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Diagnosis, Treatment, and Prevention of Lyme Disease in Children

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Abstract

The approaches to diagnosing and treating Lyme disease (LD) have been improved and refined as a result of basic and clinical research, and considerable practical experience. In addition, there have been recent studies that have allowed improvements in the ability to prevent infection with *Borrelia burgdorferi*. This paper will review the relevant literature and address recent developments in the diagnosis, treatment, and prevention of LD. Issues specifically related to the management of children will be identified. Controversies regarding treatment approaches will be examined in some detail.

Understanding the clinical manifestations, or stage, of LD is crucial when approaching both diagnosis and treatment. Early localized disease is best diagnosed by recognizing the characteristic skin lesion, erythema migrans. Early disease will frequently, but not always, be accompanied by a detectable antibody response, particularly IgM antibody to the spirochete. Late disease, chiefly arthritis, is generally associated with high levels of IgG antibody. Western blot technology allows confirmation of enzyme immunoassay results and is especially useful when the latter is in the low or equivocal range.

Early localized disease responds well to oral antibacterial therapy. Early disseminated disease, often associated with neurologic findings, may require parenteral therapy. The arthritis associated with LD frequently

responds to oral antibacterials, but some refractory cases may require intravenous therapy, and occasionally surgery. Doxycycline is the oral antibacterial of choice, while amoxicillin and cefuroxime axetil are alternatives that may be preferred in young children. Owing to its long half-life and once daily dose administration, intravenous ceftriaxone has become the accepted standard for parenteral therapy.

Tick avoidance has long been the mainstay for preventing LD. Antibacterial prophylaxis, using doxycycline, for tick bites has been shown to be an effective approach to prevention, but its relevance to pediatrics is uncertain. Vaccines designed to prevent infection have also been developed.

Lyme disease (LD) has become the most common vector-borne disease in the US, as well as in some countries in Europe. In the US, it is among the top 10 notifiable diseases in both sexes and in all age groups.[1] In endemic regions, it is considered a major public health problem. The bacteria that cause LD are spirochetes belonging to the genus *Borrelia*. Like other spirochetes, these organisms can cause persistent infection with symptoms that may persist or recur over a long period of time. A prominent host inflammatory response accounts for many of the disease manifestations. In the US, *Borrelia burgdorferi* sensu stricto is responsible for virtually all cases of LD, while in Europe, LD is also caused by *B. garinii* and *B. afzelli* (these have been the only causative agents in Asia). There are clinical differences, particularly with respect to neurologic involvement, between infections caused by these species and *B. burgdorferi*. For example, Bannwarth's syndrome (aseptic meningitis with radiculoneuritis) and acrodermatitis chronica atrophicans are primarily seen in Europe.

In most regions of the US, the vector of LD is the deer tick, *Ixodes scapularis*, which acquires the spirochete by feeding on the mouse, *Peromyscus leucopus*, the major reservoir of the bacteria. Human disease may result when there is prolonged (24–48 hours) attachment of the tick to the skin, during which time bacteria may pass into the dermis.

1. Clinical Manifestations of Lyme Disease (LD)

Following inoculation of the spirochete into skin, the characteristic skin lesion, erythema migrans (EM), appears at the site of the tick attachment in the majority of patients. EM is an annular erythematous lesion that typically enlarges over several days; it may resolve spontaneously, in days or weeks, or as a result of antibacterial treatment. EM is usually not associated with local symptoms and patients often exhibit no further disease manifestations. If the organism disseminates via lymphohematogenous routes, infection may occur in a variety of tissues, resulting in skin (multiple EM), nervous system, cardiac, ocular, and joint involvement. Even without antibacterial treatment, early disseminated disease may resolve; however, it may also progress and result in significant morbidity. Persistent infection in the joints, eyes or CNS can result in late clinical manifestations. Table I lists the main clinical manifestations according to the stage of disease. For a more detailed review on the clinical manifestations of Lyme disease please refer to Steere.[2]

2. Diagnosis

There have been considerable efforts to devise laboratory tests for the purpose of identifying borrelial infection. However, in point of fact, most human infections present with clinical findings, including exposure to vector ticks, that should suggest the possibility of LD to the clinician. The presence of EM is sufficient for

