubmed/2668788	"Borrelia burgdorferi, the etiologic agent of Lyme borreliosis, was isolated from the CSF of a patient with elevated serum IgG antibody titers against B burgdorferi and a history of multiple tick bites. The **absence of** concurrent inflammatory signs of CSF as well as **intrathecal antibody production indicates a phase of latent Lyme neuroborreliosis** in which no tissue infection or reaction has yet occurred".
Steere AC (1990) http://www.ncbi.nlm.nih.gov/pubmed/2345301	"Intrathecal antibody determinations are the most specific diagnostic test currently available for Lyme neuroborreliosis, but local antibody production in CSF is an inconsistent finding in American patients with late neurologic manifestations of the disorder"
Kaiser R (1993) http://www.ncbi.nlm.nih.gov/pubmed/8411090	"Intrathecal synthesis of IgM antibodies to B. burgdorferi was demonstrated in patients with neuroborreliosis by sonicate ELISA in 20 of 35 samples, by flagellin ELISA in 16 of 35 samples and by 14-kDa ELISA in 9 of 35 samples".
Peter O. (1993) http://www.ncbi.nlm.nih.gov/pubmed/8421774	"Isolation of Borrelia burgdorferi from the CSF is relatively rare. The present report describes the first three isolations in Switzerland. **In neither of the two CSF could intrathecal synthesis of specific antibodies be demonstrated.** In the third case, however, immunofluorescence showed IgG antibody titers of 1/128 in the CSF and 1/512 in serum".
Coyle PK (1995) http://www.ncbi.nlm.nih.gov/pubmed/7501150	"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**".
Oksi J (1996) http://www.ncbi.nlm.nih.gov/pubmed/9010017	"We conclude that cerebral lymphocytic vasculitis and multifocal encephalitis may be associated with B. burgdorferi infection. The presence of B. burgdorferi DNA in tissue samples from areas with inflammatory changes indicates that direct invasion of B. burgdorferi may be the pathogenetic mechanism for focal encephalitis in LNB".
Logigian EL et al. (1999) http://www.ncbi.nlm.nih.gov/pubmed/10395852	"Months to years after classic manifestations of Lyme disease, the 18 patients presented with memory difficulty, minor depression, somnolence, or headache. Sixteen (89%) had abnormal memory scores; 16 (89%) had cerebrospinal fluid (CSF) abnormalities, and all 7 patients tested had frontotemporal perfusion defects on single photon emission computed tomographic (SPECT) imaging…. We conclude that Lyme encephalopathy can be treated successfully with ceftriaxone".
Honegr K (2001) http://www.ncbi.nlm.nih.gov/pubmed/11233667	"In 18 patients with Lyme borreliosis the authors proved the persistence of Borrelia burgdorferi sensu lato by detection of the causal agent by immune electron microscopy or of its DNA by PCR in plasma or cerebrospinal fluid after an interval of 4-68 months. Clinical

	manifestations common in Lyme borreliosis were present in only half the patients, in the remainder non-specific symptoms were found. **In nine subjects with confirmed Borrelia burgdorferi sensu lato in the cerebrospinal fluid the cytological and biochemical finding was normal.** Examination of antibodies by the ELISA method was negative in 7 of 18 patients during the first examination and in 12 of 18 during the second examination".

Preac-Mursic V, Wilske B, Schierz G, et al. (1984) Repeated isolation of spirochetes from the cerebrospinal fluid of a patient with meningoradiculitis Bannwarth' Syndrome. Eur J Clin Microbiol 3, 564-565

Ackermann R, Gollmer E, Rehse-Kupper B. (1985) Progressive Borrelien-Enzephalomyelitis. Chronische Manifestation der Erythema-migrans Krankheit am Nervensystem. Dtsh. Med. Wochenschr.110(26), 1039-1042.

Snydman DR, Schenkein DP, Berardi VP, Lastavica CC, Pariser KM (1986) Borrelia burgdorferi in joint fluid in **chronic Lyme arthritis**. Ann Int Med 104: 798-800.

Diringer MN et al. (1987) Lyme meningoencephalitis – report of a severe, penicillin resistant case. Arthritis & Rheum. 30, 705-708

Wokke JHJ, van Gijn J, Elderson A, Stanek G. (1987) Chronic forms of Borrelia burgdorferi infection of the nervous system. Neurology 37, 1031-1034.

