

Final Report of the Lyme Disease Review Panel of the Infectious Diseases Society of America

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In April 2008, the Infectious Diseases Society of America (IDSA) entered into an agreement with Connecticut Attorney General Richard Blumenthal to voluntarily undertake a special review of its 2006 Lyme disease guidelines. This agreement ended the Attorney General's investigation into the process by which the guidelines were developed. The IDSA agreed to convene an independent panel to conduct a one-time review of the guidelines. The Review Panel members, vetted by an ombudsman for potential conflicts of interest, reviewed the entirety of the 2006 guidelines, with particular attention to the recommendations devoted to post-Lyme disease syndromes. After multiple meetings, a public hearing, and extensive review of research and other information, the Review Panel concluded that the recommendations contained in the 2006 guidelines were medically and scientifically justified on the basis of all of the available evidence and that no changes to the guidelines were necessary.

INTRODUCTION AND PURPOSE

In November 2006, Connecticut Attorney General Richard Blumenthal initiated an antitrust investigation to determine whether the Infectious Diseases Society of America (IDSA) violated antitrust laws in the promulgation of the IDSA's 2006 Lyme disease guidelines, entitled "The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America" [1]. The IDSA maintained that it had developed the 2006 Lyme disease guidelines on the basis of a proper review of the medical or scientific studies and evidence by a panel of experts in the prevention, diagnosis, and treatment

of Lyme disease. In April 2008, the Connecticut Attorney General and the IDSA reached an agreement to end the investigation [2]. Under the agreement and its attached action plan, the IDSA guidelines would remain in effect, and the IDSA agreed to convene an independent Review Panel whose task would be to determine whether the 2006 Lyme disease guidelines were based on sound medical and scientific evidence and whether these guidelines should be changed or revised.

The Review Panel was not charged with updating or rewriting the 2006 Lyme disease guidelines. Any recommendation for update or revision to the guidelines would be conducted by a separate IDSA committee. This document is a summary of the "Final Report of the Review Panel." The entire report can be found online (<http://www.idsociety.org/Content.aspx?id=16499>).

OMBUDSMAN AND POTENTIAL CONFLICTS OF INTEREST

Members of the Review Panel were selected through an open application process. Medical ethicist Howard Brody (Institute for the Medical Humanities at the

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University of Texas Medical Branch at Galveston) was jointly selected by the Connecticut Attorney General and the IDSA to serve as ombudsman. Dr Brody's role was to screen all applicants to ensure that each Review Panel member was without any conflicts of interest, including ensuring that the Review Panel chairperson was without any beneficial or financial interest related to Lyme disease, any financial relationship with an entity that has an interest in Lyme disease, and any conflict of interest. Dr Brody screened the chairperson and each Review Panel member and found that each met the required criteria.

METHODOLOGY

Data and other information collection. The Review Panel members, with the assistance of IDSA staff, conducted a comprehensive literature search and retrieval. PubMed and the Cochrane Collaboration Library databases were searched. The following terms were used in a core search: "lyme," "*B. burgdorferi*," "borreliosis," and "borrelia burgdorferi." Separate searches were conducted to combine these terms with each manifestation (eg, "arthritis"). Additional searches were conducted using the terms "babesiosis," "babesia," "HGA," and "human granulocytic anaplasmosis." Full-text articles were retrieved and provided to Review Panel members. The literature search included current practice guidelines and their supporting references by the International Lyme and Associated Diseases Society (ILADS) [3], the American Academy of Neurology [4], the European Federation of Neurological Societies [5], the European Society of Clinical Microbiology and Infectious Diseases [6], and the American College of Physicians [7], as well as the IDSA guidelines from 2006 and 2000 [1, 8].

The Review Panel held a public input period of >80 days to allow the public to submit information and to ensure that all points of view were taken into consideration. The Review Panel received submissions from ~150 individuals or organizations. Submissions from the public to the Review Panel included letters, patient medical records and laboratory reports, meeting abstracts, newspaper articles, books, a DVD, and miscellaneous correspondence. The Review Panel received and reviewed numerous written submissions that scientifically contested specific contents of the 2006 guidelines, as well as any accompanying references.

