GUIDELINES FROM THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Practice Guidelines for the Treatment of Lyme Disease

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Executive Summary

Tick bites and prophylaxis. The best currently available method for preventing infection with *Borrelia burgdorferi* is to avoid vector tick exposure. If exposure to *Ixodes scapularis* or *Ixodes pacificus* ticks is unavoidable, measures recommended to reduce the risk of infection include using both protective clothing and tick repellents, checking the entire body for ticks daily, and promptly removing attached ticks, before transmission of *B. burgdorferi* can occur (A-III [see tables 1 and 2 for recommendation categories, indicated in parentheses throughout this text]).

Routine use of either antimicrobial prophylaxis (E-I) or serological tests (D-III) after a tick bite is not recommended. Some experts recommend antibiotic therapy for patients bitten by *I. scapularis* ticks that are estimated to have been attached for >48 h (on the basis of the degree of engorgement of the tick with blood), in conjunction with epidemiological information regarding the prevalence of tick-transmitted infection (C-III). However, accurate determinations of species of tick and degree of engorgement are not routinely possible, and data are insufficient to demonstrate efficacy of antimicrobial therapy in this setting.

Persons who remove attached ticks should be monitored closely for signs and symptoms of tick-borne diseases for up to 30 days and specifically for the occurrence of a skin lesion at the site of the tick bite (which may suggest Lyme disease) or a temperature >38°C (which may suggest human granulocytic ehrlichiosis [HGE] or babesiosis). Persons who develop a skin lesion or other illness within 1 month after removing an attached tick should promptly seek medical attention for assessment of the possibility of having acquired a tick-borne disease (A-II).

Health care practitioners, particularly those in areas where Lyme disease is endemic, should become familiar with its clinical manifestations, recommended practices for testing for it, and therapy for the disease, as well as for HGE and babesiosis (A-III).

Testing of ticks for tick-borne infectious organisms is not recommended, except in research studies (D-III).

Prior vaccination with the recently licensed recombinant outer-surface protein A (OspA) vaccine preparation reduces the risk of developing Lyme disease associated with tick bites but should not alter the above recommendations (A-I).

Early Lyme disease. Administration of doxycycline (100 mg twice daily) or amoxicillin (500 mg 3 times daily) for 14–21 days is recommended for treatment of early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of neurological involvement or third-degree atrioventricular heart block (A-I). In prospective studies, these agents have been shown to be effective in treating erythema migrans and associated symptoms. Doxycycline has the advantage of being efficacious for treatment of HGE, which may occur simultaneously with early Lyme disease. Doxycycline is relatively contraindicated during pregnancy or lactation and for children aged <8 years.

Because of its higher cost, cefuroxime axetil (500 mg orally twice daily), which is as effective as doxycycline in the treatment of erythema migrans (A-I), should be reserved as an alternative agent for those patients who can take neither doxycycline nor amoxicillin. For children, we recommend amoxicillin at a dos-

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Table 1. Categories indicating the strength of each recommendation for or against use.

Category	Definition
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

NOTE. Table is adapted from [1].

age of 50 mg/kg/d, divided into 3 doses per day (maximum, 500 mg/dose), or doxycycline (for those aged ≥8 years) at a dosage of 1–2 mg/kg twice per day (maximum, 100 mg/dose) (B-II). Cefuroxime axetil, at a dosage of 30 mg/kg/d, divided into 2 doses daily (maximum, 500 mg/dose), is an acceptable alternative agent (B-III).

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 amoxicillin, doxycycline, and cefuroxime axetil. Possible regimens for adults are as follows: azithromycin, 500 mg orally daily for 7–10 days; erythromycin, 500 mg orally 4 times daily for 14–21 days; and clarithromycin, 500 mg orally twice daily for 14–21 days. Possible dosages for children are the following: azithromycin, 10 mg/kg/d (maximum, 500 mg/d); erythromycin, 12.5 mg/kg 4 times daily (maximum, 500 mg/dose); and clarithromycin, 7.5 mg/kg twice daily (maximum, 500 mg/dose). Patients treated with macrolides should be closely followed.

Ceftriaxone (2 g iv daily), although effective, is not superior to oral agents and is not recommended as a first-line agent for treatment of Lyme disease in the absence of neurological involvement or third-degree atrioventricular heart block (E-I).

The use of ceftriaxone (2 g once daily iv for 14–28 days) in early Lyme disease is recommended for acute neurological disease manifested by meningitis or radiculopathy (B-II). Intravenous penicillin G at a dosage of 18–24 million units daily, divided into doses given every 4 h (for patients with normal renal function), may be a satisfactory alternative (B-II). Cefotaxime (2 g iv every 8 h) may also be a satisfactory alternative (B-II). For adult patients who are intolerant of both penicillin and cephalosporins, doxycycline (200–400 mg/d) in 2 divided doses given orally (or iv if the patient is unable to take oral medications) for 14–28 days may be adequate (B-II).

For children, we recommend ceftriaxone (75–100 mg/kg/d) in a single daily iv dose (maximum, 2 g) (B-II) or cefotaxime (150–200 mg/kg/d) divided into 3 or 4 iv doses (maximum, 6 g/d) (B-III) for 14–28 days. An alternative is iv penicillin G (200,000–400,000 units/kg/d; maximum, 18–24 million units/d) divided into doses given every 4 h for those with normal renal function (B-II).

Patients with first- or second-degree atrioventricular heart block associated with early Lyme disease should be treated with the same antimicrobial regimens as patients with erythema migrans without carditis (see paragraphs 1 and 2 of the recommendations in this section, above) (B-III). We recommend that patients with third-degree atrioventricular heart block be treated with parenteral antibiotics such as ceftriaxone (see paragraphs 5 and 6 of the recommendations in this section, above) in the hospital, although there are no clinical trials to support this recommendation (B-III). A temporary pacemaker may also be required.

Although antibiotic treatment does not hasten the resolution of seventh-cranial-nerve palsy associated with *B. burgdorferi* infection, antibiotics should be given to prevent further sequelae (B-II). There was disagreement among panel members on the neurological evaluation of patients with seventh-cranial-nerve palsy. Some members perform a CSF examination on all patients with seventh-cranial-nerve palsy, whereas others reserve lumbar puncture for patients for whom there is strong clinical suspicion of CNS involvement (e.g., severe headache or nuchal rigidity). Patients whose CSF examinations yield normal findings may be treated with the same regimens used for patients with erythema migrans (B-III), whereas patients for whom there is clinical and laboratory evidence of CNS involvement should be treated with regimens effective against meningitis (see paragraphs 5 and 6 of the recommendations in this section, above) (B-II).

