Lyme Disease Presenting as Multiple Chronic Infectious Disease Syndrome (MCIDS/SIMC) & Co-Infections: Diagnosis and Treatment

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Dr Richard Horowitz
Hudson Valley Healing Arts Center
4232 Albany Post Road
Hyde Park, N.Y. 12538
845-229-8977

Background Data

Undergraduate: Northwestern University

Medical School: Free Univ of Brussels, Belgium 1977-1984

Residency: Mount Sinai services, Elmhurst, N.Y. 1984-1987. Board certified in Internal Medicine

Private Medical practice: Hyde Park, N.Y. 1987- 2011 (the most Lyme endemic area in NYS)

Director Hudson Valley Healing Arts Center: Treated 12,000 Chronic Lyme patients in last 24 years

Assistant Director Medicine Vassar Brothers Hospital

President elect International Lyme and Associated Diseases Society & President ILADEF (C3) education

5 Essential Scientific Points

- 1)There are 2 standards of care in the US
- 2) Defining Chronic Lyme Disease: What is it?-the difference between the “surveillance” definition and “real life” in the doctors office. Proposing a new definition: Multiple Chronic Infectious Disease Syndrome (MCIDS/ ou SIMC)
- 3) Serology and Seronegative infection
- 4) Persistent/chronic borrelial infection & the need for longer treatment courses
- 5) Optimal diagnostic and therapeutic modalities are presently undefined but treating the 15 point differentials in Multiple Chronic Infectious Disease Syndrome helps (MCIDS) (SIMC)

Chronic Lyme Disease—The Standard of Care

- Two equally legitimate but divergent standards of care currently exist for the diagnosis and treatment of Lyme disease: IDSA guidelines and ILADS guidelines

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

2) Evidence-based guidelines for the management of Lyme Disease.

Cameron, Horowitz, et al. Expert Review of Anti Infective Therapy 2(1) 2004

- Many doctors in the United States do not follow IDSA guidelines. They treat for seronegative disease, and treat for extended periods of time. "For chronic Lyme disease, 57% of responders treat 3 months or more."
- **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.

Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines

Dong Heun Lee, MD; Ole Vielemeyer, MD

- **Methods:** We analyzed the strength of recommendation and overall quality of evidence behind 41 Infectious Diseases Society of America (IDSA) guidelines released between January 1994 and May 2010. Individual recommendations were classified based on their strength of recommendation (levels A through C) and quality of evidence (levels I through III). Guidelines not following this format were excluded from further analysis. Evolution of IDSA guidelines was assessed by comparing 5 recently updated guidelines with their earlier versions.
- **Conclusions:** More than half of the current recommendations of the IDSA are based on level III evidence only. Until more data from well-designed controlled clinical trials become available, physicians should remain cautious when using current guidelines as the sole source guiding patient care decisions.

Arch Intern Med. 2011;171(1):18-22

Defining Chronic Lyme Disease: MCIDS: Differential Diagnosis

1. Infections: a)Bacterial: **Lyme** disease, Ehrlichiosis, Bartonella, Mycoplasma, Chlamydia, Rickettsia, Typhus, Tularemia, Q-Fever, Tick paralysis b) Parasites: Babesiosis and other piroplasms, filiariasis, amebiasis, giardiasis…c) Viruses: EBV, HHV-6, HHV-8, CMV, St Louis Encephalitis, W Nile, Powassan encephalitis and other viral encephalopathies, ?XMRV virus d) Candida and other fungi
2. Immune dysfunction: ANA+, RF+ ↑ HLA DR-4
3. Inflammation: ↑ IL-1, IL-6, TNF-α→ "Sickness syndrome"
4. Toxicity: Heavy Metals, Mold, and Neurotoxins
5. Allergies
6. Nutritional & Metabolic abnormalities
7. Mitochondrial dysfunction
8. Psychological disorders 9. Endocrine disorders
10. Sleep disorders 11. Autonomic nervous system dys (f)
12 Gastrointestinal disorders 13. Elevated LFT's
14. Drug Use/Addiction 15. Need for Physical Therapy

