

# Final Report of the Lyme Disease Review Panel of the Infectious Diseases Society of America (IDSA)

## INTRODUCTION AND PURPOSE

In November 2006, the Connecticut Attorney General (CAG), 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" (the 2006 Lyme Guidelines). IDSA maintained that it had developed the 2006 Lyme disease guidelines based on a proper review of the medical/scientific studies and evidence by a panel of experts in the prevention, diagnosis, and treatment of Lyme disease. In April 2008, the CAG and the IDSA reached an agreement to end the investigation. Under the Agreement and its attached Action Plan, the 2006 Lyme Guidelines remain in effect, and the Society agreed to convene a Review Panel whose task would be to determine whether or not the 2006 Lyme Guidelines were based on sound medical/scientific evidence and whether or not these guidelines required change or revision.

The Review Panel was not charged with updating or rewriting the 2006 Lyme Guidelines. Any recommendation for update or revision to the 2006 Lyme Guidelines would be conducted by a separate IDSA group.

This document is the Final Report of the Review Panel.

## REVIEW PANEL MEMBERS

**Carol J. Baker, MD**, Review Panel Chair  
Baylor College of Medicine Houston, TX

**William A. Charini, MD**  
Lawrence General Hospital, Lawrence, MA

**Paul H. Duray, MD<sup>1</sup>** (retired)  
Westwood, MA

**Paul M. Lantos, MD**  
Duke University Medical Center, Durham, NC

<sup>1</sup> Dr. Duray resigned from the Panel on October 7, 2009, due to family illness.

**Gerald Medoff, MD**

Washington University School of Medicine, St. Louis, MO

**Manuel H. Moro, DVM, MPH, PhD**

National Institutes of Health, Bethesda, MD

**David M. Mushatt, MD, MPH & TM**

Tulane University School of Medicine, New Orleans, LA

**Jeffrey Parsonnet, MD**

Dartmouth-Hitchcock Medical Center, Lebanon, NH

**Cmdr. John W. Sanders, MD**

U.S. Naval Medical Research Center Detachment, Lima, Peru

**OMBUDSMAN AND CONFLICT OF INTEREST**

Members of the Review Panel were selected through an open application process. Medical ethicist Howard Brody, MD, PhD, of the Institute for the Medical Humanities at the University of Texas Medical Branch at Galveston was jointly selected by the CAG and 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. The Action Plan provides that "a conflict of interest exists when anyone involved in the guideline process has a financial or other beneficial interest in the products or concepts addressed in the guidelines or in competing products or concepts that might bias his or her judgment. For guidance purposes, if the combined financial or beneficial interests in the products or concepts addressed in the guidelines exceed \$10,000, those interests may be considered to bias a participant's judgment."

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 the IDSA staff, conducted a comprehensive literature search and retrieval. PubMed and the Cochrane Collaboration Library were searched. The following terms were used in a core search: "lyme," "B. burgdorferi," "borreliosis," "borrelia burgdorferi." Separate searches were conducted to combine these terms with each manifestation (e.g., "arthritis"). Additional searches were conducted on "babesiosis," "babesia," "HGA," and "human granulocytic anaplasmosis." Full-text articles were retrieved and provided to Panel members.

Practice guidelines and their supporting references by the American Academy of Neurology, American College of Physicians, European Federation of Neurological Societies, European Society of Clinical Microbiology and Infectious Diseases, IDSA, and International Lyme and Associated Diseases Society (ILADS) also were reviewed.

The Review Panel held a public input period of more than 80 days to allow the public to submit information and to ensure that all points of view were taken into consideration. The Panel received submissions from approximately 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 Panel also received and reviewed numerous written summaries contesting specific contents of the **2006** Lyme Guidelines, along with supporting articles and references.

The Review Panel held an all-day open public hearing on July 30, 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 of the Review Panel, Ombudsman, CAG's Office, and the IDSA Staff was held to determine the final list of presenters for the July hearing. Two patients and 16 physicians or researchers were chosen to present:

1. Tina Garcia, Lyme Education Awareness Program Arizona (L.E.A.P. Arizona, Inc.), Mesa, AZ
2. Lorraine Johnson, JD, MBA, California Lyme Disease Association (CALDA), Ukiah, CA
3. Daniel Cameron, MD, International Lyme and Associated Diseases Society (ILADS), Mt. Kisco, NY
4. Phillip Baker, PhD, American Lyme Disease Foundation (ALDF), Bethesda, MD
5. Ben Luft, MD, The State University of New York, Stony Brook, NY
6. Allison Delong, MS, ILADS and the Center for Statistical Sciences, Brown University, Providence, RI
7. Barbara Johnson, PhD, Centers for Disease Control and Prevention, Fort Collins, CO
8. David Volkman, MD, Nissequogue, NY
9. Sam Donta, MD, Falmouth, MA
10. Eugene Shapiro, MD, IDSA and Yale University School of Medicine, New Haven, CT
11. Brian Fallon, MD, Columbia University Medical Center, New York, NY
12. Sunil Sood, MD, Schneider Children's Hospital at North Shore, Manhasset, NY
13. Ken Liegner, MD, ILADS, Armonk, NY
14. Allen Steere, MD, Massachusetts General Hospital and Harvard Medical School, Boston, MA
15. Steven Phillips, MD, ILADS, Wilton, CT
16. Arthur Weinstein, MD, Washington Hospital Center, Washington, DC
17. Raphael Stricker, MD, ILADS, San Francisco, CA
18. Gary Wormser, MD, IDSA and New York Medical College, Valhalla, NY

The hearing was broadcast live via webcast, on the IDSA website and transcripts, slides, and testimony were posted. The Review Panel also reviewed follow-up correspondence from presenters and others after the hearing.

