Relapse/Persistence of Lyme Disease Despite Antibiotic Therapy

16 September 2003

	Author	*Year*	*Title*	*Journal*
1.	**Straubinger RK.**	2000	**PCR-based quantification of Borrelia burgdorferi organisms in canine tissues over a 500-day postinfection period.**	Journal of Clinical Microbiology, 38(6):2191-2199

[Persistence:] "Antibiotic treatment resulted in the temporary disappearance of B. burgdorferi DNA. Skin samples became positive by PCR starting 60 days after treatment had ended, and additional positive samples were detected later. ...therapy with different antibiotics seems to reduce the load of B. burgdorferi infection to a level of approximately 53 to 13,078 spirochetes per 100 µg of extracted total DNA but fails to eliminate the infection. [Dogs were treated with ceftriaxone, doxycycline, or azithromycin for 30 consecutive days.]

After antibiotic therapy had ended, in some treated dogs antibody titers remained at constant levels rather than decreasing further. This argues more for the persistence of the antigenic stimulus than for the complete elimination of B. burgdorferi."

[Diagnosis:] "...DNA of heat-killed borrelia was not detectable for very long in skin tissue of an uninfected dog, implying that during natural infection the DNA of killed organisms is removed quickly and completely within a few days."

2.	**Straubinger RK; Straubinger AF; Summers BA; Jacobson RH.**	2000	**Status of Borrelia burgdorferi Infection after antibiotic treatment and the effects of corticosteroids: an experimental study.**	Journal of Infectious Diseases, 181(3):1069-1081

16 dogs were infected with Borrelia burgdorferi. 120 days after tick exposure, 12 dogs were treated with antibiotics for 30 days; 4 control dogs were not treated. "At euthanasia, single tissues of the antibiotic-treated dogs and multiple tissues of all control dogs were Borrelia-positive by polymerase chain reaction."

[Persistence:] "Do the data indicate an ongoing persistent infection in these animals or only the presence of DNA remnants of dead Borrelia...? From this study and our previous investigations (20), it appears likely that B. burgdorferi maintains a persistent infection with live organisms albeit at a very low level." (p.1079)

[Diagnosis:] "As demonstrated by the injection of heat-killed B. burgdorferi organisms into the skin of an uninfected animal, DNA of dead organisms was detectable in our hands only for 3 weeks. These results are in concordance with a study in which persistent experimental infection with Treponema pallidum, the spirochetal agent of syphilis, was identified by PCR (21). Wicher et al. [1998] discovered that DNA of dead Treponema organisms was removed from or degraded within rabbit tissue within 15-30 days after syringe inoculation." (p.1079)

"Our studies show that at least in the dog, blood is an unreliable tissue to demonstrate B. burgdorferi infection." (p.1080)

3.	**Oksi J; Marjamaki M; Nikoskelainen J; Viljanen MK.**	1999	**Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme Borreliosis.**	Annals of Medicine, 31(3):225-32

Of 165 patients treated for disseminated Lyme borreliosis with three months or more of antibiotics (including a minimum of two weeks of ceftriaxone), 32 had treatment failure. At follow-up, 13 patients with clinical relapse were PCR or culture positive (10 PCR positive, 1 culture positive, 2 PCR and culture positive). "In this study, culture or PCR-based evidence for the presence of live spirochetes was obtained in more than 40% of the patients with relapsed disease."

"The treatment caused only temporary relief in the symptoms of the patients."

"We conclude that the treatment of Lyme borreliosis with appropriate antibiotics for even more than 3 months may not always eradicate the spirochete."