Polymicrobial Infections are common in ticks

- Vector-Borne and Zoonotic Diseases. Tokarz et al, Sept 2009. Assesment of Polymicrobial Infections in Ticks in NYS: 71% harbored 1 organism, 30% had a polymicrobial inf (2), and 5% had 3 or more microbes: *Borrelia burgdorferi, Borrelia miyamotoi, Anaplasma phagoctyophilum, Babesia microti, & Powassan virus.*

- J. Clin Microbiology 1999; (37:2215-2215) Schoub et.al.; High Percentage of Ixodes ricinus ticks are co-infected with *Borrelia, Ehrlichia, and Bartonella* (Netherlands). 5-10% + for Bart by culture

- Lebech et al. Serologic evidence of *granulocytic ehrlichiosis and piroplasma WA 1* in European patients with Lyme neuroborreliosis. Seventh Intl Congress on Lyme Borreliosis 1996:390

- Minar et al. Natural foci of tick-borne encephalitis in central Europe and the relationship of the incidence of Ixodes ricinus to original ecosystems. Cent Eur J Public Health 1995;3:337

- Mycoplasma in ticks: Sapi, Horowitz, et al. Awaiting publication. University of New Haven. Multiple mycoplasma species were found in ticks, ie *M.genitalium, pneumoniae, M. fermentans*

CDC Case Definition is Not for Diagnosis

- **CDC Surveillance Case Definition -a case with EM or one objective manifestation (meningitis, cranial neuropathy, arthritis, or AV block, that is laboratory confirmed)**

- **"This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis."** Centers for Disease Control Prevention *MMWR*56(23);573-576, June 15, 2007

- Serology for Early Lyme Disease (EM): + serology in 20-50% of cases

-Wormser N Engl J Med 2006 ; Wormser Clin Vaccine Immunol 2008 ; -Lieber M'bomeyo Presse Med 2003 : **Diagnosis is clinical at this stage +Enquiry among GPs in Alsace in 2003 : 50% thought a positive serology is required**

-Assous Med Mal Infect 2007: the 2 tiered test is good, but don't do in early Lyme.

EUCALB labs: 3 problemes→Il ne doit pas y avoir plus de 5% de seropositifs dans une population donnee, ils ont determiner le valeur critique du test sur une population en bonne sante (donneurs de sang), et la sensibilite est impossible a determiner avec l'absence d'un « gold standard » (PCR, culture, signes cliniques)

Lyme Disease Diagnosis: Problems with Testing

1)Intra and Interlaboratory Variation in LD testing

-Bakken et al. JAMA 1992;268:891-895

-Marangoni J Med Microbiol 2005: 3 different commercial Elisa tests showed discrepant results. Sensitivity for the same sera 36,8% to 70.5%

-De Marteno Med Mal Infect 2007: Compared 14 Elisa test kits for the diagnosis of neuroborreliosis. Sensitivity varied from 20.9% -97.7%

2) Testing Issues: Different species of Borrelia: *Rudenko FEMS Microbiol Letter 2009 ; Bouattour Arch Inst Pasteur Tunis 2004 ; Lopes de Carvalho Clin Rheumatol 2008*⟶***Borrelia burgdorferi*** **sensu stricto (USA, Europe, North Africa),** ***Borrelia afzelii*** **(Europe, Asia)** ***Borrelia garinii*** **(several serotypes) (Europe, Asia, North Africa),** ***Borrelia valaisiana, Borrelia lusitaniae*** **(Portugal, Italy, North Africa) : vasculitis, Serology often does not cross react & can lead to false negative results (B31 + 297 improves testing in the US)**

3) Problems with 2 Tiered Testing

-Two Tiered testing using an Elisa with a confirmatory Western Blot:

-In 2005, John's Hopkins University study: found CDC two tiered testing missed 75% of positive Lyme cases Coulter,et al.,*J Clin Microbiol* 2005;43:5080-5084

Sensitivity/Specificity of Commercial Two-Tier Testing for Lyme Disease

Study/Year	Sensitivity	Specificity
Schmitz et al, 1993	66%	100%
Engstrom et al, 1995	55%	96%
Ledue et al, 1996	50%	100%
Trevejo et al, 1999	29%	100%
Nowakowski, 2001	66%	99%
Bacon et al, 2003	68%	99%
MEAN TOTAL	56%	99%

Stricker and Johnson BMJ 2007; 335:1008

AIDS testing has a sensitivity of 99.5% Would an AIDS test with a sensitivity of 56% be satisfactory?