A reference list of many of the materials reviewed by the Panel is located at the end of this document [1-1025]. This is not meant to be an all-inclusive list but rather is meant to show the breadth of materials reviewed by the Review Panel.

## Consensus Development

Each Review Panel member was assigned a section of the 2006 Lyme Guidelines and was tasked with the careful review of the evidence and other information submitted and/or presented relevant to that section. Established criteria used by the 2006 guideline development panel were also used by the Review Panel to grade the strength of the recommendation and the quality of the evidence (Table 1). Review Panel members assessed the validity and appropriateness of these designations and commented on them when they felt it was appropriate to do so.

**Table 1. Infectious Diseases Society of America-US Public Health Service Grading System for ranking recommendations in clinical guidelines.**

Category, grade	Definition
<b>Strength of recommendation</b>	
<b>A</b>	Strongly in favor
<b>B</b>	Moderately in favor
<b>C</b>	Optional
<b>D</b>	Moderately against
<b>E</b>	Strongly against
<b>Quality of evidence</b>	
<b>I</b>	Evidence from $\geq 1$ properly randomized, controlled trial
<b>II</b>	Evidence from $\geq 1$ well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from $>1$ center); from multiple time series studies; or from dramatic results from uncontrolled experiments
<b>III</b>	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE: Categories reflect the strength of each recommendation for or against use and the quality of the evidence

All Review Panel members were required to comprehensively review the section on Post-Lyme Syndromes. The Panel met several times (see below), in person and via conference call, to present the findings of their research on their assigned sections. An open discussion among Panel members took place, and each member made an individual determination as to whether or not each recommendation in the 2006 Lyme Guidelines was medically/scientifically justified in light of the evidence and information collected and provided, and whether or not a change or revision was needed. Each member's vote was recorded.

## Meetings

The Review Panel met on 16 occasions:

Date	Meeting Type	Meeting Purpose
January 22, 2009	Conference call	To conduct panel business
March 2, 2009	Conference call	To conduct panel business
April 16, 2009	Conference call	To conduct panel business
April 27, 2009	Conference call	To determine hearing presenters
May 7, 2009	Conference call	To discuss logistical plans for hearing
June 12, 2009	Conference call	To conduct panel business
July 23, 2009	Conference call	To conduct panel business
July 30, 2009	Open public hearing	To hear presentations from patients, physicians and researchers
July 31, 2009	Face-to-face meeting	To conduct panel business
September 30, 2009	Conference call	To conduct panel business
October 23, 2009	Conference call	To conduct panel business
October 29, 2009	Face-to-face meeting	To conduct panel business
November 20, 2009	Conference call	To conduct panel business
December 4, 2009	Conference call	To conduct panel business
February 9, 2010	Conference call	To conduct panel business
March 1, 2010	Conference call	To conduct panel business

## INDIVIDUAL RECOMMENDATIONS

Reprinted below are each of the recommendations within the 2006 Lyme Guidelines, including, where relevant, parenthetical notations, e.g., (B-III), on the 2006 Panel's ranking of the strength of evidence and grade of the recommendation supporting each recommendation.

Following each of the 2006 recommendations is the Review Panel's assessment and comments including parenthetical notations e.g., (8-0), indicating the Review Panel's final<sup>2</sup> vote with respect to whether the recommendation is medically/scientifically justified in light of all of the evidence and information provided.

<sup>2</sup> The Review Panel conducted an initial vote on each recommendation in which it considered, based upon the medical/scientific evidence and all of the information provided, whether to recommend that the individual recommendation be revised or rewritten and whether to recommend that the overall 2006 Lyme Guidelines be revised or rewritten. In this initial vote, the Review Panel determined that it would not recommend that any individual recommendation be revised or rewritten and that it would not recommend that the overall 2006 Lyme Guidelines be revised or rewritten. Following communications with the Connecticut Attorney General's Office, the Review Panel conducted a second vote in which it considered (1) whether each recommendation is medically/scientifically justified in light of all of the evidence and information provided and (2) whether to recommend that the overall 2006 Lyme Guidelines be revised or rewritten. The results of the second vote are set forth in this report.

## Prevention/Prophylaxis of Lyme

### **2006 Recommendation**

The best currently available method for preventing infection with *B. burgdorferi* and other *Ixodes* species-transmitted pathogens is to avoid exposure to vector ticks. If exposure to *I. scapularis* or *I. pacificus* ticks is unavoidable, measures recommended to reduce the risk of infection include the use of both protective clothing and tick repellents, checking the entire body for ticks daily, and prompt removal of attached ticks before transmission of these microorganisms can occur (B-III).

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

For prevention of Lyme disease after a recognized tick bite, routine use of antimicrobial prophylaxis or serologic testing is not recommended (E-III).

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

A single dose of doxycycline may be offered to adult patients (200 mg dose) and to children >8 years of age (4 mg/kg up to a maximum dose of 200 mg) (B-I) when all of the following circumstances exist: (a) the attached tick can be reliably identified as an adult or nymphal *I. scapularis* tick that is estimated to have been attached for >36 h on the basis of the degree of engorgement of the tick with blood or of certainty about the time of exposure to the tick; (b) prophylaxis can be started within 72 h of the time that the tick was removed; (c) ecologic information indicates that the local rate of infection of these ticks with *B. burgdorferi* is >20%; and (d) doxycycline treatment is not contraindicated. The time limit of 72 h is suggested because of the absence of data on the efficacy of chemoprophylaxis for tick bites following tick removal after longer time intervals. Infection of >20% of ticks with *B. burgdorferi* generally occurs in parts of New England, in parts of the mid-Atlantic States, and in parts of Minnesota and Wisconsin, but not in most other locations in the United States. Whether use of antibiotic prophylaxis after a tick bite will reduce the incidence of HGA or babesiosis is unknown.

