Reinfection in Patients with Lyme Disease

Robert B. Nadelman and Gary P. Wormser
Division of Infectious Diseases, Department of Medicine, New York Medical College, Valhalla

Lyme disease is the most common tick-borne infection in the United States and Europe. A surprising number of patients experience a subsequent episode of Lyme disease after the first episode has resolved. Reinfection has been well-documented only after successfully treated early infection (nearly always erythema migrans) and can often be recognized clinically by the development of a repeat episode of erythema migrans occurring at a different location on the skin during months when the principal tick vectors are abundant in the environment. Limited data suggest that the clinical and laboratory manifestations of reinfection in patients with Lyme disease with erythema migrans are not very different from those of initial infection. Patients with recurrent infections afford an opportunity to study the role of the immune response in this illness. Because patients with early Lyme disease continue to remain at high risk for reinfection, this population should be targeted for education about prevention of Lyme disease.

Lyme disease is diagnosed in nearly 20,000 persons in the United States each year [1]. This infection, transmitted by the bite of certain Ixodes ticks, is the most commonly reported vector-borne disease in the United States and is widespread in the temperate zones of much of Europe and parts of Asia [2]. Several related species of Borrelia cause Lyme disease (herein, referred to as Lyme Borrelia). Virtually all patients in the United States are infected with a single species called Borrelia burgdorferi. In contrast, persons acquiring Lyme disease in Europe may be infected with one of several different species [2].

A surprising number of patients sustain a second (and sometimes even another subsequent) episode of early Lyme disease after the first episode has resolved [3–18]. Although reinfection is well-recognized, there is little detailed information on the clinical and laboratory manifestations. Herein, we review the available clinical, epidemiological, and laboratory aspects of reinfection with Lyme Borrelia.

Reinfection is defined here as the development of a new tick-transmitted infection with Lyme Borrelia occurring after successful antimicrobial treatment of a prior episode of Lyme disease. This is distinguished from relapse, which is defined here as the presence of objective clinical and/or microbiological evidence of persistent infection with Lyme Borrelia after a non-curable course of antimicrobial treatment [19]. Reinfection has been well-documented only after successfully treated early infection (nearly always erythema migrans) and not after late manifestations of Lyme disease.

INCIDENCE AND CAUSES OF REINFECTION

Early infection produces a distinctive expanding skin lesion known as erythema migrans. Reinfection occurs regularly in patients from both the United States and Europe who are observed for 1 year after treatment of an initial episode of erythema migrans (table 1) [3–18]. It is notable that the rate at which second episodes of erythema migrans occur in closely observed cohorts may exceed the incidence of Lyme disease in the general population, even in the same region of high endemicity where the study group originates. For example, in a study conducted in Westchester County, New York, 14 (15%) of 96 patients with erythema migrans were observed to have recurrent erythema migrans when observed for a mean duration of ~5 years (i.e., a rate of ~3% per year) [10]. This rate is substantially higher than the mean reported countywide incidence of Lyme disease of 0.06% per year for the period 1995–1997, when the study was conducted [20]. There are several potential explanations for reinfection.