Treatment for pregnant patients can be identical to that for nonpregnant patients with the same disease manifestation, except that tetracyclines should be avoided (B-III).

Lyme arthritis. Lyme arthritis usually can be treated successfully with antimicrobial agents administered orally or intravenously. Administration of doxycycline (100 mg twice daily orally) or amoxicillin (500 mg 3 times daily), in each instance for 28 days, is recommended for patients without clinically evident neurological disease (B-II). For children, we recommend administration of doxycycline (1–2 mg/kg twice per day; maximum, 100 mg/dose), which can be given to patients aged ≥8 years, or amoxicillin (50 mg/kg/d, divided into 3 doses per day; maximum, 500 mg/dose) for 28 days (B-II).

Oral therapy is easier to administer than iv antibiotics, is associated with fewer serious complications, and is considerably less expensive. Its disadvantage is that some patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require iv therapy for successful treat-

Table 2. Grades indicating the quality of evidence on which recommendations are based.

Grade	Definition
I	Evidence from at least 1 properly randomized, controlled trial
II	Evidence from at least 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 of uncontrolled experiments
III	Evidence from opinions of respected authorities that is based on clinical experience, descriptive studies, or reports of expert committees

ment. Further controlled trials are needed to compare oral with iv therapy.

Neurological evaluation, including lumbar puncture, should be done for patients if there is a strong clinical suspicion of neurological involvement. Patients with both arthritis and objective evidence of neurological disease should receive iv ceftriaxone (2 g once daily for 14–28 days) (A-II). Alternative therapies include iv cefotaxime (2 g iv every 8 h) (B-III) or iv penicillin G (18–24 million units daily, divided into doses given every 4 h for patients with normal renal function) (B-II). Because of low blood levels, the long-acting benzathine preparation of penicillin is not recommended (D-III). For children, we recommend administration of ceftriaxone (75–100 mg/kg/d in a single daily iv dose; maximum, 2 g) (B-III) or cefotaxime (150–200 mg/kg/d divided into 3 or 4 iv doses; maximum, 6 g/d) (B-III) for 14–28 days. An alternative is iv penicillin G (200,000–400,000 units/kg/d; maximum, 18–24 million units/d), divided into doses given every 4 h for those with normal renal function (B-III).

For patients who have persistent or recurrent joint swelling after recommended courses of antibiotic therapy, we recommend repeat treatment with another 4-week course of oral antibiotics or with a 2- to 4-week course of iv ceftriaxone (B-III). Clinicians should consider waiting several months before initiating repeat treatment with antimicrobial agents because of the anticipated slow resolution of inflammation after treatment. If patients have persistent arthritis despite 2 courses of oral therapy or one course of iv therapy, symptomatic treatment with nonsteroidal anti-inflammatory agents is recommended; intra-articular steroids may also be of benefit (B-III). If persistent synovitis is associated with significant pain or if it limits function, arthroscopic synovectomy can reduce the period of joint inflammation (B-II).

Late neuroborreliosis affecting the CNS or peripheral nervous system. For patients with late neurological disease affecting the CNS or peripheral nervous system, treatment with ceftriaxone (2 g once a day iv for 2–4 weeks) is recommended (B-II). Alternative parenteral therapy may include administration of cefotaxime (2 g iv every 8 h) (B-II) or iv penicillin G (18–24 million units daily, divided into doses given every 4 h for patients with normal renal function) (B-II). Response to treatment is usually slow and may be incomplete. However, unless relapse is shown by reliable objective measures, repeat treatment is not recommended. For children, a 14–28-day course of treatment with ceftriaxone (75–100 mg/kg/d in a single daily iv dose; maximum, 2 g) is recommended (B-II). An alternative is cefotaxime (150–200 mg/kg/d iv, divided into 3 or 4 doses; maximum, 6 g/d) (B-II). Another alternative is iv penicillin G (200,000–400,000 units/kg/d, divided into doses given every 4 h for those with normal renal function; maximum, 18–24 million units/d) (B-II).

Chronic Lyme disease or post–Lyme disease syndrome. After an episode of Lyme disease that is treated appropriately, some persons have a variety of subjective complaints (such as myalgia, arthralgia, or fatigue). Some of these patients have been classified as having "chronic Lyme disease" or "post–Lyme disease syndrome," which are poorly defined entities. These patients appear to be a heterogeneous group. Although European patients rarely have been reported to have residual infection with *B. burgdorferi,* this has yet to be convincingly demonstrated either in a large series of appropriately treated European patients or in a study of North American patients.

Randomized controlled studies of treatment of patients who remain unwell after standard courses of antibiotic therapy for Lyme disease are in progress. To date, there are no convincing published data that repeated or prolonged courses of either oral or iv antimicrobial therapy are effective for such patients. The consensus of the Infectious Diseases Society of America (IDSA) expert-panel members is that there is insufficient evidence to regard "chronic Lyme disease" as a separate diagnostic entity.

Objective

The objective of these practice guidelines is to provide clinicians and other health care practitioners with recommendations for management of cases in which either Lyme disease has been diagnosed or the patient was bitten by an *Ixodes* tick in North America (tables 1 and 2) [1]. Lyme disease is endemic in several regions of the United States, particularly areas of the Northeast, Upper Midwest, and Northwest [2]. It is the most frequent vector-borne disease in the United States. Adults and children of both sexes can be affected. These patients are evaluated and treated by general practitioners, pediatricians, and internists, as well as by infectious disease specialists, dermatologists, rheumatologists, neurologists, orthopedists, obstetricians, and ophthalmologists. Because the genospecies of *B. burgdorferi* that cause Lyme disease in North America are different from those that cause Lyme borreliosis in Eurasia, recommendations were based, whenever possible, on studies conducted in the United States.

In the treatment of this 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 of penetration into the infected sites, and clinical studies to support the treatment regimen. The reader is referred to other sources for information on diagnostic aspects of Lyme disease [3–9].