Table I. The main clinical manifestations of Lyme disease

Disease stage	Timing after tick bite	Clinical manifestations
Early localized	3–30 days	EM (single)
		Variable constitutional symptoms (myalgia, arthralgia, fever, headache, fatigue)
		Regional lymphadenopathy
Early disseminated	3–12 weeks	EM (single or multiple)
		Constitutional symptoms
		Neck pain
		Meningitis
		Cranial neuritis, e.g. facial palsy
		Radiculoneuritis
		Carditis (variable heart block)
		Ocular involvement
Late disease	>2 months	Arthritis
		Chronic CNS involvement

EM = erythema migrans.

diagnosis of early LD. When compatible disease manifestations are observed, but EM is lacking, diagnosis may be facilitated by performing appropriate laboratory tests.

Serologic testing is the most useful modality in most cases. In the first weeks after infection, anti-borrelial IgM antibody becomes detectable, rapidly peaks, and then declines. After 1 month, most patients will also develop IgG antibody. Even after antibacterial therapy, IgG antibody may be present for many years. Both IgM and IgG are detectable using an enzyme-linked immunosorbent assay (ELISA) or immunofluorescent assay (IFA) for antibodies to *B. burgdorferi*. Some commercial tests assay for IgG or IgM alone, while others are designed to detect both. These assays are sensitive, but lack of specificity may lead to false positive results, especially in the setting of other spirochetal infections, autoimmune diseases, and certain viral infections, e.g. Epstein-Barr virus and parvovirus B19. Current recommendations[3] advocate the use of western immunoblotting to confirm results that are positive or equivocal by ELISA or IFA. The western blot technique utilizes borrelial proteins which have been separated by electrophoresis so that IgM and IgG antibody to individual antigens can be detected; interpretive criteria for western blots performed in the US have been published.[3] A recently developed ELISA test is based on a synthetic peptide (C6) and has been shown to have not only good sensitivity, but also high specificity.[4] Although approved by the US FDA, it is not yet widely used commercially.

The correct interpretation of results of LD serology is necessary for accurate diagnosis, and may also help identify the stage of infection. A positive ELISA or IFA in conjunction with a positive western blot indicates that the patient has been infected. In early infection, reactivity on IgM tests is often greater than reactivity on IgG tests. Late disease, e.g. arthritis, is usually accompanied by highly reactive IgG tests; however, IgM is occasionally seen in late disease, or long after successful treatment, therefore its presence does not always indicate recent infection.[5] A low positive ELISA or IFA with negative western blots most often represents cross-reacting antibody, rather than infection with *B. burgdorferi*. Serologic tests may be nondiagnostic in early LD, but with more long-standing infection seronegativity is rare. In fact, the most common reason for 'seronegative LD' is incorrect diagnosis. The use of antibacterials in early LD may blunt the antibody response, but persistent infection in the absence of detectable antibody is probably uncommon. On the other hand, IgG antibody is detectable for long periods of time in some patients who are successfully treated; therefore, the use of follow-up antibody tests to assess adequacy of treatment is generally not recommended. Finally, antibody can sometimes be detected by both ELISA and western blot in asymptomatic people who have no recollection of having had LD.[6,7] These results may indicate subclinical infection in the past.

Other laboratory methods have also been used to detect infection. These include culture, antigen tests, and polymerase chain reaction (PCR). *B. burgdorferi* is cultivated using the Barbour-Stoenner-Kelly medium, and its presence in a clinical specimen is diagnostic. However, cultures tend to be mainly positive in early infection, most commonly from skin biopsies of EM, and less commonly from plasma or cerebrospinal fluid (CSF). While culture is an important research tool, it is not practical for general diagnostic use.

Even though the urine antigen test has been widely used in the US to diagnose LD, especially in patients who are seronegative, the reliability of the urine antigen detection assay for LD is highly questionable.[8] Its use cannot be recommended at this time. Tests for antigen-antibody complexes in blood and CSF have been used in research settings, but are not commercially available.

