# CORRESPONDENCE

## LYME DISEASE WITHOUT ERYTHEMA MIGRANS: CAUSE FOR CONCERN?

### To the Editor:

Steere et al. (1) described "influenza-like" symptoms without a characteristic erythema migrans ("bull's eye") rash in patients who became seropositive for *Borrelia burgdorferi*, the agent of Lyme disease, during a Lyme disease vaccine trial. In that trial, 17% of patients developed persistent symptoms consistent with chronic Lyme disease despite optimal antibiotic treatment, which had been promptly administered owing to close monitoring during the trial. In a more realistic clinical setting, 64% of patients who received "adequate" therapy for Lyme disease developed persistent symptoms that prompted further treatment (2).

The salient question that arises from these studies is whether antibiotic-treated Lyme disease patients with persistent symptoms are "cured" of their infection or whether they have ongoing infection following their initial treatment. At least three lines of evidence support the latter possibility. First, studies in animals (3,4) and humans (4,5) have found evidence of persistent *B. burgdorferi* infection despite "adequate" antibiotic therapy. Second, *B. burgdorferi* can infect a broad range of tissues and cells including fibroblasts and macrophages, and the spirochetes may persist in these cells while evading the immune response and antibiotic therapy (6,7). Third, immune deficiency involving a subset of natural killer cells may persist for 10 years or more in patients with chronic Lyme disease (4). The lymphocyte deficiency is often reversible with prolonged administration of antibiotics (8).

How can we evaluate persistent infection in chronic Lyme disease? The Centers for Disease Control and Prevention recommends screening with an enzyme-linked immunosorbent assay (ELISA), although this test misses half the cases of clinically proven disease (7,9). The Food and Drug Administration supports this screening but states, "Unlike human immunodeficiency virus tests, the commercially available serologic tests for antibody to *B. burgdorferi* are not standardized against a reference serum specimen panel" (9). Newer tests, such as the polymerase chain reaction and the VlsE peptide ELISA described by Steere et al., have not been validated in controlled clinical trials. Finally, culture techniques for *B. burgdorferi* have not been clinically useful. Thus, Lyme disease testing is at present inaccurate.

Compounding the problems with *B. burgdorferi* detection is the observation by Steere et al. that 26% of patients with rashless Lyme disease had serologic evidence of coinfection with *Babesia microti* or *Anaplasma phagocytophila*, the agent of human granulocytic ehrlichiosis (1). A recent study found that 23.5% of patients with Lyme disease in California had evidence of coinfection with the *Babesia* WA-1 strain (10). Thus, tick-borne polymicrobial infection is relatively common. Studies in mice have shown that this type of polymicrobial infection may inhibit the host immune response and exacerbate the course of Lyme disease in coinfected animals (11). In the face of immune suppression, longer courses of antibiotic therapy may be necessary to eradicate Lyme disease when it is associated with other tick-borne infections (7,8,12).

In summary, after the initial mildly symptomatic illness described by Steere et al. that may pass unnoticed without a characteristic "bull's eye" rash, the development of persistent symptoms may signal a chronic infection by a cunning spirochete that is difficult to detect (6,7). This spirochetal infection may be exacerbated by coinfecting tick-borne organisms, and persistent infection may require long-term antibiotic therapy rather than standard short-term treatment (7,8,12). Given the subtle onset of *B. burgdorferi* infection described by Steere et al., better detection methods and evaluation of adequate long-term antibiotic regimens are desperately needed for Lyme disease and its coinfections.

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## LYME DISEASE PRESENTING AS AN INFLUENZA-LIKE ILLNESS

### To the Editor:

I read with interest the article by Steere et al. (1) on seroconversion to *Borrelia burgdorferi* with either immunoglobulin (Ig) G or IgM Western blot in a group of patients presenting with a summer "flu-like" illness without rash. A minority had concurrent ehrlichiosis or babesiosis, often more symptomatic than those with Lyme disease alone. The authors recommend considering Lyme disease in patients with "systemic symptoms during summer, especially when headache or arthralgia but no upper respiratory or gastrointestinal symptoms is reported" (1). A closer look at these specific symptoms demonstrates that only 63% had fever, 54% had headache, and 71% had arthralgias. The authors do not specify whether all or just some of the above symptoms are required to justify serologic testing. Although gastrointestinal or respiratory symptoms were rarely seen in the current series, these observations could be related to methodology. The source of the current report was a Lyme disease vaccine trial wherein study subjects were provided an instructional packet that encouraged reporting of flu-like illnesses "without predominant respiratory or gastrointestinal symptoms" (2,3). Additionally, the original study definition of possible Lyme disease excluded patients with "cough, coryza, diarrhea, or vomiting" (3). Thus, the absence of notable gastrointestinal or respiratory symptoms in this set of patients could be a consequence of both reporting bias and the case definition used.

Presumably a substantial fraction of patients presenting with nonspecific constitutional symptoms have viral illnesses, and clinical criteria that can separate Lyme disease without rash from viral processes are needed. A recent small prospective study by Belongia et al. (4) was not able to distinguish summertime "flu-like" illnesses due to tick-related infection from viral illnesses on the basis of clinical presentation. Although most investigators have noted a high incidence of hematologic and liver enzyme abnormalities in patients with ehrlichiosis or babesiosis (5–7), these laboratory tests were not incorporated into the current authors' diagnostic approach. Because the patients studied by Steere et al. (1) represent a subset of a much larger cohort derived from a prospective Lyme vaccine study, those patients screened for Lyme disease but who were rejected might have formed the basis of a control group against which those with "flu-like" symptoms due to Lyme disease could have been compared. Barring more complete epidemiological studies and appropriate predictive models, caution should be exercised in routinely ordering serology for *B. burgdorferi* based on nonspecific symptoms.

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### *The Reply:*

Dr. Porwancher questions whether study methodology was the reason that gastrointestinal or respiratory symptoms were rarely seen in our series of 42 patients who had systemic symptoms without erythema migrans (1). We do not think so. Early symptoms of Lyme disease were originally described in 314 patients with erythema migrans (2). These patients often had malaise and fatigue, headache, fever and chills, myalgias, or arthralgias. A few patients had cough, chest pain, or diarrhea, but these were not the predominant symptoms. In our recent study (1), the same clinical picture was observed in patients without erythema migrans.

The vaccine study was designed to identify all participants who developed *Borrelia burgdorferi* infection (3). Patients were encouraged to report to their study physician if they had any symptoms, alone or in combination, which might be due to Lyme disease, as previously described in the medical literature. During the study, more than 400 participants were evaluated for flu-like illness, but only 28 had immunoglobulin (Ig) G seroconversion to *B. burgdorferi* when these symptoms were present (1). In these patients, headache and arthralgias were common, but gastrointestinal and respiratory symptoms were not. We do not think that Lyme