Laboratory Diagnosis of Lyme Disease

Advances and Challenges

Adriana R. Marques, MD

KEYWORDS

• Lyme disease • *Borrelia burgdorferi* • Laboratory diagnosis • Serology

KEY POINTS

- It is difficult to demonstrate *Borrelia burgdorferi* by direct techniques (culture and polymerase chain reaction [PCR]). The spirochete is more easily found in the skin and plasma samples of patients with early disease (erythema migrans), and in the synovial fluid of patients with Lyme arthritis (using PCR).
- The sensitivity of antibody-based tests increases with the duration of the infection. Less than 50% of patients with erythema migrans are positive at presentation. These patients should receive treatment based on the clinical diagnosis.
- Serologic tests are most helpful in patients with clinical findings indicating later stages of Lyme disease.
- Many tests for Lyme disease are being performed in patients with low likelihood to have the disease, a situation in which a positive result is more likely to be a false-positive.
- The current assays do not distinguish between active and past infection, and patients may continue to be seropositive for years.
- The use of nonvalidated Lyme diagnostic tests is not recommended.

OVERVIEW

Lyme disease, or Lyme borreliosis, is a multisystem illness caused by the spirochete *Borrelia burgdorferi* and it is the most common tick-borne illness in the United States and Europe. Newly revised estimates from the Centers for Disease Control and Prevention (CDC) suggest that there are likely to be around 300,000 new cases of

This research was supported by the Intramural Research Program National Institute of Allergy and Infectious Diseases, NIH.
Disclaimer: The findings and conclusions in this article are those of the author and do not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases.
Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10/12C118 10 Center Drive, Bethesda, MD 20892, USA
E-mail address: amarques@niaid.nih.gov

Infect Dis Clin N Am 29 (2015) 295–307
http://dx.doi.org/10.1016/j.idc.2015.02.005 **id.theclinics.com**
0891-5520/15/$ – see front matter Published by Elsevier Inc.

Lyme disease per year in the United States.[1] *B burgdorferi* is transmitted by the bite of infected ticks of the *Ixodes ricinus* complex. In the United States, most cases of Lyme disease are caused by the blacklegged tick (*Ixodes scapularis*), occurring in the mid-Atlantic, northeast, and upper Midwest regions.

B burgdorferi is a gram-negative bacterium, and has the elongated and spiral shape of the spirochetes.[2] It varies from 10 to 30 μm in length and 0.2 to 0.5 μm in width. It has a linear chromosome and a variable number of circular and linear plasmids.[3] The *B burgdorferi* sensu lato group includes at least 20 genospecies.[4] Three genospecies are most commonly associated with human infections: *B burgdorferi* sensu stricto, which causes disease in North America and Europe; and *Borrelia afzelii* and *Borrelia garinii*, which occur in Europe and Asia.[5] Additional genospecies have been shown to at least occasionally cause human disease in Europe (eg, *Borrelia spielmanii* and *Borrelia valaisiana*).[5] There is some variation in the clinical presentation depending on the infecting genospecies, with *B burgdorferi* sensu stricto predominating in arthritis, *B garinii* in neurologic disease, and *B afzelii* in chronic skin manifestations.[6] Even within the same genospecies, there is variation in presentation and dissemination capability.[7,8]

For clinical purposes, Lyme disease is divided into early localized, early disseminated, and late stages. Lyme disease usually begins with the characteristic skin lesion, erythema migrans (EM), at the site of the tick bite.[9–11] After several days or weeks, the spirochete may disseminate and patients can develop neurologic, cardiac, and rheumatologic involvement.[12–15] The infection is characterized by low number of bacteria, which can persist in collagen-rich tissues. Although antibiotic therapy accelerates resolution of the disease, manifestations can spontaneously regress without antibiotic therapy. The resolution of disease is mediated by immune responses, which control the infection. However, without antibiotic therapy, it can recur and/or new manifestations can appear.[9,16,17]

The available laboratory methods for the diagnosis of Lyme disease are in 2 categories: direct methods to detect *B burgdorferi*, and indirect methods that detect the immune response against it (mainly the detection of antibodies against *B burgdorferi*). It is important to recognize that laboratory tests should be ordered and interpreted in the context of the clinical evaluation and the likelihood that the patient has Lyme disease. This article reviews the laboratory diagnostics for Lyme disease (with focus on the United States) and discusses current recommendations and new developments.

DIRECT METHODS FOR DETECTION OF *BORRELIA BURGDORFERI*

Laboratory tests for direct detection of *B burgdorferi* are hampered by very low numbers of spirochetes in most clinical samples. The lack of sensitive, easy, fast, direct tests for the presence of *B burgdorferi* is one of the main challenges in the laboratory diagnosis of Lyme disease. Although direct tests for *B burgdorferi* can sometimes be helpful, none are required for the diagnosis of the disease. The main direct test modalities used are culture and PCR. Histopathology has limited utility, being used mostly to exclude other diseases, and in the evaluation of suspected cases of borrelial lymphocytoma and acrodermatitis chronica atrophicans.[18,19] Detection of *B burgdorferi* is difficult and time consuming because of the extreme scarcity of organisms.[20–23] Warthin-Starry and modified Dieterle silver stains, focus-floating microscopy, as well as direct and indirect immunofluorescence assays with antiborrelial antibodies have been used, but can be difficult to interpret and require special expertise and careful use of controls.[24–26] At present, no antigen assays are recommended for the diagnosis of Lyme disease. A research test for detection of outer surface