



## International Lyme and Associated Diseases Society

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October 25, 2006

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**Subject: Retraction of “The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America.”**

Dear Dr. Gorbach:

On behalf of the membership of the International Lyme and Associated Diseases Society (ILADS), I am submitting a formal request for retraction of the article, “The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America” (hereafter referred to as the “Lyme guidelines article”), which has been published electronically in your journal (1).

ILADS is requesting retraction of the Lyme guidelines article because the authors of the article employed exclusionary data selection that substantially biased the resulting diagnosis and treatment recommendations while ignoring opposing or dissenting views about these recommendations. As with research articles tainted by data selection, the Lyme guidelines article threatens to harm patients and patient care due to the biased methodology used by the authors, and this threat can only be avoided by formal retraction of the article.

The attached analysis of key points in the Lyme guidelines article demonstrates that the authors of the article made statements that either reflected significant selection bias of published data or ignored published evidence that conflicted with their opinions. Nowhere is this more apparent than in Dr. Klemmner’s analysis of the three NIH-funded Lyme treatment studies, which elevates and relies on the findings of his own study while dismissing the results of two other studies that conflict with his findings. Other statements about the erythema migrans (EM) rash, Lyme testing methodology, antibiotic treatment of chronic Lyme disease, Lyme disease in pregnancy and Lyme disease in Southern states all reflect a biased view of Lyme disease that is either unsubstantiated or refuted by available peer-reviewed published literature.

It is disturbing that ten of the central recommendations in the guidelines are supported by evidence ranked E-III—that is, “very strong” recommendations based on the weakest

level of evidence—opinion. In light of the controversy surrounding Lyme disease diagnosis and treatment and our evolving understanding of the disease, it is inappropriate to dictate medical care based on such weak evidence. The panel of authors was selected to exclude divergent points of view from patients, from treating physicians in other medical societies, and even from physicians within IDSA itself. The failure of the authors to disclose dissenting views presents a false sense of consensus on an issue that is in fact highly controversial, misinforming patients and physicians alike about available treatment options and denying the exercise of clinical discretion and individualized medical decision-making that is central to any complex illness.

Although the Lyme guidelines article boasts 405 references, many of the dissenting references are either glossed over or ignored in the text. In addition, as of the date of publication of the Lyme guidelines article there were 18,537 articles about tick-borne diseases listed on Medline, so the referenced articles represent only 2% of the available literature. The remaining 98% of these articles often present opposing or conflicting views of Lyme disease, and thus the data selection by the authors is even more striking.

We are aware that retraction of medical publications is generally reserved for research articles that violate principles of scientific integrity (2). Scientific integrity has been defined as “commitment to truthfulness, to personal accountability and to vigorous adherence to standards of professional conduct (eg, accuracy, fairness, collegiality, transparency)” (3). Clinical guidelines from societies as powerful as IDSA are generally accepted as accurate, fair, collegial and transparent, and they rapidly become the standard of medical care in our country. It is wholly inappropriate and dangerous for guidelines to be formulated using exclusionary tactics, flagrant data selection, biased opinions and sweepingly “strong” recommendations based on the weakest category III evidence. We feel that the same principles of scientific integrity that apply to medical research should also apply to practice guidelines. In our opinion, the Lyme guidelines article does not reflect accuracy, fairness, collegiality or transparency and should be retracted.

We propose the following:

1. Immediate retraction of the published Lyme guidelines article.
2. Formal notification of the CDC and other medical societies that the guidelines article has been retracted.
3. Formation of a widely diversified Lyme guidelines committee that bases its recommendations on the strength of the underlying evidence.
4. Reformulation of the Lyme guidelines article to reflect a more balanced view of tick-borne diseases, taking into account the existing evidence-based ILADS guidelines article listed by the National Guidelines Clearinghouse (4).
5. Submission of the reformulated guidelines article for outside peer review to a medical journal that is independent of IDSA.

Sincerely,

Raphael Stricker, MD  
President, ILADS

## References

1. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klemperer MS, Krause PJ, Bakken JS, Strle F, Stanek G, Bockenstedt L, Fish D, Dumler JS, Nadelman RB. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006 Nov 1;43(9):1089-134. Epub 2006 Oct 2.
2. Warner TD, Roberts LW. Scientific integrity, fidelity and conflicts of interest in research. *Curr Opin Psychiatry*. 2004;17:381-5.
3. Institute of Medicine National Research Council of the National Academies. Integrity in scientific research. Washington, DC: The National Academies Press, 2002.
4. The ILADS Working Group. Evidence-based guidelines for the management of Lyme disease. *Expert Rev Anti-Infect Ther* 2004;2:S1-S13.