Schmidli J, Hunziker T, Moesli P, Schaad UB. (1988) Cultivation of Borrelia burgdorferi from Joint Fluid Three Months After Treatment of Facial Palsy Due to Lyme Borreliosis. (Letter). J Infect Dis 158, 905-6.

Weber K, Bratzke HJ, Neubert U et al. (1988) Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. J Pediatr Infect Dis 7, 286-9.

Schmidli J, Hunziker T, Moesli P, Schaad UB. (1988) Cultivation of Borrelia burgdorferi from joint fluid three months after treatment of facial palsy due to Lyme borreliosis. J Infect Dis 158, 905-6.

Steere AC, Duray PH, Butcher EC. (1988) Spirochetal antigens and lymphoid cell surface markers in Lyme synovitis. Comparison with rheumatoid synovium and tonsillar lymphoid tissue. Arthritis Rheum 31, 487-95.

Duray PH, Steere AC (1988) Clinical pathologic correlations of Lyme disease by stage. Ann N Y Acad Sci. 539, 65-79

Dattwyler RJ, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG. (1988) Seronegative Lyme

disease. Dissociation of specific T- and B-lymphocyte responses to Borrelia burgdorferi. N Engl J Med.

319(22), 1441-6.

Cimmino MA, Azzolini A, Tobia F, Pesce CM. (1989) Spirochetes in the spleen of a patient with chronic Lyme disease. Am J Clin Pathol 91, 95-7.

Merlo A, Weder B, Ketz E, Matter L. (1989) Locked-in state in Borrelia burgdorferi meningitis. J Neurol 236, 305-306.

Preac□Mursic V, Weber K, Pfister HW, Wilske B, Gross B, Baumann A, Prokop J. (1989) **Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis**. Infection 17, 355-9. http://www.ncbi.nlm.nih.gov/pubmed/2613324

Pfister HW, Preac-Mursic V, WilskeB et al. (1989) Latent Lyme Neuroboreliosis: presence of Borrelia burgdorferi in the cerebrospinal fluid without concurrent inflammatory signs. Neurology. 39(8) 1118-1120 http://www.ncbi.nlm.nih.gov/pubmed/2668788

Logigian EL, Kaplan RF, Steere AC. (1990) Chronic neurologic manifestations of Lyme disease. N Engl J Med. 323(21), 1438-44. http://www.ncbi.nlm.nih.gov/pubmed/2172819

Stanek G, Klein J, Bittner R, Glogar D (1990) Isolation of Borrelia burgdorferi from the myocardium of a patient with **longstanding cardiomyopathy**. N Eng J Med 322: 249-252.

Omasits M, Seiser A, Brainin M. (1990) Zur rezidivierenden und schubhaft verlaufenden Borreliose des Nervensystems. Wiener klinische Wochenschrift 102, 4-12.

MacDonald AB, Berger BW, Schwan TG (1990) Clinical implications of delayed growth of the Lyme borreliosis spirochete, Borrelia burgdorferi. Acta Trop. 48(2), 89-94.

Steere AC, Berardi VP, Weeks KE et al. (1990) Evaluation of the intrathecal antibody response to Borrelia burgdorferi as a diagnostic test for Lyme neuroborreliosis. J Infect Dis 161(6), 1203-1209 http://www.ncbi.nlm.nih.gov/pubmed/2345301

Pfister HW, Preac-Mursic V, Wilske B et al. (1991) Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. Infect Dis 163, 311-8.

Hassler D, Riedel K, Zorn J, Preac-Mursic V (1991) Pulsed high-dose cefotaxime therapy in refractory Lyme borreliosis. Lancet 338, 193

May Y et al. (1991) Intracellular localization of Borrelia burgdorferi within human endothelial cells. Infect Immun. 59, 671-678

Montgomery RR, Malavista SE et al. (1991) The fate of Borrelia burgdorferi within endothelial cells. Infect Immun. 59, 671-678

Keller TL et al. (1992) PCR detection of Borrelia burgdorferi DNA in cerebrospinal fluid of Lyme neuroborreliosis patients. Neurology. 43, 32-42

Banyas GT. (1992) Difficulties with Lyme serology. J Am Optom Assoc. 63(2), 135-9.

