

## **Scientific references by Dr Horowitz, and other authors on persistence of Lyme borreliosis:**

### **Dr Horowitz Publications /Abstracts:**

#### **Book:**

**NY Times Science Best Seller: Why Can't I Get Better? Solving the Mystery of Lyme and Chronic Disease.** Dr Richard I. Horowitz. St Martin's Press, NYC.

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Why Can't I Get Better?

Richard Horowitz, M.D.

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### **Scientific Publications of Dr Horowitz:**

Clinical Roundup: Selected Treatment Options for Lyme disease: Multiple Causative Factors in Chronic Disease. Horowitz, R. Alt and Compl Therapies. DOI:10. 1089/act.2012.18407. Mary Ann Liebert, Inc, Vol 18, No.4 Aug 2012

Human Babesiosis and Ehrlichiosis-Current Status. Shah, J., Horowitz, R., Eur Infect Dis, Vol 6, Issue 1, Spring 2012

Mycoplasma Species in Ticks. Sapi, E, Horowitz, R: Awaiting Publication

Controversy brewing over Lyme Disease testing. Phillips, Burrasano, Horowitz, Savely, Stricker. The Lancet, Vol 6 March 2006

Rash Discussions about STARI and Lyme Disease. Stricker, Horowitz, et. al. Clinical Infectious Disease, January 15, 2006 V42i2 p 306.

Lyme Disease: Scratching the Surface. Phillips, Harris, Horowitz, Johnson, Stricker. The Lancet. Vol. 2005 November 19

**Evidence-based guidelines for the management of Lyme Disease. Cameron, Horowitz, et al. Expert Review of Anti Infective Therapy 2(1) 2004**

Bartonella Henselae: Limitations of Serological Testing: Evaluation of Elisa and Polymerase Chain Reaction Testing In a Cohort of Lyme Disease Patients and Implications for Treatment. Horowitz R.I., M.D. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.

**Borrellia Burgdorferi & Bartonella Henselae: A Study Comparing Tetracyclines In Combination with Quinolones in Co-Infected Patients. Horowitz R.I.,M.D. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.**

**Mycoplasma Infections in Chronic Lyme Disease: A Retrospective Analysis of Co-Infection and Persistence Demonstrated by PCR Analysis Despite Long Term Antibiotic Treatment. Horowitz R.I.,M.D. et.al. Abstract, 16<sup>th</sup> International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.**

A Prospective Study of Heavy Metal Exposure Among Lyme Disease Patients with Chronic Persistent Symptomatology: Implications for Treatment. Horowitz R.I.,M.D. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.

**Lyme Disease and Pregnancy: Implications of Chronic Infection, PCR Testing and Prenatal Treatment. Horowitz R.I. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.**

Effects of Shifting the Acid-Base Balance Among Lyme Patients during Jarish Herxheimer Flares: A Small Prospective Study. Horowitz R.I.,M.D. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.

**Lyme Disease and Babesiosis: New Therapeutic Options for Chronic Persistent Disease. Horowitz R.I.,M.D.. Abstract, 13th Annual International Scientific Conference on Lyme Disease and other Tick-Borne Disorders. Hartford, Connecticut, March 25-26,2000.**

Mefloquine and Artemesia: A Prospective Trial of Combination Therapy in Chronic Babesiosis Horowitz R.I.,M.D.. Abstract, 13th Annual International Scientific Conference on Lyme Disease and other Tick-Borne Disorders. Hartford, Connecticut, March 25-26,2000.

**Chronic Persistent Lyme Borreliosis: PCR Evidence of Chronic Infection Despite Extended Antibiotic Therapy- A Retrospective Review Horowitz R.I.,M.D.. Abstract, 13th Annual International Scientific Conference on Lyme Disease and other Tick-Borne Disorders. Hartford, Connecticut, March 25-26,2000.**

Chronic Lyme Disease: A Symptom Complex of Multiple Co-Infections: New Diagnostic & Treatment Protocols. Horowitz, R.I.,M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York.

