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

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Evidence-based guidelines for the management of patients with Lyme disease, human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis), and babesiosis were prepared by an expert panel of the Infectious Diseases Society of America. These updated guidelines replace the previous treatment guidelines published in 2000 (Clin Infect Dis 2000; 31[Suppl 1]:1–14). The guidelines are intended for use by health care providers who care for patients who either have these infections or may be at risk for them. For each of these *Ixodes* tickborne infections, information is provided about prevention, epidemiology, clinical manifestations, diagnosis, and treatment. Tables list the doses and durations of antimicrobial therapy recommended for treatment and prevention of Lyme disease and provide a partial list of therapies to be avoided. A definition of post–Lyme disease syndrome is proposed.

EXECUTIVE SUMMARY

Background

Lyme disease is the most common tickborne infection in both North America and Europe. In the United States, Lyme disease is caused by *Borrelia burgdorferi*, which is transmitted by the bite of the tick species *Ixodes scapularis* and *Ixodes pacificus*. Clinical manifestations most often involve the skin, joints, nervous system, and heart. Extracutaneous manifestations are less commonly seen than in earlier years. Early cutaneous infection with *B. burgdorferi* is called erythema migrans, which is the most common clinical manifestation of Lyme disease. *I. scapularis* may also be infected with and transmit *Anaplasma phagocytophilum* (previously referred to as *Ehrlichia phagocytophila*) and/or *Babesia microti*, the primary cause of babesiosis. Thus, a bite from an *I. scapularis* tick may lead to the development of Lyme disease, human granulocytic anaplasmosis (HGA, formerly known as human granulocytic ehrlichiosis), or babesiosis as a single infection or, less frequently, as a coinfection. *Clinical findings are sufficient*

Received 21 August 2006; accepted 21 August 2006; electronically published 2 October 2006.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

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.

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Clinical Infectious Diseases 2006; 43:1089–134

1058-4838/2006/4309-0001$15.00

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.

Tick Bites and Prophylaxis of Lyme Disease

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) (see table 1 for recommendation categories, which are indicated in parentheses throughout this text).

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

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).

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.

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 2*A* and 2*B*) (A-III). Testing of ticks for tickborne infectious agents is not recommended, except in research studies (D-II).

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

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

Category, grade	Definition
Strength of recommendation	
A	Strongly in favor
B	Moderately in favor
C	Optional
D	Moderately against
E	Strongly against
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾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
III	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.

Figure 1. From left to right, an *Ixodes scapularis* larva, nymph, adult male tick, and adult female tick. The picture is a generous gift from Dr. Richard Falco (Fordham University).

1 month after removing an attached tick should promptly seek medical attention to assess the possibility of having acquired a tickborne infection. 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.

Early Lyme Disease

Erythema migrans. 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). 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. Antibiotics recommended for children are amoxicillin (50 mg/kg per day in 3 divided doses [maximum of 500 mg per dose]), cefuroxime axetil (30 mg/kg per day in 2 divided doses [maximum of 500 mg per dose]), or, if the patient is ⩾8 years of age, doxycycline (4 mg/kg per day in 2 divided doses [maximum of 100 mg per dose]) (A-II).

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.

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

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).

Lyme meningitis and other manifestations of early neurologic Lyme disease. 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). 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). For patients who are intolerant of β-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.

For children, ceftriaxone (50–75 mg/kg per day) in a single

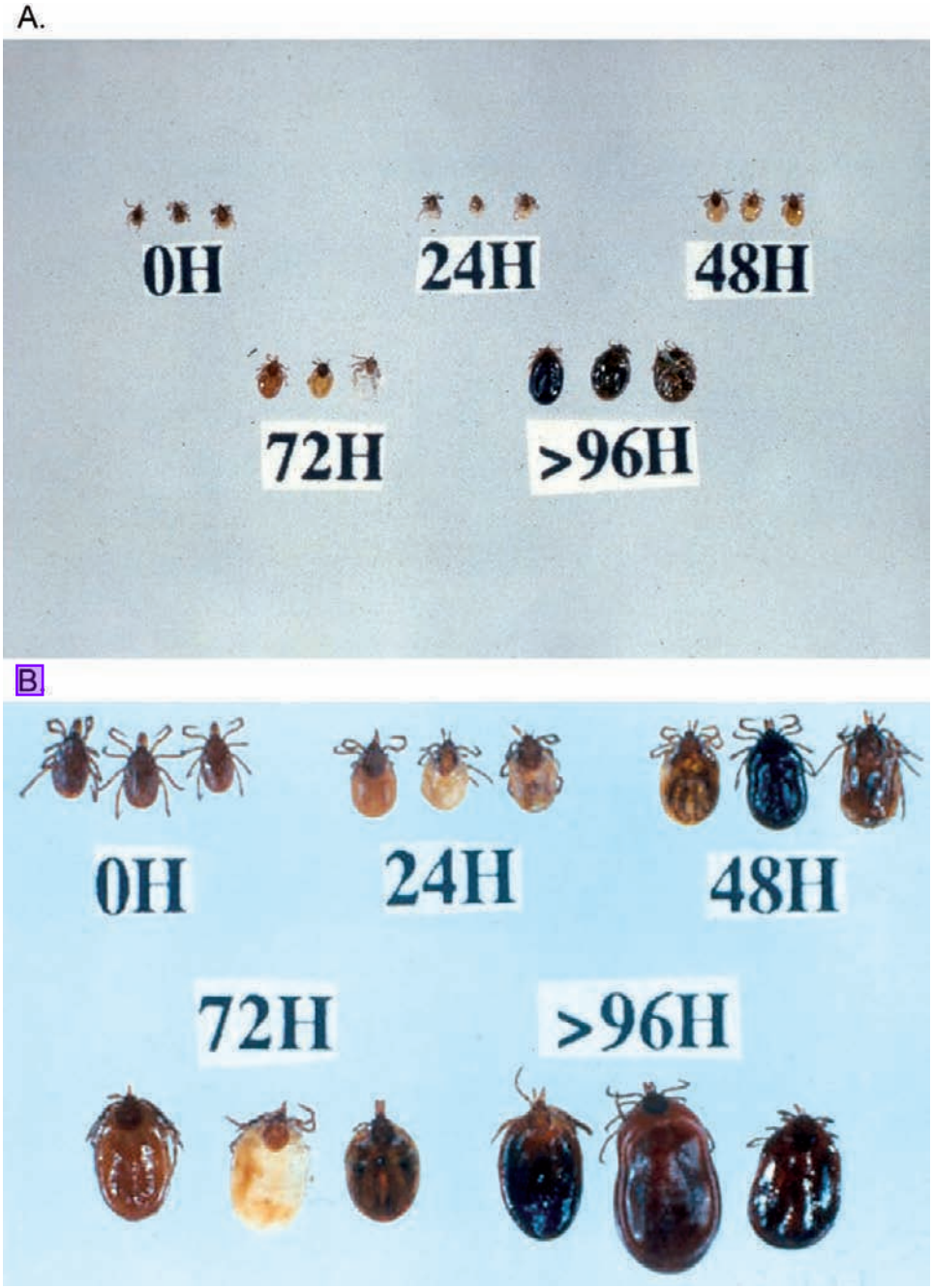

Figure 2. *Ixodes scapularis* ticks demonstrating changes in blood engorgement after various durations of attachment. *A,* Nymphal stage (reprinted from [1], with permission from Elsevier). *B,* Adult stage. The pictures are a generous gift from Dr. Richard Falco (Fordham University).

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). Children ⩾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).

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

Lyme carditis. 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 ⩾30 milliseconds, because the degree of block may fluctuate and worsen very rapidly in such 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). 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).

Borrelial lymphocytoma. Available data indicate that borrelial lymphocytoma may be treated with the same regimens used to treat patients with erythema migrans (see above) (B-II).

Pregnancy. 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).

Late Lyme Disease

Lyme arthritis. 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. 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 ⩾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 β-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.

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). For children, intravenous ceftriaxone or intravenous cefotaxime is recommended (B-III); penicillin G administered intravenously is an alternative (B-III). See the recommendations above for treatment of patients with Lyme meningitis for suggested doses of each of these antimicrobials.

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. 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. If persistent synovitis is associated with significant pain or limitation of function,

arthroscopic synovectomy may reduce the duration of joint inflammation (B-II).

Late neurologic Lyme disease. 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). 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. Ceftriaxone is also recommended for children with late neurologic Lyme disease (B-II). Cefotaxime or penicillin G administered intravenously is an alternative (B-III). See the recommendations above on the treatment of Lyme meningitis for suggested doses of each of these antimicrobials.

Acrodermatitis chronica atrophicans. 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.

Coinfection. 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). 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).

Post–Lyme Disease Syndromes

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.

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 (E-I).

Therapeutic modalities not recommended. 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).

HGA

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.

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 coinfected with *B. microti*.

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 ⩾8 years of age may be treated with a 10-day course of doxycycline. 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. 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).

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). 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 coinfected with *B. burgdorferi* should also be treated with amoxicillin or cefuroxime axetil, as used for the treatment of erythema migrans (see above) (A-I). No other antimicrobial can be recommended for the treatment of HGA (E-III).

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

Babesiosis

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

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).

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.

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.

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.

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.

OBJECTIVE

The objectives of these practice guidelines are to provide clinicians and other health care practitioners with recommendations for treatment of patients in the United States with suspected or established Lyme disease, HGA (formerly known as human granulocytic ehrlichiosis), or babesiosis. In addition, recommendations are provided for prevention of these infections, all of which may be transmitted by certain species of *Ixodes* ticks. The panel performed an extensive review of all of the randomized, controlled trials and open-label trials published in peer-reviewed, English-language journals. Previously published and widely accepted criteria were used to grade the quality of the evidence on which the recommendations were based (table 1) [2, 3].

Lyme disease, caused by the spirochete *B. burgdorferi,* is endemic in several regions of the United States, particularly areas of the Northeast, upper Midwest, and northern California [4, 5]. It is the most frequently reported vectorborne disease in the United States. The *Ixodes* tick vectors have a 3-stage life cycle: larva, nymph, and adult. The risk of human illness is highest during the time of year when the nymphal stage is seeking a blood meal. The most common clinical manifestation of Lyme disease is a skin lesion called erythema migrans that results from cutaneous infection with *B. burgdorferi.* Adults and children of both sexes may be affected. Patients with Lyme disease are evaluated and treated by general practitioners, pediatricians, and internists, as well as by infectious diseases specialists, dermatologists, rheumatologists, neurologists, cardiologists, orthopedists, gynecologists and obstetricians, otolaryngologists, and ophthalmologists. Because of the differences in the species of *Borrelia* that cause Lyme disease in North America *(B. burgdorferi),* compared with those that cause this infection in Eurasia *(B. burgdorferi, Borrelia afzelii,* and *Borrelia garinii),* recommendations were based, whenever possible, on studies conducted in the United States. In the treatment of Lyme disease, as in all infectious diseases, basic medical and scientific principles should be considered. In selecting an antibiotic, there should be evidence of activity in vitro, evidence for penetration into the infected sites, and well-designed clinical studies to support the treatment regimen.

RECOMMENDATIONS FOR THE CLINICAL ASSESSMENT, TREATMENT, AND PREVENTION OF LYME DISEASE, HGA, AND BABESIOSIS

PREVENTION OF TICK BITES

The best currently available method for preventing infection with *B. burgdorferi* and other *Ixodes*-transmitted infections is to avoid tick-infested areas [6]. If exposure to either *I. scapularis* or *I. pacificus* ticks is unavoidable, a number of measures may help to decrease the risk that ticks will attach and subsequently transmit infection. Frequent visual inspection of skin and clothes may help to identify ticks prior to attachment, thus allowing removal before infection can be transmitted. Attached ticks should be removed promptly, preferably with the aid of fine-tip forceps [7]. If a portion of the mouth parts of the tick remains embedded in the skin, only topical disinfection of the site is suggested, because attempts to remove this material can cause tissue damage and are unnecessary as the risk of Lyme disease is unaffected.

Use of protective clothing (long-sleeved shirt tucked into pants and long pants tucked into socks) may interfere with tick attachment by increasing the time required for ticks to find exposed skin, thus facilitating their recognition and removal. Wearing light-colored clothing to provide a background that contrasts with the tick is often recommended as a common sense precaution to enhance the ability to see and remove ticks before attachment. A recent study, however, suggested that an *Ixodes* tick species present in Europe *(Ixodes ricinus)* may be more attracted to light-colored than darker-colored clothing [8]. These findings require confirmation before any change in recommended practice should be considered.

Tick and insect repellents that contain N,N-diethyl-3-methylbenzamide (DEET) applied to the skin or clothing provide additional protection but may require reapplication for maximum effectiveness. The timing of reapplication depends on the specific preparation utilized [9–11]. Ticks detect DEET through olfactory sensing and are repelled [12]. Serious neurologic complications in children after excessive application of DEET-containing repellents have been reported [13], but the compound appears to be safe when used as directed in the product labels, even for young children >2 months old [14,15]. DEET need not be applied to the face or hands for prevention of tick bites and should not be applied to skin that is either

irritated or abraded. After returning indoors, skin that was treated with DEET should be washed with soap and water. Permethrin (a synthetic pyrethrin) is available in a spray solely for application to clothing (it is inactivated by skin lipids [16]) and is particularly effective because it kills ticks on contact [17]. Picaridin and IR3535 have recently been promoted as effective insect repellents, but their effectiveness against *Ixodes* ticks has not been determined [14, 18].

To date there is only limited evidence that any of the personal protective measures described above are effective in reducing the number of human cases of Lyme disease [19–22].

PROPHYLAXIS OF LYME DISEASE

Primary Management Options Considered

For persons who remove attached ticks, the management options considered included treating with antimicrobials: (1) all persons, (2) only persons believed to be at increased risk of developing Lyme disease (e.g., those removing a nymphal or adult *I. scapularis* or *I. pacificus* tick after at least 36 h of attachment), (3) only persons who develop erythema migrans or other clinical signs and symptoms of a tickborne infection, and (4) all persons who seroconvert from a negative to a positive test result for serum antibodies to *B. burgdorferi*. Management of bites by the vector ticks *I. ricinus* and *Ixodes persulcatus* was not considered by the panel, because these tick species are not present in North America.

Outcomes Evaluated

The panel weighed both the risks and consequences of developing Lyme disease (including the risk of late complications) in persons bitten by *I. scapularis* or *I. pacificus* ticks against the economic costs and adverse effects of prophylactic antimicrobials. The impact of the different strategies on quality of life was considered. In addition, the potential effect of having previously received the recombinant OspA Lyme vaccine, which was withdrawn by the manufacturer in 2002, was considered [23]. The principal desired outcome is prevention of Lyme disease. Another desired outcome is the prevention of other *Ixodes*-transmitted illnesses, including HGA (caused by *A. phagocytophilum*) and babesiosis. Either of the latter 2 infections may occur alone or in conjunction with Lyme disease, and occasionally all 3 infections may occur together [24–28].

Options Considered and Evidence To Support Recommendations

Option 1: antimicrobial therapy for all persons who remove vector ticks* (I. scapularis *or* I. pacificus) *that have become attached. Tick bites are extremely common in areas of endemicity. For example, it has been estimated that nearly 180,000 tick bites occurred annually in Westchester County, New York (total population, ~850,000), during the 1991–1994 time period [29]. In a prospective study in which individuals from this county were closely observed after a documented *I. scapularis* tick bite, a second bite occurred in ~15% of patients within just 6 weeks of the original bite [30].

Three randomized, prospective studies on the use of antibiotic chemoprophylaxis were reported through 1993 [31–33]. In each study, a 10-day course of antibiotics was compared with an identical-appearing placebo. Although none of the antibiotic-treated patients developed Lyme disease in these trials, the studies were not adequately powered to show a significant difference in efficacy compared with placebo. Thus, it remained unclear whether the use of antibiotics for prophylaxis after *I. scapularis* tick bites could actually cure incubating *B. burgdorferi* infection [34]. In a larger and more recent chemoprophylaxis trial, erythema migrans at the site of a tick bite developed in only 1 (0.4%) of 235 subjects who received a single 200-mg dose of doxycycline within 72 h of removing an attached *I. scapularis* tick, compared with 8 (3.2%) of 247 subjects who received placebo ($P < .04$) [30]. None of the subjects developed either objective evidence of extracutaneous Lyme disease or asymptomatic *B. burgdorferi* infection. Treatment efficacy was 87%, but there was a wide 95% CI (25%–98%), reflecting the small number of patients who developed Lyme disease. Although single-dose doxycycline was frequently associated with gastrointestinal upset, such as nausea or vomiting [30], the authors cited data to show that the tolerability could be improved by administration with food with only a minimal decrease in peak serum concentrations [35].

A proof-of-concept study in mice bitten by infected *I. scapularis* ticks confirmed that a single oral dose of doxycycline is effective for prevention of *B. burgdorferi* infection [36]. Although the efficacy rate was lower in the mouse study (43%), the time that the concentration of doxycycline remained above the MIC (T>MIC) of *B. burgdorferi* in the mouse model was less than one-half the estimated T>MIC in humans after receipt of a single 200-mg dose of doxycycline because of a faster rate of elimination of doxycycline in mice than in humans [30, 36, 37]. Indeed, parenteral administration of a single dose of a sustained release preparation of doxycycline in the same mouse model was 100% effective in prevention of *B. burgdorferi* infection [36].

