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There are shortcomings of single-dose therapies for LBRF. With penicillin alone, recurrence may occur in up to 20% of patients, and the frequency of JHR was higher after tetracycline than penicillin. For treatment of LBRF in adults in Ethiopia, a regimen that reduces rates of both recurrence and JHR was a single dose of 400,000 units of intramuscular penicillin G procaine followed several hours later or the next day by doxycycline (100 mg orally twice daily) or tetra cycline (500 mg or 12.5 mg/kg orally every 6 h) for 7 days.

The accumulated anecdotal reports on STRF therapy indicate a recurrence rate of ≥20% after single-dose treatment, plausibly due to the propensity of some tick-borne species to invade the CNS. Accordingly, multiple antibiotic doses are recommended. The pre ferred treatment for adults is a 10-day course of doxycycline (100 mg twice daily) or tetracycline (500 mg or 12.5 mg/kg orally every 6 h). When tetracyclines are contraindicated, the alternatives are oral penicillin V potassium (500 mg or 12.5 mg/kg every 6–8 h) or erythromycin (500 mg or 12.5 mg/kg orally every 6 h) for 10 days. If a β-lactam antibiotic is given and CNS involvement is confirmed or suspected, it is preferably administered intravenously rather than orally. For adults, the regimen is penicillin G (5 million units IV every 6 h) or ceftriaxone (2 g IV daily) for 10–14 days. The JHR during treatment of LBRF or STRF can be severe and may end in death if precautions are not in place for close monitor ing for at least 24 h and with provision of parenteral cardiovascular and volume support as needed. Apprehension, rigors, fever, and hypotension occur within 1–3 h of initiation of antibiotic treat ment and may be accompanied by a further decrease in the platelet count. The incidence of the JHR is 20–60% in LBRF after the first antibiotic dose. JHR may also be encountered when a patient with unsuspected relapsing fever is treated with other types of antibiot ics, such ciprofloxacin, that have suboptimal effects. PART 5 Infectious Diseases Experience with the treatment of B. miyamotoi or B. lonestari HTRF is limited, but these organisms likely have the same antibiotic susceptibilities as other Borrelia species. Therapy for B. miyamotoi disease follows the guidelines for Lyme disease. This would include parenteral therapy for CNS involvement. In absence of contraindi cations, doxycycline (100 mg twice daily) is the preferred choice for uncomplicated B. miyamotoi infection because of the antibiotic’s efficacy for anaplasmosis and Lyme disease. If JHR occurs, it is generally milder than is observed in relapsing fever. ■ ■PROGNOSIS The mortality rates for untreated LBRF and STRF are in the ranges of 10–70% and 4–10%, respectively, and are largely determined by coexisting conditions, such as malnutrition or another infection, and by the availability of medical support. With prompt antibiotic treat ment, the mortality rate is 2–5% for LBRF and <2% for STRF. There are no reported deaths from HTRF. Features associated with a poor prognosis of LBRF or STRF include concurrence with malaria, typhus, or typhoid; pregnancy; stupor or coma on admission; diffuse bleeding; poor liver function; myocarditis; and bronchopneumonia. The mortal ity rate from the JHR in LBRF, in the absence of adequate monitoring and resuscitation measures, is

~5%. LBRF or STRF during pregnancy frequently leads to abortion, stillbirth, or perinatal death, but con genital malformations have not been reported. Although spirochetes or their remnants may persist in the CNS or other sequestered sites after bacteremia has resolved, posttreatment sequelae and prolonged disability have not been documented for any form of relapsing fever. Partial immunity against reinfection seems to develop in residents of areas with perennial elevated risk. ■ ■PREVENTION There is no vaccine for LBRF, STRF, or HTRF. Reduction of expo sure to lice and ticks is the key strategy for prevention. LBRF can be prevented through improved personal hygiene, reduction of crowd ing, better access to hot water (≥60° C) for clothes washing, and selected use of pesticides. Clothing is an important factor in main taining the human body louse. The risk of STRF can be reduced by construction of houses with concrete or sealed plank floors and