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel recommends the careful consideration of the grading for quality of evidence. One panel member thought the quality of evidence assigned to the recommendation (I) might be too high.

## 2006 Recommendation

Doxycycline is relatively contraindicated in pregnant women and children <8 years old. The panel does not believe that amoxicillin should be substituted for doxycycline in persons for whom doxycycline prophylaxis is contraindicated because of the absence of data on an effective short-course regimen for prophylaxis, the likely need for a multiday regimen (and its associated adverse effects), the excellent efficacy of antibiotic treatment of Lyme disease if infection were to develop, and the extremely low risk that a person with a recognized bite will develop a serious complication of Lyme disease (D-III).

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel recommends removal of the modifiers “relatively” contraindicated and “excellent” efficacy.

## 2006 Recommendation

Prophylaxis after *I. pacificus* bites is generally not necessary, because rates of infection with *B. burgdorferi* in these ticks are low in almost the entire region in which the tick is endemic. However, if a higher infection rate were documented in specific local areas (>20%), prophylaxis with single-dose doxycycline would be justified if the other criteria mentioned above are met.

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## 2006 Recommendation

Protective immunity produced by the recombinant OspA Lyme disease vaccine is not long lasting. A history of having received the vaccine should not alter the recommendations above, because it is unlikely that previous vaccinations will still have a protective effect against Lyme disease. Similarly, it should not be assumed that having had a prior episode of early Lyme disease will provide protection against developing *B. burgdorferi* infection if a bite occurs from another infected tick.

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## 2006 Recommendation

To prescribe antibiotic prophylaxis selectively to prevent Lyme disease, health care practitioners in areas of endemicity should learn to identify *I. scapularis* ticks, including its stages (figure 1), and to differentiate ticks that are at least partially engorged with blood (figure 2A and 2B) (A-III).

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel recommends the careful consideration of the strength of recommendation. Although a subjective measure, two Review Panel members thought that the strength assigned to this recommendation (A) might be too high.

## **2006 Recommendation**

Testing of ticks for tickborne infectious agents is not recommended, except in research studies (D-II).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **2006 Recommendation**

Health care practitioners, particularly those in areas of endemicity, should become familiar with the clinical manifestations and recommended practices for diagnosing and treating Lyme disease, HGA, and babesiosis (A-III).

Persons who have removed attached ticks from themselves (including those who have received antibiotic prophylaxis) should be monitored closely for signs and symptoms of tickborne diseases for up to 30 days; in particular, they should be monitored for the development of an expanding skin lesion at the site of the tick bite (erythema migrans) that may suggest Lyme disease. Persons who develop a skin lesion or viral infection–like illness within 1 month after removing an attached tick should promptly seek medical attention to assess the possibility of having acquired a tickborne infection.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel recommends that consideration be given to specifying what constitutes “monitoring” and to providing anticipatory guidance for patients about possible manifestations of disseminated Lyme disease (e.g., arthritis, meningitis).

## **2006 Recommendation**

HGA and babesiosis should be included in the differential diagnosis of patients who develop fever after an *Ixodes* tick bite in an area where these infections are endemic (A-II). A history of having received the previously licensed recombinant outer surface protein A (OspA) Lyme disease vaccine preparation should not alter the recommendations above; the same can be said for having had a prior episode of early Lyme disease.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **Early Lyme Disease**

### **2006 Recommendation**

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, 10–21 days for doxycycline and 14–21 days for amoxicillin or cefuroxime axetil) is recommended for the treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations (see Lyme meningitis, below) or advanced atrioventricular heart block (A-I). Ten days of therapy is sufficient if doxycycline is used; however, given the much shorter half-life of  $\beta$ -lactam drugs, such as amoxicillin or cefuroxime axetil, it is unclear whether a 10-day course of these drugs would be as effective. Therefore,



for uniformity, a 14-day course of therapy is recommended for all of the first-line oral agents. Each of these antimicrobial agents has been shown to be highly effective for the treatment of erythema migrans and associated symptoms in prospective studies. Doxycycline has the advantage of being effective for treatment of HGA (but not for babesiosis), which may occur simultaneously with early Lyme disease. Doxycycline is relatively contraindicated during pregnancy or lactation and in children <8 years of age.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests removal of the modifiers “highly” and “relatively.”

### **2006 Recommendation**

For children, amoxicillin, cefuroxime axetil, or doxycycline (if the patient is  $\geq 8$  years of age) is recommended (tables 2 and 3) (A-II).

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Macrolide antibiotics are not recommended as first-line therapy for early Lyme disease, because those macrolides that have been compared with other antimicrobials in clinical trials have been found to be less effective (E-I). When used, they should be reserved for patients who are intolerant of, or should not take, amoxicillin, doxycycline, and cefuroxime axetil. For adults with these limitations, recommended dosage regimens for macrolide antibiotics are as follows: azithromycin, 500 mg orally per day for 7–10 days; clarithromycin, 500 mg orally twice per day for 14–21 days (if the patient is not pregnant); or erythromycin, 500 mg orally 4 times per day for 14–21 days. The recommended dosages of these agents for children are as follows: azithromycin, 10 mg/kg per day (maximum of 500 mg per day); clarithromycin, 7.5 mg/kg twice per day (maximum of 500 mg per dose); or erythromycin, 12.5 mg/kg 4 times per day (maximum of 500 mg per dose). Patients treated with macrolides should be closely observed to ensure resolution of the clinical manifestations.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

First-generation cephalosporins, such as cephalexin, are ineffective for treatment of Lyme disease and should not be used (E-II).