One cost-effectiveness analysis concluded that a 2-week course of doxycycline is indicated when the probability of infection with *B. burgdorferi* after a tick bite is ⩾3.6% and should be considered when the theoretical probability ranges from 1% to 3.5% [38]. Some experts disagree with key assumptions in the model (many of which tended to favor the use of antimicrobial prophylaxis) and consider the duration of treatment to be excessive. However, the findings do argue against routine prophylaxis of all *I. scapularis* tick bites, because the frequency of Lyme disease was <3.6% among placebo recipients in each of the 4 reported chemoprophylaxis trials [30–33].

Doxycycline is relatively contraindicated for women who are either pregnant or breast-feeding, as well as for children <8 years of age. In these patients, if chemoprophylaxis were to be used, an alternative antimicrobial, such as amoxicillin, would need to be considered. Amoxicillin is effective against *B. burgdorferi* both in vitro [39, 40] and in clinical trials of patients with Lyme disease [41–44], and it may be expected to be a useful prophylactic agent after a bite from an *I. scapularis* or *I. pacificus* tick. No cases of Lyme disease developed in 192 patients given 10 days of amoxicillin for prophylaxis after a bite from an *I. scapularis* tick in a randomized clinical trial [32], although failure of amoxicillin prophylaxis has been reported anecdotally from Europe [45]. Amoxicillin has a shorter half-life than doxycycline, and a multiday regimen would likely be necessary for prophylaxis to be effective [37].

Some practitioners prescribe a 10–14-day course of prophylactic amoxicillin for pregnant women after *I. scapularis* tick bites, because case reports have suggested that Lyme disease during pregnancy may be associated with adverse outcomes for the fetus [46]. However, a large body of data from clinical and epidemiologic studies suggest that favorable outcomes can be expected when pregnant women with Lyme disease are treated with standard antibiotic regimens [47–49]. Indeed, there is little evidence that a congenital Lyme disease syndrome occurs [50, 51].

It has been estimated that if a 10-day course of amoxicillin were routinely used for antibiotic prophylaxis after tick bites, 8 cases of drug-associated rash, including 1 severe life-threatening reaction, would occur for every 10 cases of early Lyme disease that were prevented [34]. In addition, 3 cases of minor amoxicillin-related adverse effects (e.g., diarrhea) would occur for every case of Lyme disease that was prevented. In 2 studies of prophylaxis for tick bites in which 10 days of an antimicrobial preparation was prescribed, the risk of acquiring Lyme disease after a tick bite among placebo recipients was approximately the same as the risk of developing a rash from the prophylactic antibiotic [31, 32].

In addition to *B. burgdorferi,* other potential pathogens, such as *A. phagocytophilum* or *B. microti,* may also be transmitted by *Ixodes* ticks [52, 53]. Doxycycline is effective for the treatment of patients with HGA (see the section on HGA below) but is not effective therapy for babesiosis (see the section on babesiosis below). There are no published clinical data on the efficacy of prophylaxis with doxycycline against either of these microorganisms. Amoxicillin is not active against either *A. phagocytophilum* or *B. microti* and, therefore, would be expected to be ineffective for prevention of these infections.

The prevalence of *B. burgdorferi* in nymphal *I. scapularis* ticks commonly ranges between 20% and 40% in areas of endemicity in the Northeastern and upper Midwestern United States [54–56]. However, *I. pacificus* ticks (the vector for Lyme disease in the western United States) have a much lower infection rate with *B. burgdorferi* (0%–14%) [57]. This is presumably because most *I. pacificus* ticks feed on lizards, the blood of which is bactericidal for *B. burgdorferi* [57–59].

The prevalence of *B. burgdorferi* infection in host seeking *I. scapularis* ticks in the southern United States is also extremely low; for adult stage ticks, it is 0%–4.6% [60–62], and for nymphal stage ticks, evidence of infection has not been found to date [63]. The panel is unaware of a proven case of *B. burgdorferi* infection acquired indigenously in any state south of Maryland or Virginia [64]. Patients in the southern United States may develop an erythema migrans–like skin lesion associated with mild viral infection-like symptoms resembling Lyme disease following a bite of an *Amblyomma americanum* (Lone star) tick [65]. Although 1 report associated this illness, known as Southern tick–associated rash illness (STARI), with *Borrelia lonestari* infection [66], most cases do not appear to be caused by any known *Borrelia* species [67].

Option 2: antimicrobial therapy only for persons believed to be at high risk for Lyme disease (e.g., those removing a nymphal or adult* I. scapularis *tick after ⩾36 h of attachment). Several factors associated with risk of developing Lyme disease after a tick bite can be identified. The lower risk from *Ixodes* tick bites in the western and southern United States has been discussed above. Regardless of the geographic region, larval *I. scapularis* and *I. pacificus* ticks are rarely infected with *B. burgdorferi.* Larval ticks become infected after feeding on an infected animal, rather than from transovarial transmission, and they feed only once before molting to the nymphal stage. Therefore, larval ticks do not serve as relevant vectors for Lyme disease.

Unengorged nymphal or adult *Ixodes* ticks also pose little or no risk of transmission of *B. burgdorferi.* The duration of tick attachment can be estimated on the basis of a measurement of the degree of tick engorgement with blood (scutal index) [30, 68, 69]. In the single-dose doxycycline chemoprophylaxis trial, duration of tick attachment as assessed by this measure correlated directly with risk of developing Lyme disease. Erythema migrans developed at the tick bite site in 8 (9.9%) of 81 placebo-treated subjects bitten by an *I. scapularis* nymphal tick that had at least some blood engorgement. The risk increased to 3 (25%) of 12 if the tick were highly engorged, equating to a ⩾72-h duration of attachment, compared with 0 (0%) of 59 for bites from nymphal ticks with no blood engorgement ($P = .02$ and $P = .004$, respectively) [30]. In a separate study from New York State, the risk of developing *B. burgdorferi* infection was 20% (3 of 15) among patients bitten by highly engorged nymphal or adult-stage *I. scapularis* ticks that were estimated to have been attached for ⩾72 h [68].

In the single-dose doxycycline chemoprophylaxis trial [30], the number of subjects needed to treat to prevent 1 case of Lyme disease was 36 (95% CI, 19–244) if everyone with an *I.*

scapularis tick bite were to have been treated [70]. However, this number could have been reduced to 12 (95% CI, 6–25) if prophylaxis were given only to those who removed partially or fully engorged nymphal ticks [70]. Although the *B. burgdorferi* infection rate of adult *I. scapularis* ticks may be twice that of nymphal ticks [71], most cases of Lyme disease in humans are associated with nymphal stage tick bites. This is apparently caused, at least in part, by the larger size of adult ticks that are more readily noticed and removed than nymphal *I. scapularis* ticks and, therefore, remain attached for a shorter duration of time [30, 69, 72]. In the single-dose doxycycline chemoprophylaxis trial, the estimated median duration of attachment for adult *I. scapularis* ticks was 10 h, compared with 30 h for nymphs ($P < .001$) [30].

The delay in transmission of *B. burgdorferi* observed clinically has also been demonstrated in animal studies. Experimental studies have demonstrated that *B. burgdorferi* is rarely transmitted to laboratory animals by nymphal or adult *I. scapularis* or nymphal *I. pacificus* ticks within the first 36 h of attachment [73–76]. This "grace period" is required for spirochetes in infected ticks to migrate from the tick midgut into the salivary glands once feeding commences [77]. Although *I. scapularis* and *I. pacificus* ticks that have been attached for <36 h are very unlikely to transmit *B. burgdorferi* infection, *I. ricinus* ticks in Europe that are infected with *B. afzelii* appear to transmit infection more rapidly, often within 24 h [78, 79]. Although there is also a delay in tick transmission of HGA or babesiosis infection in animal systems [80–82], *A. phagocytophilum* can be transmitted within the first 24 h of attachment of *I. scapularis* ticks [83]. Taken together, the conclusion from the human and animal studies is that expeditious removal of attached ticks may be very helpful in prevention of *Ixodes* species–transmitted infections.

The option of selectively treating persons with "high-risk" tick bites to prevent Lyme disease assumes that the species, stage, and degree of engorgement of the tick can be ascertained. This requires special expertise. Many different tick species bite humans, and some "ticks" removed from humans are actually spiders, scabs, lice, or dirt and, thus, pose no risk of Lyme disease [68, 84]. Nevertheless, health care practitioners can be taught to identify ticks (figure 1) and to estimate the degree of engorgement for use as a marker of the duration of feeding in a clinical setting (figure 2*A* and 2*B*) [85]. Independent assessment by the health care practitioner is necessary because in areas where exposure to ticks is frequent, the patient's own estimate of the duration of attachment is unreliable and usually is shorter than the actual duration of attachment [68, 86]. Methods for determining the *B. burgdorferi* infection status of ticks removed from patients are not standardized, and the results do not necessarily correlate with the risk of infection [68]. Testing of ticks removed from patients for *B. burgdorferi* is, therefore, not recommended except in research studies.

Option 3: antimicrobial therapy only for persons who develop erythema migrans or other clinical manifestations of Lyme disease or other tick-transmitted infections. The great majority of persons with *B. burgdorferi* infection present with erythema migrans [23, 87–89]. Because primary erythema migrans lesions occur at the site of a tick bite [90–93], a person who removes a tick should be specifically directed to search for and seek care for a skin lesion that subsequently develops at that location. The prognosis for patients who are treated for erythema migrans is excellent (see Early Lyme Disease, below). HGA, as well as babesiosis in areas of endemicity, should be included in the differential diagnosis of patients who develop fever or clinical illness after an *Ixodes* tick bite [94–96].

Option 4: antimicrobial therapy for all persons who seroconvert from a negative to a positive test result for serum antibodies against* B. burgdorferi *when acute and follow-up serum samples are tested simultaneously. To implement this option, acute and follow-up blood specimens need to be tested for antibodies in paired samples. The value of acute-phase and convalescent-phase serologic testing for identifying infection with *B. burgdorferi* following a tick bite, however, has not been demonstrated. There were no asymptomatic seroconversions after tick bites among untreated subjects in any of the United States chemoprophylaxis trials [30–33]. Furthermore, no objective extracutaneous manifestation of Lyme disease developed in any of the patients in the 3 studies in which patients were observed for 6 months to 3 years [31–33]. The single-dose doxycycline chemoprophylaxis trial had a 6-week follow-up period and was not designed to detect long-term outcomes [30]. In that study, nonspecific "viral-type" illnesses (i.e., without erythema migrans) were no more frequent in antibiotic-treated subjects than in untreated subjects, consistent with the probability that most of these illnesses were unrelated to *B. burgdorferi* infection. Although asymptomatic seroconversion was reported to have occurred rarely in subjects enrolled in a Lyme vaccine trial [97], mild illnesses or erythema migrans skin lesions could have gone unnoticed or unreported, because volunteers were only examined if they reported symptoms. Serologic assays for Lyme disease thus far evaluated [98–103] are of limited use in screening persons lacking objective manifestations of Lyme disease because of their poor specificity (particularly for IgM reactivity) and cost [98, 99, 101, 102, 104].

Recommendations

1. 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 infection can occur (B-III).

2. For prevention of Lyme disease after a recognized tick bite, routine use of antimicrobial prophylaxis or serologic testing is not recommended (E-III). 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 on 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 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 of the United States. Whether use of antibiotic prophylaxis after a tick bite will reduce the incidence of HGA or babesiosis is unknown.

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 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)

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

Protective immunity produced by the recombinant OspA Lyme disease vaccine is not long lasting [105]. 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.

3. 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 2*A* and 2*B*) (A-III). Testing of ticks for tickborne infectious agents is not recommended, except in research studies (D-II).

4. Health care practitioners, particularly those in areas of endemicity, should become familiar with the clinical manifestations of Lyme disease, HGA, and babesiosis and recommended practices for diagnosis and treatment (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 and, in particular, 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. HGA, as well as babesiosis in areas of endemicity, should be included in the differential diagnosis of patients who develop fever after an *Ixodes* tick bite (A-II).

EARLY LYME DISEASE

Primary Management Options Considered

The management options considered included oral antimicrobial therapy for patients with a single erythema migrans skin lesion and oral versus parenteral therapy for patients with clinical evidence of early disseminated infection (i.e., patients presenting with multiple erythema migrans lesions, carditis, cranial nerve palsy, meningitis, or acute radiculopathy). In view of the high frequency of travel between North America and Europe, borrelial lymphocytoma was addressed, despite its rarity in North America. Its primary etiologic agent is *B. afzelii,* one of the exclusively Eurasian species of Lyme borrelia, which are often referred to as *B. burgdorferi* sensu lato.

The panel was unable to provide a recommendation on treatment of seropositive patients without erythema migrans believed to have an acute viral-like illness due to *B. burgdorferi* infection because of lack of data, although recommended therapies for the treatment of erythema migrans would likely be adequate.

Outcomes Evaluated

The panel weighed both the risks and consequences of developing late complications of Lyme disease and the economic costs and possible adverse effects of antimicrobial therapy. The desired outcome is to resolve the symptoms and signs of early Lyme disease, eradicate *B. burgdorferi* infection, and prevent late complications.

Background and Diagnosis of Erythema Migrans

Primary erythema migrans is a round or oval, expanding erythematous skin lesion that develops at the site of deposition of *B. burgdorferi* by an *Ixodes* species tick [90–93, 106–111]. These skin lesions typically become apparent approximately 7–14 days (range, 3–30 days) after the tick has detached or was removed and should be at least 5 cm in largest diameter for a secure diagnosis [112].

An erythematous skin lesion present while an *Ixodes* tick is still attached or which has developed within 48 h of detachment is most likely a tick bite hypersensitivity reaction (i.e., a noninfectious process), rather than erythema migrans. Tick bite hypersensitivity reactions are usually <5 cm in largest diameter, sometimes have an urticarial appearance, and typically begin to disappear within 24–48 h. In contrast, an early primary erythema migrans lesion usually increases in size over this time frame [90, 106]. To differentiate between the 2 processes, it may be useful to mark the borders of the skin lesion with ink and then observe for 1–2 days without antibiotic therapy.

When there is >1 erythema migrans skin lesion, the secondary skin lesions are believed to arise by hematogenous dissemination from the site of primary infection [113]. Secondary erythema migrans skin lesions can be <5 cm in largest diameter, but like primary lesions, they may expand. In some patients with multiple erythema migrans skin lesions, the primary lesion cannot be identified with certainty.

Erythema migrans skin lesions can vary in appearance (figure 3). Some lesions are homogeneously erythematous, whereas others have prominent central clearing or a distinctive target-like appearance [65, 91, 110]. On the lower extremities, the lesion may be partially purpuric. Vesicles or pustules are present at the center of a primary erythema migrans lesion in ~5% of cases [115]. However, unlike contact dermatitis (e.g., from poison ivy), vesicular-appearing erythema migrans lesions are not associated with significant pruritus. Erythema migrans lesions are not scaly unless they are long-standing and fading, or topical corticosteroid creams have been applied. Erythema migrans lesions often occur at sites (e.g., axilla, popliteal fossa, and abdomen) that would be highly unusual for community-acquired bacterial cellulitis due to pyogenic bacteria.

Erythema migrans is the only manifestation of Lyme disease in the United States that is sufficiently distinctive to allow clinical diagnosis in the absence of laboratory confirmation. In a patient with a compatible epidemiologic and clinical history, the preferred means of diagnosis is visual inspection of the skin lesion. Serologic testing is too insensitive in the acute phase (the first 2 weeks of infection) to be helpful diagnostically [102, 103, 116]. Patients should be treated on the basis of clinical findings. In a minority of cases for which there may be diagnostic uncertainty, both acute-phase and convalescent-phase (i.e., 2 weeks after the acute-phase) serum samples should be tested using the 2-tier testing algorithm recommended by the Centers for Disease Control and Prevention (CDC) and the Association of State and Territorial Public Health Laboratory Directors [117]. Untreated patients who remain seronegative, despite continuing symptoms for 6–8 weeks, are unlikely to have Lyme disease, and other potential diagnoses should be actively pursued.

First-tier testing is most often performed using a polyvalent ELISA. If the first-tier assay result is positive or equivocal, then the same serum specimen is retested by separate IgM and IgG immunoblots. For patients with symptoms in excess of 4 weeks to be considered seropositive, reactivity must be present on the IgG immunoblot specifically [117]. To maintain the highest possible specificity, immunoblot interpretation in this testing scheme should only be done in qualified laboratories that follow the CDC-recommended, evidence-based guidelines on immunoblot interpretation [117–120]. Alternative recommendations for interpretation of immunoblots have not been rigorously validated and are very likely to lead to an inappropriate diagnosis. Use of single-tier testing with an immunoblot alone will also result in reduced specificity, because immunoblots are only semiquantitative, and faint bands are commonly seen in samples from healthy people without tick exposure and from patients with illnesses other than Lyme disease [119, 121]. In interpreting the results of serologic tests, it is also important to remember that the background rates of seropositivity in areas with high endemicity may exceed 4% [122]. *Therefore, the presence of seropositivity does not guarantee that a given medical condition is due to* B. burgdorferi *infection.* Although useful for documentation of *B. burgdorferi* infection in research studies, amplification of *B. burgdorferi* DNA by PCR or culture of specimens of skin or blood for *Borrelia* species is not recommended for diagnosis of erythema migrans in routine clinical care because of the cumbersome nature and expense of these test methods [103, 123, 124].

