PEDIATRICS PERSPECTIVES

Management of Pediatric Lyme Disease: Updates From 2020 Lyme Guidelines

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Lyme arthritis first was described in the United States in 1977 after a report of a cluster of children with arthritis living in Old Lyme, Connecticut.[1] In the subsequent 45 years, Lyme disease has come to be recognized as an infectious disease that if left untreated may involve multiple organ systems, including the skin, joints, heart, and nervous system, and is referred to as Lyme borreliosis. The Infectious Diseases Society of America issued guidelines for the management of Lyme disease based on a systematic review of the scientific literature in 2000 and 2006.[2,3] The American Academy of Neurology issued guidelines in 2007 for the treatment of nervous system Lyme disease.[4] Practice guidelines were affirmed in 2010.[5] The current guidelines were published in 2020 by a panel representing the Infectious Diseases Society of America, American Academy of Neurology, and American College of Rheumatology, using the Grading of Recommendations, Assessment, Development and Evaluations approach to determine both certainty of evidence and strength of the recommendations.[6] More than 33 individuals representing 9 societies, as well as patient representatives and a health care consumer representative, participated in the process.

This report extracts recommendations from the 2020 guidelines for the management of pediatric Lyme disease that differ from previous guidelines and reviews treatment recommendations that remain unchanged. Changes in the guidelines include the use of doxycycline in children <8 years of age for postexposure prophylaxis after a nymphal *Ixodes scapularis* tick bite and for treatment of neuroborreliosis. In addition, we review treatment recommendations for erythema migrans, arthritis, and cardiac disease that remain unchanged. Finally, we note the current status of second-generation vaccine development for the prevention of Lyme disease.

INTRODUCTION

In the United States, Lyme borreliosis is caused by the spirochete *Borrelia burgdorferi* sensu stricto (*B burgdorferi* in the strict sense), except for a small number of cases caused by *Borrelia mayonii* in the upper Midwest. Transmission occurs during a bite by an infected tick of the species *I scapularis* in eastern and upper midwestern states or

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Ixodes pacificus in the west coast states. Person-to-person transmission of *B burgdorferi* sensu stricto, including vertical transmission resulting in congenital disease or via transfusion of blood products, has not been documented.

Approximately 35 000 cases of Lyme borreliosis are reported annually to the Centers for Disease Control and Prevention Lyme disease surveillance program, although because of likely underreporting, the true number is estimated to be at least three- to 12-fold higher (>400 000 cases annually).[7] Lyme borreliosis presents a significant disease burden for those living in the endemic regions of the United States, including the Northeast, Mid-Atlantic, and upper Midwest (Fig 1). Minimal, if any, disease occurs in other areas of the United States except in the west coast states, where a low incidence is recognized.

Worldwide, at least 20 different genospecies of *Borrelia* are recognized and collectively, are referred to as *B burgdorferi* sensu lato (*B burgdorferi* in the general sense), although 3 genospecies account for most cases of Lyme borreliosis in humans: *B burgdorferi* sensu stricto, *Borrelia afzelii*, and *Borrelia garinii*. The latter 2 species are found in Europe and Asia and cause certain clinical syndromes such as acrodermatitis chronica atrophicans and borrelial lymphocytoma, which are not seen with *B burgdorferi* sensu stricto infection in North America. On the other hand, Lyme arthritis is much more common in North America than in Europe.

POSTEXPOSURE ANTIMICROBIAL PROPHYLAXIS

Postexposure prophylaxis is recommended for adults largely on the basis of results from a chemoprophylaxis trial published in 2001.[8] Trial results demonstrated that if specific factors are satisfied (the tick is identified as *Ixodes* species, the bite occurs in a highly endemic area, and the tick was attached for at least 36 hours), the benefit of prophylaxis outweighs the risk of a complication from doxycycline. Doxycycline traditionally has not been used in children <8 years of age because of concern about staining of permanent teeth. However, available data indicate this complication has not been associated with doxycycline, in contrast to older tetracyclines.[6] Thus, current guidelines for postexposure prophylaxis (or treatment) of Lyme borreliosis include the use of doxycycline regardless of age.[9] Doxycycline is administered as a single dose at 4.4 mg/kg for children up to a maximum of the adult dose of 200 mg (≥45 kg).

Single-dose postexposure prophylaxis with amoxicillin is not recommended because of its short half-life (~60 minutes) relative to that of doxycycline (16–22 hours). Prophylactic antibiotic therapy is not recommended for a tick bite that is equivocal or considered low risk, but the person should be followed for development of erythema migrans or other manifestations of infection. Other tick-borne infections, such as *Babesia microti*, likely are transmitted in <24 hours, emphasizing the need for prompt tick removal. Whenever possible, avoiding exposure to or prompt removal of ticks is preferred to postexposure prophylaxis.

