

Review Article

*Medical Progress*

**LYME DISEASE**

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SINCE its original description nearly 25 years ago,<sup>1</sup> Lyme disease has become recognized as an important infectious disease in the United States. The infection, which is caused by the tick-borne spirochete *Borrelia burgdorferi*, is now endemic in more than 15 states and has been responsible for focal outbreaks in some eastern coastal areas. Lyme borreliosis is also endemic in Europe and Asia, where certain aspects of the disease (erythema migrans, meningopolyneuritis, and acrodermatitis chronica atrophicans) were described in the early and mid-20th century. These syndromes were linked conclusively in 1982 and 1983 with the recovery of a previously unrecognized spirochete from the tick vector and from infected patients.<sup>2,3</sup>

Since the last review of Lyme disease in the *Journal* 12 years ago,<sup>4</sup> the number of scientific articles about this entity has increased substantially. During this period, the complete genome of the spirochete has been sequenced, animal models have been developed for studies of pathogenesis, guidelines for diagnosis and treatment have been established, and a vaccine has been developed to prevent the illness.

**EPIDEMIOLOGY AND VECTOR OF TRANSMISSION**

Since surveillance for Lyme disease was begun by the Centers for Disease Control in 1982, the number of reported cases has increased dramatically. Currently, about 15,000 cases are reported each year, making Lyme disease the most common vector-borne disease in the United States.<sup>5</sup> The disorder occurs primarily in three distinct foci: in the Northeast from Maine to Maryland, in the Midwest in Wisconsin and Minnesota, and in the West in northern California and Oregon. In Europe, Lyme borreliosis is widely established in forested areas. The highest reported frequencies of the disease are in middle Europe and Scandinavia, particularly in Germany, Austria, Slo-

venia, and Sweden.<sup>6</sup> The infection is also found in Russia, China, and Japan.

Lyme borreliosis in all locations is transmitted by ticks of the *Ixodes ricinus* complex.<sup>7,8</sup> These ticks have larval, nymphal, and adult stages; they require a blood meal at each stage. The risk of infection in a given area depends largely on the density of these ticks as well as their feeding habits and animal hosts, which have evolved differently in different locations. In the northeastern and north central United States, *I. scapularis* (also called *I. dammini*) ticks are abundant, and a highly efficient cycle of *B. burgdorferi* transmission occurs between immature larval and nymphal *I. scapularis* ticks and white-footed mice,<sup>8</sup> resulting in high rates of infection in nymphal ticks and a high frequency of Lyme disease in humans during the late spring and summer months.<sup>5</sup> The proliferation of deer, which are the preferred host of the adult tick, was a major factor in the emergence of epidemic Lyme disease in the northeastern United States during the late 20th century. In addition, *I. scapularis* is a vector for the agents of human granulocytic ehrlichiosis and babesiosis.

The vector ecology of *B. burgdorferi* is quite different in northern California and Oregon,<sup>9</sup> where the frequency of Lyme disease is low.<sup>5</sup> There, two intersecting cycles are necessary for the transmission of the disease. The spirochete is maintained in nature by the dusky-footed woodrat and *I. neotomae* ticks, which do not bite humans. Although nymphal *I. pacificus* ticks do bite humans, these ticks are usually not infected, because they prefer to feed on lizards, which are not susceptible to *B. burgdorferi* infection. Only the relatively few nymphal *I. pacificus* ticks that fed on infected woodrats when they were in the larval stage are responsible for the transmission of the spirochete to humans. Similarly, in the southeastern United States, nymphal *I. scapularis* ticks feed primarily on lizards rather than rodents, and *B. burgdorferi* infection occurs rarely, if at all, in that part of the country. There, a rash resembling erythema migrans but not caused by *B. burgdorferi* has been associated with the bite of the Lone Star tick.<sup>10</sup>

In Europe, the principal vector is *I. ricinus*, and in Asia, it is *I. persulcatus*.<sup>6</sup> These ticks are also vectors of tick-borne encephalitis virus.

**CAUSATION**

The structure of borrelia species, including *B. burgdorferi*, is similar to that of all spirochetes: a protoplasmic cylinder surrounded by periplasm containing the flagella, which is surrounded, in turn, by

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an outer membrane.<sup>11</sup> The unique feature of borrelia species is that a number of their outer-membrane proteins are encoded by plasmid genes. The complete genome of *B. burgdorferi* (strain B31) has now been sequenced.<sup>12</sup> The genome is quite small (approximately 1.5 megabases) and consists of a highly unusual linear chromosome of 950 kilobases as well as 9 linear and 12 circular plasmids.

The remarkable aspect of the *B. burgdorferi* genome is its large number of sequences for predicted or known lipoproteins,<sup>12</sup> including the plasmid-encoded outer-surface proteins (Osp) A through F. These and other differentially expressed outer-surface proteins presumably help the spirochete adapt to and survive in markedly different arthropod and mammalian environments.<sup>13</sup> In addition, during early, disseminated infection, a surface-exposed lipoprotein, called VlsE, has been reported to undergo extensive antigenic variation.<sup>14</sup> The organism has few proteins with biosynthetic activity and apparently depends on the host for most of its nutritional requirements.<sup>12</sup> The genome contains no homologues for systems that specialize in the secretion of toxins or other virulence factors. The only known virulence factors of *B. burgdorferi* are surface proteins that allow the spirochete to attach to mammalian cells.