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

When erythema migrans cannot be reliably distinguished from community-acquired bacterial cellulitis, a reasonable approach is to treat with either cefuroxime axetil or amoxicillin–clavulanic acid (dosage of amoxicillin–clavulanic acid for adults, 500 mg 3 times per day;

dosage for children, 50 mg/kg per day in 3 divided doses [maximum of 500 mg per dose]), because these antimicrobials are generally effective against both types of infection (A-III).

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests the inclusion of a comment that these agents will be ineffective against methicillin-resistant *Staphylococcus aureus* (MRSA). If community rates of MRSA are high, doxycycline could be considered because of its activity against both MRSA and *B. burgdorferi*, unless the patient is pregnant or less than 9 years old.

### **2006 Recommendation**

Ceftriaxone, while effective, is not superior to oral agents and is more likely than the recommended orally administered antimicrobials to cause serious adverse effects. Therefore, ceftriaxone is not recommended for treatment of patients with early Lyme disease in the absence of neurologic involvement or advanced atrioventricular heart block (E-I).

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Pregnant and lactating patients may be treated in a fashion identical to nonpregnant patients with the same disease manifestation, except that doxycycline should be avoided (B-III).

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of Lyme disease: first-generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-Bartonella therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others (see table 4) (E-III).

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that “lack of biological plausibility, lack of efficacy” be replaced with “lack of demonstrated efficacy in controlled studies.”

There are data demonstrating that the following are ineffective in the treatment of Lyme disease: first-generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, ketolides, isoniazid, trimethoprim-

sulfamethoxazole, fluconazole, benzathine penicillin G and combinations of antimicrobials. There are also data demonstrating that the following are potentially harmful: combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), and long-term antibiotic therapy (e.g., more than 4 weeks). There is a paucity of data regarding the safety and effectiveness of the use of the following in the treatments for Lyme disease: hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, and specific nutritional supplements, but some of these are likely to be harmful to the patient. Many of these examples, such as fever therapy and hydrogen peroxide, carry considerable risk of harm to the patient.

### **2006 Recommendation**

Coinfection with *B. microti* or *A. phagocytophilum* or both may occur in patients with early Lyme disease (usually in patients with erythema migrans) in geographic areas where these pathogens are endemic. Coinfection should be considered in patients who present with more-severe initial symptoms than are commonly observed with Lyme disease alone, especially in those who have high-grade fever for >48 h, despite receiving antibiotic therapy appropriate for Lyme disease, or who have unexplained leukopenia, thrombocytopenia, or anemia (A-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel recommends that abnormal hepatic transaminases (AST and ALT), lactate dehydrogenase, or bilirubin should also prompt evaluation for coinfection with *B. microti* or *A. phagocytophilum*.

### **2006 Recommendation**

Coinfection might also be considered in the situation in which there has been resolution of the erythema migrans skin lesion, but either no improvement or worsening of viral infection-like symptoms (B-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel recommends that consideration be given to changing “might” to “should.”

## **Early Neurologic Lyme**

### **2006 Recommendation**

For adult patients with early Lyme disease and the acute neurologic manifestations of meningitis or radiculopathy, the use of ceftriaxone (2 g once per day intravenously for 14 days; range, 10–28 days) in early Lyme disease is recommended for adult patients with acute neurologic disease manifested by meningitis or radiculopathy (B-I).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel recommends that consideration be given to the emerging data supporting the use of oral doxycycline as

first line therapy in selected patients with neurologic manifestations of Lyme disease, such as those with hypersensitivity to beta lactam antibiotics.

### **2006 Recommendation**

Parenteral therapy with cefotaxime (2 g intravenously every 8 h) or penicillin G (18–24 million U per day for patients with normal renal function, divided into doses given every 4 h), may be a satisfactory alternative (B-I).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

For patients who are intolerant of  $\beta$ -lactam antibiotics, increasing evidence indicates that doxycycline (200–400 mg per day in 2 divided doses orally for 10–28 days) may be adequate (B-I). Doxycycline is well absorbed orally; thus, intravenous administration should only rarely be needed.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

For children, ceftriaxone (50–75 mg/kg per day) in a single daily intravenous dose (maximum, 2 g) (B-I) is recommended. An alternative is cefotaxime (150–200 mg/kg per day) divided into 3 or 4 intravenous doses per day (maximum, 6 g per day) (B-II) or penicillin G (200,000–400,000 units/kg per day; maximum, 18–24 million U per day) divided into doses given intravenously every 4 h for those with normal renal function (B-I).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Children  $\geq 8$  years of age have also been successfully treated with oral doxycycline at a dosage of 4–8 mg/kg per day in 2 divided doses (maximum, 100–200 mg per dose) (B-II).

The presence of either papilledema or sixth cranial nerve palsy may indicate the presence of increased intracranial pressure. Although elevated intracranial pressure typically responds to systemic antibiotic therapy, other measures to lower pressure, such as serial lumbar punctures and use of corticosteroids or acetazolamide, may be considered in individual cases. CSF shunting was thought to be necessary in one patient to control increased intracranial pressure that appeared to be causing or contributing to loss of vision.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel recommends that it be noted that there are no clinical trials of doxycycline for pediatric patients with Lyme disease, but it is reasonable to extrapolate from the adult data in the recommendation.

