HHS Public Access

Author manuscript

Curr Opin Pediatr. Author manuscript; available in PMC 2015 May 02.

Published in final edited form as:

Curr Opin Pediatr. 2015 February ; 27(1): 100–104. doi:10.1097/MOP.0000000000000167.

Update on persistent symptoms associated with Lyme disease

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Abstract

Purpose of review—Lyme disease, caused by *Borrelia burgdorferi*, is the most common vector-borne illness in the United States. The pathogenesis, ecology, and epidemiology of Lyme disease have been well described, and antimicrobial treatment is very effective. There has been controversy about whether infection can persist and cause chronic symptoms despite treatment with antimicrobials. This review summarizes recent studies that have addressed this issue.

Recent findings—The pathogenesis of persistent nonspecific symptoms in patients who were treated for Lyme disease is poorly understood, and the validity of results of attempts to demonstrate persistent infection with *B. burgdorferi* has not been established. One study attempted to use xenodiagnosis to detect *B. burgdorferi* in patients who have been treated for Lyme disease. Another study assessed whether repeated episodes of erythema migrans were due to the same or different strains of *B. burgdorferi*. A possible cause of persistent arthritis in some treated patients is slow clearance of nonviable organisms that may lead to prolonged inflammation. The results of all of these studies continue to provide evidence that viable *B. burgdorferi* do not persist in patients who receive conventional antimicrobial treatment for Lyme disease.

Summary—Patients with persistent symptoms possibly associated with Lyme disease often provide a challenge for clinicians. Recent studies have provided additional evidence that viable *B. burgdorferi* do not persist after conventional treatment with antimicrobials, indicating that ongoing symptoms in patients who received conventional treatment for Lyme disease should not be attributed to persistent active infection.

Video abstract—http://links.lww.com/MOP/A23

Keywords

Lyme disease; post-treatment Lyme disease syndrome; xenodiagnosis

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Conflicts of interest

None.

INTRODUCTION

Lyme disease was first described in 1977 when 51 children and adults from Lyme, Connecticut, were reported to have an unusual form of recurrent arthritis. In 1982, Willy Burgdorfer was able to isolate a spirochete, later named *Borrelia burgdorferi*, which ultimately was found to be the cause of Lyme disease [1]. The organism, found in *Ixodes scapularis* ticks, has since been subclassified into several genospecies. Among those that commonly cause Lyme disease are *B. burgdorferi* sensu stricto (the sole cause of Lyme disease in the United States), *B. garinii*, and *B. afzelii*. As a group, these may be classified as part of the *B. burgdorferi sensu lato* complex.

The clinical features of Lyme disease have been well described; therapy is well tolerated and effective, and complications are rare. Several studies have detailed the accepted diagnostic criteria for and appropriate treatment of patients with Lyme disease [2,3].

Over the past decade, there has been considerable controversy regarding ongoing, nonspecific symptoms that develop or persist in patients after they are treated for Lyme disease. Such symptoms may include fatigue, arthralgia, myalgia, or perceived impaired cognition. Major points of controversy are whether *B. burgdorferi* are not being fully eradicated with recommended antimicrobial treatment and whether the persistent or new symptoms are causally related to persistent infection. A number of previous studies found no evidence of persistence of infection at the end of therapy, but little is known about why some patients with Lyme disease have ongoing nonspecific symptoms (or even whether the frequency of such symptoms is greater in patients who had been treated for Lyme disease than in the general population). In this study, we will review several recent studies that tried to assess whether infection persists in patients with Lyme disease after completion of conventional antimicrobial therapy. We will also review recent studies discussing persistence of spirochetal remnants (in the absence of viable organisms) in connective tissues and joints that may fuel an inflammatory response that might persist during and after antimicrobial treatment. In addition, we will discuss recent studies that have attempted to differentiate re-infection from relapse in repeat episodes of erythema migrans.

POST-TREATMENT LYME DISEASE SYNDROME

Therapy for Lyme disease is very effective, and objective clinical findings after completion of therapy are rare [2]. Post-treatment Lyme disease syndrome (PTLDS) has been defined as persistent subjective symptoms without objective manifestations that persist for at least 6 months after conventional treatment for Lyme disease has been completed. These are nonspecific symptoms such as fatigue, arthralgia, myalgia, or perceived cognitive impairment. Some patients and Lyme disease ‘activists,’ as well as ‘Lyme-literate’ physicians, label this syndrome as ‘chronic Lyme disease’ and believe it is due to persistence of infection that requires long-term treatment with antibiotics to alleviate the symptoms. Despite the lack of evidence to support persistence of infection [4], advocates have been lobbying to have the accepted Lyme disease treatment guidelines modified. One goal of making changes to the guidelines is to force insurance companies to pay for

prolonged courses (months to years) of parenterally administered antibiotics [5▪]. Four placebo-controlled clinical trials have been conducted to assess if there is any benefit to using prolonged antibiotic therapy for patients with PTLDS. These trials have been re-analyzed and reviewed by Klempner *et al*. [6▪], and the consensus remains that there are no significant enduring benefits, but significant risks of adverse events from long-term treatment with antibiotics. There is a large body of evidence indicating that treatment with prolonged courses of antibiotics is not indicated for patients with PTLDS.