**Lyme Disease Diagnosis and Treatment—Critique of IDSA 2006 Guidelines**

<u>Infectious Disease Society of America (IDSA) Claims</u>	<u>Fact</u>
<p><b>Position Overview:</b></p> <p>LYME DISEASE IS HARD TO CATCH, EASY TO CURE</p> <ul style="list-style-type: none"> <li>—Lyme disease is rare and occurs in limited locations</li> <li>—The disease is easy to diagnose</li> <li>—Lyme testing is reliable</li> <li>—Treatment rarely fails</li> <li>—Chronic Lyme disease does not exist</li> </ul>	<p><b>Position Overview:</b></p> <p>LYME DISEASE AND COINFECTIONS RESULT IN A COMPLEX ILLNESS THAT REQUIRES <u>CLINICAL JUDGEMENT</u> TO DIAGNOSE AND TREAT</p> <ul style="list-style-type: none"> <li>—Lyme disease and other tick-borne coinfections are spreading</li> <li>—Tick-borne coinfections make treatment of Lyme disease more difficult</li> <li>—Lyme testing is unreliable</li> <li>—<i>Borrelia burgdorferi</i> is difficult to eradicate, and treatment failure is more common than we think</li> <li>—Prolonged antibiotic therapy appears to be useful and appropriate in persistent Lyme disease</li> </ul> <p>The IDSA’s “one-size fits all” approach to Lyme diagnosis and treatment will result in the misdiagnosis and denial of care of many thousands of patients a year, creating a public health burden as many of these patients become chronically ill and disabled.</p>
<p>THE LYME BULLSEYE RASH IS ALL IMPORTANT</p> <p>“The great majority of persons with <i>B. burgdorferi</i> infection present with erythema migrans.” [a bullseye ‘EM’ rash]</p> <p>“Extracutaneous [non-rash] manifestations are less commonly seen.”</p> <p>“The more indolent forms of neurologic Lyme disease are quite rare.”</p>	<p>LYME IS FREQUENTLY A NEUROLOGICAL DISEASE, NOT A SKIN DISEASE</p> <p>Only 35-68% of Lyme patients present with a bullseye ‘EM’ rash, [1][2] but up to 40% develop neurologic involvement of either the peripheral or central nervous system.[3] The IDSA’s overemphasis on the rash and denial of many common neuropsychiatric symptoms will result in missed diagnoses and a future epidemic of late stage disease.</p> <p>-----</p> <p>Many IDSA-cited studies are flawed because of selection bias for those subjects presenting with a bullseye ‘EM’ rash. The exclusion of Lyme disease patients with no rash leads to an artificially high estimate of the incidence of the rash among patients infected with <i>B. burgdorferi</i>. Furthermore, IDSA guidelines make no reference to the large body of Lyme-related psychiatric literature, and there were no psychiatrists on the guidelines panel.</p>
<p>TESTING IS RELIABLE AND MANDATORY</p> <p>“Clinical findings alone are not sufficient for diagnosis of extracutaneous [non-rash] manifestations of Lyme disease... Diagnostic testing... is required for confirmation.”</p>	<p>CLINICAL JUDGMENT IS ESSENTIAL, BECAUSE TESTS MAY MISS OVER HALF OF POSITIVE CASES</p> <p>Diagnosis should be based on clinical signs, symptoms, history, exposure risk, and course of illness. When laboratory tests are not a “gold standard” (at least 95% sensitive), clinical discretion is essential. In the case of Lyme disease, the FDA-approved kits are 36-70% sensitive.[7] Diagnosis should be based on clinical signs, symptoms, history, exposure risk, and course of illness, with tests playing a supportive role. Since early treatment is <i>essential</i> for a favorable outcome, <u>why is the IDSA supporting an overly restrictive diagnostic protocol</u> that results in a high percentage of non-rash patients becoming chronically ill?</p> <p>-----</p> <p>NIH: “Until better tests are available, the diagnosis of Lyme disease must be based on characteristic clinical findings in which the results of laboratory tests play a supportive role.[4]</p> <p>FDA: “A patient with active Lyme disease may have a negative test result.”[5]</p> <p>The sensitivity and specificity of the currently used tests for Lyme disease are not adequate to meet the two-tier test</p>