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 [10]. If exposure to *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. The use of protective clothing (shirt tucked into pants and pants tucked into socks) may interfere with

attachment by ticks by increasing the time required for ticks to find exposed skin, thus facilitating their recognition and removal. By wearing light-colored clothing (to provide a background with which the tick contrasts), persons in areas of endemicity may also be more likely to see (and remove) ticks before they have attached.

Daily inspections of the entire body to locate (and remove) ticks also provide an opportunity to prevent transmission of tick-borne infections [11, 12]. Attached ticks should be removed promptly with fine-toothed forceps, if possible [13]. Tick and insect repellents applied to the skin and clothing provide additional protection [10, 14, 15].

Tick Bites and Prophylaxis

Primary Management Options

For patients who remove attached ticks, we considered the following management options: (1) treating all such persons; (2) treating only persons believed to be at high risk (e.g., those removing a nymphal or adult vector tick [*I. scapularis* or *I. pacificus*] after 48 h of attachment); (3) treating only persons who develop erythema migrans or other clinical signs and symptoms of tick-borne infection; and (4) treating all persons who seroconvert from negativity to positivity (optimally with a 4-fold increase in titer) for serum antibodies to *B. burgdorferi* (acute and follow-up blood specimens from all persons who are bitten would need to be collected and tested for antibodies in paired specimens).

Outcome

The panel weighed both the risks and the consequences of developing Lyme disease (including the risk of late complications) for persons bitten by vector ticks *(I. scapularis* or *I. pacificus)* against the cost and adverse effects of prophylactic antimicrobials. The effect of the different strategies on quality of life was considered. In addition, we considered the effect of the recent licensing of a recombinant OspA vaccine for prevention of Lyme disease [16]. The principal desired outcome is prevention of Lyme disease. Another desired outcome is the prevention of other *Ixodes*-borne illnesses, including babesiosis and HGE. Concurrent infection and disease with these organisms have been described [17–19].

Evidence

Option 1: treating with antimicrobials all persons who remove vector ticks (I. scapularis *or* I. pacificus) *that have become attached.* Although some practitioners routinely treat patients that have been bitten by *I. scapularis* [20], several prospective, randomized double-blind clinical trials involving persons who were bitten by *I. scapularis* ticks and then were treated with placebo, penicillin, tetracycline, or amoxicillin each led to conclusions that routine antimicrobial prophylaxis is not warranted [21–23]. A meta-analysis of these studies (in which >600 persons were enrolled) did not indicate that antimicrobial prophylaxis is effective (pooled OR, 0.0; 95% CI, 0.0–1.5; $P = .12$) [24]. The authors of the meta-analysis estimated that if amoxicillin rather than doxycycline were used (to enable small children and pregnant or lactating women to receive prophylaxis), 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 [24].

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 adverse effects of the antimicrobials used for prophylaxis were reported, the risk of acquiring Lyme disease after a tick bite was no different than the risk of developing adverse effects from the prophylactic antibiotics [21, 22].

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 ≥.036 and should be considered when the theoretical probability ranges from .01 to .035 [25]. Many experts, however, disagree with key assumptions in the model. Furthermore, doxycycline is relatively contraindicated for women who are either pregnant or breast-feeding, as well as for children aged <8 years.

Some practitioners prescribe a 10-to-14-day course of amoxicillin for pregnant women who have been bitten by *I. scapularis*, because case reports have suggested that adverse outcomes for the fetus may be associated with pregnancies complicated by Lyme borreliosis [26]. Increasing data from clinical and epidemiological studies, however, suggest that favorable outcomes can be expected when pregnant women with Lyme borreliosis are treated with standard antibiotic regimens [27–29].

In addition to *B. burgdorferi,* other potential pathogens may be present in *I. scapularis* ticks [30, 31]. Babesiosis and HGE can occur independently or together with Lyme disease [17, 18, 32]. Administration of doxycycline is effective in the treatment of patients with HGE [33] but is not recommended as therapy for babesiosis. There are no published clinical data regarding the efficacy of prophylaxis with doxycycline against either of these infections.

Option 2: treating with antimicrobials only persons believed to be at high risk (e.g., those who have removed a nymphal or adult vector tick [I. scapularis *or* I. pacificus] *after 48 h of attachment).* Entomological studies have shown that *B. burgdorferi* is rarely transmitted by *I. scapularis* within the first 48 h of attachment to laboratory animals [11, 12]. This "grace period" is required for spirochetes to migrate from the gut into the salivary glands of infected ticks once feeding commences [34]. Thus, ticks that have been attached for <48 h theoretically cannot transmit *B. burgdorferi* infection. However, this is not true for HGE or babesiosis, since the organisms that cause these diseases are

already present in the salivary glands before feeding (D. Fish, unpublished data, and [35]).

The option of treating selectively persons with "high-risk" tick bites to prevent Lyme disease assumes that the species, stage, degree of engorgement, and infection status of the tick, as well as the probability of transmission of infection, can be readily ascertained. This is rarely true. 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 [36, 37]. Methods for determining the infection status of ticks removed from patients are experimental and are not standardized. One study found that patients who removed partially engorged ticks that were calculated to have been attached for ≥72 h were significantly more likely to develop *B. burgdorferi* infection than were patients who removed ticks that had been attached for an estimated duration of <72 h ($P = .008$) [37]. However, even if the risk of Lyme disease is increased with partially engorged ticks, no study has demonstrated that antimicrobials are effective in reducing the risk of infection after a tick bite.

Option 3: treating with antimicrobials only persons who develop erythema migrans or other clinical manifestations of Lyme disease or other tick-transmitted diseases. The great majority of persons with *B. burgdorferi* infection present with erythema migrans [16, 38–40]. Since primary erythema migrans lesions occur at the site of a tick bite [41–44], a person who removes a tick would be likely to detect and to seek care for a rash that subsequently develops at that location. Patients who develop fever in the absence of erythema migrans after an *Ixodes* tick bite should be evaluated for HGE and/or babesiosis in areas where these infections are endemic [33, 45, 46].

In a placebo-treated population observed prospectively in a large, multicenter vaccine trial, some volunteers developed serological evidence of asymptomatic *B. burgdorferi* infection [16]. Whether antibiotic therapy is beneficial for such patients is unknown, a question in need of further study. (See next paragraph [option 4] for caveats concerning serological diagnosis.)

