

Articles relating to persistence of infection & seronegativity.

Authored in some cases by IDSA guideline authors who claim there is no evidence of chronic or seroneg. despite their own previous studies.

Key: green author on all 3 panels, yellow or blue author in two, grey author in one

List of IDSA authors 2000:	List of IDSA Authors 2006:	Authors of: Treatment of nervous system Lyme disease (an evidence-based review)
Gary P. Wormser	Gary P. Wormser	G.P. Wormser, MD
Eugene D. Shapiro	Eugene D. Shapiro	E.D. Shapiro, MD
Allen C. Steere	Allen C. Steere	
Durland Fish	Durland Fish	
Robert B. Nadelman	Robert B. Nadelman	
Raymond J. Dattwyler	Raymond J. Dattwyler	
	John J. Halperin	J.J. Halperin, MD
Patricia K. Coyle	Johan S. Bakken	A.L. Belman, MD
David T. Dennis	Linda Bockenstedt	C.T. Bever Jr., MD
Benjamin J. Luft	J. Stephen Dumler	L. Dotevall, MD
David H. Persing	Mark S. Klempner	G. Gronseth, MD
Daniel W. Rahn	Peter J. Krause	L. Krupp, MD
Thomas J. Rush	Gerold Stanek	E. Logigian, MD
	Franc Strle	

- The CDC published research in 2006 in which the researchers stated,

"Our results indicate that it is possible to acquire *B. burgdorferi* infection via transfused blood in a mouse model of Lyme borreliosis."

PMID: 16995409 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/16995409>

- W. Burgdorfer in 1984: Yale J Biol Med. 1984 Jul–Aug; 57(4): 515–520.

"In view of the unusual behavior (limited distribution, loss of infection intensity) of the spirochetes in ticks, the possibility that other hematophagous arthropods, such as biting flies, gnats, and mosquitoes, may play a role as mechanical vectors of ECM and Lyme disease cannot be ruled out."

PMCID: PMC2590008

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2590008/pdf/yjbm00100-0070.pdf>

## **Persistence of infection, Chronic Lyme & /or seronegativity:-**

1. Ann N Y Acad Sci. 1988;539:65-79.

### **Clinical pathologic correlations of Lyme disease by stage.**

[Duray PH](#), [Steere AC](#).

Department of Pathology, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111.

#### **Abstract**

Lyme disease is capable of producing a wide variety of clinical pathologic conditions and lesions having in common histologic features of collagen-vascular disease. The plasma cell is an omnipotent inflammatory responder in most tissues involved by Lyme disease, ranging from relatively acute to lesions that have gone on for years. Vascular thickening also seems to be prominent, and in the dermis is accompanied by scleroderma-like collagen expansion. The disease in some ways resembles the responses seen in lupus erythematosus such as mild cerebritis with lymphocytes and plasma cells in the leptomeninges. Lymphoplasmacytic panniculitis of Lyme disease resembles lupus profundus, both in the infiltrate and the plasma cell-blood vessel relationship. The onion skin thickened vessels of the synovia resemble the vessels of lupus spleens, while the sclerodermoid thickening of the dermis and various skin lesions of stage III Lyme disease suggest a collagen-vascular disorder. Finally, the perivascular lymphoid infiltrate in clinical myositis does not differ from that seen in polymyositis or dermatomyositis. All of these histologic derangements suggest immunologic damage in response to persistence of the spirochete, however few in number.

PMID: 2847622 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/2847622>

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2. [N Engl J Med](#). 1988 Dec 1;319(22):1441-6.

### **Seronegative Lyme disease. Dissociation of specific T- and B-lymphocyte responses to *Borrelia burgdorferi*.**

[Dattwyler RJ](#), [Volkman DJ](#), [Luft BJ](#), [Halperin JJ](#), [Thomas J](#), [Golightly MG](#).

Department of Medicine, State University of New York, School of Medicine, Stony Brook 11794-8161.