without thatched roofs or mud walls. Dwellings in forested areas pose a risk in western North America when rodents nest in the roof, attic, or wall spaces or under the structure. Buildings infested with Ornithodoros ticks can be treated with pesticides and then rodent-proofed. If residing in a high-risk environment, individuals should not sleep on the floor, and beds should be moved away from the wall. Individuals with recreational or occupational exposure to caves, where mammals may reside, merit advice about the risk of STRF. Following exposure at a site of STRF risk, treatment with doxycycline (a single dose of 100 mg or 200 mg on day 1 followed by 100 mg/d for 4 days) was efficacious in preventing infection in a placebo-controlled trial. Recommendations for preventing B. miya motoi infection follow those for reducing risk of Lyme disease from exposure to the vector, hard ticks (Chap. 191). ■ ■FURTHER READING Barbour AG, Schwan TG: Borrelia, in Bergey’s Manual of Systematics of Archaea and Bacteria, WB Whitman et al (eds). Hoboken, Wiley, 2015. Beeson AM et al: Soft tick relapsing fever — United States, 2012–2021. MMWR Morb Mortal Wkly Rep 72:777, 2023. Butler T: The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: A review of recent cases and our under standing of pathogenesis. Am J Trop Med Hyg 96:46, 2017. Isenring E et al: Infectious disease profiles of Syrian and Eritrean migrants presenting in Europe: A systematic review. Travel Med Infect Dis 25:65, 2018. Kahlig E et al: Louse-borne relapsing fever-A systematic review and analysis of the literature: Part 1-Epidemiology and diagnostic aspects. PLoS Negl Trop Dis 15:e0008564, 2021. Kahlig E et al: Louse-borne relapsing fever-A systematic review and analysis of the literature: Part 2-Mortality, Jarisch-Herxheimer reac tion, impact on pregnancy. PLoS Negl Trop Dis 15:e0008656, 2021. McCormick DW et al: Characteristics of hard tick relapsing fever caused by Borrelia miyamotoi, United States, 2013–2019. Emerg Infect Dis 29:1719, 2023. Vazquez LJ et al: Relapsing fever caused by Borrelia lonestari after tick bite in Alabama. Emerg Infect Dis 29:441, 2023. Warrell DA: Louse-borne relapsing fever (Borrelia recurrentis infec tion). Epidemiol Infect 147:e106, 2019. Wormser GP et al: Aggregation of data from 4 clinical studies dem onstrating efficacy of single-dose doxycycline postexposure for pre vention of the spirochetal infections: Lyme disease, syphilis, and tick-borne relapsing fever. Diagn Microbiol Infect Dis 99:115293 2021. Allen C. Steere, Jacob E. Lemieux

Lyme Borreliosis ■ ■DEFINITION Lyme borreliosis is caused by a closely related group of spirochetes, Borrelia burgdorferi sensu lato (also called Borreliella spp.), transmitted by ticks of the Ixodes ricinus complex. The infection usually begins with a characteristic expanding skin lesion, erythema migrans (EM; stage 1, localized infection). After several days or weeks, the spirochete may spread to many different sites (stage 2, disseminated infection). Possi ble manifestations of disseminated infection include additional annular skin lesions, meningitis, cranial neuritis,

radiculoneuritis, peripheral neuritis, carditis, atrioventricular nodal block, or migratory muscu loskeletal pain. Months or years later (usually after periods of latent infection), intermittent or persistent arthritis, chronic encephalopathy