Diagnosis: Laboratory Testing—5 More Studies
False Seronegativity Extensively Documented

- **Kaiser R.** False-negative serology in patients with neuroborreliosis and the value of employing of different borrelial strains in serological assays. J Med Microbiol. 2000**Pikelj F, Strle F, Mozina M.**

- Seronegative Lyme disease and transitory atrioventricular block. Ann Intern Med 1989 Jul 1;111(1):90. Oct;49(10):911-5.

- **Dejmkova H, Hulinska D, Tegzova D, Pavelka K, Gatterova J, Vavrik P.** Seronegative Lyme arthritis caused by Borrelia garinii. Clin Rheumatol. 2002 Aug;21(4):330-4.

- **Brunner M.** New method for detection of Borrelia burgdorferi antigen complexed to antibody in seronegative Lyme disease. J Immunol Methods. 2001 Mar 1;249(1-2):185-90.

- **Breier F, Khanakah G, Stanek G, Kunz G, Aberer E, Schmidt B, Tappeiner G.** 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 Feb;144(2):387-92.

Diagnosis: Laboratory Testing-5 More Studies
False Seronegativity Extensively Documented

1)Schutzer SE, Coyle PK, Belman AL, Golightly MG, Drulle J. Sequestration of antibody to *Borrelia burgdorferi* in immune complexes in seronegative Lyme disease. Lancet. 1990 Feb 10;335(8685):312-5.

2)Steere AC. Seronegative Lyme disease. JAMA. 1993 Sep 15;270(11):1369.

3)Dattwyler RJ, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG. Seronegative Lyme disease. Dissociation of specific T- and B-lymphocyte responses to *Borrelia burgdorferi*. N Engl J Med. 1988 Dec 1;319(22):1441-6.

4)Coyle PK, Schutzer SE, Deng Z, Krupp LB, Belman AL, Benach JL, Luft BJ. Detection of *Borrelia burgdorferi*-specific antigen in antibody-negative cerebrospinal fluid in neurologic Lyme disease. Neurology. 1995 Nov;45(11):2010-5.

Therefore false Negative CSF (& Seronegative Also) has also been seen

5)"…a patient with active Lyme disease may have a negative test result…"

-Brown SL, Hansen SL, Langone JJ. (FDA Medical Bulletin) Role of serology in the diagnosis of Lyme disease. JAMA. 1999 Jul 7;282(1):62-6.

Chronic Lyme Disease: Why is it chronic?
Verified Persistent Infection Despite Antibiotics

