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240 Relapsing Fever Caused by *Borrelia* Species

James M. Horton

SHORT VIEW SUMMARY

Definition
- Relapsing fever is caused by spirochetes of the *Borrelia* genus.
- The illness is characterized by relapsing fevers with spirochetes evident on a blood smear.

Organism
- *Borrelia* spp. are divided between *Borrelia burgdorferi,* which causes Lyme disease (see Chapter 241), and the *Borrelia* spp. that cause relapsing fever.
- The relapsing fever species are divided between louse-borne and tick-borne species.

Epidemiology
- Tick-borne relapsing fever occurs on almost every continent, but in the United States it is endemic in the Rocky Mountains.

Pathophysiology
- The spirochete changes surface antigens about every 7 days, causing the cyclic, relapsing fever.

Clinical Manifestations
- The patient presents with fever for 3 days alternating with afebrile periods lasting about 7 days.

Diagnosis
- Spirochetes can be seen on the peripheral blood smear during febrile periods.

Therapy
- Doxycycline or penicillin is effective treatment.
- Jarisch-Herxheimer reactions are common, and the patient should be observed in a clinic or hospital for at least 3 hours after starting antibiotic therapy.

Prevention
- Postexposure therapy with doxycycline is preventive.

Relapsing fever is characterized by recurrent fevers with spirochetemia caused by organisms of the *Borrelia* genus.[1] The spirochetes are broadly divided between endemic tick-borne species (tick-borne relapsing fever [TBRF]) and epidemic louse-borne species (louse-borne relapsing fever [LBRF]). TBRF occurs in North and South America, Europe, Africa, and Asia and can be caused by about 20 different species.[2,3] In the United States, relapsing fever is endemic in the Rocky Mountain regions of the western states but can also occur in travelers returning from other endemic areas.[4,5] LBRF was epidemic in the early 20th century but has subsided as a result of improved sanitation. Currently LBRF is found only on the Horn of Africa and possibly among the homeless in Europe.[6]

ORGANISM

The genus *Borrelia* belongs to the family Spirochaetaceae. It consists of two groups: species that cause Lyme disease and species that cause relapsing fever (Table 240.1).[7] The relapsing fever spirochetes are genetically diverse pathogens that are broadly divided between the louse-borne *Borrelia recurrentis* and the tick-borne species. The TBRF agents are maintained by soft ticks of the family Argasidae. Some species such as *Borrelia lonestari* and *Borrelia miyamotoi* group genetically with the classic relapsing fever spirochetes but are spread by other tick species.[7] *B. lonestari* is spread by the Lone Star tick, *Amblyomma americanum.* In one study it was associated with southern tick–associated rash illness by polymerase chain reaction (PCR) assay, but further studies were unable to confirm that result.[8] *B. miyamotoi,* which is spread by *Ixodes dammini* or *Ixodes scapularis,* has been described in Japan, Europe, Russia, and the United States. Molloy and coworkers[9] described 97 cases across the northeastern United States diagnosed by PCR (see Table 240.1).[8,10]

The pathogens are spirochetes that are 8 to 30 µm long and 0.2 to 0.5 µm wide.[2] The spirochetes have spontaneous antigenic variation of the outer membrane proteins called the variable major proteins (*vmp*).[11] These proteins determine the serotypes and are the mechanism for the relapsing disease. *Borrelia* strains can grow in artificial media (Barbour-Stoenner-Kelly medium),[12] although the diagnosis is usually confirmed by microscopic examination of a blood smear. The spirochetes are readily visualized with Wright or Giemsa stains, but species cannot be distinguished by the staining characteristics. The spirochetes can survive in the tick vectors for up to 12 years; ticks remain the optimal means of maintaining organisms.[13]

Ticks are divided between the soft-bodied Argasidae ticks and the hard-bodied Ixodid ticks. Soft-bodied ticks of the Argasidae family are vectors for most TBRF and are strongly associated with rodents. Ticks become infected during a blood meal on a vertebrate with spirochetemia. Humans become infected by tick bites via salivary gland secretions.[2] The hard-bodied ticks are the vectors for *B. miyamotoi*.[10]

In the Rocky Mountain western states, relapsing fever is caused predominantly by *Borrelia hermsii,* but it can also be caused by *Borrelia parkeri, Borrelia turicatae,* and *Borrelia mazzotti.* Each TBRF *Borrelia* spp. is associated with one species of transmitting soft-bodied ticks of the *Ornithodoros* genus. In the western United States, *B. hermsii* is transmitted by *Ornithodoros hermsi.*[2]