The Review Panel held an all-day public hearing on 30 July 2009 to offer a forum for the presentation of relevant information on the diagnosis and treatment of Lyme disease. An open application process was held to identify hearing presenters. Thirty-five applications were received and were reviewed by the ombudsman prior to review by the Review Panel. A conference call including the Review Panel, ombudsman, Connecticut Attorney General's Office, and the IDSA staff was held to determine the final list of presenters for the July hearing. Two patients with Lyme disease and 16 physicians or researchers

were chosen to present. The hearing was broadcast live via Web cast, and transcripts, slides, and testimony were posted on the IDSA Web site. The Review Panel also reviewed follow-up correspondence from presenters and others after the hearing. A reference list of most of the materials reviewed by the Review Panel is located in the full version of this report, which is published online (<http://www.idsociety.org/Content.aspx?id=16499>).

Consensus development. Each Review Panel member was assigned a section of the 2006 guidelines and tasked with careful review of the evidence and other information submitted and/or presented relevant to that section. All Review Panel members comprehensively reviewed the section on post-Lyme disease syndromes and the executive summary. Established criteria used by the 2006 guideline development panel were also used by the Review Panel to assess the strength of the recommendation and the quality of the evidence. The Review Panel assessed the validity and appropriateness of these designations and commented on them if they felt it was appropriate.

The Review Panel met several times in person and via many conference calls to present the findings of their research on their assigned sections. An open discussion among Review Panel members took place, and each member individually voted whether each recommendation in the guidelines was medically and scientifically justified in light of the scientific evidence and whether a change or revision was needed. In addition to voting on each separate recommendation, the panel members also voted on whether the overall guideline was medically and scientifically sound or required revision.

FINDINGS OF THE REVIEW PANEL

The recommendations in the 2006 IDSA Lyme disease guidelines are divided among the sections and subsections listed in Table 1. For each of the recommendations in the 2006 guide-

Table 1. Sections and Subsections of the 2006 Infectious Diseases Society of America Lyme Disease Guidelines

Tick bites and prophylaxis of Lyme disease
Early Lyme disease
Erythema migrans
Lyme meningitis and other manifestations of early neurologic Lyme disease
Lyme carditis
Borrelial lymphocytoma
Late Lyme disease
Lyme arthritis
Late neurologic Lyme disease
Acrodermatitis chronica atrophicans
Post-Lyme disease syndromes
Human granulocytic anaplasmosis
Human babesiosis

lines, the Review Panel found that each was medically and scientifically justified in light of all the evidence and information and required no revision. The Review Panel voted 8–0 for all but 1 recommendation (vote, 7–1). For several recommendations, the Review Panel provided commentary suggesting minor changes to language or content. The online version of this report explicitly lists all recommendations with the accompanying vote and commentary by the Review Panel.

POST-LYME DISEASE SYNDROMES

Because of the controversial nature and public profile of this subject, the Review Panel has included here its findings on the subject of Post-Lyme disease syndromes. The 2006 IDSA Lyme disease guidelines contain 2 formal recommendations on this subject, but the Connecticut Attorney General asked the panel to divide one of these into 2 considerations for the review and vote (Table 2).

The Review Panel determined that all 3 of the recommendations were medically and scientifically justified in light of all of the evidence and information provided.

The Review Panel reviewed numerous sources of evidence for this contentious topic. These included but were not limited to (1) a large volume of case reports and case series submitted by representatives of the ILADS and referenced by that society's published guideline; (2) case reports cited by representatives of ILADS and patient representatives in oral presentations to the Panel during the 30 July 2009 hearing; (3) journal correspondence published in response to several Lyme disease practice guidelines, editorials, and clinical trials; (4) patient testimony; and (5) the available randomized, placebo-controlled, clinical trials of long-term antibiotic therapy for symptoms attributed to Lyme disease.