Repeated tick bites. Many patients with Lyme disease con-
Table 1. Prospective studies in the United States in which reinfection with *Borrelia burgdorferi* was identified.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>Location</th>
<th>Study design</th>
<th>Age group</th>
<th>No. of patients with Lyme disease</th>
<th>No. (%) of patients who experienced reinfection</th>
<th>Mean duration of the study, years</th>
<th>Rate of reinfection per year, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luger et al. [16]</td>
<td>1995</td>
<td>CT, NJ, NY</td>
<td>Prospective treatment trial</td>
<td>≥12 years</td>
<td>170</td>
<td>2 (1.2)</td>
<td>1</td>
<td>1.2</td>
<td>…</td>
</tr>
<tr>
<td>Gerber et al. [12]</td>
<td>1996</td>
<td>CT</td>
<td>Prospective observational</td>
<td>Children</td>
<td>201</td>
<td>6 (3.0)</td>
<td>2</td>
<td>1.5</td>
<td>…</td>
</tr>
<tr>
<td>Smith et al. [15]</td>
<td>2002</td>
<td>b</td>
<td>Prospective vaccine trial</td>
<td>≥17 years</td>
<td>118</td>
<td>2 (1.7)</td>
<td>1.7</td>
<td>1.0</td>
<td>…</td>
</tr>
<tr>
<td>Wormser et al. [17]</td>
<td>2003</td>
<td>NY</td>
<td>Prospective treatment trial</td>
<td>≥16 years</td>
<td>180</td>
<td>13 (7.2)</td>
<td>2.5</td>
<td>2.9</td>
<td>Some patients overlap with Nowakowski et al. [10]</td>
</tr>
<tr>
<td>Nowakowski et al. [10]</td>
<td>2003</td>
<td>NY</td>
<td>Prospective observational</td>
<td>≥16 years</td>
<td>96</td>
<td>14 (14.6)</td>
<td>4.9</td>
<td>3.1</td>
<td>Among reinfected patients, 3 (21%) of 14 had a third episode of erythema migrans; 4 others (5%) who were asymptomatic experienced seroconversion; some patients overlap with Wormser et al. [17]</td>
</tr>
</tbody>
</table>

*a* No. of patients enrolled, regardless of duration of follow-up.

*b* New England, middle Atlantic states, Midwest.
tinue to live, work, and/or participate in recreation in regions where ticks are endemic. Repeated tick bites are quite common. In 1 study of persons from New York with recently recognized *Ixodes scapularis* tick bites, 59 (17.6%) of 335 subjects reported new tick bites during a 6-week follow-up period, despite receiving oral and written recommendations about how to reduce the risk of tick bites [21]. In a 14-year study of residents of Block Island, Rhode Island, tick bites were reported significantly more frequently by subjects who experienced repeated episodes of Lyme disease than by persons who had had only a single episode of infection [18].

Multiple measures are available to limit exposure to ticks, including covering bare skin and using tick repellents. However, compliance with these recommendations has been suboptimal. In a study involving >4600 persons that was conducted in Nantucket, Massachusetts, a region of high endemicity, only 53% of the study population wore protective clothing, 34% avoided tick-infested regions, and 11% used tick repellent [22]. Persons with a prior history of Lyme disease were no more likely to practice preventive behaviors than were those who had never been infected [22]. Alternative interventions designed to decrease tick density around individual homes, such as constructing fences against deer and application of acaricides to property, have not been widely adopted for a variety of reasons, including cost, inconvenience, and environmental concerns.

In certain animal studies, however, there is good evidence that multiple tick bites occurring over time may paradoxically lead to a lower risk of developing *B. burgdorferi* infection. Some [23], but not all [24], laboratory animals can be made resistant to *B. burgdorferi* infection by challenging the animals repeatedly with ticks that are free of pathogens. This implies that host immunity to ticks (even in the absence of specific immunity to spirochetes) can prevent transmission of this infection in animals. Immune responses to tick salivary antigens were believed to have interfered with tick feeding on inbred strains of mice and guinea pigs and even resulted in frequent death of the attached ticks [25, 26]. This concept has been used successfully in a vaccine for cattle directed at the *Boophilus microplus* tick. Vaccination prevents tick feeding and, possibly, decreases transmission of babesiosis and anaplasmosis [27]. Of interest, white-footed mice, which serve as the main reservoir for *B. burgdorferi*, do not develop immunity to *I. scapularis* tick bites [24].

Immunity to *I. scapularis* tick bites might occur in humans, but thus far, evidence to support this contention is based on a single retrospective study [26]. In that study, residents of a region of high endemicity for Lyme disease who experienced ≥3 pruritic tick bites were significantly less likely than those with fewer bites to develop Lyme disease [26]. It was postulated that a vigorous immune response from multiple bites led to so much pruritus that the tick was promptly recognized and removed, thereby interrupting transmission of *B. burgdorferi*, a process that normally requires >48 h [20, 26]. Alternatively, a vigorous immune response directed against tick salivary antigens might have reduced the ability of the tick to transmit the spirochete successfully [26].

