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Lyme Disease: Treatment & Prevention

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Introduction

As an emerging infectious disease, Lyme disease (LD) presents a challenge to clinicians. The Centers for Disease Control (CDC) conclude Lyme disease is currently the most common vectorborne disease in the United States.[1] The latest data published by the CDC indicate that 16,273 cases of LD were reported in 1999. Although this number is a 3% decrease from cases reported in 1998, it is a 21% increase from cases reported in 1997.[1] In 1999, most cases of LD were reported in the northeastern, mid-atlantic, and north central states. The following states reported incidences higher than the national average (6.0 cases/100,000 people): Connecticut, Rhode Island, New York, Pennsylvania, Delaware, New Jersey, Maryland, Massachusetts, and Wisconsin.[1] Florida is considered a low risk state with an incidence of 0.4 cases per 100,000 people for 1999. Also between 1990 and 1999, there were a total of 382 cases reported.[1]

Lyme disease appears to target the young (<15), and middle-aged (30-59) more frequently than other age groups.[1] It affects both sexes equally. The most frequent months of reported onset of illness are June and July.[1] Persons at highest risk of contracting LD are those living in areas where the disease is endemic, who spend time outdoors in overgrown brush or wooded areas due to occupational or recreational activities. This article will focus on the latest treatment guidelines for LD and methods of preventing transmission of the infection.

Epidemiology

Lyme disease is caused by *Borrelia burgdorferi,* a leptospire residing in the gut of infected ticks of the *Ixodes ricinus* complex. *Ixodes scapularis*, also know as the blacklegged or deer tick, is the vector in the eastern United States, whereas *Ixodes pacificus*, or the western blacklegged tick, is the vector in the western United States.[2] The nymphal stage of the tick's life cycle occurs during late spring and early summer. It is during this stage of the tick's life cycle that the majority of Lyme disease cases are transmitted to humans. The CDC estimates the prevalence of *B. burgdorferi*-infected ticks in the United States is approximately 15-30% of *I. scapularis* nymphs and up to 14% of *I. pacificus* nymphs. However, in the southern United States, the prevalence of infection in *I. scapularis* ticks is generally 0%-3%.[2] Thus the risk of contracting LD varies not only with geographic location but also with presence of *B. burgdorferi*-infected ticks in a specific area and amount of exposure to those ticks by an individual. These three factors are important aspects for clinicians to consider when deciding a patient's degree of risk for contracting Lyme disease and considering vaccination.

Transmission of Lyme disease involves a vector (*Ixodes ricinus* ticks), human hosts, and the use of an animal host (white-tailed deer) to complete the life cycle of *B. burgdorferi*. Deer are an important link in the life cycle of *B. burgdorferi* and are abundant in areas where Lyme disease is endemic.[3] *B. burgdorferi* is maintained in nature through horizontal transmission from infected nymphs (ticks) to white-tailed deer to larval ticks, which then molt to become infected nymphs. Infected nymphs are responsible for spreading *B. burgdorferi* to humans.[3]

Diagnostic Evaluation

Early

Early manifestations can appear as localized disease in the form of a solitary erythema migrans lesion, most frequently in the area surrounding the tick attachment, or patients can present with symptoms of early disseminated disease such as fever, lymphadenopathy, multiple erythema migrans lesions, carditis, cranial-nerve palsy, meningitis, or acute radiculopathy.[4] A summary of early signs and symptoms of LD are presented in Tables 1 & 2.

Late

Late manifestations of LD include arthritis (oligoarticular, commonly of the knees), encephalopathy (characterized by memory deficit, irritability, and somnolence), and neuropathy (manifested primarily by distal paresthesias or radicular pain).[4]

CNS Involvement

CNS symptoms usually include but are not limited to severe headache, nuchal rigidity, meningitis, or acute radiculopathy. Patients presenting with CNS symptoms are treated in a different manner than patients with early or late manifestations of LD. A lumbar puncture is performed along with a neurological evaluation of all patients suspected of having CNS involvement. Although patients may present with either early or late manifestations of Lyme disease in addition to CNS symptoms, patients are treated separately and more aggressively based on the emergence of CNS symptoms.