	Author	Year	Title	Journal
4.	**Breier F; Khanakah G; Stanek G; Kunz G; Aberer E; et al.**	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(2):387-392.
			[From the abstract:] "Despite treatment with four courses of ceftriaxone with or without methylprednisone for up to 20 days, progression of LSA [lichen sclerosus et atrophicus] 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." [From the article:] "The relapses she repeatedly suffered despite initially successful antibiotic treatment could be related to the observation that Borrelia may possibly be able to remain dormant in certain tissue compartments, thus escaping bactericidal antibiotic activity. This would be consistent with the fact that these relapses were always able to be treated successfully with a course of the same antibiotics as before; this is corroborated by a recent report that Bb may persist in experimentally infected dogs despite antibiotic treatment with doxycycline or amoxycillin."	
5.	**Warner G; O'Connell S; Lawton N.**	1999	**Atypical features in three patients with florid neurological Lyme disease.**	J Neurol Neurosurg Psychiatry, 67(2):275.
			"*Two [of three patients] had new symptoms/signs despite appropriate and adequate treatment; the third a remitting-relapsing course."*	
6.	**Cimperman J; Maraspin V; Lotric-Furlan S; Ruzic-Sabljic E; Strle F.**	1999	**Lyme meningitis: a one-year follow up controlled study.**	Wien Klin Wochenschr, 111(22-23):961-3
			[Abstract:] "The results of our study revealed that Lyme meningitis frequently occurs without meningeal signs and is often accompanied by additional borreliosis persisted or occurred for the first time in several patients. They were not infrequent even at the examination performed one year after therapy." [A total of 36 patients were followed.]	
7.	**Zamponi N; Cardinali C; Tavoni MA; Porfiri L; Rossi R; Manca A.**	1999	**Chronic neuroborreliosis in infancy.**	Ital J Neurol Sci, Oct;20(5):303-7
			[From the abstract:] "Lyme disease is a polymorphic and multisystemic disease caused by Borrelia burgdorferi. Neurological manifestations are found in 10%-50% of cases. We present 2 cases followed for 5 and 6 years of chronic relapsing-remitting neuroborreliosis."	
8.	**Kufko IT; Mel'nikov VG; Andreeva EA; Sokolova ZI; Lesniak OM; Beikin IaB.**	1999	**Comparative study of results of serological diagnosis of Lyme borreliosis by indirect immunofluorescence and immunoenzyme analysis.**	Klin Lab Diagn, 3:34-7
			"Patients with persistent levels of antibodies to B. burgdorferi, even without clinical signs of infection, are in need of regular check-ups, because the prognostic significance of antibodies to B. burgdorferi is unknown and relapses may occur after months and years."	
9.	**Straubinger RK; Straubinger AF; Summers BA; Jacobson RH; Erb HN.**	1998	**Clinical manifestations, pathogenesis, and effect of antibiotic treatment on Lyme borreliosis in dogs.**	Wien Klin Wochenschr, 110(24):874-81
			[Abstract:] "In three separate experiments, B. burgdorferi-infected dogs received antibiotic treatment (amoxicillin; azithromycin; ceftriaxone; doxycycline) for 30 consecutive days. ...Antibiotic treatment prevented or resolved episodes of acute arthritis, but failed to eliminate the bacterium from infected dogs. ... CONCLUSIONS: B. burgdorferi disseminates through tissue by migration following tick inoculation, produces episodes of acute arthritis, and establishes persistent infection. The spirochete survives antibiotic treatment and disease can be reactivated in immunosuppressed animals."	
10.	**Treib J; Fernandez A; Haass A; Grauer MT; Holzer G; Woessner R.**	1998	**Clinical and serologic follow-up in patients with neuroborreliosis.**	Neurology, Nov;51(5):1489-91
			[Abstract:] "The authors performed a clinical and serologic follow-up study after 4.2 +/- 1.2 years in 44 patients with clinical signs of neuroborreliosis and specific intrathecal antibody production. All patients had been treated with ceftriaxone 2 g/day for 10 days. Although neurologic deficits decreased significantly, more than half the patients had unspecific complaints resembling a chronic fatigue syndrome and showed persisting positive immunoglobulin M serum titers for Borrelia in the Western blot analysis."	
11.	**Hudson BJ; Stewart M; Lennox VA; Fukunaga M; Yabuki M; et al.**	1998	**Culture-positive Lyme borreliosis.**	Med J Aust, May 18;168(10):500-2
			"We report a case of Lyme borreliosis. Culture of skin biopsy was positive for Borrelia garinii, despite repeated prior treatment with antibiotics."	
12.	**Meier P; Blatz R; Gau M; Spencker FB; Wiedemann P.**	1998	**Pars plana vitrectomy in Borrelia burgdorferi endophthalmitis.**	Klin Monatsbl Augenheilkd, 213(6):351-4
			"Despite of [sic] intravenous application of ceftriaxon for 14 days panuveitis persisted, and endophthalmitis developed when antibiotic therapy was finished....Despite of a second intravenous ceftriaxon treatment for 14 days we observed a retinal vasculitis in the follow up of 6 months. CONCLUSIONS: Despite intravenous ceftriaxon-therapy borrelia burgdorferi must have survived in the vitreous body."	