LBRF is caused only by *B. recurrentis* and is spread by the human body louse *(Pediculus humanus).* The spirochetes do not penetrate through the louse intestine, so the disease is spread by crushing or squeezing the louse, releasing the organisms on the skin.[2,15]

EPIDEMIOLOGY AND TRANSMISSION

TBRF and its host, the *Ornithodoros* tick, occur on every continent except Australia and Antarctica (see Table 240.1).[2] Although the host and habitat of each *Ornithodoros* tick species may vary, they have some characteristics in common. The ticks are obligate blood feeders, and the spirochetes from a blood meal invade all tissues of the tick within hours. The spirochetes can persist for years in the tick salivary glands, facilitating the transmission during the short feeding period of 20 minutes. Infection of humans occurs when saliva or excrement is released during feeding. Animal reservoirs include chipmunks, squirrels, rabbits, rats, mice, owls, and lizards. The ticks inhabit rodent burrows, decaying wood, cabins, animal shelters, and caves.[16]

Intrusion of humans into the tick's environment creates the opportunity for disease transmission. In the United States, the largest epidemic occurred in 1973 when 62 campers became ill after sleeping in log cabins in Arizona.[17] In North America, TBRF occurs in the Rocky Mountain regions (Fig. 240.1) of the western states at altitudes above 1500 feet, and most cases occur during the summer months, although cases have been reported in the winter.[4,17] In Texas, most cases occur

TABLE 240.1 *Borrelia* Species That Cause Relapsing Fever

SPECIES	DISEASE	ARTHROPOD VECTOR	GEOGRAPHIC DISTRIBUTION	RESERVOIR
B. hermsii	TBRF	*Ornithodoros hermsi*	Western United States and Canada	Rodent
B. turicatae	TBRF	*Ornithodoros turicata*	Southwestern United States	Rodent
B. parkeri	TBRF	*Ornithodoros parkeri*	Western United States and Baja California	Rodent
B. mazzottii	TBRF	*Ornithodoros talaje*	Mexico and Central America	Rodent
B. venezuelensis	TBRF	*Ornithodoros rudis*	South America	Rodent
B. crocidurae	TBRF	*Ornithodoros erraticus*	Middle East, North Africa	Rodent
B. hispanica	TBRF	*Ornithodoros marocanus*	Iberian peninsula and North Africa	
B. recurrentis	LBRF	*Pediculus humanus*	Eastern Africa, previously worldwide	
B. miyamotoi[2]	Meningitis,[a] febrile illness	*Ixodes dammini* *Ixodes scapularis*	United States, Europe and Asia	Rodent
B. lonestari[a]	Illness association unclear[8]	*Amblyomma americanum*	Southern United States	Deer

[a]Presumed pathogen, Koch's postulates not fulfilled.
LBRF, Louse-borne relapsing fever; *TBRF,* tick-borne relapsing fever.
Modified from Southern PM, Sanford JP. Relapsing fever: a clinical and microbiological review. Medicine. *1969;48:129–149; and Barbour A, Hayes S. Biology of* Borrelia *species.* Microbiol Mol Biol Rev. *1986;50:381–400; based on Gugliotta JL, Goethert HK, Berardi BS, et al. Meningoencephalitis from* Borrelia miyamotoi *in an immunocompromised patient.* N Engl J Med. *2013;368:240–245.*

FIG. 240.1 Cases of tick-borne relapsing fever—United States, 1990–2011. One dot is placed randomly within county of exposure where known; shading indicates states where tick-borne relapsing fever was reportable. *(From Forrester JD, Kjemtrup AM, Fritz CL, et al. Tickborne Relapsing fever—United States 1990-2011.* MMWR Morb Mortal Wkly Rep. *2015;64:58–60. With permission from the Centers for Disease Control and Prevention.)*

during the winter and are associated with spelunking.[14]) Outbreaks have been reported in Arizona, California, Colorado, Montana, New Mexico, Washington, and British Columbia; however, most illness is sporadic.[5,12,18] Most patients have a history of exposure to a cabin or woodpile with rodent infestation. The ticks feed for less than 1 hour, and bites are painless, so many patients give no history of a tick bite.[17] The ticks feed nocturnally. TBRF occurs more commonly in male patients, and most patients are younger than 20 years.[1] TBRF has also been transmitted by transfusion, transplacentally, and by laboratory exposure.