Luft BJ et al. (1992) Invasion of the CNS by Bb in acute disseminated infection. JAMA 267, 1364-1367

Liegner KB et al. (1992) Culture-confirmed treatment failure of cefotaxime and minicycline in a case of Lyme meningoencephalomyelitis in the United States. Abstract, V Int Conference on Lyme Borreliosis, Arlington, Va, May30-June 2

Fraser DD et al (1992) Molecular detection of persistent Borrelia burgdorferi in a man with **dermatomyositis**. Clinical and Exper. Rheum. 10, 387-390

Haupl TH, Krause A, Bittig M. (1992) Persistence of Borrelia burgdorferi in chronic Lyme Disease: altered immune regulation or evasion into immunologically privileged sites? Abstract 149 Fifth International Conference on Lyme Borreliosis, Arlington, VA

Preac□Mursic V, Pfister HW, Spiegel H, Burk R, Wilske B, Reinhardt S, Böhmer R. (1993) First isolation of Borrelia burgdorferi from an iris biopsy. J Clin Neuroophthalmol 13, 155-61

Haupl T, Hahn G, Rittig M et al. (1993) Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis. Arthritis Rheum 36, 1621-6.

Liegner KB, Shapiro JR, Ramsay D, Halperin AJ, Hogrefe W, Kong L. (1993) Recurrent erythema migrans despite extended antibiotic treatment with minocycline in a patient with persisting Borrelia burgdorferi infection. J Am Acad Dermatol 28(2 Pt 2), 312-4.

Battafarano DF, Combs JA, Enzenauer RJ, Fitzpatrick JE. (1993) Chronic septic arthritis caused by Borrelia burgdorferi. Clin Orthop 297, 238-41.

Fitzpatrick JE et al. (1993) Chronic septic arthritis caused by borrelia burgdorferi. Clin Ortho. 297, 238-241

Haupl T, Hahn G, Rittig M, Krause A, Schoerner C, Schonnherr U, Kalden JR, Burmester GR (1993) Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme Borreliosis. Arthritis and Rheum 36, 1621-1626

Kaiser R, Rasiah C, Gassmann G et al (1993) Inthrathecal antibody synthesis in Lyme neuroborreliosis: use of recombinant P41 and a 14-kDa flagellin fragment in ELISA. J Med Mikrobiol.39(4), 290-297 http://www.ncbi.nlm.nih.gov/pubmed/8411090

Peter O, Bretz AG, Zenhausern R et al. (1993) Isolation of Borrelia burgdorferi in the cerebrospinal fluid of 3 children with neurological involvement. Schweiz Med Wochenschr 123(1-2), 14-19 http://www.ncbi.nlm.nih.gov/pubmed/8421774

Barbour AG, Fish D. (1993) The biological and social phenomenon of Lyme disease. Science. 260(5114), 1610–1616.

Hulínská D, Krausová M, Janovská D, Rohácová H, Hancil J, Mailer H. (1993) Electron microscopy and the polymerase chain reaction of spirochetes from the blood of patients with Lyme disease. Cent Eur J Public Health. 1(2), 81-5.

Nocton JJ, Dressler F, Rutledge BJ, Rys PN, Persing DH Steere AC (1994) Detection of Borrelia burgdorferi DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis N Engl J Med 330, 229-34.

Liegner KB, Ziska M, Agricola MD, Hubbard JD, Klempner MS, Coyle PK, Bayer ME, Duray PH. (1994) Fatal Chronic Meningoencephalomyelitis (CMEM) With Massive Hydrocephalus, In A New York State Patient With Evidence of Borrelia Burgdorferi Exposure. Program and Abstracts, VI International Conference on Lyme Borreliosis. Abstr. P041T. Bologna, Italy, June 19-22

Shadick NA, Phillips CB, Logigian EL, Steere AC, Kaplan RF, Berardi VP, Duray PH, Larson MG, Wright EA, Ginsburg KS, Katz JN, Liang MH (1994) The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. Ann Intern Med 121, 560-7.

Masters E, Lynxwiler P, Rawlings J. (1994) Spirochetemia after continuous high-dose oral amoxicillin therapy. Infect Dis Clin Prac 3, 207–208.