	<p>approach being recommended. <u>Ideally, a screening test should have a high degree of sensitivity (95%).</u>[6]          ELISA: Sensitivities of 3 commercial ELISAs ranged from 36.8% to 70.5%[7]          WESTERN BLOT: The sensitivities of the IgM and IgG immunoblot for detecting patients who were seropositive into the study period were 58.5 and 54.6% [8] Luger and Krause found up to a 56% false-negative rate. [9]          IDSA-recommended tests are antibody tests, and only 70% of the documented Lyme patients in these 2 studies had a significant antibody response.[10][11]</p>
<p>CDC “SURVEILLANCE CRITERIA” SHOULD BE USED FOR DIAGNOSIS</p> <p>“Serum samples should be tested using the 2-tier testing algorithm recommended by the Centers for Disease Control and Prevention.”</p>	<p>USING OVERLY STRICT CDC CRITERIA MISSES UP TO 75% OF POSITIVE CASES</p> <p>The CDC explicitly states that this definition is intended for surveillance purposes only, and is "not intended to be used in clinical diagnosis." [12][13]</p> <p>-----</p> <p>College of American Pathologists (CAP): ELISA assays for Lyme Disease do not have adequate sensitivity to be part of the two-tiered approach of the CDC/ASPHLD[6]          Johns Hopkins 2-yr study (2005): The CDC 2-tiered testing procedure <input type="checkbox"/> <u>misses 75% of positive Lyme cases</u>[14]          NY Dept. of Health Letter (1996): CDC’s 2-tiered testing procedure <u>misses 81% of positive Lyme cases.</u>[15]</p>
<p>14-28 DAYS OF ANTIBIOTICS WILL CURE LYME</p> <p>“There is no convincing biological evidence for the existence of symptomatic chronic <i>B. burgdorferi</i> infection among patients after receipt of recommended treatment regimens for Lyme disease.”</p>	<p>THIS SLOW-GROWING, EVASIVE SPIROCHETE OFTEN REQUIRES LONGER ANTIBIOTIC COURSES</p> <p>Substantial treatment failures occur using standard protocols. Longer term treatment may be necessary. <i>B. burgdorferi</i> may persist in humans and animals for months or years despite a robust immune response and standard antibiotic treatment, particularly when treatment is delayed and dissemination is widespread. Numerous studies have demonstrated persistence of infection despite antibiotic therapy.</p> <p>If the IDSA treatment limits are automatically adopted by insurance companies as they have been in the past, thousands of chronically ill Lyme patients will be forced to pay for expensive, possibly life-saving treatments out of pocket, risking the loss of their life savings and their good health. Quality of care will be compromised because the most needy patients will be denied care based on these IDSA “one-size-fits-all” guidelines.</p> <p>-----</p> <p>Treatment for 14-21 days results in a 26-50% failure rate. [16]          Persistence of <i>B burgdorferi</i> despite antibiotic treatment demonstrated by post-treatment isolation of the bacteria. [17]</p>