ATTEMPTS TO FIND PERSISTENT INFECTION WITH *BORRELIA BURGDORFERI*

Studies of the use of culture and PCR amplification assays to diagnose Lyme disease have consistently found that these tests are not sensitive enough to be clinically useful [7–11]. *B. burgdorferi* grows very slowly, and there are relatively few organisms in the blood or cerebrospinal fluid during infection, making recovery of the organism difficult. In addition, culturing the organism requires special media [Barbour, Stoener, Kelly (BSK)] and is time-consuming, typically requiring weeks before results become available. Consequently, testing for anti-bodies to *B. burgdorferi* has been the mainstay for diagnosis in patients with extra-cutaneous manifestations of Lyme disease. A two-tier serologic test has been recommended by the Centers for Disease Control (CDC) and usually consists of a sensitive screening test with an ELISA followed by a confirmatory Western immunoblot if the ELISA result is positive or equivocal [3].

Some experimental studies in animal models have found evidence that *B. burgdorferi* DNA and RNA may persist in tissues after antimicrobial treatment [12]. However, the presence of nucleic acids of *B. burgdorferi* does not necessarily equate to the presence of viable organisms. Nor is it clear what the relevance of these animal models is to human disease [13]. Chronic Lyme disease advocates are eager to document that viable bacteria persist in humans after a standard course of antimicrobial treatment to support the concept of chronic Lyme disease. However, efforts to isolate *B. burgdorferi* in patients with PTLDS have been unsuccessful. Recently, modified methods for culturing *B. burgdorferi* from blood and the first attempt at xeno-diagnosis of Lyme disease in humans have been reported.

In 2013, Sapi *et al*. [14▪] attempted to develop a new and more sensitive method to culture *B. burgdorferi* by modifying the BSK media. They used blood from 72 patients with Lyme disease who were seropositive by the standard 2-tier method (without adequate description of their symptoms, physical findings, or the duration of their illnesses) and 48 uninfected controls. DNA sequencing of the *pyrG* gene was used on the positive cultures to confirm the identity of the bacteria. The authors reported that they were able to grow *B. burgdorferi* from the blood of 68 (94%) of the patients with Lyme disease, but not from any of the controls. Subsequently, Johnson *et al*. [15▪] from the CDC sequenced a portion of the *pyrG* gene of the four laboratory strains of *Borrelia* used by Sapi *et al*. in their quality control, and compared these with the sequences of the strains isolated from the blood of their participants. Of the 51 sequences reported by Sapi *et al*., 29 of 51 (56%) were either *B. garinii* or *B. afzelii* – strains of bacteria that cause Lyme disease in Europe and in Asia, but that are not found in North America. In addition, they found that 80% of the *Borrelia* sp.

isolated were clones that were identical in sequence to the laboratory controls. They concluded that laboratory contamination likely was the explanation for the findings of Sapi *et al*. We agree with the warning from the CDC [16▪] that independent confirmation is crucial for new diagnostic techniques that contradict a large body of previous evidence.

Marques *et al*. [17▪▪] conducted the first human experiment exploring the use of xenodiagnosis to detect *B. burgdorferi* in patients with PTLDS. Xenodiagnosis is designed to detect vector-transmitted organisms by attaching the natural vector to a potentially infected patient and examining the vector for the presence of the organism after it has fed. A study showed that a substance in saliva of *I. scapularis* causes *B. burgdorferi* to migrate towards it, in effect acting as a chemoattractant and providing a reason to think xenodiagnosis may be a sensitive technique to detect *B. burgdorferi* [18]. The first study to detect *B. burgdorferi* in mice using xenodiagnosis was conducted in 2002 [19]. In this study, spirochetal remnants, but no viable organisms, were detected. In 2014, Marques and her group evaluated 36 participants for the presence of *B. burgdorferi* using xenodiagnosis. Of the 36 participants, 10 were seronegative healthy individuals who never had Lyme disease (controls) and one was a potentially 'positive control' individual with erythema migrans on whom the tick was placed at the same time that antimicrobial treatment was begun. In addition, there were 20 seropositive individuals; 10 asymptomatic patients who had been treated for Lyme disease and who had high titers of antibody to *B. burgdorferi*, and 10 patients who had PTLDS. Lastly, there were five patients who had completed antibiotic therapy for erythema migrans from 1 to 4 months earlier. The investigators placed 25–30 laboratory-raised, pathogen-free, larval *I. scapularis* ticks under a retention dressing on each patient. The ticks were removed after feeding for 3–7 days. Evidence for the presence of *B. burgdorferi* was sought using cultures, standard PCR assays, or isothermal amplification followed by PCR and electrospray ionization mass spectroscopy of homogenates of the ticks, of skin biopsies from the sites where ticks fed, or from immunodeficient mice on which either the ticks subsequently fed or into which homogenized ticks were inoculated. The authors were not able to recover viable organisms either from ticks or from skin biopsies from any of the patients or from the immunodeficient mice. Only two patients had detectable *B. burgdorferi* DNA by PCR. One patient was the positive control who was early in the course of antibiotic treatment for erythema migrans, and the other was a patient with PTLDS. The authors concluded that xenodiagnosis was safe and well tolerated, but that further studies are needed to determine the significance of the positive PCR assay in the patient with PTLDS. We agree that this method needs further investigation. It has been established that *B. burgdorferi* DNA can persist for months after inactivation of spirochetes [20]. A positive result on a PCR assay after antibiotic treatment is not necessarily an indication of an ongoing infection.