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13.	**Priem S; Burmester GR; Kamradt T; Wolbart K; Rittig MG; Krause A.**	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.**	Annals of the Rheumatic Diseases, 57(2):118-21
			[Persistence:] "Paired SF [synovial fluid] and SM [synovial membrane] specimens and urine samples from four patients with ongoing or recurring Lyme arthritis despite previous antibiotic therapy were investigated. RESULTS: In all four cases, PCR with either primer set was negative in SF and urine, but was positive with at least one primer pair in the SM specimens." *[Diagnosis:] "CONCLUSIONS: These data suggest that in patients with treatment resistant Lyme arthritis negative PCR results in SF after antibiotic therapy do not rule out the intraarticular persistence of B burgdorferi DNA. Therefore, in these patients both SF and SM should be analysed for borrelial DNA by PCR as positive results in SM are strongly suggestive of ongoing infection."*	
14.	**Petrovic M; Vogelaers D; Van Renterghern L; Carton D; et al.**	1998	**Lyme borreliosis – A review of the late stages and treatment of four cases.**	Acta Clinica Belgica, 53(3):178-83.
			A five-week treatment with doxycycline at a dose of 200 mg daily was prescribed. Fatigue, arthralgia en myalgia seemed to respond positively to the initiated therapy. However, they reappeared two weeks after cessation of doxycycline. ...it was decided to treat with ceftriaxone IM 2 g daily for three weeks. This resulted in a complete resolution of the general symptoms. However, three weeks later arthralgia of the knees and myalgia in both legs recurred. ... Symptoms and signs may improve only temporarily shortly after treatment, but re-emerge within weeks or months.	
15.	**Straubinger RK; Summers BA; Chang YF; Appel MJ.**	1997	**Persistence of Borrelia burgdorferi in experimentally infected dogs after antibiotic treatment.**	Journal of Clinical Microbiology, 35(1):111-6
			[From the abstract:] "In specific-pathogen-free dogs experimentally infected with Borrelia burgdorferi by tick exposure, treatment with high doses of amoxicillin or doxycycline for 30 days diminished but failed to eliminate persistent infection. Although joint disease was prevented or cured in five of five amoxicillin- and five of six doxycycline-treated dogs, skin punch biopsies and multiple tissues from necropsy samples remained PCR positive and B. burgdorferi was isolated from one amoxicillin- and two doxycycline-treated dogs following antibiotic treatment. ...[In] dogs that were kept in isolation for 6 months after antibiotic treatment was discontinued, antibody levels began to rise again, presumably in response to proliferation of the surviving pool of spirochetes."	
16.	**Straubinger RK; Straubinger AF; Jacobson RH; Chang Y; Summer BA; Hollis N; Appel M.**	1997	**Two lessons from the canine model of Lyme Disease: migration of Borrelia burgdorferi in tissues and persistence after antibiotic treatment.**	Journal of Spirochetal & Tick-borne Diseases, Vol. 4, No. 1/2
			[Persistence:] "In two studies, antibiotic treatment with amoxicillin or doxycycline for 30 days failed to eliminate persistent infection in 11 dogs. Immediately after treatment, borreliae could not be demonstrated, antibody levels declined, and joint lesions were prevented or cured. Live spirochetes, however, persisted in the tissue of at least three dogs as B. burgdorferi DNA was detected in all 11 treated dogs for up to 6 months after treatment, at which time antibody levels again began to rise." *[Diagnostic issues:] "In the dog model, we detected B. burgdorferi reliably in skin but infrequently in blood by culture and polymerase chain reaction (PCR). We found the organism in the synovium of joints but not in synovial fluids, and in meninges but not in cerebrospinal fluid."*	
17.	**Branigan P; Rao J; Rao J; Gerard H; Hudson A; Williams W; Arayssi T; Pando J; Bayer M; Rothfuss S; Clayburne G; Sieck M; Schumacher HR.**	1997	**PCR evidence for Borrelia burgdorferi DNA in synovium in absence of positive serology.**	American College of Rheumatology, Vol 40(9) Suppl, Sept, p.S270
			"PCR evidence for Borrelia has been identified in synovial biopsies of patients with clinical pictures that had not initially suggested Lyme disease. All [6 PCR-positive] patients were negative for antibodies to Borrelia and some were PCR positive in synovium despite previous treatment with antibiotics."	
18.	**Weber K.**	1996	**Treatment failure in erythema migrans: a review.**	Infection, 24:73-5.
			[From the abstract:] "Patients with erythema migrans can fail to respond to antibiotic therapy. Persistent or recurrent erythema migrans, major sequelae such as meningitis and arthritis, survival of Borrelia burgdorferi and significant and persistent increase of antibody titres against B. burgdorferi after antibiotic therapy are strong indications of a treatment failure. Most, if not all, antibiotics used so far have been associated with a treatment failure in patients with erythema migrans."	

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19.	**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.**	Human Pathology, Vol 27(10):1025-34
			[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 intracellulary and extracellulary 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)*	
20.	**Mursic VP; Wanner G; Reinhardt S; Wilske B; Busch U; Marget W.**	1996	**Formation and cultivation of Borrelia burgdorferi spheroplast L-form variants.**	Infection, 24(3):218-26
			[Persistence:] "...clinical persistence of Borrelia burgdorferi in patients with active Lyme borreliosis occurs despite obviously adequate antibiotic therapy..." "The persistence of Bb even after therapy with antibiotics has been demonstrated in cerebrospinal fluid (CSF), in skin, iris,heart and joint biopsies." *[Cysts:] In vitro investigation of morphological variants of B. burdorferi, in an effort to explain the clinical persistence of active Lyme borreliosis despite antibiotic therapy. The authors suggest that these atypical forms may allow Borrelia to survive antibiotic treatment.*	
21.	**Luft BJ; Dattwyler RJ; Johnson RC; Luger SW; Bosler EM; Rahn Rahn DW; et al.**	1996	**Azithromycin compared with amoxicillin in the treatment of erythema migrans. A double-blind, randomized, controlled trial.**	Annals of Internal Medicine, 124(9):785-91
			"Fifty-seven percent of patients who had relapse were seronegative at the time of relapse."	
22.	**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 No.5
			The urine of 74.2% of patients previously treated with antibiotics for Lyme disease was found to be positive for B. burgdorferi DNA using PCR testing. All patients (n=97) had prior documented EM rash and had received a minimum of 3 weeks to 2 months oral or intravenous antibiotics. In 4 patients, PCR results were temporarily negative after treatment, but became positive again 4-6 weeks later. All patients suffered "continuing, often gradually worsening Lyme disease-like symptoms. ...it seems to be characteristic for most of the patients in our study that, after antibiotic-free periods of a few months, they had again become increasingly ill with neurological and arthritic symptoms, so that treatment had been resumed."	
23.	**Aberer E; Kersten A; Klade H; Poitschek C; Jurecka W.**	1996	**Heterogeneity of Borrelia burgdorferi in the skin.**	American Journal of Dermatopathology, 18(6):571-9
			"Neuralgias arising 6 months after ECM in spite of antibiotic therapy were evident in a seronegative patient who showed perineural rod-like borrelia structures."	
24.	**Oksi J; Kalimo H; Marttila RJ; Marjamaki M; Sonninen P; et al.**	1996	**Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of literature.**	Brain, Dec;119 (Pt 6):2143-54.
			"In one of the six analysed brain tissue specimens [from a patient who had received more than six months of antibiotic treatment prior to death, including two 3-week courses of IV ceftriaxone], B. burgdorferi DNA was detected by PCR."	
25.	**Valesova H; Mailer J; Havlik J; Hulinska D; Hercogova J.**	1996	**Long-term results in patients with Lyme arthritis following treatment with ceftriaxone.**	Infection, 24(1):98-102
			"Long term clinical results in 26 patients at 36 months were complete response or marked improvement in 19, relapse in six and new manifestations in four of the cases, respectively."	
26.	**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(1):9-16
			[Persistence:] "...the persistence of B. burgdorferi s.l. and clinical recurrences in patients despite seemingly adequate antibiotic treatment is described." ... *[Diagnosis:] "The patients had clinical disease with or without diagnostic antibody titers to B. burgdorferi."*	