The causative agent of Lyme disease currently consists of three pathogenic species: *B. burgdorferi*, *B. afzelii*, and *B. garinii*.<sup>15</sup> Only *B. burgdorferi* strains have

been found in the United States. In contrast, most of the illness in Europe is caused by *B. afzelii* and *B. garinii*, and only these two species have been found in Asia. The basic outlines of the disease are similar worldwide, but there are regional variations, primarily between the illness found in America and that found in Europe and Asia (Table 1).

### CLINICAL MANIFESTATIONS AND PATHOGENESIS

The clinical manifestations of Lyme disease remain basically as they were presented in the *Journal* 12 years ago.<sup>4</sup> However, much new information is available about the pathogenesis of the disease, especially from animal models of the infection. Early infection consists of localized erythema migrans (stage 1), followed within days or weeks by disseminated infection that affects the nervous system, heart, or joints in particular (stage 2) and subsequently, within weeks or months, by late or persistent infection (stage 3).

#### Skin Involvement and Early Disseminated Infection

In at least 80 percent of patients in the United States, Lyme disease begins with a slowly expanding skin lesion, erythema migrans, which occurs at the site of the tick bite (Fig. 1).<sup>4</sup> The skin lesion is frequently accompanied by influenza-like symptoms, such as malaise and fatigue, headache, arthralgias, myalgias, fever, or regional lymphadenopathy, and these symp-

TABLE 1. COMPARISON OF LYME DISEASE IN NORTH AMERICA AND EUROPE AND ASIA.

VARIABLE	NORTH AMERICA ( <i>BORRELIA BURGDORFERI</i> )	EUROPE AND ASIA ( <i>B. AFZELII</i> OR <i>B. GARINII</i> )
Skin		
Acute phase	Erythema migrans faster spreading, more intensely inflamed, and of briefer duration; frequent, possibly widespread hematogenous dissemination	Erythema migrans slower spreading, less intensely inflamed, and of longer duration; less frequent hematogenous dissemination, but possible regional or contiguous spread to other sites
Chronic phase	Acrodermatitis rarely reported	Acrodermatitis chronica atrophicans, caused primarily by <i>B. afzelii</i>
Nervous system		
Acute phase	Meningitis, severe headache, mild neck stiffness, less prominent radiculoneuritis	Severe radicular pain and pleocytosis; less prominent headache and neck stiffness, caused particularly by <i>B. garinii</i>
Chronic phase	Subtle sensory polyneuropathy without acrodermatitis	Subtle sensory polyneuropathy within areas affected by acrodermatitis
	Subtle encephalopathy, cognitive disturbance, slight intrathecal antibody production	Severe encephalomyelitis, spasticity, cognitive abnormalities, and marked intrathecal antibody production, caused primarily by <i>B. garinii</i>
Cardiac		
Acute phase	Atrioventricular block and subtle myocarditis	Atrioventricular block and subtle myocarditis
Chronic phase	None reported	Dilated cardiomyopathy
Arthritis		
Acute phase	More frequent oligoarticular arthritis, more intense joint inflammation	Less frequent oligoarticular arthritis, less intense joint inflammation
Chronic phase	Treatment-resistant arthritis in about 10 percent of patients, probably due to autoimmune mechanism	Persistent arthritis rare, probably not due to an autoimmune mechanism
Asymptomatic infection	In about 10 percent of patients	In more than 10 percent of patients
Antibody response	Expansion of response to many spirochetal proteins	Expansion of response to fewer spirochetal proteins

toms may be the presenting manifestation of the illness. In Europe, erythema migrans is often an indolent, localized infection, whereas in the United States, this lesion is associated with more intense inflammation and signs that often suggest dissemination of the spirochete.<sup>16</sup> In one U.S. study, spirochetes were cultured from plasma samples in 50 percent of patients with erythema migrans.<sup>17</sup>

A number of mechanisms may aid in the dissemination of *B. burgdorferi*. For example, the sequences of OspC vary considerably among strains, and only a few of the groups of sequences are associated with disseminated disease.<sup>18</sup> Spreading through skin and other tissue matrixes may be facilitated by the binding of human plasminogen and its activators to the surface of the spirochete.<sup>19</sup> During the dissemination and homing to specific sites, the organism attaches to certain host integrins,<sup>20,21</sup> matrix glycosaminoglycans,<sup>22</sup> and extracellular-matrix proteins.<sup>23</sup> For example, borrelia decorin-binding proteins A and B bind decorin, a glycosaminoglycan on collagen fibrils, which may explain why the organism is commonly aligned with collagen fibrils in the extracellular matrix in the heart, nervous system, or joints.<sup>22</sup> In a recent report, decorin-deficient mice had more limited spirochetal colonization of joints and milder arthritis than normal mice of the same strain that expressed decorin.<sup>24</sup>