There has been controversy over how to classify and treat patients presenting with seventh cranial nerve palsy. Clinicians argue over whether this symptom, by itself, should be classified as a CNS symptom. Some clinicians treat seventh cranial nerve palsy with a lumbar puncture (LP) and follow CNS treatment protocols; others look for other evidence of CNS involvement, such as severe headache or nuchal rigidity, before choosing to treat with CNS protocols.[4]

Chronic LD or Post-Lyme Disease Syndrome

Patients who have been treated successfully and appropriately for Lyme disease may complain of residual symptoms of arthralgia, myalgia, or fatigue continuing for weeks or months beyond treatment. These patients have been classified as having "chronic Lyme disease" or "post-Lyme disease syndrome." The Infectious Disease Society of America (IDSA) does not recognize this classification as a separate diagnostic entity. They claim these symptoms are common following treatment of many infectious diseases, and are difficult to distinguish from LD because "the prevalence of fatigue and/or arthralgias in the general population is greater than ten percent."[4] Also, the IDSA concludes there are no convincing published data showing repeated or prolonged courses of oral or intravenous antimicrobial therapy are effective for such patients.

Table 1. Early Signs of Lyme Disease[3]

Sign	No. Pts (%) n=314
Erythema chronicum migrans	314 (100)*
Multiple annular lesions	150 (48)
Lymphadenopathy	
regional	128 (41)
generalized	63 (20)
Pain on neck flexion	52 (17)
Malar rash	41(13)
Erythematous throat	38 (12)
Conjunctivitis	35 (11)
Right upper quadrant tenderness	24 (8)
Splenomegaly	18 (6)
Hepatomegaly	16 (5)
Muscle tenderness	12 (4)
Periorbital edema	10 (3)
Evanescent skin lesions	8 (3)
Abdominal tenderness	6 (2)
Testicular swelling	2 (1)

*Erythema chronicum migrans was required for inclusion in the study

Testing

The diagnosis of LD is based primarily on the presence of a characteristic clinical picture, and exposure in an endemic area. Treating patients based on these findings alone is appropriate according to the CDC.[2] However, an elevated antibody response to *B. burgdorferi* can be used as diagnostic evidence or as a means of confirming a suspected LD infection. *B. burgdorferi* is most readily cultured from erythema migrans lesions because growing a culture from other sites is difficult.[3] It grows best in a Barbour-Stoenna-Kelly medium at 33C.[3]

Serologic testing has been found to be very

Table 2. Early Symptoms of Lyme Disease[3]

Symptom	Number of Pts (%) n=314
Malaise, fatigue, and lethargy	251 (80)
Headache	200 (64)
Fever and chills	185 (59)
Stiff neck	151 (48)
Arthralgias	150 (48)
Myalgias	135 (43)
Backache	81 (26)
Anorexia	73 (23)
Sore throat	53 (17)
Nausea	53 (17)
Dysesthesia	35 (11)
Vomiting	32 (10)
Abdominal pain	24 (8)
Photophobia	19 (6)
Hand stiffness	16 (5)
Dizziness	15 (5)
Cough	15 (5)
Chest pain	12 (4)
Ear pain	12 (4)
Diarrhea	6 (2)

helpful in providing valuable supportive diagnostic information in patients with manifestations of later-stage disseminated LD and in asymptomatic LD infections.[2] Less than 5% of patients who are seronegative go on to develop late manifestations.[5] This figure can be explained by the strong seroreactivity and expanded WB immunoglobin (IgG) banding patterns to diagnostic *B. burgdorferi* antigens that patients with early disseminated or late-stage LD demonstrate.[2] These findings indicate serologic testing in LD can be performed with a high degree of specificity and sensitivity.[2]

