

# **Controversies in Lyme Disease Diagnosis & Treatment**

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# Lyme Disease

## State of the Art

"We also know that there are known unknowns; that is to say, we know that there are some things we do not know. But there are also unknown unknowns - the ones that we don't know we don't know."

-Donald Rumsfeld

**From left to right: Larvae, Nymph, Female, Male Tick**  
**Tick in Nymph stage is the size of a poppy seed.**



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# Classic Features of Lyme Disease

## 1. Tickbite

- Only 50-60% of Lyme patients recall a tickbite.

## 2. Erythema migrans (“bullseye”) rash

- Only 35-60% of Lyme patients ever see a rash.
- Variable appearance and location.

## 3. Arthritis

- Only 20-30% of Lyme patients get joint swelling.
- May be masked by anti-inflammatory meds.

Stricker et al. *Expert Rev Anti Infect Ther.* 2005;3:155-65

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# Question

Is it “post-Lyme syndrome” or persistent infection?

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*B. burgdorferi*, a spiral bacteria  
that causes Lyme Disease, seen  
through a microscope.

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# Characteristics of *Borrelia burgdorferi*

- Over 1500 gene sequences
- At least 132 functioning genes (in contrast, *T. pallidum* has 22 functioning genes)
- 21 plasmids (three times more than any known bacteria)
- “Stealth” pathology: evades the immune response

Casjens S et al., *Mol Microbiol* 2000;35:490-516.

Porcella & Schwan, *J Clin Invest* 2001;107:651-6.

# *Borrelia burgdorferi*

## “Stealth” Pathology

1. **Immune Suppression**
2. **Phase & Antigenic Variation**
3. **Physical Seclusion**
  - Intracellular Sites
  - Extracellular Sites
4. **Secreted Factors**

Embers et al, *Microbes Infect* 2004;6:312-318.

# *Borrelia burgdorferi* “Stealth” Pathology

## 1. Immune Suppression

- Complement inhibition
- Inhibitory Cytokine Induction (IL-10)
- Lymphocyte/Monocyte Tolerization
- Antibody Sequestration in Immune Complexes

Embers et al, *Microbes Infect* 2004;6:312-318.

# *Borrelia burgdorferi*

## “Stealth” Pathology

### 2. Phase & Antigenic Variation

- Gene switching (Trypanosomes)
- Mutation/Recombination (HIV)
- Variable Antigen Expression (Neisseria)
- Autoinduction (Mycobacteria)
- Fibronectin binding (Staph, Strep)

Embers et al, *Microbes Infect* 2004;6:312-318.

Rhen et al, *Trends Microbiol* 2003;11:80-85

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# *Borrelia burgdorferi*

## “Stealth” Pathology

### 3. Physical Seclusion

#### – Intracellular Sites

- Multiple Cell Types
  - Synovial Cells, Endothelial Cells, Fibroblasts
  - Macrophages, Kupffer Cells
- Persistent Infection *In Vitro* (8 Weeks)
- Dormant State: Cyst Formation, Neutrophil Calprotectin

Embers et al, *Microbes Infect* 2004;6:312-318

Montgomery et al. *Infect Immun* 2006;74:2468-72

# *Borrelia burgdorferi*

## “Stealth” Pathology

### 3. Physical Seclusion

#### – Extracellular Sites

- Privileged Sites (Joints, Eyes, CNS)
- Cloaking Mechanisms (Binding to Proteoglycan, Collagen, Plasminogen, Integrin, Fibronectin)

Coburn et al, *Mol Microbiol* 2005;57:1182-95.

Coleman & Benach, *Infect Immun* 2003;71:5556-64

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# *Borrelia burgdorferi* “Stealth” Pathology

## 4. Secreted Factors

- Hemolysin (BlyB)
- Porin (Oms 28)
- Adhesin (Bgp)
- Pheromones (DPD/AI-2)
- Aggrecanase (ADAMTS-4)

Williams & Austin, *Infect Immun* 1992;60:3224-30.

