

Lyme Disease: Standards of Care

For Disseminated Lyme, 43% treat > 3 months

For Chronic Lyme, 57% treat > 3 months

Ziska MH, Donta ST, Demarest FC. Physician preferences in the diagnosis and treatment of Lyme disease in the United States. *Infection* 1996 Mar-Apr;24(2):182-6.

Two equally legitimate but divergent standards of care currently exist for the diagnosis and treatment of Lyme disease.

Johnson L, Stricker RB. Treatment of Lyme disease: a medicolegal assessment. *Expert Rev Anti Infect Ther.* 2004 Aug;2(4):533-57.

Opposing Lyme Disease Treatment Guidelines

ILADS Guidelines VS. IDSA Guidelines

“Both guidelines are evidence-based and peer reviewed, with the IDSA generally recommending standardized short-term treatment, and ILADS recommending individualized treatment based on the clinical course of the patient.”

Johnson L, Stricker RB. Treatment of Lyme disease: a medicolegal assessment. Expert Rev Anti Infect Ther. 2004 Aug;2(4):533-57.

In Favor of Antibiotics for Chronic Lyme

ILADS Guidelines

“Refractory Lyme disease is a devastating condition that usually affects patients with persistent symptomatology and long-term disability. Prompt and aggressive institution of antibiotic therapy may be essential to prevent refractory disease. Increasing evidence shows that antibiotics have a beneficial effect on the course of refractory Lyme disease even in cases where the patient is intolerant of antibiotics or when a previous regimen has failed. Several months of therapy are often required to produce clear evidence of improvement.”

Against Antibiotics for Chronic Lyme

IDSA Guidelines

ξ “To date, there is no convincing biologic evidence for the existence of symptomatic chronic B. burgdorferi infection among patients after receipt of recommended treatment regimens for Lyme disease. Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (6 months) subjective symptoms after administration of recommended treatment regimens for Lyme disease (E-I).”

Biologic Plausibility: Data NOT Cited by IDSA

ξ “Lyme disease lacks characteristics of other infections that justify longer treatment, such as... infections caused by an intracellular pathogen”

ξ IDSA Guidelines

ξ *Bb* is an intracellular pathogen

ξ Ma Y, Sturrock A, Weis JJ. Intracellular localization of Borrelia burgdorferi within human **ENDOTHELIAL CELLS**. Infect Immun 1991 Feb;59(2):671-8.

ξ Dorward DW, Fischer ER, Brooks DM. Invasion and cytopathic killing of human **LYMPHOCYTES** by spirochetes causing Lyme disease. Clin Infect Dis 1997 Jul;25 Suppl 1:S2-8.

ξ Montgomery RR, Nathanson MH, Malawista SE. The fate of Borrelia burgdorferi, the agent for Lyme disease, in mouse **MACROPHAGES**. Destruction, survival, recovery. J Immunol 1993 Feb 1;150(3):909-15.

ξ Girschick HJ, Huppertz HI, Russmann H, Krenn V, Karch H. Intracellular persistence of Borrelia burgdorferi in human **SYNOVIAL CELLS**. Rheumatol Int 1996;16(3):125-32.

ξ Livengood JA, Gilmore RD Jr. Invasion of human **NEURONAL** and **GLIAL CELLS** by an infectious strain of Borrelia burgdorferi. Microbes Infect. 2006 Nov-Dec;8(14-15):2832-40.

ξ Miklosy J, Kasas S, Zurn AD, McCall S, Yu S, McGeer PL. Persisting atypical and cystic forms of Borrelia burgdorferi and local inflammation in Lyme neuroborreliosis. J Neuroinflammation. 2008 Sep 25;5:40. [**NEURONAL** and **GLIAL CELLS**]

ξ **Klempner MS**, Noring R, Rogers RA. Invasion of human skin **FIBROBLASTS** by the Lyme disease spirochete, Borrelia burgdorferi. J Infect Dis 1993 May;167(5):1074-81.