In fact, the CDC recommends initial tests be performed with a sensitive test such as an enzyme linked immuno sorbent assay (ELISA) or an indirect fluorescent antibody test, followed by more specific testing with Western immunoblot to confirm positive or indeterminate results.[2] PCR is also helpful for amplifying genomic DNA of *B. burgdorferi* in blood, skin, CSF, and synovial fluid but has not yet been standardized for routine diagnosis.[2]

However, serologic testing early after infection will be insensitive because the specific immune response in LD develops slowly. Whereas 30-40% of patients with erythema migrans lesions are seropositive in acute phase sera, 60-70% are seropositive two to four weeks later.[3] The specific IgM response peaks between the third and sixth week of infection, while the specific IgG response develops gradually over several months.[3] After the first 4-6 weeks of infection, 90% of patients have an elevated IgG response to the spirochete.[3]

Role of Antimicrobials

Oral First Line Therapies

Doxycycline is preferred for early manifestations of Lyme disease without CNS complications.[3,4,6] It is administered at a dose of 100 mg bid to adults, and can be prescribed to children older than 8 years at a dose of 1-2 mg/kg/bid, not to exceed 100 mg/dose. Table 3 summarizes the antimicrobials used in the treatment of Lyme disease.

Another recommended oral medication in the treatment of early Lyme disease is amoxicillin.[3,4] Amoxicillin is administered to adults at a dose of 500 mg tid, and at 50 mg/kg/d divided into 3 doses, not to exceed 500 mg/dose for children. Amoxicillin is also available in a liquid formulation for those unable to take solid dosage forms.

An alternative oral medication is cefuroxime axetil at 500 mg bid for adults, and 30 mg/kg/d divided into 2 doses with a maximum of 500 mg/dose for children.[3,4] This agent can be reserved for persons unable to take amoxicillin or doxycycline, but is more costly than the other choices. Cefuroxime is also available as a liquid but has poor palatability.

Oral Second Line Therapies

Macrolide antibiotics are viewed as second line therapies, indicated when patients are unable to tolerate doxycycline, amoxicillin, or cefuroxime axetil.[3,4] They are not to be used as first line therapies. Of the macrolide class of antibiotics, the following agents are acceptable for use in the treatment of Lyme disease: azithromycin, 500 mg qd for adults, 10 mg/kg/d (maximum 500 mg/dose) for children; erythromycin, 500 mg qid for adults, 12.5 mg/kg qid (maximum 500 mg/dose) for children; or clarithromycin 500 mg bid for adults, 7.5 mg/kg bid (maximum 500 mg/dose) for children.

Table 3. Antimicrobials Used for the Treatment of Lyme Disease[4]

Drug	Adult Dosage	Duration (Days)	Pediatric Dosage
Preferred oral			
Amoxicillin	500 mg tid	14-21	50 mg/kg/d, divided into 3 doses (max 500 mg/dose)
Doxycycline	100 mg bid	14-21	= 8 years, not recommended > 8 years, 1-2 mg/kg bid (max 100 mg/dose)
Alternative oral			
Cefuroxime axetil	500 mg bid	14-21	30 mg/kg/d, divided into 2 doses (max 500 mg/dose)
Azithromycin	500 mg qd	7-10	10 mg/kg/d (max 500 mg/dose)
Clarithromycin	500 mg bid	14-21	7.5 mg/kg bid (max 500 mg/dose)
Erythromycin	500 mg qid	14-21	12.5 mg/kg qid (max 500 mg/dose)
Preferred parenteral			
Ceftriaxone	2 g qd	14-28	75-100 mg/kg qd (max 2 g)
Alternative parenteral			
Cefotaxime	2 g tid	14-28	150-200 mg/kg/d, divided into 3-4 doses (max 6 g/d)
Penicillin G	3-4 million units q4h*	14-28	200,000-400,000 units/kg/d, divided into q4h doses (max 18-24 million units/d)

*Pts with normal renal function

Intravenous First Line Therapies

Ceftriaxone is used for early or late manifestations of Lyme disease with CNS complications.[3,4] Ceftriaxone has good CSF penetration and is administered at a dose of 2 g once daily for adults. In children, ceftriaxone can be used at a dose of 75-100 mg/kg/d in a single daily intravenous dose (maximum of 2 g per day).