#### **Abstract**

The diagnosis of Lyme disease often depends on the measurement of serum antibodies to *Borrelia burgdorferi*, the spirochete that causes this disorder. Although prompt treatment with antibiotics may abrogate the antibody response to the infection, symptoms persist in some patients. We studied 17 patients who had presented with acute Lyme disease and received prompt treatment with oral antibiotics, but in whom chronic Lyme disease subsequently developed. Although these patients had clinically active disease, none had diagnostic levels of antibodies to *B. burgdorferi* on either a standard enzyme-linked immunosorbent assay or immunofluorescence assay. On Western blot analysis, the level of immunoglobulin reactivity against *B. burgdorferi* in serum from these patients was no greater than that in serum from normal controls. The patients had a vigorous T-cell proliferative response to whole *B. burgdorferi*, with a mean (  $\pm$  SEM) stimulation index of 17.8  $\pm$  3.3, similar to that (15.8  $\pm$  3.2) in 18 patients with chronic Lyme disease who had detectable antibodies. The T-cell response of both groups was greater than that of a control group of healthy subjects (3.1  $\pm$  0.5; P less than 0.001). 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.

PMID: 3054554 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/3054554>

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3. [Infection](#). 1989 Nov-Dec;17(6):355-9.

#### **Survival of *Borrelia burgdorferi* in antibioticly treated patients with Lyme borreliosis.**

[Preac-Mursic V](#), [Weber K](#), [Pfister HW](#), [Wilske B](#), [Gross B](#), [Baumann A](#), [Prokop J](#).

Neurologische Klinik Grosshadern, München, FR Germany.

#### **Abstract**

The persistence of *Borrelia burgdorferi* in patients treated with antibiotics is described. The diagnosis of Lyme disease is based on clinical symptoms, epidemiology and specific IgG and IgM antibody titers to *B. burgdorferi* in serum. Antibiotic therapy may abrogate the antibody response to the infection as shown in our patients. *B. burgdorferi* may persist as shown by positive culture in MKP-medium; 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*.

PMID: 2613324 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/2613324>

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4. [Am J Clin Pathol](#). 1989 Jan;91(1):95-7.

#### **Spirochetes in the spleen of a patient with chronic Lyme disease.**

[Cimmino MA](#), [Azzolini A](#), [Tobia F](#), [Pesce CM](#).

Istituto Scientifico di Medicina Interna, Università di Genova, Italy.

#### **Abstract**

A 54-year-old man had intermittent evening fever, arthralgia, transient erythematous macular eruption on the skin, and splenomegaly of two year's duration. Immunofluorescence tests for *Borrelia burgdorferi* serum antibodies had positive results, but G-penicillin treatment was ineffective. Splenectomy with lymph node biopsy was performed to rule out lymphoproliferative disorders. *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.

PMID: 2910019 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/2910019>

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5. [N Engl J Med](#). 1990 Nov 22;323(21):1438-44.

**Chronic neurologic manifestations of Lyme disease.**

[Logigian EL](#), [Kaplan RF](#), [Steere AC](#).

Department of Neurology, Tufts University School of Medicine, Boston, MA 02111.

**Abstract**

BACKGROUND AND METHODS: Lyme disease, caused by the tick-borne spirochete *Borrelia burgdorferi*, is associated with a wide variety of neurologic manifestations. To define further the chronic neurologic abnormalities of Lyme disease, we studied 27 patients (age range, 25 to 72 years) with previous signs of Lyme disease, current evidence of immunity to *B. burgdorferi*, and chronic neurologic symptoms with no other identifiable cause. Eight of the patients had been followed prospectively for 8 to 12 years after the onset of infection.

RESULTS: Of the 27 patients, 24 (89 percent) had a mild encephalopathy that began 1 month to 14 years after the onset of the disease and was characterized by memory loss, mood changes, or sleep disturbance. Of the 24 patients, 14 had memory impairment on neuropsychological tests, and 18 had increased cerebrospinal fluid protein levels, evidence of intrathecal production of antibody to *B. burgdorferi*, or both. Nineteen of the 27 patients (70 percent) had polyneuropathy with radicular pain or distal paresthesias; all but two of these patients also had encephalopathy. In 16 patients electrophysiologic testing showed an axonal polyneuropathy. One patient had leukoencephalitis with asymmetric spastic diplegia, periventricular white-matter lesions, and intrathecal production of antibody to *B. burgdorferi*. Among the 27 patients, associated symptoms included fatigue (74 percent), headache (48 percent), arthritis (37 percent), and hearing loss (15 percent). At the time of examination, chronic neurologic abnormalities had been present from 3 months to 14 years, usually with little progression. Six months after a two-week course of intravenous ceftriaxone (2 g daily), 17 patients (63 percent) had improvement, 6 (22 percent) had improvement but then relapsed, and 4 (15 percent) had no change in their condition.

