Prevention of Lyme Disease

ABSTRACT. Lyme disease is currently the most frequently reported vector-borne illness in the United States, accounting for more than 95% of such cases. The purpose of this report is to provide recommendations for preventing Lyme disease, including the use of a Lyme disease vaccine. Individuals can reduce their risk of Lyme disease by avoiding tick-infested habitats when in endemic areas. If exposure to tick-infested habitats cannot be avoided, individuals may reduce their risk of infection by using repellents, wearing protective clothing, and regularly checking for and removing attached ticks. Morbidity from Lyme disease can be reduced significantly by detecting and treating the infection in its early stages; early and appropriate treatment almost always results in a prompt and uncomplicated cure. A Lyme disease vaccine (LYMErix, SmithKline Beecham, Collegeville, PA) was licensed by the US Food and Drug Administration on December 21, 1998, for persons 15 to 70 years of age. This vaccine seems to be safe and effective, but whether its use is cost-effective has yet to be clearly established. Use of this vaccine causes false-positive enzyme immunoassay results for Lyme disease. Lyme disease can be diagnosed in vaccinated persons by immunoblot testing. Decisions about the use of this vaccine should be based on an assessment of a person’s risk as determined by activities and behaviors relating to tick exposure in endemic areas. This vaccine should be considered an adjunct to, not a replacement for, the practice of personal protective measures against tick exposure and the early diagnosis and treatment of Lyme disease.

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

PREVENTION OF TICK BITES

The ticks that can transmit Lyme disease (Ixodes scapularis, also known as the black-legged or deer tick in the eastern United States, and Ixodes pacificus, also known as the western black-legged tick in the western United States) are found in wooded areas, high grasses, marshes, gardens, and beach areas. In endemic residential areas, clearing brush and trees, removing leaf litter and woodpiles, and keeping grass mowed may reduce tick exposure by removing habitats suitable for ticks and their reservoir hosts. Area application of pesticides to residential properties is effective for suppressing vector ticks but may be harmful to other wildlife and people. Exclusion of deer from residential yards by fencing and maintaining tick-free pets also may reduce tick exposure.

Heavily infested tick habitats, such as wooded areas, should be avoided if possible. If not possible, then use of wide trails, not straying off the trail, and not sitting on the ground may decrease exposure. Careful attention also should be given to clothing worn in these areas. Clothing should be light-colored to make tick identification easier. Long sleeves and long pants that are tight at the wrists, ankles, and waist, and long pants tucked into light colored socks are preferable. A hat should be worn in densely wooded areas.

Tick and insect repellents that contain n,n-diethyl-m-toluamide (DEET) applied to the skin provide additional protection but require reapplication every 1 to 2 hours for maximum effectiveness. Although serious neurologic complications in children resulting from the frequent and excessive application of DEET-containing repellents have been reported, they are rare, and the risk is low when these compounds are used as directed.
are used according to product label instructions.\textsuperscript{15–17} Therefore, DEET should be applied sparingly, according to product label instructions, only to exposed skin, and not to a child’s face, hands, or skin that is irritated or abraded. After the child returns indoors, treated skin should be washed with soap and water. Concentrations of DEET greater than 30\% usually are not necessary. Permethrin (a synthetic pyrethroid) is available in a repellent spray for application to clothing only and is particularly effective because it kills ticks on contact.

Persons should be taught to inspect themselves and their children’s bodies and clothing daily after possible tick exposure. Special attention should be given to the exposed hairy regions of the body where ticks often attach, including the heads and necks of children.

Because animal studies indicate that transmission of \textit{B burgdorferi} from infected ticks usually requires a prolonged duration of attachment ($\geq 48$ hours), ticks should be removed promptly.\textsuperscript{18,19} The body of the tick should not be squeezed during removal. It should be grasped with a fine tweezers as close to the skin as possible and removed by gently pulling the tick straight out without twisting motions. If fingers are used to remove ticks, they should be protected with gloves or facial tissue and washed after removal of the tick. Analysis of ticks to determine if they are infected is not indicated because the predictive values of such tests in relation to the development of human disease are unknown.