Option 4: treating with antimicrobials all persons who seroconvert from negativity to positivity for serum antibodies to B. burgdorferi when acute and follow-up serum samples are tested simultaneously. Although assessment of acute- and convalescent-phase serologies is a standard means of identifying individuals with a variety of infectious diseases, the utility of this approach for identifying infection with *B. burgdorferi* following a tick bite is unknown. Present serological assays for Lyme disease have substantial limitations [3–7], and their use is not recommended for screening of persons lacking objective manifestations of Lyme disease [3, 4, 6, 7].

Recommendations

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

Routine use of either antimicrobial prophylaxis (E-I) or serological tests (D-III) after a tick bite is not recommended. Some experts recommend antibiotic therapy for patients bitten by *I. scapularis* ticks that are estimated to have been attached for >48 h (on the basis of the degree of engorgement of the tick with blood), in conjunction with epidemiological information regarding the prevalence of tick-transmitted diseases (C-III). However, accurate determinations of tick species and degree of engorgement are not routinely possible, and data are insufficient to demonstrate efficacy of antimicrobials in this setting.

Persons who remove attached ticks should be monitored closely for signs and symptoms of tick-borne diseases for up to 30 days and specifically for the occurrence of a skin lesion at the site of the tick bite (which may suggest Lyme disease) or a temperature >38°C (which may suggest HGE or babesiosis). Persons who develop a skin lesion or other illness within 1 month after removing an attached tick should promptly seek medical attention for assessment of the possibility of having acquired a tick-borne disease (A-II).

Health care practitioners, particularly those in areas where Lyme disease is endemic, should become familiar with the clinical manifestations of and recommended practices for testing and therapy for Lyme disease, as well as for HGE and babesiosis (A-III).

Testing of ticks for tick-borne infectious organisms is not recommended, except in research studies (D-III).

Prior vaccination with the recently licensed recombinant OspA vaccine preparation reduces the risk of developing Lyme disease associated with tick bites but should not alter the above recommendations (A-I).

Early Lyme Disease

Primary Management Options

We considered the following management options for early Lyme disease: oral antimicrobial therapy for early localized infection (i.e., solitary erythema migrans) and oral versus iv therapy for cases of early disseminated infection (i.e., patients presenting with multiple erythema migrans lesions, carditis, cranial-nerve palsy, meningitis, or acute radiculopathy). Borrelial lymphocytoma was not addressed because of its rarity in North America (its primary causative organism, *Borrelia afzelii,* is an exclusively Eurasian genospecies).

Outcome

The panel weighed both the risks and the consequences of developing late complications of Lyme disease and the possible adverse effects of antimicrobial therapy. The desired outcome is to resolve the symptoms and signs of early Lyme disease and to prevent late complications.

Evidence

At least 7 randomized prospective trials have addressed the treatment of early Lyme disease in the United States [47–53]. All studies used erythema migrans as the disease-defining criterion. Six studies recruited patients with either localized or disseminated early Lyme disease [47–52], whereas 1 study required disseminated early disease for enrollment [53]. Differing criteria were used to define treatment success and failure in the various studies. Most studies defined "failure" by the occurrence of objective clinical manifestations, but subjective symptoms were considered evidence of treatment failure in some studies.

The etiology of residual patient complaints after treatment may include an inflammatory response, unrelated to active infection, or alternative disease processes. Failure rates were not considered in the context of background complaints in an otherwise "healthy" population. For example, in a recent random telephone survey collecting self-reported health information, the prevalence of chronic joint symptoms in adults ranged from 12.3% to 22.7% [54]. In a study of adult members in a health maintenance organization in Seattle, ~20% reported fatigue of at least 6 months' duration that interfered with normal activities [55]. Twelve percent of a control group of children without Lyme disease in another study mentioned fatigue as a symptom [56]. In rheumatology practice, a prevalence of 15%–20% for fibromyalgia is common [57]. Nearly 85% of the general population may experience at least 1 somatic symptom in a 6-week period, and 81% of healthy university students and hospital staff members described at least 1 such symptom over a 3-day interval [58, 59]. Thus, the occurrence of arthralgia, myalgia, and fatigue after treatment for early Lyme disease must be evaluated in the context of background complaints for a significant proportion of patients.

In addition, the possibility of coinfection with other pathogens such as *Babesia microti* and the *Ehrlichia* species that causes HGE was not considered in any of the treatment studies of early Lyme disease. In a separate study in an area in which babesiosis is endemic, most patients who had residual complaints after treatment for early Lyme disease had evidence of coinfection with *B. microti* [17]. Specific treatment with antiparasitic agents directed against this microorganism was effective in diminishing symptoms in 1 study [60].

The first randomized clinical trial of treatment of erythema migrans compared erythromycin, tetracycline, and penicillin at dosages of 250 mg 4 times daily for 10 days and included 112 adult patients [47]. Signs and symptoms after treatment were considered to be either "minor" (headache, fatigue, supraventricular tachycardia, arthralgias, brief arthritis of <2 weeks' duration, or isolated facial palsy) or "major" (meningitis, meningoencephalitis, carditis, or recurrent attacks of arthritis). Approximately 15% of patients had transient intensification of symptoms during the first 24 h of therapy, consistent with a Jarisch-Herxheimer reaction. Erythema migrans and its associated symptoms resolved significantly faster in patients treated with penicillin or tetracycline than in patients treated with erythromycin ($P < .05$). In addition, treatment with tetracycline or penicillin was associated with a lower rate of occurrence of "major" manifestations by these criteria, compared with the occurrence rate associated with erythromycin.

Overall, "minor" posttreatment signs and symptoms occurred in ~45% of patients. Extending therapy to 20 days with tetracycline in a subsequent study by the same investigators had no effect on the frequency of posttreatment symptoms [47]. The results of these studies supported the findings of an earlier open trial of oral penicillin therapy [61]. It could be concluded that erythema migrans was responsive to antibiotic treatment but optimal therapy was not defined.

Subsequent small studies found that doxycycline and amoxicillin (plus probenecid), which are the tetracycline and β-lactam preparations most commonly prescribed in current clinical practice for patients with erythema migrans, were effective therapies, and that the efficacies of each drug regimen were similar [48, 49].