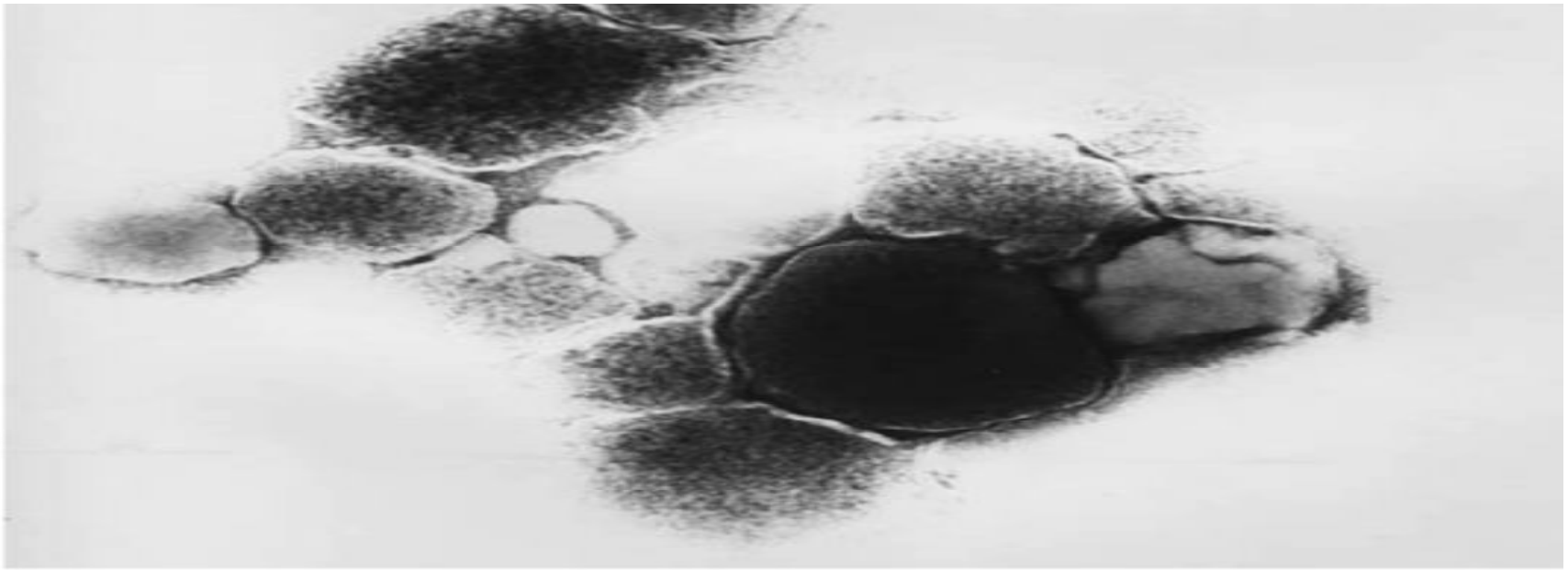
- 30% Remained PCR Positive Despite Multiple Courses of “Adequate” Antibiotic Therapy
- **Nocton J J; Dressler F; Rutledge B J; Rys P N; Persing D H; Steere A C.** Detection of Borrelia burgdorferi DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis N. Engl. J. Med. 1994 Jan, 330:4, 229-34.

