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Diagnosis, Treatment and Prevention of Pediatric Lyme disease

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ABSTRACT

Lyme disease remains a significant public health challenge in the United States, particularly in the Northeast and Midwest regions, and is likely to increase in the coming years with population growth to suburban areas and warmer weather. Lyme disease is a bacterial infection caused by the spirochete, Borrelia burgdorferi, that is transmitted to humans through deer ticks. The presentation of Lyme disease can involve multiple systems with dermatologic, neurologic, rheumatologic, and cardiac symptoms commonly described. However, there is substantial variation in the presentation of Lyme disease, creating a challenge to diagnosis and treatment. The standard treatment for Lyme disease is administration of antibacterial agents. Although the majority of pediatric patients achieve symptom resolution with treatment, a subset continues to experience fatigue, pain, and psychological disturbances known as post-treatment Lyme disease syndrome. Prevention of Lyme disease largely relies on behavioral measures such as wearing long sleeves and pants and checking for ticks given the absence of an effective vaccine. Prophylactic antibiotic treatment is also highly effective for children who have experienced a Ixodes tick bite, occurring in an endemic region with tick attachment for at least 36 hours. Although Lyme disease disproportionately impacts children, the existing literature primarily focuses on its presentation in adults. In this review, we summarize the latest literature surrounding the diagnosis, treatment, and prevention of Lyme disease with a specific emphasis on pediatric populations and the recent advancements in vaccine development.

Keywords

Diagnosis, Lyme disease, Pediatrics, Treatment, Vaccine.

Introduction

With over 30,000 cases each year, Lyme disease is the most widely diagnosed vector borne illness in the United States [1]. Lyme disease is caused by the bacterium, *Borrelia burgdorferi*, which is transmitted to humans through *Ixodes* ticks, more commonly known as deer ticks [2]. Due to the higher incidence of tick exposure associated with outdoor activities, a significant proportion of those affected by Lyme disease are children aged 5 to 9 [1,3]. With early detection and treatment, the long-term prognosis in this age group is excellent. However, many children present asymptomatically or with nonspecific symptoms, delaying diagnosis. Without early intervention, potentially severe and long-term complications can ensue. Additionally, although the clinical presentation of Lyme disease is similar in children and adults, there are several key distinctions that are important to recognize. The aim of this review is to describe the epidemiology and clinical manifestations of Lyme disease while providing a summary of the current literature pertaining to the diagnosis, treatment, and prevention of pediatric Lyme disease.

Epidemiology of Pediatric Lyme Disease

Although Lyme disease has likely been around for centuries, it was first described in Connecticut in the 1970s [4]. In 1991, Lyme disease was added to the list of notifiable diseases, requiring all cases to be reported to the Centers for Disease Control (CDC) for surveillance [1,2]. During the first year of reporting, 10,000 cases of Lyme disease were reported nationwide [5]. Over the past several decades, numbers have increased, peaking at nearly 43,000 reported cases in 2017 [2]. In 2022, the CDC revised

the reporting criteria for Lyme disease to include only cases confirmed by laboratory testing. Due to challenges surrounding laboratory testing and early diagnosis, Lyme disease cases are likely underreported [6-8]. This is supported in a recent analysis of health insurance claims in the United States from 2010-2018, which found that the true incidence of Lyme disease is likely six to eight times higher than reported cases [9].

There are two tick species that carry *Borrelia burgdorferi* in the United States: *Ixodes scapularis* and *Ixodes pacificus* [1]. The life cycle of these species includes four phases: egg, larvae, nymph, and adult [2]. During the latter three phases, a tick may become infected with *Borrelia burgdorferi* if it feeds on an infected host, typically a small mammal or bird [10]. Although adult ticks prefer to feed on deer, nymphs may feed on humans, further transmitting *Borrelia burgdorferi* [2]. It is widely accepted that a tick must be attached for at least 36 hours in order for a human to contract Lyme disease [11,12].

Due to the geographical distribution of *Ixodes* species, Lyme disease is considered endemic in fourteen states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin [2,13]. Up to 95% of all reported cases occur in these endemic regions, however, recent CDC surveillance data shows increasing rates among neighboring states, a trend that likely reflects human population moves to more suburban areas and changing climate patterns [1,2]. Based on current expansion trends, research suggests that the geographical distribution of *I. scapularis* is expected to increase by 213% by 2080, highlighting the relevance of Lyme disease for clinicians and public health workers alike [10].

