84 Lyme Disease

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Definition/Classification

Lyme disease, also known as Lyme borreliosis (LB), is a vector-borne, bacterial illness caused by the spirochete *Borrelia burgdorferi* sensu lato (*B. borgdorferi* in the general sense). Infection of the skin occurs first, but LB can disseminate to multiple organ systems.

Etiology

Historically, descriptions of dermatologic manifestations date back 100 years; however, LB was officially described in 1977 among an epidemiological cluster of patients with oligoarticular arthritis in Lyme, Connecticut, USA. In 1982, *B. burgdorferi* sensu stricto was detected and isolated in culture (see ❯ *Fig. 84.1*), and since then *B. garinii*, *B. afzelii* (both in Europe), and *B. spielmani* (Asia) species have been described with LB.

LB is transmitted to humans by infected *Ixodes* spp. ticks, which take blood meals from humans during their nymphal (more infective) and adult life stages. It is not a simple bite, but prolonged attachment (∼48 h) that transmits disease, as *Borrelia* spp. are found in the tick gut, and engorgement is associated with higher transmission rates.

Epidemiology

LB has a worldwide distribution, but the majority of literature is from Europe and North America, where it is the most common vector-borne illness. The United States has adopted epidemiological definitions and national surveillance; reporting 29,959 confirmed and 8,509 probable cases in 2009, and an incidence of 13.4/100,000 persons (Delaware reports the highest at 111.2, followed by Connecticut at 78.2) with 5–10-year-old children comprising the largest affected group. In Europe, not all countries have universal reporting; however, in 2006 reported incidence in Slovenia was 155/100,000 persons, Austria 130, Sweden 80, Bulgaria 55, and Germany 25 (with highest reported total cases at 20,700). Asian countries including China, Indonesia, Japan, Korea, and Nepal also report LB.

Pathogenesis

Borrelia spp. regulate gene expression throughout the life cycle to adapt to different host and host defenses. Upregulation of plasmid-encoded outer-surface protein (Osp) C allows the spirochete to attach to tick salivary glands to facilitate transfer to the mammalian host. Another example is the antigenic variation of lipoprotein VlsE, which helps elude host immunity. Once transmitted to humans, *Borrelia* spp. infect the skin and the ensuing inflammation gives rise to the characteristic erythema migrans (EM) rash. *Borrelia* spp. bind many host receptors, including plasminogen and its activators, to help it spread through tissue matrices. Additionally, certain gene expressions of OspC have been associated with dissemination. Although it is not known what makes certain spirochetes more neurotropic or arthritogenic, ongoing investigations continue to elucidate the spirochete–host interplay.

Humans respond to infection through both innate (complement, chemokines, Toll-like receptors) and adaptive immune responses (opsonizing antibodies). There is evidence that LB can trigger autoimmune phenomena, exemplified in patients with certain HLA-DR allotypes who develop noninfectious, recalcitrant arthritis.

Pathology

Although not clinically indicated, skin biopsy of early erythema migrans (EM) lesion reveals a dense mononuclear infiltrate, mainly of T cells, plasma cells, and occasional macrophages. Two other skin manifestations, more common in Europe, often require biopsy (in conjunction with immunohistochemistry, culture, and PCR) to establish the diagnosis: borrelial lymphocytoma is characterized by B cell infiltration and observable germinal centers in the cutis and subcutis, and acrodermatitis chronica atrophicans (ACA) is associated with an inflammatory response of T cells and macrophages.

Disseminated disease occurs from direct bacterial invasion, as animal models demonstrate spirochetes within nervous, cardiac, and synovial tissue. In arthritis,

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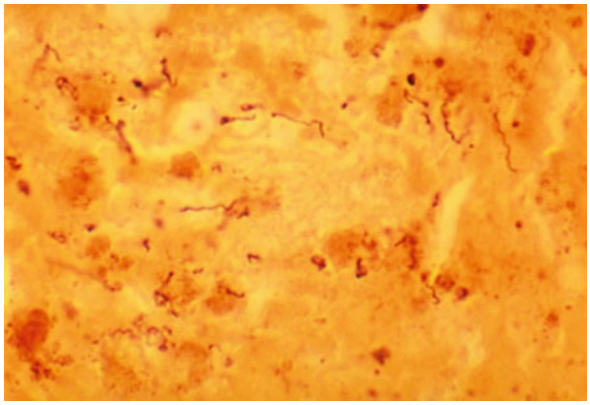

Figure 84.1
Histopathology showing *Borrelia burgdorferi* spirochetes in Lyme disease. Dieterle silver stain (Photo courtesy of CDC/Dr. Edwin P. Ewing, Jr. 1983)

joint aspiration will reveal a polynuclear leukocytosis. With meningeal involvement, cerebral spinal fluid will demonstrate a mild lymphocytic pleocytosis, moderately elevated protein, and typically normal glucose. Electrophysiological studies suggest that the bundle of His and AV node are the most commonly affected areas in cardiac disease associated with heart block.