**Bicillin Therapy and Lyme Disease: A Retrospective Study of the Safety and Efficacy of High Dose Intramuscular Bicillin in the Treatment of Chronic resistant Lyme Disease. Horowitz, R.I., M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York**

High Dose Trimethoprim-Sulfamethoxazole Therapy: A Useful Adjunct to Combination Therapy in the Treatment of Resistant Babesiosis. Horowitz, R.I.,

M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York

**Metronidazole Therapy in the Treatment of Chronic Lyme Disease. Horowitz, R.I., M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York.**

Chronic Persistent Babesiosis after Acute Treatment with Cleocin and quinine, and Atovaquone and Azithromycin Horowitz, R.I., M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York

Babesiosis in Upstate New York: PCR and RNA Evidence of Co-Infection with Babesia Microti Among Ixodidae Ticks in Dutchess County, NY. Horowitz, R.I., M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York

Atovaquone and Azithromycin Therapy: A New Treatment Protocol for Babesiosis in Co-Infected Lyme Patients. Horowitz, R.I., M.D. 11th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 25-26, 1998. New York, New York.

Alternative Therapies, 5 (5), 30-31: Rainbow Healing Arts Center: Integrating the Science of Medicine with the Art of Healing. Horowitz, R.I., M.D., September 1999.

#### **Rationale for Long Term Treatment and Studies on Persistence:**

Regarding treatment, some physicians believe that there is no reason to be treating patients beyond the 30 day course routinely recommended by the IDSA guidelines; however there are high rates of treatment failure for all stages of Lyme disease. According to the CDC, as many as 20% of patients remain ill after the short term treatment protocol recommended by the IDSA (<http://www.cdc.gov/lyme/treatment/>).

**Other studies suggest the treatment failure rate for early Lyme disease may be as high as 36%:**

- Aucott JN, et al. Post-treatment Lyme disease syndrome symptomatology and the impact on life functioning: is there something here? *Qual Life Res.* 2013 Feb;22(1):75-84

**In late Lyme disease, treatment failure rates may exceed 50%:**

- Cameron, D., Horowitz, R, et al: Treatment of Lyme disease: a medicolegal assessment. *Expert review of anti-infective therapy.* 2004 Aug;2(4):533-57

**Why do patients fail short term therapy? The peer reviewed medical literature shows chronic persistent infection despite intensive antibiotics:**

- Bradley JF, et al, The Persistence of Spirochetal Nucleic Acids in Active Lyme Arthritis. *Ann Int Med* 1994;487-9
- Bayer ME, Zhang L, Bayer MH. *Borrelia burgdorferi* DNA in the urine of treated patients with chronic Lyme Disease symptoms. A PCR study of 97 cases. *Infection* 1996. Sept-Oct;24(5):347-53
- Diringer MN, et al, Lyme meningoencephalitis- report of a severe, penicillin resistant case. *Arthritis & Rheum,* 1987;30:705-708
- Donta, ST, Tetracycline therapy in chronic Lyme disease. *Chronic Infectious Diseases,* 1997; 25 (Suppl 1): 552-56
- Fitzpatrick JE, et al. Chronic septic arthritis caused by *Borrelia burgdorferi*. *Clin Ortho* 1993 Dec;(297):238-41
- Georgilis K, Peacocke M, & Klempner MS. Fibroblasts protect the Lyme disease spirochete, *Borrelia burgdorferi*, from ceftriaxone in vitro. *J Infect Dis* 1992;166: 440-444
- Fallon BA, et al. Repeated antibiotic treatment in chronic Lyme disease, *Journal of Spirochetal and Tick-borne Diseases,* 1999; 6 (Fall/Winter):94-101
- Fraser DD, et al. Molecular detection of persistent *Borrelia burgdorferi* in a man with dermatomyositis. *Clinical and Exper Rheum.* 1992;10:387-390