Although Lyme disease can affect individuals across age groups, it is commonly described as having a bimodal distribution with peak incidence occurring in individuals 5-9 and 45-59 years of age [1,2,13]. The data consistently demonstrate a higher prevalence of Lyme disease in males compared to females, regardless of age group [1]. This finding is potentially due to behavioral variances (job related), which may result in higher levels of tick exposures among males [2].

Lyme disease incidence peaks during the summer months, with 50% of all cases occurring in June and July [1,2,14]. This timing is due to a combination of both the life cycle of *Ixodes* species and human behavioral patterns. Risk factors that put patients at risk of developing Lyme disease include time spent outdoors, amount of forest cover when outdoors, landscaping practices including the amount of leaf litter, and density of deer located near the home [2]. One study in Connecticut found the risk of acquiring Lyme disease is correlated with time spent outside at home, while a report from Minnesota suggests that weekend travel and recreational activities are associated with increased risk [15,16].

Clinical Manifestations

The clinical presentation of Lyme disease varies substantially, with symptoms appearing anywhere from four days to eighteen weeks following an initial tick bite [17]. Symptoms are often described in three phases: early localized, early disseminated, and late-stage disease [3,6]. Patients may present at any phase along this spectrum. The most common early presentation of Lyme disease among children is erythema migrans: a flat, red, skin lesion at the site of the tick bite that often presents as a bullseye like image [3,18]. Unlike adults, who commonly exhibit skin lesions on their legs or abdomen, children most frequently present with erythema migrans in the head or neck region [6,13,19]. This observation is important to note, as it may go unnoticed in the presence of hair. Depending on factors such as skin pigmentation, lesion color, and lesion shape, there can be significant variation in the presentation of erythema migrans, creating a challenge for early diagnosis [7]. Typically, pediatric patients present with a singular lesion. However, if treatment is delayed, multiple lesions may develop [13]. Additionally, erythema migrans may be accompanied by flu-like symptoms such as fever, fatigue, headache, and arthralgia [3,13].

The second phase of Lyme disease, early-disseminated disease, can present as multiple skin lesions, neuroborreliosis, or carditis. Lyme neuroborreliosis is the term used to describe the neurologic symptoms associated with Lyme disease. It is estimated that if left untreated, 15-20% of those infected with Lyme disease will develop Lyme neuroborreliosis, although studies in Europe estimate this rate to be higher in pediatric populations [13,17]. The most common manifestations of Lyme neuroborreliosis in children are cranial nerve palsies and meningitis [3]. Of the cranial nerve palsies, the facial nerve is most frequently affected [3]. However, clinically these symptoms can be attributed to Bell's Palsy, and the connection to Lyme disease may be missed. Therefore, it is important to consider Lyme disease in the differential diagnosis for facial nerve palsy in pediatric patients presenting in the summer months [6]. A significant subset of children will develop bilateral facial nerve palsy, a presentation that is nearly exclusively associated with Lyme disease [12]. Overall, facial nerve palsy in pediatric patients has a favorable prognosis, as 95% of cases resolve regardless of whether treatment is pursued [13].

Contrary to facial nerve palsy, Lyme meningitis may go unnoticed and often presents nonspecifically with headache, neck pain, or fever [20]. This can be especially challenging to detect in young children. It is also worth recognizing that it can be difficult to distinguish Lyme meningitis from other forms of meningitis [21]. Clinically, the "rule of 7s" is used to describe patients who are at low risk of Lyme meningitis, a form of lymphocytic meningitis. These patients are described as having the following characteristics: cerebrospinal fluid with less than or equal to 70% mononuclear cells, no cranial nerve VII palsy, and headaches that have persisted for less than seven days [21,22]. Patients who do not fit the definition of low risk should be monitored with a lumbar puncture to ultimately prevent increased intracranial pressure and subsequent complications [13].

Although carditis occurs in 1-8% of adult cases, most literature describes it as an uncommon manifestation of Lyme disease in

children [3,13]. However, a study of 207 pediatric patients in Connecticut identified 33 cases of Lyme carditis, approximately 16% of the study cohort. After multivariate analysis, this study noted several associations among children who developed carditis including age greater than ten and presenting with arthralgia and meningitis [23]. Most reported cases of pediatric carditis present with atrioventricular block, ranging from first degree to third degree [13]. In these instances, a child may present with palpitations, chest pain, syncope, or they may remain completely asymptomatic [3]. While Lyme carditis is a rare manifestation, it should not be overlooked due to the potential mortality associated with severe arrythmias.