<p><b>ANTIBIOTICS DON'T HELP CHRONIC LYME PATIENTS</b></p> <p>“Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (≥6 months) subjective symptoms after recommended treatment regimens for Lyme disease.”</p> <p>“In many patients, posttreatment symptoms appear to be more related to the aches and pains of daily living rather than to either Lyme disease or a tickborne coinfection.”</p>	<p><b>MOST CHRONIC PATIENTS IMPROVE WITH TREATMENT</b></p> <p>Clinical and research evidence shows that long-term antibiotics can significantly improve the quality of life for patients with chronic Lyme disease. The potential harm in letting a persistent Lyme infection go untreated far outweighs the potential side-effects of long-term antibiotic use. If long-term oral antibiotic therapy is considered safe enough for acne patients, its use is certainly justified for chronic Lyme patients. Intravenous therapy is justified for serious, refractory cases or those with clear central nervous system involvement. Risks are minimized by skilled clinicians who take appropriate precautions.</p> <p>-----</p> <p>Two NIH-funded double-blind studies support retreatment of those failing short-term approaches. Recently completed trial (not yet published) at Columbia University showed the efficacy of at least 10 weeks of IV treatment.[18] Krupp showed efficacy of retreatment in terms of fatigue.[19] Five uncontrolled studies support longer treatment approaches.[20-24]</p>
<p><b>PREGNANT WOMEN SHOULDN'T WORRY ABOUT HAVING LYME DISEASE</b></p> <p>“There is little evidence that a congenital Lyme disease syndrome occurs.”</p>	<p><b>PREGNANT WOMEN SHOULD BE FULLY INFORMED OF THE RISKS OF TICK-BORNE DISEASES</b></p> <p>Lyme disease, as well as other tick-borne infections, can be transmitted from an infected mother to fetus through the placenta during pregnancy, possibly resulting in complications or stillbirth.[25-26]</p> <p>-----</p> <p>“46 cases of adverse outcomes ...of gestational Lyme borreliosis were found, including miscarriage, stillbirth, perinatal death, congenital anomalies, systemic illness, early-onset fulminant or mild sepsis and later-onset chronic progressive infection.”[27]</p> <p>Transmission to the fetus demonstrated in murine model.[28]</p> <p><i>B burgdorferi</i> DNA has been detected in human breast milk.[29]</p>
<p><b>THERE IS NO LYME DISEASE IN THE SOUTH</b></p> <p>“The panel is unaware of a proven case of <i>B. burgdorferi</i> infection acquired indigenously in any state south of Maryland or Virginia.”</p>	<p><b>THERE ARE NUMEROUS DOCUMENTED CASES OF INDIGENOUS LYME DISEASE IN THE SOUTH</b></p> <p>Indigenous Lyme disease has been documented by clinicians, military bases, and health departments across the southern states. With early treatment being <i>essential</i> for a favorable outcome, it behooves southern physicians and epidemiologists to remain open-minded about Lyme disease as a differential diagnosis, especially with the ease by which it can be acquired while traveling out of state. If front-line physicians are told Lyme is rare, based on <i>opinion only</i>, it could result in missed diagnoses and a future epidemic of late stage disease.</p> <p>-----</p> <p>From 1984–1989, 104 indigenous cases of Lyme disease were reported in North Carolina. [30-31]</p> <p>From 1997-2000, there were 44 cases of Lyme disease on Navy and Marine bases in North Carolina. [32]</p> <p>The U.S. Army conducts regular Lyme Disease Risk Assessments (LDRAs) at military installations and has determined that these southern states have been designated as HIGH RISK for Lyme (AR, CA); MODERATE RISK (NC, SC, CA, FL, KY) and SOME RISK (FL, GA, LA, MO, OK). [33]</p> <p>In 2005, the CDC reported 313 cases of Lyme disease in states south of Virginia.[34]</p>

NIH, National Institute of Health; CDC, Centers for Disease Control & Prevention; FDA, Food & Drug Administration; ELISA, enzyme-linked immunosorbent assay

## References

1. Stricker RB et al: Lyme disease without erythema migrans: cause for concern? *Am J Med* 2003; 115:72.
2. Centers for Disease Control and Prevention (CDC). Lyme Disease – USA, 2001–2002. *Morb Mortal Wkly Rep* 2004;53(17):365–369.
3. Fallon BA, Nields JA. Lyme disease: a neuropsychiatric illness. *Am J Psychiatry* 1994;151:1571-1583
4. National Institute of Allergies and Infectious Diseases (National Institute of Health). How Lyme Disease Is Diagnosed.1999. Available from: <http://www.niaid.nih.gov/dmid/lyme/diagnosis.htm>
5. Food & Drug Administration. Lyme disease test kits: potential for misdiagnosis. FDA Medical Bulletin, 1999, Summer, Final Issue. <http://www.fda.gov/medbull/summer99/Lyme.html>
6. Bakken LL, Callister SM, Wand PJ, Schell RF. Interlaboratory comparison of test results for detection of Lyme disease by 516 participants in the Wisconsin State Laboratory of Hygiene/College of American Pathologists Proficiency Testing Program. *J Clin Microbiol* 1997; 35(3):537-43.
7. Marangoni A, Sparacino M, Cavrini F, Storni E, Mondardini V, Sambri V, Cevenini R. Comparative evaluation of three different ELISA methods for the diagnosis of early culture-confirmed Lyme disease in Italy. *J Med Microbiol* 2005;54:361-367
9. Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. *J Clin Microbiol* 1995;33(2):419-27.
8. Luger SW, Krauss PJ. Serologic tests for Lyme disease: interlaboratory variability. *Arch Intern Med* 1990;150:761-763.
10. Agüero-Rosenfeld ME, Nowakowski J, McKenna DF, Carbonaro CA, Wormser GP. Serodiagnosis in early Lyme disease. *J Clin Microbiol* 1993;31:3090-3095.
11. Agüero-Rosenfeld ME, Nowakowski J, McKenna DF, Carbonaro CA, Wormser GP. Evolution of the serologic response to *Borrelia burgdorferi* in treated patients with culture-confirmed erythema migrans. *J Clin Microbiol* 1996;34:1-9.
12. Lyme Disease (*Borrelia burgdorferi*): 1996 Case Definition. CDC Case Definitions for Infectious Conditions under Public Health Surveillance.
13. CDC Testimony before the Connecticut Department of Health and Attorney General's Office. CDC's Lyme Prevention and Control Activities. <http://www.hhs.gov/asl/testify/t040129.html>
14. Coulter P, Lema C, Flayhart D, Linhardt AS, Aucott JN, Auwaerter PG, Dumler JS. Two-Year Evaluation of *Borrelia burgdorferi* Culture and Supplemental Tests for Definitive Diagnosis of Lyme Disease. *J Clin. Microbiol* 2005;43:5080-5084
15. Letter from B. DeBuono of NY Dept. of Health to C. Fritz of CDC. April 15, 1996.
16. Wahlberg P, Granlund H, Nyman D, Panelius J, Seppala I. Treatment of late Lyme borreliosis. *J Infect* 1994;29(3):255-61.
17. Oksi J, Marjamaki M, Nikoskelainen J, Viljanen M. *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. *Ann Med* 1999; 31(3): 225-32.
18. Fallon BA. Laboratory findings in chronic Lyme disease and results of the controlled treatment study. Lyme & Other Tick-Borne Diseases:Technology Leading the Way Conference; 2004 October 22, 2004; Rye Town, NY.
19. Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S,Dattwyler R, Chandler B. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology* 2003; 60(12):1923-30.
20. Donta ST. Macrolide therapy of chronic Lyme Disease. *Med Sci Monit* 2003;9(11):136-42. PMID 14586290.