Human Persistent *Bb* Infection Studies Cited by The Guidelines, but Pertinent Findings Omitted

ξ *“the detection of Osp A DNA in joint fluid indicates the presence of viable spirochetes”*

<u>Patients</u>	<u>Treatment Received</u>	<u>SF PCR Positive After Treatment</u>
<u>12</u>	<u>< 1 month PO antibiotics</u>	<u>12 out of 12 (100%)</u>
<u>19</u>	<u>30-60d PO antibiotics and/or IV up to 3 wks</u>	<u>7 out of 19 (37%)</u>
<u>10</u>	<u>“multiple courses of antibiotic therapy”</u>	<u>3 out of 10 (30%)</u>

ξ None of the above discussed in The Guidelines

ξ American patients, therefore sensu stricto

ξ Nocton J J; Dressler F; Rutledge B J; Rys P N; Persing D H; Steere A C. Detection of Borrelia burgdorferi DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis N. Engl. J. Med. 1994 Jan, 330:4, 229-34.

Human Persistent *Bb* Infection Studies Cited by The Guidelines, but Pertinent Findings Omitted

ξ 38 treated Lyme patients – Long term outcomes

ξ 26% relapsed by 1 year and required re-treatment

ξ 34% had long term morbidity despite treatment

ξ Patient #12 treated with 2 weeks IV penicillin

ξ Despite treatment, severe neurologic illness

ξ Re-treated--2 weeks IV ceftriaxone without effect

ξ She died. On autopsy, brain tissue: Spirochetes demonstrated with mononuclear inflammation

ξ None of the above discussed in The Guidelines

ξ American patients, therefore sensu stricto

ξ Shadick NA, Phillips CB, Logigian EL, Steere AC, Kaplan RF, Berardi VP, Duray PH, Larson MG, Wright EA, Ginsburg KS, Katz JN, Liang MH. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. Ann Intern Med. 1994 Oct 15;121(8):560-7.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

ξ 12 Lyme patients failed antibiotics

ξ Spirochetes in synovium: 6 of 12 patients (50%)

ξ "...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."

ξ Steere AC, Duray PH, Butcher EC. Spirochetal antigens and lymphoid cell surface markers in Lyme synovitis. Comparison with rheumatoid synovium and tonsillar lymphoid tissue. Arthritis Rheum. 1988 Apr;31(4):487-95.

ξ 67 yr old woman died – ARDS attributed to Lyme

ξ Failed 2 weeks tetracycline, 10 days IV penicillin, & a 2nd course IV penicillin, duration unspecified

ξ Autopsy: Lymph nodes – Spirochetes consistent with *Bb*

ξ Kirsch M, Ruben FL, Steere AC, Duray PH, Norden CW, Winkelstein A. Fatal adult respiratory distress syndrome in a patient with Lyme disease. JAMA 1988 May 13; 259(18): 2737-9.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

- ξ 15 yr old girl – Tick bite, Bell's palsy, Positive serologies
 - ξ Amoxicillin/clavulanic acid – 12 d, Doxycycline – 2 wks
 - ξ Two months later, arthritis of the knee
- ξ *Bb* culture synovial fluid: Positive – Bound mAb H5332
 - ξ Most likely sensu stricto based on monoclonal ab
- ξ Schmidli J, Hunziker T, Moesli P, Schaad UB. Cultivation of *Borrelia burgdorferi* from joint fluid three months after treatment of facial palsy due to Lyme borreliosis. J Infect Dis 1988 Oct; 158(4): 905-6.
- ξ 54 yr old man – 2 yrs of fevers, arthralgias, circular rashes
 - ξ Positive Lyme serologies
 - ξ After 3 wks IV penicillin, still febrile & anemic
- ξ *Bb* demonstrated in the spleen
 - ξ Cimmino MA, Azzolini A, Tobia F, Pesce CM. Spirochetes in the spleen of a patient with chronic Lyme disease. Am J Clin Pathol 1989 Jan;91(1):95-7.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

- ξ 24 year old woman – EM after camping in PA
 - ξ Years later – arthritis, needed several surgeries
 - ξ Ultimately, seropositive Lyme arthritis diagnosed
 - ξ 2 courses IV penicillin, 3 of IV ceftriaxone, & 1 of IM penicillin all resulted in “dramatic reduction” of arthritis, but relapses after discontinuation of each
 - ξ Doxycycline for 13 months, sulfasalazine for 1 year, & arthroscopic synovectomy did not help
- ξ Despite multiple antibiotic treatments, synovial tissue & synovial fluid silver stain revealed copious spirochetes; synovial fluid Lyme PCR positive
- ξ Battafarano DF, Combs JA, Enzenauer RJ, Fitzpatrick JE. Chronic septic arthritis caused by *Borrelia burgdorferi*. Clin Orthop 1993 Dec(297): 238-41.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