Because TBRF occurs on almost every continent (see Table 240.1), the diagnosis should be considered in a febrile patient returning from

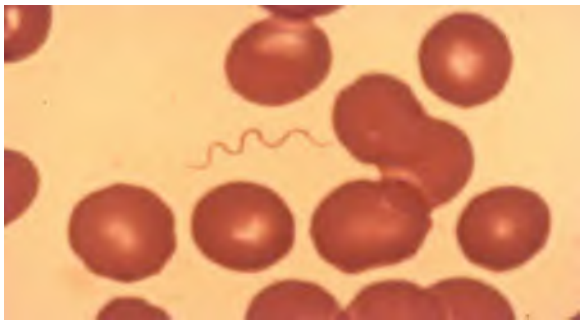

FIG. 240.2 Peripheral blood smear from a patient with tick-borne relapsing fever acquired in Idaho (wright stain). *(From Rhee KY, Johnson WD. Borrelia species (relapsing fever). In Mandell GL, Bennett JE, Dolin R, eds.* Principles and Practice of Infectious Diseases. *6th ed. Philadelphia: Churchill Livingstone; 2005.)*

Central America, Africa, the Middle East, or southern Europe. In West Africa, as the number of cases of malaria has decreased, the percentage of febrile patients with TBRF has increased to 7.3%. In some districts, cases of TBRF exceed malaria.[43]

LBRF was epidemic in the early 20th century throughout Eurasia and Africa. The last major epidemic occurred during World War II in Africa and Europe when an estimated 50,000 people died of the infection under conditions of crowding, such as in displaced-person camps. Today it is largely confined to Ethiopia and the surrounding area, where an estimated 10,000 people a year have LBRF.[20,21] LBRF has been suspected to cause illness in homeless people in France and has been described among refugees from northeast Africa to Europe.[19,22]

PATHOPHYSIOLOGY

Perhaps the most interesting aspect of this disease is the relapsing pattern of fever and the antigenic changes in the spirochete. During the febrile periods, spirochetes are dividing rapidly and become visible on the blood smear (Fig. 240.2).[1] With LBRF, concentrations of more than 100,000 organisms/mm^3 of blood have been described.[24] With the development of a specific immune response to the dominant *vmp*, the organisms are cleared from the blood, resulting in the afebrile period; however, the spirochete then express a different *vmp*, resulting in recurrent spirochetemia and fever. Type-specific immunity suppresses this new antigenic pathogen, and the cycle of fever and afebrile periods begins again. The cyclic process of antigenic variation followed by specific antibody production is responsible for the relapsing course of the illness.[1,2]

TABLE 240.2 Summary of Clinical Features of Relapsing Fever

FEATURE	MEAN VALUE OR INCIDENCE	
	Louse-Borne Disease	Tick-Borne Disease
Case-fatality rate	4%–40%	2%–5%
Incubation period	8 days (range, 4–18 days)	7 days (range, 4–18 days)
Duration of first febrile attack	5.5 days	3 days
Duration of afebrile interval	9 days	7 days
Duration of relapses	2 days	2–3 days
Number of relapses	1–2 (range, 1–5)	3 (range, 0–13)
Maximal temperature	101°F–102°F	105°F
Splenomegaly	77%	41%
Hepatomegaly	66%	17%
Jaundice	6%	7%
Rash	8%	28%
Respiratory symptoms	34% (cough)	16%
Central nervous system involvement	30%	9%

Modified from Southern PM, Sanford JP. Relapsing fever: a clinical and microbiological review. Medicine. *1969;48:129–149.*

TABLE 240.3 Treatment of *Borrelia* Relapsing Fever

ORGANISM	TREATMENT	DOSE	DURATION
LBRF[a]	Tetracycline	500 mg	Once
	Doxycycline	200 mg	Once
	Procaine penicillin G	400,000–800,000 U IM	Once
	Erythromycin	500 mg	Once
TBRF[b]	Tetracycline	500 mg qid	10 days
	Doxycycline	100 mg bid	10 days
	Erythromycin	500 mg qid	10 days
TBRF involving central nervous system[c]	Penicillin G	3 million U IV q4h	10–14 days
	Ceftriaxone	2 g/day IV or 1 g bid IV	10–14 days

[a]Based on clinical trials.[21,39]
[b]Based on review of sporadic cases.[4,16]
[c]Based on case reports and extrapolation from other spirochetal diseases of the central nervous system.[27]
IM, Intramuscular; *IV,* intravenous; *LBRF,* louse-borne relapsing fever; *TBRF,* tick-borne relapsing fever.

