TABLE 210-1 ALGORITHM FOR TESTING FOR AND TREATING LYME DISEASE

Pretest Probability	Example	Recommendation
High	Patients with erythema migrans	Empirical antibiotic treatment without serologic testing
Intermediate	Patients with oligoarticular arthritis	Serologic testing and antibiotic treatment if test results are positive
Low	Patients with nonspecific symptoms (myalgias, arthralgias, fatigue)	Neither serologic testing nor antibiotic treatment

Source: Adapted from the recommendations of the American College of Physicians (G Nichol et al: Ann Intern Med 128:37, 1998, with permission).

Lyme disease may cause diagnostic confusion. According to an algorithm published by the American College of Physicians (Table 210-1), serologic testing for Lyme disease is recommended only for patients with at least an intermediate pretest probability of Lyme disease, such as those with oligoarticular arthritis. It should not be used as a screening procedure in patients with pain or fatigue syndromes. In such patients, the probability of a false-positive serologic result is higher than that of a true-positive result.

For serologic analysis of Lyme disease in the United States, the CDC recommends a two-step approach in which samples are first tested by enzyme-linked immunosorbent assay (ELISA) and equivocal or positive results are then tested by western blotting. During the first weeks of infection, both IgM and IgG responses to the spirochete should be determined, preferably in both acute- and convalescent-phase serum samples. Approximately 20–30% of patients have a positive response detectable in acute-phase samples, whereas ~70–80% have a positive response during convalescence (2–4 weeks later). After 4–8 weeks of infection (by which time most patients with active Lyme disease have disseminated infection), the sensitivity and specificity of the IgG response to the spirochete are both very high—in the range of 99%—as determined by the two-test approach of ELISA and western blot. At this point and thereafter, a single test (that for IgG) is usually sufficient. In persons with illness of >2 months' duration, a positive IgM test result alone is likely to be false-positive and therefore should not be used to support the diagnosis.

According to current criteria adopted by the CDC, an IgM western blot is considered positive if two of the following three bands are present: 23, 39, and 41 kDa. However, the combination of two such bands may still represent a false-positive result. Misuse or misinterpretation of IgM blots has been a factor in the incorrect diagnosis of Lyme disease in patients with other illnesses. An IgG blot is considered positive if 5 of the following 10 bands are present: 18, 23, 28, 30, 39, 41, 45, 58, 66, and 93 kDa. In European cases, no single set of criteria for the interpretation of immunoblots results in high levels of sensitivity and specificity in all countries.

The most promising second-generation serologic test is the VlsE C6 peptide IgG ELISA, which employs a 26-mer of the sixth invariant region of the VlsE lipoprotein of *B. burgdorferi*. The results achieved with this test are similar to those obtained with the standard two-test approach (sonicate IgM and IgG ELISA and western blot). The principal advantage of the C6 peptide ELISA is the early detection of an IgG response, which renders an IgM test unnecessary. However, not all patients with late Lyme disease have a response to the C6 peptide, and this test is not quite as specific as sonicate western blot. Thus, at present, a two-test approach that includes western blot is still recommended. Blotting can also be helpful in assessing the duration of current or past disease.

After successful antibiotic treatment, antibody titers decline slowly but responses (including that to the VlsE C6 peptide) may persist for years. Moreover, not only the IgG but also the IgM response may persist for years after therapy. Therefore, even a positive IgM response cannot be interpreted as confirmation of recent infection or reinfection unless the clinical picture is appropriate.

DIFFERENTIAL DIAGNOSIS

Classic EM is a slowly expanding erythema, often with partial central clearing. If the lesion expands little, it may represent the red papule of an uninfected tick bite. If the lesion expands rapidly, it may represent cellulitis (e.g., streptococcal cellulitis) or an allergic reaction, perhaps to tick saliva. Patients with secondary annular lesions may be thought to have erythema multiforme, but neither the development of blistering mucosal lesions nor the involvement of the palms or soles is a feature of *B. burgdorferi* infection. In the eastern United States, an EM-like skin lesion, sometimes with mild systemic symptoms, may be associated with *Amblyomma americanum* tick bites. However, the cause of this Southern tick-associated rash illness (STARI) has not yet been identified. This tick may also transmit *Ehrlichia chaffeensis*, a rickettsial agent (Chap. 211).

As stated above, *I. scapularis* ticks in the United States may transmit not only *B. burgdorferi* but also *B. microti*, a red blood cell parasite (Chap. 249); *A. phagocytophilum*, the agent of human granulocytotropic anaplasmosis (Chap. 211); *Ehrlichia* species Wisconsin; *B. miyamotoi*, a relapsing fever spirochete (Chap. 209); or (rarely) Powassan encephalitis virus (the deer tick virus, which is closely related to European tick-borne encephalitis virus) (Chap. 233). Although babesiosis and anaplasmosis are most often asymptomatic, infection with any of these agents may cause nonspecific systemic symptoms, particularly in the young or elderly, and co-infected patients may have more severe or persistent symptoms than patients infected with a single agent. Standard blood counts may yield clues regarding the presence of co-infection with *Anaplasma* or *Babesia*. Anaplasmosis may cause leukopenia or thrombocytopenia, and babesiosis may cause thrombocytopenia or (in severe cases) hemolytic anemia. IgM serologic responses may confuse the diagnosis. For example, *A. phagocytophilum* may elicit a positive IgM response to *B. burgdorferi*. The frequency of co-infection in different studies has been variable. In one prospective study, 4% of patients with EM had evidence of co-infection.

Facial palsy caused by *B. burgdorferi*, which occurs in the early disseminated phase of the infection (often in July, August, or September), is usually recognized by its association with EM. However, in rare cases, facial palsy without EM may be the presenting manifestation of Lyme disease. In such cases, both the IgM and the IgG responses to the spirochete are usually positive. The most common infectious agents that cause facial palsy are herpes simplex virus type 1 (Bell's palsy; Chap. 216) and varicella-zoster virus (Ramsay Hunt syndrome; Chap. 217).

Later in the infection, oligoarticular Lyme arthritis most resembles reactive arthritis in an adult or the pauciarticular form of juvenile idiopathic arthritis in a child. Patients with Lyme arthritis usually have the strongest IgG antibody responses seen in Lyme borreliosis, with reactivity to many spirochetal proteins.

The most common problem in diagnosis is to mistake Lyme disease for chronic fatigue syndrome (Chap. 464e) or fibromyalgia (Chap. 396). This difficulty is compounded by the fact that a small percentage of patients do in fact develop these chronic pain or fatigue syndromes in association with or soon after Lyme disease. Moreover, a counterculture has emerged that ascribes pain and fatigue syndromes to chronic Lyme disease when there is little or no evidence of *B. burgdorferi* infection. In such cases, the term *chronic Lyme disease*, which is equated with chronic *B. burgdorferi* infection, is a misnomer, and the use of prolonged, dangerous, and expensive antibiotic treatment is not warranted.

TREATMENT LYME BORRELIOSIS

ANTIBIOTIC TREATMENT

As outlined in the algorithm in Fig. 210-2, the various manifestations of Lyme disease can usually be treated successfully with orally administered antibiotics; the exceptions are objective neurologic abnormalities and third-degree atrioventricular heart block, which are generally treated with IV antibiotics, and arthritis that does not