ξ 7 Lyme patients with neurologic & urologic findings

ξ All treated with ceftriaxone, 3 wk mean

ξ 4 of 7 patients (57%) relapsed despite treatment

ξ Relapsers re-treated with ceftriaxone for 2-3 wks

ξ Antibiotics helpful in all, but 5 of 7 patients (71%) remained symptomatic

ξ Patient #2, despite 3 weeks ceftriaxone:

Relapsed – *Bb* demonstrated in bladder biopsy, confirmed with monoclonal antibodies

ξ Chancellor MB, McGinnis DE, Shenot PJ, Kiilholma P, Hirsch IH. Urinary dysfunction in Lyme disease. J Urol. 1993 Jan;149(1):26-30.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

- ξ 58 year old woman, no history of tick bite or EM; neurologic manifestations
 - ξ Seronegative, CSF Lyme antibody negative
 - ξ CSF intermittently positive for *Bb* immune complexes, Osp A free antigen, and PCR
 - ξ 3 out of 7 LP's, (43%) were negative by CSF PCR
Patient treated anyway and improved from treatment
 - ξ 7 rounds of IV antibiotics & 3 years continuous oral
 - ξ Severe Herxheimer reactions upon re-initiation of each antibiotic therapy, followed by improvements

ξ Lawrence C, Lipton RB, Lowy FD, Coyle PK. Seronegative chronic relapsing neuroborreliosis. Eur. Neurol. 1995;35(2):113-7.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

- ξ 3 CNS Lyme patients – brain biopsy proven persistent infection after antibiotics
- ξ Patient #1
 - ξ Seronegative, CSF antibody negative, no pleocytosis
 - ξ CSF cultured positive for *Bb* sensu lato
- ξ Treated with 3 wks ceftriaxone, partial improvement
- ξ Treated with 8 months doxy, patient relapsed, Lyme PCR positive in both plasma & bone marrow
- ξ Ceftriaxone re-started, but patient died. On autopsy, brain tissue was Lyme PCR positive
- ξ Oksi J, Kalimo H, Marttila RJ, Marjamaki M, Sonninen P, Nikoskelainen J, Viljanen MK. Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of literature. Brain 1996 Dec; 119 (Pt 6): 2143-54.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

ξ Patient #2

- ξ Initially IgM seropositive, IgG seronegative, then both seronegative despite disease progression
- ξ CSF repeatedly negative for Lyme antibodies & PCR
- ξ Brain biopsy PCR positive in 3 separate samples

- ξ Failure of 7 weeks ceftriaxone & almost 9 months various, often high dose oral antibiotics
- ξ After stopping antibiotics, multiple relapses with recurrent brain lesions & a positive plasma Lyme PCR

- ξ After another 100 days ceftriaxone, all brain lesions resolved. Patient remained well. MRI and PCR negative on long term follow up.

- ξ Oksi J, Kalimo H, Marttila RJ, Marjamaki M, Sonninen P, Nikoskelainen J, Viljanen MK. Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of literature. Brain 1996 Dec; 119 (Pt 6): 2143-54.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

- ξ 48 year old woman with choroiditis 2 months after a tick bite & rash – Lyme serologies initially positive
 - ξ After 6 weeks doxycycline the choroiditis resolved
- ξ “The IgG titer rapidly decreased within a few weeks after the first antibiotic therapy, and remained negative in both the IF and ELISA evaluations, despite progression of the disease.”
- ξ 4 weeks post-antibiotics, arthritis in hands & EKG with newly inverted P-waves
 - ξ CSF – Negative for pleocytosis, protein, or Lyme antibody
- ξ Ceftriaxone for 2 weeks – Resolution of arthritis and rhythm disturbance
- ξ Haupt T, Hahn G, Rittig M, Krause A, Schoerner C, Schonherr U, Kalden JR, Burmester GR. Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. *Arthritis Rheum* 1993 Nov; 36(11): 1621-6.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

- ξ 2 months post-ceftriaxone, choroiditis returned
 - ξ Treated – Roxithromycin & TMP/SMX
 - ξ Upon starting antibiotics, severe exacerbation of hand pain
- ξ Biopsy of flexor retinaculum – “The ligament tissue was found to be heavily infiltrated by spirochetes.”
- ξ Positive culture for *B. burgdorferi sensu stricto*
 - ξ PCR positive, amplified product hybridized using Southern blot
 - ξ Both negative and positive controls were appropriately used throughout the procedure
- ξ Haupt T, Hahn G, Rittig M, Krause A, Schoerner C, Schonherr U, Kalden JR, Burmester GR. Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. *Arthritis Rheum* 1993 Nov; 36(11): 1621-6.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

