Problems with Diagnosis and Treatment of Lyme Disease

Presentation to the IDSA Lyme Guidelines Review Panel

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Raphael Stricker, MD

Past President, International Lyme & Associated Diseases Society

1. Challenge to Laboratory Diagnostic Test Requirement and Restrictions on the Use of Clinical Judgment—Pages 1089-1090

"*Clinical findings are sufficient for the diagnosis of erythema migrans, but clinical findings alone are not sufficient for diagnosis of extracutaneous manifestations of Lyme disease….Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extracutaneous Lyme disease….*"

2. Challenge to Implausibility of Persistent Infection--Page 1118

"The notion that symptomatic, chronic *B. burgdorferi* infection can exist despite recommended treatment courses of antibiotics in the absence of objective clinical signs of disease, is highly implausible…."

3. Challenge to Early Lyme Disease Treatment Duration--Recommendation 1, Page 1104

"Doxycycline (100 mg twice per day), amoxicillin (500 mg 3 times per day), or cefuroxime axetil (500 mg twice per day) *for 14 days (range for doxycycline, 10–21 days; range for amoxicillin or cefuroxime axetil, 14–21 days) is* recommended for treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans in the absence of specific neurologic manifestations (see Early Neurologic Lyme Disease) or advanced atrioventricular heart block (tables 2 and 3) (A-I)….*Each of the recommended antimicrobial agents has been shown to be highly effective in the treatment of erythema migrans and associated symptoms in prospective studies*."

4. Challenge to Late Neurologic Lyme Disease Treatment--Recommendation 3, Page 1113

"Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone (*2 g once per day intravenously for 2–4 weeks*) (tables 2 and 3) (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-II). *Response to treatment is usually slow and may be incomplete. Re-treatment is not recommended unless relapse is shown by reliable objective measures*."

Issues to Address in IDSA Guidelines

- Lyme disease is easy to diagnose
- Lyme disease is easy to treat
- Persistent infection following short-course antibiotic therapy is “highly implausible”
- Alleged danger of prolonged antibiotic treatment

1. Challenge to Laboratory Diagnostic Test Requirement and Restrictions on the Use of Clinical Judgment—Pages 1089-1090

"*Clinical findings are sufficient for the diagnosis of erythema migrans, but clinical findings alone are not sufficient for diagnosis of extracutaneous manifestations of Lyme disease….Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extracutaneous Lyme disease….*"

Challenge to Laboratory Testing/Clinical Judgment

1. A study by Bakken et al. (1997) comparing interlaboratory variation among 516 participants in the Wisconsin State Laboratory of Hygiene/College of American Pathologists Proficiency Testing Program reached the following conclusion: **“Our data indicated that the sensitivity and specificity of the currently used tests for Lyme disease are not adequate to meet the two-tier test approach being recommended.”**

   Because of the poor performance of these tests, the study went on to say: **“In conclusion, our results suggest that stronger measures need to be taken by the Food and Drug Administration to control the quality of commercially available Lyme disease assay kits.”**

Challenge to Laboratory Testing/Clinical Judgment

2. Brown et al. (1999) from the Food and Drug Administration (FDA) reviewed studies of Lyme test performance published through 1998 and reached the following conclusion:

   “Given the results seen with different manufacturers’ test kits, interlaboratory results predictably show poor agreement. A test in 4 laboratories, which used either IFA or ELISA, indicated that neither interlaboratory nor intralaboratory testing were reliable.”

Challenge to Laboratory Testing/Clinical Judgment

3. A study by Hunfeld et al. (2002) involving 337 microbiology laboratories in Europe reached the following conclusion: "**Quantification of test results and reporting of specific immunoblot bands showed high variability.** Moreover, for some assays a high number of false positive and false negative test results were reported by the participants….**In view of our results further standardisation of Lyme disease serology is not just desirable but is urgently needed. Moreover, stronger criteria for the validation of available test kits must be applied."**

Challenge to Laboratory Testing/Clinical Judgment

4. A review by Stricker and Johnson (2007) of North American case-control studies of commercial two-tier Lyme testing reached the following conclusion: "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."**

   An updated analysis including more recent studies found that the sensitivity of the two-tier test system was even worse (46%). This sensitivity is far below the 95% cutoff required for an accurate diagnostic test, and much worse than the 99.5% sensitivity of commercial HIV testing.