On reviewing this abundance of material, and after lengthy discussions among the Review Panel members, the following conclusions were reached:

1. The prospective, controlled clinical trials of extended antibiotic treatment of Lyme disease have demonstrated considerable risk of harm, including potentially life-threatening adverse events, attributable both to antibiotic treatment and to intravascular access devices. Such events include intravenous catheter infection, including septicemia (line sepsis), venous thromboembolism, drug hypersensitivity reactions, and drug-induced cholecystitis. Minor adverse events, such as diarrhea and candidiasis, were also more common among antibiotic-treated patients [9–13]. In a recent cohort of 200 patients, catheter-associated adverse events, such as thrombosis and infection, occurred a mean of 81 days into therapy, underscoring the cumulative risk of adverse events with increasing time [14].

2. Prospective, controlled clinical trials have demonstrated little benefit from prolonged antibiotic therapy. Nearly all pri-

Table 2. Recommendations in the Post-Lyme Disease Syndromes Section of the 2006 Infectious Diseases Society of American Lyme Disease Guidelines

"There is no well-accepted definition of post-Lyme disease syndrome. This has contributed to confusion and controversy and to a lack of firm data on its incidence, prevalence, and pathogenesis. In an attempt to provide a framework for future research on this subject and to reduce diagnostic ambiguity in study populations, a definition for post-Lyme disease syndrome is proposed in these guidelines. Whatever definition is eventually adopted, having once had objective evidence of *B. burgdorferi* infection must be a condition sine qua non. Furthermore, when laboratory testing is done to support the original diagnosis of Lyme disease, it is essential that it be performed by well-qualified and reputable laboratories that use recommended and appropriately validated testing methods and interpretive criteria. Unvalidated test methods (such as urine antigen tests or blood microscopy for *Borrelia* species) should not be used."

"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 recommended treatment regimens for Lyme disease."

NOTE. From [1, p 1094].

mary outcome measures failed to demonstrate an advantage to prolonged antibiotic therapy. Statistically significant improvements in treatment groups were not demonstrated across studies, were nonspecific, were of unclear clinical importance, and in one case, were not sustained at the end of the trial [9–13].

3. The risk/benefit ratio for prolonged antibiotic therapy discourages prolonged antibiotic courses for Lyme disease. Several presenters in the 30 July hearing argued that patients with symptoms attributed to chronic Lyme disease confer considerable societal cost. This argument, however, was not accompanied by quantitative evidence from controlled trials that prolonged antibiotic therapy could even partly reduce this cost. The Review Panel concluded that a societal benefit was at best hypothetical based on current evidence.

It has been argued that prolonged parenteral antibiotics are considered sufficiently safe for their routine use in such infections as osteomyelitis and endocarditis [14]. The Review Panel does not agree with this comparison, however, because in these conditions clinical trials have decisively shown a clinical and mortality benefit. On the other hand, in the case of Lyme disease, there has yet to be a single high-quality study that demonstrates comparable benefit to prolonging antibiotic therapy beyond 1 month. Therefore, the Review Panel concluded that *in the case of Lyme disease*, inherent risks of long-term antibiotic therapy were not justified by clinical benefit.

This conclusion was reached despite the large volume of case reports, case series, anecdotes, and patient testimonials re-

viewed that attested to perceived clinical improvement during antibiotic therapy. Such evidence is by its nature uncontrolled and highly subject to selection and reporting biases. In many published case reports, patients did not receive initial Lyme disease therapy consistent with the current standard of care, so it was impossible to be sure that shorter-duration therapy had failed. In some cases, the diagnosis of Lyme disease was doubtful, on the basis of clinical presentations consistent with other illnesses. Many reports included patients whose diagnosis was made before the implementation of the Center for Disease Control and Prevention's recommendation for 2-tier serological testing, and were based on less stringent criteria. Finally, caution should be used in extrapolating results from European studies to North American patients, because of the well-established microbiological and clinical distinctions in Lyme borreliosis on the 2 continents.

In the end, such sources of evidence were felt to be fertile material for hypothesis generation but intrinsically incapable of hypothesis testing. By contrast, the prospective, randomized, controlled trials were formal hypothesis tests with strict recruitment criteria, prospectively defined outcome measures, and independent oversight.

The Review Panel's conclusions, which are consistent with those reached by guidelines panels from the IDSA and from other societies, represent the state of medical science at the time of writing. Only high-quality, prospective, controlled clinical trial data demonstrating both benefit and safety will be sufficient to change the current recommendations.