Asch ES, Bujak DI, Weiss M, Peterson MGE, Weinstein A. (1994) Lyme disease: an infectious and postinfectious syndrome. Journal of Rheumatology. 21(3), 454–461. http://www.ncbi.nlm.nih.gov/pubmed/8006888

Bradley JF et al. (1994) The Persistence of Spirochetal Nucleic Acids in Active Lyme Arthritis. Ann Int Med 487-489

Wahlberg P, Granlund H, Nyman D, Panelius J, Seppälä I. (1994) Treatment of late Lyme borreliosis. J Infect. 29(3), 255-6

Lawrence C, Lipton RB, Lowy FD, Coyle PK (1995) Seronegative chronic relapsing neuroborreliosis. Eur Neurol 35, 113-117. http://www.ncbi.nlm.nih.gov/pubmed/7796837

vonStedingk LT, Olsson I, Hanson HS, Asbrink E, Hovmark A (1995) Polymerase chain reaction for detection of Borrelia burgdorferi DNA in skin lesions of early and **late Lyme borreliosis**. Eur J Clin Microbiol Infect Dis 14: 1-5.

Patmas, MA. (1995) Persistence of Borrelia burgdorferi despite antibiotic treatment. Journal of Spirochetal and Tick-Borne Diseases. 2(1), 101

Waniek C, Prohovnik I, Kaufman MA, Dwork AJ. (1995) Rapidly progressive frontal-type dementia associated with Lyme disease. J Neuropsychiatry Clin Neurosci. 7(3), 345-7.

Sala-Lizarraga JA. Salcede-Vivo J, Ferris J, Lopez-Andreu JA (1995) Lyme borrelioiosis. Lancet, Vol 345, 1436-37

Keszler K, Tilton RC (1995) Persistent PCR Positivity in a Patient Being Treated for Lyme Disease. Jnl of Spirochetal and Tick-Borne Diseases. 2(3), 57-58

Fallon BA et al. (1995) LateStage Neuropsychiatric Lyme Borreliosis. Case Reports. Psyhosomatics. 36, 295-300

Strle F et al. (1995) Persistence of Borrelia burgdorferi Sensu Lato in Resolved Erythema Migrans Lesions. Clin Inf Dis. 23, 380-389

Coyle PK, Schutzer SE, Deng Z et al. (1995) Detection of Borrelia burgdorferi-specific antigen in antibody negative cerebrospinal fluid in neurologic lyme disease. Neurology. 45(11) 2010-2015 http://www.ncbi.nlm.nih.gov/pubmed/7501150

Bujak et al. (**1996**) Clinical and neurocognitive features of the **post Lyme syndrome**. J. Rheumatol 23, 1392-1397

Bayer ME, Zhang L, Bayer MH. (1996) Borrelia burgdorferi DNA in the urine of treated patients with chronic Lyme disease symptoms. A PCR study of 97 cases. Infection 24, 347–353.

Nocton JJ, Bloom BJ, Rutledge BJ, Persing DH, Logigian EL, Schmid CH, Steere AC. (1996) Detection of Borrelia burgdorferi DNA by polymerase chain reaction in cerebrospinal fluid in Lyme neuroborreliosis. J Infect Dis 174, 623-7.

Preac Mursic V, Marget W, Busch U, Pleterski Rigler D, Hagl S. (1996) Kill kinetics of Borrelia burgdorferi and bacterial findings in relation to the treatment of Lyme borreliosis. Infection 24, 9-16.

Oksi J, Kalimo H, Marttila RJ et al. (1996) Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of literature. Brain 119, 2143-54. http://www.ncbi.nlm.nih.gov/pubmed/9010017

Girschick HJ et al. (1996) Intracellular persistence of Borrelia burgdorferi in human synovial cells. Rheumatol Int. 16(3), 125-132

Nanagara R, Duray PH, Schumacher HR Jr. (1996) Ultrastructural demonstration of spirochetal antigens in synovial fluid and synovial membrane in chronic Lyme disease: possible factors contributing to persistence of organisms. Hum Pathol. 27(10), 1025-34

Karma A et al. (1996) Long term follow-up of chronic Lyme neuroretinitis. Retina 16, 505-509

Priem S, Wolbart K, Rittig MG, Burmester GR et. al. (1996) Detection of Borrelia burgdorferi by PCR in Synovial Membrane, but Not in Synovial Fluid in Patients with Lyme Arthritis. (Abstract#D661). Proceedings VII International Congress on Lyme Borreliosis. June 16-21, San Francisco, CA.

Liegner KB et al. (1997) Lyme disease and the clinical spectrum of antibiotic responsive chronic meningoencephalomyelitides. Journal of Spirochetal and Tick-Borne Dis. 61-73

Donta ST (1997) Tetracycline therapy in chronic Lyme diseases. 25 (Suppl1) 552-556

Priem S, Burmester GR, Kamradt T et al. (1998) Detection of Borrelia burgdorferi by polymerase chain reaction in synovial membrane, but not in synovial fluid from patients with persisting Lyme arthritis after antibiotic therapy. Ann Rheum Dis 57,118-21.