Table 1: Sensitivity/Specificity of Commercial Two-tier Testing for Convalescent/Late-stage Lyme Disease*

Study/Year	Location	Patients/Controls	Sensitivity (%)	Specificity (%)
Schmitz et al., 1993[a]	US	25/28	66	100
Engstrom et al., 1995[b]	US	55/159	55	96
Ledue et al., 1996[c]	US	41/53	44	100
Tilton et al., 1997[d]	US	23/23	45	100
Trevejo et al., 1999[e]	US	74/38	29	100
Bacon et al., 2003[f]	US	106/559	67	99
Binnicker et al., 2008[g]	US	35/5	49	100
Steere et al., 2008[h]	US	76/86†	18	99
Totals	US: 8	435/951	46	99

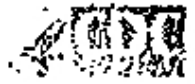
**Limited to studies from the US that included negative controls.*
†Non-commercial enzyme-linked immunosorbent assay (ELISA).
a. Schmitz et al., Eur J Clin Microbiol Infect Dis, *1993;12:419–24.; b. Engstrom et al.,* J Clin Microbiol, *1995;33:419–27.; c. Ledue et al.,* J Clin Microbiol, *1996;34:2343–50.; d. Tilton et al.,* Clin Infect Dis, *1997;25(Suppl. 1):S31–4.; e. Trevejo et al.,* J Infect Dis, *1999;179:931–8.; f. Bacon et al.,* J Infect Dis, *2003;187:1187–99.; g. Binnicker et al.,* J Clin Microbiol, *2008;46:2216–21.; h. Steere et al.,* Clin Infect Dis, *2008;47:188–95.*

Sensitivity of 2-tiered Testing
Good in Later Stages of Disease

Stage of Lyme disease	n	EIA %	2-tier %
Acute (EM)	80	60	38
Early convalescent	106	91	67
Early neurologic	15	100	**87**
Arthritis	33	97	**97**
Late neurologic	11	100	**100**

Bacon, *et al.* (2003) *JID*

Johnson, *et al.* (2004) *JID*



From Johnson BJ, Canadian Lyme Consensus Conference, 2006

BUT…

"For late disease, the case definition requires at least one late manifestation **and laboratory confirmation of infection**, and therefore the possibility of **selection bias** toward reactive samples cannot be discounted."

Bacon et al, *J Infect Dis* 2003;187:1187-99

Limitations of 2-tiered Testing

- Insensitive in acute EM; early neuro ?
- Lacks antigens expressed only in mammals
- Complex, technically demanding, costly
- Hard to standardize
  - Reading Wbs requires judgment and experience
  - Wbs are only semi-quantitative
  - Faint bands are difficult to interpret
- May require 2 blood samples
- Appropriate use of IgM blots requires knowledge of date of disease onset; IgM blots less specific than IgG blots
- Some labs are inexperienced in properly setting blot development cut-off controls

From Johnson BJ, Canadian Lyme Consensus Conference, 2006

Limitations of Two-Tier Testing

"Relatively few studies using currently available commercial
tests have evaluated the performance of the recommended
two-tier testing on well-characterized sera from patients with extracutaneous manifestations of Lyme borreliosis. Comparison of sensitivities and specificities between studies is difficult due to the use of different antigen preparations and test methods and inclusion of sera from Lyme borreliosis patients with undefined disease duration and treatment history."

Aguero-Rosenfeld et al, *Clin Microbiol Rev* 2005;18:484-509

Sensitivity of 2nd Generation C6 EIA Preliminary Results*

	n	C6 EIA %	2-tier %
Acute early Ld (mainly EM)	69**	68.1	50.7
Disseminated Ld (mainly neuroß and Lyme arthritis)	91**	94.5	81.3
All Ld patients, all stages	275	77.8	(62.5)*

*Some Wb tests incomplete, not included in analyses

**Samples for which Wb testing is complete

From Johnson BJ, Canadian Lyme Consensus Conference, 2006

Questionable Basis of Two-Tier Testing for Lyme Disease

The IDSA guidelines rely on the CDC surveillance criteria for use and interpretation of Lyme testing. The CDC in turn cites two pivotal studies to support the current commercial test system, one by **Engstrom et al**. for positive IgM results and the other by **Dressler et al**. for positive IgG results.