21. Donta ST. Tetracycline therapy for chronic Lyme disease. *Clin Infect Dis* 1997;25(Suppl 1):S52-6. PMID 9233665.
22. Wahlberg P, Granlund H, Nyman D, Panelius J, Seppala I. Treatment of late Lyme borreliosis. *J Infect* 1994;29(3):255-61. PMID 7884218.
23. Oksi J, Nikoskelainen J, Viljanen MK. Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. *Eur J Clin Microbiol Infect Dis* 1998;17 (10):715-9. PMID 9865985.
24. Fallon BA, Tager F, Fein L, Liegner K, Keilp J, Weiss N, Liebowitz M. Repeated antibiotic treatment in chronic Lyme disease. *J Spirochet Tick-Borne Dis* 1999;6(3):94-102.
25. MacDonald AB. Gestational Lyme borreliosis. Implications for the fetus. *Rheum Dis Clin North Am* 1989;15(4):657-77.
26. Schlesinger PA, Duray PH, Burke BA, Steere AC, Stillman MT. Maternal-fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*. *Ann Intern Med* 1985;103 (1): 67-8.
27. Gardner T. Lyme disease. In: Remington JS and Klein JO, editor(s). *Infectious diseases of the fetus and newborn infant*. Philadelphia: Saunders; 1995. p. 447-528.
28. Silver RM, Yang L, Daynes RA, Branch DW, Salafia CM, Weis JJ. Fetal outcome in murine Lyme disease. *Infect Immun* 1995;63(1):66-72.
29. Schmidt BL, Aberer E, Stockenhuber C, Klade H, Breier F, Luger A. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in the urine and breast milk of patients with Lyme borreliosis. *Diagn Microbiol Infect Dis* 1995; 21(3):121-8.
30. Levine JF, Apperson CS, Spiegel RA, Nicholson WL, Staes CJ. Indigenous cases of Lyme disease diagnosed in North Carolina. *South Med J* 1991;84(1):27-31.
31. Pegram PS, Sessler CN, London WL. Lyme disease in North Carolina. *South Med J* 1983;76(6):740-2.
32. McGinnis J, Bohnker BK, Malakooti M, Mann M, Sack DM. Lyme disease reporting for Navy and Marine Corps (1997-2000). *Mil Med*. 2003;168(12):1011-4.
33. U.S. Army Lyme Disease Assessment Reports 1983-1996. <http://members.utech.net/users/10766/lyme.htm>
34. CDC. Summary of notifiable diseases, United States, 2005. *Morb Mortal Wkly Rep* 2005;53(53)



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