Clinical Manifestations

Despite early and late clinical manifestations, symptoms do not necessarily present in a progressive linear fashion; however, the vast majority of patients (>90% in children) present with early localized disease, manifest by a single, circular, expanding (over days, at least 5 cm), macular, sometimes centrally-clearing (occasionally targetoid) lesion known as EM (see *Fig. 84.2*). EM typically occurs at the site of the tick bite approximately 10 days later (3–32 days), it can vary greatly in shape and infrequently can have a vesicular, scaly, or necrotic center. Careful examination is necessary as EM can be entirely within the hairline. Constitutional symptoms of myalgia, arthralgia, malaise, and/or headache can accompany EM or rarely be the only presenting symptoms. EM in Europe spreads slower, persists longer, and is associated with less symptoms of acute inflammation.

Multiple EM lesions are the most common presentation of early disseminated disease. Appearing days to weeks after a single EM in ~15–20% of cases, they are smaller, can

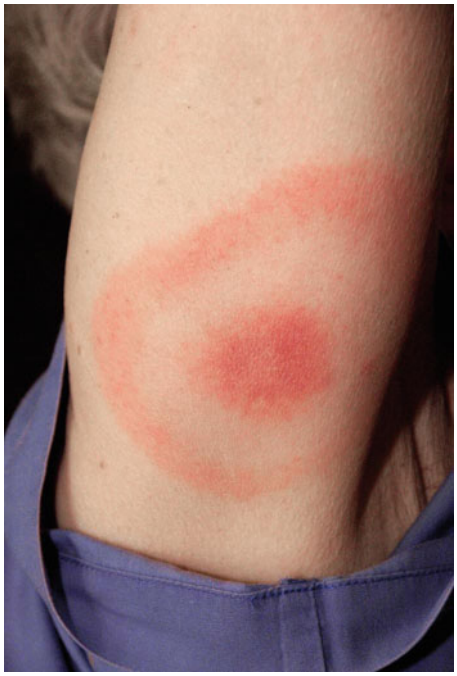

Figure 84.2
Erythema migrans rash with targetoid appearance (Photo courtesy of CDC/James Gathany 2007)

appear more linear, more often lack central clearing, and are often accompanied by constitutional symptoms. Neurological manifestations include isolated peripheral neuropathy, most commonly the facial nerve. Nuchal rigidity should prompt lumbar puncture for the evaluation of meningitis, but persistent and severe headaches are more typical. Increased intracranial pressure and papilledema, sometimes associated with abducens palsy, is well described in children with Lyme meningitis. Optic neuritis can also be seen. Cardiac involvement occurs in less than 1%, and presents as first-, second-, or third-degree heart block. Myocarditis can occur, but is less likely. An extremely rare and difficult to diagnose skin finding is borrelial lymphocytoma, which presents as a bluish-red swelling, mimicking a benign tumor, on the ear lobe or areola of the breast.

Arthritis, typically occurring months after infection, is the chief presentation of late disease and more common in North America (~10%). Monoarticular infection of the knee is most common; there is tremendous swelling with only mild-to-moderate pain and infrequently erythema overlies the joint. Occasionally, as described above, as a subset (~10%) of patients develop chronic arthritis. Polyneuropathy/ridiculoneuritis (Bannwarth syndrome)

is especially rare in children but should be suspected in endemic European areas when symptoms include muscle weakness, neuralgia, and/or paresthesias. Encephalomyelitis or encephalopathy (subtle cognitive dysfunction) is extremely rare in pediatrics, especially with better detection and earlier treatment. Also exceedingly rare (case reports in pediatrics), but historically important, ACA presents (typically in older women with *B. afzelii*) with a bluish-red lesion, atrophic skin, prominent vessels, and associated neuropathy.

Diagnosis

Serological testing is the mainstay for the diagnosis of LB. In North America, a two-tier testing system with excellent sensitivity and specificity has been adopted. Enzyme immunoassays (EIA) detect Lyme-specific antibodies quantitatively and if equivocal or positive (false positives occur), should be reflexed to a confirmatory Western immunoblot assay. The immunoblotting is considered positive if there are at least five of ten IgG bands or at least two of three IgM bands. Since immunoblotting can persist indefinitely after adequate treatment, a test which is positive by IgM alone would be considered false if symptoms had been present for longer than 1 month. Because of this, interpretation of testing can be very confusing, and testing should never be done for vague nonspecific symptoms, especially when the positive predictive value is low.

A clinical diagnosis of EM is pathognomonic for early localized disease, and serological testing should not be performed as it is unreliable at this stage.

Serological testing is invariably positive in early disseminated and late LB, although multiple EM is also specific enough to diagnose clinically. Especially in Europe where LB is more neurotropic, an antibody index or ratio of Lyme-specific immunoglobulins in the spinal fluid compared to the serum can elucidate neurological involvement.