A multicenter study that compared cefuroxime axetil (500 mg twice daily for 20 days) with doxycycline (100 mg 3 times daily for 20 days) in 123 patients with erythema migrans demonstrated satisfactory outcomes for ~90% of patients followed for 1 year after treatment [50]. Seventy-one percent of patients in the cefuroxime group and 76% in the doxycycline group were completely cured, whereas 19% and 16% of patients, respectively, had persistent subjective complaints but their conditions improved. Although treatment was considered to have failed for 10% of patients, most of these patients did not have objective evidence of continuing active infection.

A second multicenter study, in which 232 patients with erythema migrans were randomized to receive either cefuroxime or doxycycline for 20 days, confirmed that the 2 drugs had comparable efficacy [51]. Consistent with earlier reports, a Jarisch-Herxheimer–like reaction occurred during the first 24 h of therapy in 12% of patients in each treatment group.

A multicenter, double-blind, randomized prospective trial compared azithromycin (500 mg once daily for 7 days) with amoxicillin (500 mg 3 times daily for 20 days) in the treatment of patients with erythema migrans [52]. Amoxicillin was found to be significantly more effective than azithromycin in resolving the acute manifestations of erythema migrans completely and in preventing relapse within a 6-month period. Of 217 evaluable patients, only 4% of those treated with amoxicillin relapsed,

Table 3. Recommended antimicrobial regimens for treatment of patients with Lyme disease.

Recommendation, drug	Dosage for adults	Dosage for children
Preferred oral		
Amoxicillin	500 mg t.i.d.	50 mg/kg/d divided into 3 doses (maximum, 500 mg/dose)
Doxycycline	100 mg b.i.d. [a]	Age <8 y: not recommended; age ≥8 y: 1–2 mg/kg b.i.d. (maximum, 100 mg/dose)
Alternative oral		
Cefuroxime axetil	500 mg b.i.d.	30 mg/kg/d divided into 2 doses (maximum, 500 mg/dose)
Preferred parenteral		
Ceftriaxone	2 g iv once daily	75–100 mg/kg iv per day in a single dose (maximum, 2 g)
Alternative parenteral		
Cefotaxime	2 g iv t.i.d.	150–200 mg/kg/d iv divided into 3 or 4 doses (maximum, 6 g/d)
Penicillin G	18–24 million units iv/d divided into doses given q4h[b]	200,000–400,000 units/kg/d, divided into doses given q4h[b] (maximum, 18–24 million units/d)

[a] Tetracyclines are relatively contraindicated for pregnant or lactating women.
[b] The penicillin dosage should be reduced for patients with impaired renal function.

compared with 16% of those treated with azithromycin (P = .005). A higher symptom score before treatment correlated with persistent symptoms after treatment.

Only 1 study has specifically addressed the treatment of acute disseminated nonneurological Lyme disease. This prospective, randomized multicenter trial revealed that in the absence of clinically apparent CNS involvement, oral doxycycline (100 mg twice daily for 3 weeks) was similar in efficacy to iv ceftriaxone (2 g daily for 2 weeks) [53].

In most of the controlled trials, patients assigned to be treated with either doxycycline or amoxicillin received therapy for ~3 weeks. However, similar success rates have been reported in studies in which 14-day treatment courses with these antibiotics were used [62, 63]. Although none of the prospective studies included pregnant patients, there are no data to suggest that these patients should be treated differently from other patients with Lyme disease, except that tetracycline therapy should be avoided [64].

Several conclusions can be drawn from these trials. Doxycycline, amoxicillin, and cefuroxime axetil are efficacious in the treatment of early Lyme disease. Most patients respond promptly and completely. Some individuals have persistent subjective complaints despite therapy that otherwise appears curative. Less than 10% of infected individuals fail to respond to antibiotic therapy, as evidenced by objective manifestations of persistent infection, and repeat treatment is rarely 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. Coinfection with other tick-borne infections or inadequately recognized CNS infection at the time of institution of antibiotic therapy may be the explanation for antibiotic failures in some circumstances.

Despite excellent activity against *B. burgdorferi* in vitro [65], the macrolides that have been studied systematically, namely, erythromycin [47] and azithromycin [52] in the United States and roxithromycin [66] in Europe, are less effective than other therapeutic agents (reviewed in [67]). Clarithromycin has not been studied in a controlled trial [68].

All antimicrobials effective in early Lyme disease are associated with a low frequency of serious adverse effects. Drug-induced rashes occur with both amoxicillin [52] and cefuroxime [50, 51]. Doxycycline may cause photosensitivity [50, 51], which may be problematic since 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. In addition, doxycycline is relatively contraindicated for children aged <8 years and for women who are pregnant or breast-feeding.

Cefuroxime axetil is much more expensive than doxycycline or amoxicillin; therefore, its administration is not recommended as first-line therapy (table 3).

In contrast to the second-generation cephalosporin cefuroxime and certain third-generation cephalosporins (e.g., ceftriaxone), first-generation cephalosporins such as cephalexin are inactive in vitro against *B. burgdorferi* and are ineffective clinically [69, 70].

Available evidence regarding treatment of acute neurological Lyme disease in the United States is based on small case series. Patients with Lyme meningitis or acute radiculopathy respond to iv penicillin [71], although ceftriaxone is more widely used for this indication because of its convenient once-daily dosing [72]. European trials have found iv penicillin to be as effective as cefotaxime or ceftriaxone [73, 74] and cefotaxime to be as effective as ceftriaxone [75]. Doxycycline administered orally or iv has also been used successfully in Europe [76–79], but

Table 4. Recommended therapy for patients with Lyme disease.

Indication	Treatment	Duration, d
Tick bite	None recommended; observe	
Erythema migrans	Oral regimen[a,b]	14–21
Acute neurological disease		
Meningitis or radiculopathy	Parenteral regimen[a,c]	14–28
Cranial-nerve palsy	Oral regimen[a]	14–21
Cardiac disease		
1st or 2d degree heart block	Oral regimen[a]	14–21
3d degree heart block	Parenteral regimen[a,d]	14–21
Late disease		
Arthritis without neurological disease	Oral regimen[a]	28
Recurrent arthritis after oral regimen	Oral regimen[a] or	28
	parenteral regimen[a]	14–28
Persistent arthritis after 2 courses of antibiotics	Symptomatic therapy	
CNS or peripheral nervous system disease	Parenteral regimen[a]	14–28
Chronic Lyme disease or post–Lyme disease syndrome	Symptomatic therapy[e]	

[a] See table 3.