Electrocardiograms are not generally performed for patients with erythema migrans in the absence of symptoms or signs suggestive of cardiac disease (see below).

Evidence to support treatment recommendations. In vitro studies have shown that *B. burgdorferi* is highly susceptible to several antimicrobial drug classes, including tetracyclines, most penicillins, and many second- and third-generation cephalosporins [39, 40, 125–132]. *B. burgdorferi* is resistant to certain fluoroquinolones, rifampin, and first-generation cephalosporins [39, 40, 125, 127, 133]. Macrolides may or may not be active in vitro, depending on the borrelial strain tested and the assay technique utilized [39, 134–136].

There have been at least 9 randomized, prospective trials addressing the treatment of early Lyme disease in the United States [41–43, 137–142]. All studies used erythema migrans as the disease-defining criterion. Eight studies recruited patients

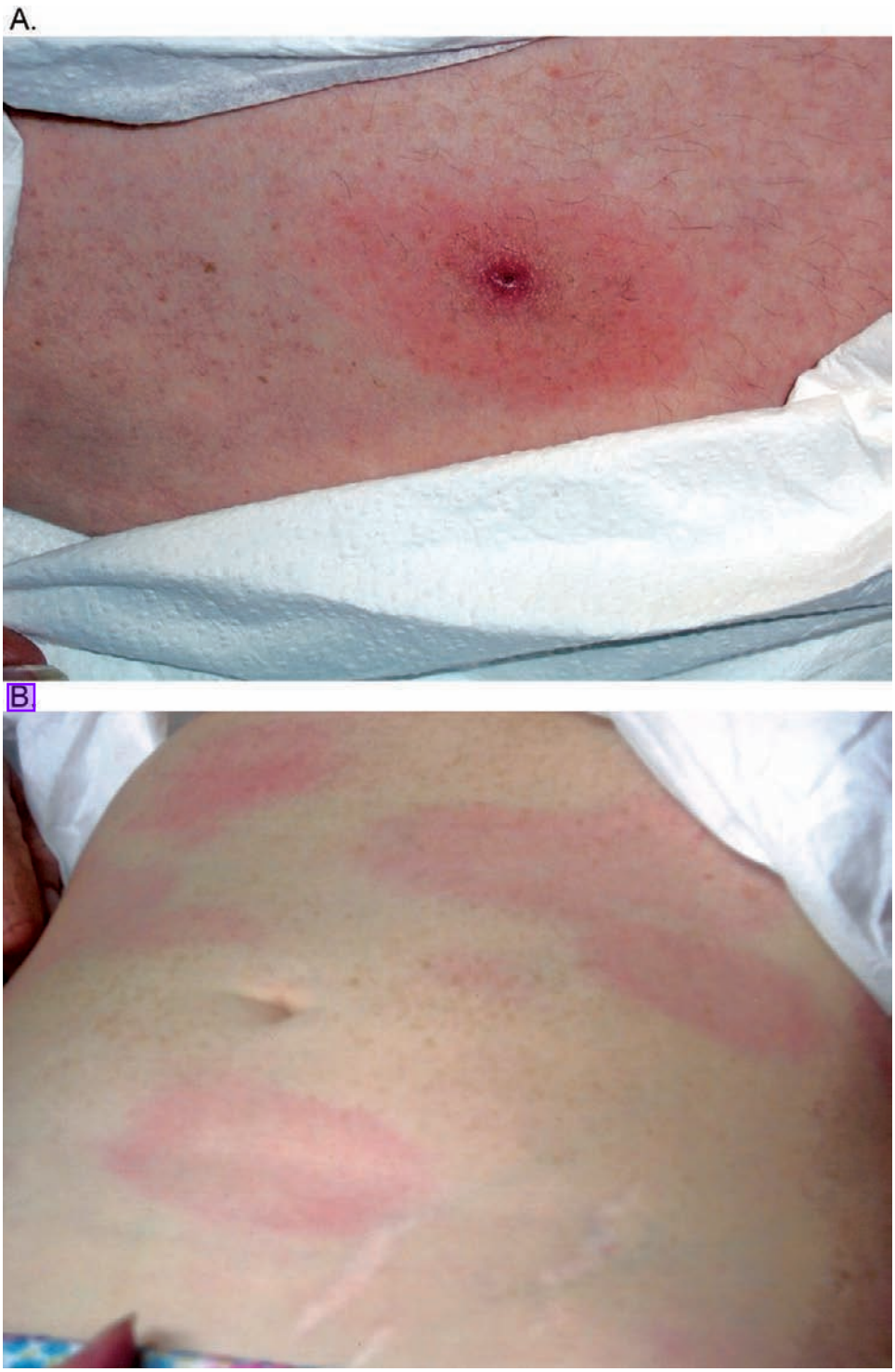

Figure 3. Illustrative examples of culture-confirmed erythema migrans. *A,* A single erythema migrans lesion of 8.5 × 5.0 cm on the abdomen. The lesion is homogeneous in color, except for a prominent central punctum (presumed site of preceding tick bite). *B,* Patient with >40 erythema migrans lesions found. Note the prominent central clearing of the lesions present on the abdomen. Reprinted with permission from [114]. (Copyright 2006, Massachusetts Medical Society. All rights reserved.)

with either localized or disseminated early Lyme disease [41–43,137–139, 141, 142], whereas 1 study required disseminated early disease for enrollment [140]. Differing criteria were used to define treatment failure in the various studies. Most defined "failure" as the persistence of objective clinical manifestations despite therapy, whereas others used the persistence of subjective symptoms.

The etiology of residual patient complaints after treatment may include an inflammatory response unrelated to active infection or may be due to alternative disease processes. The possibility that these symptoms may have been related to a tick-transmitted coinfection was not evaluated in any of the studies. Importantly, failure rates were not considered in the context of the high frequency of background complaints present in an otherwise "healthy" population. Both of these factors have likely contributed to a misconception by some that recommended treatment courses are associated with a relatively poor outcome. This has helped to foster highly speculative theories on how *B. burgdorferi* might survive in patients treated with a standard course of antimicrobial therapy. These issues are discussed in greater detail below in the section on post–Lyme disease syndromes.

The first randomized clinical trial on the treatment of erythema migrans compared erythromycin, tetracycline, and penicillin at dosages of 250 mg 4 times per day for 10 days in 112 adult patients [137]. Signs and symptoms after treatment were considered to be either "minor" (headache, fatigue, supraventricular tachycardia, arthralgias, brief arthritis of <2 weeks duration, and isolated facial palsy) or "major" (meningitis, meningoencephalitis, carditis, or recurrent attacks of arthritis). Approximately 15% of patients had a transient intensification of symptoms during the first 24 h of therapy, consistent with a Jarisch-Herxheimer–like reaction. These usually mild reactions have only been well-documented at the start of treatment. There is no evidence that they can last for >24 h or that they can recur. They have no diagnostic value, and they have not been shown to be predictive of outcome.

Erythema migrans and its associated symptoms resolved more rapidly in penicillin- or tetracycline-treated patients, compared with those who were given erythromycin ($P < .05$) [137]. In addition, treatment with tetracycline or penicillin was associated with a lower rate of occurrence of "major" manifestations by these criteria, compared with erythromycin. Overall, "minor" signs and symptoms after treatment occurred in ~45% of patients. Extending therapy to 20 days with tetracycline in a subsequent study by the same authors had no effect on the frequency of posttreatment symptoms [137]. The results of these studies supported the findings of a previous open trial of oral penicillin therapy for early Lyme disease [143]. It could be concluded from these studies that erythema migrans was responsive to penicillin and tetracycline, erythromycin was less effective, and optimal therapy had not been defined.

Subsequent small studies found that doxycycline and amoxicillin (plus probenecid), the tetracycline and β-lactam preparations most commonly prescribed in current clinical practice for patients with erythema migrans, were effective therapies, and each drug regimen had efficacy comparable to the other [41, 42].

Two of the largest studies of the treatment of erythema migrans in adults compared cefuroxime axetil with doxycycline [138, 139]. The first was a multicenter study in which 123 patients with erythema migrans were randomized to receive cefuroxime axetil (500 mg twice per day for 20 days) or doxycycline (100 mg 3 times per day for 20 days). This study demonstrated comparable efficacy, with satisfactory outcomes in ~90% of patients observed for 1 year after treatment [138]. Although 10% of subjects were considered to have experienced treatment failure on the basis of the presence of continuing symptoms, most of these patients did not have any objective clinical finding. Similar results were observed in a second multicenter study of 232 patients with erythema migrans who were also randomized to receive 20 days of either cefuroxime or doxycycline [139]. In a separate randomized trial of 43 children with erythema migrans, 2 different dosage regimens of cefuroxime axetil (20 mg/kg per day or 30 mg/kg per day) were found to have efficacy comparable to amoxicillin (50 mg/kg per day) [141].

A multicenter, double-blind, randomized, prospective trial compared azithromycin (500 mg once per day for 7 days) with amoxicillin (500 mg 3 times per day for 20 days) for the treatment of patients with erythema migrans [43]. Amoxicillin was found to be significantly more effective than azithromycin for complete resolution of the acute manifestations of erythema migrans and for prevention of relapse in a 6-month period. Of 217 evaluable subjects, only 4% of those treated with amoxicillin experienced relapse, compared with 16% of those treated with azithromycin ($P = .005$). A higher symptom score prior to treatment correlated with persistent symptoms after treatment.

Only 1 study has specifically addressed the treatment of acute disseminated nonneurologic Lyme disease, which was defined by the presence of either multiple erythema migrans lesions or an objective nonneurologic extracutaneous manifestation. Patients with objective CNS involvement were excluded. This prospective, randomized multicenter trial of 140 patients demonstrated that oral doxycycline (100 mg twice per day for 3 weeks) and intravenous ceftriaxone (2 g per day for 2 weeks) were equally effective [140]. Importantly, none of the patients in this study developed a significant late complication.

In most of the controlled trials, patients assigned treatment with either doxycycline or amoxicillin received ~3 weeks of

therapy. However, comparable success rates have been reported in studies in which shorter treatment courses with these antibiotics were used [144]. Duration of antibiotic therapy for erythema migrans was addressed in a prospective, randomized, double-blind, placebo-controlled clinical trial of 180 patients [142]. Patients were randomized into 3 treatment groups: doxycycline (100 mg twice per day by mouth for 10 days); a single 2-g intravenous dose of ceftriaxone, followed by doxycycline (100 mg twice per day by mouth for 10 days); and doxycycline (100 mg twice per day by mouth for 20 days). The rate of complete resolution of signs and symptoms was similar for all 3 treatment groups in both on-study and intention-to-treat analyses. Despite the potential for *B. burgdorferi* to disseminate to the CNS in some patients with erythema migrans [145], the addition of a single dose of ceftriaxone to a 10-day course of doxycycline did not improve outcome. The single ceftriaxone dose, however, was associated with a 4-fold increase in the frequency of diarrhea ($P < .001$) [142].

Although none of the prospective studies enrolled pregnant subjects with Lyme disease, there are no data to suggest that these patients should be treated differently from other patients with Lyme disease, except that doxycycline therapy should be avoided [146].

Several conclusions can be drawn from these trials. Doxycycline, amoxicillin, and cefuroxime axetil are effective for the treatment of early Lyme disease. Most patients respond promptly and completely. Some individuals have persistent subjective complaints, despite receiving therapy that otherwise appears curative. Less than 10% of individuals do not respond to antibiotic therapy, as evidenced by the presence of objective clinical manifestations, and rarely is re-treatment required. In general, patients who are more systemically ill (e.g., febrile with significant constitutional complaints) at the time of diagnosis take longer to have a complete response to therapy. Inadequately recognized CNS infection at the time of institution of antibiotic therapy may be the explanation for antibiotic failures in some circumstances.

The macrolides that have been systematically studied are less effective than the other antibiotic therapies noted above. Erythromycin [137] and azithromycin [43] have been studied in the United States, and roxithromycin [147] has been studied in Europe. Clarithromycin has not been studied in a controlled trial [148]. Because of these findings, macrolides cannot be recommended as first-line therapy.

In contrast to the second-generation cephalosporin cefuroxime and to certain third-generation cephalosporins (e.g., ceftriaxone), first-generation cephalosporins, such as cephalexin, are inactive in vitro against *B. burgdorferi* and are ineffective clinically [125, 133].

All antimicrobials effective in early Lyme disease are associated with a low frequency of serious adverse effects. Drug-induced rashes occur with both amoxicillin [43] and cefuroxime axetil [138, 139]. Doxycycline may cause photosensitivity [138, 139], which is a concern, because early Lyme disease occurs most commonly during the summer months. Individuals treated with doxycycline are advised to avoid exposure to the sun while receiving therapy. Doxycycline should be taken with 8 ounces of fluid to reduce the risk of esophageal irritation and with food to reduce gastrointestinal intolerance. In addition, doxycycline is relatively contraindicated in children <8 years of age and in women who are pregnant or breast-feeding.

Recommendations

1. Doxycycline (100 mg twice per day), amoxicillin (500 mg 3 times per day), or cefuroxime axetil (500 mg twice per day) for 14 days (range for doxycycline, 10–21 days; range for amoxicillin or cefuroxime axetil, 14–21 days) is recommended for treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans in the absence of specific neurologic manifestations (see Early Neurologic Lyme Disease) or advanced atrioventricular heart block (tables 2 and 3) (A-I). Ten days of therapy is sufficient if doxycycline is used; however, given the much shorter half-life of β-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 the recommended antimicrobial agents has been shown to be highly effective in 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. For children, amoxicillin, cefuroxime axetil, or doxycycline (if the patient is ⩾8 years of age) is recommended (tables 2 and 3) (A-II).

2. Macrolide antibiotics are not recommended as first-line therapy for early Lyme disease (E-I). When used, they should be reserved for patients who are intolerant of, or should not take, amoxicillin, doxycycline, and cefuroxime axetil (table 3). Patients treated with macrolides should be closely observed to ensure resolution of the clinical manifestations.

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

Table 2. Recommended antimicrobial regimens for treatment of patients with Lyme disease.

Drug	Dosage for adults	Dosage for children
Preferred oral regimens		
Amoxicillin	500 mg 3 times per day[a]	50 mg/kg per day in 3 divided doses (maximum, 500 mg per dose)[a]
Doxycycline	100 mg twice per day[b]	Not recommended for children aged <8 years For children aged ⩾8 years, 4 mg/kg per day in 2 divided doses (maximum, 100 mg per dose)
Cefuroxime axetil	500 mg twice per day	30 mg/kg per day in 2 divided doses (maximum, 500 mg per dose)
Alternative oral regimens		
Selected macrolides[c]	For recommended dosing regimens, see footnote *d* in table 3	For recommended dosing regimens, see footnote in table 3
Preferred parenteral regimen		
Ceftriaxone	2 g intravenously once per day	50–75 mg/kg intravenously per day in a single dose (maximum, 2 g)
Alternative parenteral regimens		
Cefotaxime	2 g intravenously every 8 h[d]	150–200 mg/kg per day intravenously in 3–4 divided doses (maximum, 6 g per day)[d]
Penicillin G	18–24 million U per day intravenously, divided every 4 h[d]	200,000–400,000 U/kg per day divided every 4 h[d] (not to exceed 18–24 million U per day)

[a] Although a higher dosage given twice per day might be equally as effective, in view of the absence of data on efficacy, twice-daily administration is not recommended.
[b] Tetracyclines are relatively contraindicated in pregnant or lactating women and in children <8 years of age.
[c] Because of their lower efficacy, macrolides are reserved for patients who are unable to take or who are intolerant of tetracyclines, penicillins, and cephalosporins.
[d] Dosage should be reduced for patients with impaired renal function.

dose]), because these antimicrobials are generally effective against both types of infection (A-III).

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).

4. Pregnant or 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).

5. 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).

6. 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 (see the sections below on post-Lyme disease syndromes, HGA, and babesiosis). 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 antibiotic therapy appropriate for Lyme disease or who have unexplained leukopenia, thrombocytopenia, or anemia (A-III). Coinfection might also be considered in patients who have resolved their erythema migrans skin lesion but have had no improvement or worsening of viral infection–like symptoms (B-III).

Background and Diagnosis of Early Neurologic Lyme Disease

Manifestations of acute peripheral nervous system involvement in Lyme disease include radiculopathy, cranial neuropathy, and mononeuropathy multiplex (multifocal involvement of anatomically unrelated nerves) [107–109, 111, 149–151]. CNS involvement includes lymphocytic meningitis and, rarely, encephalomyelitis (parenchymal inflammation of brain and/or spinal cord, with focal abnormalities evident on neurologic

Table 3. Recommended therapy for patients with Lyme disease.

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

NOTE. Regardless of the clinical manifestation of Lyme disease, complete response to treatment may be delayed beyond the treatment duration. Relapse may occur with any of these regimens; patients with objective signs of relapse may need a second course of treatment.

[a] See text.

[b] A single dose of doxycycline may be offered to adult patients and to children ⩾8 years of age when *all* of the following circumstances exist: (1) the attached tick can be reliably identified as an adult or nymphal *Ixodes 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, (2) prophylaxis can be started within 72 h after the time that the tick was removed, (3) ecologic information indicates that the local rate of infection of these ticks with *Borrelia burgdorferi* is ⩾20%, *and* (d) doxycycline is not contraindicated. For patients who do not fulfill these criteria, observation is recommended.