**Immunologic factors.** It is clear that the normal human immune response is not fully protective against reinfection in patients with early Lyme disease associated with erythema migrans who are treated with antibiotics. This parallels syphilis, in which virtually all persons with a prior history of early syphilis who had been treated with penicillin could be reinfected [28]. As with syphilis, reinfection in patients with Lyme disease appears to be extremely rare following late manifestations (e.g., arthritis) after an expanded immune response develops, including antibody responses to outer surface protein A (OspA), decorin-binding protein, or other antigens [29–31]. Although recurrent infection manifested by “typical erythema migrans” has been reported in 2 instances after putative Lyme arthritis [32], the evidence presented was not sufficiently compelling to justify the authors’ diagnosis of reinfection in either case.

Whether being immunocompromised increases the risk of reinfection has not been extensively studied. In a European study of patients with erythema migrans, immunocompromised patients were 3 times more likely than otherwise healthy control subjects to have had a prior episode of erythema migrans (6 [9%] of 67 patients vs. 2 [3%] of 67 control subjects), but this difference was not statistically significant (*P* = .27) [33].

Although all of the essential components of a protective immune response to *B. burgdorferi* infection in humans or animals have not been identified, several lines of evidence suggest that antibody to OspA can be protective (OspA was the antigen used in the Lyme disease vaccine) [31]. However, OspA antibodies do not account for the short-lived resistance to reinfection observed in 1 animal model of infection [34]. After antibiotic treatment, animals were initially resistant to reinfection via tick feeding. However, within months, animals became susceptible to reinfection with the same strain of *B. burgdorferi*. The mechanism for the temporary immunity was determined not to be correlated with the level of antibodies to OspC or whole *Borrelia* sonicate. In addition, an immune response to OspA was absent in this study, which was expected because this antigen is not expressed by *B. burgdorferi* during early infection [31, 34].

**Microbiological variation.** Strain variability may be a means by which Lyme *Borrelia* species circumvent the host’s immune response to a previous infection and cause reinfection. In Europe, some reinfections are caused by a species of *Borrelia* that is distinctly different from the one that caused the original infection (F. Strle, personal communication). However, there may also be considerable strain variation within a particular
species of Lyme Borrelia. For instance, when strains are classified according to the allele at the highly variable OspC gene, there are at least 17 subtypes of B. burgdorferi in the United States that are associated with clinical illness (I. Schwartz, personal communication). In 1 experiment, mice immunized with OspC derived from a particular strain of B. burgdorferi were protected from infection with the homologous strain but not from challenge with 2 heterologous strains [35]. The role of microbiological variation as a predisposing factor for reinfection deserves further study.

**RECURRENT LYME DISEASE: REINFECTION VERSUS RELAPSE**

*Erythema migrans.* During both the initial infection and subsequent episodes, the majority of patients with Lyme disease manifest the distinctive skin lesion erythema migrans. In untreated patients, erythema migrans resolves spontaneously within a median of 28 days, but relapse may occur, usually within a year of the appearance of the initial lesion [36]. After treatment with presently recommended antibiotic regimens, however, persistence, progression, or recurrence of the skin lesion or the development of objective extracutaneous manifestations of Lyme disease is exceedingly rare [2, 7, 9, 10, 12, 15–17, 36–40]. Relapse has been well-documented (on the basis of recovery of B. burgdorferi by culture) only in patients treated with antibiotics (e.g., cephalaxin) known to have poor activity in vitro against this microorganism [19], although some patients treated with certain macrolides also appear to experience relapse clinically [37]. Thus, the development of a new erythema migrans lesion in a person with a prior history of Lyme disease who was treated with recommended regimens [40] is prima facie evidence for reinfection. Clinical features that suggest reinfection rather than relapse include the development of an erythema migrans lesion at a site different from that of the original lesion and the presence of a punctum in the lesion (figure 1A, table 2). A punctum is a small raised or depressed point near the center of a primary erythema migrans lesion, representing the site from which the tick detached. In the United States, repeat episodes of erythema migrans due to reinfection almost always develop in a subsequent transmission season during the late spring or summer (R.B.N., unpublished data) [18], at the time when nymphal stage (i.e., the stage that is the principal vector for Lyme disease) Ixodes scapularis or Ixodes pacificus ticks are most abundant [41, 42]. In Eurasia, reinfection, usually transmitted by nymphal Ixodes ricinus or adult Ixodes persulcatus, is also expected to occur mostly during the late spring or summer. In contrast, cases of relapse of preexisting infection would not necessarily be expected to occur in a seasonal pattern and would be likely to arise within a few weeks to several months after the initial episode [18].