Late-stage Lyme disease in children typically presents as arthritis. Due to the challenges of diagnosing early-stage pediatric Lyme disease, arthritis is often the initial symptom that prompts medical intervention. In children, arthritic symptoms are typically reported in a single, large, weight-bearing joint, with 90% of cases affecting the knee [1,3]. The onset of arthritis is variable, as it may occur several weeks to years following an initial infection [3]. This variable timing provides yet another challenge to diagnosis, as children with late-stage Lyme disease may present in the winter months [14]. Following antibiotic treatment, arthritic symptoms typically resolve [3].

Diagnosis and Laboratory Testing

Laboratory testing for the diagnosis of Lyme disease has many well described challenges. Currently, the CDC recommends a two-tier testing procedure. The first step is an enzyme-linked immunosorbent assay (ELISA) or immunofluorescence assay (IFA) to screen for a *B. burgdorferi* antibody response [12,24]. If this initial screening is positive, a western blot test analyzing IgG and IgM antibodies or a secondary tier enzyme immunoassay is used to confirm the diagnosis [6]. A western blot is considered positive if it has 2 of 3 IgM bands present within 4 weeks of initial symptoms or if it has 5-10 IgG bands present at any point in time [12]. Since the test measures the immune response rather than the presence of the infectious organism, early testing may reveal false negatives [1,9]. For this reason, current clinical guidelines suggest laboratory testing be utilized only in the case of suspected disseminated Lyme disease [24,25]. Another limitation of current testing procedures is difficulty distinguishing ongoing infection from past infection. This distinction is largely up to clinician judgment and can lead to misdiagnosis [7]. Due to the limitations associated with laboratory testing, Lyme disease is largely considered a clinical diagnosis with assessment of symptoms, geographic location, and travel history all playing an important role [3].

Treatment and Management

The most recent clinical practice guidelines for the treatment of Lyme disease were published in 2020. These comprehensive guidelines include input from the Infectious Disease Society of America, the American Academy of Neurology, and the American College of Rheumatology [25]. According to these guidelines, post exposure prophylaxis is recommended for pediatric patients who have a high-risk tick bite, defined as displaying the following three characteristics: a known *Ixodes* bite, occurring in an endemic region, and tick attachment for at least 36 hours [8]. Prophylactic treatment is given as a single dose of doxycycline (4.4 mg/kg up to a maximum dose of 200mg) within 72 hours of exposure [8,25]. A study of 482 adult patients who were given prophylactic treatment following a tick bite, found that it reduced Lyme infection rates by 87% [2]. It is worth noting that previous recommendations advised against treating children under the age of 8 with doxycycline due to tooth staining [8]. However, recent studies have found these concerns to be minimal [26,27].

Although erythema migrans typically resolves without treatment, antibiotic therapy is recommended to prevent chronic disease [3]. There are several antibiotics that may be utilized including amoxicillin, doxycycline, cefuroxime, and azithromycin [8]. Selection should be made based on clinical judgment and include considerations such as presence of additional symptoms, known drug allergies or reactions, frequency of dosing, and likelihood of co-infection with other infectious organisms [8,25]. All factors considered, the first line agent for children under the age of 8 is amoxicillin and the first line agent for children over the age of 8 is doxycycline. The American Academy of Pediatrics recommended dosages are included in Table 1 [8].

Table 1: Treatment Guidelines for Pediatric Lyme Disease from the American Academy of Pediatrics [7].

Oral Antibiotic	Pediatric Dosage
Amoxicillin	50 mg/kg/day in 3 equal doses (max 500mg/dose)
Doxycycline	4.4 mg/kg/day in 2 equal doses (max 200mg/dose)
Cefuroxime axetil	30 mg/kg/day in 2 equal doses (max 500mg/dose)
Azithromycin	10mg/kg/day in 1 dose (max 500mg/dose)
IV Therapy	Pediatric Dosage
Ceftriaxone	50-75 mg/kg/day in 1 dose (max 2.0 g/d)
Penicillin G	200,000-400,000 U/kg/day in 6 equal doses (max 24 million U/d)

It is recommended that treatment of early disseminated Lyme disease is guided by clinical presentation. Neurological symptoms should be treated with an oral doxycycline regimen [8]. Corticosteroid therapy for cranial neuropathy is not recommended for children under the age of 16 [25]. In a patient with suspected Lyme carditis, an electrocardiogram should be performed with PR prolongation or other signs of arrythmia prompting hospitalization [23,25]. In cases of hospitalized carditis, IV ceftriaxone should be administered followed by a course of oral antibiotics [8].