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27.	**Lawrence C; Lipton RB; Lowy FD; Coyle PK.**	1995	**Seronegative chronic relapsing neuroborreliosis.**	European Neurology, 35(2):113-7

[From the abstract:] This article reports a Lyme disease patient "who experienced repeated neurologic relapses despite aggressive antibiotic therapy." The patient was seronegative. "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."

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

[From the 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 [Lyme disease] must be considered even in cases with purely psychiatric presentation, and prolonged antibiotic therapy may be necessary."

29.	**Steere AC.**	1995	**Musculoskeletal manifestations of Lyme disease.**	American Journal of Medicine, 88:4A-44S-51S.

"...a 1-month course of oral antibiotics may not always eradicate viable spirochetes."

30.	**Vartiovaara I.**	1995	**Living with Lyme.**	Lancet, 345:842-4

A Finnish physician's account of his experiences that beginning with a tick bite in Vancouver in 1987. Dr. Vartiovaara resigned from his position with the Finnish Medical Journal in 1992, due to disabilities caused by Lyme disease.

[Persistence:] "After that [a positive result on a T-cell proliferation test at Stony Brook Hospital] I had two months' heavy treatment with oral doxycycline 300mg a day. I was a little better after it, but only for about two months. Then it started all over again, and got worse. ...We sent blood and spinal fluid to Dr. Oksi and they turned out to be positive [by PCR]--in other words, the spirochaete was still alive in my body after six years, despite the antibiotics." Dr. Vartiovaara was then treated aggressively with a combination of antibiotics, including four weeks of ceftriaxone, for six months. Some time after the cessation of treatment however, he found that "My symptoms are on the move again."

[Diagnosis:] "What should be done when a patient has the typical Lyme disease history but negative serology? This is still a hot question especially in the USA. My strong opinion is that oral antibiotics should be given in such cases. Ordinary laboratory tests cannot be relied upon and the PCR is too expensive for routine use. When the whole picture leans towards Lyme borreliosis it is both ethically and medically right to treat." (p.844)

31.	**Ferris J; Lopez-Andreu JA; Salcede-Vivo J; Sala-Lizarraga JA.**	1995	**Lyme borrelioiosis. [Letter]**	Lancet, Vol 345: 1436-37

"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."