PCR has been used to detect borrelial DNA in clinical specimens, including skin biopsies, plasma, synovial fluid, CSF, and urine. In patients with treatment-resistant Lyme arthritis, PCR has been shown to be superior to culture and has been used to guide management decisions.[9] Despite early claims of high sensitivity of PCR in the diagnosis of Lyme neuroborreliosis, more current experience suggests that the usefulness of this test on CSF samples is more limited. The finding of urinary borrelial DNA by PCR has been shown to correlate with disease activity,[10] but the sensitivity of the test in this setting is not sufficiently high for routine diagnostic use.

The clinician must be aware that laboratories differ in their methodologies and reporting of results. Some laboratories have developed notoriety for high rates of positive results, including cultures, which may not be reproducible in other laboratories. Positive serologic tests in persons without past or current clinical findings of LD may need to be interpreted cautiously with these points in mind. Hence, one must use care in both ordering and interpreting tests for *B. burgdorferi*.

Table II. Antibacterials useful for treating Lyme disease (LD), based on clinical situation[a]

Clinical manifestation	Usual treatment	Alternative agents	Dosages
Early localized LD	Doxycycline PO[b]	Macrolides (erythromycin, clarithromycin, azithromycin)	Doxycycline: 100mg bid (pediatric: 2–4 mg/kg/day divided bid) Erythromycin: 250mg qid (pediatric: no data for LD) Clarithromycin: 500mg bid (pediatric: no data for LD) Azithromycin: 500mg day 1 and 250mg od (pediatric: no data for LD)
	Amoxicillin[b]		Amoxicillin: 500mg tid (pediatric: 50 mg/kg/day divided tid)
	Cefuroxime axetil		Cefuroxime axetil 500mg bid (pediatric: 20–30 mg/kg/day divided bid)
Early disseminated LD			
No CNS involvement, no more than first-degree heart block	Doxycycline PO[b] Amoxicillin Cefuroxime axetil	Macrolides	Doxycycline: as above Amoxicillin: as above Cefuroxime axetil: as above
With CNS involvement, symptomatic carditis, PR interval >0.3 seconds, or second- or third-degree heart block	Ceftriaxone IV[b]	Penicillin G (benzylpenicillin) IV Doxycycline IV, PO	Ceftriaxone: 2g od (pediatric: 100 mg/kg/day) Penicillin G: 20 million units/day divided q4–6h (pediatric: 200 000–400 000/kg/day divided q4–6h) Doxycycline: as above
Late LD			
Arthritis	Doxycycline PO[b]	Ceftriaxone IV[c]	Doxycycline and ceftriaxone: as above
	Amoxicillin[b]	Penicillin G IV[c]	Amoxicillin and penicillin G: as above
CNS involvement	Ceftriaxone IV[b]	Penicillin G IV	Ceftriaxone and penicillin G: as above
		Doxycycline IV, PO	Doxycycline: as above

a See text for details and duration of treatment.

b Agent of choice.

c For patients with severe or refractory disease.

bid = twice daily; **IV** = intravenously; **od** = once daily; **PO** = orally; **PR** = PR interval on the ECG; **qid** = four times daily; **q*x*h** = every *x* hour; **tid** = three times daily.

3. Treatment: Antibacterials

A variety of antibacterials show good *in vitro* activity against *B. burgdorferi*.[11-13] These include penicillin and amoxicillin, several third-generation cephalosporins, macrolides, and tetracyclines, particularly doxycycline. Fluoroquinolones are less active than other antibacterials *in vitro*.

Most of the current published treatment recommendations derive from US and European studies, and from expert opinion. The most important considerations in antibacterial selection for a given situation are the clinical manifestations and organ system involvement. For example, aggressive therapy using parenteral antibacterials is recommended for more serious disease, such as CNS involvement or third-degree heart block, while early localized disease usually responds well to a course of oral therapy. Recommendations for the treatment of LD, based on clinical situation, are given in table II.