The antigenic shift is due to a "loose form of programming," with the antigens usually occurring in the same sequence.[25] With the third episode, the spirochete has mixtures of serotypes.[25] The *vmp* genes reside on linear plasmids, and activation of a new *vmp* results from recombination between different plasmids.[25]

Pathologic findings at autopsy include hepatitis, miliary splenic abscesses, and central nervous system hemorrhages with perivascular infiltrates. Hemorrhagic gastrointestinal and renal lesions have been described.[1]

CLINICAL MANIFESTATIONS

After a median incubation period of 7 days (range, 2–18 days), the patient has fever lasting about 3 days (range, 2–7 days), alternating with afebrile periods lasting about 7 days (range, 4–14 days) (Table 240.2).[1] If untreated, a patient with TBRF can have 30 relapses of the febrile illness, whereas LBRF is usually associated with only 1 relapse. Most patients have at least two relapses of fever before the disease is diagnosed.[16] The febrile episodes can be accompanied by myalgias, arthralgias, headache, dizziness, and vomiting.[16] Lymphadenopathy, hepatosplenomegaly, and a rash occur in less than one-third of patients.[1] Neurologic complications include lymphocytic meningitis, altered mental status, Bell palsy, other cranial nerve palsies, paralysis, and seizures.[1,26,27] Uveitis and endophthalmitis have been reported.[28] Acute respiratory distress syndrome from relapsing fever has been reported in the United States.[29] Myocarditis occurs infrequently and can cause arrhythmias.[5] Systemic inflammatory response syndrome has been reported and can be associated with abnormal liver enzymes, azotemia, hypoxia, and acute respiratory distress syndrome.[5] In some cases the patient presents with a sepsis syndrome from a Jarisch-Herxheimer reaction after receiving an empirical antibiotic such as ciprofloxacin or amoxicillin for a presumed bacterial infection.[30,31] Usually, each febrile relapse becomes less severe. Relapsing fever during pregnancy is associated with increased maternal and fetal mortality and has been associated with spontaneous abortions.[1,4]

TBRF must be differentiated from Colorado tick fever, brucellosis, tularemia, plague, juvenile rheumatoid arthritis, leptospirosis, and occult malignancy.[32] Relapsing fever and Lyme disease share similar neurologic manifestations[33]; the serologic assays cross react, making the differentiation between these two diseases difficult.[16] In one series, 7 of 16 patients with TBRF in Idaho had false-positive test results for Lyme disease.[16]

For LBRF, the differential diagnosis includes typhus, malaria, typhoid fever, leptospirosis, hepatitis, and dengue. In patients from tropical countries, relapsing fever must be differentiated from malaria, and the two illnesses can occur simultaneously.[34] A coexisting louse-borne typhus epidemic can make early diagnosis difficult. The relapsing fever, epidemiology, and spirochetes on smear will confirm the LBRF diagnosis.[1]

On laboratory testing, the leukocyte count ranges from 3000 to 16,000 cells/mm^3.[1] In patients with neurologic symptoms, the cerebrospinal fluid has a pleocytosis (15–2200 cells/mm^3 with a protein elevation up to 160 mg/dL).[1] Spirochetes are found in the cerebrospinal fluid on microscopy in 12% of patients with neurologic symptoms.[1] Elevated lactate dehydrogenase and creatine kinase levels have been reported.[35]

DIAGNOSIS

Relapsing fever is diagnosed by identifying the spirochetes on a Giemsa or Wright blood smear (see Fig. 240.2).[1] An acridine orange stain can also identify the spirochetes on the smear.[4,36] The diagnosis of TBRF is sometimes first suspected by the hematology laboratory technician.[17] The sensitivity of the blood smear during the febrile period is about 70% in TBRF.[1] The sensitivity of the blood smear is less during the afebrile periods, and thick smears might have a higher susceptibility.[1]