Engstrom et al. and Dressler et al. pegged positive test results to high specificity (92-94% and 99%, respectively) at the expense of sensitivity (44-75% and 83%, respectively). **Thus the two-tier surveillance test system, although highly specific, lacks the sensitivity required for an accurate diagnostic test.**

Should Lyme Testing take Precedence over Clinical Judgment?

Positive Predictive Value of Lyme Testing

Guidelines (p. 1117): “Regardless of the nature of the symptom(s), **a low positive predictive value can be anticipated if serologic testing is done for patients who do not reside in or travel to a geographic area where Lyme disease is endemic.** Under these circumstances, the majority of patients with a positive test result will not have active *B. burgdorferi* infection and, accordingly, would be unlikely to obtain a durable response from antibiotic treatment directed at this infection.”

Positive Predictive Value of Lyme Testing

Reed KD. Laboratory testing for Lyme disease: Possibilities and practicalities. J Clin Microbiol 2002;40:319-3

“Because Lyme disease incidence rates and vector abundance vary widely between different geographic areas, it can be difficult for physicians to have sufficient information to allow accurate assessment of pretest probability of Lyme disease for individual patients.”

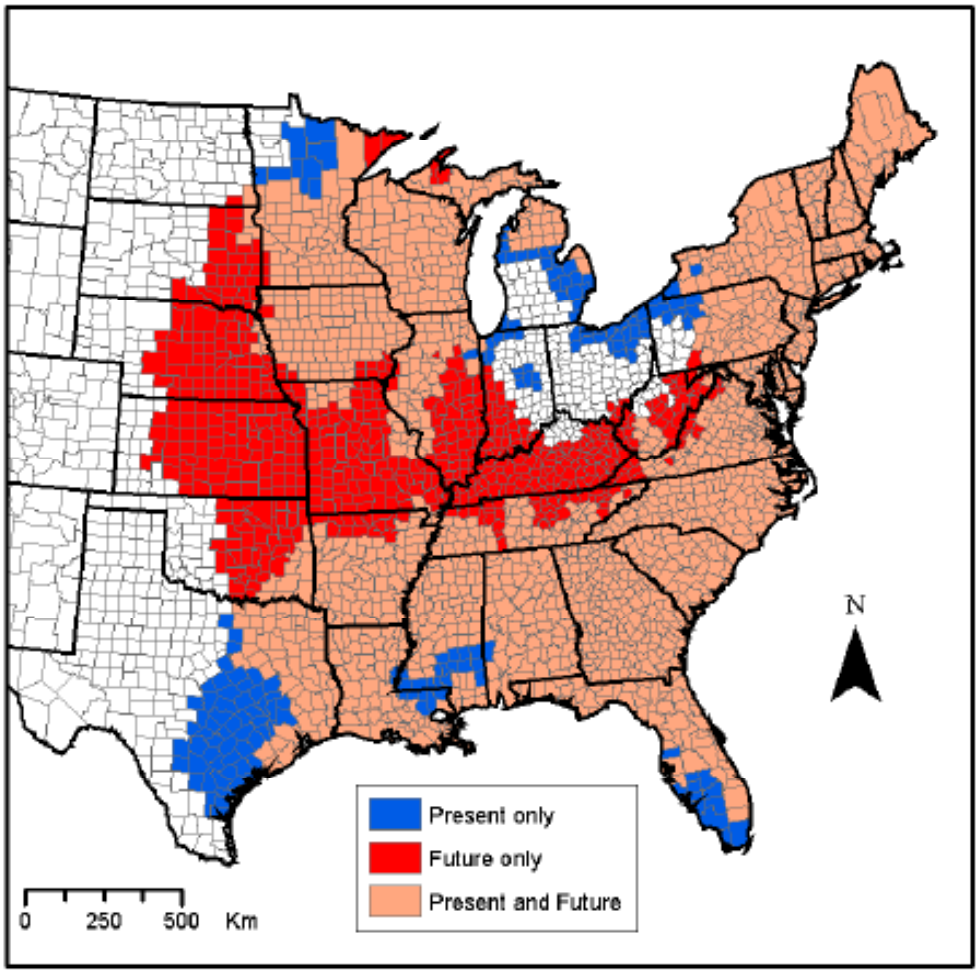


Figure 3.
Change in county-based distribution of *I. scapularis* from present to the 2080s. The future distribution based on climate change data, which considers the effects of both greenhouse ga and sulfate aerosols, was overlaid on the current predicted distribution. The map reveals futur suitable (in red) and unsuitable (in blue) counties. Counties that remain suitable over time (i pink) are also displayed.