## **2006 Recommendation**

Although antibiotic treatment may not hasten the resolution of seventh cranial nerve palsy associated with *B. burgdorferi* infection, antibiotics should be given to prevent further sequelae (A-II).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **2006 Recommendation**

Cranial nerve palsies in patients with Lyme disease are often associated with a lymphocytic CSF pleocytosis, with or without symptoms of meningitis. Panel members differed in their approach to the neurologic evaluation of patients with Lyme disease-associated seventh cranial nerve palsy. Some perform a CSF examination on all such patients. Others do not because of the good clinical response with orally administered antibiotics (even in the presence of CSF pleocytosis) and the absence of evidence of recurrent CNS disease in these patients. There was agreement that lumbar puncture is indicated for those in whom there is strong clinical suspicion of CNS involvement (e.g., severe or prolonged headache or nuchal rigidity). Patients with normal CSF examination findings and those for whom CSF examination is deemed unnecessary because of lack of clinical signs of meningitis may be treated with a 14-day course (range, 14–21 days) of the same antibiotics used for patients with erythema migrans (see above) (B-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **2006 Recommendation**

Those with both clinical and laboratory evidence of CNS involvement should be treated with regimens effective for Lyme meningitis, as described above (B-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **Cardiac Manifestations of Lyme**

### **2006 Recommendation**

Patients with atrioventricular heart block and/or myopericarditis associated with early Lyme disease may be treated with either oral or parenteral antibiotic therapy for 14 days (range, 14–21 days). Hospitalization and continuous monitoring are advisable for symptomatic patients, such as those with syncope, dyspnea, or chest pain. It is also recommended for patients with second- or third-degree atrioventricular block, as well as for those with first-degree heart block when the PR interval is prolonged to  $\geq 300$  milliseconds, because the degree of block may fluctuate and worsen very rapidly in such patients.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **2006 Recommendation**

For hospitalized patients, a parenteral antibiotic, such as ceftriaxone, is recommended as initial treatment of hospitalized patients (see recommendations for treatment of Lyme meningitis above) (B-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **2006 Recommendation**

For patients with advanced heart block, a temporary pacemaker may be required; expert consultation with a cardiologist is recommended. Use of the pacemaker may be discontinued when the advanced heart block has resolved. An oral antibiotic treatment regimen should be used for completion of therapy and for outpatients, as is used for patients with erythema migrans without carditis (see above) (B-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **Borrelial Lymphocytoma**

### **2006 Recommendation**

Available data indicate that borrelial lymphocytoma may be treated with the same treatment regimens used to treat patients with erythema migrans (see tables 2 and 3) (B-II).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **Late Lyme Arthritis**

### **2006 Recommendation**

Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally.

Doxycycline (100 mg twice per day) (B-I), amoxicillin (500 mg 3 times per day) (B-I), or cefuroxime axetil (500 mg twice per day) (B-III) for 28 days is recommended for adult patients without clinical evidence of neurologic disease.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that careful consideration be given to the current quality of evidence for amoxicillin. Two Review Panel members thought that the quality of evidence assigned to doxycycline in this recommendation (I) might be too high based on the available evidence.

## **2006 Recommendation**

For children amoxicillin (50 mg/kg per day in 3 divided doses [maximum of 500 mg per dose]) (B-I), cefuroxime axetil (30 mg/kg per day in 2 divided doses [maximum of 500 mg per dose]) (B-III), or, if the patient is  $\geq 8$  years of age, doxycycline (4 mg/kg per day in 2 divided doses [maximum of 100 mg per dose]) (B-I) is recommended. Oral antibiotics are easier to administer than intravenous antibiotics, are associated with fewer serious complications, and are considerably less expensive.

However, it is important to recognize that a small number of patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require intravenous therapy with a  $\beta$ -lactam antibiotic (see the paragraph below) for successful resolution. Further controlled trials are needed to compare the safety and efficacy of oral versus intravenous therapy for Lyme arthritis.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that careful consideration be given to the current quality of evidence for amoxicillin. Two Review Panel members thought that the quality of evidence assigned to this recommendation (I) might be too high based on the available evidence.

## **2006 Recommendation**

Neurologic evaluation that may include lumbar puncture should be performed for patients in whom there is a clinical suspicion of neurologic involvement.

Adult patients with arthritis and objective evidence of neurologic disease should receive: parenteral therapy with ceftriaxone (A-II) for 2-4 weeks. Cefotaxime or penicillin G administered parenterally is an acceptable alternative (B-II).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests consideration of specifying neurological issues that should be included/excluded. In addition, the Review Panel suggests that “evidence of neurologic disease” be defined and that the adjective “objective” be deleted. Clarifying the language to indicate that penicillin is inferior to cefotaxime in this clinical setting should also be considered when the guideline is next updated.

## **2006 Recommendation**

For children intravenous ceftriaxone or intravenous cefotaxime is recommended (B-III); penicillin G administered intravenously is an alternative (B-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that consideration be given to clarifying the language to indicate that penicillin is inferior to cefotaxime.

### **2006 Recommendation**

For patients who have persistent or recurrent joint swelling after a recommended course of oral antibiotic therapy, we recommend re-treatment with another 4-week course of oral antibiotics or with a 2–4-week course of ceftriaxone IV (B-III) (for dosages of oral agents, see the recommendations above for treatment of erythema migrans, and for dosages of parenteral agents, see the recommendations above for treatment of Lyme meningitis). A second 4-week course of oral antibiotic therapy is favored by panel members for the patient whose arthritis has substantively improved but has not yet completely resolved, reserving intravenous antibiotic therapy for those patients whose arthritis failed to improve at all or worsened. Clinicians should consider waiting several months before initiating re-treatment with antimicrobial agents because of the anticipated slow resolution of inflammation after treatment.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

During this period, NSAIDs may be used, but intra-articular injections of corticosteroids are not recommended (D-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information collected and provided (8-0).