For early disease not involving the CNS, a tetracycline is the agent of choice. Advantages of tetracyclines include their good *in vitro* activity against *B. burgdorferi*, and their long, established track record in clinical trials and practice. Doxycycline is often considered the best drug in this class, based on its excellent bioavailability, ease of dose administration (twice daily), and better tolerability. Because it is lipophilic, doxycycline also has reasonably good CNS penetration (up to 26% of plasma levels[14]). Two studies from Europe involving patients with early neuroborreliosis have shown the efficacy of doxycycline to be comparable

with that of parenteral penicillin G (benzylpenicillin)[15] or ceftriaxone;[16] similar studies have not been performed in the US. Doxycycline also compared favorably with parenteral ceftriaxone for early disseminated LD, not involving the CNS.[17] A retrospective study suggested that tetracycline, given for a mean of 4 months, was successful in treating chronic infection.[18] In patients with early disseminated disease, which can involve the CNS, doxycycline is preferred over alternative oral antibacterials which do not attain adequate CNS levels (if CNS infection is established, parenteral therapy is recommended – see below). Another advantage of doxycycline is that it is considered the agent of choice for treating human granulocytic ehrlichiosis, which is transmitted by deer ticks and may occur simultaneously with LD in some geographic areas. Disadvantages of the tetracyclines include the potential hazards to the fetus and young child, photosensitivity reactions, and esophageal ulcerations. Although tetracyclines are usually avoided in the young child, therapeutic courses of doxycycline can be given with minimal risk of dental staining;[19] however, prolonged and repeated courses should be avoided.

Of the oral β-lactam antibiotics, amoxicillin and cefuroxime axetil have been the most extensively studied in clinical trials of LD. The combination of amoxicillin with probenecid (to increase serum antibiotic levels) demonstrated efficacy comparable to doxycycline in a trial of adult patients with early LD,[20] and in adults with Lyme arthritis.[21] However, in the latter study, subsequent neurologic involvement appeared more frequently in patients who received amoxicillin. Based on its *in vitro* activity and on limited published studies, amoxicillin is considered the oral agent of choice for children <8 years of age. One recent prospective study appears to support the efficacy of amoxicillin in treating early LD in that population.[22]

Cefuroxime axetil has been compared with doxycycline in adults with early LD[23,24] and appears to have equal efficacy, with fewer adverse reactions. A pediatric trial[22] showed the efficacy and safety of cefuroxime axetil to be comparable with those of amoxicillin. Cefuroxime axetil is more expensive than doxycycline or amoxicillin. Oral third-generation cephalosporins have been less well studied.

Erythromycin is active *in vitro* against *B. burgdorferi*, but has not been found to perform well in clinical practice.[25] It is generally considered a third-line agent. Clarithromycin has been evaluated in one noncomparative pilot study[26] which found efficacy similar to that reported for other agents in early LD. In some studies, the efficacy of azithromycin has been shown to be comparable to that of amoxicillin/probenecid and doxycycline;[27,28] however, another trial demonstrated amoxicillin to be more effective in resolving acute manifestations and preventing additional symptoms than azithromycin.[29] A potential drawback to the use of macrolides is their relatively poor penetration into the CNS.

The parenteral agents that have been most extensively evaluated are penicillin G and the third-generation cephalosporins, cefotaxime and ceftriaxone. The latter agents have better *in vitro* activity against *B. burgdorferi*, attain higher serum concentrations, and have superior penetration into the CNS. Studies comparing the efficacy of these agents have generally favored the cephalosporins for early disseminated and late LD. For patients with CNS involvement, they are considered the agents of choice. The ease of once daily dose administration has made ceftriaxone a suitable agent for outpatient intravenous therapy. While it can be relatively safe to use, the prolonged use of ceftriaxone in the treatment of LD has been reported to result in biliary complications, including among patients with unsubstantiated diagnoses.[30] The literature generally does not support the use of ceftriaxone for courses longer than 4 weeks.[31]