As shown definitively in mice, inflammatory innate immune responses are critical in the control of early, disseminated infection.<sup>25,26</sup> Spirochetal lipoproteins, which bind the CD14 molecule and toll-like receptor 2 on macrophages, are potent activators of the innate immune response, leading to the production of macrophage-derived inflammatory cytokines.<sup>27</sup> In addition, type 1 helper T (Th1) cells, which are part of the adaptive immune response, are prominent early in the infection in mice.<sup>28</sup> In humans, infiltrates of macrophages and T cells in erythema migrans lesions express messenger RNA for both inflammatory and antiinflammatory cytokines.<sup>29</sup> Particularly in disseminated infection, adaptive T-cell and B-cell responses in lymph nodes lead to the production of antibody against many components of the organism.<sup>30,31</sup>

Despite the innate and adaptive immune responses, *B. burgdorferi* may sometimes survive in certain sites. In European patients, especially elderly women with *B. afzelii* infection, a chronic, slowly progressive skin condition called acrodermatitis chronica atrophicans may develop on sun-exposed acral surfaces. The organism has been cultured from such lesions as long as 10 years after the onset of the disease.<sup>32</sup> In one study, the infiltrates of T cells and macrophages in these lesions had a restricted cytokine profile, with little or no production of interferon- $\gamma$ ,<sup>29</sup> which may explain in part why the immune response is ineffective in eradicating the spirochete. Consistent with this hypothesis, ultraviolet B irradiation of C3H mice infected with *B. burgdorferi* decreased the Th1 response.<sup>33</sup>

## Neurologic Involvement

Within weeks, during or shortly after the period of early, disseminated infection, objective signs and symptoms of acute neuroborreliosis develop in about 15 percent of untreated patients in the United States.<sup>4</sup> Possible manifestations include lymphocytic meningitis with episodic headache and mild neck stiffness, subtle encephalitis with difficulty with mentation, cranial neuropathy (particularly unilateral or bilateral facial palsy), motor or sensory radiculoneuritis, mononeuritis multiplex, cerebellar ataxia, or myelitis.<sup>34,35</sup> In children, the optic nerve may also be affected because of inflammation or increased intracranial pressure, which may lead to blindness.<sup>36</sup> Even in untreated patients, acute neurologic abnormalities typically improve or resolve within weeks or months.

The spread of *B. burgdorferi* within the nervous system has been demonstrated in nonhuman primates,<sup>37</sup> the only known animal model of neuroborreliosis. In immunosuppressed monkeys, which had a larger spirochetal burden than did immunocompetent animals, *B. burgdorferi* infiltrated the leptomeninges, motor and sensory nerve roots, and dorsal-root ganglia, but not the brain parenchyma.<sup>38</sup> In the peripheral nervous system, spirochetes were seen in the perineurium, the connective-tissue sheath surrounding each bundle of peripheral-nerve fibers.

In up to 5 percent of untreated patients, *B. burgdorferi* may cause chronic neuroborreliosis, sometimes after long periods of latent infection.<sup>39</sup> In both the United States and Europe, a chronic axonal polyneuropathy may develop, manifested primarily as spinal radicular pain or distal paresthesias.<sup>35,40</sup> Electromyograms typically show diffuse involvement of both proximal and distal nerve segments. In Europe, *B. garinii* may cause chronic encephalomyelitis, characterized by spastic paraparesis, cranial neuropathy, or cognitive impairment with marked intrathecal production of antibodies against the spirochete.<sup>35</sup> In the United States, a mild, late neurologic syndrome has been reported, called Lyme encephalopathy, manifested primarily by subtle cognitive disturbances.<sup>39,41</sup> Although there are no inflammatory changes in the cerebrospinal fluid, the intrathecal production of antibodies against the spirochete can often be demonstrated. Neither single-photon-emission computed tomography of the brain nor neuropsychological tests of memory have sufficient specificity to be helpful in the diagnosis. Lyme encephalopathy may be treated successfully with a one-month course of intravenous ceftriaxone therapy,<sup>42</sup> but immune-mediated or postinfectious phenomena may also play a part in the pathogenesis of these syndromes. One unusual case of *B. burgdorferi*-induced meningoencephalitis and cerebral vasculitis has been reported that was unresponsive to antibiotics.<sup>43</sup> In this case, a T-cell clone recovered from the cerebrospinal fluid responded both to spirochetal epitopes and to autoantigens.