	Author	Year	Title	Journal
32.	**Wahlberg P; Granlund H; Nyman D; Panelius J; Seppala I.**	1994	**Treatment of late Lyme borreliosis.**	Journal of Infection, 3:255-61
	[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 intraveous ceftriaxone and continuing with amoxycillin plus probenecid or with cephadroxil were useful in the treatment of late Lyme borreliosis." (pp. 260-1)*			
33.	**Malawista SE; Barthold SW; Persing DH.**	1994	**Fate of Borrelia burgdorferi DNA in tissues of infected mice after antibiotic treatment.**	Journal of Infectious Diseases, 170:1312-1316
	The mice receiving antibiotic treatment in this study were given ceftriaxone. *[Persistence:] 2 out of 5 mice tested 60 days after treatment were found to be positive on culture; 1 of these mice was also positive by PCR. The authors speculate that this could be due to: (a) reinfection (which they consider "highly unlikely"), (b) contamination, or (c) the "resurgence of spirochetes in animals not completely sterilized by antibiotics. This last possibility will bear further scrutiny because late recurrences of Lyme disease without obvious reinfection may occur in humans."* *[Diagnosis:] Positive PCR results were found to suggest active infection. "Unless some patients with Lyme disease have a defect in their ability to degrade spirochetal DNA, these results suggest that persisting PCR positivity indicates persisting infection."*			
34.	**Bradley JF; Johnson RC; Goodman JL.**	1994	**The persistence of spirochetal nucleic acids in active Lyme arthritis.**	Annals of Internal Medicine, 120(6):487-9
	"Our results show the intra-articular persistence of B. burgdorferi nucleic acids in Lyme arthritis and suggest that persistent organisms and their components are important in maintaining ongoing immune and inflammatory processes even among some antibiotic-treated patients. Further studies are needed to determine the microbiologic state of these organisms and their therapeutic and prognostic implications." (p.489)			
35.	**Asch ES; Bujak DI; Weiss M; Peterson MG; Weinstein A.**	1994	**Lyme disease: an infectious and postinfectious syndrome.**	Journal of Rheumatology, 3:454-61
	[From the abstract:] "Patients were seen at a mean of 3.2 years after initial treatment. A history of relapse with major organ involvement had occurred in 28% and a history of reinfection in 18%. Anti-Borrelia antibodies, initially present in all patients, were still positive in 32%. At followup, 82 (38%) patients were asymptomatic and clinically active Lyme disease was found in 19 (9%). Persistent symptoms of arthralgia, arthritis, cardiac or neurologic involvement with or without fatigue were present in 114 (53%) patients." *[From the article:] "...18 patients (8%) received intravenous antibiotics (penicillin in 14 and ceftriaxone in 4) as initial therapy and 6 (33%) of these patients relapsed. ...Subsequent courses of antibiotic therapy were used in 51 (24%) patients. Many received repeated courses of antibiotic therapy for disease relapse and had full or partial response to this treatment."*			
36.	**Shadick NA; Phillips CB; Logigian EL; Steere AC; Kaplan RF; Berardi AB; 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.**	Annals of Internal Medicine, 121(8): 560-7.
	"*Ten of the 38 patients with Lyme disease reported relapses within 1 year of treatment... and had had repeated antibiotic treatment (5 patients with intravenous ceftriaxone). ...Patient 4, in addition, had had second degree atrioventricular block with acute Lyme disease that resolved with penicillin treatment. Her irregular rhythm recurred 2 years later, resolved temporarily with ceftriaxone treatment, but progressed to complete heart block requiring a pacemaker. ...Patient 12... was treated with 2 weeks of parenteral penicillin. She later developed a progressive speech disorder, bradykinesia, and abnormal ocular motor function. Magnetic resonance imaging of the brain showed scattered white matter lesions in the hemispheres and pons... she was re-treated with 2 weeks of parenteral ceftriaxone in 1989 that had no effect on her neurologic symptoms. During the time of observation, this patient died. At autopsy... [using] Dieterle silver stain, a spirochete was present in the cortex and another was exterior to a leptomeningeal vessel."*			
37.	**Lopez-Andreu JA; Ferris J; Canosa CA; Sala-Lizarraga JA.**	1994	**Treatment of late Lyme disease: a challenge to accept.**	Journal of Clinical Microbiology, 32:1415-16.
	"[The patient] received 2 g of ceftriaxone daily for 4 weeks. Marked early clinical improvement was observed and continued for 3 weeks after therapy was discontinued. He received 6 additional courses of intravenous antibiotics for 3 to 5 weeks' duration (penicillin, doxycycline [two courses], and ceftriaxone [three courses]), and 1 oral antibiotic (azithromycin). His general condition improved, but each antibiotic course was followed by a relapse."			

	Author	Year	Title	Journal
38.	**Preac-Mursic V; Pfister HW; Spiegel H; Burk R; Wilske B; ReinhardtS; BohmerR.**	1993	**First isolation of Borrelia burgdorferi from an iris biopsy.**	Journal of Clinical Neuroophthalmology, Sep;13(3):155-61; discussion 162
			"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."	
39.	**Klempner MS; Noring R; Rogers RA.**	1993	**Invasion of human skin fibroblasts by the Lyme disease spirochetes, Borrelia burgdorferi.**	Journal of Infectious Diseases, 167:1074-1081
			This study found that B. burgdorferi spirochetes can survive antibiotic treatment through intracellular sequestion within fibroblasts. "In these experiments, we demonstrated that fibroblasts and keratinocytes were able to protect B. burgdorferi from the action of this B-lactam antibiotic [ceftriaxone] even at antibiotic concentrations > or = 10 times the MBC of the antibiotic. The protective effect was sustained for < or = 14 days and required viable fibroblast monolayers... We have demonstrated the presence of intracellular B. burgdorferi within HF [human fibroblasts] using laser scanning confocal microscopy... The observation of viable spirochetes within fibroblasts coupled to protection of B. burgdorferi from extracellular microbicidal antibiotics by fibroblasts [19] suggests that B. burgdorferi may be among the small number of bacteria that can cause chronic infection by localizing within host cells where they remain sequestered from some antimicrobial agents and the host humoral immune response."	
40.	**Haupl T; Hahn G; Rittig M; Krause A; Schoerner C; Schonherr U; Kalden JR; Burmester GR.**	1993	**Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis.**	Arthritis & Rheumatism, 36(11):1621-6
			[Persistence:] "Repeated antibiotic treatment [6 weeks oral doxycycline, 2 weeks intravenous ceftriaxone, 2 weeks combination of oral roxithromycin/sulfamethoxazole/trimethoprim] was necessary to stop the progression of disease, but obviously did not completely eliminate B burgdorferi from all sites of infection. This was confirmed by the culture of viable B burgdorferi from a ligament sample obtained surgically. [The cultured bacteria were identified as B. burgdorferi by reactions with specific immune sera and monoclonal antibodies, and by polymerase chain reaction amplification and Southern blot hybridization techniques.] *...These data indicate that vital B burgdorferi persisted (a) despite several courses of antibiotic therapy, (b) even when clinical symptoms subsided, and (c) even when no humoral immune response was detectable by ELISA or by IF." (p. 1625)* *[Treatment:] "The hypothesis of evasion [to explain the survival of Bb] supports the use of more aggressive therapy as described in recent reports (19), in which 3-4 weeks of intravenous antibiotics was suggested as first-line treatment when systemic manifestations develop, such as the choroiditis in our patient." (p.1626)* *[Intracellular:] "Electron microscopy of the ligament revealed spirochetes situated between collagen fibers or associated with fibroblasts, deeply invaginating these cells." (p.1625)* *[Diagnosis:] [From the abstract:] "The initially significant immune system activation was followed by a loss of the specific humoral immune response and a decrease in the cellular immune response to B burgdorferi over the course of the disease." [From the article:] "Interestingly, the cellular immune responses were also directed against the surface protein OspA during each recurrence of clinical symptoms, even though anti-OspA antibodies were not detectable by immunoblot." (p.1625)*	
41.	**Chancellor MB; McGinnis DE; Shenot PJ; Kiilholma P; Hirsch IH.**	1993	**Urinary dysfunction in Lyme disease.**	Journal of Urology, Jan;149(1):26-30
			[From the abstract:] "Neurological and urological symptoms in all patients were slow to resolve and convalescence was protracted. Relapses of active Lyme disease and residual neurological deficits were common."	