- Fried MD et al, *Borrelia burgdorferi* persists in the gastrointestinal tract of children and adolescents with Lyme Disease, *JNL of Spirochetal and Tick-borne Diseases*, Spring/Summer 2002; 9:11-15
- Girschick HJ, et al. Intracellular persistence of *Borrelia burgdorferi* in human synovial cells. *Rheumatol Int* 1996;16(3):125-132
- Hassler D, et al. Pulsed high-dose cefotaxime therapy in refractory Lyme Borreliosis (letter). *Lancet* 1991;338:193
- Horowitz RI. Chronic Persistent Lyme Borreliosis: PCR evidence of chronic infection despite extended antibiotic therapy: A Retrospective Review. Abstract XIII Intl Sci Conf on Lyme Disease. Mar 24-26, 2000.
- Haupl T, et al. Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. *Arthritis Rheum* 1993;36:1621-1626
- Karma A, et al. Long term follow-up of chronic Lyme neuroretinitis. *Retina* 1996;16:505-509
- Keller TL, et al. PCR detection of *Borrelia burgdorferi* DNA in cerebrospinal fluid of Lyme neuroborreliosis patients. *Neurology* 1992;43:32-42
- Masters EJ, et al. Spirochetemia after continuous high-dose oral amoxicillin therapy. *Infect Dis Clin Practice* 1994;3:207-208
- Ma Y, et al. Intracellular localization of *Borrelia burgdorferi* within human endothelial cells. *Infect Immun* 1991;59:671-678
- Meier P, et al. Pars plana vitrectomy in *Borrelia burgdorferi* endophthalmitis. *Klin Monatsbl Augenheilkd* 1998 Dec;213(6):351-4
- Preac-Mursic V, et al. Survival of *Borrelia burgdorferi* in antibioticly treated patients with Lyme borreliosis. *Infection* 1989;17:355-359.
- Preac-Mursic V, et al. Persistence of *Borrelia burgdorferi* and Histopathological Alterations in Experimentally Infected Animals. A comparison

with Histopathological Findings in Human Lyme Disease. *Infection* 1990;18(6):332-341

- Straubinger RK, et al. Persistence of *Borrelia burgdorferi* in Experimentally Infected Dogs after Antibiotic Treatment. *J Clin Microbiol* 1997;35(1):111-116
- Embers, M. et al. Persistence of *Borrelia burgdorferi* in Rhesus Macaques following Antibiotic treatment of Disseminated Infection. *PLoS ONE* 7(1): e29914. doi:10.1371/journal.pone

**Chronic persistent infection with Bb despite intensive antibiotics was also proven in two recent Xenodiagnosics studies. The first was in mice:**

- Hodzic E, Barthold SW (2014) Resurgence of Persisting Non-Cultivable *Borrelia burgdorferi* following Antibiotic Treatment in Mice. *PLoS ONE* 9(1): e86907.

Results confirmed previous studies: Bb could not be cultured from tissues, but low copy numbers of Bb flaB DNA were detectable in tissues up to 8 months after completion of treatment & RNA transcription of genes was seen with visualized spirochetes.

In humans, a recent NIH study by Dr Marques showed that among ten patients who had high levels of antibodies against *B. burgdorferi* after antibiotic treatment, two of those patients had “indeterminate results”, and one patient with Post Treatment Lyme disease syndrome (PTLDS) had a positive result, confirming evidence of ongoing *Borrelia* DNA in these patients:

- Marques, A. et al. Xenodiagnosis to Detect *Borrelia burgdorferi* Infection: A First-in-Human Study. *Clinical Infectious Diseases* DOI: 10.1093/cid/cit939 (2014).