ξ 165 patients, all initially met CDC case definition

ξ Antibiotics – Median duration of 16 weeks

ξ Despite antibiotics 32 of 165 (19%) relapsed

ξ 13 of 32 (41%) positive by culture, PCR, or both; 85% having received ceftriaxone as well as oral antibiotics

ξ 3 patients were culture positive

ξ All 13 patients re-treated– After at least 4 to 6 weeks IV ceftriaxone, 69% improved.

ξ One of the 3 cultures was *Bb sensu stricto*

ξ Oksi J, Marjamaki M, Nikoskelainen J, et al. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med. 1999 Jun;31(3):225-232.

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

- ξ Pre-antibiotics, 12 of 13 eventual relapsers (92%) were initially seropositive
- ξ Post-antibiotics, during relapse with PCR and/or culture confirmed persistent infection, only 6 of 12 relapsers (50%) IgG seropositive
 - ξ Persistent infection despite diminishing serologies
- ξ Immediately post-antibiotics but before clinical relapse, only 1 of 13 eventual relapsers (8%) was PCR positive
- ξ During clinical relapse, 12 of 13 patients (92%) were PCR positive
 - ξ Increased PCR over time consistent with replication
- ξ Oksi J, Marjamaki M, Nikoskelainen J, et al. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med. 1999 Jun;31(3):225-232.

Human Persistence Data NOT Cited by IDSA & New Data Published After IDSA Guidelines

Persistent *Bb* infection despite:

- ξ Single rounds of recommended antibiotic therapy;
- ξ Multiple rounds of recommended antibiotic therapy; and
- ξ Aggressive, ie, more than 3 months of antibiotic therapy
- ξ Confirmed by culture, and/or PCR & Immuno-electron microscopy
- ξ Pícha D, Moravcová L, Holecková D, Zd'árský E, Valesová M, Maresová V, Hercogová J, Vanousová D. Examination of specific DNA by PCR in patients with different forms of Lyme borreliosis. *Int J Dermatol*. 2008 Oct;47(10):1004-10.
- ξ Hulinska D, Votypka J, Valesova M. Persistence of *Borrelia garinii* and *Borrelia afzelii* in patients with Lyme arthritis. *Zentralbl Bakteriol* 1999 Jul;289(3):301-18.
- ξ Svecová D, Gavornik P. Recurrent erythema migrans as a persistent infection. *Epidemiol Mikrobiol Imunol*. 2008 Aug;57(3):97-100.
- ξ Hulinska D, Krausova M, Janovska D, Rohacova H, Hancil J, Mailer H. Electron microscopy and the polymerase chain reaction of spirochetes from the blood of patients with Lyme disease. *Cent Eur J Public Health* 1993 Dec; 1(2): 81-5.
- ξ Aberer E, Breier F, Schmidt B. Success and failure in the treatment of acrodermatitis chronica atrophicans. *Infection* 1996;24:85-7.
- ξ Maraspin V, Ruzic-Sabljić E, **Strle F**, et al. Persistence of *Borrelia burgdorferi* after treatment with antibiotics. *Alpe Adria Microbiol J* 1995;3:211-6.
- ξ Preac-Mursic V, Wilske B, Schierz G, et al. Repeated isolation of spirochete from the cerebrospinal fluid of a patient with meningoradiculitis Bannwarth. *Eur J Clin Microbiol* 1984;3:564-5.

Human Persistence Data NOT Cited by IDSA & New Data Published After IDSA Guidelines

Persistent *Bb* infection despite:

- ξ Single rounds of recommended antibiotic therapy;
- ξ Multiple rounds of recommended antibiotic therapy; and
- ξ Aggressive, ie, more than 3 months of antibiotic therapy
- ξ Confirmed by culture, and/or PCR & Immuno-electron microscopy

ξ Priem S, Burmester GR, Kamradt T, Wolbart K, Rittig MG, Krause A. Detection of *Borrelia burgdorferi* by polymerase chain reaction in synovial membrane, but not in synovial fluid from patients with persisting Lyme arthritis after antibiotic therapy. *Ann Rheum Dis.* 1998 Feb;57(2):118-21.