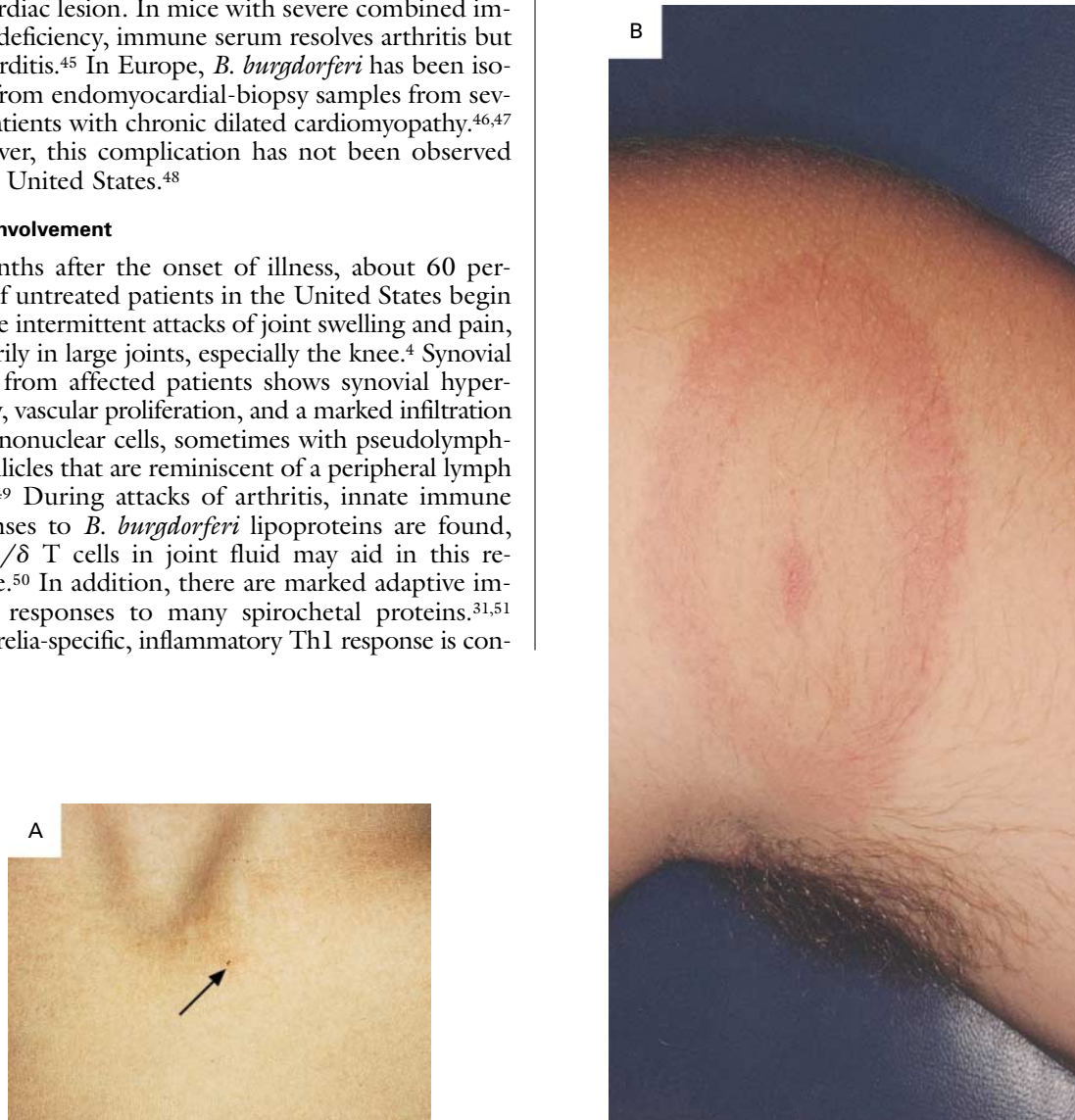
### Cardiac Involvement

Within several weeks after the onset of disease, about 5 percent of untreated patients have acute cardiac involvement — most commonly fluctuating degrees of atrioventricular block, occasionally acute myopericarditis or mild left ventricular dysfunction, and rarely cardiomegaly or fatal pancarditis.<sup>4</sup> In C3H mice, cardiac infiltrates of macrophages and T cells secrete inflammatory cytokines.<sup>44</sup> In these mice, the killing of spirochetes through cellular immune mechanisms seems to be the dominant factor in the resolution of the cardiac lesion. In mice with severe combined immunodeficiency, immune serum resolves arthritis but not carditis.<sup>45</sup> In Europe, *B. burgdorferi* has been isolated from endomyocardial-biopsy samples from several patients with chronic dilated cardiomyopathy.<sup>46,47</sup> However, this complication has not been observed in the United States.<sup>48</sup>

### Joint Involvement

Months after the onset of illness, about 60 percent of untreated patients in the United States begin to have intermittent attacks of joint swelling and pain, primarily in large joints, especially the knee.<sup>4</sup> Synovial tissue from affected patients shows synovial hypertrophy, vascular proliferation, and a marked infiltration of mononuclear cells, sometimes with pseudolymphoid follicles that are reminiscent of a peripheral lymph node.<sup>49</sup> During attacks of arthritis, innate immune responses to *B. burgdorferi* lipoproteins are found, and  $\gamma/\delta$  T cells in joint fluid may aid in this response.<sup>50</sup> In addition, there are marked adaptive immune responses to many spirochetal proteins.<sup>31,51</sup> A borrelia-specific, inflammatory Th1 response is con-

centrated in joint fluid,<sup>52,53</sup> but antiinflammatory (Th2) cytokines are also present.<sup>53</sup> Furthermore, patients with Lyme arthritis usually have higher borrelia-specific antibody titers than patients with any other manifestation of the illness, including late neuroborreliosis.<sup>31,54</sup>