Cluss et al. *Infect Immun* 2004;72:6279-86.

Babb et al. *J Bacteriol* 2005;187:3079-87

Behera et al. *Arth Rheum* 2006;54:3319-29

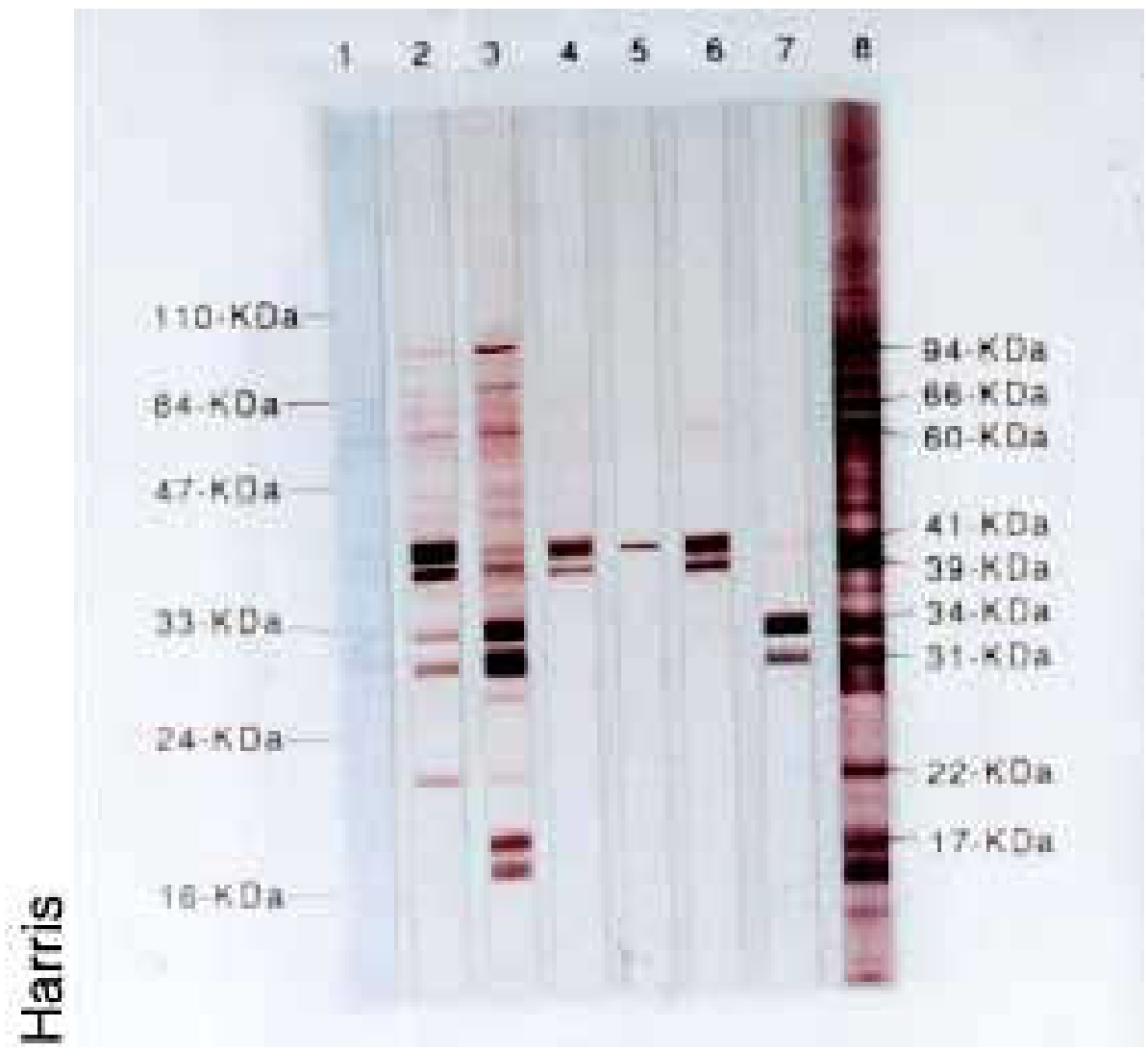
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Nasty Bug!

