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 doctor’s 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.


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.”

Method: 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, filariasis, 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. Assessment 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 phagocytophilum, 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


- 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 MMWR56(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.

  EU CALB labs: 3 problems → Il ne doit pas y avoir plus de 5% de seropositifs dans une population donnée, ils ont déterminer le valeur critique du test sur une population en bonne santé (donneurs de sang), et la sensibilité est impossible à déterminer 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
<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>Schmitz et al, 1993</td>
<td>66%</td>
<td>100%</td>
</tr>
<tr>
<td>Engstrom et al, 1995</td>
<td>55%</td>
<td>96%</td>
</tr>
<tr>
<td>Ledue et al, 1996</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Trevejo et al, 1999</td>
<td>29%</td>
<td>100%</td>
</tr>
<tr>
<td>Nowakowski, 2001</td>
<td>66%</td>
<td>99%</td>
</tr>
<tr>
<td>Bacon et al, 2003</td>
<td>68%</td>
<td>99%</td>
</tr>
<tr>
<td><strong>MEAN TOTAL</strong></td>
<td><strong>56%</strong></td>
<td><strong>99%</strong></td>
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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


Pikelj F, Strle F, Mozina M.


False Seronegativity Extensively Documented


5) “... a patient with active Lyme disease may have a negative test result…”

Chronic Lyme Disease: Why is it chronic?

Verified Persistent Infection Despite Antibiotics

- 30% Remained PCR Positive Despite Multiple Courses of “Adequate” Antibiotic Therapy

- “....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.”

- 74% Remained PCR Positive Despite Extended Antibiotic Therapy
Treatment failures due to Persistence of Lyme Borreliosis: Atypical Forms/Cystic Forms


- Alban PS et al, Serum-starvation induced changes in protein synthesis and morphology of Borrelia burgdorferi, Microbiology (2000), 146:119-27


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.

**Granules within the cyst**

**Cyst Form**

**Granular Change in Spirochete**
Treatment Failure—Intracellular B. burgdorferi


“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.”

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)
Chronic Persistent Infection with Bb Despite Intensive AB’s

- Donta, ST, Tetracycline therapy in chronic Lyme disease. Chronic Infectious Diseases, 1997; 25 (Suppl 1): 552-56
Persisense of Lyme Borreliosis

Treatment Outcomes:
High Failure Rates in Late Disease

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

- 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


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
<table>
<thead>
<tr>
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<th>Treatment</th>
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<td>- EM rash</td>
<td>- ELISA / C6 peptide</td>
<td>- Cell Wall:</td>
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<td>- Migratory Joint &amp; muscle pain</td>
<td>(B31/297 yield better results. ? 23, 31, 34, 39,83-93 bands..)</td>
<td>Cephalosporins,</td>
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<tr>
<td>- Fatigue</td>
<td>- PCR: urine and blood</td>
<td></td>
</tr>
<tr>
<td>- HA</td>
<td>- Lyme Dot Blot / RWB</td>
<td>- Cystic:</td>
</tr>
<tr>
<td>- Paresthesias come&amp;go</td>
<td>- Lyme Serum Antigen</td>
<td>Hydroxychloroquine,</td>
</tr>
<tr>
<td>- Cognitive dysfunction</td>
<td>- Lymphocyte Transformation test</td>
<td>Grapefruit Seed,</td>
</tr>
<tr>
<td>- Psych abnormalities</td>
<td>- Testing for co-inf’s</td>
<td>Metronidazole,</td>
</tr>
<tr>
<td>- Sleep disorder</td>
<td>Rarely:</td>
<td>Tinidazole</td>
</tr>
<tr>
<td>- Neck stiffness</td>
<td>- biopsy &amp; culture</td>
<td>Intracellular:</td>
</tr>
<tr>
<td>- Photophobia &amp; phonophobia</td>
<td>- silver staining</td>
<td>Macrolides,</td>
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<td>- Fluctuating symptoms</td>
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- Migratory Joint & muscle pain
- Fatigue
- HA
- Paresthesias come&go
- Cognitive dysfunction
- Psych abnormalities
- Sleep disorder
- Neck stiffness
- Photophobia & phonophobia
- Fluctuating symptoms

**Testing**
- 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
- biopsy & culture
- silver staining

**Treatment**
- 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.”