PMID: 2172819 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/2172819>

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6. [Acta Trop](#). 1990 Dec;48(2):89-94.

**Clinical implications of delayed growth of the Lyme borreliosis spirochete, *Borrelia burgdorferi*.**

[MacDonald AB](#), [Berger BW](#), [Schwan TG](#).

Department of Pathology, Southampton Hospital, New York 11968.

**Abstract**

Lyme borreliosis, a spirochetal infection caused by *Borrelia burgdorferi*, may become clinically active after a period of latency in the host. Active cases of Lyme disease may show clinical relapse following antibiotic therapy. The latency and relapse phenomena suggest that the Lyme disease spirochete is capable of survival in the host for prolonged periods of time. We studied 63 patients with erythema migrans, the pathognomonic cutaneous lesion of Lyme borreliosis, and examined in vitro cultures of biopsies from the active edge of the erythematous patch. Sixteen biopsies yielded spirochetes after

prolonged incubations of up to 10.5 months, suggesting that *Borrelia burgdorferi* may be very slow to divide in certain situations. 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.

PMID: 1980573 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/1980573>

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7. [J Am Optom Assoc.](#) 1992 Feb;63(2):135-9.

#### **Difficulties with Lyme serology.**

[Banyas GT.](#)

#### **Abstract**

Lyme disease is a multisystem infection characterized by dermatologic, neurologic, and arthritic findings. Like syphilis, Lyme borreliosis may imitate several other infectious and non-infectious diseases. Diagnosis is dependent on a reliable history (if available), clinical findings, and blood serology findings. A major problem has been seronegativity in persons possessing the disease (false negatives). 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.

PMID: 1583267 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/1583267>

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8. [J Am Acad Dermatol.](#) 1993 Feb;28(2 Pt 2):312-4.

#### **Recurrent erythema migrans despite extended antibiotic treatment with minocycline in a patient with persisting *Borrelia burgdorferi* infection.**

[Liegner KB](#), [Shapiro JR](#), [Ramsay D](#), [Halperin AJ](#), [Hogrefe W](#), [Kong L](#).

Department of Medicine, Northern Westchester Hospital Center, Mount Kisco, NY.

#### **Abstract**

Erythema migrans recurred in a patient 6 months after a course of treatment with minocycline for Lyme disease. Polymerase chain reaction on heparinized peripheral blood at that time demonstrated the presence of *Borrelia burgdorferi*-specific DNA. The patient was seronegative by Lyme enzyme-linked 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. Reinfection was not believed to have occurred. Further treatment with minocycline led to resolution of the erythema migrans.

PMID: 8436647 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/8436647>

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9. [Cent Eur J Public Health](#). 1993 Dec;1(2):81-5.

**Electron microscopy and the polymerase chain reaction of spirochetes from the blood of patients with Lyme disease.**

[Hulínská D](#), [Krausová M](#), [Janovská D](#), [Roháčová H](#), [Hancil J](#), [Mailer H](#).

Department of Electron Microscopy, National Institute of Public Health, Prague, Czech Republic.

**Abstract**

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.

PMID: 8004045 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/8004045>

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10. [J Clin Neuroophthalmol](#). 1993 Sep;13(3):155-61; discussion 162.

**First isolation of Borrelia burgdorferi from an iris biopsy.**

[Preac-Mursic V](#), [Pfister HW](#), [Spiegel H](#), [Burk R](#), [Wilske B](#), [Reinhardt S](#), [Böhmer R](#).

Max v. Pettenkofer Institut für Hygiene u. Medizinische Mikrobiologie, LM-Universität München, Germany.

**Abstract**

The persistence of Borrelia burgdorferi in six patients is described. Borrelia burgdorferi has been cultivated from iris biopsy, skin biopsy, and cerebrospinal fluid also after antibiotic therapy for Lyme borreliosis. Lyme Serology: IgG antibodies to B. burgdorferi were positive, IgM negative in four patients; in two patients both IgM and IgG were negative. Antibiotic therapy may abrogate the antibody response to the infection as shown by our results. Patients may have subclinical or clinical disease without diagnostic antibody titers. Persistence of B. burgdorferi cannot be excluded when the serum is negative for antibodies against it.

PMID: 8106639 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/8106639>

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11. [Ann Intern Med](#). 1994 Oct 15;121(8):560-7.