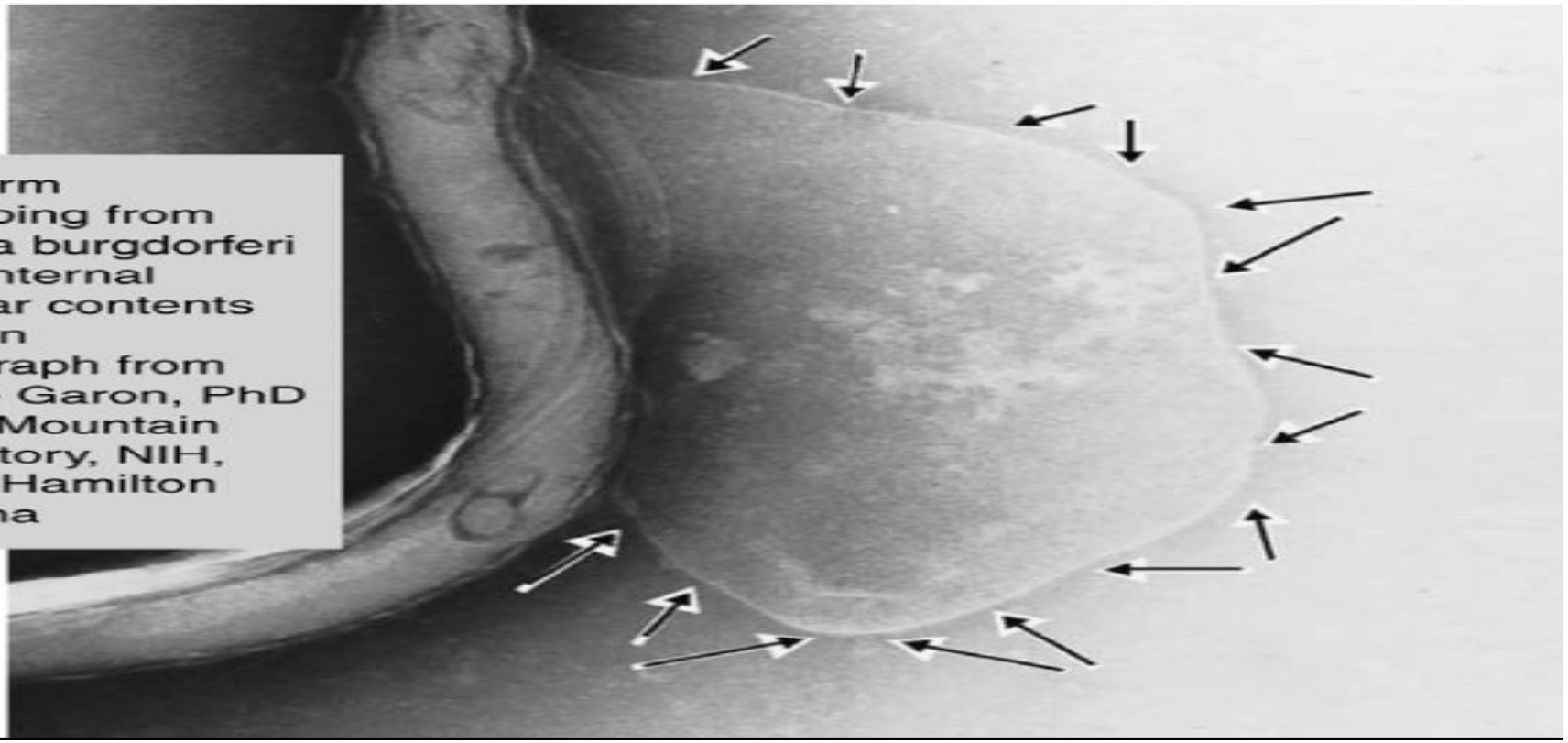
- **“....DNA of heat-killed borrelia was not detectable for very long in skin tissue of an uninfected dog, implying that during natural infection the DNA of killed organisms is removed quickly and completely within a few days."**
- **Straubinger RK.** PCR-Based quantification of Borrelia burgdorferi organisms in canine tissues over a 500-Day postinfection period. J Clin Microbiol. 2000 Jun;38(6):2191-9.

- 74% Remained PCR Positive Despite Extended Antibiotic Therapy
- **Bayer M E; Zhang L; Bayer M H.** Borrelia burgdorferi DNA in the urine of treated patients with chronic Lyme disease symptoms. A PCR study of 97 cases. Infection. 1996 Sep, 24:5, 347-53.