Negative blood smears, even when repeated, do not exclude relapsing fever.[31] In LBRF the number of spirochetes may be too low to be detected by routine blood smear; an acridine orange stain of the buffy coat technique was more sensitive in one report.[37] The spirochetes were concentrated in the red blood cell layer.[37]

Acute and convalescent serologic testing with indirect fluorescent antibody and enzyme-linked immunosorbent assay can be used in patients with negative blood smears.[20] Cross-reactivity of the serology tests with *Borrelia burgdorferi* has been reported in one case.[26] Positive serologic tests for syphilis (Venereal Disease Research Laboratory test) occur in 5% of patients with relapsing fever and are thought to represent false-positive results.[1] PCR assay has been used to diagnose *B. hermsii* bloodstream infection.[38] The diagnosis can also be confirmed by mouse inoculation or culture in modified Kelly medium.[12]

THERAPY

Doxycycline, tetracycline, and penicillin are the preferred antibiotic agents for relapsing fever.[1,16] The in vitro susceptibilities indicate that the minimal inhibitory concentrations to penicillin and tetracycline are less than 0.1 mEq/mL.[31] Macrolides, cephalosporins, and chloramphenicol have in vitro activity, but clinical data on their use are limited. The spirochetes are usually resistant in vitro to fluoroquinolones, sulfonamides, and aminoglycosides (Table 240.3).

Antibiotic selection for TBRF is based on case reports and retrospective series.[4,16] Most patients with TBRF are treated for 7 to 10 days with doxycycline (100 mg twice a day) or tetracycline (500 mg four times a day). If tetracyclines are contraindicated, erythromycin (500 mg four times a day) may be used. Relapses may occur with shorter courses of

antibiotics.[1,4] Animal studies suggest that relapses might be due to residual spirochetes in the central nervous system. The placenta can be a reservoir for spirochetes in pregnant patients.[4] Meningitis or encephalitis should be treated with parenteral antibiotics such as penicillin G or ceftriaxone for 14 days. The spirochetes should clear from the blood within 8 hours.

LBRF treatment is based on larger clinical trials.[39] Tetracycline in a single oral dose (0.5 g) is the preferred therapy for LBRF.[21,39] Doxycycline (200 mg) or penicillin G procaine (400,000–800,000 U intramuscularly) has been used.[21,39] For pregnant women or small children, erythromycin, 0.5 g in a single dose, is also effective.[21] Again, the spirochetes should clear from the blood within 8 hours.

Jarisch-Herxheimer reactions with rigors, fever, and leukopenia occur in about half of the patients after the first antibiotic dose.[4,16] Although the reaction usually occurs within 2 hours of the first antibiotic dose, it can occur more than 3 hours later, so all patients should be observed for several hours after the initial antibiotic dose.[4,16] This complication can be accompanied by hypotension, respiratory distress syndrome, and death.[4,16,24] One study reported that patients with microhematuria are less likely to have a Jarisch-Herxheimer reaction, but the pathophysiology of this association is not known.[16] Other factors such as age, sex, proteinuria, the presence of juvenile (band) neutrophils on the white blood cell differential, and choice of antibiotic do not affect the risk for Jarisch-Herxheimer reactions in TBRF.[16] One study found that low-dose penicillin was less likely than tetracycline to provoke a Jarisch-Herxheimer reaction in LBRF, but the patients had a higher relapse rate.[40] Prior administration of hydrocortisone does not prevent the reaction. Persistence of fever in a patient with relapsing fever from a tropical country should prompt a search for a coinfection such as malaria or typhoid fever.[33,34]

Without treatment, the mortality rate of TBRF approaches 10%,[17] but the average mortality rate is about 3%. Untreated epidemic LBRF has a mortality of 40%.[1] The prognosis is worse in LBRF, with altered consciousness, jaundice, pulmonary edema, rash, Jarisch-Herxheimer reaction, vomiting, and delay in treatment.[34]

PREVENTION

Prevention of relapsing fever requires avoidance or elimination of the arthropod vectors. In developed countries, avoidance of cabins and woodpiles with rodents, elimination of rodent nests, and use of insect repellents containing DEET (*N,N*-diethyl-*m*-toluamide) can prevent TBRF.[17] Fumigation with pyrethrin or permethrin has been used, but failures to prevent disease have been reported.[17] Good personal hygiene and, if necessary, delousing procedures prevent LBRF. DDT (dichlorophenyltrichloroethane) was widely used during World War II, but DDT-resistant louse strains have subsequently developed. Other insecticides such as dimethyl dithiophosphate (malathion) are now used for delousing (see Chapter 292).[41] LBRF can be controlled by basic hygiene including washing of clothes of refugees from endemic countries.[23] Postexposure prophylaxis with doxycycline, 200 mg on day 1 followed by 100 mg daily for 4 days, has been effective in preventing TBRF.[42]