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# Laboratory Testing for Lyme Disease



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# Two-Tier Testing in Lyme Disease

Diagnostic test (Stage of disease)	Sensitivity (%)	Specificity (%)
ELISA/IFA (Early stage)	59	93
ELISA/IFA (Late stage)	95	81
ELISA/IFA + WB (Early & late stage)	50-75	99-100

Depietropaolo et al. *Am Fam Phys* 2005;72:297

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# Treatment Failure in Lyme Disease

Culture-confirmed failure of antibiotic treatment was first reported in 1989:

“Antibiotic therapy may abrogate the antibody response to the infection as shown in our patients. *B. burgdorferi* may persist as shown by positive culture in MKP-medium; patients may have subclinical or clinical disease without diagnostic antibody titers to *B. burgdorferi*.”

Preac-Mursic V et al. Survival of *Borrelia burgdorferi* in antibioticly treated patients with Lyme borreliosis. *Infection* 1989;17:355-9.

“There is no credible scientific evidence for the persistence of symptomatic *Borrelia burgdorferi* infection after antibiotic treatment.”

Gary P. Wormser, M.D.

Raymond J. Dattwyler, M.D.

*New York Times*, June 9, 2006

# Animal Models of Persistent Lyme Disease

## 1. Mice

- 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;150:909-15.

“Persistence of spirochetes within macrophages provides a possible pathogenetic mechanism for chronic or recurrent Lyme disease in man.”

- Bockenstedt LK, Mao J, Hodzic E, Barthold SW, Fish D. Detection of attenuated, noninfectious spirochetes in *Borrelia burgdorferi*-infected mice after antibiotic treatment. *J Infect Dis* 2002;186:1430-7.

“Nine months after treatment, low levels of spirochete DNA could be detected by real-time PCR in a subset of antibiotic-treated mice.”

# Animal Models of Persistent Lyme Disease

## 2. Dogs

- Straubinger RK; Summers BA; Chang YF; Appel MJ. Persistence of *Borrelia burgdorferi* in experimentally infected dogs after antibiotic treatment. *J Clin Microbiol* 1997;35:111-6.

“In 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.”

- Straubinger RK. PCR-based quantification of *Borrelia burgdorferi* organisms in canine tissues over a 500-day postinfection period. *J Clin Microbiol* 2000;38:2191-9.

“At the end of the experiment, *B. burgdorferi* DNA was detectable at low levels ( $10^2$  to  $10^4$  organisms per 100 microgram of extracted DNA) in multiple tissue samples regardless of treatment.”

# Animal Models of Persistent Lyme Disease

## 3. Monkeys

- Pachner AR, Cadavid D, Shu G, Dail D, Pachner S, Hodzic E, Barthold Central and peripheral nervous system infection, immunity, and inflammation in the NHP model of Lyme borreliosis. *Ann Neurol.* 2001;50:330-8.

“These data demonstrate that Lyme neuroborreliosis is a persistent infection, that spirochetal presence is a necessary but not sufficient condition for inflammation, and that antibody measured in serum may not predict the severity of infection.”

- Pachner AR, Dail D, Narayan K, Dutta K, Cadavid D. Increased expression of B-lymphocyte chemoattractant, but not pro-inflammatory cytokines, in muscle tissue in rhesus chronic Lyme borreliosis. *Cytokine.* 2002;19:297-307.

“This study is the first to extensively characterize cytokine gene expression in chronically inflamed tissue in Lyme borreliosis.”

# Animal Models of Persistent Lyme Disease

## 3. Monkeys

- Cadavid D, Bai Y, Hodzic E, Narayan K, Barthold SW, Pachner AR. Cardiac involvement in non-human primates infected with the Lyme disease spirochete *Borrelia burgdorferi*. *Lab Invest.* 2004;84:1439-50.  
“We conclude that carditis in NHPs infected with *B. burgdorferi* is frequent and can persist for years but is mild unless they are immunosuppressed.”
- Miller JC, Narayan K, Stevenson B, Pachner AR. Expression of *Borrelia burgdorferi* erp genes during infection of non-human primates. *Microb Pathog.* 2005;39:27-33.  
“The majority of erp genes were detectably transcribed after more than 3 months of mammalian infection.”