[c] See table 2.

[d] For adult patients intolerant of amoxicillin, doxycycline, and cefuroxime axetil, 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) may be given. 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); and 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.

[e] Ten days of therapy is effective if doxycycline is used; the efficacy of 10-day regimens with the other first-line agents is unknown.

[f] For nonpregnant adult patients intolerant of β-lactam agents, doxycycline (200–400 mg/day orally [or intravenously, if the patient is unable to take oral medications]) in 2 divided doses may be adequate. For children ⩾8 years of age, the dosage of doxycycline for this indication is 4–8 mg/kg per day in 2 divided doses (maximum daily dosage of 200–400 mg).

[g] See text. Patients without clinical evidence of meningitis may be treated with an oral regimen. Parenteral antibiotic therapy is recommended for patients with both clinical and laboratory evidence of coexistent meningitis. Most of the experience in the use of oral antibiotic therapy is for patients with seventh cranial nerve palsy. Whether oral therapy would be as effective for patients with other cranial neuropathies is unknown. The decision between oral and parenteral antimicrobial therapy for patients with other cranial neuropathies should be individualized.

[h] A parenteral antibiotic regimen is recommended at the start of therapy for patients who have been hospitalized for cardiac monitoring; an oral regimen may be substituted to complete a course of therapy or to treat ambulatory patients. A temporary pacemaker may be required for patients with advanced heart block.

[i] Antibiotic-refractory Lyme arthritis is operationally defined as persistent synovitis for at least 2 months after completion of a course of intravenous ceftriaxone (or after completion of two 4-week courses of an oral antibiotic regimen for patients who are unable to tolerate cephalosporins); in addition, PCR of synovial fluid specimens (and synovial tissue specimens, if available) is negative for *B. burgdorferi* nucleic acids.

[j] Symptomatic therapy might consist of nonsteroidal anti-inflammatory agents, intra-articular injections of corticosteroids, or other medications; expert consultation with a rheumatologist is recommended. If persistent synovitis is associated with significant pain or if it limits function, arthroscopic synovectomy can reduce the period of joint inflammation.

examination and imaging studies) [107–109, 111, 149–152]. Encephalomyelitis will be discussed in the section on late nervous system Lyme disease.

Although, in the 1980s, early neurologic Lyme disease was reported to occur in approximately 10%–15% of untreated patients with Lyme disease in the United States [107, 153, 154], the frequency of this manifestation is less in recent series [23, 26, 87–89], possibly because of bias of ascertainment in early studies or improved recognition and treatment of patients with erythema migrans. In the United States, cranial neuropathy is the most common manifestation of early neurologic Lyme disease [4]. Seventh nerve palsy is the most common of the cranial neuropathies, and bilateral involvement may occur [155, 156]. In areas where Lyme disease is endemic, ~1 in 4 patients who present with seventh nerve palsy in nonwinter months can be shown to have Lyme disease [157]. Seventh nerve palsy due to Lyme disease can develop in patients who have no recollection of an erythema migrans lesion or of a tick bite.

Table 4. Selected antimicrobials, drug regimens, or other modalities *not* recommended for the treatment of Lyme disease.

Doses of antimicrobials far in excess of those provided in tables 2 and 3
Multiple, repeated courses of antimicrobials for the same episode of Lyme disease or a duration of antimicrobial therapy prolonged far in excess of that shown in table 3
Combination antimicrobial therapy
Pulsed-dosing (i.e., antibiotic therapy on some days but not on other days)
First-generation cephalosporins, benzathine penicillin G, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, trimethoprim-sulfamethoxazole, amantadine, ketolides, isoniazid, or fluconazole
Empirical antibabesiosis therapy in the absence of documentation of active babesiosis
Anti-*Bartonella* therapies
Hyperbaric oxygen therapy
Fever therapy (with or without malaria induction)
Intravenous immunoglobulin
Ozone
Cholestyramine
Intravenous hydrogen peroxide
Vitamins or nutritional managements
Magnesium or bismuth injections

Two case-control studies of pediatric patients in the United States systematically compared selected clinical and laboratory features of Lyme meningitis with viral meningitis [158, 159]. In these studies, patients with Lyme meningitis were less likely to be febrile [158] but were more likely to have been ill for a longer duration of time (median duration, >7 days), compared with patients with viral meningitis (median duration of headache, 2 days) [159]. The presence of erythema migrans, cranial nerve palsy, or papilledema was helpful in differentiating the 2 entities; ⩾1 of these 3 physical findings was observed in ~90% of patients with Lyme meningitis but in none of the patients with viral meningitis [158, 159]. In contrast to children, however, papilledema appears to be uncommon in adults with Lyme meningitis [160, 161]. The proportion of polymorphonuclear leukocytes in the CSF of patients with Lyme meningitis is typically <10% and is significantly lower than that observed in viral meningitis [158, 159].

The vast majority of patients with early neurologic Lyme disease are seropositive [157, 162–164]. Patients should have a total body skin examination to look for a concurrent erythema migrans lesion and should be questioned to determine whether one had been present within the preceding 1–2 months. For the small proportion of patients who have neurologic Lyme disease but are found to be seronegative by 2-tier testing, a convalescent-phase serum sample obtained ~2 weeks after the acute-phase sample will usually yield positive results.

Another diagnostic test that may be helpful in selected cases is a test for the presence of intrathecal production of antibody to *B. burgdorferi* [103, 152, 165, 166]. Tests to determine specific intrathecal production of antibody are required, because there may be passive transfer to the CSF of serum antibody to *B. burgdorferi.* Amplification of *B. burgdorferi* DNA in CSF using PCR by a laboratory with excellent quality control can also be useful [103, 124, 167], but few laboratories are capable of accurately performing this test. In the absence of erythema migrans, neurologic manifestations are too nonspecific to warrant a purely clinical diagnosis; laboratory support for the diagnosis is required.

Evidence to support treatment recommendations. Available evidence regarding treatment of acute neurologic Lyme disease in the United States is derived from small case series [168]. Patients with Lyme meningitis or acute radiculopathy respond to intravenous penicillin [169], although ceftriaxone is more widely used for this indication because of its convenient once-daily dosing [170]. European trials have found that cefotaxime or ceftriaxone is as effective as intravenous penicillin [171, 172] and that cefotaxime is as effective as ceftriaxone [173]. Although experience with the use of oral doxycycline for the treatment of meningitis due to Lyme disease is limited in the United States, this drug, administered orally or intravenously, has been used successfully in Europe in adults and in children ⩾8 years of age [174–179]. These studies, however, have included few patients with encephalomyelitis [178]. In one prospective, open-label, randomized trial from Europe [176], patients with neuroborreliosis were treated for 14 days with either oral doxycycline (200 mg per day; $n = 31$) or intravenous penicillin (~20 million U per day; $n = 23$). No significant differences were found in clinical outcome or post-treatment CSF test results between the study groups. In another prospective, open-label, nonrandomized trial from Europe, the rate of improvement in clinical outcome or in CSF cell counts was similar for adult patients treated for 10–14 days with either ceftriaxone (2 g intravenously once per day) ($n = 29$) or doxycycline (200 mg orally twice per day) ($n = 36$) [179]. Although duration of therapy has not been systematically compared in studies of acute neurologic Lyme disease, it is noteworthy that 10–14 days of antibiotic therapy has been associated with highly favorable outcomes in both adults [171, 176, 179, 180] and children [178].

Cranial nerve palsy has been treated satisfactorily with oral antibiotics [107, 155, 175]. One study suggested that the frequency and rate of recovery of seventh nerve palsy in patients treated with antibiotics appear to be the same as in untreated patients or in patients treated with corticosteroids, with or without concomitant antibiotic therapy [155]. In a study conducted in Europe, the authors concluded that oral doxycycline was effective for treatment of Lyme disease–associated seventh nerve palsy in patients with CSF pleocytosis [175]. Although

seventh nerve palsy usually resolves with or without antibiotic treatment, untreated patients may be at especially high risk for development of Lyme arthritis, which was observed in 14 (87.5%) of 16 patients, according to one report [181]. Therefore, all patients with cranial nerve palsy in association with Lyme disease should receive antibiotic therapy, not primarily for the purpose of expediting recovery from the paralysis, which will usually resolve within a few weeks regardless of whether antimicrobial therapy is given, but rather to prevent later complications [181].

Recommendations

1. 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) is recommended (tables 2 and 3) (B-I). Parenteral therapy with cefotaxime or penicillin G may be a satisfactory alternative (B-I). For patients who are intolerant of β-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.

For children, ceftriaxone (B-I) or cefotaxime (B-II) administered parenterally is recommended (tables 2 and 3); intravenous penicillin G is an alternative (B-I). 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 [160, 161]. 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 [160].

2. 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). 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 seventh cranial nerve palsy. Some perform a CSF examination on all patients with Lyme disease–associated seventh cranial nerve palsy. Others do not, because of the good clinical response with orally administered antibiotics (even in the presence of a 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 examinations and those in 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 (B-III). Those with both clinical and laboratory evidence of CNS involvement should be treated with regimens effective against meningitis, as in recommendation number 1 above (tables 2 and 3) (B-III).

Background and Diagnosis of Cardiac Manifestations of Lyme Disease

Patients with symptomatic cardiac involvement associated with Lyme disease usually present with the acute onset of varying degrees of intermittent atrioventricular heart block, sometimes in association with clinical evidence of myopericarditis [182–188]. Electrophysiologic studies have usually demonstrated block occurring above the bundle of His, often involving the atrioventricular node, but heart block may occur at multiple levels [182–184]. Severe or fulminant congestive heart failure or development of valvular heart disease is not associated with Lyme disease [183]. In the United States, there is no convincing evidence that Lyme disease is a cause of chronic cardiomyopathy [189, 190].

Although Lyme carditis had earlier been reported to occur in 4%–10% of untreated United States patients with Lyme disease, the frequency of this manifestation is much lower in more recent series [183, 191]. This change, like that observed for acute neurologic manifestations, could possibly be the result of a bias of ascertainment in early studies or improved recognition and treatment of patients with erythema migrans. No evidence of carditis was found among 233 case patients diagnosed with definite Lyme disease in 2 prospective studies on the evaluation of a recombinant OspA vaccine [23, 89]. Because carditis usually occurs within 2 months after onset of infection, erythema migrans [182, 186, 187] or neurologic Lyme disease [182, 187] may occur concomitantly or in close proximity, which may be helpful diagnostically. In the absence of concomitant erythema migrans (present in up to 85% of cases [186]), the clinical manifestations of Lyme carditis are too nonspecific to warrant a purely clinical diagnosis. Under these circumstances, support for the diagnosis requires the presence of *B. burgdorferi* antibody in acute- or convalescent-phase (2–4 weeks after the acute phase) serum specimens. The vast majority of patients with cardiac manifestations of Lyme disease are seropositive at the time of presentation [183, 192].

Because of the potential for life-threatening complications, hospitalization and continuous monitoring are advisable for symptomatic patients (e.g., those with syncope, dyspnea, or chest pain). These interventions are also suggested 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 ⩾30 milliseconds, because the degree of block may fluctuate and worsen very rapidly in such patients [182].

Evidence to support treatment recommendations. No studies have specifically addressed the treatment of Lyme carditis. Although there is no evidence that antibiotic therapy hastens the resolution of cardiac abnormalities, antibiotic therapy is recommended for patients with Lyme carditis with this purpose in mind and to prevent later manifestations of Lyme disease [183]. There are no comparative treatment trials in carditis, and there is no evidence to suggest that parenteral antibiotic therapy is more effective than oral antibiotic therapy. A temporary pacemaker may be required in patients with advanced heart block for the duration of the block [183, 187]. Complete heart block generally resolves within 1 week, and lesser conduction disturbances resolve within 6 weeks [182, 186, 187].

Recommendations

1. 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 ⩾30 milliseconds, because the degree of block may fluctuate and worsen very rapidly in such patients.

For hospitalized patients, a parenteral antibiotic, such as ceftriaxone (see recommendation above for treatment of meningitis) (table 2), is recommended as initial treatment, although there are no clinical trials to support this recommendation (B-III). For patients with advanced heart block, a temporary pacemaker may be required; expert consultation with a cardiologist is recommended. The pacemaker may be discontinued when the advanced heart block has resolved. An oral antibiotic regimen should be used for completion of therapy and for outpatients, as is used for patients with erythema migrans without carditis (tables 2 and 3) (B-III).

Background and Diagnosis of Borrelial Lymphocytoma

Borrelial lymphocytoma is a rare cutaneous manifestation of Lyme disease in Europe, which presents as a solitary bluish-red swelling with a diameter of up to a few centimeters [109, 193–196]. The most common site of borrelial lymphocytoma is the ear lobe in children and the breast, on or near the nipple, in adults. Mild, localized discomfort often accompanies the skin lesion. Borrelial lymphocytoma is characterized histologically by a dense polyclonal and predominantly B lymphocytic infiltration of the cutis and subcutis, frequently with germinal center formation [109, 197]. Borrelial lymphocytoma may be the only sign of Lyme disease or merely one of several manifestations during the course of the illness. It often appears near the site of a prior tick bite and frequently arises in the vicinity of a previous or concurrent erythema migrans lesion, but compared with erythema migrans, it usually emerges later and lasts longer (untreated borrelial lymphocytoma may persist for many months or even for >1 year) [109, 193, 194, 197].

In general, diagnosing borrelial lymphocytoma is more challenging than diagnosing erythema migrans, largely because of lack of awareness of this rare condition. It is easiest when the location of the lesion is on the ear lobe, much more difficult if on the breast, and even more difficult if in other (atypical) locations [194]. The diagnosis is supported by the history or presence of erythema migrans, and the majority of patients are seropositive [109, 193, 195, 198, 199]. Histological examination is recommended in patients with suspected borrelial lymphocytoma at a location other than the ear lobe. Borrelial lymphocytoma on the breast must be differentiated from malignancy [109].

Evidence to support treatment recommendations. There are no prospective, randomized studies on the treatment of borrelial lymphocytoma. When borrelial lymphocytoma is the only manifestation of Lyme disease or is associated with erythema migrans, it is usually treated with antimicrobial regimens that are used for therapy of erythema migrans (tables 2 and 3). Such a therapeutic approach resulted in complete recovery within 1–12 weeks (median, 2 weeks) in a group of 52 adults and children [200]. Two (4%) of these patients, however, developed an objective extracutaneous manifestation of Lyme disease after treatment; both were among the 19 patients in this study who had been treated with phenoxymethylpenicillin. Another study revealed similar findings [194]. Among 63 adult patients with borrelial lymphocytoma treated with oral antibiotics for 14 days, the lesion disappeared within 4 weeks after the start of therapy in 49 patients (78%) and within 6 weeks in 59 patients (94%) [194]. Both reports indicated that resolution of the lesion was faster in patients with a shorter duration of borrelial lymphocytoma prior to institution of antimicrobial therapy [194, 200].

Recommendations

1. 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).

LATE LYME DISEASE

Primary Management Options Considered

The panel considered various oral and parenteral antimicrobial regimens for treatment of the late manifestations of Lyme dis-

ease. Late manifestations include arthritis, encephalopathy, encephalomyelitis, and peripheral neuropathy. In view of the high frequency of travel between North America and Europe, acrodermatitis chronica atrophicans was addressed, despite its rarity in North America. Dermatologic manifestations that are even less common or less–well substantiated were not considered [201]. The panel did not make recommendations on keratitis and other possible ocular manifestations of Lyme disease because of the lack of evaluable data on ophthalmologic complications, which are very rare [160, 202]. Because of lack of data, the panel was also unable to provide a recommendation on treatment of asymptomatic individuals who are seropositive for antibodies to *B. burgdorferi* but have no history of Lyme disease.

The response to treatment of late manifestations may be slow, and weeks to months may be required for improvement or resolution of symptoms after treatment. However, appropriate antibiotic treatment leads to recovery in most patients.

Outcomes Evaluated

The panel compared the risks and consequences of ineffective treatment of late Lyme disease with the problems resulting from adverse effects of antimicrobial therapies. The desired outcome is to treat effectively the late complications of Lyme disease while minimizing the adverse effects from antibiotic therapy and economic costs. The effects of the different treatment strategies on quality of life were considered.

Background and Diagnosis of Rheumatologic Manifestations of Lyme Disease

Although Lyme arthritis was reported to occur in 60% of untreated patients in the United States with Lyme disease nearly 20 years ago [153], the frequency of this manifestation has been ⩽10% in recent series [23, 26, 87–89], probably because of improved recognition and earlier treatment of patients with early Lyme disease. However, the frequency of arthritis among the 40,792 cases of Lyme disease reported to the CDC for the years 2001–2002 was at least 24.8% [4]. Possible explanations for the higher proportion of arthritis cases in national reporting include reporting bias favoring the tabulation of seropositive Lyme disease cases, confusion between arthritis and arthralgia by the treating health care provider [203], and inaccuracy of Lyme disease diagnosis [203]. In addition, surveillance report forms differ by state, and reported seropositivity in support of a diagnosis of Lyme arthritis is not necessarily based on 2-tier testing [112].

Lyme arthritis is a monoarticular or oligoarticular form of arthritis that typically involves the knee [107, 111, 153, 204–206]. However, other large joints or the temporomandibular joint may be involved. Large knee effusions that are out of proportion to the pain are typical. A Baker's cyst may develop and may rupture. Lyme arthritis is often intermittent in nature if untreated, with episodes of joint inflammation spontaneously resolving after a few weeks to a few months. Persistent swelling of the same joint for ⩾12 months would be an unusual presenting manifestation of Lyme arthritis.