**Figure 1.** The Nymphal *Ixodes scapularis* Tick (Panel A) and Various Erythema Migrans Lesions (Panels B, C, and D).

Lyme disease usually begins with a slowly expanding skin lesion, erythema migrans, which occurs at the site of a tick bite. Panel A shows a tiny (1 to 2 mm in diameter), nymphal *I. scapularis* tick (arrow) attached near the neck of a child. Panel B shows a classic erythema migrans lesion (9 cm in diameter) near the axilla. The lesion has partial central clearing, a bright red outer border, and a target center. Panel C shows a pale, homogeneous erythema migrans lesion (12 cm in diameter) on the back of a knee. Panel D shows an erythema migrans lesion (10 cm in diameter) with a vesicular center on the back of a knee. In each instance, *Borrelia burgdorferi* was isolated from a skin-biopsy sample of the lesion. (Photographs provided courtesy of Dr. Vijay Sikand, East Lyme, Conn., and the SmithKline Beecham Lyme Disease Vaccine Trial.)



The infection of inbred strains of mice has shown the importance of genetic factors in determining the severity of arthritis.<sup>25</sup> Severe, acute arthritis develops in C3H/HeJ mice that are infected with *B. burgdorferi*<sup>55</sup>; antibody against a 37-kd arthritis-resolving protein is critical in the resolution of the arthritis.<sup>56</sup> In contrast, arthritis does not develop in *B. burgdorferi*-infected C57BL/6 mice.<sup>55</sup> The components of the immune response that account for these differences between strains are not yet clear, but effective innate immune responses seem to be important in resistance to arthritis.<sup>25,26</sup>

After several brief attacks of arthritis, some patients may have persistent joint inflammation. In about 10 percent of patients, particularly those with HLA-DRB1\*0401 or related alleles,<sup>57</sup> the arthritis persists

in the knees for months or even several years after 30 days of intravenous antibiotic therapy or 60 days of oral antibiotic therapy.<sup>58</sup> In my experience, polymerase-chain-reaction (PCR) tests for *B. burgdorferi* DNA in synovium or joint fluid are almost always negative after this treatment,<sup>59,60</sup> suggesting that the live spirochetes have been eradicated. Treatment-resistant arthritis and treatment-responsive arthritis differ primarily in the cellular and humoral immune responses to OspA.<sup>51,61</sup> Such responses may be perpetuated after antibiotic treatment by OspA antigens that have been retained in the patients' dendritic cells. However, OspA antigens are not detectable in the synovial tissue of such patients by immunoperoxidase techniques.<sup>60</sup>

Autoimmunity may develop within the inflammatory milieu of affected joints in these patients be-

cause of molecular mimicry between an immunodominant T-cell epitope of OspA (OspA<sub>165-173</sub>) of *B. burgdorferi* and human-lymphocyte-function-associated antigen 1 (hLFA-1 $\alpha$ <sub>L332-340</sub>),<sup>62</sup> an adhesion molecule that is highly expressed on T cells in synovium. T cells that react to OspA<sub>165-173</sub> are concentrated in the joints of these patients.<sup>63</sup> When hLFA-1 $\alpha$ <sub>L332-340</sub> is processed and presented by the HLA-DRB1\*0401 molecule, this self peptide may behave as a partial agonist for such cells.<sup>64</sup> However, it may not be the only relevant autoantigen in treatment-resistant Lyme arthritis.

### DIAGNOSIS

The culture of *B. burgdorferi* from specimens in Barbour–Stoenner–Kelly medium permits a definitive diagnosis. However, except in the case of a few patients with acrodermatitis, positive cultures have been obtained only early in the illness, primarily from biopsy samples of erythema migrans lesions,<sup>65</sup> less often from plasma samples,<sup>17</sup> and only occasionally from cerebrospinal fluid samples in patients with meningitis.<sup>34</sup> Later in the infection, PCR testing is greatly superior to culture in the detection of *B. burgdorferi* in joint fluid.<sup>59</sup> *B. burgdorferi* has not been isolated from the cerebrospinal fluid of patients with chronic neuroborreliosis, and *B. burgdorferi* DNA has been detected in cerebrospinal fluid samples in only a small number of such patients.<sup>66</sup> The Lyme urine antigen test, which has given grossly unreliable results,<sup>67</sup> should not be used to support the diagnosis of Lyme disease.

