

Lyme Disease: Diagnosis and Management in Military Treatment Facilities

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Key Issues

- Current status of diagnostic testing for *Borrelia burgdorferi* infection
- Current status of IDSA guidelines
- IDSA versus ILADS guidelines for diagnosis and management of Lyme disease

Infectious Diseases Society of America (IDSA)

The International Lyme and Associated Diseases Society (ILADS)

Reason Presented to DHB

- Provide information on current diagnosis and management of Lyme disease in military medical treatment facilities

Background Information: Diagnosis of Lyme Disease

- Multiple diagnostic methods utilized
 - Clinical diagnosis
 - Two-tier testing
 - Screening Enzyme Linked Immunoassay (ELISA)
 - Confirmatory Western Blot (WB)
 - Polymerase Chain Reaction (PCR)
 - Cerebrospinal fluid testing

118 cases of EM with culture or PCR confirmed
Borrelia burgdorferi infection EM rashes were:



Homogenous – 59%

Central erythema – 32%

“classic” EM

Central clearing ‘bulls eye’ – only 9%

N Engl J Med 2006;354:2794-801

Ann Intern Med 2002; 136:421

Background Information: Two-Tier Testing

- Screening test
 - Polyvalent ELISA
 - Insensitive in *first two weeks* of infection
 - If positive or indeterminate, confirmatory done
- Confirmatory test
 - Immunoblot of both IgM and IgG
 - CDC criteria used for interpretation

Background Information: Two-Tier Testing

- DOD uses only FDA approved testing
- IGeneX, Inc. in Palo Alto, California
 - Used by Washington, D.C. non-DOD practitioners who claim expertise in Lyme
 - Not FDA-approved
 - Claim “internal validation assays”
 - DOD beneficiaries pay out of pocket

LYME WARS

Let's tackle the testing

The two tier testing system endorsed by the Centers for Disease Control and Prevention (CDC) has a high specificity (99%) and yields few false positives. But the tests have a uniformly miserable sensitivity (56%)—they miss 88 of every 200 patients with Lyme disease (table). By comparison, AIDS tests have a sensitivity of 99.5%—they miss only one of every 200 AIDS cases. In simple terms, the chance of a patient with Lyme disease being diagnosed using the commercial tests approved by the Food and Drug Administration and sanctioned by the CDC is about getting heads or tails when tossing a coin, and the poor test performance assures that many patients with Lyme disease will go undiagnosed.

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British Medical Journal
November 2007

Background Information: Two-Tier Testing

Sensitivity of screening test used at National Naval Medical Center

Stage	Total	LIAISON [®] <i>Borrelia burgdorferi</i>			
		Pos	Eqv	Neg	Sensitivity (95% Confidence Intervals)
Early Localized EM	19	13	0	6	68.4% (47.0 – 85.2)
Early Convalescent	21	17	0	4	81.0% (61.6 – 93.2)
Early Neurologic	20	14	0	6	70.0% (49.2 – 86.1)
Total	60	44	0	16	

Package Insert

LIAISON[®] *Borrelia burgdorferi* (310870)

Background Information: Treatment of Lyme Disease

- Treatment durations well studied
- Military MTF physicians follow IDSA guidelines for Lyme diagnosis and therapy
- ILADS guidelines discussed in Infectious Diseases conferences

The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America

IDSA GUIDELINES

Clinical Infectious Diseases 2006;43:1089-134

Practice Parameter: Treatment of nervous system Lyme disease (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

ABSTRACT Objective: To provide evidence-based recommendations on the treatment of nervous system Lyme disease and post-Lyme syndrome. Three questions were addressed: 1) Which antimicrobial agents are effective? 2) Are different regimens preferred for different manifestations of nervous system Lyme disease? 3) What duration of therapy is needed? Methods: The authors analyzed published studies (1983-2003) using a structured review process to classify the evidence related to the questions posed. Results: The panel reviewed 353 abstracts which yielded 112 potentially relevant articles that were reviewed, from which 37 articles were identified that were included in the analysis. Conclusions: There are sufficient data to conclude that, in both adults and children, this nervous system infection responds well to penicillin, ceftriaxone, cefotaxime, and doxycycline (Level B recommendation). Although most studies have used parenteral regimens for neuroborreliosis, several European studies support use of oral doxycycline in adults with meningitis, cranial neuritis, and radiculitis (Level B), reserving parenteral regimens for patients with parenchymal CNS involvement, other severe neurologic symptomatology, or failure to respond to oral regimens. The number of children (≥ 8 years of age) enrolled in rigorous studies of oral vs parenteral regimens has been smaller, making conclusions less statistically compelling. However, all available data indicate results are comparable to those observed in adults. In contrast, there is no compelling evidence that prolonged treatment with antibiotics has any beneficial effect in post-Lyme syndrome (Level A). **NEUROLOGY 2007;69:91-102**

Neurology 2007; 69:91-102

Background Information: Treatment of Lyme Disease

Table 3. Recommended therapy for patients with Lyme disease.