	Author	*Year*	*Title*	*Journal*
42.	**Reik L Jr.**	1993	**Stroke due to Lyme disease.**	Neurology, 43(12):2705-7
	[From the abstract:] "A 56-year-old Connecticut woman suffered multiple strokes 18 months after antibiotic treatment for early Lyme disease with facial palsy. Pleocytosis, intrathecal synthesis of anti-Borrelia burgdorferi antibody, and the response to antibiotic treatment substantiated the diagnosis of neuroborreliosis."			
43.	**Battafarano DF; Combs JA; Enzenauer RJ; Fitzpatrick JE.**	1993	**Chronic septic arthritis caused by Borrelia burgdorferi.**	Clinical Orthop, 297:238-41
	"A patient had chronic septic Lyme arthritis of the knee for seven years despite multiple antibiotic trials and multiple arthroscopic and open synovectomies. Spirochetes were documented in synovium and synovial fluid (SF). Polymerase chain reaction (PCR) analysis of the SF was consistent with Borrelia infection."			
44.	**Liu AN.**	1993	**Lyme disease in China and its ocular manifestations.**	Chung Hua Yen Ko Tsa Chih, 5:271-3
	"Early cases may be cured by oral antibiotics while intravenous drip of large dosage is needed for advanced cases, with a relapsing rate of 16%."			
45.	**Georgilis K; Peacocke M; Klempner MS.**	1992	**Fibroblasts protect the Lyme disease spirochete, Borrelia burgdorferi, from ceftriaxone in vitro.**	Journal of Infectious Diseases, 166(2):440-4
	[From the abstract:] "The Lyme disease spirochete, Borrelia burgdorferi, can be recovered long after initial infection, even from antibiotic-treated patients, indicating that it resists eradication by host defense mechanisms and antibiotics. *...Human foreskin fibroblasts protected B. burgdorferi from the lethal action of a 2-day exposure to ceftriaxone at 1 microgram/mL, 10-20 x MBC. In the absence of fibroblasts, the organisms did not survive. ...Fibroblasts protected B. burgdorferi for at least 14 days of exposure to ceftriaxone. Mouse keratinocytes, HEp-2 cells, and Vero cells but not Caco-2 cells showed the same protective effect. Thus, several eukaryotic cell types provide the Lyme disease spirochete with a protective environment contributing to its long-term survival."* *[From the article:] "An intracellular site of survival would provide protection, since many of the antibiotics are much less concentrated in the cells than in extracellular spaces. ...Possibly fibroblasts and keratinocytes are the initial sites of this intracellular survival. This is especially relevant in that the first contact between the spirochete and the host in Lyme disease occurs in the skin." (p.443)*		
46.	**Cooke WD; Dattwyler RJ.**	1992	**Complications of Lyme borreliosis.**	Annual Review of Medicine, 43:93-103
	"The diversity of the symptoms [of Lyme arthritis], from a mild self-limited illness to a severe chronic arthritis that persists despite antibiotic treatment, suggests that host factors are important in the pathogenesis."			
47.	**Feder HM Jr; Gerber MA; Luger SW; Ryan RW.**	1992	**Persistence of serum antibodies to Borrelia burgdorferi in patients treated for Lyme disease.**	Clinical Infectious Diseases, Nov;15(5):788-93
	[From the abstract:] "...we recalled 32 patients with Lyme disease from a primary care practice a mean of 16 months after treatment... Nine of the 32 patients had persistent or recurrent symptoms, and ELISA and immunoblot were not helpful for identifying these nine patients."			

	Author	Year	Title	Journal
48.	**Dinerman H; Steere AC.**	1992	**Lyme disease associated with fibromyalgia.**	Annals of Internal Medicine, 117:281-5

15 patients with Lyme disease and symptoms of fibromyalgia were followed in a long-term study. "None of the patients had had fibromyalgia before the onset of Lyme disease." All patients received antibiotic therapy, in most cases 2 g/d intravenous ceftriaxone for 2 to 4 weeks.

[Persistence:] "Case Report: [After 2 weeks ceftriaxone] The knee swelling gradually resolved over the next 3 months, but he [the patient] began to have symptoms of fibromyalgia including marked fatigue and more diffuse pain and stiffness in the wrists, elbows, shoulders, and knees. Because his symptoms persisted, he was given a second 2-week course of ceftriaxone 1 year later. Although his symptoms improved somewhat with treatment, his fatigue and joint pain worsened again within several months, and he also experienced intermittent headache, memory difficulties, and irritability... Because of the slight spinal fluid pleocytosis and because he had already received two courses of ceftriaxone, he was treated with imipenim, 250 mg, every 8 hours for 30 days. His symptoms again improved for several months, but then worsened. During the subsequent year, in addition to his previous symptoms, he developed radicular pain along the chest wall, numbness and sensitivity on the right side of the face, and numbness in the left hand and foot."

