Lyme Disease: Standards of Care

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


Two equally legitimate but divergent standards of care currently exist for the diagnosis and treatment of Lyme disease.

ILADS Guidelines
VS. IDSA Guidelines

“Both guidelines are evidence-based and peer reviewed, with the IDSA generally recommending standardized short-term treatment, and ILADS recommending individualized treatment based on the clinical course of the patient.”

“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).”
“Lyme disease lacks characteristics of other infections that justify longer treatment, such as... infections caused by an intracellular pathogen”

IDSA Guidelines

*Bb* is an intracellular pathogen


**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"

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment Received</th>
<th>SF PCR Positive After Treatment</th>
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<tbody>
<tr>
<td>12</td>
<td>&lt; 1 month PO antibiotics</td>
<td>12 out of 12 (100%)</td>
</tr>
<tr>
<td>19</td>
<td>30-60d PO antibiotics and/or IV up to 3 wks</td>
<td>7 out of 19 (37%)</td>
</tr>
<tr>
<td>10</td>
<td>“multiple courses of antibiotic therapy”</td>
<td>3 out of 10 (30%)</td>
</tr>
</tbody>
</table>

None of the above discussed in The Guidelines

American patients, therefore sensu stricto

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

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.”


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

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

15 yr old girl — Tick bite, Bell’s palsy, Positive serologies
- Amoxicillin/clavulanic acid — 12 d, Doxycycline — 2 wks
- Two months later, arthritis of the knee

*Bb* culture synovial fluid: Positive — Bound mAb H5332
- Most likely sensu stricto based on monoclonal ab


54 yr old man — 2 yrs of fevers, arthralgias, circular rashes
- Positive Lyme serologies
- After 3 wks IV penicillin, still febrile & anemic

*Bb* demonstrated in the spleen

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

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

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

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

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.

48 year old woman with choroiditis 2 months after a tick bite & rash—Lyme serologies initially positive

After 6 weeks doxycycline the choroiditis resolved

“The IgG titer rapidly decreased within a few weeks after the first antibiotic therapy, and remained negative in both the IF and ELISA evaluations, despite progression of the disease.”

4 weeks post-antibiotics, arthritis in hands & EKG with newly inverted P-waves

CSF—Negative for pleocytosis, protein, or Lyme antibody

Ceftriaxone for 2 weeks—Resolution of arthritis and rhythm disturbance

Human Studies Documenting Persistent *Bb* Infection, but NOT Cited by The Guidelines

- 2 months post-ceftriaxone, choroiditis returned
  - Treated — Roxithromycin & TMP/SMX
  - Upon starting antibiotics, severe exacerbation of hand pain

- Biopsy of flexor retinaculum — “The ligament tissue was found to be heavily infiltrated by spirochetes.”

- Positive culture for *B. burgdorferi sensu stricto*
  - PCR positive, amplified product hybridized using Southern blot
  - Both negative and positive controls were appropriately used throughout the procedure

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

Pre-antibiotics, 12 of 13 eventual relapsers (92%) were initially seropositive.

Post-antibiotics, during relapse with PCR and/or culture confirmed persistent infection, only 6 of 12 relapsers (50%) IgG seropositive.

Persistent infection despite diminishing serologies.

Immediately post-antibiotics but before clinical relapse, only 1 of 13 eventual relapsers (8%) was PCR positive.

During clinical relapse, 12 of 13 patients (92%) were PCR positive.

Increased PCR over time consistent with replication.

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

Persistent *Bb* infection despite:
- Single rounds of recommended antibiotic therapy;
- Multiple rounds of recommended antibiotic therapy; and
- Aggressive, ie, more than 3 months of antibiotic therapy

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

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### Early Lyme: Objective vs. Subjective

74 patients with EM

<table>
<thead>
<tr>
<th>Objective Findings</th>
<th>Subjective Symptoms</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>EM as Entry Criteria</td>
<td>Fatigue</td>
<td>56.8%</td>
</tr>
<tr>
<td>No A-V Block</td>
<td>Myalgias</td>
<td>43.2%</td>
</tr>
<tr>
<td>No Meningitis</td>
<td>Headache</td>
<td>39.2%</td>
</tr>
<tr>
<td>No Cranial Neuritis</td>
<td>Chills</td>
<td>35.1%</td>
</tr>
<tr>
<td>No encephalomyelitis</td>
<td>Joint pain</td>
<td>35.1%</td>
</tr>
<tr>
<td>Joint swelling in only 10.8% (without swelling)</td>
<td></td>
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</tr>
</tbody>
</table>

Asymptomatic & Subjective Only

Lyme Vaccine Study—

11% of New Seroconversion by IgG 5 Band Western Blot was Asymptomatic

16% of ‘Definite Lyme’ had only Subjective Symptoms

*Asymptomatic Lyme disease proven—So notion that Lyme disease cannot occur without objective features is untenable*


**Human Persistent Bb Infection, NOT Cited by The Guidelines—Objective vs. Subjective**

- **18 late Lyme disease patients — Failed IV antibiotics, sometimes repeatedly**
  - Despite antibiotics, all patients demonstrated:
    - Positive *Bb* PCR and/or immuno-electron microscopy
    - Initial testing: 7 of 18 patients (39%) seronegative
    - Repeat testing: 12 of 18 patients (67%) seronegative
  - 9 of 18 (50%): Non-specific symptoms at any point
  - 12 of 18 (67%): Non-specific symptoms in later stages

8 patients--originally met CDC case definition

- Myalgia despite treatment in all, 75% met American College of Rheumatology criteria for fibromyalgia

- Treated patients: 43%--muscle biopsy Lyme PCR positive
  - Most had received repeated courses of oral antibiotics & 1 course of ceftriaxone
  - All were seronegative by CDC 2-tiered evaluation.

- PCR methods-3 different labs, none contained previous Bb
  - All 14 negative controls remained negative

- Underscores the need for caution in diagnosing “Not-Lyme, but fibromyalgia”

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

Randomized Controlled Trials

Open Label Trials
Review of the 4 NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials


Review of the 4 NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials


Unrealistic Design Assumptions to Assess Primary Outcomes

Trials Were Underpowered to Detect Clinically Meaningful Treatment Effects

Inappropriate Minimum Clinically Important Difference – To detect a treatment effect, it would have required participants to improve to a level of health which was a full standard deviation superior to that of the general population

Review of the 4 NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials


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 Primary Outcome: Fatigue

- Demonstrated Benefits to Fatigue After Treatment
- No Evidence of Unblinding

Review of the 4 NIH Sponsored Chronic Lyme Re-tx Randomized Controlled Trials


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

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.
For More Information Visit
ILADS.ORG