**The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study.**

[Shadick NA](#), [Phillips CB](#), [Logigian EL](#), [Steere AC](#), [Kaplan RF](#), [Berardi VP](#), [Duray PH](#), [Larson MG](#), [Wright EA](#), [Ginsburg KS](#), [Katz JN](#), [Liang MH](#).

Department of Rheumatology-Immunology, Brigham & Women's Hospital, Boston, MA 02115.

## Abstract

**OBJECTIVE:** To ascertain the prevalence of and risk factors for long-term sequelae from acute Lyme disease.

**DESIGN:** Population-based, retrospective cohort study.

**SETTING:** A coastal region endemic for Lyme disease.

**PARTICIPANTS:** Patients with a history of Lyme disease who were previously treated with antibiotics were compared with randomly selected controls.

**MEASUREMENTS:** A standardized physical examination, health status measure (Short Form 36), psychometric test battery, and serologic analysis.

**RESULTS:** Compared with the control group (n = 43), the Lyme group (n = 38; mean duration from disease onset to study evaluation, 6.2 years) had more arthralgias (61% compared with 16%; P < 0.0001); distal paresthesias (16% compared with 2%; P = 0.03); concentration difficulties (16% compared with 2%; P = 0.03); and fatigue (26% compared with 9%; P = 0.04), and they had poorer global health status scores (P = 0.04). The Lyme group also had more abnormal joints (P = 0.02) and more verbal memory deficits (P = 0.01) than did the control group. Overall, 13 patients (34%; 95% CI, 19% to 49%) had long-term sequelae from Lyme disease (arthritis or recurrent arthralgias [n = 6], neurocognitive impairment [n = 4], and neuropathy or myelopathy [n = 3]). Compared with controls, patients who had long-term sequelae had higher IgG antibody titers to the spirochete (P = 0.03) and received treatment later (34.5 months compared with 2.7 months; P < 0.0001).

**CONCLUSIONS:** 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 long-term morbidity.

PMID: 8085687 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/8085687>

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12. [J Infect.](#) 1994 Nov;29(3):255-6

### **Treatment of late Lyme borreliosis.**

[Wahlberg P](#), [Granlund H](#), [Nyman D](#), [Panelius J](#), [Seppälä I](#).

Department of Medicine, Åland Central Hospital, Mariehamn, Finland.

[From the abstract:] "Short periods of treatment were not generally effective."

[From the article:] "Symptoms and signs often improve temporarily shortly after treatment but reappear within weeks or months. ...To conclude, we have shown that long-term treatments beginning with intravenous ceftriaxone and continuing with amoxicillin plus probenecid or with cephadroxil were useful in the treatment of late Lyme borreliosis." (pp. 260-1)

PMID: 7884218 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/7884218>

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13. [Eur Neurol](#). 1995;35(2):113-7.

**Seronegative chronic relapsing neuroborreliosis.**

[Lawrence C](#), [Lipton RB](#), [Lowy FD](#), [Coyle PK](#).

Department of Medicine, Albert Einstein College of Medicine, New York, N.Y., USA.

**Abstract**

We report an unusual patient with evidence of *Borrelia burgdorferi* infection who experienced repeated neurologic relapses despite aggressive antibiotic therapy. Each course of therapy was associated with a Jarisch-Herxheimer-like reaction. 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.

[From the article:] "Before her 6th hospital admission this patient had received four courses of ceftriaxone, one of cefotaxime and two of doxycycline (of 19 and 8 weeks). Increasing right hemiparesis and dyspnea with right intercostal muscle weakness prompted her 6th admission to the hospital. Following intravenous ceftriaxone for 2 weeks, it was decided to place the patient on long-term therapy [22 months] with clarithromycin. Although there is no information on the penetration of clarithromycin into the CNS, it achieves high concentrations within macrophages [18] a known sanctuary for the *Bb* spirochete [19]. The clinical response to clarithromycin in this patient has now been sustained for over 22 months."

"...Survival of *Bb* in humans despite aggressive antibiotic therapy has been previously reported [2,22]. We believe this to be an example of a patient with chronic relapsing *Bb* infection. It is important to evaluate unusual patients like this thoroughly in order to determine the effectiveness of prolonged oral antibiotics as a therapeutic option."

PMID: 7796837 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/7796837>

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14. [J Neuropsychiatry Clin Neurosci](#). 1995 Summer;7(3):345-7.