Brownstein et al. *Ecohealth* 2005;2:38-46.

2. Challenge to Implausibility of Persistent Infection--Page 1118

"The notion that symptomatic, chronic *B. burgdorferi* infection can exist despite recommended treatment courses of antibiotics in the absence of objective clinical signs of disease, is highly implausible…."

Zoonotic Infection with *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.

Table 1. "Stealth" pathology of *Borrelia burgdorferi*.

Immunosuppression
Tick saliva components
Complement inhibition
Inhibitory cytokine induction (IL-10)
Lymphocyte/monocyte tolerization
Antibody sequestration in immune complexes
Genetic, phase, and antigenic variation
Gene switching (trypanosomes)
Mutation/recombination (HIV)
Variable antigen expression (*Neisseria* species)
Dormant state, autoinduction (*Mycobacterium* species)
Fibronectin binding (*Staphylococcus* and *Streptococcus* species)
Physical seclusion
Intracellular sites
Multiple cell types (synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and nerve cells)
Persistent infection in vitro (8 weeks)
Extracellular sites
Privileged sites (joints, eyes, and CNS)
Cloaking mechanisms (binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin)
Secreted factors
Hemolysin (BlyB)
Porin (Oms 28)
Adhesin (Bgp)
Pheromones (DPD/AI-2)
Aggrecanase (ADAMTS-4)

Stricker, *Clin Infect Dis* 2007;45:149-157

Persistence Despite Treatment

Study	Culture and/or PCR Evidence of Persistent Infection
Breier (2001)	Despite repeated treatment, Bb cultured from skin of enlarging lichen sclerosus lesions.
Oksi (1999)	Thirteen of 32 patients (40%) had PCR- or culture-confirmed relapses after treatment.
Bayer (1996)	97 previously treated chronic Lyme patients were PCR- positive in urine samples.
Preac Mursic (1996)	Isolation of Bb by culture in 5 patients, 4 of whom were seronegative on previous occasions.
Battafarano (1993)	Despite repeated treatment, Bb documented in synovium and synovial fluid of a patient with arthritis of the knee after 7 years.
Preac-Mursic (1993)	Bb cultured from iris biopsy 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 geereralized ulcertating bullous lichen sclerosus et atrophicus. Br J Dermatol 2001;144:387-392; Oksi J, et al. *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med 1999;**31:** 225-32; 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**:347-53; Preac-Mursic V, et al. Formation and cultivation of Borrelia burgdorferi spheroplast L-form variants. Infection 1996;**24**:218-26; Battafarano DF, et al. Chronic septic arthritis caused by *Borrelia burgdorferi*. Clin Orthoped 1993;297:238-41; Preac-Mursic et al. First isolation of *Borrelia burgdorferi* from an iris biopsy. J Clin Neuroophthalmol 1993;13:155–61

3. Challenge to Early Lyme Disease Treatment Duration--Recommendation 1, Page 1104

"*Each of the recommended antimicrobial agents has been shown to be highly effective in the treatment of erythema migrans and associated symptoms in prospective studies*."

Early Lyme Disease Treatment

Guidelines (p. 1104) state: "Doxycycline, amoxicillin, or cefuroxime **for 14 days** is recommended for treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans".

Amoxicillin: None of the trials cited by the guidelines used amoxicillin alone for less than 20 days.

Cefuroxime: All 3 of the cited trials employed a 20-day cefuroxime treatment regimen.