# Treatment Relapses and Failures

<b>Persistent Symptoms after Short Term Therapy</b>	
<b>Study (Failure %)</b>	<b>Comments</b>
Dvorakova (2004) (50%) [1]	Chronic Lyme disease: Antibiotics are only successful in 50% of cases.
Kaiser (2004) (80%) [2]	Twelve months after treatment, 93% of patients with acute, but only 20% with chronic neuroborreliosis were cured.
Berglund 2002 (25%) [3]	25% of the patients suffered from residual neurological symptoms 5 years post-treatment.
Shadick (1999) (37%) [4]	69 of 184 treated patients (37%) reported relapse of disease.
Treib (1998) (>50%) [5]	After 4.2 years, >50% of 44 treated neuroborreliosis patients with specific intrathecal antibodies were symptomatic.

1. Dvorakova J, et al. [Pharmacological aspects of Lyme borreliosis]. Ceska Slov Farm. 2004; 53(4): 159-64.
2. Kaiser R. [Clinical courses of acute and chronic neuroborreliosis following treatment with ceftriaxone]. Nervenarzt. 2004; 75(6): 553-7.
3. Berglund J, et al. Five-year follow-up study of patients with neuroborreliosis. Scand J Infect Dis. 2002; 34(6): 421-5.
4. Shadick NA, et al. Musculoskeletal and neurologic outcomes in patients with previously treated Lyme disease. Ann Intern Med. 1999; 131(12): 919-26.
5. Treib J, A, et al. Clinical and serologic follow-up in patients with neuroborreliosis. Neurology. 1998; 51(5): 1489-91.

# Treatment Relapses and Failures

<b>Persistent Symptoms after Short Term Therapy</b>	
<b>Study (Failure %)</b>	<b>Comments</b>
Valesova (1996) (38%) [1]	At 36 months, 10 of 26 patients (38%) had relapsed or progressed (relapse in 6, and new symptoms in 4).
Shadick (1994) (26%) [2]	Ten of 38 patients(26%) relapsed within 1 year of treatment.
Asch (1994) (28%) [3]	At a mean of 3.2 years after treatment, 28% of 215 patients had relapsed. Persistent symptoms (fatigue, arthralgia) in 114 patients (53%).
Pfister (1991) (37%) [4]	After a mean of 8.1 months, 10 of 27 neuroborreliosis patients (37%) were symptomatic & Bb persisted in the CSF of one.
Logigian (1990) (37%) [5]	After 6 months, 10 of 27 patients (37%) relapsed or failed treatment.

1. Valesova H, et al. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. *Infection*. 1996; 24(1): 98-102.
2. Shadick NA, et al. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. *Ann Intern Med*. 1994; 121(8): 560-7.
3. Asch ES, et al. Lyme disease: an infectious and postinfectious syndrome. *J Rheumatol*. 1994; 21(3): 454-61.
4. Pfister HW, et al. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. *J Infect Dis*. 1991; 163(2): 311-8.
5. Logigian EL, et al. Chronic neurologic manifestations of Lyme disease. *N Engl J Med*. 1990; 323(21): 1438-44.

# Persistence Despite Treatment

Study	Culture and/or PCR Evidence of Persistent Infection
Breier et al (2001)	Despite repeated treatment, <u>Bb cultured from skin</u> of enlarging lichen sclerosus lesions
Oksi (1999)	<u>40% (13 of 32) patients had PCR- or culture-confirmed relapses</u>
Bayer (1996)	<u>97 previously treated chronic Lyme patients were PCR- positive .</u>
Preac Mursic (1996)	<u>Isolation of Bb by culture in 5 patients</u> , 4 of whom were seronegative on previous occasions
Battafarano et al. (1993)	Despite repeated treatment, <u>Bb documented in synovium and synovial fluid</u> of a patient with arthritis of the knee after 7 years
Preac-Mursic (1993)	<u>Bb cultured from iris biopsy</u> of treated patient with blurred vision & persistent symptoms lasting several years.