Intravenous Alternative Therapies

Alternative intravenous therapies include penicillin G at a dose of 18-24 million units daily, divided into doses given every four hours for adult patients with normal renal function.[3,4] For children with normal renal function, penicillin G is given at a dose of 200,000-400,000 units/kg/d (max. 18-24 million units/d) divided into doses given every four hours.

Another alternative is cefotaxime at a dose of 2 g every eight hours for adults, or 150-200 mg/kg/d divided into 3 or 4 doses (maximum 6 g/d) in children.[3,4]

For adults and children (>8 yrs) who cannot tolerate penicillin or cephalosporins because of a beta lactam allergy or otherwise, parenteral doxycycline is acceptable. Doxycycline should be administered at a dose of 200-400 mg/d in two divided doses.[4]

Guidelines for Treatment

There is some debate over which individuals exposed to tick bites should receive treatment for Lyme disease. The newest IDSA guidelines developed four options to this dilemma and evaluated the advantages versus disadvantages of treating individuals according to each option.

Option 1

Treating with antimicrobials all persons who remove vector ticks that have become attached. This option involves liberal management of exposed individuals which not only is costly, but was found by the IDSA to have greater risks of antibiotic-associated adverse reactions than benefits from treating the infection. Also, patients treated according to this option were no more likely to develop LD from a tick bite than they were to have an antibiotic-associated adverse reaction.[4]

Option 2

Treating with antimicrobials only persons believed to be at high risk. Although this option narrows the amount of potentially treatable patients, it still examines a large group of candidates and could be costly. Also, this option becomes difficult to fol-

low because one cannot always be certain the bite or wound was inflicted by a tick, or that the tick was the species Ixodes, or that the tick was from the species Ixodes and was infected with *B. burkdorferi*. In addition, there is no standardized method for screening ticks for evidence of infection with *B. burkdorferi.* Even if patients in this category were given prophylactic antibiotics based on the assumption that any tick was attached for greater than 72 hours, no studies have shown that antibiotics can reduce the development of infection after a tick bite has occurred.

Option 3

Treating with antimicrobials only persons who develop erythema migrans or other clinical manifestations of Lyme disease. Again, progression from option 2 to option 3 has narrowed the percentage of treatable patients; however, this option requires patients show symptoms of a tick-borne illness. While option 3 is beneficial for patients who develop erythema migrans or other symptoms, it provides no treatment for individuals who are asymptomatic with active LD.

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. Option 4 does not appear to be the best option due to limitations of currently available serological assays for detecting LD and current recommendations by IDSA not to use serological testing as a method of screening individuals exposed to a tick bite.

Recommendations

After reviewing all options, the IDSA reached the following conclusions. "Routine use of antimicrobial prophylaxis or serological tests after a tick bite is not recommended."[4] "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."[4] "Persons who develop a skin lesion or other illness within one month after removing an attached tick should promptly seek medical attention for assessment of the possibility of having acquired a tick-borne disease."[4] The CDC makes similar recommendations regarding who should and should not be treated for a potential Lyme disease infection.[2]

Duration of Treatment

Length of treatment is a highly disputed issue surrounding Lyme disease, and continues to be challenged by practitioners. Most controlled trials have been conducted in adults using doxycycline or amoxicillin with treatment durations of 3 weeks (20 days) for early and late manifestations of LD without evidence of CNS complications.[4] However, Nowakowski showed that 14-day regimens of doxycycline were as efficacious, with similar adverse events, as 20-day regimens of doxycycline.[6] Looking at these findings, one would argue 20-day regimens are unnecessary, more costly, and could put patients at greater risk for experiencing adverse events. Because of the controversy and emerging findings like Nowakowski's, the IDSA has left room in their recently published guidelines for clinicians to individualize treatment rather than follow a directed duration. The IDSA Guidelines recommend treating patients for 14-21 days with any of the three preferred oral antimicrobials.[4]