Limited data are available regarding the clinical manifestations of second episodes of erythema migrans in patients with Lyme disease who have reinfection. A recent report described 28 patients from Block Island, Rhode Island, who had repeated episodes of erythema migrans and were believed to have been reinfected with B. burgdorferi [18] (5 additional persons had only “flu-like illnesses” as either their first or second episode of infection but were considered to have Lyme disease on the basis of seroconversion). None of the patients had clinical evidence of immunodeficiency. Persons with reinfection were equally distributed by sex; however, 6 (86%) of 7 persons who experienced a third episode of Lyme disease were female. This finding is difficult to explain but is consistent with the observations in a recent Swedish study, in which the investigators found that 27 of 31 reinfected persons were women aged >44 years [43].

As one would predict, nearly all cases of recurrent infection in the Block Island study occurred during the late spring or summer [18]. The number and severity of symptoms were similar in the first and second episodes and tended to be less severe during the third episode, although these findings were
not statistically significant. Surprisingly, patients with recurrent Lyme disease did not seek medical attention sooner than did those who had only a single episode.

A preliminary report summarized findings for 11 men and 11 women who each experienced 2 episodes of erythema migrans and were seen at our institution; the episodes occurred a mean (±SD) of 3.25 ± 2.65 years apart (figure 1) [44]. A prior tick bite at the site of erythema migrans was recalled with similar frequency in patients who experienced first and second episodes. Patient symptoms (including fever), diameter of erythema migrans, abnormal findings on physical examination, and laboratory results (complete blood count, transaminase levels, and erythrocyte sedimentation rate) during second episodes were similar to those during first episodes. These findings were also similar to those for contemporaneous control subjects who experienced single episodes of erythema migrans. This study obviously had insufficient power to detect relatively small differences.

In this study, patients were >2 times as likely to have multiple erythema migrans skin lesions (a marker of hematogenous dissemination of *B. burgdorferi* infection) during their first episode of Lyme disease than during their second episode (7 [32%] patients during the first episode vs. 3 [14%] patients during the second episode; *P* = .15) [44]. Although this finding could be a chance event, alternatively, it could be related to the development of partial host immunity, leading to protection from hematogenous dissemination after reinfection (see “Extracutaneous disease”).

**Extracutaneous disease.** Duration of infection is not easily determined for patients who have only extracutaneous manifestations of Lyme disease, such as oligoarthritis or lymphocytic meningitis. Because such manifestations may relapse without adequate treatment, it may be particularly difficult to distinguish reinfection from relapse when a second episode of clinical illness is not associated with erythema migrans. At least 1 patient with a history of treated extracutaneous Lyme disease has been reported to have had reinfection with *B. burgdorferi*, based on new extracutaneous findings associated with the detection of specific antibodies [45]. According to this report from Germany, an 11-year-old girl developed a second episode of facial nerve palsy 5 years after experiencing facial nerve palsy on the contralateral side. Both episodes developed within a few weeks after a recognized tick bite and were associated with CSF pleocytosis and detectable IgM antibodies to *B. burgdorferi* in both serum and CSF specimens [45]. The patient had been healthy between episodes, with complete resolution of signs and symptoms and reversion to seronegativity after receiving treatment with intravenous penicillin for 10 days at the time of the first illness. Other reported cases of reinfection manifested by extracutaneous disease without erythema migrans have been less well-documented [46]. A lower incidence of hematogenous dissemination in reinfection might contribute, in part, to the observation that second infections with *B. burgdorferi* are almost always characterized by erythema migrans without objective extracutaneous manifestations. In 1 study of patients with erythema migrans, *B. burgdorferi* was significantly less likely to be recovered from blood samples of those with a prior history of Lyme disease, implying that partial immunity may protect against disseminated infection [47].