### **2006 Recommendation**

If patients have no resolution of arthritis despite intravenous therapy and if PCR results for a sample of synovial fluid (and synovial tissue if available) are negative, symptomatic treatment is recommended (B-III). Symptomatic therapy might consist of nonsteroidal anti-inflammatory agents, intra-articular injections of corticosteroids, or disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine; expert consultation with a rheumatologist is recommended.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

If persistent synovitis is associated with significant pain or limitation of function, arthroscopic synovectomy may reduce the duration of joint inflammation (B-II).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests careful consideration be given to the current strength assigned to this recommendation. Although a subjective measure, two Review Panel members thought that the strength of recommendation assigned to this recommendation (B) might be too high.



## Late Neurologic Lyme

### **2006 Recommendation**

Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with intravenous ceftriaxone for 2 to 4 weeks (B-II).

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

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.

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that consideration be given to adding a rating for strength of recommendation and level of evidence to the last part of this recommendation. Consideration should also be given to providing examples of reliable “objective measures.”

### **2006 Recommendation**

Ceftriaxone is also recommended for children with late neurologic Lyme disease (B-II).

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Cefotaxime or penicillin G administered intravenously is an alternative (B-III).

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## Acrodermatitis Chronica Atrophicans

### **2006 Recommendation**

Available data indicate that acrodermatitis chronica atrophicans may be treated with a 21-day course of the same antibiotics (doxycycline [B-II], amoxicillin [B-II], and cefuroxime axetil [B-III]) used to treat patients with erythema migrans (see above). A controlled study is warranted to compare oral with parenteral antibiotic therapy for the treatment of acrodermatitis chronica atrophicans.

*Panel Determination/Discussion* – The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## Post Lyme Syndromes

### **2006 Recommendation**

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.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that the sentence that begins with “Whatever definition” be modified as follows: “Whatever definition is eventually adopted, having once had objective clinical or laboratory evidence of *B. burgdorferi* infection must be a condition sine qua non until a syndrome is formally defined.”

### **2006 Recommendation**

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.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (7-1).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that consideration be given to changing the phrase “no convincing biologic evidence” to something more specific, such as “Reports purporting to show the persistence of viable *B. burgdorferi* organisms after treatment with recommended regimens for Lyme disease have not been conclusive or corroborated by controlled studies.” It has been proposed by some that there are hardy, drug-tolerant reservoirs of *B. burgdorferi*, including intracellular cystic forms. To date, this has not been shown to correlate with symptom persistence, nor has eradication of these forms been shown to correlate with symptom improvement.

### **2006 Recommendation**

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 (E-I).

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

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 International Lyme and Associated Diseases Society (ILADS) and referenced by that society's published guidelines; 2) case reports cited by representatives of ILADS and patient representatives in oral presentations to the Panel during the Hearing on July 30, 2009; 3) journal correspondence published in response to several Lyme disease practice guidelines, editorials, and clinical trials; 4) patient testimony; and 5) the available placebo-controlled randomized clinical trials of long-term antibiotic therapy for symptoms attributed to Lyme disease.

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

1. **The prospective, controlled clinical trials for extended antibiotic treatment of Lyme disease have demonstrated considerable risk of harm, including potentially life-threatening adverse events.** 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 in antibiotic-treated patients [286, 438, 459, 493, 666]. In a recent cohort of 200 patients, catheter-associated adverse events such as thrombosis and infection occurred on average 81 days into therapy, underscoring the cumulative risk of adverse events with increasing time [895].

In clinical trials evaluating prolonged IV antibiotics for Lyme disease, there has been a lower rate of line sepsis in patients receiving IV ceftriaxone than those receiving IV placebo. It must be emphasized however, this adverse event is directly related to the intravenous access device. As ceftriaxone is intrinsically inactive against many common causes of line sepsis, including *Enterococcus*, *Candida*, *methicillin-resistant Staphylococcus aureus* (MRSA), and coagulase-negative *Staphylococci*, it should not be seen as mitigating the potential risk of septicemia due to long term intravenous lines.

2. **Prospective, controlled clinical trials have demonstrated little benefit from prolonged antibiotic therapy.** Nearly all primary outcome measures have failed to demonstrate a benefit 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, not sustained at the end of the trial [286, 438, 459, 493, 666].
3. **The risk/benefit ratio from prolonged antibiotic therapy strongly discourages prolonged antibiotic courses for Lyme disease.** Several presenters in the July 30<sup>th</sup> 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 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 [895]. The 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 clinical study that demonstrates comparable benefit to prolonging antibiotic therapy beyond one 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 reviewed 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 based on clinical presentations consistent with other illnesses. Some patients were abnormal hosts and not representative of the general population. Many reports included patients whose diagnosis was made before the implementation of the CDC recommendation for 2-tier serological testing, and were therefore based on less stringent criteria. Finally, caution should be used in extrapolating results from European studies to North American patients, due to the well-established microbiological and clinical distinctions in Lyme borreliosis on the two 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 Panel's conclusions, which are consistent with those reached by guidelines panels from the IDSA as well as 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.

## HGA

### **2006 Recommendation**

All symptomatic patients suspected of having HGA should be treated with antimicrobial therapy because of the risk of complications (A-III). Suspicion of HGA is based on the acute onset of unexplained fever, chills, and headache, often in association with thrombocytopenia, leukopenia, and/or increased liver enzyme levels in patients with exposure to *I. scapularis* or *I. pacificus* ticks within the prior 3 weeks. Confirmation of the diagnosis is based on laboratory testing (see the HGA section of the text), but antibiotic therapy should not be delayed in a patient with a suggestive clinical presentation pending the results. Identification of the characteristic intragranulocytic inclusions on blood smear is the most rapid diagnostic method, but such inclusions are often scant in number or sometimes absent; in addition, other types of inclusions unrelated to HGA or overlying platelets can be misinterpreted by inexperienced observers. Testing for antibodies to *A. phagocytophilum* is the most sensitive diagnostic method, but only if a convalescent-phase serum sample is assayed.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that PCR diagnostic tests be considered for inclusion in this recommendation.