Synovial fluid usually shows mild-to-moderate inflammation, with a median leukocyte count of 24,250 leukocytes/mm^3 in one study [204]; typically, there is a predominance of granulocytes [204, 206]. In the vast majority of patients, the clinical manifestations are too nonspecific to warrant a purely clinical diagnosis of Lyme arthritis. Confirmation of the diagnosis requires serologic testing. All patients should be determined to be seropositive by 2-tier testing that includes an ELISA and IgG immunoblot [162, 206]. In a seropositive patient, a positive PCR test result on a synovial fluid specimen adds increased diagnostic certainty [206, 207]. Positive PCR results for a joint fluid specimen from a seronegative patient, however, should be regarded with skepticism [103].

Background and Diagnosis of Late Neurologic Lyme Disease

Late neurologic Lyme disease may present as encephalomyelitis, peripheral neuropathy, or encephalopathy [149–152, 208–212]. Because most patients with Lyme disease are now diagnosed and treated early in the course of infection, these more indolent forms of neurologic Lyme disease are quite rare. Encephalomyelitis is a unifocal or multifocal inflammatory CNS disease [152, 213]. Collectively, only 1 patient with encephalomyelitis has been diagnosed over the past 5 years by panel members (G.P.W., J.J.H., R.B.N., R.J.D., A.C.S., E.D.S., M.S.K., P.J.K., J.S.B., and L.B.), in spite of both community-based and referral clinical practices. This severe neurologic manifestation of Lyme disease has been diagnosed primarily in Europe.

In untreated patients, encephalomyelitis has been monophasic and slowly progressive, principally involving white matter. Two-tier (ELISA and IgG immunoblot) seropositivity with serum samples and evidence of intrathecal antibody production to *B. burgdorferi* are expected [149, 162, 213]. Intrathecal antibody production, however, may persist for years following successful treatment, so this parameter does not provide a useful marker of disease activity [214]. CSF examination typically shows a lymphocytic pleocytosis, a moderately elevated protein level, and a normal glucose level [149, 213]. Sensitivity of PCR for detection of *B. burgdorferi* DNA in the CSF of such patients is extremely low. MRI of the affected part of the neuraxis can demonstrate areas of inflammation, typically with increased signal on T2 and FLAIR imaging and enhancement following contrast administration [149, 215].

Lyme encephalomyelitis may be confused clinically with a first episode of relapsing-remitting multiple sclerosis or primary progressive multiple sclerosis, but appropriate CSF and serum

studies for *B. burgdorferi*–specific antibody should differentiate between these entities in most instances [216–218].

Late neurologic Lyme disease–associated peripheral neuropathy typically presents as a mild, diffuse, "stocking glove" process. Only 9 such patients have been diagnosed by panel members (G.P.W., J.J.H., R.B.N., R.J.D., A.C.S., E.D.S., M.S.K., P.J.K., J.S.B., and L.B.) over the past 5 years. Patients typically complain of intermittent limb paresthesias, and some patients complain of radicular pain. The most frequent abnormality found on neurologic examination is reduced vibratory sensation of the distal lower extremities. Electrophysiologic studies show findings consistent with a mild confluent mononeuritis multiplex [219]. Nerve biopsy reveals small perivascular collections of lymphocytes, without spirochetes [220, 221]. Serum IgG antibody to *B. burgdorferi* detected by the 2-tier approach is expected in patients with Lyme disease–associated peripheral neuropathy. The absence of antibody should lead to an alternative diagnosis [149]. Because the pathophysiologic process usually occurs outside the subarachnoid space, CSF findings are often normal, without evidence of intrathecal antibody production to *B. burgdorferi*.

Lyme disease–associated encephalopathy is an imprecisely defined clinical entity characterized by mild abnormalities of memory and cognitive functions that are demonstrable either by a careful mental status examination or by formal neuropsychologic testing [211, 222]. Panel members (G.P.W., J.J.H., R.B.N., R.J.D., A.C.S., E.D.S., M.S.K., P.J.K., J.S.B., and L.B.) have diagnosed only 7 patients over the past 5 years. In the past, certain patients with this condition had concomitant Lyme arthritis [211]. In such patients, CSF examination findings were often normal, and the process may have been related to general illness rather than CNS infection (i.e., "toxic-metabolic" in origin). Other patients have had evidence of intrathecal antibody production to *B. burgdorferi* and/or increased CSF protein levels, with or without a mild CSF pleocytosis [208, 211, 222]. In these cases, the encephalopathy may actually be a mild form of encephalomyelitis. Cranial imaging studies may occasionally demonstrate focal areas of presumed parenchymal inflammation. Most often, findings are normal or demonstrate only minor, nonspecific abnormalities; consequently, cranial imaging plays little if any role in the diagnosis or follow-up of patients with this entity [223]. In serum, 2-tier IgG seropositivity is expected [149, 208, 211, 222, 223].

The panel has differentiated between early and late neurologic Lyme disease in these guidelines, as is customary. There is little evidence to support a pathophysiological basis for this distinction, however, and differences may be related more to the degree of involvement [208, 217, 219].

Evidence to support treatment recommendations. The first study of antibiotic treatment in patients with Lyme arthritis was initiated in 1980 [224]. The regimens tested were those used for the treatment of tertiary syphilis, and the study design was a double-blind, placebo-controlled trial. Study patients had intermittent or chronic Lyme arthritis primarily affecting the knees, and all were subsequently shown to be seropositive for antibodies to *B. burgdorferi*. In the first phase of the study, 40 patients were randomized to receive either intramuscular benzathine penicillin G (7.2 million U) or placebo. In the second phase, 20 patients were treated with intravenous penicillin G (20 million U per day for 10 days); oral or intramuscular antibiotic treatment had already failed for 6 of these patients. Of the 20 patients who received intramuscular benzathine penicillin, 7 (35%) had complete resolution of joint involvement within 1 month of initiation of treatment, compared with none of 20 patients who were given placebo ($P < .02$). Of the 20 patients treated with intravenous penicillin G, 11 (55%) had complete resolution of arthritis soon after treatment. It was concluded that parenteral penicillin was often effective in the treatment of Lyme arthritis, but a substantial percentage of patients did not respond.

Subsequently, a series of studies was begun to test the efficacy of intravenous ceftriaxone in the treatment of late Lyme disease. Compared with penicillin, the advantages of ceftriaxone are its excellent CSF penetration and long serum half-life, which permits once-per-day dosing. In 1987, a case series of 7 patients with Lyme arthritis or chronic neuroborreliosis, who were refractory to oral or intravenous penicillin therapy, were then treated with intravenous ceftriaxone (2 or 4 g per day for 2 weeks) [225]. All 5 patients who had arthritis responded to ceftriaxone therapy, and 5 of the 6 patients with limb paresthesias experienced a reduction in their symptoms and had improvement in nerve conduction studies. In a follow-up study, 23 patients with Lyme arthritis or late neuroborreliosis were randomly assigned to receive penicillin (20 million U per day intravenously for 10 days) or ceftriaxone (4 g per day intravenously for 14 days) [226]. Of the 13 patients who received ceftriaxone, none had objective evidence of persistent disease after treatment, although 3 had mild arthralgias, and 1 complained of fatigue and memory difficulty. In contrast, 5 of the 10 patients who received intravenous penicillin continued to have fatigue, memory deficit, or recurrent oligoarthritis at 3 months after treatment. Four of these 5 patients had resolution of their symptoms after re-treatment with ceftriaxone.

In a subsequent study, 31 patients with Lyme arthritis or late neuroborreliosis were treated with either 2 g or 4 g per day of ceftriaxone for 2 weeks (the first 17 patients enrolled received the 4-g dose and the next 14 patients received the 2-g dose) [226]. Following treatment, 3 of the 31 patients had persistent encephalopathy, 2 had persistent neuropathy, and 3 had no improvement in their arthritis. The overall frequency of persistent symptoms among patients was 13%, which was similar in both dosage groups. Duration of ceftriaxone treatment was

investigated in an open-label, randomized, multicenter study. In this study, 143 evaluable patients with manifestations of late Lyme disease (primarily Lyme arthritis) were treated with intravenous ceftriaxone (2 g per day for either 2 or 4 weeks) [227]. In this study, assessment was done at 3-month intervals for 12 months; primary assessment of outcome was at the time point of last evaluation. There was no significant difference in the clinical cure rates between the 2-week and 4-week treatment groups (76% and 70%, respectively). The most common persistent symptoms were arthralgia, pain, weakness, malaise, and fatigue. At time of the last evaluation, 5 patients in the 2-week treatment group had no apparent response to therapy, compared with none in the 4-week group ($P = .07$). The later the time point of evaluation, the higher the proportion of patients who were categorized as cured. A greater proportion of patients in the 4-week treatment group than in the 2-week group had therapy prematurely discontinued because of adverse events ($P < .02$). The principal conclusion of these 2 studies is that daily parenteral administration of ceftriaxone at a dosage of 2 g per day for 2 weeks is effective in resolving illness in the majority of patients with late Lyme disease. However, some patients have persistent symptoms despite receiving ceftriaxone treatment.

At the same time that studies were being performed to assess parenteral antibiotic regimens, oral therapy was also found to be effective in the treatment of patients with Lyme arthritis. In 1983 and 1984, a total of 14 children with Lyme arthritis were treated orally with either phenoxymethyl penicillin or tetracycline for 10–30 days [228]. Thirteen experienced no further attacks of arthritis at follow-up 4–24 months after treatment, while 1 patient's symptoms did not resolve until after he received a 10-day course of intravenous penicillin.

From 1986 through 1991, a total of 48 adult and pediatric patients with Lyme arthritis were randomly assigned to receive a 30-day course of doxycycline (100 mg orally twice per day) or amoxicillin plus probenecid (500 mg of each 4 times per day) [44]. Eighteen of the 20 evaluable patients treated with doxycycline and 16 of the 18 evaluable patients who completed the amoxicillin-probenecid regimen had resolution of arthritis 1–3 months after study entry. However, neuroborreliosis later developed in 5 patients, 4 of whom received the amoxicillin-probenecid regimen. The concomitant use of probenecid with amoxicillin may be inadvisable, because probenecid may impair penetration of β-lactam antibiotics into brain parenchyma [170, 229]. In retrospect, all 5 patients reported subtle distal paresthesias or memory impairment at the time of study entry. It was concluded that patients with Lyme arthritis can usually be treated successfully with oral antibiotics, but practitioners must be aware of subtle neurologic symptoms, which may require treatment with intravenous β-lactam antibiotics.

In a cost-effectiveness analysis, intravenous therapy was found to be no more cost-effective than oral therapy for patients with Lyme arthritis; intravenous therapy was more likely to result in serious complications and was substantially more expensive [230]. Thus, the authors concluded that oral antibiotics are preferred in the initial treatment of Lyme arthritis in the absence of concomitant neurologic involvement.

Not all patients with Lyme arthritis respond to 2–4-week courses of oral or intravenous antibiotic therapy. In one treatment trial, 16 patients with Lyme arthritis who had continuous joint swelling for at least 3 months, despite receiving 4-week courses of oral antibiotics, did not have resolution of arthritis when they were subsequently treated with intravenous ceftriaxone (2 g per day for 2 weeks) either [44]. These 16 patients were found to have distinctive immunogenetic and immune markers, including a high frequency of the HLA-DR4 allele and of antibody reactivity with OspA of the spirochete. More recent data based on PCR testing of serial joint fluid samples suggest that arthritis may persist in a small number of patients, despite apparent eradication of the spirochete (i.e., absence of amplifiable *B. burgdorferi* DNA by PCR) [205, 207, 231]. In these patients, it has been postulated that a T cell epitope of OspA may cross-react with a human protein, leading to an autoimmune response as a possible explanation for the persistent joint inflammation [205, 232]. This form of arthritis is termed "antibiotic-refractory Lyme arthritis" [233]. It can be operationally defined as persistent synovitis for at least 2 months after completion of a course of intravenous ceftriaxone (or after completion of two 4-week courses of an oral antibiotic for patients unable to tolerate cephalosporins), in conjunction with negative results of PCR of synovial fluid specimens, and of synovial tissue specimens if available [231, 234]. Arthroscopic synovectomy has been used successfully in the treatment of patients with antibiotic refractory Lyme arthritis. Of 20 patients who underwent this procedure for refractory chronic Lyme arthritis of the knee, 16 (80%) had resolution of joint inflammation during the first month after surgery or soon thereafter [235]. The remaining 4 patients (20%) had persistent or recurrent synovitis. No patient, however, has been documented to have persistent joint inflammation of >5 years' duration [236]. Anecdotally, some patients with antibiotic-refractory arthritis have appeared to benefit from intraarticular injections of corticosteroids, systemic administration of nonsteroidal anti-inflammatory agents (NSAIDs), or DMARDs, primarily hydroxychloroquine [206, 237, 238].

Patients with late Lyme disease associated with prominent neurologic features also respond to antibiotic therapy. In a trial conducted from 1987 through 1989, a total of 27 adult patients with Lyme encephalopathy, polyneuropathy, or both were treated with intravenous ceftriaxone (2 g per day for 2 weeks) [208]. In addition to clinical signs and symptoms, outcome measures included CSF analyses and neuropsychological tests

of memory. Response to therapy was usually gradual and did not begin until several months after treatment. When measured 6 months after treatment, 17 patients (63%) had uncomplicated improvement, 6 (22%) had improvement but then had relapse, and 4 (15%) had no change in their condition.

In a subsequent study, the same investigators treated 18 adult patients with Lyme encephalopathy with intravenous ceftriaxone (2 g per day for 30 days) [222]. Of the 18 patients, 16 had abnormal verbal or visual memory scores on neuropsychologic tests, and 16 had CSF abnormalities, most commonly intrathecal antibody production to *B. burgdorferi* or an elevated total protein level. As determined 6 months after treatment, 14 (93%) of the 15 patients examined had improvement in symptoms; verbal memory scores in the 15 patients were significantly improved ($P < .01$). The total CSF protein values were significantly less in the 10 patients who had follow-up analyses ($P < .05$). At 12–24 months, all patients were back to normal or improved (1 of the 18 patients was re-treated after 8 months). It was concluded that Lyme encephalopathy may be associated with active infection of the nervous system and that the infection can be treated successfully in most patients with a 30-day course of intravenous ceftriaxone. Whether a 30-day course is superior to 14 days of treatment is unclear. Although the data are much more limited, children with neurocognitive abnormalities attributed to Lyme disease also appear to improve after 2–4 weeks of intravenous ceftriaxone [239].

The third-generation cephalosporin cefotaxime has been tested in Europe and has been found to be effective in the treatment of late Lyme disease [240]. Although cefotaxime must be administered 3–4 times per day, compared with once-daily administration for ceftriaxone, it does not cause the biliary complications that have been associated with ceftriaxone therapy [241].

Recommendations

1. Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally (tables 2 and 3). Doxycycline (B-I), amoxicillin (B-I), or cefuroxime axetil (B-III) for 28 days is recommended for adult patients without clinical evidence of neurologic disease. For children, amoxicillin (B-I), cefuroxime axetil (B-III), or doxycycline (if ≥8 years of age) (B-I) is recommended (tables 2 and 3). Oral therapy is easier to administer than intravenous antibiotics, is associated with fewer serious complications, and is 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 β-lactam antibiotic for successful resolution. Further controlled trials are needed to compare the safety and efficacy of oral therapy with intravenous therapy for Lyme arthritis. 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 plus objective evidence of neurologic disease should receive parenteral therapy with ceftriaxone (tables 2 and 3) (A-II). Cefotaxime or penicillin G administered parenterally is an acceptable alternative (B-II). For children, intravenous ceftriaxone or intravenous cefotaxime is recommended (B-III); penicillin G administered intravenously is an alternative (B-III) (tables 2 and 3).

2. Patients who have persistent or recurrent joint swelling after a recommended course of oral antibiotic therapy should be re-treated with another 4-week course of oral antibiotics or with a 2–4-week course of intravenous ceftriaxone (B-III) (tables 2 and 3). 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. During this period, NSAIDs may be used, but intra-articular injections of corticosteroids are not recommended (D-III). 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 NSAIDs, intra-articular injections of corticosteroids, or DMARDs, such as hydroxychloroquine; expert consultation with a rheumatologist is recommended. If persistent synovitis is associated with significant pain or limitation of function, arthroscopic synovectomy may reduce the duration of joint inflammation (B-II).

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

Background and Diagnosis of Acrodermatitis Chronica Atrophicans

Acrodermatitis chronica atrophicans is a late skin manifestation of Lyme disease that develops insidiously several years after initial infection (range, 0.5–8 years) [109, 242].

Approximately 20% of patients have a history of a preceding erythema migrans lesion, usually of the same extremity [242]. Acrodermatitis chronica atrophicans is diagnosed most frequently in women >40 years of age. Although any of the species

of Lyme *Borrelia* may cause the lesion, by far the most common etiologic agent is *B. afzelii*. Therefore, this manifestation is much more common in Europe than in the United States [243–246].