**Rapidly progressive frontal-type dementia associated with Lyme disease.**

[Waniek C](#), [Prohovnik I](#), [Kaufman MA](#), [Dwork AJ](#).

New York State Psychiatric Institute, NY 10032, USA.

**Abstract**

The authors report a case of fatal neuropsychiatric Lyme disease (LD) that was expressed clinically by progressive frontal lobe dementia and pathologically by severe subcortical degeneration. Antibiotic treatment resulted in transient improvement, but the patient relapsed after the antibiotics were discontinued. LD must be considered even in cases with purely psychiatric presentation, and prolonged antibiotic therapy may be necessary.

PMID: 7580195 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/7580195>

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15. 1995 Lyme borreliosis. [Letter] Lancet, Vol 345: 1436-37

**Sala-Lizarraga JA. Salcedo-Vivo J; Ferris J; Lopez-Andreu JA;**

“Our patient received during 2 years seven short-term antibiotic treatments, achieving transitory improvements. Nonetheless, his condition greatly deteriorated. In October, 1993, he started a different antibiotic regimen (ceftriaxone, 2 g per day intravenously for 12 months, oral roxithromycin 150 mg per day for 2 months, and oral ciprofloxacin, 500 mg per 12 hours for 2 months). After ceftriaxone he has continued with oral minocycline, 100 mg per 12 hours for 7 months. His quality of life has greatly improved and the treatment is more tolerable than the borreliosis.”

“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.”

<http://www.lymeinfo.net/medical/LDPersist.pdf> (no 34)

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16. 9th Annual International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders

### **Chronic Lyme Disease: An Evolving Syndrome**

**Benjamin J. Luft**, M.D. Professor

Chair (acting) Department of Medicine, State University of New York at Stony Brook

Abstract:

Lyme disease, initially described as an arthritic disease, has unfolded over the past 15 years as a multistage, multisymptom disease of great complexity and variability. Several key factors are involved in the development of Lyme disease; the spirochetal agent, the tick and the host. The spirochete shows strain heterogeneity with at least three major genospecies: *Borrelia burgdorferi*, *B. garinii* and *B. afzelii*. Different genospecies appear to be associated with distinct clinical manifestations. Multiple strains of *B. burgdorferi* can infect the same tick and human infection can include single or multiple spirochete strains. In the case of the ticks, environmental factors such as temperature, humidity and source of blood meal may alter the major outer surface proteins (Osp) of the spirochete within the tick vector. This can affect the spirochete infectivity. Ticks can be co-infected with multiple organisms, including *Babesia* and *Ehrlichia* species. The immune response plays a definite role in the infectivity and pathogenesis of *B. burgdorferi*. Osp A, a major outer surface protein with relative molecular mass of 31,000, stimulates B cells and cytokine production. Humans with chronic arthritis are more likely to show an immune response to Osp A.

Chronic Lyme disease has become an increasing concern for health care providers. Retrospective studies confirm that a proportion of patients treated for Lyme disease experience prolonged post treatment problems. Persistent complaints are generally non-specific and include arthralgias, myalgias, cognitive difficulties, fatigue, malaise, dizziness, stiff neck and photophobia. Chronic Lyme disease patients may be seropositive or seronegative with or without a documented history of Lyme disease.

Since Lyme disease is a clinical diagnosis, research must continue to improve diagnostic assays using recombinant proteins which are more sensitive and specific than the whole organism sonicate used for both ELISA and Western blots. Possible biological markers of chronic Lyme disease, such as

positive Borrelial antigen, Borrelial DNA and pleocytosis in the CSF or synovial fluid, need to be assessed and validated. Elimination of biological markers in combination with sensitive indices of neuropsychological symptoms will be useful for the evaluation of treatment modalities.

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17. Hum Pathol. 1996 Oct;27(10):1025-34

**Ultrastructural demonstration of spirochetal antigens in synovial fluid and synovial membrane in chronic Lyme disease: possible factors contributing to persistence of organisms.**

[Nanagara R](#), [Duray PH](#), [Schumacher HR Jr](#).

Allergy-Immunology-Rheumatology Division, Department of Medicine, Faculty of Medicine, KhonKaen University, Thailand.