Breier F, et al. Isolation and polymerase chain reaction typing of *Borrelia afzelii* from a skin lesion in a seronegative patient with geeneralized ulcertating bullous lichen sclerosus et atrophicus. 2001. Br J Dermatol, 144(2):387-392; 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; Bayer, M.E., te al. *Borrelia burgdorferi* DNA in the urine of treated patients with chronic Lyme disease symptoms. A PCR study of 97 cases. Infection, 1996. 24(5): p. 347-53; Preac-Mursic, V., et al., *Formation and cultivation of Borrelia burgdorferi spheroplast L-form variants*. Infection, 1996. 24: p. 218-26; Battafarano DF, Combs JA, Enzenauer RJ, Fitzpatrick JE. 1993. Chronic septic arthritis caused by *Borrelia burgdorferi*. Clin Orthop 297:238-41; Preac-Mursic et al. First isolation of *Borrelia burgdorferi* from an iris biopsy. J Clin Neuroophthalmol 1993;13:155-61

# Treatment May Suppress But Not Eradicate Bb

Breier (2001)	Patient with Lyme disease and lichen sclerosus et atrophicus had relapses of skin lesions for up to 1 year; treated successfully with a course of the same antibiotics previously used for Lyme disease.
Petrovic (1998)	Despite repeated treatment, symptoms improved only temporarily after treatment, but re-emerged within weeks or months.
Bayer (1996)	97 patients with chronic Lyme disease confirmed by PCR: '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 to be resumed.'
Ferris (1996)	Despite repeated treatment over a 2-year period, the patient's condition deteriorated. Twelve months of IV antibiotics followed by 11 months of oral antibiotics significantly improved the quality of life.

Petrovic M, et al. Lyme borreliosis--a review of the late stages and treatment of four cases. *Acta Clin Belg.* 1998; 53(3): 178-83; Breier F, et al. 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.* 2001; 144(2): 387-92; Bayer ME, et al. *Borrelia burgdorferi* DNA in the urine of treated patients with chronic Lyme disease symptoms. A PCR study of 97 cases. *Infection.* 1996; 24(5): 347-53; Ferris J, et al. Lyme Borreliosis (Letter). *Lancet.* 1995; 345: 1436-37.

**Does longer antibiotic treatment help  
in persistent Lyme disease?**

## Non-Controlled Studies Supporting Longer Treatment of Persistent Lyme Disease

Study	Comments
Oksi (1999)	9/13 patients (69%) with disseminated Lyme disease initially treated for 3 months with oral or IV antibiotics subsequently relapsed. Good response to retreatment with IV ceftriaxone for 4-6 weeks.
Donta (1997)	277 patients with chronic Lyme treated for 1-11 months (mean, 4 months): 20% were cured, 70% improved and 10% had treatment failure.
Oksi (1998)	30 patients with disseminated Lyme treated for 100 days. 90% had good or excellent responses.

Oksi, J., et al., *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. *Ann Med*, 1999. **31**:225-32; Donta, S.T., *Tetracycline therapy for chronic Lyme disease*. *Clin Infect Dis*, 1997. **25 Suppl 1**:S52-6; 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**:715-9.

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# Donta Study

<b>Tetracycline Treatment Duration</b>	<b>Symptom Improvement</b>
<b>2 Months</b>	<b>33%</b>
<b>3 Months</b>	<b>61%</b>

Donta ST. Tetracycline therapy for chronic Lyme disease.  
*Clin Infect Dis* 1997; 25 (Suppl 1):S52-6

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# Non-Controlled Studies Supporting Longer Treatment of Persistent Lyme Disease

Study	Comments
Wahlberg (1994)	Success rates for 100 patients with late Lyme disease: 31% (4/13) with 14 days of ceftriaxone; 89% (50/56) with ceftriaxone, then 100 days of amoxicillin and probenecid; and 83% (19/23) with ceftriaxone, then 100 days of cefadroxil.
Fallon (1999)	18 patients retreated with intravenous, intramuscular or oral antibiotics scored better on measures of cognition. Those retreated with IV therapy showed greatest improvement.