Acrodermatitis chronica atrophicans occurs most often on the extensor surfaces of the hands and feet, and early lesions are characterized by a slight bluish-red discoloration and doughy swelling. Initially unilateral, the lesion may later become bilateral. The lesion enlarges slowly over months to years, in association with resolution of the edema and development of skin atrophy (figure 4) (sometimes referred to as "cigarette paper skin"). Nodules may develop over bony prominences, such as the elbow or patella [197, 242, 247]. In some patients, sclerosing lesions develop. Because of atrophy of the skin, the veins become prominent, which may lead to a misdiagnosis of venous insufficiency [109, 197, 242]. Approximately two-thirds of patients have an associated peripheral neuropathy, typically involving the affected extremity, manifested primarily as local sensory loss [248, 249].

The diagnosis of acrodermatitis chronica atrophicans is based on appropriate epidemiology, clinical characteristics, histological findings, and IgG seropositivity. Histopathology shows a pronounced lymphoplasmacellular infiltration of the skin and sometimes also of the subcutis, with or without atrophy [195].

Evidence to support treatment recommendations. Acrodermatitis chronica atrophicans does not appear to resolve spontaneously. There are no prospective, randomized studies on treatment. Oral or parenteral antimicrobial therapy (table 2) given for 3 weeks (range, 2–4 weeks) has resulted in improvement in pain and swelling, diminution in fibrous nodules, and gradual fading of the lesion within 2–6 months [250–252]. Atrophic areas often persist, and little objective improvement can be demonstrated in the neuropathy in uncontrolled studies, regardless of whether antibiotics are administered parenterally. However, progression of neurologic involvement is halted, and the neuropathic symptoms of pain and paresthesia are improved [251, 252]. In the United States, treatment of Lyme disease–associated peripheral neuropathy with intravenous ceftriaxone usually results in improvement. The reasons for the differences in the experience with this manifestation of the disease in the United States and Europe are not clear.

Recommendations

1. 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], or cefuroxime axetil [B-III]) used to treat patients with erythema migrans (tables 2 and 3). A controlled study is warranted to compare oral with parenteral antibiotic therapy for the treatment of acrodermatitis chronica atrophicans.

Figure 4. Illustrative example of a patient with acrodermatitis chronica atrophicans. The picture is a generous gift from Dr. Franc Strle (University Medical Center, Ljubljana, Slovenia).

POST–LYME DISEASE SYNDROMES

Primary management options considered. The focus of this section is on patients with unexplained chronic subjective symptoms following treatment with recommended antibiotic regimens for a previous objective manifestation of Lyme disease (e.g., erythema migrans). The management options considered included oral versus parenteral antimicrobial therapy (including prolonged treatment), versus symptomatic therapy only.

Outcomes evaluated. The panel weighed the potential benefits and risks associated with antimicrobial therapy, including adverse effects of antimicrobial therapy [241, 253] and complications associated with the use of intravenous catheters [254]. Also considered were the inconvenience of prolonged therapies, the potential impact of the indiscriminate use of antibiotics on the development of antibiotic resistance in the community, and the economic costs [255]. The desired outcome is to eliminate or alleviate symptoms without causing harm to the patient.

Background and diagnosis of patients with post–Lyme disease syndromes. Shortly after treatment with conventional courses of antibiotics for Lyme disease (tables 2 and 3), a minority of patients continue to report symptoms or signs. On the basis of numerous studies of patients with erythema migrans, it can be expected that few—if any—patients who are compliant with antibiotic therapy will have persistence or recurrence of the skin lesion. A rare patient, however, will develop an objective extracutaneous manifestation of Lyme disease, such as a new seventh nerve palsy or meningitis [138, 142]. Seventh nerve palsy typically occurs during the first week of therapy and, in most cases, appears to be benign; in an otherwise stable patient, this event does not mandate a change in treatment [138]. In contrast, if Lyme meningitis develops during or

shortly after completion of a course of oral antimicrobial therapy, the patient should be re-treated with ceftriaxone or a comparable parenteral antibiotic (table 2) [142, 256].

In some patients treated for objective extracutaneous manifestations of Lyme disease, there will be slow or even incomplete resolution of that manifestation. This is well illustrated by the treatment of patients with neuroborreliosis who have seventh nerve palsy. A small proportion of such patients will have mild residual weakness of facial muscles [155]. A similar phenomenon can probably occur with any other site of neurologic impairment, attributable not to persistent infection but to residual, irreversible neurologic damage. In ~10% of patients with Lyme arthritis, joint swelling (usually of a single joint) will persist after recommended antimicrobial treatment courses (table 3) [153, 205]. Chronic joint swelling in these circumstances, if not treated with other approaches (such as synovectomy) [235], will eventually disappear, but it has lasted for up to 4–5 years in a few patients [236]. *B. burgdorferi* has not been demonstrated to persist in such patients.

Objective clinical manifestations are uncommon after treatment of patients with Lyme disease. A much more likely scenario after treatment is the persistence or development of subjective symptoms without any residual or new objective manifestation. In patients treated for early or late Lyme disease, the frequency of subjective symptoms is at least partially dependent on when after treatment the patient is assessed [142, 227]. On the basis of an intention-to-treat analysis of 1 study of patients treated for erythema migrans, subjective symptoms were present in 35% of patients at day 20, in 24% at 3 months, and in 17% at 12 months ($P < .002$, for the comparison of the frequency of symptoms across the 3 time points) [142]. The presence of such symptoms during the first several weeks to months after treatment most often appears to be due to slow resolution of an inflammatory process associated with a highly symptomatic or disseminated *B. burgdorferi* infection [257]. Furthermore, evidence from 3 randomized trials [137, 142, 227] and 1 retrospective study [144] of patients treated for either early or late Lyme disease indicates that a more prolonged initial treatment course of antibiotics does not improve the rate of resolution of symptoms (see the sections on early and late Lyme disease above for more details).

In some patients, symptoms may be due, at least in part, to a tickborne coinfection. When compared with patients with Lyme disease alone, patients coinfected with babesiosis were more symptomatic at the time of diagnosis and were more likely to remain ill during the first 1–3 months or longer into convalescence [24, 26]. Coinfection, however, does not appear to worsen long-term outcome [258]. Furthermore, *Babesia* coinfection is unlikely to explain persistent symptoms for the majority of patients with Lyme disease because of the limited geographic distribution of this zoonosis. The impact of coinfection with HGA on posttreatment symptoms is less clear than for babesiosis. One report suggested that coinfected patients also had a more delayed convalescence, but the number of study subjects was small [26]. A second small study found little difference in symptom frequency for coinfected patients, compared with those with Lyme disease alone [27]. A third study found that HGA, with or without concurrent Lyme disease, was associated with more fatigue and certain other symptoms 1–3 years after the onset of illness, compared with an uninfected control group, but HGA was not associated with functional disability [259]. Because of the lack of persistence of antibodies to *A. phagocytophilum,* the authors of that study regarded this process as a postinfectious syndrome of unknown etiology [259]. *Bartonella* DNA has been found in some *Ixodes* species, but there is no convincing evidence that *Bartonella* infections can be transmitted to humans by a tick bite [260].

In many patients, posttreatment symptoms appear to be more related to the aches and pains of daily living rather than to either Lyme disease or a tickborne coinfection. Put simply, there is a relatively high frequency of the same kinds of symptoms in "healthy" people. For example, 20%–30% of adults complain of chronic fatigue [261–263], and in the 2003 National Health Interview Survey, the frequency of doctor-diagnosed arthritis cases among adults was 21.5% [264]. A study in England found a point prevalence of 11.2% for the presence of self-reported chronic widespread pain among adults that was frequently associated with feelings of depression and anxiety, fatigue, and somatic symptoms [265]. A recent study of the general adult United States population estimated a point prevalence of self-reported serious pain (level 3) to be 3.75%–12.10%, depending on the assessment tool used; for level 3 emotional or cognitive dysfunction, it was 2.17%–3.42% [266]. Population-based surveillance in the United States indicates a mean of 6.1 self-reported unhealthy days during the preceding month [267]. Thus, the presence of arthralgia, myalgia, fatigue, and other subjective symptoms after treatment for Lyme disease must be evaluated in the context of "background" complaints in a significant proportion of individuals.

Some patients with post–Lyme disease symptoms are found to have multiple tender points on physical examination, in addition to their reported widespread pain, and fulfill clinical criteria for a diagnosis of fibromyalgia [268, 269]. Whether Lyme disease triggered the fibromyalgia or whether the 2 conditions coincided as simply the result of chance, given the relatively high prevalence of fibromyalgia (2%) in the general population [270, 271], is unknown and deserves further study.

A recent meta-analysis attempted to determine whether the frequency of post–Lyme disease symptoms exceeds that of similar symptoms in control groups without Lyme disease [272]. Because none of the prospective studies of the outcome of Lyme disease included control populations, the authors of the meta-

analysis instead chose to analyze certain early retrospective studies of patients principally diagnosed during the 1980s [273–277]. The meta-analysis found that the frequency of post–Lyme disease symptoms exceeded that of the control populations by ⩾5% [272]. Unfortunately, the findings of this meta-analysis cannot be considered reliable, because the majority of the studies that were analyzed included "Lyme disease" cases that were poorly characterized or were diagnosed on the basis of less-reliable serologic testing methods than are currently recommended [278, 279]. In addition, patients were included in these studies who were not treated with antibiotics at all, who were treated after a prolonged delay of months to years, or who were treated with antibiotic regimens that are not currently recommended. Recall bias was also a potential limitation of the studies evaluated, given the possibility that a person with Lyme disease would be more likely to recall and/or to report subsequent symptoms, such as arthralgias, myalgias, or fatigue, than would another person with the same symptoms who was never diagnosed with Lyme disease [280]. More recent prospective studies of patients with Lyme disease have revealed that outcome is substantially better than reported in studies considered in the meta-analysis [87, 110, 139, 140, 142, 257, 278, 279]. Subjects in the prospective studies were well characterized. Most had localized or disseminated early Lyme disease associated with erythema migrans (the most common presentation of definite *B. burgdorferi* infection [23, 88, 89]) and were promptly treated with appropriate antibiotic regimens. Moreover, in some of the prospective studies, posttreatment symptoms occurred in <5% of patients [87, 110, 278]. A controlled, prospective study would be preferable to a meta-analysis for determination of whether the frequency of symptoms after treatment for Lyme disease exceeds that of similar symptoms in persons without Lyme disease.

Previous studies of various infectious diseases have suggested that delayed convalescence can be related to the emotional state of the patient before onset of the illness [281, 282]. In those studies, fatigue was often a persistent symptom [281, 282]. Consistent with these observations, one study of patients with Lyme disease found that poor outcome was associated with prior traumatic psychological events and/or past treatment with psychotropic medications [283]. This is an important consideration for future investigations.

To summarize, it can be expected that a minority of patients with Lyme disease will be symptomatic following a recommended course of antibiotic treatment as a result of the slow resolution of symptoms over the course of weeks to months or as a result of a variety of other factors, such as the high frequency of identical complaints in the general population.

Post–Lyme disease syndrome, posttreatment chronic Lyme disease, and chronic Lyme disease. Post–Lyme disease syndrome, posttreatment chronic Lyme disease, and chronic Lyme disease are terms intended to describe patients who have had well-documented Lyme disease and who remain symptomatic for many months to years after completion of appropriate antibiotic therapy. Considerable confusion and controversy exist over the frequency and cause of this process and even over its existence. This is because of a lack of a standardized case definition or a biologic marker to identify patients [284–287]. Some have classified untreated and treated patients with objective evidence of late Lyme disease, such as arthritis or encephalopathy, as having chronic Lyme disease, instead of using the preferred terminology of late Lyme disease. More often, patients categorized as having post–Lyme disease syndrome have subjective symptoms alone, such as musculoskeletal pains, cognitive complaints, and/or fatigue without objective abnormalities on physical examination. Thus, it is not surprising that studies of patients with post–Lyme disease complaints have used different case definitions and enrollment criteria. Thus, the study populations have varied.

The largest of the controlled treatment trials of patients with post–Lyme disease complaints (which included separate treatment studies for seropositive and seronegative patients) defined post–Lyme disease syndrome as the presence of any of the following symptoms: widespread musculoskeletal pain, cognitive complaints, radicular pain, paresthesias, or dysesthesias, provided the symptoms interfered with the ability to function [288]. The symptoms also had to begin within 6 months after the initial diagnosis and treatment of *B. burgdorferi* infection and had to persist for at least 6 months. Although not a formal component of the definition, 90% of the patients in this particular trial also complained of fatigue [289]. All patients in this trial reported some cognitive impairment at baseline, and >70% gave cognitive dysfunction as their primary symptom [290]. However, the study population had normal baseline neuropsychological test scores, including objective measures of attention and memory [290]. Although objective evidence of cognitive dysfunction has been reported in patients with post–Lyme disease symptoms [291, 292], these findings come from a few relatively small studies in which there may have been some degree of referral bias and/or differences in the neuropsychologic testing criteria used to diagnose cognitive impairment [290, 293]. Standardization of a case definition for the syndrome will be needed to address more specifically what constitutes cognitive dysfunction and whether patients with objective evidence of cognitive impairment should preferably be classified as having late neurologic Lyme disease. Self-reported cognitive dysfunction is clearly not a reliable indicator of objective evidence of impairment based on neuropsychological testing [290].

In another published, controlled treatment trial of patients with post–Lyme disease complaints, the case definition required the presence of severe fatigue (as defined by a specific 11-

question fatigue severity scale), in which the onset coincided with the diagnosis of Lyme disease and persisted for at least 6 months after the patients were originally treated with antibiotics [294].

None of the published studies of patients with early or late Lyme disease characterized partial responders using either of the definitions above. Some of the prospective studies of the treatment of early Lyme disease regarded patients as incomplete responders if the patients had any unexplained subjective symptoms when they were assessed, regardless of symptom severity or whether the symptoms necessarily originated within the first 6 months after initiation of antibiotic treatment [142, 257].

Unfortunately, it is apparent that the term "chronic Lyme disease" is also being applied to patients with vague, undiagnosed complaints who have never had Lyme disease. *When adult and pediatric patients regarded as having chronic Lyme disease have been carefully reevaluated at university-based medical centers, consistently, the majority of patients have had no convincing evidence of ever having had Lyme disease, on the basis of the absence of objective clinical, microbiologic, or serologic evidence of past or present* B. burgdorferi *infection* [253, 268, 295–298]. In one study, >50% of such patients actually had other treatable disorders, such as depression, rheumatoid arthritis, bursitis, and myasthenia gravis [253]. If serologic testing for Lyme disease is done for chronically ill patients who only have fatigue or musculoskeletal complaints without any objective manifestation of Lyme disease, the test results have a poor positive predictive value [98, 99, 101, 102, 104, 270]. Regardless of the nature of the symptom(s), a low positive predictive value can also be anticipated if serologic testing is done for patients who do not reside in or travel to a geographic area where Lyme disease is endemic. Under these circumstances, the majority of patients with a positive test result will not have active *B. burgdorferi* infection and, accordingly, would be unlikely to obtain a durable response from antibiotic treatment directed at this infection. The fact that some antibiotic classes (e.g., tetracyclines and macrolides) have significant anti-inflammatory effects exclusive of their antimicrobial effects [299, 300] can explain, in part, why uninfected patients with inflammatory conditions might also improve transiently while receiving these drugs.

Do viable *B. burgdorferi* persist in tissues despite antibiotic treatment? There is no convincing evidence in North America for the persistence of *B. burgdorferi* in the skin of humans after treatment with antibiotic regimens known to be active against *B. burgdorferi* in vitro. In the 2 US studies in which this question has been investigated systematically, skin biopsy samples from sites of a prior, resolved erythema migrans lesion were cultured. In one study, none of 18 biopsy cultures for 13 patients with erythema migrans grew *B. burgdorferi* (5 patients had negative skin biopsy culture results on 2 separate occasions 3–5 months apart), although all of these patients were culture positive prior to treatment with an antibiotic [301]. In the second study, 13 previously culture-positive patients were all culture negative when an additional biopsy specimen from the site of the resolved erythema migrans lesion was evaluated [302].

In several other US studies, cultures were performed of various extracutaneous sites in patients with persistent symptoms after antimicrobial therapy. One study reported the results of blood cultures performed for 47 patients who had been extensively treated with antimicrobials for symptoms of "chronic Lyme disease" [303]. This study reported a 97% blood culture positivity rate using a novel culture medium specifically requiring Detroit tap water as a constituent. This publication did not present the PCR data necessary to confirm that the visualized spirochetal forms were actually *B. burgdorferi.* This was an important omission, because the appearance of cellular debris may be confused with spirochetes on microscopic examination of culture supernatants [304]. A subsequent study, which evaluated 10 patients with post–Lyme disease symptoms using the same novel culture method, in addition to standard techniques for growing Lyme *Borrelia,* failed to grow *B. burgdorferi* from any blood culture [305]. In contrast to the conventional medium used to grow Lyme *Borrelia,* the novel culture medium was also unable to support the growth of a laboratory-adapted strain of *B. burgdorferi* for more than a few days. Another study similarly was unsuccessful in recovering *B. burgdorferi* from the blood of 12 patients with chronic post–Lyme disease symptoms, using both conventional and hypertonic media (M.S.K., unpublished data) [288]. The latter study also cultured 128 CSF specimens for *B. burgdorferi* and evaluated blood specimens and CSF specimens by PCR. None of the 843 specimens tested in total was either culture or PCR positive [288, 289]. Therefore, the most plausible explanation for the positive results using the novel blood culture method reported by a single group of investigators [303] is that the microscopic findings were not, in fact, due to *B. burgdorferi.*

In another study, *B. burgdorferi* DNA was detected by PCR in urine samples of 74.2% of 97 United States patients who were diagnosed as having "chronic Lyme disease" and who were previously treated with antibiotics for extended periods of time [306]. Few additional details were provided by the authors as to the characteristics of the patient population. Because the authors did not sequence the amplicons to confirm their identity, the results should be regarded as questionable in the absence of confirmation by other investigators. Nonspecific amplification in urine PCR using different targets has been observed previously [103]. The results also appear to be inconsistent with more recent assessments of the utility of PCR for detection of *B. burgdorferi* DNA in urine samples, in which the sensitivity of the assay was shown to be only 8% (1 of 12)

for untreated patients with objective evidence of Lyme disease (erythema migrans) [307].