[From the abstract:] “Electron microscopy [both EM and IEM were used] adds further evidence for persistence of spirochetal antigens in the joint in chronic Lyme disease. Locations of spirochetes or spirochetal antigens both intracellularly and extracellularly in deep synovial connective tissue as reported here suggest sites at which spirochaetes may elude host immune response and antibiotic treatment.”

[From the article:] “If spirochetes are already sequestered in tissue that is inaccessible to antibiotics such as in the fibrinous and collagen tissue or within fibroblasts, high-dose parenteral antibiotics, or combination therapies with long duration may be needed to kill the living spirochetes.” (p.1032)

PMID: 8892586 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/8892586>

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18. [Infection](#). 1996 Jan-Feb;24(1):9-16.

**Kill kinetics of Borrelia burgdorferi and bacterial findings in relation to the treatment of Lyme borreliosis.**

[Preac Mursic V](#), [Marget W](#), [Busch U](#), [Pleterski Rigler D](#), [Hagl S](#).

Max v. Pettenkofer Institut, Ludwig-Maximilians-Universität München, Germany.

**Abstract**

For a better understanding of the persistence of Borrelia burgdorferi sensu lato (s.l.) after antibiotic therapy the kinetics of killing B. burgdorferi s.l. under amoxicillin, doxycycline, cefotaxime, ceftriaxone, azithromycin and penicillin G were determined. The killing effect was investigated in MKP medium and human serum during a 72 h exposure to antibiotics. Twenty clinical isolates were used, including ten strains of Borrelia afzelii and ten strains of Borrelia garinii. The results show that the kinetics of killing borreliae differ from antibiotic to antibiotic. The killing rate of a given antibiotic is less dependent on the concentration of the antibiotic than on the reaction time. Furthermore, the data show that the strains of B. afzelii and B. garinii have a different reaction to antibiotics used in the treatment of Lyme borreliosis and that different reactions to given antibiotics also exist within one species. The B. garinii strains appear to be more sensitive to antibiotics used in therapy. 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.

PMID: 8852456 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/8852456>

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19. [Acta Clin Belg.](#) 1998 Jun;53(3):178-83.

**Lyme borreliosis--a review of the late stages and treatment of four cases.**

[Petrovic M](#), [Vogelaers D](#), [Van Renterghem L](#), [Carton D](#), [De Reuck J](#), [Afschrift M](#).

Department of Internal Medicine, University Hospital Ghent, Belgium.

**Abstract**

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. These difficulties clinical cases of Lyme borreliosis. The different clinical cases illustrate 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 and typical presentations of late Lyme disease, such as lymphocytic meningo-encephalitis and polyradiculoneuritis.

PMID: 9701852 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/9701852>

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20. [Graefes Arch Clin Exp Ophthalmol.](#) 1999 Mar;237(3):225-30.

**The laboratory diagnosis of ocular Lyme borreliosis.**

[Mikkilä H](#), [Karma A](#), [Viljanen M](#), [Seppälä I](#).

Department of Ophthalmology, Helsinki University Central Hospital, Finland.

**Abstract**

**BACKGROUND:** A study was carried out to evaluate indirect enzyme-linked immunosorbent assay (ELISA), immunoblot analysis, and polymerase chain reaction (PCR) in the diagnostic work-up of ocular Lyme borreliosis.

**METHODS:** Twenty patients with ocular Lyme borreliosis were examined. IgG and IgM antibodies to *Borrelia burgdorferi* were measured by ELISA in serum, and in cerebrospinal fluid (CSF) when indicated, and immunoblot analysis of *B. burgdorferi* IgG antibodies in serum was performed. A nested PCR was used to detect a segment of a gene coding for *B. burgdorferi* endoflagellin. The samples used in PCR testing were serum and CSF and in isolated cases conjunctiva and vitreous.

**RESULTS:** Seventeen patients had elevated *Borrelia* antibodies in serum or CSF by ELISA. Seven patients, including two with negative ELISA, had a positive immunoblot. Seven of the 13 patients in whom PCR was examined during clinically active disease had a positive PCR result. Immunoblot analysis gave a negative result from the sera of five PCR-positive patients.

CONCLUSIONS: 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.

PMID: 10090586 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/10090586>

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21. [Ann Med.](#) 1999 Jun;31(3):225-32.

**Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis.**

[Oksi J](#), [Marjamäki M](#), [Nikoskelainen J](#), [Viljanen MK](#).