[b] For adult patients who are intolerant of amoxicillin, doxycycline, and cefuroxime axetil, alternatives are azithromycin (500 mg orally daily for 7–10 days), erythromycin (500 mg orally 4 times per day for 14–21 days), or clarithromycin (500 mg orally twice daily for 14–21 days [except during pregnancy]). The recommended dosages of these agents for children are as follows: azithromycin, 10 mg/kg daily (maximum, 500 mg/d); erythromycin, 12.5 mg/kg 4 times daily (maximum, 500 mg/dose); clarithromycin, 7.5 mg/kg twice daily (maximum, 500 mg/dose). Patients treated with macrolides should be closely followed.

[c] For nonpregnant adult patients intolerant of both penicillin and cephalosporins, doxycycline (200–400 mg/d orally [or iv if oral medications cannot be taken], divided into 2 doses) may be adequate.

[d] A temporary pacemaker may be required.

[e] See the discussion of Chronic Lyme Disease or Post–Lyme Disease Syndrome in the text.

experience with this agent for the treatment of patients with meningitis due to Lyme disease in the United States is limited.

Cranial-nerve palsy has been treated satisfactorily with oral antibiotics [38, 80]. There was disagreement among panel members, however, on the neurological evaluation of patients with seventh-cranial-nerve palsy. Some members perform a lumbar puncture for all individuals with Lyme disease–associated seventh-cranial-nerve palsy. Others reserve lumbar puncture for those patients for whom there is strong clinical evidence of CNS involvement (e.g., severe headache or nuchal rigidity).

Patients whose CSF examinations yield normal findings may be treated with the same regimens used for patients with erythema migrans, whereas those with clinical and laboratory evidence of CNS involvement should be treated with regimens effective against meningitis. Since the frequency and rate of recovery of seventh-cranial-nerve palsy in patients treated with antibiotics appear to be the same as in untreated patients, the principal goal of therapy is to prevent the development of later clinical manifestations [80].

No studies have specifically addressed the treatment of carditis. Cardiac involvement in North American Lyme disease primarily manifests as atrioventricular heart block and usually occurs within the first several weeks of infection, often in conjunction with erythema migrans [81]. First- and second-degree atrioventricular heart blocks resolve during therapy with oral antibiotics. Because of the potential for life-threatening complications, patients with third-degree atrioventricular heart block should be closely monitored in the hospital. Most panel members treat such patients with iv ceftriaxone, although there is no evidence that parenteral therapy is more effective than oral therapy. Insertion of a temporary pacemaker may be necessary for patients with third-degree heart block in some circumstances.

Recommendations

Administration of doxycycline (100 mg twice daily) or amoxicillin (500 mg 3 times daily) for 14–21 days is recommended for treatment of early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of neurological involvement or third-degree atrioventricular heart block (tables 3 and 4) (A-I). In prospective studies, these agents have been shown to be effective in the treatment of erythema migrans and associated symptoms.

Doxycycline has the advantage of being efficacious for treatment of HGE, which may occur simultaneously with early Lyme disease. Doxycycline is relatively contraindicated during pregnancy or lactation and for children aged <8 years. Because of its higher cost, cefuroxime axetil, which is as effective as doxycycline in the treatment of erythema migrans (A-I), should be reserved as an alternative agent for those patients who can take neither doxycycline nor amoxicillin. For children, amoxicillin or doxycycline (for those aged ≥8 years) is recommended (tables 3 and 4) (B-II). Cefuroxime axetil is an acceptable alternative agent (B-III).

Administration of macrolide antibiotics is not recommended as first-line therapy for early Lyme disease (E-I). When used, they should be reserved for patients who are intolerant of amoxicillin, doxycycline, and cefuroxime axetil (table 4). Patients treated with macrolides should be closely followed.

Ceftriaxone (2 g iv daily), although effective, is not superior to oral agents and is therefore not recommended for treatment of Lyme disease in the absence of neurological involvement or third-degree atrioventricular heart block (E-I).

The use of ceftriaxone (2 g once daily iv for 14–28 days) in early Lyme disease is recommended for acute neurological disease manifested by meningitis or radiculopathy (tables 3 and 4) (B-II). Parenteral therapy with penicillin G or cefotaxime may be a satisfactory alternative (B-II). For adult patients who are intolerant of both penicillin and cephalosporins, doxycycline (200–400 mg/d in 2 divided doses orally [or iv if the patient is unable to take oral medications]) for 14–28 days may be adequate (B-II).

For children, iv ceftriaxone (B-II) or cefotaxime (B-III) is recommended (tables 3 and 4); penicillin G given iv is an alternative (B-II).

Patients with first- or second-degree atrioventricular heart block associated with early Lyme disease should be treated in the same manner as patients with erythema migrans without carditis (tables 3 and 4) (B-III). We recommend that patients with third-degree atrioventricular heart block be treated with parenteral antibiotics such as ceftriaxone (table 3) in the hospital, although there are no clinical trial data to support this recommendation (B-III). A temporary pacemaker may also be required.

Although antibiotic treatment does not hasten the resolution of seventh-cranial-nerve palsy associated with *B. burgdorferi* infection, antibiotics should be given to prevent further sequelae (B-II). There was disagreement among panel members on the neurological evaluation of patients with seventh-cranial-nerve palsy. Some members perform a CSF examination of all patients with seventh-cranial-nerve palsy, whereas others reserve lumbar puncture for those in whom there is strong clinical evidence of CNS involvement (e.g., severe headache or nuchal rigidity).

Patients whose CSF examinations yield normal findings may be treated with the same regimens used for patients with erythema migrans (B-III). Those with clinical and laboratory evidence of CNS involvement should be treated with regimens effective against meningitis (tables 3 and 4) (B-II).

Treatment for pregnant patients can be identical to that for nonpregnant patients with the same disease manifestation, except that tetracyclines should be avoided (B-III).