Borrelia miyamotoi

B. miyamotoi is genetically similar to the other relapsing fever spirochetes but has significant differences in clinical presentation and diagnosis. It is transmitted by the hard-shelled *Ixodes* ticks that also transmit Lyme disease.[44] It is associated with the small rodents that are also associated with Lyme disease in eastern North America, Asia, and Europe[45,46] and so occurs mostly in the spring and summer. Cases have been reported in the United States, Europe, Russia, and Japan.[47] In areas endemic for Lyme disease, antibodies to *B. miyamotoi* are found in 1% of healthy blood donors and 3% of patients with suspected Lyme disease.[48] In The Netherlands, 10% of forestry workers are seropositive for *B. miyamotoi*.[49] The incubation period is 12 to 16 days followed by symptoms of nonspecific fever, myalgia, arthralgias, and headache.[50] Less common presentations include lymphadenopathy, relapsing fever, neurologic symptoms, and cognitive symptoms.[23,47] A relapsing fever course was present in 11% of patients.[50] Nine of 48 patients (20%) had erythema migrans skin lesions, but some may have had coinfection with Lyme disease.[50] Laboratory findings include mild leukopenia and transaminase elevation.[50] Patients with central nervous system involvement can have a lymphocytic pleocytosis on cerebrospinal fluid analysis.[7] In most immunocompetent patients, *B. miyamotoi* has no long term sequelae, but two cases of cognitive decline and gait disturbances over months have been described.[7,47] Coinfections with other *Ixodes*-transmitted pathogens have occurred including Lyme disease, babesiosis, human granulocytic anaplasmosis, and relapsing fever.[47] The diagnosis is confirmed by PCR testing or immunoassay (enzyme-linked immunosorbent assay or bead assay). The spirochete has been observed in blood smears during the febrile illness, but the sensitivity of the test is not known.[7] The spirochete has been seen on Giemsa staining of a cytospin of the cerebrospinal fluid.[47] Based on case reports, the treatment consists of doxycycline 100 mg twice a day for 14 days.[47] If the patient has central nervous system involvement, ceftriaxone 2 g daily for 14 to 28 days or penicillin G (24 million U/day) has been reported to be successful in case reports.[7,47] A Jarisch-Herxheimer reaction was observed in 15% of patients; in one case the reaction occurred within 9 hours.[7,50] Prevention consists of taking measures to avoid tick bites.[47] Patients with *B. miyamotoi* live in areas of Lyme disease, so they often receive doxycycline prophylaxis after a tick bite. There are no randomized trials of the efficacy of doxycycline prophylaxis for *B. miyamotoi* infection.

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The complete reference list is available online at Expert Consult.

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241 Lyme Disease (Lyme Borreliosis) Due to *Borrelia burgdorferi*

Allen C. Steere

SHORT VIEW SUMMARY

Definition
- A tick-borne infection caused by the spirochete *Borrelia burgdorferi* sensu lato leading to a multisystem illness primarily in the skin, joints, nervous system, heart, or a combination of these.

Epidemiology
- The vectors of Lyme disease are 14 closely related ixodid tick species that are part of the *Ixodes ricinus* complex.
- The disease occurs in parts of North America, Europe, and Asia.
- The disorder in the United States occurs primarily in three distinct foci: in the Northeast from Maine to North Carolina; in the Midwest in Wisconsin, Minnesota, and Michigan; and in the West, primarily in northern California.
- The peak onset of early infection is in the summer months.
- About 30,000 cases are reported yearly in the United States, but the actual number is estimated to be ~300,000 cases annually, mostly from the northeastern United States.

Clinical Characteristics
- Without antibiotic therapy, Lyme borreliosis generally occurs in stages, with different clinical manifestations at each stage, although patients may not express all stages.
- Stage 1 usually consists of a slowly expanding skin lesion, erythema migrans, which may be accompanied by flulike symptoms.
- Stage 2, which occurs weeks later includes manifestations of early disseminated infection, particularly neurologic or cardiac involvement.
- In the United States, stage 3, which occurs usually occurs months after disease onset, is commonly characterized by intermittent or persistent arthritis in one or a few joints, most commonly the knees, over a period of several years, whereas in Europe, acrodermatitis chronica atrophicans is the most common late manifestation of the illness.