**MANAGEMENT OF TICK BITES**

In many areas of the United States, the economic impact of inappropriate use of prophylactic antimicrobial agents and serologic testing for Lyme disease after deer tick bites has been substantial.\textsuperscript{20} Antibiotic Prophylaxis

Routine use of antimicrobial agents to prevent Lyme disease after a deer tick bite, even in highly endemic areas, is not recommended because it is of unproven value and is associated with potential risks and costs.\textsuperscript{21–24} Most deer ticks (70\%–80\%), even in highly endemic areas for Lyme disease, are not infected with \textit{B burgdorferi},\textsuperscript{24} and the risk of infection after a recognized deer tick bite in an endemic area is estimated to be only about 1.4\%.\textsuperscript{23} Furthermore, almost all persons who become infected from a recognized deer tick bite will develop erythema migrans at the site of the bite, which is easily recognized and diagnostic of early Lyme disease. Children with this stage of disease can be treated easily and effectively with little risk of long-term complications.\textsuperscript{25} Based on current data, the risk of developing late Lyme disease from a recognized deer tick bite that was not treated with an antimicrobial agent and was not followed by the appearance of erythema migrans is extremely low.\textsuperscript{20} Three prospective controlled studies comparing placebo and antimicrobial prophylaxis management of tick bites have been unable to demonstrate the effectiveness of antimicrobial prophylaxis for preventing Lyme disease because of the low risk of infection or disease.\textsuperscript{22} Because the majority of tick bites are unrecognized, empiric therapy after recognized tick bites is unlikely to reduce the overall number of cases.\textsuperscript{22} Furthermore, the nature and duration of a prophylactic regimen have not been established, and prophylactic antimicrobial agents may be associated with adverse reactions and increased health care costs.

**Serologic Testing**

Serologic testing for Lyme disease at the time of a recognized tick bite is not recommended.\textsuperscript{20} There is little or no chance that a patient would have detect-
able antibodies to B burgdorferi from a new infection at the time of the tick bite, and antibodies present at the time would likely represent a false-positive result or evidence of an earlier infection. Although some physicians obtain a serum sample at the time of a tick bite and 6 to 8 weeks later for antibody testing to provide reassurance in the absence of erythema migrans and antibiotic therapy, this practice usually is unnecessary, especially with evidence that the tick was attached for less than 48 hours, and the results may be misleading because of the inaccuracy of serologic testing for Lyme disease in many laboratories. There is a high probability of a false-positive serologic test result for Lyme disease when the probability of the presence of Lyme disease is low.

LYME DISEASE VACCINE

Animal studies have demonstrated that purified recombinant proteins, particularly of certain outer surface proteins (Osp) of B burgdorferi, such as Osp A, B, and C, induce antibody responses that are highly protective. The most extensively studied of the single Osp vaccines and the one currently licensed contains recombinant OspA (rOspA), which is highly protective in the mouse model when the challenge strain is homologous or closely related to the isolate from which the OspA was derived. However, when the challenge strain is different from the isolate from which the OspA was derived, protection to challenge is minimal or nonexistent.

MECHANISM OF ACTION

The rOspA vaccine seems to have a unique mode of action. Antibodies directed against the OspA are lethal to the organism, although the exact mechanism by which the antibody kills B burgdorferi is unknown. OspA is expressed by B burgdorferi residing in the midguts of dormant ticks, but expression is later downregulated in response to a blood meal. Therefore, patients with natural B burgdorferi infection have little exposure to OspA and minimal or absent antibody responses to OspA. Data from animal models suggest that protective OspA antibodies from the immunized host destroy B burgdorferi in the midgut of the tick, preventing transmission to the host. The vaccine-induced protection thus occurs primarily before the B burgdorferi enters the host.

Antigenic differences in OspA have been observed between and within B burgdorferi genospecies, including B burgdorferi sensu stricto, Borrelia afzelii, and Borrelia garinii. In addition, strains with mutations, frame shifts, or recombinations between OspA and Osp B have been isolated. Therefore, there has been concern that a single OspA antigen cloned from a single isolate, may be insufficient to provide broad cross-protective immunity, and it may be necessary to use different OspAs in the development of vaccines intended for use in North America and Europe. However, the diversity of OspA among isolates is greatest among European strains. Isolates in the United States seem to be much more homogeneous, suggesting that a single OspA antigen may be sufficient for a vaccine in this country.