Some physicians feel that there is no evidence of prolonged antibiotics helping symptoms. We know that:

**Short term antibiotics fail in 25%-71% of patients with late stage disease:**

- Berglund J, Stjernberg L, Ornstein K, Tykesson-Joelsson K, Walter H. 5-y Follow-up study of patients with neuroborreliosis. Scand J Infec Dis. 2002;34(6):421-5.
- Valesová H, Mailer J, Havlík J, Hulínská D, Hercogová J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. Infection. 1996 Jan-Feb;24(1):98-102

These frequent treatment relapses and failures with short term therapy are documented by other authors:

- Logigian (1990) : After 6 mo's of therapy, 10/27 patients treated with IV AB's relapsed or had treatment failure.
- Pfister (1991): 33 patients with neuroborreliosis were treated with IV AB's. After a mean of 8.1 months 10/27 were symptomatic and borrelia persisted in the CSF in 1 patient.
- Shadick (1994) : 10/38 pts relapsed (5 with IV) within 1 year of treatment, and had repeated AB treatment.
- Asch (1994) : 28% relapsed w/ major organ involvement 3.2 years after initial treatment

Many doctors use IDSA guidelines to base their conclusions to not treat sick patients with long term antibiotics. However only three NIH-funded trials have been conducted on the treatment of chronic Lyme disease:

- Klempner M, Hu L, Evans J, Schmid C, Johnson G, Trevino R, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. The New England journal of medicine. 2001 Jul 12:85-92
- Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, et al. 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, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology*. 2008 Mar 25;992-1003

These were inadequate treatment trials as sample sizes were extremely small, ranging from 37 to 78 patients. Critics have pointed out that studies this small lack sufficient statistical power to measure clinically relevant improvement:

- Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. *Expert Review Anti-Infective Therapy*. 2014 Sep;12(9):1103-35.
- Institute of Medicine. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011. Available from: [http://books.nap.edu/openbook.php?record\\_id=1305](http://books.nap.edu/openbook.php?record_id=1305)

**Nevertheless, two of the three clinical trials demonstrated that retreatment improved some patients' measures, such as fatigue and pain (Krupp, Fallon). Others have shown improvement in cognitive function, in those with Lyme encephalopathy (Fallon).**

- Fallon BA, Petkova E, Keilp J, Britton C. A reappraisal of the U.S. clinical trials of Post-Treatment Lyme Disease Syndrome. *Open Neurology Journal*. 2012;6(Supp. 1-M2):79-87.
- Delong et al. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: A biostatistical review of randomized, placebo controlled, clinical trials. *Contemporary Clinical Trials* 33 (2012), 1132-1142

**The medical literature does in fact show a benefit to using longer treatment regimens for disseminated Lyme Disease:**

- 1. Wahlberg, P. et al, Treatment of late Lyme borreliosis. *J Infect*, 1994. 29(3): p255-61 →31% improved w/ 14 days of Rocephin, 89% improved w/

Rocephin + 100d of Amoxicillin and Probenecid, 83% improved w/ Rocephin, then 100 days of cephadroxil

- 2. Donta, ST., Tetracycline therapy for chronic Lyme disease. Clin Infect Dis, 1997. 25 Suppl 1: p.S52-6. →277 pts with chronic LD treated between 1-11 months: 20% cured, 70% improved, 10% failed
- 3. Oksi, J et al., Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. Eur J Clin Microbiol Infect Dis, 1998. 17(10) :p 715-9→ 30 pts w/ chronic Lyme disease were treated for 100 days, and 90% had good or excellent responses
- 4. Oksi, J., et al. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med, 1999. 31(3):p.225-32→32/165 patients with disseminated Lyme were treated for 1 or more months of antibiotics, and showed that even more than 3 months of treatment may not eradicate the spirochete, and that longer term therapy may be necessary.

This last study detected chronic persistent Lyme by both PCR and culture, the “gold standard” for proving chronic infection.

In conclusion, the scientific literature shows: unreliable blood tests, persistence of borrelia despite short term treatment, and peer reviewed clinical trials showing benefit of longer term antibiotic therapies. It is therefore incumbent on the physician to use their best clinical judgment in treating their patients.

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