### **2006 Recommendation**

Doxycycline is recommended as the treatment of choice for patients who are suspected of having symptomatic HGA (A-II). The dosage regimen for adults is 100 mg given twice per day by mouth (or intravenously for those patients unable to take an oral medication) for 10 days. This treatment regimen should be adequate therapy for patients with HGA alone and for patients who have coinfection with *B. burgdorferi*. Persistence of fever for >48 h after initiation of doxycycline treatment suggests that the diagnosis of HGA is incorrect or, more remotely, that the patient may be coinfecting with *B. microti*.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Although a 10-day treatment course of doxycycline may be offered to all children as well (C-III), the panel preferred a modified approach in which severity of illness, age of the child, and the presence or absence of coinfection with *B. burgdorferi* were each considered, to minimize an already low risk of drug toxicity. The suggested dosage of doxycycline for children with HGA is 4 mg/kg per day in 2 divided doses (maximum of 100 mg per dose) given orally (or intravenously for children unable to take an oral medication). Children at least 8 years of age may be treated with a 10-day course of doxycycline.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

For severely ill children <8 years of age without concomitant Lyme disease, the panel recommended an abbreviated treatment course of 4–5 days (i.e., for 3 days after resolution of fever) (B-III). Children treated with an abbreviated course of therapy should be closely observed to ensure resolution of clinical and laboratory abnormalities.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

If the child has concomitant Lyme disease, then amoxicillin (50 mg/kg per day in 3 divided doses [maximum of 500 mg per dose]) or cefuroxime axetil (30 mg/kg per day in 2 divided doses [maximum of 500 mg per dose]) should be initiated at the conclusion of the course of doxycycline to complete a 14-day total course of antibiotic therapy (B-III).

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Patients with mild illness due to HGA who are not optimally suited for doxycycline treatment because of a history of drug allergy, pregnancy, or age <8 years, may be treated with rifampin for 7–10 days using a dosage regimen of 300 mg twice per day by mouth for adults and 10 mg/kg twice per day for children (maximum of 300 mg per dose) (B-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Rifampin-treated patients should be closely observed to ensure resolution of clinical and laboratory abnormalities. Because rifampin is not effective therapy for Lyme disease, patients coinfecting with *B. burgdorferi* should also be treated with amoxicillin or cefuroxime axetil, as used for the treatment of erythema migrans (see above) (A-I).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

No other antimicrobial can be recommended for the treatment of HGA (E-III)

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Persistence of fever for >48 h after initiation of doxycycline suggests that the diagnosis of HGA is incorrect or, more remotely, that the patient is coinfecting with *B. microti*.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that consideration be given to adding a rating for strength of recommendation and level of evidence to this recommendation.

### **2006 Recommendation**

Treatment is not recommended for asymptomatic individuals who are seropositive for antibodies to *A. phagocytophilum* (E-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## **Babesiosis**

### **2006 Recommendation**

All patients with active babesiosis should be treated with antimicrobials because of the risk of complications (A-III). Diagnostic criteria for active babesial infection should include the presence of viral infection–like symptoms *and* identification of babesial parasites in blood by smear evaluation or by PCR amplification of babesial DNA.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Symptomatic patients whose serum contains antibody to babesia but whose blood lacks identifiable babesial parasites on smear or babesial DNA by PCR should not receive treatment (E-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Treatment is also not recommended for asymptomatic individuals, regardless of the results of serologic examination, blood smears, or PCR (E-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Asymptomatic patients with positive babesial smears and/or PCR should have these studies repeated, and a course of treatment should be considered if parasitemia persists for >3 months (B-III).

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

The combination of either atovaquone plus azithromycin or clindamycin plus quinine for 7–10 days is the initial therapy that should be considered for patients with babesiosis (A-I). Clindamycin and quinine should be given for those with severe babesiosis (A-III). In such patients, clindamycin should be administered intravenously rather than orally, and exchange transfusion should be considered. Longer duration of antimicrobial therapy may be necessary in highly and persistently symptomatic patients until parasitemia is cleared, but no controlled studies exist that define the risk-benefit ratio of more prolonged therapy.

The dosage regimen of atovaquone plus azithromycin for adults is atovaquone, 750 mg orally every 12 h, and azithromycin, 500–1000 mg on day 1 and 250 mg orally once per day thereafter. For immunocompromised patients with babesiosis, higher doses of azithromycin (600–1000 mg per day) may be used. The dosages for children are atovaquone, 20 mg/kg

every 12 h (up to a maximum of 750 mg per dose), and azithromycin, 10 mg/kg once per day on day 1 (up to a maximum of 500 mg per dose) and 5 mg/kg once per day (up to a maximum of 250 mg per dose) orally thereafter.

The dosage regimen of clindamycin plus quinine for adults is clindamycin, 300–600 mg every 6 h intravenously or 600 mg every 8 h orally, and quinine, 650 mg every 6–8 h orally. Dosages for children are clindamycin, 7–10 mg/kg given intravenously or orally every 6–8 h (up to a maximum of 600 mg per dose) and quinine 8 mg/kg given orally every 8 h (up to a maximum of 650 mg per dose).