**Asymptomatic seroconversion.** In a study of 96 patients observed for ~5 years after presenting with culture-confirmed erythema migrans, 3 asymptomatic participants (3.1%) experienced seroconversion (defined as increased bands on immunoblot, resulting in seroconversion on the basis of IgM criteria in 1 patient or of IgG criteria in 2 patients) 2–5 years after their initial episode [10]. Another patient developed new IgG bands but did not meet criteria for seropositivity. Because these patients were seen only on a yearly basis, it is possible that some of the patients had erythema migrans lesions that were unrecognized or not recalled at the time of the follow-up visit. The clinical significance of such a change in seroreactivity deserves further study.

**LABORATORY DIAGNOSIS OF REINFECTION: USE OF SEROLOGICAL TESTING**

How best to use serological testing for the diagnosis of reinfection is unclear. Although the presence of IgM antibodies...
often suggests a new infection in the context of many illnesses, including Lyme disease, this is not always true. IgM reactivity may represent a false-positive result associated with a variety of cross-reacting antibodies [48]. In addition, prolonged seroreactivity (including persistent IgM antibodies to *B. burgdorferi* detected for months to years) has been described in patients with Lyme disease who were thought to have had a complete clinical response to antibiotic treatment, with presumed eradication of infection [49].

It would be expected that a change from seronegativity to seropositivity or the development of a 4-fold increase in antibody titer directed against Lyme *Borrelia* would suggest a new infection. However, this has not been well studied. In a preliminary investigation, the incidence of seroconversion was specifically studied in patients with exactly 2 clinically recognized episodes of erythema migrans. These patients had been prospectively observed after their first episode, and serial serum samples were obtained [50]. Serum samples were tested by a polyvalent whole-cell ELISA and by the C6 antibody test (Immunetics) [51], but immunoblot testing was not performed. Of the patients who became seronegative, according to whole-cell ELISA findings, after resolution of the first episode of erythema migrans, most (9 [82%] of 11 patients) were seropositive, having seroconverted (as determined by either assay) by the time they presented with a second episode. Considering the limited available data, it can be concluded that no pattern of serological response has been identified that would differentiate reinfection from initial infection with *B. burgdorferi*. Further study of larger populations is indicated to better understand the sensitivity and specificity of available serological assays for the diagnosis of reinfection.

**SUMMARY**

Reinfection with *B. burgdorferi* can often be recognized clinically by the development of a repeat episode of erythema migrans occurring at a different skin site during months when the nymphal stage of the principal tick vectors (or the adult stage of *I. persulcatus*) are plentiful in the environment. Reinfection is more reliably diagnosed in patients with recurrent erythema migrans lesions than in patients with extracutaneous manifestations of disease. Limited available data suggest that the clinical manifestations of reinfection in patients with Lyme disease with erythema migrans are not very different from manifestations during initial infection. Future investigation is warranted to better characterize the clinical characteristics and serological response associated with separate episodes of Lyme disease. Patients who have recurrent infections also afford an opportunity to study the role of the immune response in this illness. Such research will be aided by an understanding of the intrinsic differences, detected on a molecular basis, among different strains of *Borrelia* causing Lyme disease that are isolated by culture of samples from patients who have experienced multiple episodes of infection. Because patients with early Lyme disease continue to remain at high risk for reinfection, this population should be targeted for education regarding strategies for prevention of Lyme disease.

**Acknowledgments**

We thank Mario Philipp, Gul Seyidoglu Madison, Adriana Gaidici, John Nowakowski, L. Frank Cavaliere, Charles Pavia, Dionysius Liveris, Ira Schwartz, Maria Aguero-Rosenfeld, Donna McKenna, Diane Holmgren, Susan Bittker, Denise Cooper, Carol Scavarda, Kathy O’Keefe (deceased), and Susan Hallperin, for contributions to patient care, laboratory testing, and/or data analysis, and Richard Falco, Franc Strle, Stephen Wikle, Robert Smith, and Peter Krause, for providing helpful background information.

**Financial support.** National Institutes of Health (RO3 AI 008275-101 to G.P.W.).

**Potential conflicts of interest.** G.P.W. received a research grant from Immunetics and expects to receive a research grant from BioRad. R.B.N.: no conflicts.

**References**