Lyme Disease: Standards of Care

For Disseminated Lyme, 43% treat for > 3 months
For Chronic Lyme, 57% treat for > 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.

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

- "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)."

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

"the detection of Osp A DNA in joint fluid indicates the presence of viable spirochetes"

Patients	Treatment Received	SF PCR + After Treatment
12	<1 month oral antibiotics	12 out of 12 (100%)
19	1-2 months oral antibiotics and/or IV antibiotics up to 3 weeks	7 out of 19 (37%)
10	"multiple courses of antibiotic therapy"	3 out of 10 (30%)

None of the above discussed in The Guidelines

- **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

- 38 treated Lyme patients—Long term outcomes
  - 26% relapsed by 1 year and required re-treatment
  - 34% had long term morbidity despite treatment
    - Patient #12 treated with 2 weeks IV penicillin
    - Despite treatment, severe neurologic illness
    - Re-treated--2 weeks IV ceftriaxone without effect
  - She died. On autopsy, brain tissue: Spirochetes demonstrated with mononuclear inflammation
- None of the above discussed in The Guidelines
- American patients, therefore sensu stricto
- 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

- 12 Lyme patients failed antibiotics
- Spirochetes in synovium: 6 of 12 patients (50%)
- "…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."
- **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.

- 67 yr old woman died—ARDS attributed to Lyme
  - Failed 2 weeks tetracycline, 10 days IV penicillin, & a 2nd course IV penicillin, duration unspecified
- Autopsy: Lymph nodes—Spirochetes consistent with *Bb*
- **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

- 24 year old woman—EM after camping in PA
  - Years later—arthritis, needed several surgeries
  - Ultimately, seropositive Lyme arthritis diagnosed
  - 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
  - Doxycycline for 13 months, sulfasalazine for 1 year, & arthroscopic synovectomy did not help
- Despite multiple antibiotic treatments, synovial tissue & synovial fluid silver stain revealed copious spirochetes; synovial fluid Lyme PCR positive
- 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

- 7 Lyme patients with neurologic & urologic findings
  - All treated with ceftriaxone, 3 wk mean
  - 4 of 7 patients (57%) relapsed despite treatment
  - Relapsers re-treated with ceftriaxone for 2-3 wks
  - Antibiotics helpful in all, but 5 of 7 patients (71%) remained symptomatic
- Patient #2, despite 3 weeks ceftriaxone: Relapsed—*Bb* demonstrated in bladder biopsy, confirmed with monoclonal antibodies
- 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

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

- 3 CNS Lyme patients—brain biopsy proven persistent infection after antibiotics
- Patient #1
  - Seronegative, CSF antibody negative, no pleocytosis
  - CSF cultured positive for *Bb* sensu lato
- Treated with 3 wks ceftriaxone, partial improvement
- Treated with 8 months doxy, patient relapsed, Lyme PCR positive in both plasma & bone marrow
- Ceftriaxone re-started, but patient died. On autopsy, brain tissue was Lyme PCR positive
- 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

- Patient #2
  - Initially IgM seropositive, IgG seronegative, then both seronegative despite disease progression
  - CSF repeatedly negative for Lyme antibodies & PCR
  - Brain biopsy PCR positive in 3 separate samples
- Failure of 7 weeks ceftriaxone & almost 9 months various, often high dose oral antibiotics
- After stopping antibiotics, multiple relapses with recurrent brain lesions & a positive plasma Lyme PCR
- After another 100 days ceftriaxone, all brain lesions resolved. Patient remained well. MRI and PCR negative on long term follow up.
- 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

- 165 patients, all initially met CDC case definition
  - Antibiotics—Median duration of 16 weeks
- Despite antibiotics 32 of 165 (19%) relapsed
  - 13 of 32 (41%) positive by culture, PCR, or both; 85% having received ceftriaxone as well as oral antibiotics
    - 3 patients were culture positive
  - All 13 patients re-treated– After at least 4 to 6 weeks IV ceftriaxone, 69% improved.
- One of the 3 cultures was *Bb* sensu stricto
- 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:

- **Recommended and/or long term antibiotic therapy;**

Confirmed by culture, and/or PCR & Immuno-electron microscopy

- Aberer E, Breier F, Schmidt B. Success and failure in the treatment of acrodermatitis chronica atrophicans. Infection 1996;24:85–7.
- Maraspin V, Ruzic-Sabljic E, **Strle F**, et al. Persistence of Borrelia burgdorferi after treatment with antibiotics. Alpe Adria Microbiol J 1995;3:211–6.
- 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.
- 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.
- 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.

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

Persistent *Bb* infection despite:

- **Recommended and/or long term antibiotic therapy;**

Confirmed by culture, and/or PCR & Immuno-electron microscopy

- 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.
- 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.
- 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.
- 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.
- Haupl 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 Persistence Data NOT Cited by IDSA & New Data Published After IDSA Guidelines

Persistent *Bb* infection despite:

- Recommended and/or long term antibiotic therapy;

- **Confirmed by culture, and/or PCR & Immuno-electron microscopy**

- Svecová D, Gavornik P. Reccurent erythema migrans as a persistent infection. Epidemiol Mikrobiol Imunol. 2008 Aug;57(3):97-100.
- 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.
- 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.
- 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.
- 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.

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

Randomized Controlled Trials

- Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn 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.

Open Label Trials

- Donta ST. Macrolide therapy of chronic Lyme disease. Med Sci Monit 2003; 9:PI136–42.
- Donta ST. Tetracycline therapy for chronic Lyme disease. Clin Infect Dis 1997 Jul;25 Suppl 1:S52-6.
- 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, Ahnn 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.

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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—Improvement to a level of health which was a full standard deviation superior to that of the general population to detect a treatment effect

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 Primaru 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 by subgroup analysis

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

- 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.

- 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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