of Lyme disease. Serum antibody (serology) testing is highly sensitive in patients with common extracutaneous manifestations that develop weeks to months after initial infection [20, 21]. Immunoglobulin G (IgG) seronegativity in an untreated patient with months to years of symptoms essentially rules out the diagnosis of Lyme disease, barring laboratory error or a rare humoral immunodeficiency state. Serologic testing is also highly specific when performed and interpreted according to current guidelines [21, 22]. Serum antibody tests should be performed using clinically validated assays in a conventional 2-tiered testing protocol, in which an enzyme immunoassay (EIA) or indirect fluorescent antibody test (IFA) is followed by immunoglobulin M (IgM) and IgG immunoblots, or in a modified 2-tiered testing protocol, in which 2 different EIAs are performed sequentially or concurrently without the use of immunoblots [23–27]. Serologic tests are intended for use in 2-tiered testing protocols, rather than as stand-alone assays, as this improves specificity [25]. Predictive value is increased when results are correlated with clinical features, patient history and risk factors.

As an indirect detection method, antibody testing for Lyme disease has some important limitations. Results can be falsely negative in the first days to weeks following initial exposure because a detectable antibody response takes time to develop [21, 28, 29]. This is often the case in patients with erythema migrans, an early manifestation of Lyme disease, who are tested <2 weeks after the development of the skin lesion [21, 28, 29].

In a seropositive patient, it can be difficult to determine whether antibody reactivity is due to past infection versus active/current infection. In part, this is because both IgM and IgG *B. burgdorferi*-specific antibody responses can persist for years or even decades after the infection has been eradicated [8, 30, 31]. Furthermore, patients can be infected multiple times [32], especially if the initial infection is promptly treated at an early stage, and an expanded humoral immune response does not develop. If there is a known or suspected past history of Lyme disease in a seropositive patient with new symptoms, the diagnosis may be primarily reliant on clinical features and exclusion of alternative diagnoses. Some individuals with no prior exposure to *B. burgdorferi* may have positive serologic tests, sometimes due to cross-reactive antibodies to other microbes or due to autoimmune disease. Because of this potential for false positive results, clinicians should be selective when ordering tests in patients with a low probability of Lyme disease.

To address these limitations, numerous nonserologic methods have been proposed or developed, including nucleic acid amplification tests, culture methods, and antigen detection assays, among others. At present, few nonserologic testing methods are useful or practical for clinical diagnosis, and those that are—primarily nucleic acid amplification tests—are mostly beneficial as adjunctive tests in select clinical scenarios when 2-tiered serologic testing is positive. This document provides guidance about when to consider ordering a nonserologic test, such as a polymerase chain reaction (PCR) assay, but providers may be faced with many options when choosing, for example, a PCR test. As a rule, an assay should only be used for diagnostic purposes if its analytical and clinical validity has been demonstrated reproducibly in comparison to an appropriate reference standard. Assessing the validity of a particular nonserologic test for Lyme disease is especially challenging because none has yet been cleared or approved by the US Food and Drug Administration (FDA). Before requesting a non-FDA-cleared test for diagnostic purposes, providers are strongly encouraged to (1) verify that the diagnostic laboratory offering the test is certified under Clinical Laboratory Improvement Amendments (CLIA) for high-complexity diagnostic testing, and (2) ensure that validation studies, whether published or unpublished, confirm analytical and clinical performance that is substantially equivalent in comparison to an appropriate reference standard. In making this assessment, consultation with an independent clinical laboratory director with experience in Lyme disease diagnostics is advised. In some cases, the CDC may serve as a resource for this assessment [33]. Some commercially available laboratory testing methods, including nonstandard serology interpretation, urine antigen, DNA testing, the use of a lymphocyte transformation test [34], or quantitative CD57 lymphocyte assay [35] should be avoided for clinical use due to lack of systematic, independent, reproducible validation studies [36].

Treatment of Lyme Disease

Lyme disease is treated with antimicrobials with activity against *B. burgdorferi* (see Tables 3 and 4). The goals of treatment are the eventual resolution of signs and symptoms of infection, with prevention of relapsed active infection or new complications of infection. Patients with erythema migrans are treated with 7–14 days of an appropriate antibiotic depending on which drug is prescribed; other clinical manifestations are typically treated with 14–28 days of an appropriate antibiotic with duration of treatment based on which clinical manifestation is being treated.

B. burgdorferi is susceptible to antimicrobials from several classes. The antibiotics most commonly used to treat *B. burgdorferi* infection in North America include doxycycline, amoxicillin, cefuroxime, ceftriaxone, and azithromycin. Under most circumstances, oral therapy is effective and preferred over intravenous (IV) therapy due to equivalent efficacies, better tolerability, and lower cost. However, indications for IV therapy, such as treatment of a hospitalized patient, are discussed in this guideline.

The choice of antibiotic depends on a number of factors that include age, the presence of extracutaneous manifestations of Lyme disease, such as neurologic Lyme disease; drug allergy, side effect profile, or tolerability; frequency of administration; sun exposure (sun exposure will increase the risk of