TREATMENT OF PEDIATRIC ERYTHEMA MIGRANS

A person with a potential tick exposure in an endemic area who develops erythema migrans should be treated on the basis of the clinical findings. Laboratory testing

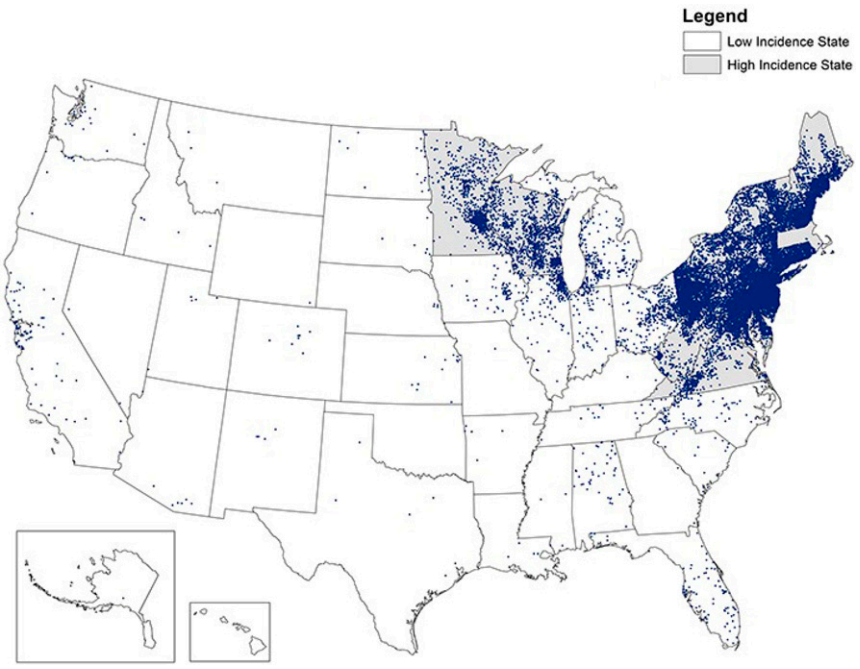

FIGURE 1
Reported cases of Lyme disease: United States, 2019. Each dot represents 1 case of Lyme disease and is placed randomly in the patient's county of residence. The presence of a dot in a state does not necessarily mean that Lyme disease was acquired in that state. (Reprinted from Centers of Disease Control and Prevention. Reported Cases of Lyme Disease—United States, 2019. Available at: https://www.cdc.gov/lyme/datasurveillance/maps-recent.html. Accessed November 22, 2021.)

is not recommended because most people will be seronegative during the early stage of Lyme borreliosis.

Selection of an antimicrobial agent for the treatment of erythema migrans (amoxicillin, doxycycline, cefuroxime axetil, or azithromycin) should be based on the following considerations: the presence of extracutaneous manifestations of infection, particularly neurologic involvement (for which doxycycline is the drug of choice); drug allergy history; drug adverse effects; ability to minimize sun exposure (photosensitivity may be associated with doxycycline use); frequency of administration (doxycycline and cefuroxime are administered twice a day, amoxicillin is administered 3 times a day); and the likelihood of coinfection with *Anaplasma phagocytophilum* or an *Ehrlichia muris*–like agent (which are sensitive to doxycycline but not to β-lactam antibiotics (Table 1). In most circumstances, a child <8 years of age is treated with oral amoxicillin, and a patient >8 years of age is treated with oral doxycycline.

Treatment of erythema migrans results in resolution of the rash within several days of antibiotic initiation and almost always prevents the development of later stages of disease. Among untreated adult patients who had erythema migrans before the cause of the disease was known, ~5% developed Lyme carditis (mainly atrioventricular conduction abnormalities), 15% develop early neuroborreliosis within weeks, and ~60% develop monoarticular or pauciarticular arthritis (mostly large joints, particularly the knees) within months.[10]

MANAGEMENT OF PEDIATRIC LYME ARTHRITIS

Patients with possible Lyme arthritis should undergo serum antibody testing rather than polymerase chain reaction or culture of blood or synovial tissue. For patients with Lyme arthritis, oral antibiotic therapy for 28 days is recommended. As with therapy for erythema migrans, children <8 years of age are usually treated with oral amoxicillin and those >8 years of age are treated with oral doxycycline. For patients with Lyme arthritis who have minimal or no response to the initial course of oral antibiotic therapy, a 2- to 4-week course of intravenous (IV) ceftriaxone is recommended over a second course of oral antibiotic. Although rare, especially in prepubertal children, a postinfectious proliferative synovitis may develop after oral and IV therapy. Referral to a rheumatologist is recommended for consideration of treatment with disease-modifying antirheumatic drugs.