ADDITIONAL REVIEW OF EXECUTIVE SUMMARY STATEMENT

In addition to reviewing all of the recommendations of the 2006 guidelines, as called for in the Action Plan, the Review Panel also reviewed the following statement from the Executive Summary at the request of the Connecticut Attorney General's Office:

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 or for diagnosis of HGA or babesiosis. Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extracutaneous Lyme disease, HGA, and babesiosis.

This statement was subject to lengthy discussion by the Review Panel. As written, it does not distinguish whether it applies equally to all patients irrespective of their prior probability of having Lyme disease. For example, a young patient from coastal New England presenting with a cranial nerve palsy would have a high probability of having Lyme disease, compared with a patient from an area of low endemicity who presents only with fatigue. Because the statement could be considered differently

in different clinical and epidemiologic contexts, it was felt to be problematic by some members of the Review Panel. Ultimately, the Review Panel was evenly split on whether this statement would benefit from modification or clarification.

This statement appears to be an admonition to practitioners against overdiagnosing Lyme disease and other tick-borne infections, particularly if the diagnosis is based only on vague and nonspecific symptoms, in patients unlikely to have been exposed to ticks in areas of endemicity, and in patients who are not seropositive by established criteria. When interpreted in isolation, this statement might be seen as constraining an individual practitioner's latitude in evaluating a patient, but this interpretation is acknowledged in other parts of the 2006 guidelines, including in the disclaimer on the first page:

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances [1, p 1089].

Clinical judgment is critical to all responsible medical practice, including the recognition of disease patterns and the rational ordering of diagnostic tests and therapy. However, the point of departure for all clinical assessments is to find a "best fit" association between a patient's illness and a likely diagnosis as established by medical evidence. On the basis of current research, for patients with nonspecific symptoms that may be seen in many illnesses (such as subjective complaints of fatigue, musculoskeletal pains and neurocognitive dysfunction), it would be a deviation from this "best fit" to attribute such symptoms to Lyme disease in the absence of more specific clinical features or laboratory results.

All Lyme-associated clinical findings, even including erythema migrans, can be seen in diseases other than Lyme disease. Symptoms that are commonly attributed to chronic or persistent Lyme, such as arthralgias, fatigue, and cognitive dysfunction, are seen in many other clinical conditions and are, in fact, common in the general population. This remains true regardless of whether they are also features of Lyme disease. It would thus be clinically imprudent to make the diagnosis of Lyme disease using these nonspecific findings alone.

On the other hand, the Review Panel felt that, in clinical practice, the presence of certain classic complications of Lyme disease, such as aseptic meningitis, atrioventricular nodal block, inflammatory arthritis, and cranial or peripheral neuropathies, in a patient with epidemiologic risk of Lyme disease and in whom alternative diagnoses have been excluded or are unlikely, may be sufficiently convincing as to constitute an exception to the statement in the Executive Summary.

The Review Panel suggests that, in future guideline iterations, the authors should directly account for the occasional patient with a high prior probability of Lyme disease but equivocal results of diagnostic testing or in whom such testing is not immediately available. In addressing this concern, the Review Panel suggests that the authors of future guidelines be clear and more specific about what is meant by such terms as “confirmation” and “diagnostic testing.”

REVIEW PANEL VOTE ON OVERALL GUIDELINES

Based on its review of all the evidence and information provided, the Review Panel determined that no changes or revisions to the 2006 Lyme disease guideline are necessary at this time (8–0). The Review Panel suggests consideration of the following when the guideline is next updated: an expanded section on diagnostic testing for Lyme disease, and a new section on the southern tick-associated rash illness.

CONCLUSIONS

The Review Panel finds that the 2006 Lyme disease guidelines were based on the highest-quality medical and scientific evidence available at the time and are supported by evidence that has been published in more recent years. The Review Panel did not find that the 2006 guidelines authors had failed to consider or cite relevant data and references that would have altered the published recommendations. In addition to the review by this panel, the recommendations in the 2006 IDSA guidelines are further corroborated by guidelines and statements by other independent bodies from the United States and Europe. It is expected that the IDSA will review the 2006 Lyme disease guidelines on a regular basis to consider any new evidence that would warrant a substantive change to the current recommendations.

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