Wahlberg, P., et al., *Treatment of late Lyme borreliosis*. J Infect, 1994. **29**:255-61;

Fallon, B.A., *Repeated antibiotic treatment in chronic Lyme disease*. J Spirochet Tick Borne Dis, 1999. **6**:94-101.

# Controlled Studies of Persistent Lyme Disease

Study	Treatment	Results	Comment
Krupp et al. (2003)	Ceftriaxone IV for 4 weeks vs. placebo	64% showed improvement in fatigue; no improvement in cognition.	Cognition finding criticized because subjects were not selected based on cognitive impairment. Improvement on this scale would not be expected since no initial impairment was demonstrated.
Klempner et al. (2001)	Ceftriaxone IV for 4 weeks, then oral doxycycline for 2 months vs. placebo	No improvement in fatigue or quality of life.	Study criticized because subjects were not selected based on fatigue. Improvement on this scale would not be expected since no initial impairment was demonstrated. ILADS has issued a position paper outlining substantial criticisms of the study ( <a href="http://www.ilads.org">www.ilads.org</a> ).

Krupp LB, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology*. 2003; 60(12): 1923-30;

Klempner M, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001; 345(2): 85-92.

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## Controlled Studies of Persistent Lyme Disease

Study	Treatment	Results	Comment
Cameron et al. (2005)	Oral amoxicillin for 3 months vs. placebo	Retreatment was successful in 2/3 of patients with worst quality of life.	Results presented at Columbia/LDA conference 2005.
Fallon et al. (2005)	Ceftriaxone IV for 10 weeks vs. placebo	Significant cognitive improvement	Results presented at Columbia/LDA conference 2005; publication expected this year.

Cameron D. Results from Lyme disease treatment trial. Columbia University/LDA Conference, Lyme & Other Tick-Borne Diseases: Emerging Tick-Borne Diseases; October 28, 2005; Philadelphia, PA

Fallon BA. Preliminary results of Columbia controlled Lyme treatment study (NIH funded). Columbia University/LDA Conference, Lyme & Other Tick-Borne Diseases: Emerging Tick-Borne Diseases; October 28, 2005; Philadelphia, PA

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# Tickborne Coinfections

- Babesia (Piroplasma)
- Anaplasma
- Ehrlichia
- Bartonella
- WA-1, MO-1, EU-1
- Rickettsia/Coxiella
- Tularemia
- Spiroplasma?

**“If somebody comes back in follow-up and has symptoms that have persisted or symptoms that have gotten worse, it may be because they are coinfecting and you have treated *Borrelia*, but you haven't treated *Babesia* or *Ehrlichia*.”**

Raymond J. Dattwyler, M.D.  
FDA Advisory Committee Meeting  
July 30, 1998

# Coinfection Exacerbates Lyme Disease

1. Thomas V, Anguita J, Barthold SW, Fikrig E. Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis alters murine immune responses, pathogen burden, and severity of Lyme arthritis. *Infect Immun* 2001;69:3359-71.
2. Zeidner NS, Dolan MC, Massung R, Piesman J, Fish D. Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis suppresses IL-2 and IFN gamma production and promotes an IL-4 response in C3H/HeJ mice. *Parasite Immunol* 2000;22:581-8.