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

A body of evidence is growing that certain immunocompromised persons are at risk of treatment failures and of severe babesiosis. A recent retrospective case control study has shown that such patients often require more prolonged or repeated courses of therapy [478].

When the 2006 Lyme Guidelines are next updated, the Review Panel suggests that consideration be given to enumeration of important high risk groups, and possibly, a recommendation of treatment until 2 weeks after resolution of parasitemia by blood smear in such patients.

### **2006 Recommendation**

Partial or complete RBC exchange transfusion is indicated for persons with severe babesiosis, as indicated by high-grade parasitemia (>10%), significant hemolysis, or renal, hepatic, or pulmonary compromise (A-III). No data are available to determine whether partial exchange transfusion is preferable to whole blood exchange; expert consultation with an infectious diseases expert and a hematologist is recommended.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Patients with moderate-to-severe babesiosis should be monitored closely during therapy to ensure clinical improvement and improvement of parasitemia and other laboratory abnormalities (A-III). In patients with mild-to-moderate babesiosis, clinical improvement should occur within 48 h after the start of antiprotozoal therapy, and symptoms should completely resolve within 3 months after the initiation of therapy. In severely ill patients, the hematocrit and percentage of parasitized erythrocytes should be monitored daily or every other day until the patient has improved and the level of parasitemia has decreased to <5% of erythrocytes. Some patients may have persistence of low-grade parasitemia for months after specific antimicrobial therapy.

***Panel Determination/Discussion*** - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).



### **2006 Recommendation**

Physicians should consider the possibility of coinfection with *B. burgdorferi* or *A. phagocytophilum* or both in patients with especially severe or persistent symptoms, despite administration of appropriate anti-babesial therapy (A-III). Patients found to have coinfection should be treated with additional antimicrobial therapy, as described above. An underlying immunodeficiency (including asplenia or prior splenectomy, malignancy, or HIV infection) also should be considered in patients with severe or prolonged episodes of babesiosis.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

### **2006 Recommendation**

Re-treatment of patients with antibabesial therapy, as outlined above, should be considered if babesial parasites or amplifiable babesial DNA are detected in blood 3 months after initial therapy, regardless of symptom status (A-III). However, such assays need not be done routinely for immunocompetent patients who are asymptomatic.

*Panel Determination/Discussion* - The Review Panel determined that this recommendation is medically/scientifically justified in light of all of the evidence and information provided (8-0).

## ADDITIONAL REVIEW OF EXECUTIVE SUMMARY STATEMENT

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

*“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.”*

**Panel Determination/Discussion** – 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 very high prior probability of Lyme disease as compared with a patient from a low endemicity area who presents only with fatigue. Because the statement could be considered differently in light of different clinical and epidemiologic contexts, it was felt to be problematic by some members of the Review Panel. Ultimately the Panel was evenly split on whether this statement would benefit from modification or clarification.

This statement appears to be an admonition to practitioners against “over-diagnosing” Lyme disease and other tick-borne infections, particularly when the diagnosis is based only on vague and nonspecific symptoms, in patients unlikely to have been exposed to ticks in endemic areas, 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.”

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. Based on 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 whether or not 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 Panel felt that in clinical practice, the presence of certain classic complications of Lyme disease such as aseptic meningitis, AV 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 when the 2006 Lyme Guidelines are next updated, 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 Guidelines are necessary at this time (8-0).

The Review Panel suggests consideration of the following when the 2006 Lyme Guidelines are next updated:

- Expansion of the background section to include an overview of the currently available diagnostic tests for Lyme disease, including the advantages and limitations of the currently recommended 2-tier serological tests. Formal recommendations about the utility and appropriate use of alternative tests should be added, with accompanying discussion and references. Such alternative tests should include the following:
  - Cerebrospinal fluid (CSF) serology
  - PCR of blood, CSF, and synovial fluid
  - Serum C6 peptide
  - Inclusion of the VIsE band in the IgG Western blot
- A discussion of the effect of antibiotic exposure (particularly for patients previously treated with suboptimal regimens) on the development or persistence of seropositivity.
- Directly addressing whether some patients with late Lyme disease may be seronegative before treatment.
- A discussion of the Southern Tick-Associated Rash Illness (STARI), how its geographic distribution compares with that of human Lyme disease cases, and recommendations as to how an EM-like rash should be managed in geographic areas where STARI has been described.
- A discussion about non-antimicrobial modalities that have been explored for patients who attribute chronic symptoms to persistent Lyme disease.

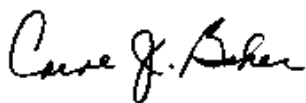
## CONCLUSION

Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances [Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines, 1990]. Among the goals of guidelines are to enhance appropriate clinical practice, improve the quality of patient care, and identify areas requiring further investigation. Guidelines are not intended to be (and cannot be) rigid dicta, inflexible rules, or requirements of practice.

The Review Panel finds that the 2006 Lyme Guidelines were based on the highest-quality medical/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 authors of the 2006 Lyme Guidelines 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 Lyme Guidelines are further corroborated by guidelines and statements by other independent bodies in the United States and Europe.

It is expected that the IDSA will review the 2006 Lyme Guidelines on a regular basis to determine the need for updating based on any newly available evidence that would warrant a substantive change to the current recommendations.

I hereby certify that the foregoing Final Report of the Lyme Disease Review Panel of the Infectious Diseases Society of America has been prepared in accordance with the requirements of the Action Plan attached as Exhibit 1 to the Agreement Between the Attorney General of the State of Connecticut and the Infectious Diseases Society of America dated April 30, 2008.



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Carol J. Baker, MD  
Review Panel Chairperson

April 22, 2010

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Date

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