Late manifestations without CNS complications involving complaints primarily of arthritis involve extending treatment for a full 28 days.[4] Some argue whether 28 days is long enough to see resolution of symptoms. New opinions suggest patients with late LD should be treated until clinical symptoms resolve, regardless of duration.[7] Guidelines adopted by the Lyme Disease Foundation (LDF) recommend treating patients with early disseminated disease for a minimum of 4-6 weeks, and late LD for a minimum of 4-6 months.[8] LDF's lengthy treatment recommendation is based on the claim that LD patients experience cyclic flares occurring every 4 weeks. It is postulated that these flares are part of the organism's cell cycle. Similar to antineoplastic treatment strategies, antibiotics target killing in the growth phase of the organism and therefore must be administered for at least 4 weeks in order to ensure a growth phase has occurred.[8] However, the phenomenon of cyclic flaring and targeted antibiotic killing is not embraced by the IDSA and CDC.

CNS complications in LD warrant the use of intravenous ceftriaxone for good penetration into the CSF, at high doses to ensure good tissue levels

for a longer duration (14-28 days) than other LD therapies.[3,4] Again, LDF guidelines recommend treating these patients until symptoms resolve rather than set an endpoint. These extra measures, including the extended duration of treatment, reflect the high risk of this patient population and the necessity to provide concentration-dependent and time-dependent killing to maximize outcomes for patients with CNS complications.

Prevention

Personal Measures

The simplest way to prevent infection of LD is to minimize exposure to ticks by avoiding tick-infested areas.[4] If avoidance is not possible, the next best option to reduce transmission of infection is to wear light-colored protective clothing. Long sleeves and pants tucked into boots expose less skin to the environment and keeps tick-attachment to a minimum. Light-colored articles help to visualize ticks. The use of an insect repellant such as DEET (n,n diethyl m-toluamide) has been shown to reduce tick attachment.[2] Permethrin has been shown to kill ticks on contact and therefore its application to clothing also increases protection.[2]

A visual inspection of the body should be performed after exposure to tick infested areas. Those residing in endemic areas should perform this examination on a daily basis. Prompt tick removal is important since attachment for longer than 48 hours is necessary for transmission of *B. burgdorferi*. The area surrounding a tick bite should be carefully watched for up to one month after the bite occurred for signs of LD infection (see Tables 1 & 2).

Vaccination

A vaccine for the prevention of Lyme disease has been developed and received FDA approval in December 2000.[9] LYMErix uses recombinant *B. burgdorferi* lipidated outer-surface protein A (rOspA) as immunogens.[2] This vaccine is administered as a series of 3 shots: at 0, 1 month, and 1 year. Although phase III clinical trials showed LYMErix to be nearly 80% effective in preventing Lyme disease, information on safety and efficacy beyond the third shot is not yet available nor is it known if additional boosters will be necessary to maintain immunity.[9] The vaccine is indicated for persons age 15-70. The most common adverse event occurring in Phase III clinical trials was soreness at the injection site, followed by LD-like symptoms of myalgia, influenza-like illness, fever and chills. Among the 10,936 subjects in these phase III clinical trials, there were no reported episodes of immediate hypersensitivity in the vaccine group.[2] Efficacy of LYMErix against symptomatic LD was shown to be 49% and 76% after two and three shots respectively. Efficacy against asymptomatic LD infection was 83% one year after receiving the vaccination and 100% two years after receiving the vaccination.[2]

