fluctuating degree of atrioventricular block (first-degree, Wenckebach, or complete heart block). Some patients have more diffuse cardiac involvement, including electrocardiographic changes indicative of acute myopericarditis, left ventricular dysfunction evident on radionuclide scans, or (in rare cases) cardiomegaly or fatal pancarditis. Cardiac involvement lasts for only a few weeks in most patients but may recur in untreated patients. Chronic cardiomyopathy caused by *B. burgdorferi* has been reported in Europe.

During this stage, musculoskeletal pain is common. The typical pattern consists of migratory pain in joints, tendons, bursae, muscles, or bones (usually without joint swelling) lasting for hours or days and affecting one or two locations at a time.

Late Infection: Stage 3 (Persistent Infection) Months after the onset of infection, ~60% of patients in the United States who have received no antibiotic treatment develop frank arthritis. The typical pattern comprises intermittent attacks of oligoarticular arthritis in large joints (especially the knees), lasting for weeks or months in a given joint. A few small joints or periarticular sites also may be affected, primarily during early attacks. The number of patients who continue to have recurrent attacks decreases each year. However, in a small percentage of cases, involvement of large joints—usually one or both knees—is persistent and may lead to erosion of cartilage and bone.

White cell counts in joint fluid range from 500 to 110,000/μL (average, 25,000/μL); most of these cells are polymorphonuclear leukocytes. Tests for rheumatoid factor or antinuclear antibodies usually give negative results. Examination of synovial biopsy samples reveals fibrin deposits, villous hypertrophy, vascular proliferation, microangiopathic lesions, and a heavy infiltration of lymphocytes and plasma cells.

Although most patients with Lyme arthritis respond well to antibiotic therapy, a small percentage in the northeastern United States have persistent (*antibiotic-refractory*) arthritis for months or even for several years after receiving oral and IV antibiotic therapy for 2 or 3 months. Although more often these patients are initially infected with RST1 strains of *B. burgdorferi*, this complication is not thought to result from persistent infection. Results of culture and polymerase chain reaction (PCR) for *B. burgdorferi* in synovial tissue obtained in the postantibiotic period have been uniformly negative. Rather, infection-induced autoimmunity, retained spirochetal antigens, or both may play a role in this outcome. Antibiotic-refractory arthritis is associated with a higher frequency of certain class II major histocompatibility complex molecules (particularly HLA-DRBI*0401 or -*0101 molecules); the Toll-like receptor 1 polymorphism 1805GG, which leads to exceptionally high levels of cytokines and chemokines in affected joints; and low frequencies of FoxP3+ T regulatory cells in synovial fluid, which correlate with longer posttreatment durations of arthritis. The recent identification of a novel human autoantigen, endothelial cell growth factor, as a target of T and B cell responses in patients with Lyme disease provided the first direct evidence of autoimmune T and B cell responses in this illness. However, multiple spirochetal or additional yet-to-be identified autoantigens may have a role in antibiotic-refractory arthritis.

Although rare, chronic neurologic involvement also may become apparent from months to several years after the onset of infection, sometimes after long periods of latent infection. The most common form of chronic central nervous system involvement is subtle encephalopathy affecting memory, mood, or sleep, and the most common form of peripheral neuropathy is an axonal polyneuropathy manifested as either distal paresthesia or spinal radicular pain. Patients with encephalopathy frequently have evidence of memory impairment in neuropsychological tests and abnormal results in CSF analyses. In cases of polyneuropathy, electromyography generally shows extensive abnormalities of proximal and distal nerve segments. Encephalomyelitis or leukoencephalitis, a rare manifestation of Lyme borreliosis associated primarily with *B. garinii* infection in Europe, is a severe neurologic disorder that may include spastic paraparesis, upper motor-neuron bladder dysfunction, and, rarely, lesions in the periventricular white matter.

Acrodermatitis chronica atrophicans, the late skin manifestation of Lyme borreliosis, has been associated primarily with *B. afzelii* infection in Europe and Asia. It has been observed especially often in elderly women. The skin lesions, which are usually found on the acral surface of an arm or leg, begin insidiously with reddish-violaceous discoloration; they become sclerotic or atrophic over a period of years.

The basic patterns of Lyme borreliosis are similar worldwide, but there are regional variations, primarily between the illness found in North America, which is caused exclusively by *B. burgdorferi*, and that found in Europe, which is caused primarily by *B. afzelii* and *B. garinii*. With each of the *Borrelia* species, the infection usually begins with EM. However, *B. burgdorferi* strains in the eastern United States often disseminate widely; they are particularly arthritogenic, and they may cause antibiotic-refractory arthritis. *B. garinii* typically disseminates less widely, but it is especially neurotropic and may cause borrelial encephalomyelitis. *B. afzelii* often infects only the skin but may persist in that site, where it may cause several different dermatoborrelioses, including acrodermatitis chronica atrophicans.

Post–Lyme Syndrome (Chronic Lyme Disease) Despite resolution of the objective manifestations of the infection with antibiotic therapy, ~10% of patients (although the reported percentages vary widely) continue to have subjective pain, neurocognitive manifestations, or fatigue symptoms. These symptoms usually improve and resolve within months but may last for years. At the far end of the spectrum, the symptoms may be similar to or indistinguishable from chronic fatigue syndrome (Chap. 464e) and fibromyalgia (Chap. 396). Compared with symptoms of active Lyme disease, post-Lyme symptoms tend to be more generalized or disabling. They include marked fatigue, severe headache, diffuse musculoskeletal pain, multiple symmetric tender points in characteristic locations, pain and stiffness in many joints, diffuse paresthesias, difficulty with concentration, and sleep disturbances. Patients with this condition lack evidence of joint inflammation, have normal neurologic test results, and may exhibit anxiety and depression. In contrast, late manifestations of Lyme disease, including arthritis, encephalopathy, and neuropathy, are usually associated with minimal systemic symptoms. Currently, no evidence indicates that persistent subjective symptoms after recommended courses of antibiotic therapy are caused by active infection.

DIAGNOSIS

The culture of *B. burgdorferi* in Barbour-Stoenner-Kelly (BSK) medium permits definitive diagnosis, but this method has been used primarily in research studies. Moreover, with a few exceptions, positive cultures have been obtained only early in the illness—particularly from biopsy samples of EM skin lesions, less often from plasma samples, and occasionally from CSF samples. Later in the infection, PCR is greatly superior to culture for the detection of *B. burgdorferi* DNA in joint fluid; this is the major use for PCR testing in Lyme disease. However, because *B. burgdorferi* DNA may persist for at least weeks after spirochetal killing with antibiotics, detection of spirochetal DNA in joint fluid is not an accurate test of active joint infection in Lyme disease and cannot be used reliably to determine the adequacy of antibiotic therapy. The sensitivity of PCR determinations in CSF from patients with neuroborreliosis has been much lower than that in joint fluid. There seems to be little if any role for PCR in the detection of *B. burgdorferi* DNA in blood or urine samples. Moreover, this procedure must be carefully controlled to prevent contamination.

Because of the problems associated with direct detection of *B. burgdorferi*, Lyme disease is usually diagnosed by the recognition of a characteristic clinical picture accompanied by serologic confirmation. Although serologic testing may yield negative results during the first several weeks of infection, almost all patients have a positive antibody response to *B. burgdorferi* after that time. The limitation of serologic tests is that they do not clearly distinguish between active and inactive infection. Patients with previous Lyme disease—particularly in cases progressing to late stages—often remain seropositive for years, even after adequate antibiotic treatment. In addition, ~10% of patients are seropositive because of asymptomatic infection. If these individuals subsequently develop another illness, the positive serologic test for