PERSISTENT *BORRELIOSIS* OR PERSISTENCE OF *BORRELIA* ANTIGENS?

It has been suggested that persistence of inactivated organisms after antimicrobial treatment might cause residual symptoms. Wormser *et al*. [21] proposed the 'amber theory' of Lyme arthritis. This theory might explain findings in a patient with Lyme arthritis from whom they identified (in synovial fluid) dead but morphologically well preserved spirochetes enmeshed in a matrix. The authors go on to propose that killed *B. burgdorferi* or antigens of *B.*

burgdorferi can be sequestered in a host-derived fibrinous material after infecting synovial fluid. They suggest that the persistence of dead spirochetes and spontaneous release of spirochetal antigens into the synovial fluid after treatment could explain the occasional recurrence of arthritis in the same joint. This would also explain why recurrent episodes of Lyme arthritis typically are not ameliorated with longer courses of antibiotics, but significant improvement often is seen with use of anti-inflammatory drugs.

REPEAT ERYTHEMA MIGRANS: REINFECTION OR RELAPSE?

Although it is well recognized that patients may have repeated episodes of erythema migrans, the question of whether these are relapses of the prior infection or a new infection has not been assessed. If persistent infection with *B. burgdorferi* after treatment occurs, then it might be expected that at least some of the repeat episodes of erythema migrans are recurrences of the prior infection. Nadelman *et al*. [22] identified 22 paired episodes of culture-positive erythema migrans in patients and analyzed the genotype of all of the strains of *B. burgdorferi* that were isolated. The authors found that in the paired episodes, none of the subsequent episodes of erythema migrans in the patient were due to the same strain of *B. burgdorferi* as the initial infecting strain. The authors concluded that recurrent episodes of erythema migrans after standard courses of antibiotics are due to re-infection rather than to relapse of the previously treated infection. Khatchikian *et al*. [23▪] evaluated the data from Nadelman *et al*.'s study and found that, using multinomial probabilities and stochastic simulation modeling, it is highly likely that patients who are infected with *B. burgdorferi* develop strain-specific immunity. In addition, in their simulations, they found that strain-specific immunity would likely last for at least 6–9 years. Knowing that strain-specific immunity develops after early Lyme disease and that recurrent erythema migrans is likely from a different strain of *B. burgdorferi* supports the accepted guidelines that prolonged or unconventional antimicrobials are not necessary for recurrent erythema migrans.

CONCLUSION

Lyme disease is the most common vector-borne illness in the United States. Therapy is well tolerated and effective, and complications are rare. There has been no evidence that demonstrates that viable *B. burgdorferi* persist in patients after conventional treatment for Lyme disease. Patients with vague, nonspecific symptoms for at least 6 months after treatment of Lyme disease, termed PTLDS, do not benefit from prolonged treatment with antibiotics which is associated with significant adverse effects. Further research is needed to document whether xenodiagnosis of patients with PTLDS will detect evidence of residual nucleic acids of *B. burgdorferi*. The presence of *B. burgdorferi* DNA after antibiotic treatment does not indicate ongoing infection. Nevertheless, persistence of *Borrelia* antigens might explain the inflammation that occurs in some patients. Repeated episodes of erythema migrans are due to re-infection with different strains of *B. burgdorferi* and not to a relapse of previously treated infection. There is substantial evidence that active infection with *B. burgdorferi* does not persist in patients with Lyme disease who receive conventional treatment with antibiotics.

Acknowledgements

C.R.O. wrote the first draft of the manuscript.

Financial support and sponsorship

None.

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▪ of special interest

▪▪ of outstanding interest

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KEY POINTS

- There is no evidence to support claims of persistent infection with bacteria that cause Lyme disease after conventional treatment with antimicrobials.
- Patients with post-treatment Lyme disease syndrome get no enduring benefits from long-term antibiotic treatment, yet there is a significantly increased risk of adverse events.
- New diagnostic techniques with results that contradict a large body of previous evidence need independent confirmation before they are accepted.
- Immunity from early Lyme disease is likely strain-specific and lasts for at least 6–9 years. Recurrent erythema migrans is the result of re-infection with a different strain of *Borrelia burgdorferi* and is not a relapse of previously treated infection.