Department of Medicine, Turku University Central Hospital, Finland. jarmo.oksi@utu.fi

**Abstract**

A total of 165 patients with disseminated Lyme borreliosis (diagnosed in 1990-94, all seropositive except one culture-positive patient) were followed after antibiotic treatment, and 32 of them were regarded as having a clinically defined treatment failure. Of the 165 patients, 136 were tested by polymerase chain reaction (PCR) during the follow-up. PCR was positive from the plasma of 14 patients 0-30 months after discontinuation of the treatment, and 12 of these patients had a clinical relapse. In addition, *Borrelia burgdorferi* was cultured from the blood of three patients during the follow-up. All three patients belonged to the group with relapse, and two of them were also PCR positive. This report focuses on the 13 patients with clinical relapse and culture or PCR positivity. Eight of the patients had culture or PCR-proven initial diagnosis, the diagnosis of the remaining five patients was based on positive serology only. All 13 patients were primarily treated for more than 3 months with intravenous and/or oral antibiotics (11 of them received intravenous ceftriaxone, nine for 2 weeks, one for 3 weeks and one for 7 weeks, followed by oral antibiotics). The treatment caused only temporary relief in the symptoms of the patients. All but one of them had negative PCR results immediately after the first treatment. The patients were retreated usually with intravenous ceftriaxone for 4-6 weeks. None of them was PCR positive after the retreatment. 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. By using PCR, it is possible to avoid unnecessary retreatment of patients with 'post-Lyme syndrome' and those with 'serological scars' remaining detectable for months or years after infection.

PMID: 10442678 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/10442678>

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22. [Infection.](#) 1998 Nov-Dec;26(6):364-7.

**A proposal for the reliable culture of *Borrelia burgdorferi* from patients with chronic Lyme disease, even from those previously aggressively treated.**

[Phillips SE](#), [Mattman LH](#), [Hulínská D](#), [Moayad H](#).

Greenwich Hospital, CT 06830, USA.

## Abstract

Since culture of *Borrelia burgdorferi* from patients with chronic Lyme disease has been an extraordinarily rare event, clarification of the nature of the illness and proving its etiology as infectious have been difficult. A method for reliably and reproducibly culturing *B. burgdorferi* from the blood of patients with chronic Lyme disease was therefore sought by making a controlled blood culture trial studying 47 patients with chronic Lyme disease. All had relapsed after long-term oral and intravenous antibiotics. 23 patients with other chronic illness formed the control group. Positive cultures were confirmed by fluorescent antibody immuno-electron microscopy using monoclonal antibody directed against Osp A, and Osp A PCR. 43/47 patients (91%) cultured positive. 23/23 controls (100%) cultured negative. Although persistent infection has been, to date, strongly suggested in chronic Lyme disease by positive PCR and antigen capture, there are major problems with these tests. 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. This discovery should help to reestablish the gold standard in laboratory diagnosis of Lyme disease.

PMID: 9861561 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/9861561>

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23. [Br J Dermatol.](#) 2001 Feb;144(2):387-92.

**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.**

[Breier F](#), [Khanakah G](#), [Stanek G](#), [Kunz G](#), [Aberer E](#), [Schmidt B](#), [Tapeiner G](#).

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## Abstract

A 64-year-old woman presented with bullous and ulcerating lichen sclerosus et atrophicus (LSA) on the neck, trunk, genital and perigenital area and the extremities. Histology of lesional skin showed the typical manifestations of LSA; in one of the biopsies spirochaetes were detected by silver staining. 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. After one further 28-day course of ceftriaxone the lesions stopped expanding and sclerosis of the skin was diminished. At this time cultures for spirochaetes and PCR of lesional skin for *B. afzelii* DNA remained negative. These findings suggest a pathogenetic role for *B. afzelii* in the development of LSA and a beneficial effect of appropriate antibiotic treatment.

PMID: 11251580 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/11251580>

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24. [Minerva Med.](#) 2001 Feb;92(1):29-33.

### **Reliability of a polymerase chain reaction (PCR) technique in the diagnosis of Lyme borreliosis**

[Article in Italian]

[Grignolo MC](#), [Buffrini L](#), [Monteforte P](#), [Rovetta G](#).

DISEM, Cattedra di Reumatologia, Istituto E. Bruzzone, ASL n. 3 Genovese, Centro Reumatologico, Gruppo Italiano per lo Studio della Malattia di Lyme (GISML), Università degli Studi, Genoa, Italy.