Hudson BJ, Stewart M, Lennox VA et al. (1998) Culture-positive Lyme borreliosis. Med J Aust 168, 500-2.

Petrovic M, Vogelaers D, Van Renterghem L, Carton D, De Reuck J, Afschrift M (1998) Lyme borreliosis – a review of the late stages and treatment of four cases. Acta Clin. Belg. 53, 178-183

Wolbart K, Priem S et al (1998) Detection of Borrelia burgdorferi by PCR in synovial membrane, but not in synovial fluid from patients with persistent Lyme arthritis after antibiotic therapy. Ann Rheum Dis. 57(2) 118-121

Fallon BA, Kochevar JM, Gaito A, Nields JA. (1998) The Underdiagnosis of Neuropsychiatric Lyme Disease in Children and Adults. Psychiat Clin NA 21, 693-703.

Logigian EL et al. (1999) Successfull Treatment of Lyme Encephalopathy with iv.Ceftriaxone, J. infect. Dis. 180, 377-383 http://www.ncbi.nlm.nih.gov/pubmed/10395852
Commentary: http://www.praxis-berghoff.de/dokumente/Behandlungsparameter_der_Neuroborreliose.pdf

Oksi J, Marjamäki M, Nikoskelainen J, Viljanen MK (1999) Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med 31, 225-232.

Mikkilä H, Karma A, Viljanen M, Seppälä I. (1999) The laboratory diagnosis of ocular Lyme borreliosis. Graefes Arch Clin Exp Ophthalmol. 237(3, 225-30.

Fallon BA et al. (1999) Repeated antibiotic treatment in chronic Lyme disease. Journal of Spirochetal and Tick-borne Diseases. 6, 94-101

Shadick NA, Phillips CB, Sangha O, et al. (1999) Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease. Annals of Internal Medicine. 131(12), 919–926. http://www.ncbi.nlm.nih.gov/pubmed/10610642

Phillips SE, Mattman LH, Hulínská D, Moayad H. (1998) A proposal for the reliable culture of Borrelia burgdorferi from patients with chronic Lyme disease, even from those previously aggressively treated. Infection. 1998 Nov-Dec;26(6):364-7.

Wormser GP et al, (2000) Practice guidelines for the treatment of Lyme disease. The Infectious Diseases Society of America, Clin. Infekt. Dis. 31 (Suppl. 1), 1-14
http://www.ncbi.nlm.nih.gov/pubmed/10982743

Seltzer EG. (2000) Long-term Outcomes of Persons With Lyme Disease. JAMA. 283(5), 609-616. http://www.ncbi.nlm.nih.gov/pubmed/10665700

Horowitz RI. (2000) Chronic Persistent Lyme Borreliosis: PCR evidence of chronic infection despite extended antibiotic therapy: A rRetrospective Review. Abstract XII Int Sci Cinf on Lyme Disease. March 24-26

Breier F, Khanakah G, Stanek G, Kunz G, Aberer E, Schmidt B, Tappeiner G (2001) Isolation and polymerase chain reaction typing of Borrelia afzelii from a skin lesion in a seronegative patient with generalized ulcerating bullous lichen sclerosus et atrophicus. Br J Dermatol 144:387-92.

Grignolo MC, Buffrini L, Monteforte P, Rovetta G. (2001) Reliability of a polymerase chain reaction (PCR) technique in the diagnosis of Lyme borreliosis. Minerva Med. 92(1), 29-33.

Honegr K, Hulinska D, Dostal V et al. (2001) Persistence of Borrelia burgdorferi sensu lato in patients with Lyme borreliosis. Epidemiol Mikrobiol Immunol 50(1), 10-16
http://www.ncbi.nlm.nih.gov/pubmed/11233667

Steere et al. (**2001**) **Autoimmune mechanisms** in antibiotic treatment-resistent Lyme arthritis JAI. 16, 263-266

Mattman L. (2001) **Cell Wall Deficient Forms. Stealth Pathogens**. CRC Press ISBN 0-8493-8767-1 1. L-form bacteria – Pathogenicity. 1. Title.