4. Specific Treatment Issues

4.1 Facial Palsy

Peripheral facial nerve palsy (PFNP) is, by far, the most common and well studied of the LD-associated cranial neuropathies. In LD endemic areas, LD is probably the most common identifiable cause of PFNP (particularly if the palsy is bilateral).[32] Standard recommendations have advocated oral antibacterial therapy for patients with isolated PFNP. However, it should be noted that among both adult[33] and pediatric[34] patients with PFNP, CSF abnormalities are frequently observed, including the presence of lymphocytic pleocytosis, antibody to *B. burgdorferi*, and borrelial DNA. The significance of this from a treatment perspective is not absolutely clear. In fact, a retrospective European study of patients who had had PFNP in the era before LD was recognized and treated with antibacterials, found no pattern of neurologic or other sequelae attributable to LD, even though a number of them probably had LD-associated PFNP.[35] However, the potential exists for significant CNS sequelae in some patients with PFNP, just as with LD-associated meningitis. Experts are divided on the issue of whether all cases of LD-associated PFNP should have a CSF evaluation.[31] Clearly, however, the clinician practicing in an

endemic area should evaluate patients with PFNP carefully, including obtaining LD serology, and perform lumbar puncture if the symptom history or physical signs suggest CNS involvement. Oral doxycycline can be used to treat such patients, but if CSF abnormalities are discovered, parenteral ceftriaxone would offer the best chance for eradication of CNS infection.

4.2 LD-Associated Arthritis

Approximately 90% of patients with arthritis respond to a 4-week course of oral antibacterials.[21] Some patients may continue to have joint swelling and other symptoms at the completion of treatment, but most of these resolve with time and can be treated symptomatically with NSAIDs. Patients whose symptoms do not resolve may require a second course of oral antibacterial or a course of intravenous antibacterial. PCR testing of synovial fluid has been used to guide treatment decisions in such situations. If there is evidence of concomitant CNS involvement, parenteral therapy with ceftriaxone may offer a better cure rate.[36] A small minority of patients have an antibacterial treatment-resistant arthritis. These patients usually have the HLA-DR4 haplotype[2] (this genetic marker is found in about 20% of the general population, and testing for it is rarely needed in clinical practice).

4.3 Duration of Treatment

Antibacterial therapy can hasten clinical resolution and prevent the occurrence of late complications, but no studies have clearly defined the optimum duration of treatment. Furthermore, surveys of physicians' practices suggest that there is no consensus among practitioners.[37,38] A 1989 study from Europe suggested that a 10-day course of oral antibacterials for early LD could result not only in a poor clinical response, but also in the ability to cultivate *B. burgdorferi* from affected tissues in some such patients.[39] Other research has indicated that treatment of LD-associated meningitis for only 10 days has been associated with a high rate of residual symptoms.[40,41] Most standard recommendations give a minimum duration of treatment, for any disease manifestation, of 2 weeks. Uncomplicated early disease is generally treated for 2–4 weeks with an oral antibacterial. As arthritis can be slow to resolve, and because of the small failure rate of oral therapy in arthritis, a 4-week course is usually recommended. Aseptic meningitis should be treated with a minimum of 2 weeks of intravenous ceftriaxone; treatment may be extended 1–2 weeks, depending on the response of the patient.

LD-associated chronic neurologic disease (often manifested by subtle cognitive impairment) is challenging to define and manage. Some experts question whether chronic CNS infection actually exists as a diagnostic entity.[31] Patients with 'chronic LD', as it is often called, have been treated with prolonged and often inappropriate therapy,[30,31,37] sometimes with significant adverse drug reactions. Oral doxycycline, given for 1–11 months, was reported to be efficacious in one uncontrolled study of patients diagnosed with chronic LD.[18] A recent placebo-controlled study involving adult patients with persistent symptoms and a history of LD was unable to demonstrate any benefit from a 30-day course of intravenous ceftriaxone, followed by a 60-day course of oral doxycycline.[42] With respect to neurocognitive functioning, children who have had LD appear to have a good prognosis,[43,44] possibly better than that of adults with LD.

4.4 LD in Pregnancy

Transmission of *B. burgdorferi* from mother to fetus has been described, but appears to be extremely uncommon. The literature has suggested that proven vertical infections (which are rare) have been associated with pronounced, even fatal, abnormalities of the fetus and newborn. However, the evidence that LD in pregnancy can have adverse effects on pregnancy outcome has been recently reviewed,[45] with the conclusion that no clear-cut pattern of teratogenic effects or neonatal infection has been identified. Pregnant women should be treated in accordance with treatment recommendations for nonpregnant adults, with the exception that tetracyclines should be avoided because of their effect on fetal bones and teeth. The well appearing infant of a mother who has had LD probably needs no special evaluation or treatment.