[Diagnosis:] "None of the patients had an elevated erythrocyte sedimentation rate."

[Seronegativity:] "The small percentage of patients who are seronegative by enzyme-linked immunosorbent assay (ELISA) later in the illness usually have positive Western blots or cellular immune responses to borrelial antigens (9,10)."

49.	**Pfister HW; Preac-Mursic V; Wilske B; Schielke E; Sorgel F; Einhaupl KM.**	1991	**Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis.**	Journal of Infectious Diseases, Feb;163(2):311-8

33 patients with Lyme neuroborreliosis were treated for 10 days with either IV ceftriaxone or IV cefotaxime. Follow-up examinations were conducted after a mean of 8.1 months.10 of 27 patients examined were symptomatic at follow-up and borreliae persisted in the CSF of one patient. The authors conclude that "a prolongation of therapy may be necessary."

50.	**Agger W; Case KL; Bryant GL; Callister SM.**	1991	**Lyme disease: clinical features, classification, and epidemiology in the upper midwest.**	Medicine (Baltimore) Mar;70(2):83-90

"Despite longer and more frequent parenteral therapy, late Lyme disease frequently required retreatment, owing to poor clinical response (p less than .05)."

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

"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."

52.	**Logigian EL; Kaplan RF; Steere AC.**	1990	**Chronic neurologic manifestations of Lyme disease.**	New England Journal of Medicine, Nov 22; 323(21):1438-44

[From the abstract:] "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."

[From the article:] "Discussion.....These chronic neurologic abnormalities began months to years after the onset of infection, sometimes after long periods of latency, as in neurosyphilis....The typical response of our patients to antibiotic therapy supports the role of spirochetal infection in the pathogenesis of each of the syndromes described here.....The likely reason for relapse is failure to eradicate the spirochete.....This is reminiscent of far advanced neurosyphilis..... This last article is one of many studies that show continuing symptoms are most likely due to persistence of the spirochete."

	Author	*Year*	*Title*	*Journal*
53.	**Sigal LH.**	1990	**Summary of the first 100 patients seen at a Lyme disease referral center.**	American Journal of Medicine, 88:577-581
			[Relapse:] "Nine patients were seen who had a preceding history of Lyme disease and previous successful therapy, but the nonspecific symptoms had returned."	
54.	**Nadelman RB; Pavia CS; Magnarelli LA; Wormser GP.**	1990	**Isolation of Borrelia burgdorferi from the blood of seven patients with Lyme disease.**	American Journal of Medicine, 88:21-26
			[Persistent Symptoms:] "Five of seven patients remained symptomatic at a median of four months after treatment..."	
55.	**Schoen RT.**	1989	**Treatment of Lyme disease.**	Connecticut Medicine, Vol 53(6):335-337
			[Treatment/Relapse:] "As in other spirochetal infections, antibiotic therapy is most effective early in the illness. ... TREATMENT PROBLEMS...Late Disease: Not all patients with neurologic manifestations or with arthritis respond to oral or intravenous antibiotic therapy (19), and in many of these individuals, retreatment may be necessary. Retreatment is also appropriate in individuals who relapse, for example, with recurrent arthritis. ...Late in the illness, cases refractory to antibiotic therapy may be encountered."	
56.	**Dieterle L; Kubina FG; Staudacher T; Budingen HJ.**	1989	**Neuro-borreliosis or intervertebral disk prolapse?**	Dtsch Med Wochenschr, 114(42):1602-6.
			"Despite antibiotic treatment (usually 10 mega U penicillin three times daily) six patients had a recurrence by April, 1989, treated with penicillin again or with twice daily 100 mg doxycycline or 2 g ceftriaxon."	
57.	**Preac-Mursic V; Weber K; Pfister HW; Wilske B; et al.**	1989	**Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis.**	Infection, 17(6):355-9
			[From the abstract:] "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." *[Persistence:] "However, some patients later developed symptoms of the disease despite antibiotic treatment (9-11). Because of these observations it has become questionable if a definite eradication of B. burgdorferi with antibiotics is possible." (p.357) ..."The central nervous system invasion by spirochetes and a persistence of Treponema pallidum after penicillin G therapy is common in neurosyphilis (22,23)." (p.358)* *[Treatment:] "In view of the hitherto failure of treatment, low CSF concentration of penicillin G, survival of B. burgdorferi in patients treated with antibiotics, the moderate penicillin G susceptibility of the organism and unpredictable progression of the disease, it seems appropriate to treat patients with substantially larger doses of antibiotics and/or longer than is provided in present treatment regimens." (p.358)* *[Seronegativity:] "As shown, negative antibody-titers do not provide evidence for successful therapy; antibody-titers may become negative despite persistence of B. burgdoferi." (p.358)*	
58.	**Kohler J; Schneider H; Vogt A.**	1989	**High-dose intravenous penicillin G does not prevent further progression in early neurological manifestation of Lyme borreliosis.**	Infection, 17(4):216-7.
			[From the abstract:] "We report two cases of Lyme borreliosis (LB) with erythema migrans (EM) and simultaneous meningopolyneuritis... EM and pain disappeared completely under high-dose penicillin G therapy within few a days. Pathological findings in CSF improved. Nevertheless, during and after therapy, neurological signs of LB developed: cranial nerve palsies as well as paresis of extremity muscles with radicular distribution."	