In patients in the United States, the diagnosis is usually based on the recognition of the characteristic clinical findings, a history of exposure in an area where the disease is endemic, and except in patients with erythema migrans, an antibody response to *B. burgdorferi* by enzyme-linked immunosorbent assay (ELISA) and Western blotting, interpreted according to the criteria of the Centers for Disease Control and Prevention and the Association of State and Territorial Public Health Laboratory Directors (Table 2).<sup>68,69</sup> In Europe, where there is less expansion of the antibody response, no single set of criteria for the interpretation of immunoblots results in high levels of sensitivity and specificity in all countries.<sup>70</sup>

Serodiagnostic tests are insensitive during the first several weeks of infection. In the United States, approximately 20 to 30 percent of patients have positive responses, usually of the IgM isotype, during this period,<sup>54,71</sup> but by convalescence two to four weeks later, about 70 to 80 percent have seroreactivity, even after antibiotic treatment. After one month, the majority of patients with active infection have IgG antibody responses.<sup>54</sup> In persons who have been ill for longer than one month, a positive IgM test alone is likely to represent a false positive result; therefore, such a response should not be used to support the di-

**TABLE 2.** CASE DEFINITION OF LYME DISEASE FOR NATIONAL SURVEILLANCE.\*

Erythema migrans, observed by a physician. This skin lesion expands slowly over a period of days or weeks to form a large, round lesion, often with central clearing. To be counted for surveillance purposes, a solitary lesion must reach a size of at least 5 cm.
At least one subsequent manifestation and laboratory evidence of infection
Nervous system: Lymphocytic meningitis, cranial neuritis, radiculoneuropathy, or rarely, encephalomyelitis, alone or in combination. For encephalomyelitis to be counted for surveillance purposes, there must be evidence in cerebrospinal fluid of the intrathecal production of antibody against <i>Borrelia burgdorferi</i> .
Cardiovascular system: Acute-onset, high-grade (2nd- or 3rd-degree) atrioventricular conduction defects that resolve in days or weeks and are sometimes associated with myocarditis.
Musculoskeletal system: Recurrent, brief attacks (lasting weeks to months) of objectively confirmed joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints.
Laboratory evidence: Isolation of <i>B. burgdorferi</i> from tissue or body fluid or detection of diagnostic levels of antibody against the spirochete by the two-test approach of enzyme-linked immunosorbent assay and Western blotting, interpreted according to the criteria of the Centers for Disease Control and Prevention and the Association of State and Territorial Public Health Laboratory Directors.†

\*Adapted from recommendations made by the Centers for Disease Control and Prevention.<sup>68,69</sup>

†In a person with acute disease of less than one month's duration, IgM and IgG antibody responses should be measured in serum samples obtained during the acute and convalescent phases. A Western blot for IgM antibodies is considered positive if at least two of the following three bands are present: 23, 39, and 41 kd. A blot for IgG antibodies is considered positive if at least 5 of the following 10 bands are present: 18, 23, 28, 30, 39, 41, 45, 58, 66, and 93 kd. Only the IgG response should be used to support the diagnosis after the first month of infection; after that time, an IgM response alone is likely to represent a false positive result.

agnosis after the first month of infection. In patients with acute neuroborreliosis, especially those with meningitis, the intrathecal production of IgM, IgG, or IgA antibody against *B. burgdorferi* may often be demonstrated by antibody-capture enzyme immunoassay,<sup>72</sup> but this test is less often positive in those with chronic neuroborreliosis.

After antibiotic treatment, antibody titers fall slowly, but IgG and even IgM responses may persist for many years after treatment.<sup>73</sup> Thus, even an IgM response cannot be interpreted as a demonstration of recent infection or reinfection unless the appropriate clinical characteristics are present. In addition, *B. burgdorferi* may cause asymptomatic infection. In a trial of Lyme disease vaccine in the United States in which subjects were followed prospectively for 20 months, IgG seroconversion was demonstrated on Western blotting in about 10 percent of subjects who had no symptoms of the infection.<sup>74</sup> In a study of seroprevalence in Sweden, more than half the subjects who were seropositive by ELISA did not remember having symptoms of Lyme borreliosis.<sup>75</sup> In tests that use whole, sonicated spirochetes as the antigen preparation, vaccination for Lyme disease may cause positive IgG results by ELISA, but vaccine-induced antibody responses can usually be differentiated from infec-

tion-induced responses by Western blotting.<sup>74</sup> If patients with past or asymptomatic infection or vaccine-induced immunity have symptoms caused by another illness, there is a danger that the symptoms will be attributed incorrectly to Lyme disease. Several second-generation tests that use recombinant spirochetal proteins or synthetic peptides have shown promising results.<sup>76,77</sup>

## TREATMENT AND OUTCOME

Evidence-based treatment recommendations for Lyme disease, similar to those reported in the *Journal* 12 years ago,<sup>4</sup> were recently presented by the Infectious Diseases Society of America.<sup>78</sup> The American College of Physicians has also developed an algorithm to guide testing and treatment according to the probability of Lyme disease before testing.<sup>79</sup> For early localized or disseminated infection, treatment with doxycycline for 14 to 21 days is recommended in persons older than eight years of age, except for pregnant women (Table 3). An advantage of doxycycline is its efficacy against the agent of human granulocytic ehrlichiosis, a possible coinfecting agent. Amoxicillin, the second-choice alternative, should be used in children and pregnant women. In patients who are allergic to either of these drugs, cefuroxime axetil is a third-choice alternative. Erythromycin or its congeners, which are fourth-choice alternatives, are recommended only for patients who are unable to take doxycycline, amoxicillin, or cefuroxime axetil. Because maternal-fetal transmission of *B. burgdorferi* seems to occur rarely, if at all,<sup>81</sup> standard therapy for the manifestation of the illness is recommended for pregnant women; doxycycline should be avoided in pregnant women.