Indication	Treatment	Duration, days (range)
Tick bite in the United States	Doxycycline, 200 mg in a single dose ^{a,b} ; 4 mg/kg in children ≥ 8 years of age) and/or observation	...
Erythema migrans	Oral regimen ^{c,d}	14 (14–21) ^e
Early neurologic disease		
Meningitis or radiculopathy	Parenteral regimen ^{c,f}	14 (10–28)
Cranial nerve palsy ^{a,g}	Oral regimen ^c	14 (14–21)
Cardiac disease	Oral regimen ^{a,h} or parenteral regimen ^{a,h}	14 (14–21)
Borrelial lymphocytoma	Oral regimen ^{c,d}	14 (14–21)
Late disease		
Arthritis without neurologic disease	Oral regimen ^c	28
Recurrent arthritis after oral regimen	Oral regimen ^{a,c} or parenteral regimen ^{a,c}	28 14 (14–28)
Antibiotic-refractory arthritis ⁱ	Symptomatic therapy ^j	...
Central or peripheral nervous system disease	Parenteral regimen ^c	14 (14–28)
Acrodermatitis chronica atrophicans	Oral regimen ^c	21 (14–28)
Post-Lyme disease syndrome	Consider and evaluate other potential causes of symptoms; if none is found, then administer symptomatic therapy ^k	...

IDSA Guidelines • CID 2006;43 (1 November)

The International Lyme and Associated Diseases Society

Evidence-based guidelines for the management of Lyme disease

The ILADS Working Group
 ILADS, P.O. Box 341461
 Bethesda, MD 20827-1461, USA
www.ILADS.org

Expert Rev. Anti-infect. Ther. 2(1), (2004)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

A Critical Appraisal of “Chronic Lyme Disease”

Henry M. Feder, Jr., M.D., Barbara J.B. Johnson, Ph.D., Susan O’Connell, M.D.,
Eugene D. Shapiro, M.D., Allen C. Steere, M.D., Gary P. Wormser, M.D.,
and the Ad Hoc International Lyme Disease Group*

N ENGL J MED 357;14 WWW.NEJM.ORG OCTOBER 4, 2007

Clinical Cases

Clinical Case #1

- 35 year old male pilot Patuxent River, MD
- Fatigue, difficulty concentrating, headaches three times per week
- Lyme screening test negative Pax River

Clinical Case #1

- Daughter (2 yrs old) was recently hospitalized for Lyme arthritis
- Whole family seeks evaluation at National Integrated Health (Washington, D.C.)

Clinical Case #1

- Family also sees “Lyme specialist” in Connecticut
- NNMC two tier testing negative
- IGeneX Western Blot testing
 - “Indeterminate”
 - National Integrated Health provider recommends prolonged antibiotic therapy
- Patient fills >8 months of amoxicillin and azithromycin at MTF pharmacies

Clinical Case #2

- 41 year old male active duty Army O5
- Tick bite January 2004
 - Empiric doxycycline given for 2 weeks
 - No EM rash present
- Evaluated by Neurology December 2004
 - Lyme serum testing negative
 - Lyme cerebrospinal fluid testing negative
 - Empiric doxycycline for 30 days

Clinical Case #2

- Lyme serologies in 2006 again negative
- Sees civilian provider in Fairfax, VA
 - IGeneX testing positive
 - Recommends prolonged (≥ 6 months) IV therapy
- WRAMC Infectious Diseases consult
 - July 2007
 - Repeatedly negative testing
 - “Not unreasonable” to give 4 weeks of intravenous ceftriaxone 2 g per day for unexplained neurologic symptoms

Data Presentation

- Up to 25% of patients experience fatigue or muscle aches after antibiotic therapy
- Over time most patients return to normal
- In prospective studies of patients with erythema migrans rash
 - 0.5 to 13.1% experienced subjective symptoms of unknown cause for ≥ 1 year
 - Whether this prevalence exceeded that of such symptoms in the general population is not known
 - None of these studies included a control group

Data Presentation

- Two placebo-controlled trials in patients with persistent symptoms and a history of Lyme disease

TWO CONTROLLED TRIALS OF ANTIBIOTIC TREATMENT IN PATIENTS WITH PERSISTENT SYMPTOMS AND A HISTORY OF LYME DISEASE

- 78 patients seropositive for *B. burgdorferi*
- 51 patients seronegative
- All patients had antecedent objective signs of Lyme disease (most EM rash)

N Engl J Med, Vol. 345, No. 2 · July 12, 2001

TWO CONTROLLED TRIALS OF ANTIBIOTIC TREATMENT IN PATIENTS WITH PERSISTENT SYMPTOMS AND A HISTORY OF LYME DISEASE

- Treated with either
 - 1 month intravenous ceftriaxone followed by 2 months oral doxycycline
- OR
- Identical-appearing intravenous and then oral placebos

N Engl J Med, Vol. 345, No. 2 · July 12, 2001

TWO CONTROLLED TRIALS OF ANTIBIOTIC TREATMENT IN PATIENTS WITH PERSISTENT SYMPTOMS AND A HISTORY OF LYME DISEASE

- Assessed at enrollment and 3 months after completion of therapy
- Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36)
- No significant differences in scores between antibiotic or placebo groups

N Engl J Med, Vol. 345, No. 2 · July 12, 2001

Policy Recommendations

- Recommend continued use of IDSA guidelines
- Expert panel re-review of guidelines based on lawsuit by Connecticut Attorney General currently underway
- Await outcome of this review by IDSA

Conclusion

- Although sensitivity of screening tests for Lyme disease not 100%
 - MTF physicians utilize multiple clinical and laboratory parameters in evaluation of tickborne disease
 - Military Infectious Diseases physicians see many consults of both Lyme seronegative and seropositive patients
- Military Infectious Diseases specialists available 24 hours a day in all services for expert consultation
- ILADS guidelines expose our patients to potential iatrogenic harm without durable benefit based on best available evidence