Review

Lyme disease—another transfusion risk?

S. K. AOKI AND P. V. HOLLAND

Lyme disease (or Lyme borreliosis) is caused by a spirochetal bacteria, *Borrelia burgdorferi*. Increased recognition of the disease and increased exposure to the vector (ticks) capable of spreading *B. burgdorferi* from animal hosts have resulted in a rise in the number of cases of Lyme borreliosis reported in the United States. There are three stages of the clinical course of Lyme borreliosis; however, not all those infected will have typical manifestations of each stage, such as the arthritis of the third stage. Routine blood cultures will rarely document bacteremia and serologic testing is not yet reliable. Early treatment can prevent later stages of Lyme borreliosis. There is evidence that transmission of *B. burgdorferi* by blood transfusion is possible, but, to date, there has been no documentation of transfusion-associated Lyme borreliosis. Thus, no new recommendations for screening donors to identify possible carriers of *B. burgdorferi* are suggested at this time. **TRANSFUSION** 1989;29:646–650.

NAMED AFTER AN epidemic of arthritis in Old Lyme, Connecticut in 1975,[1] Lyme disease has come to be recognized as a potentially serious, bacterial, systemic illness of world-wide distribution.[2,3] More than 1500 cases per year are reported in the United States,[4] but many more cases may go undiagnosed. Lyme disease (or Lyme borreliosis) is now the most common tick-transmitted infection in the United States. The disease is not a new one: the skin lesion associated with it, erythema chronicum migrans, was described in Europe in 1909.[5] Lyme borreliosis can also produce an acute illness with fever, myalgias, and fatigue;[6] neurologic disease including meningitis, encephalitis, and cranial nerve palsies (such as Bell's palsy); and myocarditis.[1] Recently, unusual manifestations of Lyme borreliosis, such as panophthalmitis,[7] hepatitis,[8] and adult respiratory distress syndrome, have been reported.[9]

Because recognition of Lyme borreliosis is increasing and because the disease can lead to a chronic infection, the possibility of its transmission by transfusion has become a concern. Once again, blood bank professionals are faced with an unusual infection about which they need to become informed.

Etiology and Distribution

Agent

Lyme borreliosis is caused by the spirochete, *Borrelia burgdorferi*. This bacteria was first described and cultured from a tick in 1982;[10] in 1983, it was identified from the blood of patients with Lyme disease.[11,12] The family *Spirochaetaceae* includes *Treponema*, such as *Treponema pallidum*, the agent of syphilis, and various *Borreliae*, including those that cause relapsing fever. Cases of transmission of *T. pallidum* by blood transfusion have been reported,[13] and, although review of the literature does not reveal any reports of relapsing fever transmitted by blood transfusion, it has been a theoretical possibility for some time.[14]

Culture characteristics of spirochetes vary considerably. *T. pallidum*, the agent of syphilis, cannot be kept alive, even in tissue culture, for more than a short time[15] and survives under blood bank refrigerator conditions for less than 4 days.[16] In contrast, *B. burgdorferi*, the agent of Lyme borreliosis, can be cultured in a special medium called Barbour-Stoenner-Kelly (BSK) and survives many subcultures.[17,18] Culture of *B. burgdorferi* from the blood of mammalian hosts is more difficult than culture from ticks, and routine blood cultures are not satisfactory in their detection of bacteremia in humans. Recently, Baranton and Saint-Girons[19] reported that *B. burgdorferi* inoculated into anticoagulated whole blood is still viable after storage for 60 days at 4° C.

Geographic distribution

Lyme borreliosis has been reported in all parts of the United States. Major endemic areas are the New England and New York coastal areas, Texas, Wisconsin, Minnesota, and northern California.[20] The incidence of the disease is increasing, in part because of better recognition of the disease, but also because of increased transmission as humans, deer, or other hosts venture in greater numbers into the ticks' breeding areas.[21–23]

Transmission

Vector

There are at least four Ixodid ticks that carry the *Borrelia* of Lyme borreliosis, including, in the United States, *Ixodes dammini, I. scapularis*, and *I. pacificus* and, in Europe, *I. ricinis*.[24] The ticks *Dermacentor variabilis* and *Amblyomma americanum* also may be vectors in the United States.[25] *B. burgdorferi* infection has been noted at all stages of the tick's life cycle. In ticks, the infection can be passed transovarially, but this may

From the Sacramento Medical Foundation Blood Center, Sacramento, California.