ξ Pfister HW, Preac-Mursic V, Wilske B, Schielke E, Sorgel F, Einhaupl KMJ. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. *Infect. Dis.* 1991 Feb;163(2):311-8.

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

ξ Hudson BJ, Stewart M, Lennox VA, Fukunaga M, Yabuki M, Macorison H, Kitchener-Smith J. Culture-positive Lyme borreliosis. *Med J Aust.* 1998 May 18;168(10):500-2.

ξ Preac Mursic V, Marget W, Busch U, Pleterski Rigler D, Hagl S. Kill kinetics of *Borrelia burgdorferi* and bacterial findings in relation to the treatment of Lyme borreliosis. *Infection.* 1996 Jan-Feb;24(1):9-16.

Early Lyme: Objective vs. Subjective

ξ 74 patients with EM

<u>Objective Findings</u>	<u>Subjective Symptoms</u>
<u>EM as Entry Criteria</u>	<u>Fatigue</u> <u>56.8%</u>
<u>No A-V Block</u>	<u>Myalgias</u> <u>43.2%</u>
<u>No Meningitis</u>	<u>Headache</u> <u>39.2%</u>
<u>No Cranial Neuritis</u>	<u>Chills</u> <u>35.1%</u>
<u>No encephalomyelitis</u>	<u>Joint pain</u> <u>35.1%</u>
<u>Joint swelling in only 10.8%</u>	<u>(without swelling)</u>

Trevejo RT, Krause PJ, Sikand VK, Schriefer ME, Ryan R, Lepore T, Porter W, Dennis DT. Evaluation of two-test serodiagnostic method for early Lyme disease in clinical practice. . J Infect Dis. 1999 Apr;179(4):931-8 .

Asymptomatic & Subjective Only

Lyme Vaccine Study –

11% of New Seroconversion by IgG 5 Band Western Blot was Asymptomatic

16% of 'Definite Lyme' had only Subjective Symptoms

ξ *Asymptomatic Lyme disease proven – So notion that Lyme disease cannot occur without objective features is untenable*

Steere AC, Sikand VK, Meurice F, Parenti DL, Fikrig E, Schoen RT, Nowakowski J, Schmid CH, Laukamp S, Buscarino C, Krause DS. Vaccination against Lyme disease with recombinant Borrelia burgdorferi outer-surface lipoprotein A with adjuvant. N Engl J Med. 1998 Jul 23;339(4):209-15.

Steere AC, Dhar A, Hernandez J, Fischer PA, Sikand VK, Schoen RT, Nowakowski J, McHugh G, Persing DH and the Lyme disease vaccine study group. Systemic symptoms without erythema migrans as the presenting picture of early Lyme disease. Am J Med. 2003 Jan;114(1):58-62.

Human Persistent *Bb* Infection, NOT Cited by The Guidelines—Objective vs. Subjective

ξ 18 late Lyme disease patients – Failed IV antibiotics, sometimes repeatedly

ξ Despite antibiotics, all patients demonstrated:

ξ Positive *Bb* PCR and/or immuno-electron microscopy

ξ Initial testing: 7 of 18 patients (39%) seronegative

ξ Repeat testing: 12 of 18 patients (67%) seronegative

ξ 9 of 18 (50%): Non-specific symptoms at any point

ξ 12 of 18 (67%): Non-specific symptoms in later stages

ξ Honegr K, Hulínská D, Beran J, Dostál V, Havlasová J, Cermáková Z. Department of Infectious diseases, University Hospital, Hradec Králové, Long term and repeated electron microscopy and PCR detection of *Borrelia burgdorferi* sensu lato after an antibiotic treatment. Cent Eur J Public Health. 2004 Mar;12(1):6-11.

Human Persistent *Bb* Infection, NOT Cited by The Guidelines—Objective vs. Subjective

ξ 8 patients--originally met CDC case definition

ξ Myalgia despite treatment in all, 75% met American College of Rheumatology criteria for fibromyalgia

ξ Treated patients: : 43%--muscle biopsy Lyme PCR positive

ξ Most had received repeated courses of oral antibiotics & 1 course of ceftriaxone

ξ All were seronegative by CDC 2-tiered evaluation.