Klempner MS, Hu LT, Evans J, et al. (2001) Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med 345 (2), 85–92. http://www.ncbi.nlm.nih.gov/pubmed/11450676
Commentary: http://www.praxis-berghoff.de/dokumente/Behandlungsparameter_der_Neuroborreliose.pdf

Klempner MS. (2002) Controlled trials of antibiotic treatment in patients with post-treatment chronic Lyme disease. Vector Borne and Zoonotic Diseases. 2(4), 255–263. http://www.ncbi.nlm.nih.gov/pubmed/12804167

Tylewska-Wierzbanowska S, Chmielewski T. (2002) **Limitation of serologic testing for Lyme borreliosis: evaluation of ELISA and western blot in Comparison.** Wien Klin Wochenschr. 114(13-14), 601-5. http://www.ncbi.nlm.nih.gov/pubmed/12422608

Fried MD, Pietrucha D, Madigan G, Bal A (2002) Borrelia burgdorferi Persists in the Gastrointestinal tract of Children and Adolescents with Lyme Disease. Journal of Spirochetal and Tick-Borne Diseases. 9(1), 11-15

Kaplan R et al. (2003) Cognitive function in post-treatment Lyme disease: do additional antibiotics help? Neurology 60, 1916-1922
http://www.ncbi.nlm.nih.gov/pubmed/12821733
Commentary: http://www.praxis-berghoff.de/dokumente/Behandlungsparameter_der_Neuroborreliose.pdf

Krupp LB, Hyman LG, Grimson R, et al. (2003) Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 60(12), 1923–1930. PubMed http://www.ncbi.nlm.nih.gov/pubmed/12821734
Commentary: http://www.praxis-berghoff.de/dokumente/Behandlungsparameter_der_Neuroborreliose.pdf

Wormser GP, Ramanathan R, Nowakowski J, et al. (2003) Duration of antibiotic therapy for early Lyme disease: a randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine. 138(9), 697–704. http://www.ncbi.nlm.nih.gov/pubmed/12729423

Diterich I, Rauter C, Kirschning CJ, Hartung T. (2003) Borrelia burgdorferi-induced tolerance as a

model of persistence via immunosuppression. Infect Immun. 71(7), 3979-87.

Latov et al. (2004) Neuropathy and **cognitive impairment following vaccination with OSPA** protein of Borrelia burgdorferi. J. Periph Ner Sys 9, 165-167

Miklossy J, Khalli K, Gern L, Ericson RL, Darekar P, Bolle L, Hurliman J, Paster J (2004) Borrelia burgdorferi persists in the brain in **chronic Lyme neuroborreliosis** and may be associated with Alzheimer disease. J Alzheimers Dis 6: 639-649.

Aledini, Latov (2005) Antibodies against OSPA epitops of Borrelia burgdorferi cross react with neuronal tissue. Journal of Neuroimmunology 159, 192-195

Hunfeld KP, Ruzic-Sabljic E, Norris DE, Kraiczy P, Strle F.(2005) In vitro susceptibility testing of Borrelia burgdorferi sensu lato isolates cultured from patients with erythema migrans before and after antimicrobial chemotherapy. Antimicrob Agents Chemother 49, 1294–301.

Raveche et al. (2005) Evidence of Borrelia **autoimmunity**-induced component of Lyme carditis and arthritis. J Clin Mikrob 43, 850-856

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 (**2006**) **The clinical assessments reatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America**. Clinical Infectious Diseases. 43(9):1089–1134. http://www.ncbi.nlm.nih.gov/pubmed/17029130

Yrjänäinen H, Hytönen J, Söderström K-O, Oksi J, Hartiala K, Viljanen MK. (2006) Persistent joint swelling and borrelia-specific antibodies in Borrelia garinii-infected mice after eradication of vegetative spirochetes with antibiotic treatment. Microbes and Infection. 8(8), 2044–2051. http://www.ncbi.nlm.nih.gov/pubmed/16797205

Livengood JA, Gilmore RD Jr. (2006) Invasion of human neuronal and glial cells by an infectious strain of Borrelia burgdorferi. Microbes and Infection.

Seidel MF, Domene AB, Vetter H (2007) Differential diagnoses of suspected Lyme borreliosis or post-Lyme-disease syndrome. Eur J Clin Microbiol Infect Dis 26(9), 611-7. http://www.unboundmedicine.com/medline/citation/17605053/abstract/Differential_diagnoses_of_suspected_Lyme_borreliosis_or_post_Lyme_disease_syndrome_

FederJr HM, Johnson JB, O'Connell S, Shapiro ED, Steere AC, Wormser GP (2007) A critical appraisal of "**chronic Lyme disease**". N Engl J Med 357, 1422-1430.