MANAGEMENT OF PEDIATRIC LYME CARDITIS

An electrocardiogram is recommended for patients with signs or symptoms consistent with Lyme carditis, including dyspnea, edema, palpitations, lightheadedness, chest pain, or syncope. Patients with PR interval prolongation >300 milliseconds or other arrhythmias or signs of myopericarditis should be hospitalized for continuous electrocardiographic monitoring. Hospitalized patients with Lyme carditis should be treated with IV ceftriaxone, followed by an oral antibiotic once evidence of clinical improvement is present. An outpatient with Lyme carditis may receive an oral antibiotic instead of an IV antibiotic.

MANAGEMENT OF CHILDREN AND ADOLESCENTS WITH NEUROLOGIC INVOLVEMENT OF LYME BORRELIOSIS

Treatment of neuroborreliosis often is the same whether meningitis is present, so the decision to perform a lumbar puncture should be individualized. Performance of a cerebrospinal fluid analysis in patients with suspected neurologic disease is indicated for excluding bacterial, viral, or other etiologies of inflammation. In addition, children with neuroborreliosis may experience a pseudotumor-like syndrome, which can be diagnosed on the basis of the finding of increased intracranial pressure. Children who present with developmental, behavioral, or psychiatric disorders are not recommended to undergo routine testing for Lyme borreliosis, as *B burgdorferi* infection is unlikely to cause such disorders. For patients with Lyme borreliosis–associated meningitis or cranial neuropathy, oral antibiotic therapy with doxycycline generally is recommended over IV treatment because of ease of administration, a lower likelihood of adverse effects, and evidence of equivalent outcome in European studies.[11] For patients with the very rare condition of Lyme disease encephalomyelitis (parenchymal involvement of the brain or spinal

TABLE 1 Recommended Treatment Regimens for Lyme Disease in Children

Drug	Pediatric Dosing
Oral regimens	
Amoxicillin	50 mg/kg per day in 3 equal doses (maximum 500 mg/dose)
Doxycycline	4.4 mg/kg per day in 2 equal doses (maximum 200 mg/dose)[a]
Cefuroxime axetil	30 mg/kg per day in 2 equal doses (maximum 500 mg/dose)
Azithromycin	10 mg/kg per day in a single daily dose (maximum 500 mg/dose)
IV therapies	
Ceftriaxone	50–75 mg/kg per day in a single dose (maximum 2.0 g/d)
Penicillin G	200 000–400 000 U/kg per day in 6 equal doses (maximum 24 million U/d)

[a] Limited data are available on the safety of doxycycline when used for ≥21 d in children <8 y of age.

cord), IV ceftriaxone is recommended over oral antibiotic therapy. Routine use of corticosteroid therapy for children <16 years of age with cranial neuropathy is not recommended on the basis of lack of evidence of benefit.[12]

Prospects for Lyme Immunization

Once diagnosed, Lyme borreliosis is a treatable disease, but if misdiagnosed or untreated, the infection can result in complications, excessive health care usage, inappropriate long-term antibiotic administration, and overuse of diagnostic testing. Thus, the burden of disease in endemic areas demonstrates the need for effective prevention strategies. Two recombinant vaccines based on the outer surface protein A (OspA) of the spirochete were developed in the 1990s, and one was licensed for prevention of Lyme borreliosis in 1998 for people 15 to 70 years of age living in areas with high rates of disease.[13,14] The licensed vaccine (LYMErix; GlaxoSmithKline) was evaluated in a 3-dose series in a randomized placebo-controlled trial wherein 2 doses were administered in the first year with a booster dose 1 year later. Vaccine efficacy was >75% in the second season of the trial, confirming that serum concentration of antibody against OspA correlated with protection against *B burgdorferi* infection. However, unsubstantiated concerns about adverse reactions contributed to poor sales of the vaccine, and the vaccine was voluntarily withdrawn by the manufacturer in 2002.[15]

In early-phase trials for preexposure disease prevention, researchers currently are evaluating both active immunization with a modified recombinant OspA vaccine or passive immunization with a long-half-life monoclonal antibody. An investigational, multivalent, subunit, adjuvanted Lyme vaccine (VLA15; produced in a collaboration between Valneva and Pfizer) has received fast-track designation by the US Food and Drug Administration and is being evaluated in an observer-blind, placebo-controlled phase 2 trial (ClinicalTrials.gov identifier: NCT04801420) of seropositive and seronegative participants ≥5 years of age treated with a 2- and 3-dose regimen.[16]

As an alternative to active immunization, seasonal passive administration of a protective antibody at the start of tick season could be an effective strategy for prophylaxis in endemic areas.[17] A monoclonal antibody that binds to a protective epitope on OspA may provide protection similar to that of a vaccine. A single dose of a long-half-life antibody at the beginning of the season theoretically would offer immediate protection that persists for the duration of seasonal exposure risk, but the injection would need to be repeated in each subsequent year.

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ABBREVIATIONS

IV: intravenous
OspA: outer surface protein A

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