or polyneuropathy, or acrodermatitis may develop (stage 3, persistent infection). Most patients experience early symptoms of the illness dur ing the summer, but the infection may not become symptomatic until it progresses to stage 2 or 3. Lyme disease was recognized as a separate entity in 1976 because of a geographic cluster of children in Lyme, Connecticut, who were thought to have juvenile rheumatoid arthritis. It became apparent that Lyme disease was a multisystem illness that affected primarily the skin, nervous system, heart, and joints. Epidemiologic studies of patients with EM implicated certain Ixodes ticks as vectors of the disease. Early in the twentieth century, EM had been described in Europe and attributed to I. ricinus tick bites. In 1982, a previously unrecognized spirochete, now called Borrelia burgdorferi, was recovered from Ixodes scapularis ticks and then from patients with Lyme disease. The entity is now called Lyme disease or Lyme borreliosis. ■ ■ETIOLOGIC AGENT B. burgdorferi, the causative agent of Lyme disease, is a fastidious microaerophilic bacterium. The spirochete’s genome is quite small (~1.5 Mb) and consists of a highly unusual genome organi zation with a linear chromosome of 950 kb and 17–21 linear and circu lar plasmids. The most remarkable aspect of the B. burgdorferi genome is that there are sequences for more than 100 known or predicted lipoproteins—a larger number than in almost any other organism. Most of these lipoproteins are encoded on plasmids and exported to the outer leaflet of the outer membrane, where they interact with the infected host or tick vector. The spirochete has few proteins with bio synthetic activity and depends on its host for most of its nutritional requirements. It has no sequences for recognizable toxins. Currently, 20 closely related borrelial species are collectively referred to as B. burgdorferi sensu lato (i.e., “B. burgdorferi in the general sense”) or Borreliella spp. The human infection Lyme borreliosis is caused primarily by four pathogenic genospecies: B. burgdorferi sensu stricto (“B. burgdorferi in the strict sense,” hereafter referred to simply as B. burgdorferi), Borrelia garinii, Borrelia bavariensis, and Borrelia afzelii. B. burgdorferi is the major cause of the infection in the United States; all four genospecies are found in Europe, and B. garinii, B. Afzelii, and B. bavariencis are the major causes in Asia. Strains of B. burgdorferi have been subdivided according to several typing schemes: one based on sequence variation of outer-surface protein C (OspC), a second based on differences in the 16S–23S rRNA intergenic spacer region (RST or IGS), a third called multilocus sequence typing, and a fourth based on whole genome sequencing (WGS). From these typing systems, it is apparent that strains of B. burgdorferi differ in pathogenicity. WGS type A, which includes OspC type A (RST1) strains, has the largest pangenome and the largest number of plasmidencoded lipoproteins, which are often immunogenic, and is especially likely to disseminate. Thus, this strain is particularly virulent and may have played a role in the emergence of Lyme disease in epidemic form in the northeastern United States in the late twentieth century. ■ ■EPIDEMIOLOGY The >20 known genospecies of B. burgdorferi sensu lato live in nature in enzootic cycles involving 14 species of ticks that are part of the I. ricinus complex. I. scapularis (Fig. 472-1) is the principal vector in the eastern United States from Maine to Georgia and in the midwestern states of Wisconsin, Minnesota, Indiana, and Michigan. I. pacificus is the vector in the western states of California and Oregon. The disease is acquired throughout Eurasia, from Ireland and Great Britain to Scan dinavia to western Russia, where I. ricinus is the vector, and in eastern Russia, China, and Japan, where I. persulcatus is the vector. These ticks may transmit other agents as well. In the United States, I. scapularis also transmits Babesia microti, Anaplasma phagocytophilum, Ehrlichia muris–like agent, Borrelia

miyamotoi, Borrelia mayonii, and Powassan virus (the deer tick virus) (see “Differential Diagnosis,” below). In Europe and Asia, I. ricinus and I. persulcatus also transmit tick-borne encephalitis virus. Ticks of the I. ricinus complex have larval, nymphal, and adult stages. They require a blood meal at each stage. The risk of infection

FIGURE 191-1 A classic erythema migrans lesion (9 cm in diameter) is shown near the right axilla. The lesion has partial central clearing, a bright red outer border, and a target center. (Courtesy of Vijay K. Sikand, MD; with permission.) in a given area depends largely on the density of these ticks as well as their feeding habits and animal hosts, which have evolved differently in different locations. For I. scapularis in the northeastern United States, the white-footed mouse and certain other rodents are the preferred hosts of the immature larvae and nymphs. It is critical that both of the tick’s immature stages feed on the same host because the life cycle of the spirochete depends on horizontal transmission: in early summer from infected nymphs to mice and in late summer from infected mice to lar vae, which then molt to become the infected nymphs that will begin the cycle again the following year. It is the tiny nymphal tick that is primar ily responsible for transmission of the disease to humans, which peaks during the early summer months. White-tailed deer, which are not involved in the life cycle of the spirochete, are the preferred host for the adult stage of I. scapularis and seem to be critical to the tick’s survival. CHAPTER 191 Lyme Borreliosis Lyme disease is now the most common vector-borne infection in the United States and Europe. Since surveillance was begun by the Centers for Disease Control and Prevention (CDC) in 1982, the number of cases in the United States has increased dramatically. More than 30,000 new cases are now reported each summer, but the number of true cases is estimated at 476,000 annually. In Europe, reported frequencies of the disease are highest in the middle of the continent and in Scandinavia. ■ ■PATHOGENESIS AND IMMUNITY To maintain its complex enzootic cycle, B. burgdorferi must adapt to two markedly different environments: the tick and the mammalian host. The spirochete expresses outer-surface protein A (OspA) in the midgut of the tick, whereas OspC is upregulated as the organism travels to the tick’s salivary gland. There, OspC binds a tick salivary-gland pro tein (Salp15), which is required for infection of the mammalian host. The tick usually must be attached for at least 24 h for transmission of B. burgdorferi. After injection into the human skin, the spirochete downregulates OspC and upregulates the VlsE lipoprotein. This protein undergoes extensive antigenic variation, which is necessary for spirochetal survival. After several days to weeks, B. burgdorferi may migrate out ward in the skin, producing EM, and may spread hematogenously or in the lymph to other organs. The only known virulence factors of