Cabello FC, Godfrey HP, Newman SA (2007) Hidden in plain sight: Borrelia burgdorferi and the extracellular matrix. Trends Microbiol 15(8), 350-4. http://www.unboundmedicine.com/medline/citation/17600717/abstract/Hidden_in_plain_sight:_Borrelia_burgdorferi_and_the_extracellular_matrix_

Halperin JJ, Shapiro ED, Logigian E, et al. (2007) Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 69(1), 91–102. http://www.ncbi.nlm.nih.gov/pubmed/17522387

Miklossy J, Kasas S, Zurn AD, et al. (2008) **Persisting atypical and cystic forms** of Borrelia burgdorferi and local inflammation in Lyme neuroborreliosis. J Neuroinflammation 40. http://www.unboundmedicine.com/medline/citation/18817547/abstract/Persisting_atypical_and_cystic_forms_of_Borrelia_burgdorferi_and_local_inflammation_in_Lyme_neuroborreliosis_

Marques A. (2008) Chronic Lyme disease: a review. Infect Dis Clin North Am. 22(2), 341–360. http://www.ncbi.nlm.nih.gov/pubmed/18452806

Fallon BA, Keilp JG, Corbera KM, et al. (2008) A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 70(13), 992–1003. http://www.ncbi.nlm.nih.gov/pubmed/17928580

Cameron DJ. (2008) An appraisal of ‘‘chronic Lyme disease.’’ N Engl J Med 358:429-30.

Marques A. (2008) Chronic Lyme disease: a review. Infect Dis Clin N Am 22, 341-360

Berghoff W (2008) Liquordiagnostik bei Lyme-Neuroborreliose und chronischer Lyme-Borreliose mit Encephalopathie. http://www.praxis-berghoff.de/dokumente/Liquordiagnostik_bei_LNB.pdf
„Bei der chronischen Lyme-Borreliose mit Encephalopathie sind die Liquorveränderungen selten und wenig ausgeprägt. Die Liquoruntersuchung in dieser Situation (chronische LB mit Encephalopathie) ist daher diagnostisch nicht hilfreich und somit nicht indiziert“.

Wormser GP, Shapiro ED, Halperin JJ et al. (2009) Analysis of a flawed double-blind, placebo-controlled, clinical trial of patients claimed to have persistent Lyme disease following treatment. Minerva Med 100(2), 171-172

Cameron DJ. (2009) Clinical trials validate the severity of persistent Lyme disease symptoms. Medical Hypotheses. 72(2), 153–156. http://www.ncbi.nlm.nih.gov/pubmed/19013025

Cameron DJ. (2009) Insufficient evidence to deny antibiotic treatment to chronic Lyme disease patients. Medical Hypotheses. 72(6), 688–691. http://www.ncbi.nlm.nih.gov/pubmed/19268485

Klemann W., Huismans B.D. (2009) Patienten mit Erreger-Direktnachweis bei chronischer Lyme-Borreliose: Klinik, Labordiagnostik, Antibiotika-Therapie und Krankheitsverlauf. Eine retrospektive Studie. Umwelt-medizin-gesellschaft 22 (2) 132-138

Cameron DJ (2010) Proof That Chronic Lyme Disease Exists. Interdiscip Perspect Infect Dis. 2010, 876450.

Fallon et al. (2010) Inflammation and central nervous system Lyme disease. Neurology of Disease 37, 534-541

Baker CJ (2010) **Chronic Lyme disease**: in defense of the scientific enterprise. FASEB J 24, 4175-4177.

Cerar D. (2010) Subjective Symptoms after Treatment of Early Lyme Disease. Am J Medicine 123(1), 79–86. http://www.ncbi.nlm.nih.gov/pubmed/20102996

Chandra et al. (2010) **Anti-neural antibody reactivity** in patients with a history of Lyme borreliosis and persistent symptoms. Brain Behav Imm. 24, 1018-1024

Stricker RB, Johnson L. (2011) Lyme disease: the next decade. Infect Drug Resist. 4, 1–9.