In one US study in which *B. burgdorferi* could be recovered on culture after antibiotic treatment, the spirochete was cultured from skin biopsy or blood samples from 5 (45%) of 11 patients with Lyme disease with persistent or recurrent erythema migrans skin lesions, despite previous treatment with cephalexin [133]. This result was not surprising, because cephalexin, like other first-generation cephalosporins, is not active in vitro against *B. burgdorferi* [125, 133]. The findings of this study are also important, because they suggest that when culture results are positive, there is likely to be concordance with objective clinical failure.

Several studies in Europe have reported anecdotal instances in which *B. burgdorferi* was recovered from specimens from patients who had been treated with antimicrobials active against this spirochete [308, 309]. In none of the studies, however, could reinfection or laboratory contamination be excluded. In a European study in which patient specimens were recultured systematically to determine persistence of *B. burgdorferi,* the spirochete was recovered from a skin biopsy sample of normal appearing skin at the site of a resolved erythema migrans lesion in 19 (1.7%) of 1148 patients; all of these patients also had a positive culture result for a skin biopsy sample obtained prior to antibiotic therapy [310]. Of the 5 cases in which isolates from both the first and second biopsy samples were available for analysis, plasmid and other typing methods suggested that the isolates were not identical for at least 4 of the pairs [310]. In one case, the isolates were not even from the same species. Strain differences might be interpreted as indicating reinfection or possibly multiplicity of infecting borrelia in the original infection [311, 312]. Unfortunately, the authors did not report any data on the specificity of the culture technique. Without this information or without confirmation of persistent infection with an independent test method such as PCR, one cannot exclude the possibility that a low frequency of culture contamination had occurred. Culture contamination would be consistent with the absence of clinical findings at the skin site, the observation that the rate of positive culture results after repeated biopsy was similar regardless of which antibiotic class the patient had received for treatment (F.S., unpublished data) [313] and the lack of antibiotic resistance in the reisolated borrelial strains [310, 313]. Culture contamination has occurred before in laboratories growing *B. burgdorferi* (G.W., unpublished data) and is a well-known phenomenon in laboratories growing *Mycobacterium tuberculosis* [314].

The notion that symptomatic, chronic *B. burgdorferi* infection can exist despite recommended treatment courses of antibiotics (tables 2 and 3) in the absence of objective clinical signs of disease, is highly implausible as evidenced by (1) the lack of antibiotic resistance in this genus [39, 40, 310], (2) the lack of correlation of persistent symptoms with laboratory evidence of inflammation or with the eventual development of objective physical signs [223, 257, 288, 289], and (3) the lack of precedent for such a phenomenon in other spirochetal infections [315–317]. Additional compelling evidence against the hypothesis that persistent symptoms are the result of persistent infection is the fact that the concentrations of antibodies against *B. burgdorferi* in many of these patients diminish to undetectable levels [257, 286, 288, 318]. The panel is unaware of any chronic infection in which antibody titers diminish despite persistence of the causative organism. In syphilis, patients who are regarded as having treatment failure typically have persistent or rising titers of antibodies [319]. Finally, Lyme disease lacks characteristics of other infections that justify longer treatment courses, such as infections in immunodeficient hosts, infections in which a pathogen is inhibited but not killed by antimicrobial therapy or in which available antimicrobials are minimally active in vitro, infections caused by an intracellular pathogen, infections involving a biofilm, infections on a heart valve, or infections involving a clinical site in which there is ischemia, a foreign body, a sequestrum, or frank pus [170]. The "cystic" forms of *B. burgdorferi* that have been seen under certain growth conditions in vitro have not been shown to have any clinical significance [320].

Animal models may be useful to determine whether *B. burgdorferi* infection can persist despite antimicrobial treatment [36, 126, 321–327]. T>MIC appears to be the most relevant pharmacodynamic parameter with regard to the killing action of β-lactam antibiotics against *B. burgdorferi* and other spirochetes [328, 329]. Consequently, the dose and pharmacokinetic parameters of the drug in animals would be expected to be integrally related to drug efficacy.

The importance of drug dosage on antibiotic efficacy is illustrated by a study of gerbils in which 2 of 4 animals that were treated with once-daily ceftriaxone at a dose of 50 mg/kg remained culture positive, whereas *B. burgdorferi* could not be recovered from any of the 8 animals that were treated with a single daily dose of at least 200 mg/kg [126]. The importance of pharmacokinetic parameters is illustrated by a study in which 2 different preparations of doxycycline were administered to mice shortly after they had become infected with *B. burgdorferi* by a tick bite. A single dose of doxycycline was 43% effective in treating incubating *B. burgdorferi* infection when administered orally to 13 mice, but it was 100% effective when administered to 12 mice by a single subcutaneous injection of a sustained release preparation of the drug [36]. Similar maximum plasma concentrations were achieved with either treatment regimen, but by 48 h, doxycycline was absent from plasma in orally treated animals, whereas low plasma concentrations were maintained for 19 days in mice that were treated with the sustained release preparation.

Studies indicate that antibiotics can cure *B. burgdorferi* infection in infected animals [36, 126, 321–323]—even those that are highly immunocompromised [321, 322]—but rare animals may remain culture positive [324], and a substantial proportion of animals will remain PCR positive in some [325–327], but not all, studies [324]. The significance of continued PCR positivity needs to be better understood, but this phenomenon should not necessarily be construed to indicate persistence of viable *B. burgdorferi.* Unless proven otherwise, culture should be regarded as the gold standard to address viability of *B. burgdorferi* [330, 331]. This is especially true for animal studies in which access to tissues, both in amount and number of sites examined, is not limiting. The studies also show no evidence for recrudescence or persistence of clinical or histologic findings of an active inflammatory process consistent with *B. burgdorferi* infection when antibiotic-treated animals are immunosuppressed [325, 327]. Therefore, even if a few residual *B. burgdorferi* spirochetes or their DNA debris persist after antibiotic treatment in animal systems, they no longer appear to be capable of causing disease.

Possible failure to recapitulate the T>MIC found in humans receiving antibiotic treatment is a potentially serious limitation of almost all of the reported treatment studies of animals. In patients receiving recommended courses of treatment, antibiotic levels would be expected to be sustained above the MIC of *B. burgdorferi* for most of each 24-h period. For future studies of animals to provide information more directly applicable to the treatment of humans, dosing schedules will need to be designed to address the often marked disparities in drug disposition between animals and humans.

Evidence to support treatment recommendations. Several controlled treatment trials of patients with post–Lyme disease symptoms have been published. The largest study consisted of 2 separate multicenter trials conducted between 1997 and 2000; one trial included only patients who at the time of enrollment were seropositive by IgG immunoblot, and the other included only those who were seronegative [288]. The definition of post–Lyme disease symptoms used by these investigators is mentioned above. In these double-blind studies, patients were randomized to receive either intravenous ceftriaxone (2 g per day for 30 days) followed by oral doxycycline (200 mg per day for 60 days) or matching intravenous and oral placebos. Both trials combined had a target enrollment of 260 patients, but the data and safety monitoring board recommended that the studies be discontinued after a planned interim analysis. Statistical analysis at that time indicated that a significant difference in treatment efficacy favoring antimicrobial therapy would be unlikely if additional patients were entered.

The primary outcome measure in these studies was improvement in the patients' health-related quality of life, which was measured by means of the medical outcome study 36-item short-form General Health Survey (SF-36) [288]. Specimens of CSF obtained at baseline and plasma specimens obtained at baseline and at days 3, 5, 21, and 45 were tested by PCR for the presence of *B. burgdorferi* DNA. CSF samples were cultured for *B. burgdorferi.* Some blood samples were cultured for *B. burgdorferi* in hypertonic medium.

A total of 129 patients were enrolled in the trials (78 were seropositive, and 51 were seronegative) [288]. The average duration of symptoms exceeded 4 years. None of the patients was PCR or culture positive for *B. burgdorferi.* Serologic testing did not suggest that coinfection with either *B. microti* or *A. phagocytophilum* contributed to the patients' symptoms [289].

Patients were assessed 6 months after study entry (3 months after completion of the antibiotic regimens) [288]. There were no significant differences in the primary outcome measure of the health-related quality of life between the patients in the antibiotic groups and those in the placebo groups in the seropositive study, the seronegative study, or both studies combined. Of note, 36% of patients in the combined placebo groups had significant improvement in their SF-36 score, suggesting a substantial placebo effect in this patient population. Although deficits in physical health status (as measured by the SF-36) for the patients enrolled were equivalent to those previously found in patients with congestive heart failure or osteoarthritis, it is important to point out that the entry criteria for the study stipulated that the patients had to have symptoms that interfered with normal functioning.

Although the patients in these trials uniformly reported cognitive difficulties, the study population had normal baseline neuropsychological test scores [290]. There was no significant difference in degree of change in these scores between baseline and later assessments at 90 and 180 days after study entry for antibiotic- versus placebo-treated patients [290].

A smaller, single-center controlled treatment trial conducted between 1997 and 1999 compared 28 days of intravenous ceftriaxone with an identical-appearing placebo [294]. Entry criteria required the presence of severe fatigue for ⩾6 months, as discussed above. On the basis of the hypothesis that the etiology for this syndrome was inadequately treated neuroborreliosis, there were 3 coprimary outcome measures: improvement in the score on an 11-item fatigue questionnaire, improvement in cognitive function, and clearance of OspA from CSF, an experimental measure of CSF infection. Fifty-five patients were enrolled into the trial (28 in the ceftriaxone group and 27 in the placebo group). Of the 512 patients screened by telephone, most were excluded because of the absence of a documented history of Lyme disease.

Fatigue improved in both groups at the 1-month assessment, but improvement was sustained at 6 months only in the ceftriaxone group [294]. There was no treatment effect in cognitive function or in clearance of OspA from CSF. OspA was detected

in the CSF in only 16% of the patients in this study, a finding contrary to the original study hypothesis that the patients had active neuroborreliosis. The report is unclear as to whether the patients had objective evidence of significant cognitive impairment. The authors stated that the patients showed cognitive slowing, compared with historical healthy control subjects, but that the deficits were relatively mild. There was no significant difference between groups in the degree of improvement in fatigue or pain, as assessed by visual analogue scales in which the patients were asked to record the intensity of these symptoms for the prior 2 weeks, or in perceived health changes using the SF-36 health survey. Four (7%) of the patients experienced a serious adverse event requiring hospitalization, including intravenous catheter sepsis in 3 patients and anaphylaxis in 1.

Several methodologic issues may have had a negative impact on the validity of the findings in this study [294]. One of these was the potential unmasking of patients noted by the investigators, because patients receiving ceftriaxone were more likely to guess their treatment group correctly. A second concern was the loss of up to one-third of the on-study patients in the placebo group. Of the 27 patients randomized to receive placebo, 3 withdrew prior to receipt of any treatment, 3 (in retrospect) did not meet entry criteria for the study, and 3 developed intravenous catheter sepsis and treatment was prematurely discontinued.

The authors of this study concluded that repeated courses of antibiotic treatment are not indicated for persistent symptoms following Lyme disease, including symptoms related to fatigue and cognitive dysfunction, particularly in light of the frequency of serious adverse events [294].

Another controlled treatment trial enrolled patients with persistent cognitive symptoms, despite having been previously treated for Lyme disease with at least 3 weeks of intravenous antibiotics [332]. This study has been completed, but the results have not been published. In this small trial, 37 patients were randomized to receive 10 weeks of intravenous ceftriaxone (2 g per day) versus an intravenous placebo. Entry criteria differed from previous studies [288, 294] because of the requirement for the patients to have objective cognitive abnormalities, blurring the distinction between Lyme encephalopathy and post–Lyme disease syndrome, as discussed above. Preliminary findings indicate the absence of sustained improvement in cognitive function in the antibiotic-treated group at 14 weeks after therapy, although some patients reported continued improvement in physical functioning [332]. Of concern, 7 (18.9%) of the study subjects experienced serious adverse events, the majority of which were related to the intravenous catheter [332].

Several open-label studies have reported individual practitioner's experiences in treating chronic Lyme disease [318, 333, 334]. Open-label studies for an illness that has no objective findings need to be viewed with a high degree of skepticism. Moreover, many of these studies did not follow currently recommended standards for serologic testing for Lyme disease [117] and were likely to have included patients who had never been infected with *B. burgdorferi.* One report that might be regarded as representative described 235 patients who were ill for at least 3 months with any 2 of the following symptoms: unexplained fatigue, neurological symptoms, or musculoskeletal symptoms [333]. Patients were treated with a macrolide plus hydroxychloroquine for an indefinite period until the patient's symptoms resolved or improved; a minimum course of therapy was 3 months. Apparently, the rationale for this combined regimen was the speculation that the reason chronic Lyme disease is refractory to antibiotic therapy is that *B. burgdorferi* is localized to an acidic endosome within some cell population. The activity of the macrolide would be enhanced by alkalinization of this endosomal compartment, which, in turn, would be accomplished through the action of hydroxychloroquine. In this study, ~10% of patients were regarded as cured and slightly more than 75% were regarded as improved after a median duration of treatment of 6 months (range, 1–18 months). A fundamental limitation of this study was that the data presented did not convincingly demonstrate that the patients ever had Lyme disease. Neither detection of borrelial antibody by 2-tier serologic testing nor recommended interpretive criteria for immunoblots was used [117]. If patients without Lyme disease were enrolled, which is likely, clinical improvement might have been due in part to the anti-inflammatory properties of both the macrolide [300] and hydroxychloroquine, rather than by an antimicrobial effect. In addition, contrary to the study premise, most biologic data indicate that *B. burgdorferi,* like other spirochetes, is principally an extracellular pathogen [335, 336].

Recommendations

1. 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 table 5. 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 [117, 118]. Unvalidated test methods (such as urine antigen tests or blood microscopy for detection of *Borrelia* species) should not be used [337].

2. To date, there is no convincing biologic evidence for the existence of symptomatic chronic *B. burgdorferi* infection

Table 5. Proposed definition of post–Lyme disease syndrome.

Inclusion criteria
An adult or child with a documented episode of early or late Lyme disease fulfilling the case definition of the Centers for Disease Control and Prevention [112]. If based on erythema migrans, the diagnosis must be made and documented by an experienced health care practitioner.
After treatment of the episode of Lyme disease with a generally accepted treatment regimen [146] (tables 2 and 3), there is resolution or stabilization of the objective manifestation(s) of Lyme disease.
Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6 month period after completion of antibiotic therapy:
Fatigue
Widespread musculoskeletal pain
Complaints of cognitive difficulties
Subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social, or personal activities.
Exclusion criteria
An active, untreated, well-documented coinfection, such as babesiosis.
The presence of objective abnormalities on physical examination or on neuropsychologic testing that may explain the patient's complaints. For example, a patient with antibiotic refractory Lyme arthritis would be excluded. A patient with late neuroborreliosis associated with encephalopathy, who has recurrent or refractory objective cognitive dysfunction, would be excluded.
A diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease.
A prolonged history of undiagnosed or unexplained somatic complaints, such as musculoskeletal pains or fatigue, before the onset of Lyme disease.
A diagnosis of an underlying disease or condition that might explain the patient's symptoms (e.g., morbid obesity, with a body mass index [calculated as weight in kilograms divided by the square of height in meters] ⩾45; sleep apnea and narcolepsy; side effects of medications; autoimmune diseases; uncontrolled cardiopulmonary or endocrine disorders; malignant conditions within 2 years, except for uncomplicated skin cancer; known current liver disease; any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa or bulimia nervosa; and active drug abuse or alcoholism at present or within 2 years).
Laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from post–Lyme disease syndrome, such as a highly elevated erythrocyte sedimentation rate (>50 mm/h); abnormal thyroid function; a hematologic abnormality; abnormal levels of serum albumin, total protein, globulin, calcium, phosphorus, glucose, urea nitrogen, electrolytes, or creatinine; significant abnormalities on urine analysis; elevated liver enzyme levels; or a test result suggestive of the presence of a collagen vascular disease.
Although testing by either culture or PCR for evidence of *Borrelia burgdorferi* infection is not required, should such testing be done by reliable methods, a positive result would be an exclusion.

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 administration of recommended treatment regimens for Lyme disease (E-I).

HGA

Primary management options considered. The management options that were considered included oral or parenteral antimicrobial therapy for patients diagnosed with symptomatic HGA.

Outcomes evaluated. The panel weighed both the risks and consequences of developing acute and late complications of HGA and the economic costs and possible adverse effects of antimicrobial therapy. The desired outcome is to resolve the symptoms and signs of HGA while minimizing the adverse effects of antimicrobial therapy.