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not happen often.[26] Most cases of *B. burgdorferi* infection in the northeastern United States are due to the bite of the tick in the nymphal stage, and thus the onset of disease occurs in June and July. The nymphs are very small (1–2 mm), and, as the bite is painless, it often goes unnoticed. There is evidence that the longer the tick remains on the host, the more likely it is to transmit the *Borrelia* infection.[27] In warmer climates, the onset of the disease may not be confined to the early summer, and transmission by adult ticks may play a more important role. Humans are exposed while walking in the grassy areas of woods or beaches or when pet cats[28] or dogs bring the ticks home. In the wild, the primary reservoir of the *Borrelia* is mice,[29] while deer are the most important host for Ixodid ticks. However, many other animals can be infected with *B. burgdorferi*, including birds,[30] hamsters,[31] raccoons, and rabbits.[10]

Transplacental transmission

Transplacental transmission has been documented in three cases of women who acquired Lyme borreliosis in the first trimester of pregnancy.[32,33] In each case, spirochetes were identified in various organs of the infant such as the brain, liver, spleen, or bone marrow. Congenital abnormalities have not been clearly due to Lyme borreliosis in any of these infants.

Clinical Course

The clinical course of Lyme borreliosis resembles in many respects that of the more common spirochetal disease, syphilis, in that both may have protean manifestations during three disease stages.[34] The disease can vary greatly with each spirochetal infection, as some patients manifest only some stages of the disease, while others show symptoms of all stages.

The primary, early stage of Lyme borreliosis is an acute illness that begins 2 days to 2 weeks after a tick bite; in 40 to 60 percent of victims, the disease presents as the unique skin lesion originally named erythema chronicum migrans.[6,34] The newer terminology, erythema migrans, reflects the acute nature of the process. The lesion begins as a macule or papule that occurs at the site of the tick bite. Typically, the area of redness expands (up to 20 cm in diameter) and the skin at the center of the lesion clears. Satellite skin lesions may also occur. Berger et al.[35] were able to culture the organism from biopsy of the leading edge of the skin lesion in 6 of 14 patients. Erythema migrans is often associated with a flu-like illness of fever, fatigue, myalgias, arthralgias, and stiff neck. During this initial phase, organisms can spread via the blood stream to other organs, where they can remain viable for years. In most cases, treatment with antibiotics at the acute stage prevents the occurrence of the late stages of the disease.[36] Unfortunately, up to 40 percent of patients do not recall a tick bite, erythema migrans, or a primary illness, and they present with one of the later stages of the disease.

The second stage of Lyme borreliosis occurs infrequently (in one study, in only 15% of patients) and consists of neurologic or cardiac symptoms developing weeks to months after the acute illness.[34] Meningitis and encephalitis can occur and about one half of the patients with neurologic involvement have facial (Bell's) palsy, which is often bilateral.[37–40] At times, this Bell's palsy is the only manifestation of the disease. Neurologic disease responds to high-dose intravenous antibiotics, which suggests that the symptoms reflect the continued presence of the organism in the nervous system. In one case of chronic meningoencephalitis, *Borrelia* was cultured from the cerebrospinal fluid 70 days after the onset of erythema migrans.[11] Myocarditis, often with conduction abnormalities such as atrioventricular block, occurs in 4 to 10 percent of Lyme disease cases.[41] Cardiac manifestations begin soon after the onset of erythema migrans, are associated with fever in one half of the cases, and are frequently accompanied by neurologic findings.[42] Reznick et al.[43] reported that the *Borrelia* organism was visible in the myocardial biopsy of a symptomatic patient.

The third stage of Lyme borreliosis is manifested primarily by arthritis, often of the knees alone or of multiple large joints, that develops weeks to years after the acute illness.[44,45] Approximately 60 percent of patients will develop this arthritis if the initial stage of their disease was not treated with antibiotics. If the subsequent Lyme arthritis is not treated with high-dose antibiotics, it can become chronic or recurrent and lead to erosion of bone and cartilage. In about one half of all patients, the arthritis is accompanied by systemic symptoms similar to those seen in the acute illness: fatigue, fever, sore throat, and myalgias. *B. burgdorferi* has been visualized in synovial biopsies 6 months after the onset of the arthritis[46] and cultured from joint fluid more than 1 year after untreated erythema migrans.[47]