B. burgdorferi are surface proteins that allow the spirochete to attach to mammalian proteins, integrins, glycosaminoglycans, or glycoproteins. For example, spread through the skin and other tissue matrices may be facilitated by the binding of human plasminogen and its activators to the surface of the spirochete. Several Borrelia strains bind components of complement, such as Factor H and other complement regulators, which help to protect spirochetes from complement-mediated lysis. Dissemination of the organism in the blood is facilitated by binding to the fibrinogen receptor (αIIbβ3) on activated platelets and the vit ronectin receptor (αvβ3) on endothelial cells. As the name indicates, spirochetal decorin-binding proteins A and B bind decorin, a glycos aminoglycan on collagen fibrils, and B. burgdorferi also binds directly

to native type 1 collagen lattices. This binding may explain why the organism is commonly aligned with collagen fibrils in the extracellular matrix in the heart, nervous system, or joints.

To control and eradicate B. burgdorferi, the host mounts both innate and adaptive immune responses, resulting in macrophage- and antibody-mediated killing of the spirochete. As part of the innate immune response, complement may lyse the spirochete in the skin. Cells at affected sites release potent proinflammatory cytokines, including interleukin 6, tumor necrosis factor α, interleukin 1β, and interferon γ (IFN-γ). Patients who are homozygous for a Toll-like receptor 1 polymorphism (1805GG), particularly when infected with highly inflammatory B. burgdorferi RST1 strains, have exceptionally high levels of proinflammatory cytokines. The purpose of the adaptive immune response appears to be the production of specific antibodies, which opsonize the organism—a step necessary for optimal spirochetal killing. Studies with protein arrays expressing ~1200 B. burgdorferi proteins detected antibody responses to a total of 120 spirochetal proteins (particularly outer-surface lipoproteins) in a population of patients with Lyme arthritis. Histologic examination of all affected tis sues reveals an infiltration of lymphocytes, macrophages, and plasma cells with some degree of vascular damage, sometimes including oblit erative microvascular lesions. In enzootic infection, B. burgdorferi spirochetes must survive this immune assault only during the summer months before returning to larval ticks to begin the cycle again the following year. In contrast, infection of humans is a dead-end event for the spirochete. Within sev eral weeks or months, innate and adaptive immune mechanisms—even without antibiotic treatment—control widely disseminated infection, and generalized systemic symptoms wane. Thus, immune mechanisms seem to succeed eventually in the near or total eradication of B. burg dorferi from selected niches, including the joints or nervous system, and symptoms resolve in most patients. However, without antibiotic therapy, spirochetes may survive in localized niches for several more years. For example, B. burgdorferi infection in the United States may cause persistent arthritis or, in rare cases, subtle encephalopathy or polyneuropathy, and B. afzelii may cause acrodermatitis. PART 5 Infectious Diseases ■ ■CLINICAL MANIFESTATIONS Early Infection: Stage 1 (Localized Infection) Because of the small size of nymphal ixodid ticks, most patients do not remember the preceding tick bite. After an incubation period of 3–32 days, EM usually begins as a red macule or papule at the site of the tick bite that expands slowly to form a large annular lesion (Fig. 191-1). As the lesion increases in size, it often develops a bright red outer border and partial central clearing. The center of the lesion sometimes becomes intensely erythematous and indurated, vesicular, or necrotic. In other instances, the expanding lesion remains an even, intense red; several red rings are found within an outside ring; or the central area turns blue before the lesion clears. Although EM can be located anywhere, the thigh, groin, and axilla are particularly common sites. The lesion is warm but not often painful. Approximately 20% of patients do not exhibit this characteristic skin manifestation. Early Infection: Stage 2 (Disseminated Infection) In cases in the United States, B. burgdorferi often spreads hematogenously to many sites within days or weeks after the onset of EM. In these cases, patients may develop secondary annular skin lesions similar in appearance to the initial lesion. Skin involvement is commonly accompanied by severe headache, mild stiffness of the neck, fever, chills, migratory musculoskel etal pain, arthralgias, and profound malaise and fatigue. Less common manifestations include generalized lymphadenopathy or splenomegaly, hepatitis, sore throat, nonproductive cough, conjunctivitis, iritis, or orchitis. Except for fatigue and lethargy, which are often constant, the early signs and symptoms of Lyme disease are typically intermittent and changing. Even in untreated patients, the early symptoms usually become less severe or disappear within several weeks. In ~15% of patients, the infection presents with these nonspecific systemic symptoms. Symptoms suggestive of meningeal irritation may develop early in Lyme disease when EM is present but usually are not associated with