4.5 Adjunctive Therapies

In addition to antibacterial therapy of the infection, some patients may benefit from supplementary therapies. NSAIDs are often used to treat constitutional symptoms, as well as arthritis. Topical eye care is often required for patients who are unable to close their eyelids due to facial palsy. Increased intracranial pressure associated with acute CNS disease may respond to acetazolamide. Synovectomy may be necessary in a small minority of patients with arthritis refractory to antibacterial therapy.[46]

4.6 Economics of Treatments for LD

Costs of laboratory diagnosis, office visits, antibacterial acquisition and administration, possible morbidity, and cost of treatment failures must be considered in a cost-effectiveness analysis. Oral doxycycline given for 3 weeks was compared with intravenous ceftriaxone administered at home for 2 weeks in a model which evaluated multiple possible scenarios.[47] Doxycycline proved to be considerably more cost effective. Another study evaluated several testing/treatment strategies for patients with suspected LD.[48] In this study, for patients with only constitutional symptoms, the no test/no treatment approach was the most cost effective. For patients with an EM rash, empiric doxycycline therapy without testing was the best strategy. For patients with constitutional symptoms, and a history of tick bite and nondiagnostic rash, the most cost effective approach was serologic testing, with doxycycline provided only for those with positive results.

Prolonged intravenous treatment of LD can be a very costly proposition, in addition to posing hazards of adverse drug reactions.

5. Prevention

5.1 Anti-Tick Measures

Until recently, the emphasis on the prevention of LD has focused on efforts to reduce the likelihood of tick attachment. Avoidance of tick infested areas is often recommended, but evidence suggests that many people acquire infection in their home environment.[49] Removal of leaf litter (larval deer ticks attach to leaves) can reduce the risk of acquiring LD at home. Personal protective measures include wearing light colored clothing, wearing long sleeves and long pants, tucking pants legs into socks, and application of DEET (diethyltoluamide) or other tick repellants to skin or clothing; although frequently recommended, these measures have not been demonstrated to reliably prevent LD in case-control studies. Tick checks, in order to identify and remove *Ixodes* ticks, should be performed after potential exposures. If a deer tick is found, it should be grasped with forceps or tweezers close to the mouth parts and pulled directly outward. If the attachment is <24 hours, human infection can usually be prevented.

5.2 Antibacterial Prophylaxis for Tick Attachments

In a study of antibacterial prophylaxis in an endemic area (Connecticut, USA), it was reported that, while the risk of acquiring LD from a given deer tick attachment was 1.2%, no efficacy of prophylaxis could be established.[50] A meta-analysis of several studies comparing antibacterial prophylaxis to placebo also concluded that antibacterials were not significantly effective in preventing clinical LD.[51] The adverse effects associated with antibacterial usage were noted in these studies.

A recent study conducted in a hyperendemic area of New York, USA compared a single 200mg oral dose of doxycycline with placebo in individuals ≥12 years who had documented *Ixodes scapularis* attachments.[52] In that study, EM developed in 0.4% of doxycycline recipients compared with 3.2% in the placebo group, which was a significant difference. No extracutaneous manifestations of LD occurred in any participant and there were no asymptomatic seroconversions. Nausea and vomiting were common in doxycycline recipients.

The cost-effectiveness of prophylaxis has been studied[53] with the authors suggesting that antibacterials would be clearly justified only if the risk of infection after a tick bite were >3.6%; this level of risk may apply in a few communities. In the New York study,[52] a minimum of 40 deer tick attachments would need to be treated to prevent one case of EM. The clinical utility and cost-effectiveness in less endemic regions would be questionable.

