

Rash Decisions: Lyme Disease, or Not?

David T. Dennis

Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins

(See the article by Wormser et al. on pages 958–65)

More than a syndrome, Lyme disease (Lyme borreliosis) is a specific tickborne zoonosis caused in North America by infection with a single spirochetal agent, *Borrelia burgdorferi* sensu stricto [1]. Natural transmission cycles of *B. burgdorferi* involve various rodents as principal reservoirs of infection and distinct species of hard ticks in the *Ixodes ricinus* complex as vectors. In the Northeast, Mid-Atlantic, and upper Midwest regions of the United States, transmission occurs by means of the black-legged (deer) tick (*Ixodes scapularis*) and, in restricted areas of the far West, by means of the western black-legged tick (*Ixodes pacificus*). Humans may become incidentally infected when they intrude into the ecological niches of these vector ticks, and the spatial clustering of confirmed Lyme disease cases correlates highly with the presence of intense enzootic cycles of *B. burgdorferi* [2, 3]. The rapid and continuing emergence of Lyme disease in the United States is a result of increasing deer and deer tick populations and of socio-demographic factors, such as suburban residence and outdoor activities that place persons at increased risk of exposure. Despite considerable underre-

porting, ~20,000 cases are now recorded annually in the United States [4]; much larger numbers of patients are treated presumptively for the disease, often with only tenuous support for the diagnosis. Diagnostic uncertainties can result because of the complex natural history Lyme disease, its varied and often nonspecific manifestations, and difficulties in obtaining laboratory confirmation in the early stages of infection, when most patients first seek medical attention. The decision to treat is, therefore, most often made empirically on the basis of clinical presentation and epidemiological or ecological context [5, 6]. Ready confirmation or rejection of diagnosis by routine laboratory testing is still problematic during the early stages of infection, when most patients seek medical attention, and the decision to treat is most often made empirically on the basis of clinical presentation and epidemiological and/or ecological context.

In this issue of *Clinical Infectious Diseases*, Wormser et al. [7] report on a prospective clinical comparison between patients presenting with erythema migrans (EM)-like lesions in an area of New York where Lyme disease is highly endemic and patients with similar rashes in southeastern Missouri, where Lyme disease is not known to occur. EM, an expanding, erythematous, annular rash is the cardinal and characteristic sign of early, localized Lyme disease, occurring at the site of an infective tick bite within a few days to weeks after exposure. In areas where it is

endemic, EM has such a high positive predictive value that it is appropriately used there to trigger presumptive treatment [8, 9]. It is also the most important marker in identifying cases for national surveillance statistics [10]. However, although characteristic, EM is not pathognomonic; even in areas where EM is known to be endemic, $\geq 10\%$ of patients with lesions meeting descriptive criteria lack evidence of infection with *B. burgdorferi* [11, 12]. An important predicate of the report of EM-like lesions by Wormser et al. [7] is that, although *B. burgdorferi* can be isolated from most patients with EM-like rashes in New York and is easily isolated from enzootic cycles there [12, 13], similar confirmations have not been made in Missouri, despite numerous investigations.

Although persons in Missouri and other south-central and southern states are only rarely exposed to bites by *Ixodes* ticks, they are commonly bitten by other tick species (especially the lone star tick, *Amblyomma americanum*) that do not carry *B. burgdorferi* but may be associated with the development of EM-like lesions at bite sites [14]. This has caused diagnostic confusion throughout a broad range of the lone star tick, from Texas in the West to southeastern Atlantic coastal states in the East, resulting in the treatment and reporting of considerable numbers of cases of rash illness as Lyme disease in a region where risk of exposure to *B. burgdorferi* is minimal or absent. Further complicating the situation is the presence of a spirochete

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Reprints or correspondence: Dr. David T. Dennis 1012 Breakwater Dr., Fort Collins, CO 80525 (epicurve@aol.com).

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distinct from *B. burgdorferi* sensu lato in a small percentage of questing *A. americanum* ticks collected in Missouri and elsewhere in its range [15]. Only recently culturable, this spirochete was named *Borrelia lonestari* on the basis of PCR amplification of the flagellin and 16S rRNA genes of organisms recovered from *Amblyomma* tick mid-guts [16]; recent phylogenetic studies have shown it to be more closely related to members of the relapsing fever group of borreliae, *Borrelia miyamotoi* and *Borrelia theileri* (the agent of bovine borreliosis), than it is to *B. burgdorferi* [17]. PCR evidence of *B. lonestari* or a closely related bacterium has been demonstrated in a single case of EM-like rash lesion in a patient who was probably exposed in Maryland and in an *A. americanum* tick that was found to be attached at the center of the rash [18].

The report by Wormser et al. [7] in this issue is the latest in a series from the past 15 years that has attempted to establish the etiology and to describe the natural history of illness in persons with EM-like rashes in Missouri and elsewhere in the southern United States, termed, for want of a better descriptor, southern tick-associated rash illness (STARI). An early retrospective epidemiological and diagnostic study conducted by the Centers for Disease Control and Prevention (CDC) [19] in Missouri reported signs and symptoms of STARI that were similar to those of patients with a diagnosis of EM in areas where Lyme disease is endemic, and it identified several risk factors that could be surrogates of tick exposure. Results of serologic tests for evidence of Lyme disease and some other arthropod-borne diseases were negative, as were results of cultures of biopsy specimens of EM-like lesions in media used to grow *Borrelia* species. Patients with STARI were found to have mild constitutional manifestations without complications and quick resolution of illness following initiation of antimicrobial treatment. CDC investigators concluded that without evidence of infection with known pathogens, EM-like lesions in pa-

tients in Missouri should be considered idiopathic, suggesting the need for studies to rule out allergic or toxic reactions to tick bite or infection with an unidentified agent as possible causes of the rash. Their clinical observations have been supported by results of studies of patients with EM-like rashes in Georgia and South Carolina [20] and North Carolina [21], and by the studies of Missouri patients reported in this issue [7]. Detailed microbiological and serologic evaluations have shown that EM-like rashes in patients in Missouri are highly unlikely to be caused by infection with either *B. burgdorferi* or *B. lonestari* [12, 22]. As noted in the prospective clinical comparison described in this issue (and highlighted by accompanying photographs), there are considerable similarities in the qualitative features of lesions in patients from the 2 areas. Group comparisons do, however, demonstrate some interesting differences that are also observable in previously published illustrated series from respective regions [14, 23], and a blinded evaluation of photographs by a panel of dermatologists might identify discriminatory markers useful to primary care providers.

The bottom line is that the finding of a rash lesion satisfying criteria of EM does not alone establish a diagnosis of Lyme disease. Confirmation relies on microbiological evidence of *B. burgdorferi* infection. The preponderance of evidence indicates that Lyme disease occurs rarely, if at all, in states south of Maryland and Virginia, and it is unfortunate that throughout a large region of the United States many patients are treated for suspected Lyme disease and its complications, sometimes with long courses of intravenous antimicrobial agents, in the absence of an evidence-based rationale. Placebo-controlled trials of antimicrobial efficacy in patients with STARI have not been conducted, and it is unknown whether treatment alters the course of illness in these patients. Until studies indicate otherwise, physicians who observe EM-like rashes in patients who do not have known endemic

B. burgdorferi exposures should be highly circumspect of a diagnosis of Lyme disease or other infectious condition and should question the use of antimicrobials in its treatment.

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