cerebrospinal fluid (CSF) pleocytosis or an objective neurologic deficit. After several weeks or months, ~15% of untreated patients develop frank neurologic abnormalities, including meningitis, subtle encepha litic signs, cranial neuritis (most commonly involving the facial nerve, resulting in unilateral or bilateral facial palsy), motor or sensory radiculoneuropathy, peripheral neuropathy, mononeuritis multiplex, cerebellar ataxia, or myelitis—alone or in various combinations. In children, the optic nerve may be affected because of inflammation or increased intracranial pressure, and these effects may lead to blindness. In the United States, the usual pattern consists of fluctuating symptoms of meningitis accompanied by facial palsy and peripheral radiculo neuropathy. Lymphocytic pleocytosis (~100 cells/μL) is found in CSF, often along with elevated protein levels and normal or slightly low glucose concentrations. In Europe and Asia, the first neurologic sign is characteristically radicular pain, which is followed by the development of CSF pleocytosis (meningopolyneuritis or Bannwarth's syndrome); meningeal or encephalitic signs are frequently absent. These early neu rologic abnormalities usually resolve completely within months, but in rare cases, chronic neurologic disease may occur later. Within several weeks after the onset of illness, ~8% of patients develop cardiac involvement. The most common abnormality is a 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 radionu clide 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. A few cases of mitral or aortic valve endocarditis have been reported, in one case occurring years after acute cardiac involvement of Lyme disease. 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, primar ily 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 persis tent and may lead to erosion of cartilage and bone. White cell counts in joint fluid range from 500 to 110,000/μL (aver age, 25,000/μL); most of these cells are polymorphonuclear leukocytes. Tests for rheumatoid factor or antinuclear antibodies usually give negative results, but a low-titer antinuclear antibody value may occur. 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 persis tent postinfectious (also called postantibiotic or antibiotic-refractory) Lyme 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 OspA type A (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, the basic pathogenetic feature of postinfectious Lyme arthritis is the development of an excessive, dysregulated proinflammatory immune response during the infection, characterized by exceptionally high IFN-γ levels, which persist in the postinfectious period. Risk factors for excessively high IFN-γ responses include presentation of an epitope of B. burgdorferi OspA (OspA164-175)

by certain class II major histocompatibility complex molecules

(particularly HLA-DRBI∗0401); a Toll-like receptor 1 polymorphism 1805GG in patients who were infected with OspC type A (RST1)

B. burgdorferi strains; and an imbalance of the CD4+ T effector/

regulatory cell ratio in which the majority of CD4+CD25+ T cells, which are ordinarily regulatory T cells, become IFN-γ-secreting T effector cells. The consequences of this excessive proinflammatory response in Lyme synovia include vascular damage, autoimmune and cytotoxic processes, and tumor-like fibroblast proliferation and fibrosis. An important driver of innate immune responses may be persistence of

B. burgdorferi peptidoglycan in synovial fluid, which may be especially difficult to clear. In addition, seven autoantigens that are targets of T- and B-cell responses in patients with Lyme disease, particularly those with postinfectious arthritis, have now been identified. These include three autoantigens associated with the vasculature (i.e., endothelial cell growth factor, apolipoprotein B-100, and annexin A2) and four extracellular matrix (ECM) proteins (i.e., matrix metalloproteinase 10, fibronectin-1, laminin B2, and collagen Vα1). Autoantibodies against vascular antigens are associated with obliterative microvascular lesions, and T-cell responses to epitopes of ECM proteins are associated with significantly longer durations of postinfectious arthritis. Although rare, chronic neurologic involvement also may become apparent months to several years after the onset of infection, some times after long periods of latent infection. The most common form of chronic central nervous system involvement is subtle encepha lopathy 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 abnor malities 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 dis order that may include spastic paraparesis, upper motor neuron blad der 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 discolor ation; 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, B. garinii, and B. bavariensis. 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 especially OspC type A (RST1) strains may lead to postinfectious arthritis. B. garinii and B. bavariensis typically disseminate less widely, but are especially neurotropic, are more likely to cause typical neu roborreliosis (Bannwarth's syndrome) and rarely 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. Posttreatment Lyme Disease Syndrome (PTLDS) Despite resolution of the objective manifestations of the infection with antibi otic therapy, ~10% of patients (although the reported percentages vary widely) continue to have subjective pain, neurocognitive manifesta tions, or fatigue symptoms. This disabling problem has been known for years following certain other infections but has been brought to fore recently with postacute sequelae of COVID-19. In Lyme disease, 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. 461) and fibromyalgia (Chap. 385). 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 mani festations 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. Randomized controlled trials have shown than repeated courses of antibiotics do not improve the symptoms of PTLDS and are not recommended.