In multicenter studies of patients with erythema migrans, similar results were obtained with doxycycline, amoxicillin, and cefuroxime axetil, and more than 90 percent of patients had satisfactory outcomes.<sup>82,83</sup> Although some patients had subjective symptoms after treatment, objective evidence of persistent infection or relapse was rare, and retreatment was usually not needed. Intravenous ceftriaxone, although effective, was not superior to oral agents as long as the patient did not have objective evidence of neurologic involvement.<sup>84</sup> In contrast to second- and third-generation cephalosporin antibiotics, first-generation cephalosporins, such as cephalexin, were ineffective.<sup>85</sup>

For patients with objective evidence of neurologic abnormalities, a two-to-four-week course of intravenous ceftriaxone is most commonly given.<sup>39,42,86</sup> Parenteral therapy with cefotaxime or penicillin G may be a satisfactory alternative.<sup>87</sup> The signs and symptoms of acute neuroborreliosis usually resolve within weeks, but those of chronic neuroborreliosis improve slowly over a period of months. Objective evidence of relapse is rare after a four-week course of therapy. In Europe, oral doxycycline may be adequate therapy for acute neuroborreliosis.<sup>88</sup> Although this medication may be

used successfully in the United States in patients with facial palsy alone, it is important to assess whether such patients have more diffuse involvement of the nervous system, which is best treated with intravenous therapy. In my experience, doxycycline is not effective for the treatment of chronic neuroborreliosis. In patients with atrioventricular nodal block with a PR interval greater than 0.3 second, therapy with one of the intravenous regimens for at least part of the course and cardiac monitoring are recommended, but the insertion of a permanent pacemaker is not necessary.

Either the oral or intravenous regimens, most often oral doxycycline or intravenous ceftriaxone, are usually effective for the treatment of Lyme arthritis.<sup>58,86</sup> Oral therapy is easier to administer, is associated with fewer side effects, and is considerably less expensive.<sup>89</sup> Its disadvantage is that some patients treated with oral agents have subsequently had overt neuroborreliosis, which may require intravenous therapy for successful treatment.<sup>58</sup> Despite treatment with either oral or intravenous antibiotic therapy, about 10 percent of patients in the United States have persistent joint inflammation for months or even several years after two months or more of oral antibiotic therapy or one month or more of intravenous antibiotic therapy.<sup>58</sup> If patients have persistent arthritis despite this treatment and if the results of PCR testing of joint fluid are negative, they may be treated with antiinflammatory agents or arthroscopic synovectomy.

After appropriately treated Lyme disease, a small percentage of patients continue to have subjective symptoms — primarily musculoskeletal pain, neurocognitive difficulties, or fatigue — that may last for years. This disabling syndrome, which is sometimes called “chronic Lyme disease” or “post-Lyme disease syndrome,” is similar to chronic fatigue syndrome or fibromyalgia.<sup>90</sup> This postinfectious syndrome occurs more frequently in patients whose symptoms are suggestive of early dissemination of the spirochete to the nervous system, particularly if treatment is delayed.<sup>91,92</sup> However, in a large study, the frequency of symptoms of pain and fatigue was no greater in patients who had had Lyme disease than in age-matched subjects who had not had this infection.<sup>93</sup>

In a study of patients with post-Lyme disease syndrome who received either intravenous ceftriaxone for 30 days followed by oral doxycycline for 60 days or intravenous and oral placebo preparations for the same duration, there were no significant differences between the groups in the percentage of patients who said that their symptoms had improved, gotten worse, or stayed the same.<sup>94</sup> Such patients are best treated symptomatically rather than with prolonged courses of antibiotic therapy. Prolonged ceftriaxone therapy for unsubstantiated Lyme disease has resulted in biliary complications<sup>95</sup>; and in one reported case, the prolonged administration of cefotaxime resulted in death.<sup>96</sup>