Late Lyme Disease

Options

The panel considered various oral and parenteral antimicrobial regimens for treatment of the late manifestations of Lyme disease. Late manifestations include arthritis (oligoarticular), encephalopathy (characterized primarily by memory deficit, irritability, and somnolence), and neuropathy (manifested primarily by distal paresthesias or radicular pain). Acrodermatitis chronica atrophicans was not addressed because of its rarity in North America (its primary causative organism, *B. afzelii,* is an exclusively Eurasian genospecies). Because of the lack of evaluable data on ophthalmologic complications, which are very rare, the panel was unable to make recommendations concerning keratitis and other possible ocular manifestations of Lyme disease.

The response to treatment of late manifestations is typically slow, and improvement or resolution of symptoms may take weeks or months. However, appropriate antibiotic treatment results in eventual recovery in most patients.

Outcome

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 of antibiotic therapy. It has not been shown nor is it anticipated that *B. burgdorferi* will develop resistance to antibiotics, but the indiscriminate use of antibiotics exacerbates the problem of antibiotic-resistant community-acquired infections with other bacteria.

Evidence

The first study of antibiotic treatment in patients with Lyme arthritis was initiated in 1980 [82]. The regimens tested were those used for the treatment of tertiary syphilis, and the study design was a double-blind, placebo-controlled trial. The patients had intermittent or chronic Lyme arthritis primarily affecting the knees, and all patients were subsequently shown to be seropositive for antibodies to *B. burgdorferi*. In the first phase of the study, 40 patients were randomized to receive im benzathine penicillin G (7.2 million units) or placebo. In the second phase, 20 patients were treated with iv penicillin G (20 million units per day for 10 days). Of the 20 patients who received im benzathine penicillin, 7 (35%) had complete resolution of joint involvement soon after treatment, compared with none of 20 patients who were given placebo ($P < 0.02$). Of the 20 patients treated the following year with iv penicillin G, 11 (55%) had complete resolution of the arthritis soon after treatment. It was concluded that parenteral penicillin was often effective in the treatment of Lyme arthritis, but a number of patients failed to respond.

Subsequently, a series of studies was begun to test the efficacy of iv ceftriaxone in the treatment of late Lyme disease. In comparison with penicillin, the advantages of ceftriaxone are its excellent CSF penetration and long serum half-life, which permits once-a-day dosing for outpatient management. In 1987, a case series of 7 patients with Lyme arthritis or chronic neuroborreliosis, who were refractory to oral or iv penicillin therapy, were then treated with iv ceftriaxone (2 or 4 g/d for 2

weeks) [83]. All 5 patients who had arthritis responded to ceftriaxone therapy, and for 5 of the 6 patients with limb paresthesias, a reduction in symptoms and improvement of nerve-conduction study findings were noted.

In a follow-up study, 23 patients with Lyme arthritis or late neuroborreliosis were randomly assigned to receive penicillin (20 million units per day iv for 10 days) or ceftriaxone (4 g/d iv for 14 days) [84]. 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 iv penicillin continued to have fatigue, memory deficit, or recurrent oligoarthritis. For 4 of these 5 patients, symptoms resolved after repeat treatment with ceftriaxone.

In a subsequent study, 31 patients with Lyme arthritis or chronic neuroborreliosis were randomly assigned to receive 2 or 4 g/d of ceftriaxone for 2 weeks [84]. After treatment, 3 of the 31 patients had persistent encephalopathy, 2 had persistent neuropathy, and 3 had no diminishment of their arthritis. The overall frequency of persistent symptoms among patients was 13%, which was similar in both treatment groups. In an open-label, randomized, multicenter study, 143 evaluable patients with manifestations of late Lyme disease, primarily Lyme arthritis, were treated with iv ceftriaxone (2 g/d for either 2 or 4 weeks) [85]. In 76% of those treated for 2 weeks and 70% of those treated for 4 weeks, symptoms resolved after treatment (the *P* value was not significant). The most common persistent symptoms were arthralgia, pain, weakness, malaise, and fatigue.

The principal conclusions of these 2 studies were that the efficacy of iv ceftriaxone at a dosage of 2 g/d was equivalent to that at a dosage of 4 g/d, and a 2-week course was as efficacious as a 4-week course for the treatment of late Lyme disease. However, some patients had persistent symptoms despite ceftriaxone treatment.

At the same time that studies were being carried out 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, 14 children with Lyme arthritis were treated orally with either phenoxymethyl penicillin or tetracycline for 10–30 days [86]. Thirteen experienced no further attacks of arthritis at follow-up at 4–24 months after treatment, whereas 1 patient's symptoms did not resolve until after a 10-day course of iv penicillin.

From 1986 through 1991, 48 adult and pediatric patients with Lyme arthritis were randomly assigned to receive either doxycycline (100 mg orally twice a day) or amoxicillin and probenecid (500 mg of each 4 times a day), in each instance for 30 days [87]. Eighteen of the 20 evaluable patients treated with doxycycline and 16 of the 18 evaluable patients who completed the amoxicillin regimen had resolution of arthritis within 13 months after enrollment in the study. However, neuroborreliosis later developed in 5 patients, 4 of whom were treated with 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 [72, 88].

In retrospect, it was noted that all 5 patients reported subtle distal paresthesias or memory impairment at the time of enrollment. It was concluded that patients with Lyme arthritis can usually be treated successfully with oral antibiotics, but practitioners must be aware of subtle neurological symptoms that may require treatment with iv antibiotics.

In a cost-effectiveness analysis, iv therapy was found to be no more cost-effective than oral therapy for patients with Lyme arthritis; iv therapy was more likely to result in serious complications and was substantially more expensive [89]. Therefore, the authors concluded that oral antibiotics are to be preferred in the initial treatment of Lyme arthritis in the absence of concomitant neurological involvement.

Not all patients with Lyme arthritis respond to antibiotic therapy. In 1 treatment trial, none of the 16 patients with Lyme arthritis who were treated with iv ceftriaxone (2 g daily for 2 weeks) had resolution of arthritis within 3 months after completion of therapy [87]. That study's enrollment requirement of continuous joint swelling for at least 3 months despite treatment with other recommended parenteral or oral antibiotic regimens differed from requirements in previous studies.