#### **Abstract**

[From the abstract:] "50% of the PCR positive results, obtained with serum and cerebrospinal fluid samples corresponded to patients who were true positives at clinical examination but negatives at serologic tests. 62.5% of urine samples positive results belonged to patients who had negative serologic and serum PCR RESULTS.

CONCLUSIONS: The obtained results suggested a good reliability of positive results obtained with the PCR technique used in this study and allowed the false negatives of serologic tests to be detected, more specifically when urine samples were used."

PMID: 11317136 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/11317136>

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25. [Wien Klin Wochenschr.](#) 2002 Jul 31;114(13-14):601-5.

### **Limitation of serologic testing for Lyme borreliosis: evaluation of ELISA and western blot in comparison**

[Tylewska-Wierzbanowska S](#), [Chmielewski T](#).

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#### **Abstract**

The aim of the study was to evaluate a one-step procedure using an ELISA test of high specificity and a two-step procedure using immunoblot as a confirmation test, and to compare the results of serological testing with detection of bacterial DNA and living spirochetes. Sera, synovial (SF) and cerebro-spinal fluids (CSF) were obtained from 90 patients with clinical symptoms of Lyme borreliosis. Serum samples were tested with recombinant ELISA and Western blot assay. Citrated blood, cerebrospinal and synovial fluids samples were cultured in cell line and tested by PCR to detect spirochetes. No correlation was found between levels of specific *B. burgdorferi* antibodies detected with a recombinant antigen ELISA and the number of protein fractions developed with these antibodies by immunoblot. Moreover, Lyme borreliosis patients who have live spirochetes in body fluids have 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.

PMID: 12422608 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/12422608>

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26. [Infect Immun](#). 2003 Jul;71(7):3979-87.

### **Borrelia burgdorferi-induced tolerance as a model of persistence via immunosuppression.**

[Diterich I](#), [Rauter C](#), [Kirschning CJ](#), [Hartung T](#).

Biochemical Pharmacology, Faculty of Biology, University of Konstanz, Konstanz, Germany.

#### **Abstract**

If left untreated, infection with *Borrelia burgdorferi sensu lato* may lead to chronic Lyme borreliosis. 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 (I. Diterich, L. Härter, D. Hassler, A. Wendel, and T. Hartung, *Infect. Immun.* 69:687-694, 2001)

PMID: 12819085 [PubMed - indexed for MEDLINE]

<http://www.ncbi.nlm.nih.gov/pubmed/12819085>

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- *Annals of Internal Med.* 1985:(Vol 103) 67-68

### **Maternal-fetal transmission of the Lyme disease spirochete *Borrelia burgdorferi***

Schlesinger P, Duray P, Burke B, [Steere A](#), Stillman A.

In 1985, researchers published the first proof of maternal-fetal transmission of *Borrelia burgdorferi* (Bb): A baby died shortly after birth and Bb spirochetes were found in the infant's spleen, kidney, and bone marrow.

[http://www.canlyme.com/Schlesinger\\_1985.pdf](http://www.canlyme.com/Schlesinger_1985.pdf)

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- World Health Organisation Europe & Stockholm university

### **Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures**

Elisabet Lindgren Thomas G.T. Jaenson

LB is the most common vector-borne disease in temperate zones of the northern hemisphere. About 85 000 cases are reported annually in Europe (estimated from available national data). However, this number is largely underestimated as case reporting is highly inconsistent in Europe and many LB infections go undiagnosed.

[http://www.euro.who.int/\\_data/assets/pdf\\_file/0006/96819/E89522.pdf](http://www.euro.who.int/_data/assets/pdf_file/0006/96819/E89522.pdf)

Sources (with thanks):

Author PJ Langhoff	<a href="http://www.allegorypress.com/books.html">http://www.allegorypress.com/books.html</a>
CanLyme	<a href="http://www.canlyme.com/Schlesinger_1985.pdf">http://www.canlyme.com/Schlesinger_1985.pdf</a>
Lyme Info.net	<a href="http://www.lymeinfo.net/lymefiles.html">http://www.lymeinfo.net/lymefiles.html</a>
Lyme Disease Action	<a href="http://www.lymediseaseaction.org.uk/articles/persistence.htm">http://www.lymediseaseaction.org.uk/articles/persistence.htm</a>