CLINICAL TRIALS IN HUMANS

Early clinical trials, including subjects with a history of Lyme disease, demonstrated that rOspA was immunogenic and well-tolerated. Lyme disease vaccines have been produced by 2 manufacturers and field tested for safety and efficacy in humans. Both vaccines are made from a rOspA expressed in Escherichia coli and purified. A lipid moiety was added after translation. LYMErix (Smith-Kline Beecham, Collegeville, PA) is prepared by using the OspA gene from B burgdorferi and contains 30 µg of purified rOspA lipidated protein combined with 0.5 mg of aluminum adjuvant. LYMErix is the only licensed Lyme disease vaccine at this time. The recommendations in the present statement apply only to the use of LYMErix; supplemental information will be provided as additional Lyme disease vaccines are licensed. A vaccine produced by Pasteur Mérieux Connaught (Swiftwater, PA), ImmuLyme, contains 30 µg of purified rOspA lipidated protein without adjuvant and is under review by the US Food and Drug Administration.

ROUTE OF ADMINISTRATION, IMMUNIZATION SCHEDULE, AND DOSAGE

Three doses of 0.5 mL (30 µg) of rOspA vaccine administered by intramuscular injection are required for optimal protection; the second dose is given 1 month later, and a third dose is given 12 months after the first dose. Dosages should be timed so that the second and the third doses are given several weeks before the start of the Lyme disease transmission season, which usually begins in April.

Preliminary data suggest that other immunization schedules (eg, 0, 1, 6 months) are safe and induce antibody responses similar to the 0, 1, 12 month schedule. However, at this time, only the 0, 1, 12 month schedule is approved by the US Food and Drug Administration.

Efficacy

Steere and coworkers conducted a multicenter, double-blind, randomized, placebo-controlled trial involving 10 936 subjects between 15 and 70 years of age. LYMErix or placebo was administered at enrollment and 1 and 12 months later. In the first year after 2 injections, the vaccine efficacy for preventing clinical Lyme disease was 49% (95% confidence interval, 15%–69%). In the second year after the third injection, the vaccine efficacy for preventing clinical Lyme disease was 76% (95% confidence interval, 58%–86%). Serologic testing was performed on study subjects at entry and 12 and 20 months later to detect asymptomatic infections with B burgdorferi. The efficacy of this vaccine for preventing asymptomatic infection was 83% in the first year after 2 doses and 100% in the second year after 3 doses. There was no evidence that the vaccine produced partial protection or mild or asymptomatic disease that could be reactivated later.

IMMUNOGENICITY

In the study by Steere and coworkers, a subset of adult subjects was evaluated longitudinally over 20 months for serum concentrations of anti-OspA anti-
bodies. At month 2 (1 month after the second injection), the geometric mean antibody titer (GMT) of immunoglobulin G anti-OspA antibodies was 1227 enzyme-linked immunosorbent assay (ELISA) units per milliliter. At month 12 (before the third injection), the GMT was 116 ELISA units per milliliter. At month 13 (1 month after the third injection), the GMT was 6006 ELISA units per milliliter, but by month 20, the GMT was 1991 ELISA units per milliliter. Although not yet established, attempts are being made to determine a correlate of protection.37

Whether protective immunity will last longer than 1 year beyond the month 12 dose is unknown. These data suggest that boosters beyond the month 12 booster may be necessary.33,37 However, additional data are needed before recommendations about immunization with more than 3 doses of rOspA vaccine can be made.

