Reply

Sir—We appreciate the comments of Hung and Hsiao [1] on our recent article [2]. We agree that the epidemiologic characteristics of the subjects will significantly affect the prevalence of isolated hepatitis B core antigen (anti-HBc) in a population. However, we are not certain how to interpret their results because of a number of discrepancies in the table of data in their letter. Hung and Hsiao [1] report that 98 subjects in their study have chronic hepatitis B virus (HBV) infection (that is, that they have test results that are positive for hepatitis B surface antigen (HBsAg), negative for antibody to hepatitis B surface antigen [anti-HBs], and positive for anti-HBc). They calculate the prevalence of chronic HBV infection to be 13.7% (98 of 716 subjects), but we believe that the true prevalence should be 23.6% (98 of 416 subjects), because the authors indicate that only 416 subjects were tested. Similar discrepancies affect the prevalence of HBV infection among subjects in the other groups discussed in their analysis. In addition, for group 4, the number of subjects classified by CD4 cell count category (10 subjects with a CD4 cell count of <50 cells/mm^3, 16 subjects with 50–99 cells/mm^3, 3 subjects with 100–199 cells/mm^3, 5 subjects with 200–349 cells/mm^3, and 3 subjects with 350 cells/mm^3) does not add up to the 27 subjects classified as being in group 4. Thus, it is difficult to fully evaluate their results because of these discrepancies. The cohort described by Hung and Hsiao [1] has a lower prevalence of HCV infection than our cohort. In fact, only 1 subject in their study had both positive test results for HCV infection and negative test results for HBsAg, anti-HBs, and anti-HBc, and only 12 subjects who tested positive for HCV had isolated anti-HBc. With such low numbers, we do not believe their study would have the power to allow them to detect an association between HCV infection and the isolation of anti-HBc. Finally, the median CD4 cell count among their subjects with isolated anti-HBc does not differ from that among subjects with negative test results for HBsAg, anti-HBs, and anti-HBc, which agrees with our findings.

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Coinfection in Patients with Lyme Disease: How Big a Risk?

Sir—In their study of coinfections in patients with Lyme disease, Steere et al. [1] found a 4% rate of coinfection with Babesia microti or Anaplasma phagocytophila in patients with erythema migrans rash that was culture-positive for Borrelia burgdorferi. This coinfection rate was significantly lower than the average rate (21%) reported in other studies cited by Steere et al. [1], and the authors explain the discrepancy by alluding to “methodology” as a principal factor. Their explanation is probably correct, but not in a positive sense.

In studying only patients with an erythema migrans rash, the authors excluded perhaps >40% of patients with Lyme disease who do not develop this rash [2, 3]. In fact, the same investigators previously reported a 26% rate of coinfection with B. microti or A. phagocytophila in patients with rashless Lyme disease [3]. Furthermore, Steere et al. [1] excluded 19% of patients with erythema migrans rashes that were culture-negative for B. burgdorferi. Because patients with Lyme disease do not always have positive skin culture results using current techniques [4–6], this patient group should have been included in the analysis.

A bigger problem with the study concerns the timing of serologic testing for coinfections. This testing was only performed at the time of erythema migrans appearance and then again after 3 weeks of antibiotic therapy. Serologic testing in this manner probably occurred too early or too late to detect an antibody response to the coinfecting agents [6]. Finally, it appears that PCR testing was only performed for patients who were seropositive for B. microti or A. phagocytophila. Because of the possibility of false-negative results of serologic testing, as described above, all patients should have been tested by PCR at repeated intervals to screen for coinfections. Thus, the low coinfection rate may have been due to methodological flaws in the study.

The results presented by Steere et al. [1] give a false impression that coinfections are rare in patients with Lyme disease, and this erroneous assumption may persuade health care providers to ignore persistent symptoms of polymicrobial infection in these patients. Coinfection with B. microti or A. phagocytophila in a mouse model of Lyme disease is associated with an altered immune response and exacerbation of symptoms of disease [7, 8]. Furthermore, newer coinfecting agents need to be considered in cases of Lyme disease, including the Babesia species WA-1 strain and Bartonella henselae [9, 10]. A recent study from California found a serologic prevalence of 23.5% for Babesia WA-1 in patients with Lyme disease in that state [9]. The true risk of polymicrobial infection in patients with Lyme disease requires better evaluation with more thorough serologic and molecular testing for known and emerging tickborne coinfections.
Reply

Sir—Stricker et al. [1] are concerned that methodological flaws may have led to an underestimation of the frequency of coinfection in our recent 4-year prospective study of patients with erythema migrans [2]. We disagree. The point of our study was to use rigorous criteria to support the diagnosis of coinfection in patients with erythema migrans and to exclude, as much as possible, confounding variables that might interfere with the interpretation of results. Our goal was not to identify all patients with coinfection in a given geographic population.

The greatest problem in the diagnosis of coinfection is the interpretation of serologic test results. First, anaplasmosis, by itself, may cause a false-positive IgM serologic response for Lyme disease [3], and patients with erythema migrans often have only an IgM response to Borrelia burgdorferi [4]. Second, a single serologic test result does not allow coinfection and sequential infection to be distinguished. Therefore, in our study, we required documentation by culture of skin biopsy samples of erythema migrans lesions to prove that patients had B. burgdorferi infection. For documentation of simultaneous Anaplasma phagocytophilum or Babesia microti infection, we required that patients have a positive PCR test result for a blood sample or IgG serocconversion between acute- and convalescent-phase samples obtained 3–4 weeks apart. Contrary to what is said by Stricker et al. [1], both PCR and serologic tests in our study were performed for all patients with culture-proven erythema migrans. In addition, our results do not suggest that serocconversion was missed when samples were obtained within this time period. In our study, the results of PCR and serologic tests, which are performed independently, were usually concordant. Three of the 4 coinfected patients had positive PCR results, and 2 of these patients had IgG serocconversion to A. phagocytophilum or B. microti. Only 1 patient had IgG serocconversion to B. microti with a negative PCR result. With use of this methodology, the data showed that 4 (4%) of 93 patients with culture-proven erythema migrans had evidence of coinfection.

We would like to correct several other statements. Stricker et al. [1] state that approximately 40% of patients do not develop erythema migrans. In the SmithKline Beecham Lyme disease vaccine trial, which was designed to identify all cases of Lyme disease that occurred in the nearly 11,000 study participants during a 20-month study period, erythema migrans was found in 78% of patients with definite symptomatic cases of Lyme disease [5]. Among patients in the vaccine trial who presented with systemic symptoms without erythema migrans, 4 (14%) of the 28 patients with definite cases (not 26%) had evidence of coinfection with A. phagocytophilum or B. microti [6].

Our data show that the frequency of coinfection in these study populations was low. However, we do not suggest that health care providers should ignore the problem of polymicrobial infection. Our recent article [2] concluded with the statement that it is important for physicians to be aware of the possibility of coinfection in patients with erythema migrans, because, in certain cases, the coinfecting agents may cause severe or even life-threatening illness.

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