Serology

As with syphilis, the results of serologic testing in Lyme borreliosis do not always indicate the state of the disease or the presence of infection. The enzyme-linked immunosorbent assay (ELISA) is negative for Lyme disease in up to 60 percent of tests during the first 3 weeks of the acute illness, but anti-*Borrelia* IgM usually appears by 3 weeks and IgG by 6 weeks.[48,50] A new antibody capture assay of the serum[51] or a new antigen test of the urine may aid in earlier diagnosis[52], but neither is commercially available at this time. In most early cases of Lyme borreliosis, prompt treatment with antibiotics will prevent an antibody response or reverse a positive Lyme serology, but this result does not guarantee that the

organism has been eradicated totally from the body.[53] Distinguishing reinfection with *B. burgdorferi* from relapse is difficult, as the IgM class of antibody, which usually lasts only 6 weeks, may, in this disease, persist for up to 2 years.[49] A positive rheumatoid factor can interfere with serologic testing for Lyme disease, as can current or past infection with relapsing fever (louse- or tick-borne), syphilis, yaws, pinta, and leptospirosis.[51,54,55] There is no species-specific serologic test for antibody to *B. burgdorferi* at this time.[56] On the other hand, infection with *B. burgdorferi* does not cause a reactive rapid plasma reagin (RPR) test for syphilis.[55] Therefore, routine screening of blood donors for syphilis with the RPR (or Venereal Disease Research Laboratory, VDRL) test does not lead to deferral of those with chronic Lyme borreliosis.

Treatment

Early treatment of the acute stage of Lyme borreliosis can prevent the later stages. Oral penicillin and tetracycline were initially found to be effective; erythromycin may be used in persons with a penicillin allergy, but it appears less effective. Treatment with high dose (20 million units daily) intravenous penicillin or ceftriaxone is indicated in cases with neurologic or with cardiac manifestations. Reports of relapses indicate that the optimum antibiotic dose and route of administration are still to be determined.[36,57]

Possibility of Transmission by Transfusion?

Transmission by transfusion is theoretically possible. The minimum infectious dose of *B. burgdorferi* may be small, considering that the organism appears to be transmitted chiefly by the entrance of tick feces into a tick bite wound. Bacteremia, although not visible on blood smear, does occur early in the disease.[11,12] (In relapsing fever, the causative *Borrelia* is found in such high numbers that it is visible on peripheral blood smear, but in Lyme borreliosis and most common bacteremias, the organisms present are not sufficient to make examination of a peripheral blood smear a useful test.) With *B. burgdorferi*, there has not yet been enough success with artificial culture media to determine precisely the magnitude and duration of the initial bacteremia or to rule out chronic or recurrent bacteremia. Blood cultures using modified Kelly's medium were positive in only 1 of 28 patients in one study,[11] 1 of 40 in another,[58] and 2 of 36 patients in the primary stage of disease in another.[12] These four positive blood cultures were drawn from 2 to 7 days after the onset of erythema migrans. All these patients had fever and myalgias, three had joint pain, and one had aseptic meningitis. Thus, the few patients who have had positive blood cultures have been quite symptomatic and would not have qualified to be blood donors at that time. Despite the low rate of positive blood cultures early in Lyme borreliosis, bacteremia may occur more frequently; in one study, 26 of 41 persons seen within 1 month of onset had disseminated disease.[45]

B. burgdorferi has been shown to survive in aliquots of whole blood kept refrigerated at 4° C for up to 60 days under simulated blood bank conditions and to be viable on subculture.[19] The inocula used in these experiments were large and their relation to the level of bacteremia in Lyme borreliosis is not known. Further, it is known that *B. burgdorferi* can persist at room temperature in platelet packs[59] much as *T. pallidum*, the agent of syphilis, can.[13] Since *B. burgdorferi* is not cell-associated, it may be able to persist in either plasma or cellular products. In many ways, *B. burgdorferi* is no different from many bacteria that cause bacteremia during acute illness and seed a protected site, thus engendering chronic focal infection. Diseases such as chronic osteomyelitis, salmonellosis, and syphilis follow such a pattern. It is not yet known if, during the third stage of *B. burgdorferi* infection, i.e., the arthritis stage, there is periodic seeding of the blood stream with organisms such as may occur in chronic osteomyelitis.