# Coinfection Exacerbates Lyme Disease

1. Moro MH, Zegarra-Moro OL, Bjornsson J, Hofmeister EK, Bruinsma E, Germer JJ, Persing DH. Increased arthritis severity in mice coinfecting with *Borrelia burgdorferi* and *Babesia microti*. *J Infect Dis* 2002;186:428-31.
2. Krause PJ, Telford SR 3rd, Spielman A, Sikand V, Ryan R, Christianson D, Burke G, Brassard P, Pollack R, Peck J, Persing DH. Concurrent Lyme disease and babesiosis. Evidence for increased severity and duration of illness. *JAMA* 1996;275:1657-60.
3. Oleson CV, Sivalingam JJ, O'Neill BJ, Staas WE. Transverse myelitis secondary to coexistent Lyme disease and babesiosis. *J Spinal Cord Med* 2003;26:168-71.

# Evidence for Persistent Coinfections

1. Krause PJ, Spielman A, Telford SR, Sikand VK, McKay K, Christianson D, Pollack RJ, Brassard P, Magera J, Ryan R, Persing DH. Persistent parasitemia after acute babesiosis. *N Engl J Med* 1998;339:160-5.
2. Allred DR. Babesiosis: persistence in the face of adversity. *Trends Parasitol* 2003;19:51-5.
3. Harrus S, Waner T, Aizenberg I, Foley JE, Poland AM, Bark H. Amplification of ehrlichial DNA from dogs 34 months after infection with *Ehrlichia canis*. *J Clin Microbiol* 1998;36:73-6.
4. Dumler JS, Bakken JS. Human granulocytic ehrlichiosis in Wisconsin and Minnesota: a frequent infection with the potential for persistence. *J Infect Dis* 1996;173:1027-30.
6. Chomel BB, Kasten RW, Sykes JE, Boulouis HJ, Breitschwerdt EB. Clinical impact of persistent *Bartonella* bacteremia in humans and animals. *Ann N Y Acad Sci* 2003;990:267-78.

# Prevalence of Coinfections in *Ixodes* Ticks, New Jersey 2004

Organism	Prevalence (%)
<i>Borrelia burgdorferi</i>	33.6
<i>Babesia microti</i>	8.4
<i>Anaplasma phagocytophilum</i>	1.9
<i>Bartonella</i> spp.	34.5

Adelson et al. *J Clin Microbiol* 2004;42:2799

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# Evaluation & Management of Chronic Lyme Disease

- Repeat testing for Lyme disease and tick-borne coinfections, including Bb (Western blot), Babesia, Anaplasma, Ehrlichia, Bartonella and WA-1
- Testing for other disease markers: Hg<sup>++</sup> toxicity, thyroid disease, ANA, rheumatoid factor, complement levels, B12 deficiency
- CD57 natural killer cell level; ?C4a level
- SPECT brain scan if neuropsychiatric symptoms are significant
- Formal neuropsychiatric testing if indicated

# Evaluation & Management of Chronic Lyme Disease

- Treat coinfections first; success defined as fourfold drop in serology (usually undetectable)
- Oral antibiotic therapy for predominantly musculoskeletal Lyme symptoms
- Parenteral antibiotics for predominantly neuropsychiatric Lyme symptoms
- Rotate open-ended antibiotic regimens
- Monitor CD57 NK level, ?C4a level

**44. Table 1. Comparison of key IDSA and ILADS guidelines.**

<b>Condition</b>	<b>IDSA</b>	<b>ILADS</b>
Lyme arthritis	B - II	A - II
Encephalopathy	A - II	A - II
Retreatment	None	A - II
Prolonged antibiotics	None	A - II
Benzathine penicillin	D - III	B - III
Intra-articular steroid	B - III	D - III
Arthroscopic Synovectomy	B - II	D - II
Coinfection	B - III	B - III
Seronegative Lyme disease	None	A - III
Combination treatment	None	B - III
Empiric treatment	None	B - III

# Conclusions

- Lyme disease and coinfections are spreading.
- *Borrelia burgdorferi* is difficult to eradicate.
- Lyme testing is not as sensitive as we are told.
- Lyme treatment failure is more common than we think.
- Prolonged antibiotic therapy appears to be useful and appropriate in persistent Lyme disease.

# **Information about Tick-Borne Diseases**

**ILADS Website**

**[www.ilads.org](http://www.ilads.org)**