Background and diagnosis of HGA. HGA is a rickettsial infection of neutrophils [338, 339]. The infectious agent, *A. phagocytophilum,* is transmitted by the bite of infected *Ixodes* ticks, and human infection occurs in areas in the United States and Europe where Lyme disease is endemic [340–343]. In contrast to Lyme disease, however, HGA is infrequently diagnosed in children.

Clinical manifestations are nonspecific and may include fever, chills, headache, and myalgias [94, 95, 341–344]. The incubation period is 5–21 days [344]. Laboratory features may include leukopenia, lymphopenia, thrombocytopenia, and mild elevation of liver enzyme levels. In most cases, HGA is a mild, self-limited illness, and all clinical signs and symptoms resolve in most patients within 30 days, even without antibiotic therapy [340]. However, serious manifestations of infection, including a fatal outcome, have been reported in patients with factors known to suppress the immunologic response to infection, such as advanced age, immunosuppressive therapy, chronic inflammatory illnesses, or underlying malignant diseases [340, 345, 346]. Chronic infection due to *A. phagocytophilum* has not been described in humans.

Prior to initiation of antibiotic therapy, *A. phagocytophilum*

can be detected in blood samples by smear examination, PCR, or culture using HL60 cells [94, 345, 347–349]. 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 [349]. The most sensitive diagnostic method is acute-phase *and* convalescent-phase serologic testing using an indirect fluorescent antibody assay (acute-phase testing alone is not sufficiently sensitive) [348–350]. Serologic testing is often the only way to diagnose a patient who has already begun to receive antibiotic treatment. Immunostaining of *A. phagocytophilum* antigen in a tissue sample is an uncommonly used diagnostic modality [344]. Doxycycline therapy leads to clinical improvement in 24–48 h [340, 345, 346, 351]. Thus, patients who do not respond to treatment within this time frame should be reevaluated for alternative diagnoses and treatment, including coinfection with *B. microti* in certain geographic areas (see Babesiosis below).

Evidence to support treatment recommendations. There are no controlled clinical trials on the use of antibiotics for treatment of HGA. Doxycycline and rifampin are both highly active against *A. phagocytophilum* in vitro [352–354], and recommendations for therapy have been based on published reports of the clinical response to these drugs. It is generally accepted that all symptomatic patients should be treated with an appropriate antimicrobial agent, because it may be very difficult to distinguish patients who will have a self-limited illness from those who will develop a complicated or fatal course of HGA [351].

Most of the clinical experience in treatment of adults has been with doxycycline at a dosage of 100 mg twice per day given orally [340, 345, 351]. There is only limited experience in the use of doxycycline for treatment of HGA in children [355–360] or pregnant women [357]. Doxycycline was used successfully to treat a pregnant woman who developed symptomatic HGA during parturition [357]. Her newborn child was subsequently diagnosed with HGA and was also treated successfully with doxycycline. In addition, a 5-year-old boy, who had simultaneous HGA and Lyme disease, was treated successfully with doxycycline [359]. Recently a 38-year-old woman was diagnosed with HGA 10 days after she had delivered a healthy baby [355]. She was treated with doxycycline for 2 weeks while breast-feeding, and both mother and baby were well at a later follow-up examination. Although the American Academy of Pediatrics has recommended doxycycline as the preferred antibiotic for treatment of children diagnosed with clinically apparent HGA [361], a small number of pediatric-age patients and pregnant women have also been treated successfully with rifampin [358, 362, 363].

The optimal duration of antimicrobial therapy for HGA has not been established. At first, patients were treated empirically with doxycycline for 10–14 days, and the recommendations for duration of treatment followed the guidelines for treatment of Lyme disease. Clinical experience, however, has shown that adult patients who have been treated for 7–10 days experienced complete resolution of their infections, and relapse or chronic infection has not been demonstrated [27, 94, 95, 341, 343]. A shorter course of doxycycline (4–7 days) has been advocated for patients <8 years of age because of the potential risk for adverse effects from this drug (dental staining) in young children [340, 351, 364, 365].

There is no published clinical experience on the use of clarithromycin or azithromycin for treatment of HGA. Certain fluoroquinolones, such as levofloxacin, are active against *A. phagocytophilum* in vitro [352–354], but a single case report and a small study of immunodeficient mice (severe combined immune deficient [SCID]) have suggested that this class of drugs may not be curative of infection [366]. Chloramphenicol is inactive against *A. phagocytophilum* in vitro [352–354] and has been ineffective for treatment of horses infected with *A. phagocytophilum* [367].

Recommendations

1. All symptomatic patients suspected to have HGA should be treated with antimicrobial therapy because of the risk of complications (A-III). Suspicion for 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 above), but antibiotic therapy should not be delayed in a patient with a suggestive clinical presentation pending the results.

2. Doxycycline is recommended as the treatment of choice for patients who are suspected to have 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 are coinfected with *B. burgdorferi.*

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 [365]. The suggested dosage of doxycycline for children with HGA is 4 mg/kg per day in 2 divided doses (maximum, 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. 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. If the child has concomitant Lyme disease, then amoxicillin (50 mg/kg per day in 3 divided doses; maximum, 500 mg per dose) or cefuroxime axetil (30 mg/kg per day in 2 divided doses; maximum, 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). Recommended management of less-severely ill children with HGA is discussed below.

3. Patients with mild illness due to HGA who are not optimally suited for doxycycline treatment due to 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, 300 mg per dose) (B-III). Rifampin-treated patients should be closely observed to ensure resolution of clinical and laboratory abnormalities. Because rifampin is not effective therapy for Lyme disease, coinfected patients should also be treated with amoxicillin or cefuroxime axetil as used for the treatment of erythema migrans (see tables 2 and 3) (A-I). No other antimicrobial can be recommended for the treatment of HGA (E-III).

4. 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 coinfected with *B. microti*.

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

BABESIOSIS

Primary management options considered. The management options considered included oral or parenteral antimicrobial therapy and exchange transfusion for patients diagnosed with symptomatic babesiosis.

Outcomes evaluated. The panel weighed both the risks and consequences of developing acute and late complications of babesiosis and the economic costs and possible adverse effects of antimicrobial therapy and exchange transfusion. The desired outcome is to resolve the symptoms and signs of babesiosis and prevent relapse while minimizing the adverse effects of both antimicrobial therapy and exchange transfusion.

Background and diagnosis of babesiosis. Babesiosis is caused by intraerythrocytic protozoa. Although several different species of *Babesia* have been found to infect humans, *B. microti* is the most common cause of infection in the United States. *B. microti* is transmitted by *I. scapularis* ticks, which may also transmit *B. burgdorferi* and *A. phagocytophilum* [368–370]. Infection due to *B. microti* occurs in parts of New England, New York State, New Jersey, Minnesota, and Wisconsin [368–371]. Infection has been recognized, however, in a only limited portion of the geographic areas where Lyme disease is endemic, and the number of reported cases of babesiosis is less than that of Lyme disease in these areas [372]. High-incidence areas include coastal southern New England and the chain of islands off the coast that include Martha's Vineyard and Nantucket Island, MA; Block Island, RI; and eastern Long Island and Shelter Island, NY.

Other species of *Babesia* have been found to cause disease in California and Washington State (WA-1) and Missouri (MO-1) [373, 374]. Sporadic cases of babesiosis have also been reported in Europe (*Babesia divergens* and *B. microti*), Africa, Asia, and South America [375–379].

The clinical features of babesiosis are similar to those of malaria and range in severity from asymptomatic to rapidly fatal. Most patients experience a viral infection–like illness with fever, chills, sweats, myalgia, arthralgia, anorexia, nausea, vomiting, or fatigue [24, 96, 371–375, 380–384]. On physical examination, fever, splenomegaly, hepatomegaly, or jaundice may be observed [371, 380, 381, 384]. Laboratory findings may include hemolytic anemia with an elevated reticulocyte count, thrombocytopenia, proteinuria, and elevated levels of liver enzymes, blood urea nitrogen, and creatinine [96, 380, 381]. Complications of babesiosis include acute respiratory failure, disseminated intravascular coagulation, congestive heart failure, coma, and renal failure [96, 381]. Immunocompromised patients, such as those who lack a spleen, have a malignancy or HIV infection, or who exceed 50 years of age, are at increased risk of severe babesiosis [381–383]. Approximately one-quarter of infected adults and one-half of children experience asymptomatic infection or such mild viral–like illness that the infection is only incidentally diagnosed by laboratory testing [372, 384–386]. In both untreated and treated patients, parasitemia may occasionally persist, resulting either in subsequent recrudescence weeks or months later (primarily in immunocompromised hosts) or, rarely, in transmission of the pathogen to others through blood transfusion [387, 388].

The diagnosis of babesiosis is based on epidemiologic, clinical, and laboratory information. Babesiosis only occurs in patients who live in or travel to areas of endemicity or who have received a blood transfusion containing the parasite within the previous 9 weeks [388]. Because the clinical findings are nonspecific, laboratory studies are necessary to confirm the diagnosis. Specific diagnosis of babesiosis is made by microscopic identification of the organism on Giemsa stains of thin blood smears [389]. On thick blood smears, the organisms appear as simple chromatin dots that might be mistaken for stain precipitate or iron inclusion bodies. Consequently, this method

should only be performed by someone with extensive experience in interpreting thick smears. Multiple blood smears should be examined, because only a few erythrocytes may be infected in the early stage of the illness when most people seek medical attention. Because *Babesia* species may be confused with malarial parasites on blood smear, confirmation of the diagnosis and identification of the specific babesial pathogen may require additional laboratory testing. Also, it is important to have other supportive laboratory results if only a few ring-like structures are observed by microscopy. Both IgG and IgM antibodies to *Babesia* can be detected by indirect fluorescent antibody assay [390, 391]. Virtually all infected patients will have detectable antibodies in an acute-phase serum sample or a convalescent-phase sample obtained 4–6 weeks later. PCR detection of *Babesia* DNA in blood has been shown to be slightly more sensitive than microscopic detection of parasites on blood smear [392, 393].

In summary, the diagnosis of babesiosis is most reliably made in patients who have lived in or traveled to an area where babesiosis is endemic, experience viral infection–like symptoms, and have identifiable parasites on blood smear and anti-babesial antibody in serum. The diagnosis of active babesial infection based on seropositivity alone is suspect. PCR is a useful laboratory adjunct, but as with smear and antibody testing, it should only be performed in laboratories that are experienced in such testing and meet the highest laboratory performance standards.

Evidence to support treatment recommendations. The combination of clindamycin and quinine was initially used in 1982 to treat a newborn infant with transfusion-transmitted babesiosis and subsequently became the first widely used antimicrobial therapy for human babesiosis [394, 395]. This combination, however, is frequently associated with untoward reactions, such as tinnitus, vertigo, and gastrointestinal upset [382, 387, 396]. These adverse effects were substantive enough to prompt earlier recommendations that treatment of babesiosis be reserved for seriously ill patients and that less ill patients should be observed without therapy [395]. Treatment failures have been reported in patients who have had splenectomy, HIV infection, or concurrent corticosteroid therapy [373, 382, 397].

The successful use of atovaquone and azithromycin for treating malaria in humans and babesiosis in a hamster infection model suggested that this drug combination might also be useful for treatment of human babesiosis [398, 399]. Atovaquone and azithromycin were compared with clindamycin and quinine in a prospective, nonblinded, randomized therapeutic trial of 58 adult patients with non–life-threatening babesiosis [396]. Atovaquone (750 mg every 12 h) plus azithromycin (500 mg on day 1, then 250 mg per day thereafter) was found to be as effective in clearing parasitemia and resolving symptoms as the combination of clindamycin (600 mg every 8 h) and quinine (650 mg every 8 h). Both drug combinations were given orally for 7 days. After 3 months, there was no evidence of parasites on blood smear or amplifiable *B. microti* DNA in either group. Significantly fewer adverse effects were associated with the atovaquone and azithromycin combination. Three-fourths of patients receiving clindamycin and quinine experienced adverse drug reactions, and one-third had to decrease the dose or discontinue the medication. In contrast, only 15% of patients in the azithromycin and atovaquone group were noted to have adverse effects from the drugs, and only 1 patient required a decrease in dosage or discontinuation of medication. It was concluded that the atovaquone and azithromycin drug combination was preferable to the combination of clindamycin and quinine because of improved tolerability [396]. For immunocompromised patients with babesiosis, successful outcome has been reported using atovaquone combined with higher doses of azithromycin (600–1000 mg per day) [400].

Other antimicrobials have been used to treat babesiosis. The combination of pentamidine and trimethoprim-sulfamethoxazole was found to be moderately effective in clearing parasitemia and symptoms due to *B. divergens* [401]. Potential adverse reactions of pentamidine, however, limit the use of this combination. Azithromycin, in combination with quinine, was used successfully in 2 patients who had not improved after clindamycin and quinine therapy [402, 403]. A severely immunosuppressed HIV-infected patient with chronic babesiosis who did not respond to clindamycin and quinine was successfully treated with clindamycin, doxycycline, and azithromycin [382].

Partial or complete RBC exchange transfusion is a potentially life-saving adjunct to antimicrobial therapy and is indicated for patients with high-grade parasitemia (≥10%), significant hemolysis, or renal, hepatic, or pulmonary compromise [381, 404, 405]. There are, however, no published trials systematically comparing antimicrobial therapy alone with the combination of antimicrobial therapy and exchange transfusion.

Recommendations

1. All patients with active babesiosis should be treated with antimicrobial therapy 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. 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). Treatment is also not recommended for asymptomatic individuals regardless of the results of serologic tests, blood smears, or PCR (E-III). Asymptomatic patients with positive babesial smear and/or PCR results should have these studies repeated, and a course

of treatment should be considered if parasitemia persists for >3 months (B-III).

2. 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 to those with severe babesiosis (A-III). In such patients, clindamycin should be administered intravenously rather than orally, and exchange transfusion should be considered (see below). 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 once per day thereafter by the oral route. For immunocompromised patients with babesiosis, higher doses of azithromycin (600–1000 mg per day) may be used. The doses for children are atovaquone, 20 mg/kg every 12 h (up to a maximum of 750 mg per dose), and azithromycin, 10 mg/kg per day 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) thereafter orally.

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. Doses for children are clindamycin, 7–10 mg/kg given every 6–8 h (up to a maximum of 600 mg per dose) intravenously or orally, and quinine, 8 mg/kg given every 8 h (up to a maximum of 650 mg per dose) orally.

3. Partial or complete RBC exchange transfusion is indicated for those 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.

4. 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 antiprotozoal therapy is begun, and symptoms should completely resolve within 3 months of 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.

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

6. Re-treatment of patients with antibabesial therapy, as outlined above, should be considered if babesial parasites or amplifiable babesial DNA is 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.

Acknowledgments

We thank Lisa Giarratano and Richard Minott for assistance in the preparation of this manuscript. The following individuals served as consultants to the Infectious Diseases Society of America panel in the development of these guidelines: Maria Aguero-Rosenfeld, Stephen W. Barthold, Susan O'Connell, Volker Fingerle, Jerry Green, Barbara J. Johnson, Richard Kaplan, Jooyun Lee, Muhammad Morshed, Jose Munoz, Benjamin H. Natelson, John Nowakowski, Mario Philipp, Joseph F. Piesman, Arthur Weinstein, and Bettina Wilske. The Expert Panel also wishes to express its gratitude to Paul G. Auwaerter, Michael A. Gerber, and Leonard H. Sigal for their thoughtful review of an earlier draft of these guidelines.

Potential conflicts of interest. G.P.W. has received consulting fees from Baxter and research support from Immunetics, and he is a founder of Diaspex, a company that does not offer products or services. R.J.D. has served as a speaker for Pfizer and is part owner of Biopeptides, a biotech company that develops vaccines and laboratory diagnostics, including products for *Borrelia burgdorferi*. J.J.H. has served as an expert witness on behalf of Lymerix (GlaxoSmithKline). A.C.S. has received consulting fees from Baxter. P.J.K. has a patent pending with a university on a babesiosis diagnostic procedure that is not yet on the market. All other authors: no conflicts.

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An error appeared in an article published in the 1 November 2006 issue of the journal (Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, Krause PJ, Bakken JS, Strle F, Stanek G, Bockenstedt L, Fish D, Dumler JS, Nadelman RB. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43:1089–134). Throughout the article, the PR interval should be given as 300 milliseconds (*not* 30 milliseconds). The authors regret this error.

An error appeared in an article published in the 1 July 2007 issue of the journal (Dube MP, Parker RA, Mulligan K, Tebas P, Robbins GK, Roubenoff R, Grinspoon SK. Effects of potent antiretroviral therapy on free testosterone levels and fat-free mass in men in a prospective, randomized trial: A5005s, a substudy of AIDS Clinical Trials Group Study 384. Clin Infect Dis 2007;45:120–6). In the second sentence of the first paragraph of the Results section, the difference between the nelfinavir and efavirenz groups with respect to median baseline free testosterone levels was misreported as being statistically insignificant. The median baseline free testosterone levels were actually significantly higher in the group randomized to receive nelfinavir (104.8 pg/mL; interquartile range, 86.2–128.9 pg/mL), compared with the group randomized to receive efavirenz (87.4 pg/mL; interquartile range, 64.2–108.3 pg/mL; $P = .006$). The authors regret this error.

Clinical Infectious Diseases 2007; 45:941

1058-4838/2007/4507-0024$15.00
DOI: 10.1086/522848