Miklossy (2011) Alzheimer's disease - a neurospirochetosis.Analysis of the evidence following Koch's and Hill's criteriaJournal of Neuroinflammation 8, 90 http://www.jneuroinflammation.com/content/8/1/90

Greco Jr TP, Conti-Kelly AM, Greco TP (2011) Antiphospholipid antibodies in patients with purported 'chronic Lyme disease' Lupus 0, 1–6 http://lup.sagepub.com/content/early/2011/07/05/0961203311414098

DiCarlo EF, Kahn LB (2011) Inflammatory diseases of the bones and joints. Semin Diagn Pathol 28(1), 53-64.
http://www.unboundmedicine.com/medline/citation/21675377/abstract/Inflammatory_diseases_of_the_bones_and_joints_

Shor S. (2011) Retrospective analysis of a cohort of internationally case defined chronic fatigue syndrome patients in a lyme epidemic area. Bulletin of the IACFS/ME 18(4), 109-123
http://www.iacfsme.org/BULLETINWINTER2011/Winter2011ShorABSTRACT/tabid/459/Default.aspx

Barbour A. (2012) **Remains of infection**. J Clin Invest. doi:10.1172/JCI63975
http://www.jci.org/articles/view/63975

Stricker R. (2012, pers. Mitteilung) **"One of the benefits of doing C3a and C4a testing in a Lyme patient with positive ANA is that if the C3a is normal prior to antibiotic treatment, the patient is unlikely to have an autoimmune disease no matter how high the ANA titer is. Like the ANA, C4a is an inflammatory marker that can be high in any condition that involves inflammation."**

Stricker RB (2012) Lyme Disease: The Hidden Epidemic. House Committee on Foreign Affairs, Subcommittee on Africa, Global Health, and Human Rights.
http://foreignaffairs.house.gov/112/HHRG-112-FA16-WState-StrickerR-20120717.pdf

Albrecht P, Henke N, Lehmann HC et al. (2012) A case of relapsing-remitting neuroborreliosis? Challenges in the differential diagnosis of recurrent myelitis. Case Reports in Neurology 4, 47-53
http://www.ncbi.nlm.nih.gov/pubmed/22649342

Katz A (2012) Field hearing of the Senate Committee on Health, Education, Labor, and Pensions addressing Lyme and tick-borne illnesses Chaired By Richard Blumenthal (D-CT). Written testimony. Thursday, August 30th, 2012, UConn – Stamford, Connecticut
http://www.help.senate.gov/hearings/hearing/?id=53342b1c-5056-9502-5d05-aa0c57233aed

Fallon BA, Petkova E, Keilp JG, Britton CB (2012) A Reappraisal of the U.S. Clinical Trials of Post-Treatment Lyme Disease Syndrome. The Open Neurology Journal, 6, (Suppl 1-M2) 79-87 http://benthamscience.com/open/toneuj/articles/V006/SI0078TONEUJ/79TONEUJ.htm

Stricker RB, Johnson L (2012) Spirochetal **'debris'** versus persistent infection in chronic Lyme disease: from semantics to science. Future Microbiol. 7(11), 1243–1246

DeLong A, Blossom B, Maloney E et al (2012) **Antibiotic retreatment of Lyme disease** in patients with persistent symptoms: A biostatistical review of randomized, placebo-controlled, clinical trials. Contemporary Clin Trials. 33(6), 1132-42. doi: 10.1016/j.cct.2012.08.009. Epub 2012 Aug 19. http://www.ncbi.nlm.nih.gov/pubmed/22922244

Barthold SW (2012) Persistence of Non-Cultivable Borrelia burgdorferi Following Antibiotic Treatment: Critical Need for Further Research
http://foreignaffairs.house.gov/112/HHRG-112-FA16-WState-BartholdS-20120717.pdf

Iyer R, Mukherjee P, Wang K et al. (2012) Detection of Borrelia burgdorferi nucleic acid after antibiotic treatment does not confirm viability. J.Clin Microbiol http://www.ncbi.nlm.nih.gov/pubmed/23269733
"It is unclear whether our findings can be extrapolated to B. burgdorferi infections in vivo. It has been suggested that B. burgdorferi may be sequestered in protective niches during animal infection such that antibiotics might be less effective."

Unbound MEDLINE results for: borrelia persistence AND human
http://www.unboundmedicine.com/medline?in=kw%257Cborrelia%2520persistence&in=jn%257C&in=au%257C
119 journal articles in the PubMed database

BDH, July 2012. Latest Revision January 2013. www.Huismans.de.vu