SAFETY

The rOspA vaccine seems to be safe. In the study by Steere and coworkers,33 soreness at the injection site was the most frequently reported adverse event, reported without solicitation by 24% of the recipients of vaccine and 8% of the recipients of placebo (P < .001). Redness and swelling at the injection site also were reported in significantly more recipients of vaccine (2%) than of placebo (1%). In addition, significantly more recipients of vaccine than placebo reported systemic symptoms (eg, myalgias, achiness, fever, chills), but none of these symptoms was reported by more than 3% of the subjects in either group. These adverse reactions usually occurred within 48 hours after immunization and lasted a median of 3 days. The type and frequency of symptoms 30 days or more after the injections did not differ significantly between recipients of vaccine and placebo. Symptoms were usually mild or moderate in severity, and the severity usually did not increase with subsequent injections. No hypersensitivity reactions were noted. There was no evidence that the rOspA vaccine exacerbated prior Lyme arthritis, caused arthritis in subjects with a history of Lyme disease or those without such a history, or caused neurologic disease.

The possibility that a rOspA vaccine could predispose to arthritis in selected persons with a genetic predisposition to this disorder exists, but no evidence of this effect has been noted. Approximately 10% of adults and fewer than 5% of children with Lyme arthritis develop inflammatory joint disease that does not respond to antimicrobial agents and typically affects 1 knee for months to years.38,39 Because of the increased frequency of certain HLA-DR4 alleles in these patients, an autoimmune mechanism has been proposed. Gross and coworkers40 showed that the immunodominant T-cell epitope of OspA bound by the HLA-DRB1*0401 molecule was antigenically cross-reactive with human leukocyte function-associated antigen-1, which could be a potential autoantigen. Persons with antibiotic treatment–resistant Lyme arthritis generated responses to OspA, human leukocyte function-associated antigen-1, and their closely related peptide epitopes, supporting a possible autoimmune mechanism involving OspA antigen associated with B burgdorferi.

Arthritis occurred no more often in vaccine recipients than in the placebo recipients, including patients who had had Lyme disease and those who carry the HLA DR4 allele, although the number of such patients was limited. Thus, there is no evidence that rOspA vaccine predisposes to chronic arthritis.

Safety and efficacy of rOspA vaccine has not been established in persons older than 70 years of age or younger than 15 years of age. Therefore, this vaccine is licensed only for use in persons 15 to 70 years of age. Studies are in progress to determine the safety and immunogenicity of rOspA vaccine for children 5 to 15 years of age.41

DIAGNOSIS OF LYME DISEASE IN VACCINE RECIPIENTS

Recipients of the rOspA vaccine have a positive ELISA test result because whole-cell B burgdorferi is used as the antigen. The interpretation of Western immunoblot results are not affected by immunization because antibody to specific protein antigens allows identification of non-OspA antibodies, and antibody to OspA is not part of the criteria for a positive immunoblot result.42 Therefore, immunoblot testing for non-OspA antibody reactivity is essential for establishing or excluding the diagnosis of Lyme disease in rOspA vaccine recipients.

COST-EFFECTIVENESS ANALYSIS

Although the cost of Lyme disease has been evaluated,43 there are few published cost-effectiveness analyses of using rOspA vaccines to prevent Lyme disease. A recent analysis by the CDC indicates that the cost of immunizing exceeds the cost of not immunizing unless the incidence of Lyme disease is more than 1% per year.44 This analysis did not consider the costs of overdiagnosis and incorrect treatment of disorders falsely attributed to Lyme disease. Most endemic states and counties report Lyme disease incidence rates that are well below 1% per year. However, some studies suggest that only 10% to 15% of physician-diagnosed cases of Lyme disease are reported to state authorities in highly endemic areas.45,46

ASSESSING THE RISK OF LYME DISEASE

The decision to recommend Lyme disease vaccine should be based on a determination of risk of being bitten by tick vectors infected with B burgdorferi. This likelihood is affected by the density of vector ticks in the environment, the prevalence of B burgdorferi infection among those ticks, and individual behavior. The geographic areas of the United States with a high density of infected vector ticks are concentrated within a few northeastern and north-central states (Fig 1). However, the risk of Lyme disease within these states differs greatly, not only from one county to another, but even within counties and townships. Detailed information on the distribution of Lyme disease risk within specific areas is best obtained from local and state health departments. The accompanying map (Fig 1) identifies counties as high, moderate, low, or no risk for Lyme disease based on density of infected vector ticks and reported human cases. Activities that involve frequent or prolonged ex-
pros to tick-infested habitats (eg, wooded, brushy, or overgrown grassy areas) substantially increase risk. Avoidance of tick-infested habitats and use of repellents may substantially reduce risk. When preventive measures have failed, morbidity from Lyme disease can be reduced substantially by detecting and treating persons with Lyme disease in the early stages.