Although a vaccine is now available, its role in the treatment and prevention of LD is controversial due to published low cost-effectiveness data. Information compiled by the CDC indicates that use of the vaccine results in a net cost to society of $5692 per case averted, and $35,375 per complicated neurologic or arthritic case avoided. This data also reveals that the cost of vaccinating will exceed the cost of not vaccinating until incidence of LD is greater than 1973 cases per 100,000 persons per year.[2] The overall incidence of LD reported in the United States in 1999 was 6 cases per 100,000 population. However, certain geographic areas show higher risk. The county with the highest incidence of LD was Nantucket County, Massachusetts, at 950.7 cases per 100,000 population. Twenty-four other counties reported incidences of LD exceeding 100 cases per 100,000 population. These counties were located in Connecticut, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin.[1] Although the reported cases for 1999 remain below that which establishes the vaccine as cost-effective, they are not far from the mark. Thus, use of the vaccine should be based on an individual's risk for contracting LD.[2] This recommendation is supported by the Advisory Committee on Immunization Practice, Public Health Service, U.S. Department of Health and Human Services.[2]

Meltzer and colleagues also published similar cost-effectiveness results on the LD vaccine.[10] His report concluded that communities with average individual probabilities of less than 0.01 of contracting LD may benefit from interventions that improve the probability of early diagnosis and treatment.[10] Meltzer's article mentions results from a forthcoming Institute of Medicine report which

Table 4. Cost Comparison of Adult IV and PO Regimens

Drug Regimen	Formulation	Cost ($)*
Amoxicillin		
500 mg tid x20 d	500 mg capsules	17
Doxycycline		
100 mg bid x20 d	100 mg capsules	17
Cefuroxime axetil		
500 mg bid x20 d	500 mg tablets	284
500 mg bid x20 d	250 mg/5 ml suspension	243
Azithromycin		
600 mg qd x6 d#	600 mg tablets	101
500 mg qd x8 d	200 mg/5 ml suspension	118
Clarithromycin		
500 mg bid x20 d	500 mg tablets	131
500 mg bid x20 d	250 mg/5 ml suspension	288
Erythromycin		
500 mg qid x20 d	500 mg tablets (base)	22
Ceftriaxone		
2 g q24h x28 d	2 g bag	1172
Cefotaxime		
2 g q8h x28 d	2 g bag	2236
Pen G x28 d		
20 million U/d q4h	20 million U vial	224

*Prices obtained from drugstore.com (March, 2001)
#Regimen differs from recommended guideline

uses cost per quality-adjusted life year (QALY) saved to judge economic benefit of the vaccine. The authors of this report estimate costs greater than $100,000 per QALY saved if the vaccine were administered "…to resident infants born in, and immigrants of any age to, geographically defined high risk areas." Thus, the authors conclude universal use of the vaccine is "less favorable," the lowest ranking priority for vaccine development and a paralleled finding in many of these studies.[10]

Comparative Cost

Comparative costs of the various recommended oral and parenteral agents are presented in Table 4.

Summary

Lyme disease is an emerging infectious disease that requires early recognition for maximum outcomes. *Borrelia burgdorferi*, the causative organism causes an infection through vector ticks of the Ixodes species. These ticks have been found in various areas of the United States. Lyme disease involves multiple stages including early and late manifestations and CNS involvement. Diagnosis is based upon clinical subjective findings and/or serologic testing. The Infectious Disease Society of America (IDSA) published updated guidelines for the treatment of Lyme disease in July 2000.[4] The IDSA recommends treating patients who present with subjective complaints of LD, such as erythema migrans, and a documented exposure (tick bite) rather than prophylactically treating all persons with a documented tick bite. Preventive measures such as avoidance of tick-infested areas and the use of protective clothing and repellants to deter tick attachment are encouraged. Persons residing in endemic areas should perform a daily body check for attached ticks. LYMErix, a vaccine for the prevention of LD in persons aged 15-70, was developed and received FDA approval in February 2000. Early reports on the cost-effectiveness of this vaccine indicate it should be reserved for use in individuals at high risk of contracting LD and not used universally. Because of its complicated infectious process and symptoms mimicking other infectious diseases such as rheumatoid arthritis and malaria, early recognition, treatment, and prevention of Lyme disease will continue to be a challenge for clinicians in the years to come.

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