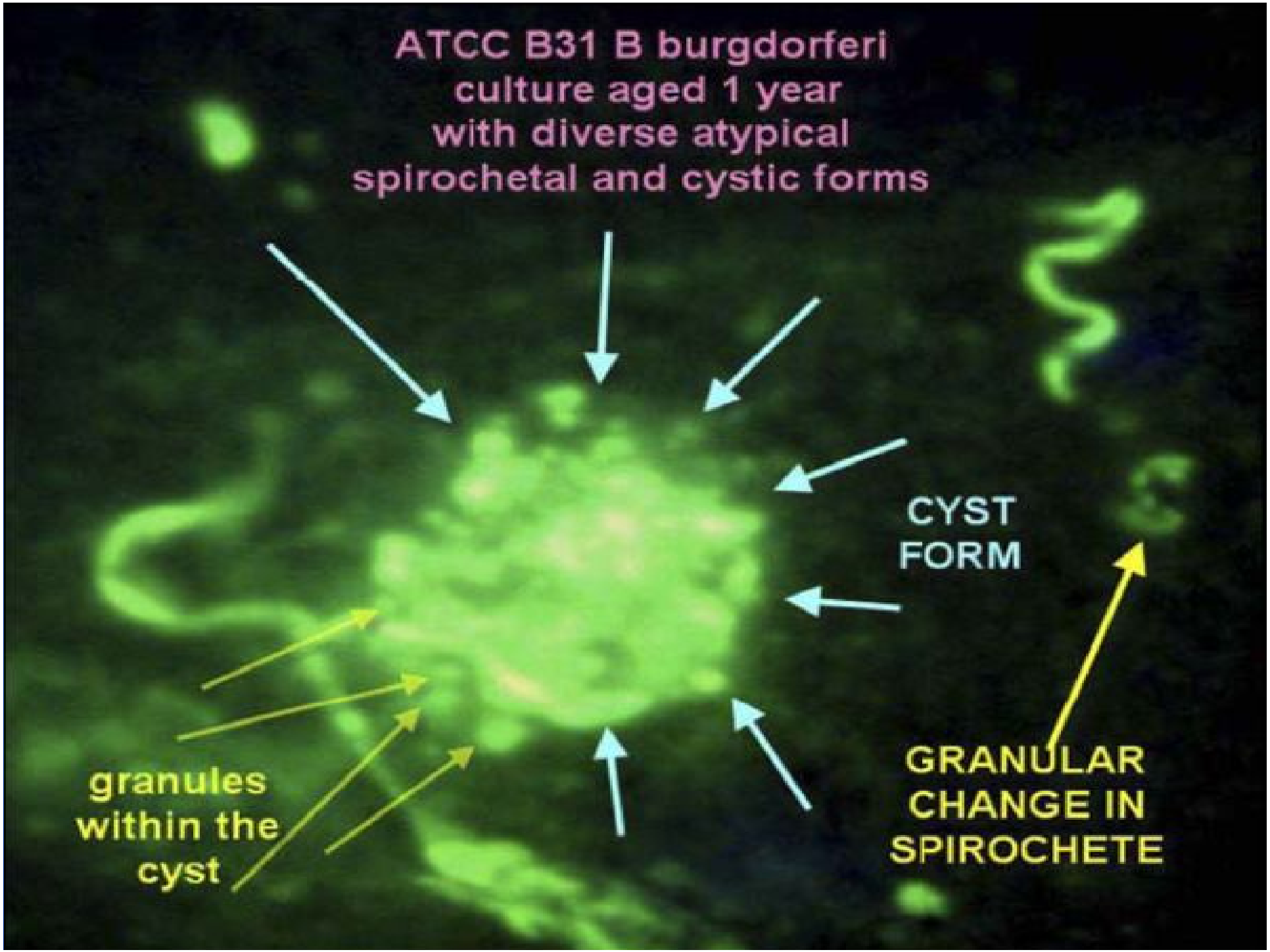
Treatment failures due to Persistence of Lyme Borreliosis: Atypical Forms/Cystic Forms

- Preac-Mursic, V et al, Formation and Cultivation of Borrelia burgdorferi Spheroplast-L-form Variants, Infection 24 (1996);No 3:218-26
- Brorson,O et al, Transformation of cystic forms of Borrelia burgdorferi to normal, mobile spirochetes, Infection 25 (1997); No 4:240-45.
- Alban PS et al, Serum-starvation induced changes in protein synthesis and morphology of Borrelia burgdorferi, Microbiology (2000), 146:119-27
- MacDonald, A. Concurrent Neocortical Borreliosis and Alzheimer's Disease: Demonstration of a Spirochetal Cyst Form. Ann NY Acad Sci. 1988. 468-470
- MacDonald A. Spirochetal cyst forms in neurodegenerative disorders,…hiding in plain sight. Med Hypotheses (2006)





Cyst form developing from Borrelia burgdorferi Note: Internal floccular contents Electron micrograph from Claude Garon, PhD Rocky Mountain Laboratory, NIH, NIAID, Hamilton Montana


ATCC B31 B burgdorferi
culture aged 1 year
with diverse atypical
spirochetal and cystic forms
CYST
FORM
granules
within the
cyst
GRANULAR
CHANGE IN
SPIROCHETE

Treatment Failure—Intracellular B. burgdorferi

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

2) 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.