■ ■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 occa sionally from CSF samples. Later in the infection, PCR is greatly supe rior 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 kill ing 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 neurobor reliosis has been much lower than that in joint fluid. With current methods, there seems to be little if any role for PCR in the detection of B. burgdorferi DNA in blood or urine samples. CHAPTER 191 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 when a two-test approach of enzyme-linked immunosorbent assay (ELISA) and Western blot or a protocol of two enzyme immunoassays (EIAs) is used. The limita tion of serologic tests is that they do not clearly distinguish between active and inactive infection. After antibiotic therapy, the amount of antibody declines but the results of

Western blot, a nonquantitative test, do not change much (or very slowly). Thus, patients with previous Lyme disease—particularly in cases progressing to late stages—often remain seropositive for years, even after adequate antibiotic therapy. In addition, ~10% of patients are seropositive because of asymptom atic infection. If individuals with past or asymptomatic B. burgdorferi infection subsequently develop another illness, the positive serologic test for Lyme disease may cause diagnostic confusion. According to an algorithm published by the American College of Physicians (Table 191-1), 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 screen ing 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. Lyme Borreliosis TABLE 191-1 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).

For serologic analysis of Lyme disease in the United States, the CDC recommends a two-step approach in which samples are first tested by ELISA, and equivocal or positive results are then tested by Western blot. This is called the conventional two-test approach. During the first weeks of infection, both IgM and IgG responses to the spirochete should be determined, preferably in both acute- and convalescentphase serum samples. Approximately 20–30% of patients have a positive response detectable in acute-phase samples (usually only a positive IgM response), whereas ~70–80% have a positive response during convales cence (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 pres ent: 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 dis ease 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. A new methodology called the modified two-test approach, which is now approved by the U.S. Food and Drug Administration, is a two-test approach using two EIAs, thereby dispensing with the Western blot. One such method employs a whole–B. burgdorferi sonicate ELISA followed by a VlsE C6 peptide IgG ELISA. This approach, which gives simply a positive or a negative result, increases sensitivity during the first several weeks of infection without compromising specificity. For more complex cases or in those with late infection, it is still valuable to determine antibody specificities to multiple spirochetal proteins, as is done with Western blots. More recently, line immunoblots or other multiplexed

antibody platforms have been developed as substitutes for Western blots. These assays allow more objective interpretation, and some platforms can provide quantitative data about antibody responses to many spirochetal proteins. 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. PART 5 Infectious Diseases ■ ■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. 192). As stated above, I. scapularis ticks in the United States may transmit not only B. burgdorferi but also B. microti, the red blood cell parasite causing babesiosis (Chap. 232); A. phagocytophilum, the agent of human granulocytotropic anaplasmosis (Chap. 192); B. miyamotoi, a relapsing fever spirochete (Chap. 190); B. mayonii and E. muris–like agent, newly recognized species that occur in the upper midwestern United States; or less commonly, Powassan virus (the deer tick virus, which is closely related to European tick-borne encephalitis virus), which may cause fatal infection (Chap. 215). Babesiosis, anaplasmosis,