These 16 patients were also found to have distinctive immunogenetic and immune markers, including a high frequency of human leukocyte antigen–DR4 specificity 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 eradication of the spirochete [90]. The observation that there are epitopes of OspA that cross-react with human leukocyte function–associated antigen-1 [91] suggests that immune phenomena might explain the persistent joint inflammation in these cases.

Arthroscopic synovectomy has been used successfully in the treatment of patients whose arthritis persists despite antibiotic therapy. 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 following surgery or soon thereafter [92]. The remaining 4 patients (20%) had persistent or recurrent synovitis.

Patients with late Lyme disease associated with prominent neurological features also respond to antibiotic therapy. In trials conducted from 1987 through 1989, 27 adult patients with Lyme encephalopathy, polyneuropathy, or both were treated with iv ceftriaxone (2 g/d for 2 weeks) [93]. 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 response was measured 6 months after treatment, 17 patients (63%) had uncomplicated improvement, 6 (22%) had improvement but then relapsed, and 4 (15%) had no change in their condition.

In a subsequent study, the same investigators treated 18 adult patients with Lyme encephalopathy with iv ceftriaxone (2 g/d for 30 days) [94]. Of the 18 patients, 16 had abnormal verbal or visual memory scores on neuropsychological tests and 16 had CSF abnormalities, most commonly production of intrathecal antibody to *B. burgdorferi* or an elevated total protein level. As determined 6 months after treatment, 14 (93%) of the 15 patients examined had diminished symptoms, and verbal memory scores for the 15 patients were significantly improved ($P < .01$). The total CSF protein values were significantly less for the 10 patients who had follow-up analyses ($P < .05$). At 12–24 months, all patients' conditions were back to normal or improved (1 of the 18 patients was given repeat treatment after 8 months).

It was concluded that Lyme encephalopathy may be associated with active infection of the nervous system and that the infection in most patients can be treated successfully with a 30-day course of iv ceftriaxone. Whether a 30-day course is superior to 14 days of treatment is unclear. Although the data are much more limited, the conditions of children with neurocognitive abnormalities attributed to Lyme disease also appear to improve after 2–4 weeks of iv ceftriaxone [95].

The third-generation cephalosporin cefotaxime has been tested in Europe and has been found to be effective in the treatment of late Lyme disease [96]. Although cefotaxime has to be administered 3–4 times daily (compared with once daily administration of ceftriaxone), it does not cause the biliary complications that have been associated with ceftriaxone therapy [97].

Recommendations

Lyme arthritis. Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally or iv (tables 3 and 4). Administration of doxycycline or amoxicillin, in each instance for 28 days, is recommended for patients without clinical evidence of neurological disease (B-II). For children, doxycycline (for those aged ≥8 years) or amoxicillin is recommended (tables 3 and 4) (B-II). Oral therapy is easier to administer than iv antibiotics, is associated with fewer serious complications, and is considerably less expensive. Its disadvantage is that some patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require iv therapy for successful treatment. Further controlled trials are needed to compare oral with iv therapy.

Neurological evaluation, including lumbar puncture, should be done for patients for whom there is a strong clinical suspicion of neurological involvement. Patients with arthritis and objective evidence of neurological disease should receive parenteral therapy with ceftriaxone (tables 3 and 4) (A-II). Alternative parenteral agents include cefotaxime (B-III) and penicillin G (B-II). The long-acting benzathine preparation of penicillin achieves only low levels in the blood and therefore is not recommended (D-III). For children, ceftriaxone iv (B-III) or cefotaxime (B-III) is recommended (tables 3 and 4); penicillin G administered iv is an alternative (B-III).

For patients who have persistent or recurrent joint swelling after recommended courses of antibiotic therapy, we recommend repeat treatment with another 4-week course of oral antibiotics or with a 2- to 4-week course of ceftriaxone iv (tables 3 and 4) (B-III). Clinicians should consider waiting several months before initiating repeat treatment with antimicrobial agents, because of the anticipated slow resolution of inflammation after treatment. If patients have persistent arthritis despite 2 courses of oral therapy or 1 course of iv therapy, symptomatic treatment with nonsteroidal anti-inflammatory agents is recommended; intra-articular steroids may also be of benefit (B-III). If persistent synovitis is associated with significant pain or if it limits function, arthroscopic synovectomy can reduce the period of joint inflammation (B-II).

Late neuroborreliosis affecting the CNS or the peripheral nervous system. For patients with late neurological disease affecting the CNS or peripheral nervous system, treatment with ceftriaxone (2 g once a day iv for 2–4 weeks) is recommended (tables 3 and 4) (B-II). Alternative parenteral therapy may include administration of cefotaxime (B-II) or penicillin G (B-II). Response to treatment is usually slow and may be incomplete. However, unless relapse is shown by reliable objective measures, repeat treatment is not recommended. For children, treatment with ceftriaxone is recommended (tables 3 and 4) (B-II). Cefotaxime or penicillin G administered iv are alternatives (B-II).

Chronic Lyme Disease or Post–Lyme Disease Syndrome

Following an episode of Lyme disease that is treated appropriately, some persons have a variety of subjective complaints (such as myalgia, arthralgia, or fatigue). Some of these patients have been classified as having "chronic Lyme disease" or "post–Lyme disease syndrome," which are poorly defined entities. These patients appear to be a heterogeneous group. Although European patients rarely have been reported to have residual infection (or perhaps reinfection) with *B. burgdorferi* [98], this has yet to be substantiated either in a large series of appropriately treated European patients or in a study of North American patients. Residual subjective symptoms that last weeks or months also may persist after other medical diseases (both infectious and noninfectious). It has also been recognized that the prevalence of fatigue and/or arthralgias in the general population is >10% [52–56, 58, 59, 99].

In areas of endemicity, coinfection with *B. microti* or the *Ehrlichia* species that causes HGE may explain persistent symptoms for a small number of these patients [17, 19]. Randomized controlled studies of treatment of patients who remain unwell after standard courses of antibiotic therapy for Lyme disease are in progress. To date, there are no convincing published data

showing that repeated or prolonged courses of oral or iv antimicrobial therapy are effective for such patients. The consensus of the IDSA expert-panel members is that there is insufficient evidence to regard "chronic Lyme disease" as a separate diagnostic entity.

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