The majority of authorities have recommended that for most instances of tick attachment, the patient should be advised to be vigilant about rashes and constitutional symptoms and to seek medical care if they occur, and that antibacterials should not be given prophylactically. Circumstances in which prophylactic antibacterials might be more prudent include: (i) people who have multiple simultaneous tick attachments; (ii) tick bites in which the tick was engorged, indicating prolonged attachment and greater risk;[54] and (iii) patients with neurologic conditions or arthritis. If a course of antibacterial prophylaxis is deemed necessary, it should be given promptly; single dose doxycycline would be reasonable for older children and adults, but safety and efficacy of a regimen for younger children and pregnant women has not been established.

5.3 Vaccination

Most efforts to develop a LD vaccine have focused on the outer surface protein A (ospA) of *B. burgdorferi*. This protein is ex-

pressed by organisms residing in the tick vector, but is largely replaced by the expression of ospC after the spirochete enters the human host. OspA vaccines are believed to work in the following unique fashion: after immunization, the human responds with production of IgG antibody, which is ingested by the tick during its blood meal; antibody to ospA is lethal to the spirochete within the tick, so that viable organisms never reach the human. Recombinant ospA vaccines are produced in an *Escherichia coli* vector, purified, and in the case of the recently marketed vaccine, combined with an aluminum hydroxide adjuvant.

Two studies involving intramuscularly administered ospA vaccines, which were simultaneously reported,[6,55] demonstrated impressive efficacy in preventing LD. As a result of the pivotal trial of the ospA vaccine manufactured by GlaxoSmithKline, LYMErix™[1] was licensed in late 1998 for use in adults. In that trial by Steere et al.,[6] volunteers aged between 15 and 70 years were randomized to receive either placebo or 30μg doses of ospA at 0, 1, and 12 months. The vaccine was shown to be immunogenic, with a significant anamnestic response following the third dose. After the third dose, vaccine efficacy was 76%. A study involving 4000 US children aged between 4 and 18 years compared three doses of ospA 30μg versus placebo given at 0, 1, and 12 months.[56] The vaccine was highly immunogenic, with antibody titers far exceeding those demonstrated in adult trials. This study did not examine vaccine efficacy.

The role of vaccination against LD has been debated and, although the vaccine was generally considered to be well tolerated in clinical trials, theoretical concerns about its safety have been articulated. Due to economic considerations, the manufacturer has recently discontinued production and marketing of the vaccine.

A note of caution should be made concerning the effect of the LD vaccine on serologic testing in patients who have been vaccinated, in that the ospA antibody can cause the standard ELISA test to be positive. The western blot will also have a 31kD band corresponding to ospA antibody, but theoretically no other bands should appear in the absence of natural infection with *B. burgdorferi*. Hence, the western blot is the critical serologic test in immunized individuals who are suspected of having LD. However, some western blot tests have given unusual patterns of reactivity in patients who have been immunized.[57] This phenomenon requires further study and may incur the need for alternative serologic methods. The C6 ELISA antibody test, which does not involve the ospA protein, may prove useful in this setting.

6. Conclusions

LD has become a major public health problem in many geographic areas. Approaches to diagnosis, patient management, and prevention of disease must take into account the epidemiology, the biology of *B. burgdorferi*, natural history of the infection, and scientific studies of the host response and the use of antibacterial therapy.

Accurate diagnosis of LD is usually possible with careful attention to physical findings, and the use of standard ELISA and western blot technology. Newer diagnostic modalities have refined the ability to identify infection in certain clinical situations. Understanding the limitations of various diagnostic tests is important for clinicians who may wish to verify or rule out a diagnosis of LD.

Most patients with early LD respond favorably to oral antibacterial therapy. However, early neurologic involvement and higher degrees of cardiac conduction disturbance should be treated with parenteral therapy. LD-associated arthritis also can be treated with oral agents, but some patients may require more aggressive treatment.

Prevention of LD occurs at the level of the individual patient, as well as at the societal level. Modifying the environment to be less favorable to the tick life cycle, modifying behaviors to avoid contact with ticks, and timely removal of attached ticks are methods that may reduce the occurrence of LD. Antibacterial prophylaxis for tick attachments offers protection in certain situations. Preventing LD by vaccination has been successful in the past; development and implementation of new vaccine strategies will require further research.

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1 The use of tradenames is for product identification purposes only and does not imply endorsement.

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