	Author	*Year*	*Title*	*Journal*
59.	**Steere AC; Duray PH; Butcher EC.**	1988	**Spirochetal antigens and lymphoid cell surface markers in Lyme synovium and tonsillar lymphoid tissue.**	Arthritis & Rheumatism, 31:487-495

[Persistence:] "Synovial tissue was obtained from 12 patients with Lyme disease who underwent arthroscopic synovectomy between 1984 and 1986. ...All patients had received antibiotic therapy and nonsteroidal antiinflammatory drugs (NSAIDs) prior to arthroscopic synovectomy. (p.488) ..."Using monoclonal antibodies to the 31- or 41-kd polypeptides of B burgdorferi, a few spirochetes and globular antigen deposits were seen in and around normal or injured blood vessels in areas of lymphocytic infiltration, in 6 of the 12 patients (Figure 4)." (p.492)

"Similarly [as in tertiary syphilis or tuberculoid leprosy], the antigenic stimulus in Lyme arthritis would appear to be a small number of live spirochetes, demonstrated here by monoclonal antibodies, which may persist in the synovial lesion for years." (p.494)

60.	**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.**	New England Journal of Medicine, 319(22):1441-6

[From the abstract:] "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."

61.	**Schmidli J; Hunziker T; Moesli P; et al.**	1988	**Cultivation of Borrelia burgdorferi from joint fluid three months after treatment of facial palsy due to Lyme borreliosis.**	Journal of Infectious Diseases, 158:905-906

"Despite clinical resolution of paralysis, subsequent arthritic complication occurred. To our knowledge, this is the first report of the successful isolation of B. burgdorferi from synovial fluid and the subsequent propagation through serial passage. This positive culture strongly suggests that the spirochetes were not eradicated by the initial antimicrobial regimens [12 days amoxicillin-clavulanate followed by two weeks of doxycycline, 200 mg/d]. ...Other possible explanations of treatment failure, such as insufficient patient compliance or reinfection by B. burgdorferi, were excluded by close medical and parental supervision." The patient was subsequently treated with 14 days intravenous ceftriaxone. Her arthritic symptoms resolved, and she remained symptom-free during an 11-month follow-up period.

62.	**Berger BW.**	1988	**Treatment of erythema chronicum migrans of Lyme disease.**	Annals of the New York Academy of Sciences, 539:346-51

"Two of 80 patients with a minor form of the illness and 17 of 81 patients with a major form of the illness required retreatment."

63.	**Weber K; Bratzke HJ; Neubert U; Wilske B; Duray PH.**	1988	**Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy.**	Pediatric Infectious Disease Journal, 7:286-9

"We now demonstrate B. burgdorferi in the brain and liver of a newborn whose mother had been treated with oral penicillin for LB [Lyme borreliosis] during the first trimester of pregnancy. ...The death of the newborn was probably due to a respiratory failure as a consequence of perinatal brain damage."

64.	**Dattwyler RJ; Halperin JJ.**	1987	**Failure of tetracycline therapy in early Lyme disease.**	Arthritis & Rheumatism, 30:448-450

"We describe the clinical courses of 5 patients with Lyme disease who developed significant late complications, despite receiving tetracycline early in the course of their illness. All 5 patients had been treated for erythema chronicum migrans with a course of tetracycline that met or exceeded current recommendations.

65.	**Berger BW.**	1986	**Treating erythema chronicum migrans of Lyme disease.**	Journal of Am Acad Dermatology, Sep;15(3):459-63

"Fourteen of sixty-one patients with a major form of the illness required retreatment, and five developed posttreatment late manifestations of Lyme disease consisting of Bell's palsy and persistent joint pain."

	Author	*Year*	*Title*	*Journal*
66.	**Steere AC; Hutchinson GJ; Rahn DW; Sigal LH; Craft JE; DeSanna ET; Malawista SE.**	1983	**Treatment of the early manifestations of Lyme disease.**	Annals of Internal Medicine, Jul;99(1):22-6
	[From the abstract:] "However, with all three antibiotic agents nearly half of the patients had minor late symptoms such as headache, musculoskeletal pain, and lethargy. These complications correlated significantly with the initial severity of illness."			
67.	**Steere AC; Malawista SE; Hardin JA; Ruddy S; Askenase PW; Andiman WA.**	1977	**Erythema chronicum migrans and Lyme arthritis. The enlarging clinical spectrum.**	Annals of Internal Medicine, 86:685-698
	"We remain skeptical that antibiotic therapy helps... Eight of our patients received penicillin, erythromycin, or cephalexin before entering the study because of the skin lesion. In one of them, the lesion persisted for 2 months despite therapy, longer than in any of the other study patients, and seven of the eight patients still developed joint, neurologic, or cardiac abnormalities."			

"Particularly puzzling has been the observation that organisms are extremely difficult to find in infected tissue, using either microbiologic or morphologic techniques. However, in many instances continued infection appears to be essential for symptoms to persist, no matter how small the number of organisms, as antimicrobial therapy is generally followed by clinical improvement."

John J. Halperin, MD and Melvin P. Heyes, PhD.
Neuroactive kynurenines in Lyme borreliosis.
Neurology, (42):43-50. 1992.