3) 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.

4) 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.

- "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."

5) 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.

Treatment failures due to Persistence of Lyme Borreliosis: Sequestration in Antibiotically Privileged Sites

- Skin: fibroblasts (Klempner)
- Eye (Preac-Mursic, Meier)
- Ligamentous tissue (Haupl)
- Joints (Priem, Bradley, Fitzpatrick)
- CNS (Coyle, Leigner)
- Endothelial cells and macrophages (Ma et al, Infect Immun 1991 Feb;59(2):671-8; Malawista SE et al, J Immunol 1993 Feb 1;150(3):909-15)

Chronic Persistent Infection with Bb Despite Intensive AB's

- 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
- 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
- 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.

Persistence of Lyme Borreliosis

- 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
- Lawrence C, Lipton RB, Lowy RD, and Coyle PK. Seronegative Chronic Relapsing Neuroborreliosis. Eur Neurol. 1995;35:113-117
- Liegner KB, et al. Recurrent erythema migrans despite extended antibiotic treatment with minocycline in a patient with persisting Borrelia borgdorferi infection. J Am Acad Dermatol 1993;2:312-314
- Preac-Mursic V, et al. Survival of *Borrelia burgdorferi* in antibiotically treated patients with Lyme borreliosis. Infection 1989;17:355-359.
- Straubinger RK, et al. Persistence of Bb in Experimentally Infected Dogs after Antibiotic Treatment. J Clin Microbiol 1997;35(1):111-116

Treatment Outcomes: High Failure Rates in Late Disease

-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.

- -There are frequent treatment relapses and failures with short term therapy:
- 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 pt
- 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

Benefit of Longer treatment Regimes 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 d Rocephin, 89% improved w/ Rocephin + 100d of Amox 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 chr LD treated between 1-11 mo: 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/ chr Lyme treated for 100 d, 90% w/ 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 pts w/ disseminated Lyme treated for 1 or more months of AB's showed that even > 3 mo of treatment may not eradicate the spirochete, longer term therapy may be necessary

Lyme Disease: Optimal Diagnosis & Treatment Regimens: Treat all 3 forms, co-inf's & Address the 15 pt differential diagnostic categories

Symptoms	Testing	Treatment
-EM rash -Flu-like sx -Migratory Joint & muscle pain -Fatigue -HA -Paresthesias come&go -Cognitive dysfunction -Psych abnormalities -Sleep disorder -Neck stiffness -Photophobia & phonophobia -Fluctuating symptoms	-ELISA / C6 peptide -Western Blot: IgG, IgM (B31/297 yield better results. ? 23, 31, 34, 39,83-93 bands..) -PCR: urine and blood -Lyme Dot Blot / RWB -Lyme Serum Antigen -Lymphocyte Transformation test -Testing for co-inf's Rarely: -biopsy & culture -silver staining	-Cell Wall: Penicillins, Cephalosporins, -Cystic: Hydroxychloroquine, Grapefruit Seed Extract,Metronidazole Tinidazole Intracellular: Macrolides, Tetracyclines, Quinolones, Rifampin

Summary

- There are 2 standards of care for Lyme Disease.
- There are significant problems with serology and therefore sero negativity is common
- Persistence of borrelia has been proven in scientific studies. Intracellular location, cystic forms & sequestration in antibiotically privileged sites are among the difficulties in completely eradicating the organism. Longer treatment courses have been shown to be effective
- Optimal diagnostic and treatment modalities are unknown
- Multiple Chronic Infectious Disease Syndrome (SIMC) would better explain resistant symptomatology among patients. Chronic Lyme Disease, co-infections, auto-immunity, inflammation, environmental toxicities (including heavy metal toxicity), sleep disorders, and neuropsychiatric issues are the most common medical problems we find in this population of 12,000 patients treated. Treatment resistant patients often improve once the above issues are adequately treated.

“Wisdom is the marriage of knowledge and experience bound by compassion.”