**TABLE 3. TREATMENT AND VACCINATION REGIMENS FOR LYME DISEASE.\***

VARIABLE	REGIMEN
Early infection (local or disseminated)	
Adults	Doxycycline, 100 mg orally twice daily for 14 to 21 days Amoxicillin, 500 mg orally three times daily for 14 to 21 days
In case of doxycycline or amoxicillin allergy	Cefuroxime axetil, 500 mg orally twice daily for 14 to 21 days Erythromycin, 250 mg orally 4 times a day for 14 to 21 days
Children	Amoxicillin, 250 mg orally 3 times a day or 50 mg per kilogram of body weight per day in 3 divided doses for 14 to 21 days
In case of penicillin allergy	Cefuroxime axetil, 125 mg orally twice daily or 30 mg per kg per day in 2 divided doses for 14 to 21 days Erythromycin, 250 mg orally 3 times a day or 30 mg per kg per day in 3 divided doses for 14 to 21 days
Neurologic abnormalities (early or late)	
Adults	Ceftriaxone, 2 g IV once a day for 14 to 28 days Cefotaxime, 2 g IV every 8 hr for 14 to 28 days Penicillin G sodium, 3.3 million U IV every 4 hr (20 million U per day) for 14 to 28 days
In case of ceftriaxone or penicillin allergy	Doxycycline, 100 mg orally 3 times a day for 30 days†
Facial palsy alone	Oral regimens may be adequate
Children	Ceftriaxone, 75 to 100 mg per kg per day (maximum, 2 g) IV once a day for 14 to 28 days Cefotaxime, 150 mg per kg per day in 3 or 4 divided doses (maximum, 6 g) for 14 to 28 days Penicillin G sodium, 200,000 to 400,000 U per kg per day in 6 divided doses for 14 to 28 days
Arthritis (intermittent or chronic)	Oral regimens listed above for 30 to 60 days or IV regimens listed above for 14 to 28 days
Cardiac abnormalities	
First-degree atrioventricular block	Oral regimens listed above for 14 to 21 days
High-degree atrioventricular block (PR interval >0.3 sec)	IV regimens listed above and cardiac monitoring‡
Pregnant women	Standard therapy for manifestation of the illness; avoid doxycycline
Vaccination	L-OspA in adjuvant, 30 µg intramuscularly, at 0, 1, and 12 months (or 0, 1, and 2 months)§

\*The recommendations for antibiotics are based on the guidelines of the Infectious Diseases Society of America.<sup>78</sup> The recommendations regarding vaccine are based on the results of a phase 3 efficacy and safety trial<sup>74</sup> and on the recommendations of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention.<sup>80</sup> IV denotes intravenously.

†This regimen may be ineffective for late neuroborreliosis.

‡Once the patient's condition has stabilized, the course may be completed with oral therapy.

§The third dose should be given in April. Booster injections may be necessary every one to three years to maintain protection. L-OspA is full-length OspA to which the lipid moiety has been added after translation.

Should *I. scapularis* tick bites be treated with antibiotic prophylaxis? In studies, the frequency of Lyme disease after a recognized tick bite has been only about 1 percent,<sup>97</sup> perhaps because the tick must usually be attached for at least 24 hours for transmission to occur.<sup>98</sup> Thus, if an attached tick is removed quickly, no other treatment is usually necessary. However, a single 200-mg dose of doxycycline effectively prevents Lyme disease when given within 72 hours after the tick bite occurs.<sup>99</sup>

### PREVENTION

Protective measures for the prevention of Lyme disease may include the avoidance of tick-infested areas, the use of protective clothing, the use of repellents and acaricides, tick checks, and modifications of landscapes in or near residential areas.<sup>80</sup> In addition, a vaccine for Lyme disease, consisting of recombi-

nant OspA in adjuvant, is now commercially available in the United States (Table 3). In a phase 3 efficacy and safety trial, the efficacy of the vaccine in the prevention of definite Lyme disease was 49 percent after two injections and 76 percent after three injections.<sup>74</sup> The most important factor in protection was the strength of the antibody response to the protective epitope of OspA. Injection of the vaccine was associated with mild-to-moderate local or systemic reactions lasting a median of three days. Although T-cell responses to OspA have been associated with treatment-resistant Lyme arthritis,<sup>51,62</sup> recipients of vaccine and placebo did not differ significantly in the development of arthritis or any other late syndrome after vaccination. Thus, vaccination seems not to duplicate the conditions necessary for the induction of autoimmunity in joints that can occur in the natural infection.

The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention advises that vaccination for Lyme disease should be considered by persons 15 to 70 years old who live in or visit high-risk areas and have frequent or prolonged exposure to *I. scapularis* ticks.<sup>80</sup> Vaccination is not recommended for persons with minimal or no exposure to such ticks. Patients who are treated for erythema migrans may become reinfected and are candidates for vaccination. However, patients with Lyme arthritis usually have high antibody titers to many spirochetal proteins and seem not to become reinfected. Therefore, vaccination is probably not necessary in these patients. To achieve a protective response, it is recommended that persons receive three injections, the second vaccination 1 month after the first and the third 12 months after the first, although equivalent antibody titers can be obtained by giving the third injection at 2 months.<sup>100</sup> The third injection should be given in April so that the patient will have sufficient antibody titers against OspA during the summer.

Since antibody titers wane rather quickly,<sup>74</sup> booster injections may need to be given every one to three years to maintain protection, but official recommendations have not yet been made regarding this issue. Because the vaccine was tested in healthy subjects, little information is available regarding the safety of vaccination in persons with other diseases, such as rheumatoid arthritis. The vaccine has not yet been approved for use in children.

It is a personal decision whether to take a preventive approach to Lyme disease that involves vaccination and repeated booster injections or to take a reactive approach that requires antibiotic treatment only if symptoms of tick-borne infection develop. Either way, vigilance for tick bites must continue, since the vaccine is not always effective against Lyme disease and does not protect against other possible tick-borne infections.

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