Suggested Research

Several lines of research may yield answers to the question of possible transmission of *B. burgdorferi* by transfusion. (1) An additional testing of the ability of the organism of Lyme borreliosis to survive in various blood components should be carried out to define what is physically possible. This testing might include studies of washed or white cell-poor red cells, as well as of components such as frozen red cells and cryoprecipitate that are kept frozen. (2) An intensive search for transfusion-associated cases of Lyme borreliosis in an endemic area should be undertaken, using both lookback and follow-up techniques. Identification of a transfusion-associated case may be made difficult by the lack of erythema migrans or history of tick bite to suggest the diagnosis, by the time delay between the acute nonspecific primary illness and the later symptoms of arthritis, meningitis, or carditis, and perhaps by the distance of the patient from an endemic area. The presentation of a patient with a recent onset of arthritis (especially of the knees alone), carditis, or meningitis and a history of receiving a blood transfusion in the last year should prompt a lookback investigation of each donor's medical history and serologic status. Alternatively, discovery that a blood donor has been diagnosed as having Lyme borreliosis should prompt a follow-up history and serologic testing of all recipients of the donor's potentially infectious blood components. Just such a follow-up of two recipients of blood products from a Sacramento donor recently diagnosed as having Lyme borreliosis found no *Borrelia* infection in either (L. Fernando, oral communication, September 1988). (3) If a more reliable serologic test or culture method for *B.*

burgdorferi is developed, it might be used to test units of blood collected in an endemic area as well as to test transfusion recipients before transfusion and again 6 weeks later. Recipients of blood units thought to be carrying *B. burgdorferi* should be compared to those receiving units that were negative for *B. burgdorferi*. (4) Serial attempts should be made to document the presence or absence of bacteremia at various stages of Lyme borreliosis by inoculating patient's blood into mice. A return to this expensive culture method may be the best way to document or rule out recurrent or silent bacteremia due to *B. burgdorferi*. Similarly, cultures using artificial media or mouse inoculation could be carried out with blood from blood donors who are found to be asymptomatic but who have serologic evidence of *B. burgdorferi* infection.

Recommendations

No case of Lyme disease due to transfusion has been reported to date. Thus, at this time there is no need for new blood banking procedures, let alone standards, to reduce the risk of transfusion-transmitted *B. burgdorferi*, nor would it be appropriate to defer asymptomatic blood donors from the large geographic areas endemic for Lyme borreliosis, even during the summer months. In every documented case of *B. burgdorferi*-induced spirochetemia to date, clinical symptoms were present. If the spirochetemia is always symptomatic, donors with acute Lyme borreliosis should be eliminated by the usual blood donor history, temperature recording, and examination of all skin rashes. Recommendations to that effect were recently issued by the American Red Cross.[60] It seems prudent at this time to regard Lyme borreliosis as a potentially serious, chronic, bacterial infection similar to chronic osteomyelitis and not to permit blood donation by individuals diagnosed with Lyme borreliosis until they have completed a course of antibiotics and are totally asymptomatic. In addition persons carrying out donor screening should be made aware of the signs and symptoms of Lyme disease so as to defer donors with those findings.

The blood banking community has become very knowledgeable in techniques for identifying, tracking, and reducing the risk of transmission of infections by blood transfusion. Proof that an infectious disease is transmitted by transfused blood or components requires evidence that (1) the organism remains viable under blood banking conditions, (2) the donor was infected with the organism at the time of donation, (3) the recipient was uninfected before transfusion, (4) the organism or markers of infection appeared in the recipient soon after the transfusion, and (5) other methods of acquiring the organism can be ruled out. Needless to say, these criteria for documenting blood transfusion as the method of transmission of infection require the availability of a reliable assay to define the presence and the absence of the infection. No large-scale testing of blood from healthy donors aimed at eliminating transmission of a disease agent should begin until there is both proof of transmission by blood and availability of a reliable testing method. Neither of these conditions has been met for *B. burgdorferi*, the causal agent of Lyme borreliosis.

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Susan K. Aoki, MD, Staff Physician, Sacramento Medical Foundation Blood Center.

Paul V. Holland, MD, Medical Director/CEO, Sacramento Medical Foundation Blood Center, Sacramento, California, and Clinical Professor of Medicine, University of California at Davis Medical School, Davis. [No reprints available]