ξ PCR methods-3 different labs, none contained previous *Bb*

ξ All 14 negative controls remained negative

ξ Underscores the need for caution in diagnosing “Not-Lyme, but fibromyalgia”

ξ Frey M, Jaulhac B, Piemont Y, Marcellin L, Boohs PM, Vautravers P, Jesel M, Kuntz JL, Monteil H, Sibilia J. Detection of *Borrelia burgdorferi* DNA in muscle of patients with chronic myalgia related to Lyme disease. Am J Med 1998 Jun;104(6):591-4.

Antibiotic Re-Treatment of Chronic Lyme Patients: Studies Demonstrating Benefits

ξ Randomized Controlled Trials

- ξ Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahn S, **Dattwyler R**, Chandler B. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30.
- ξ Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, Slavov I, Cheng J, Dobkin J, Nelson DR, Sackeim HA. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2008 Mar 25;70(13):992-1003.
- ξ Cameron D. Severity of Lyme disease with persistent symptoms. Insights from a double-blind placebo-controlled clinical trial. Minerva Med. 2008 Oct;99(5):489-96.

ξ Open Label Trials

- ξ Donta ST. Macrolide therapy of chronic Lyme disease. Med Sci Monit 2003; 9:PI136-42.
- ξ Donta ST. Tetracycline therapy for chronic Lyme disease. Clin Infect Dis 1997 Jul;25 Suppl 1:S52-6.
- ξ Clarissou J, Song A, Bernede C, Guillemot D, Dinh A, Ader F, Perronne C, Salomon J. Efficacy of a long-term antibiotic treatment in patients with a chronic Tick Associated Poly-organic Syndrome (TAPOS). Med Mal Infect. 2009 Feb;39(2):108-15.

Review of the 4 NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials

[Klempner MS](#), Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, Norton D, Levy L, Wall D, McCall J, Kosinski M, Weinstein A. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001 Jul 12;345(2):85-92.

Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahn S, [Dattwyler R](#), Chandler B. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology*. 2003 Jun 24;60(12):1923-30.

Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, Slavov I, Cheng J, Dobkin J, Nelson DR, Sackeim HA. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology*. 2008 Mar 25;70(13):992-1003.

Delong AK, Blossom B, Maloney EL, Phillips SE. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: a biostatistical review of randomized, placebo-controlled, clinical trials. *Contemp Clin Trials*. 2012 Nov;33(6):1132-42.

Review of the 4 NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials

Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, Norton D, Levy L, Wall D, McCall J, Kosinski M, Weinstein A. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001 Jul 12;345(2):85-92.

Unrealistic Design Assumptions to Assess Primary Outcomes
Trials Were Underpowered to Detect
Clinically Meaningful Treatment Effects

Inappropriate Minimum Clinically Important Difference –
To detect a treatment effect, it would have required participants to
improve to a level of health which was a full standard deviation
superior to that of the general population

DeLong AK, Blossom B, Maloney EL, Phillips SE. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: a biostatistical review of randomized, placebo-controlled, clinical trials. Contemp Clin Trials. 2012 Nov;33(6):1132-42.

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Design Assumptions to Assess 2 Primary Outcomes Were Unrealistic
Trial Was Underpowered to Detect
Clinically Meaningful Treatment Effects

Design Assumption & Analysis Appropriate for the 3rd Primary Outcome: Fatigue

Demonstrated Benefits to Fatigue After Treatment

No Evidence of Unblinding

DeLong AK, Blossom B, Maloney EL, Phillips SE. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: a biostatistical review of randomized, placebo-controlled, clinical trials. Contemp Clin Trials. 2012 Nov;33(6):1132-42.

Review of the 4 NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials

Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, Slavov I, Cheng J, Dobkin J, Nelson DR, Sackeim HA. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. 2008 Mar 25;70(13):992-1003.

Design Assumption & Analysis Appropriate for Cognitive Function
Demonstrated Benefits to Cognitive Function After Treatment
Relapse of Cognitive Dysfunction on Stopping Antibiotics

Benefits Also Demonstrated for Fatigue and Body Pain After Antibiotic Therapy

DeLong AK, Blossom B, Maloney EL, Phillips SE. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: a biostatistical review of randomized, placebo-controlled, clinical trials. Contemp Clin Trials. 2012 Nov;33(6):1132-42.

IDSA Guidelines – Proposed Recommendation

- ξ There is convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after the receipt of recommended antibiotic treatment regimens for Lyme disease.
- ξ In my opinion, there are egregious oversights in the IDSA Guidelines, in that they have not included volumes of published data which documents persistent infection after antibiotic therapy, inclusive of the IDSA Guidelines authors' own published works.



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