Conclusion: The recommendation to reduce treatment duration for amoxicillin and cefuroxime to 14 days lacks explicit evidence that effectiveness is maintained with the shorter regimens. **This portion of the recommendation should be revised.**

Slide courtesy of E. Maloney, MD

Early Lyme Disease Treatment

Doxycycline 100mg BID/TID x 20-21 days

Intent-to-Treat Analysis

Study	N	Success	Improve	Uneval	Failed	Total Failed
Dattwyler et al 1990	37	35 (95%)	-	2 (5%)	-	2 (**5%**)
Dattwyler et al 1997	72	58 (81%)	-	13 (18%)	1 (1%)	14 (**19%**)
Nadelman et al 1992	45	29 (64%)	6 (13%)	7 (16%)	3 (7%)	10 (**22%**)
Luger et al 1995	89	48 (54%)	5 (6%)	36 (40%)	-	36 (**40%**)
Wormser et al 2003	59	30 (51%)	10 (17%)	19 (32%)	-	19 (**32%**)

Slide courtesy of E. Maloney, MD

Early Lyme Disease Treatment

Doxycycline 100mg BID x 10 days

Intent-to-Treat Analysis

Author	N	Success	Improved	Uneval	Failed	Total Failed
Massarotti 1992	26	14 (54%)	-	4 (15%)	8 (31%)	12 (**46%**)
Wormser* 2003	61	36 (59%)	6 (10%)	18 (29%)	1 (2%)	19 (**31%**)

* Data from 12 month evaluation

Slide courtesy of E. Maloney, MD

Early Lyme Disease Treatment

Doxycycline 10-day Treatment Arm

Evaluation Point	% Response	On-Study	Intent-to-Treat
Baseline	NA	61 patients	61 patients
20 days	71%	34/48 (71%)	34/61 (56%)
3 months	77%	36/47 (77%)	36/61 (59%)
12 months	84%	36/43 (84%)	36/61 (59%)
30 months	90%	28/31 (90%)	28/61 (46%)

Wormser et al. *Ann Intern Med* 2003;138:697-704.

4. Challenge to Late Neurologic Lyme Disease Treatment--Recommendation 3, Page 1113

"Response to treatment is usually slow and may be incomplete. Re-treatment is not recommended unless relapse is shown by reliable objective measures."

Late Neurologic Lyme Treatment

Insufficient evidence

- 4 open-label trials cited by IDSA guidelines
- 96 patients
- Variable duration of ceftriaxone treatment

Evidence misapplied

- Poor outcomes:

  Only 7-35% returned to pre-morbid baseline
- Restrictive treatment recommendation not supported

Dattwyler RJ. J Infect Dis 1987;155:1322–5. Dattwyler RJ. Lancet 1988; 1:1191–4.
Logigian EL. N Engl J Med 1990; 323:1438–44. Logigian EL. J Infect Dis 1999; 180:377–83.

Slide courtesy of E. Maloney, MD

Safety of Intravenous Therapy in Lyme Disease

Study	Patients	Days of IV Antibiotic/Placebo Therapy (Range)	Total IVD Days	Significant Adverse Events* (%)	Adverse Event Rate/1,000 IVD Days (Range)
Klempner et al. 2001	129	30	3,870	2 (2)	0.5
Krupp et al. 2003	55	30	1,650	4 (7)	2.4
Oksi et al. 2007	145	21	3,045	2 (1)	0.7
Fallon et al. 2008	37	70	2,590	7 (19)	2.7
TOTAL	**366**	**38 (21-70)**	**11,115**	**15 (4)** †	**1.3 (0.5-2.7)**

*Significant adverse events included medication-related complications (allergic reactions, gallbladder toxicity, *Clostridium difficile* enterocolitis, renal failure) and catheter-related complications (skin infiltration, infection and thrombosis). IVD, intravascular device

†Significant adverse events occurred in 10/260 patients (4%) receiving IV antibiotics and 5/106 patients (5%) receiving IV placebo.

Systematic Errors and Misleading Statements in IDSA Lyme Guidelines

Problem	Example
Exaggeration	“Vast majority” translates into 60-65% of patients with early neurologic, cardiac and arthritic symptoms of Lyme disease
Circular reasoning	Define a condition with positive test, then say test has 100% sensitivity
Small sample sizes	Late Lyme disease diagnosis & treatment
Data selection/exclusion	Treatment success & failure
Reliance on Expert Opinion	Panel bias against chronic Lyme disease

Conclusions

- Science does not support the inadequate diagnostic testing for Lyme disease recommended by the IDSA guidelines
- Science does not support the inadequate treatment of Lyme disease recommended by the IDSA guidelines
- Persistent infection causing persistent symptoms is plausible in chronic Lyme disease
- Prolonged antibiotic treatment is relatively safe and justifiable in chronic Lyme disease