B. miyamotoi, and B. mayonii typically cause an influenza-like syn drome with fever, myalgias, and cytopenia, but symptoms may range from asymptomatic infection to severe or even fatal disease, particu larly in the young or the elderly. 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. Anaplasmosis and B. miyamotoi may cause leukopenia or thrombocytopenia, and babesiosis may cause thrombocytopenia and hemolytic anemia. IgM serologic responses may confuse the diagnosis. For example, A. phagocytophilum may elicit a positive IgM response to B. burgdorferi. PCR of blood is the diagnostic test of choice for co-infection with A. phagocytophilum, B. microti, or B. miyamotoi. Alternatively, examination of a peripheral blood smear can be used to detect B. microti, but blood smear analysis is insensitive for A. phago cytophilum and B. miyamotoi. The frequency of co-infection in differ ent studies has been variable. In one prospective study, 4% of patients with EM had evidence of co-infection, although this appears to be an increasing problem in early infection. Facial palsy caused by B. burgdorferi, which occurs in the early dis seminated phase of the infection (often in July, August, or September), is usually recognized by its association with EM. However, 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. 197) and varicella-zoster virus (Ramsay Hunt syndrome; Chap. 198). Later in the infection, oligoarticular Lyme arthritis most resembles peripheral spondyloarthropathy 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 bor reliosis, with reactivity to many spirochetal proteins. The most common problem in the

diagnosis of early Lyme disease is to miss the diagnosis, either because of an atypical morphology of EM or the erroneous assumption that a negative serologic test for B. burgdorferi excludes acute disease. Clinicians should be aware of the typical and atypical manifestations of EM, recognize the limited value of serologic testing in evaluating patients with early Lyme disease, and understand that the diagnosis of early Lyme disease is a clinical one. The most common problem in diagnosis of late-stage Lyme disease is to mistake chronic fatigue syndrome (Chap. 461) or fibromyalgia (Chap. 385) for Lyme disease. This difficulty is compounded by the fact that a small percentage of patients with Lyme disease 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 repeated courses of antibiotic treatment is not warranted. Well-controlled randomized trials have found no benefit to antibiotic therapy for PTLDS, whereas there is well-documented risk of harm. TREATMENT Lyme Borreliosis ANTIBIOTIC TREATMENT As outlined in the algorithm in Fig. 191-2, the various manifes tations of Lyme disease can usually be treated successfully with orally administered antibiotics; the exceptions are severe objective neurologic abnormalities and third-degree atrioventricular heart block, which are generally treated with IV antibiotics, and arthri tis that does not respond to oral therapy. For early Lyme disease, doxycycline is effective and can be administered to men, non pregnant women, and children older than age 8. An advantage of this regimen is that it is also effective against A. phagocytophilum,

B. miyamotoi, and B. mayonii, which are transmitted by the same tick that transmits the Lyme disease agent. Amoxicillin, cefuroxime axetil, and erythromycin or its congeners are second-, third-, and

Skin Erythema migrans Acrodermatitis Joint Arthritis* Heart AV block Nervous system Facial palsy alone Meningitis Radiculoneuritis Encephalopathy Polyneuropathy 1˚, 2˚ 3˚ Oral therapy First choice Age ≥9 years, not pregnant: doxycycline, 100 mg bid Age <9 years: amoxicillin, 50 mg/kg per day Second choice for adults: amoxicillin, 500 mg tid Third choice for all ages: cefuroxime axetil, 500 mg bid Fourth choice for all ages: erythromycin, 250 mg qid Intravenous therapy First choice: ceftriaxone, 2 g qd Second choice: cefotaxime, 2 g q8h Third choice: Na penicillin G, 5 million U q6h Guidelines for duration of therapy Localized skin infection: 14 days Early disseminated infection: 21 days Acrodermatitis: 30 days Arthritis: 30−60 days** Neurologic involvement: 14–28 days Cardiac involvement: 28 days; complete course with oral therapy when patient is no longer in high-degree AV block FIGURE 191-2 Algorithm for the treatment of the various early or late manifestations of Lyme borreliosis. AV, atrioventricular. *For arthritis, oral therapy should be tried first; if arthritis is unresponsive, IV therapy should be administered. **For Lyme arthritis, IV ceftriaxone (2 g given once a day for 14–28 days) also is effective and is necessary for patients who do not respond to oral therapy. However, compared with oral treatment, this regimen is less convenient to administer, has more side effects, and is more expensive. fourth-choice alternatives, respectively, for the treatment of Lyme disease. In children, amoxicillin is effective (not >2 g/d); in cases of penicillin allergy, cefuroxime axetil or erythromycin may be used. In contrast to second- or third-generation cephalosporin antibiot ics, first-generation cephalosporins, such as cephalexin, are not effective. For patients with infection localized to the