Spirochete can be detected in affected sites by immunohistochemistry and culture, both with significant limitations to clinical practice. PCR has proven useful in diagnosing arthritis (not in meningitis).

Differential Diagnosis

The differential for EM includes, but is not limited to, other insect bites, granuloma annulare, nummular eczema, urticaria, pityriasis, tinea, drug eruption, erythema nodosum, and erythema multiforme. The expanding nature and persistence of EM, including the lack of scaliness and pruritus, help to distinguish it from the other rashes.

Lyme meningitis is indistinguishable from other forms of aseptic meningitis, but a larger percentage of monocytes in the spinal fluid, longer duration of symptoms, papilledema, and facial nerve palsy can be more telling.

Lyme arthritis can be mistaken for suppurative arthritis, reactive arthritis, juvenile idiopathic arthritis, rheumatic fever, or osteomyelitis with joint involvement. Ability to ambulate and only moderate pain, differentiate Lyme arthritis from suppurative arthritis, but serology (PCR if fluid is tapped) will decipher Lyme.

Coinfection (especially in North America) with other tick-borne illness like babesiosis should be considered in more severely ill-appearing patients and if leukopenia and thrombocytopenia are present ehrlichiosis should be suspected.

Treatment

Medication and duration are specific to the presenting symptoms of LB, best depicted in *Table 84.1*.

The use of macrolides (azithromycin 10 mg/kg/day (max 500 mg/day), clarithromycin 15 mg/kg/day in two divided doses (max 1,000 mg/day), erythromycin 50 mg/kg/day in 4 divided doses (max 2,000 mg/day)) should be reserved for those with true allergies to preferred regimens. Some patients may develop paradoxical worsening of symptoms soon after treatment begins that lasts about 24 h (Jarisch–Herxheimer). Few patients may have persistence of vague symptoms including fatigue, arthralgia, and headache that can last weeks to months after treatment. These post-Lyme syndromes are noninfectious, and should be treated supportively with nonsteroidal anti-inflammatory analgesic medications and reconditioning (there is no indication for prolonged antibiotics). For the few patients with recalcitrant arthritis, synovectomy or immune-modulating medications, like methotrexate, are treatment options.

Prognosis

LB has often been misdiagnosed, and has led to some confusion on treatment outcomes. Published data suggest that LB in children is completely treatable and outcomes for early and late disease are excellent.

Table 84.1
Treatment options based on symptomatology

Symptom	Drug	Duration
EM rash	1. Doxycycline[a] PO 4 mg/kg/day divided in two daily doses (max 200 mg/day) 2. Amoxicillin PO 50 mg/kg/day in three divided doses (max 1,500 mg/day) 3. Cefuroxime axetil PO 30 mg/kg/day in two divided doses (max 1,000 mg/day)	14 days (10–21 days)
Multiple EM rash	Same as for EM rash	21 days (21–28 days)
Borrelial lymphocytoma	Same as for EM rash	14 days (14–28 days)
Heart block/cardiac disease[b]	Same as for EM rash	21 days (21–28 days)
Isolated facial palsy	Same as for EM rash	28 days (14–28 days)
Meningitis,[c] polyneropathy, ridiculoneuritis, and other late neurological disease	1. Ceftriaxone 75–100 mg/kg/day IV once daily (max 2,000 mg/day) 2. Cefotaxime 150 mg/kg/day IV in three divided doses (max 6,000 mg/day) 3. Penicillin G 0.2–0.4 million units/kg/day in six divided doses (max 20 million units/day)	28 days (14–28 days)
Arthritis[d]	Same as for EM rash	28 days
ACA	Same as for EM rash	21 days

EM erythema migrans, PO per os, ACA acrodermatitis chonica atrohpicans
[a]Do not use in children <8 year and pregnant women due to teeth discoloration
[b]Third-degree heart block and severe cardiac disease requires hospitalization, sometimes pacing, and parenteral therapy initially
[c]Doxycycline has been studied extensively in Europe and can be used for acute uncomplicated neurological disease
[d]If arthritis needs to be re-treated some experts chose parenteral therapy

Prevention

The best way to prevent LB is to avoid tick-infested areas. In endemic residential areas, it is suggested to remove leaf litter and woodpiles, keep grass short, and apply pesticides. Using repellents such as DEET directly on the skin, and insecticides like permethrin on clothes, tents, and camping gear can be helpful. Also when anticipating exposure, wear long sleeves and tuck long pants into socks. Performing a careful skin inspection daily, when exposed, with prompt removal of ticks is most important as this dramatically decreases transmission rates (1–3%). Prophylaxis is not routinely recommended, only doxycycline has shown benefit in adults, and should be reserved for those who remove engorged ticks in endemic areas (children older than 8 years could take 4 mg/kg once, max 200 mg). Otherwise, patients who have been bitten should be monitored over the next month for the development of EM or constitutional symptoms and treated as needed.

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