Lyme arthritis, or late-stage Lyme disease, should be treated with a 28-day regimen of oral antibiotics [25]. Similar to other guidelines, the first line agent is typically amoxicillin for children under the age of 8 and doxycycline for children over the age of 8 [8]. If symptom resolution is not achieved through an initial course of antibiotics, 2-4 weeks of IV ceftriaxone may be utilized [25].

Although the vast majority of pediatric patients achieve symptom resolution with treatment, a small subset continue to experience fatigue, pain, and psychological disturbances [28]. The term,

post-treatment Lyme disease syndrome (PTLD), has been coined to describe this phenomenon [20]. In order for a diagnosis of PTLD to be made, a patient must have a documented episode of Lyme disease, achieve resolution or stabilization of symptoms following antibiotic therapy, and then continued to experience relapsing, non-specific symptoms for at least six months after treatment [7,28]. A recent study of 89 children who received treatment for Lyme disease found that 9% of children likely met the definition for PTLD and an additional 13% of children had at least one PTLD symptom [28]. Despite its estimated prevalence, little is known about the etiology of PTLD, highlighting the need for further research. Additionally, PTLD has received increasing media coverage in recent years, which may cause anxiety for patients. Therefore, it is important for clinicians to recognize PTLD and validate these concerns. However, if initial treatment is not effective, long-term antibacterial treatment for PTLD is not recommended as benefits have not been demonstrated. Instead, efforts should focus on treating individual symptoms [20].

Prevention

Due to the challenging nature and widespread prevalence of Lyme disease in endemic regions, it is important to counsel children and parents on prevention techniques. Some behavioral strategies that can reduce the incidence of exposure include wearing long sleeves and long pants tucked into white socks when going outdoors and drying clothes with high heat after outdoor activities [2,3,12]. Insect repellant with 30% DEET may also be effective for preventing tick bites, and it is safe to use in all children over the age of 2 months [3]. Other strategies discussed in the literature include bathing immediately after outdoor activities and regular tick checks. However, the latter may not be reliable, as *Ixodes* species are often small and difficult to detect [2,7]. Overall, there is not one method that is perfect at preventing tick exposure and a combination approach is recommended.

Another area of interest in Lyme disease prevention is the ongoing development of an effective vaccine. In 1998, the FDA approved LYMErix for people age 15-70 who lived in endemic regions [7]. However, despite its 75% efficacy, there was low demand for the vaccine, and four years later it was voluntarily removed from the market [2,7]. More recent efforts have been focused on a developing a recombinant vaccine against OspA, an outer surface protein on *Borrelia burgdorferi I* [29]. These vaccines utilize an antibody response to block bacterium transmission following a tick bite. Although there have been several efforts to utilize this mechanism, the recombinant vaccine (VLA15) is currently the only vaccine in human clinical trials [7]. Developed by Pfizer and Valneva, VLA15 uses 6 different OspA serotypes and requires three doses and a follow up booster. As of June 2023, VLA15 completed its phase 2 clinical trial, although it is not expected to be submitted for full FDA approval until 2026 [30].

As an alternative to vaccination, passive administration of monoclonal antibodies that bind to OspA has been proposed [2]. Proven effective in mice and nonhuman primates, this method is seasonal and would require repeat injections each year [31]. However, clinical trials are needed before this method could become commercially available.

Conclusion

Lyme disease poses a significant disease burden, especially among endemic regions in the United States. With a large subset of affected patients under the age of 9, it is especially relevant for pediatricians to recognize the presentation of Lyme disease in this population. When compared to adults, pediatric Lyme disease is more likely to present with erythema migrans in the head or neck region, facial nerve palsy, or as late-stage arthritic disease. Although the majority of children fully recover from Lyme disease, it is important for providers to administer early treatment in order to avoid severe complications such as carditis, lymphocytic menigitis, and arthritis. Treatment for Lyme disease should follow the latest recommendations published in 2020. Lastly, although recent clinical trials have yielded promising results, there is currently no vaccine available for the prevention of Lyme disease. Therefore, providers who practice in endemic regions should counsel patients and their caregivers on behavioral measures that can be used to help reduce tick exposure.

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