skin, a 10-day course of doxycycline or a 14-day course of amoxicillin is generally sufficient; in contrast, for patients with early disseminated infec tion, a 14- to 21-day course is recommended. Approximately 15% of patients experience a Jarisch-Herxheimer-like reaction during the first 24 h of therapy. In multicenter studies, >90% of patients whose early Lyme disease was treated with these regimens had satisfactory outcomes. Although some patients reported symptoms after treat ment, objective evidence of persistent infection or relapse was rare, and re-treatment was usually unnecessary. Oral administration of doxycycline or amoxicillin for 30 days is recommended for the initial treatment of Lyme arthritis in patients who do not have concomitant neurologic involvement. Among patients with arthritis who have an incomplete response to oral antibiotics, a second, 30-day course of oral antibiotics may be suc cessful. However, among patients with arthritis who have minimal or no response to oral antibiotics, re-treatment with IV ceftriaxone for 28 days is appropriate. In patients with arthritis in whom joint inflammation persists for months or even several years after both oral and IV antibiotics, treatment with nonsteroidal anti-inflammatory agents, therapy with disease-modifying antirheumatic drugs, or synovectomy may be successful. In the United States, parenteral antibiotic therapy is usually used for severe objective neurologic abnormalities. Patients with such abnormalities are most commonly treated with IV ceftriaxone for 14–28 days, but IV cefotaxime or IV penicillin G for the same

duration also may be effective. In Europe, similar results have been obtained with oral doxycycline and IV antibiotics in the treatment of acute neuroborreliosis. Although systematic trials have not been conducted in the United States, oral doxycycline is now used by many clinicians in this country for the treatment of patients with less severe neurologic abnormalities, such as facial palsy alone or uncomplicated Lyme meningitis. In patients with high-degree atrio ventricular block or a PR interval of >0.3 s, IV therapy for at least part of the course and cardiac monitoring are recommended, but the insertion of a permanent pacemaker is not necessary.

It is unclear how and whether asymptomatic infection should be treated, but patients with such infection are often given a course of oral antibiotics. Because maternal–fetal transmission of B. burgdorferi seems to occur rarely (if at all), standard therapy for the manifesta tions of the illness is recommended for pregnant women. Long-term persistence of B. burgdorferi has not been documented in any large series of patients after treatment with currently recommended regi mens, but there are a few case reports of persistent infection after such regimens. Although an occasional patient requires a second course of antibiotics, there is no indication for multiple, repeated antibiotic courses in the treatment of Lyme disease. CHRONIC LYME DISEASE After appropriately treated Lyme disease, a small percentage of patients continue to have subjective symptoms, primarily musculo skeletal pain, neurocognitive difficulties, or fatigue. This syndrome, termed posttreatment Lyme disease syndrome (PTLDS), is sometimes a disabling condition that is similar to chronic fatigue syndrome or fibromyalgia. Five double-blind, placebo-controlled trials conducted in the United States and Europe have failed to show benefit of further antibiotic therapy in these patients. For example, in a large study, one group of patients with PTLDS received IV ceftriaxone for 30 days

followed by oral doxycycline for 60 days, while another group received IV and oral placebo preparations for the same durations. No significant differences were found between groups in the numbers of patients reporting that their symptoms had improved, become worse, or stayed the same. Such patients are best treated for the relief of symptoms rather than with prolonged courses of antibiotics. PROPHYLAXIS AFTER A TICK BITE The risk of infection with B. burgdorferi after a

recognized tick bite is so low that antibiotic prophylaxis is not routinely indicated. However, if an attached, engorged I. scapularis nymph is found or if follow-up is anticipated to be difficult, a single 200-mg dose of doxycycline, which usually prevents Lyme disease when given within 72 h after the tick bite, may be administered. CHAPTER 191 Lyme Borreliosis ■ ■PROGNOSIS The response to treatment is best early in the disease. Later treatment of Lyme borreliosis is still effective, but the period of convalescence may be longer. Eventually, most patients recover with minimal or no residual deficits. ■ ■REINFECTION Reinfection may occur after EM when patients are treated with antimi crobial agents. In such cases, the immune response is not adequate to provide protection from subsequent infection. However, patients who develop an expanded immune response to the spirochete over a period of months (e.g., those with Lyme arthritis) have protective immunity for a period of years and rarely, if ever, acquire the infection again. ■ ■PREVENTION Protective measures for the prevention of Lyme disease may include the avoidance of tick-infested areas, the use of repellents and acari cides, tick checks, and modification of landscapes in or near residential areas. Although a vaccine for Lyme disease used to be available, the manufacturer has discontinued its production. Another company is currently testing a similar vaccine in both the United States and Europe. However, no vaccine is currently available commercially for the prevention of this infection.

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