Because of the limited time of exposure, travelers to endemic areas generally are expected to be at lower risk of Lyme disease than persons who permanently reside in those areas. The desirability of immunization for travelers to areas of high risk during Lyme disease transmission season depends on the anticipated exposure to vector ticks. Travelers may obtain some protection from 2 doses of vaccine, but a full series of 3 doses, beginning 1 year before anticipated exposure, is necessary to achieve optimal protection.

The Lyme disease vaccine should be considered an adjunct to, not a replacement for, the practice of personal protective measures against tick exposure and the early diagnosis and treatment of Lyme disease. Decisions about immunization to prevent Lyme disease should be based on an assessment of risk of exposure to infected ticks, use of personal protective measures against tick bites, and vaccine efficacy and costs. Lyme disease vaccine does not provide protection against other tick-borne diseases.

RECOMMENDATIONS FOR PREVENTION OF LYME DISEASE

1. Attempts to minimize exposure to vector ticks in residential areas is encouraged. Heavily tick-infested areas should be avoided, if possible. If not possible, then personal protective measures (eg, wearing specific types of clothing, use of repellents, frequent checks for ticks), and early detection and treatment of disease manifestations are encouraged.

2. Routine use of antimicrobial agents to prevent Lyme disease after a deer tick bite, even in highly endemic areas, is not recommended. Serologic testing for Lyme disease at the time of a recognized tick bite also is not recommended.

3. Use of Lyme disease vaccine

   a. The vaccine should be considered for administration to the following persons who are 15 years of age or older:
      1) Those who reside, work, or recreate in geographical areas of high or moderate risk (Fig 1) and whose activities result in frequent or prolonged exposure to vector ticks.
      2) Those who visit geographical areas of high risk (Fig 1) during the peak Lyme disease transmission season and whose activities result in frequent or prolonged exposure to vector ticks.

   b. The vaccine may be given to persons who reside, work, or recreate in geographical areas of high or moderate risk and whose activities result in some, but neither frequent nor prolonged exposure to vector ticks. However, the benefits of vaccine for these persons compared with those of personal protective measures and early treatment of Lyme disease are unclear.

   c. The vaccine is not recommended for the following:
      1) Those who reside, work, or recreate in areas of high or moderate risk but who have minimal or no exposure to infected ticks.
      2) Persons who reside, work, and recreate in geographical areas of low or no risk (Fig 1).
      3) Children younger than 15 years of age until data about the safety and immunogenicity of this vaccine in this age group are available and the US Food and Drug Administration has approved the product for use in this age group.

   d. Persons with a history of Lyme disease

      Immunization should be considered for persons with a history of Lyme disease who are at continued high risk. However, persons with antibiotic treatment-resistant Lyme arthritis should not be immunized because of the association between this condition and immune reactivity to OspA. Persons with chronic joint or neurologic illness related to Lyme disease, as well as those with second or third degree atrioventricular block were excluded from the phase III safety and efficacy trial, and, thus, the safety and efficacy of Lyme disease vaccine for such persons is unknown.

   e. Simultaneous administration with other vaccines

      The safety and efficacy of the simultaneous administration of rOspA vaccine with other vaccines have not been established. Administration of rOspA vaccine should not interfere with the administration of routinely recommended immunizations. If rOspA vaccine is to be given concurrently with other vaccines, each should be administered in a separate syringe at a separate site.

   f. Persons with immunodeficiencies

      Data are lacking on the safety and efficacy of rOspA vaccines in persons with immunodeficiencies. General guidelines for administration of inactivated or subunit vaccines should be followed (see current edition of the Red Book).

   g. Vaccine use in pregnancy

      Because the safety of rOspA vaccine administered during pregnancy has not been established, immunization of women known to be pregnant is not recommended. A vaccine pregnancy registry has been established by SmithKline Beecham Pharmaceuticals. In the event that a pregnant woman is immunized, health care professionals are encouraged to register this immunization by calling (800) 366-8900, extension 5231.

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