Microbiology
- The genus *Borrelia* currently includes 20 closely related species known collectively as *Borrelia burgdorferi* sensu lato (*B. burgdorferi* in the general sense).
- The human infection is caused primarily by three pathogenic species: *B. burgdorferi* sensu stricto (*B. burgdorferi* in the strict sense) is the sole cause in the United States, whereas *Borrelia afzelii* and *Borrelia garinii* are the primary causes of the infection in Europe.

Diagnosis
- Culture of *B. burgdorferi* in Barbour-Stoenner-Kelly medium permits definitive diagnosis but has been possible reliably only from biopsies of erythema migrans skin lesions, an early disease manifestation.
- Diagnosis is usually based on characteristic clinical findings and a positive immunoglobulin G serologic test result, using a two-test approach of enzyme-linked immunosorbent assay and Western blot.

Therapy
- For early infection, appropriate oral antibiotic therapy (usually doxycycline, 100 mg twice daily or amoxicillin, 500 mg three times daily) for 14 to 21 days is usually successful.
- For some patients with neurologic involvement or arthritis, intravenous antibiotic therapy (often ceftriaxone, 2 g daily) for 28 days may be necessary.

Prevention
- Personal protection methods to avoid tick bites and carry out tick checks after exposure in endemic areas are the major prevention strategies.
- A vaccine for Lyme disease consisting of recombinant OspA with adjuvant was shown to be safe and effective, but the vaccine is not now available.

Lyme disease or Lyme borreliosis, which is caused by the tick-borne spirochete *Borrelia burgdorferi* (sensu lato), occurs in temperate regions of North America, Europe, and Asia.[1,2] It is now the most common vector-borne disease in the United States and Europe.[3] The illness usually begins in summer (stage 1) with a characteristic expanding skin lesion, called erythema migrans (EM), which occurs at the site of the tick bite.[1,4] Within several days to weeks (stage 2), the spirochete may spread to other sites, particularly to other skin sites, the nervous system, heart, or joints. After months to years (stage 3), sometimes following periods of latent infection, the spirochete may cause persistent disease, most commonly affecting the joints, nervous system, or skin. Serologic testing is the most practical laboratory aid in diagnosis. All stages of the disorder are usually curable by appropriate antibiotic therapy, but in patients who develop postinfectious syndromes, complete recovery may be delayed.

Lyme disease was recognized as a separate entity in 1976 because of close geographic clustering of affected children in Lyme, Connecticut, who were thought to have juvenile rheumatoid arthritis.[5] However, parts of the illness were recognized previously in Europe and were given different names, including erythema chronicum migrans, Bannwarth syndrome, or acrodermatitis chronica atrophicans.[4] These syndromes were linked conclusively in 1982 and 1983 with the recovery of a previously unrecognized spirochete from the tick vector[6] and from infected patients.[4] The basic outlines of the disease are similar worldwide, but there are regional variations, primarily between the illness found in America and that in Europe and Asia.[1]

CAUSATIVE ORGANISM

The agents of Lyme borreliosis belong to the eubacterial phylum of spirochetes, which are vigorously motile, corkscrew-shaped bacteria. The spirochete cell wall consists of a cytoplasmic membrane surrounded by peptidoglycan and flagella and then by a loosely associated outer membrane (Fig. 241.1).[7] Of the *Borrelia* spp., *B. burgdorferi* is the longest (20–30 µm) and narrowest (0.2–0.3 µm), and it has fewer flagella (7–11). The complete genome of *B. burgdorferi* has been sequenced. *B. burgdorferi* strains have a small, linear chromosome (≈950 kilobases)[8] and 17 to 21 linear and circular plasmids, which comprise about 40% of its DNA.[9]

The remarkable aspect of the *B. burgdorferi* genome is the large number of sequences for predicted and known lipoproteins,[8,9] including the plasmid-encoded outer-surface proteins (Osp) A through F. These and other differentially expressed outer-surface proteins presumably help the spirochete adapt to, survive in, and persist in markedly different arthropod and mammalian environments. In addition, during the disseminated phase of the infection, another surface-exposed lipoprotein,

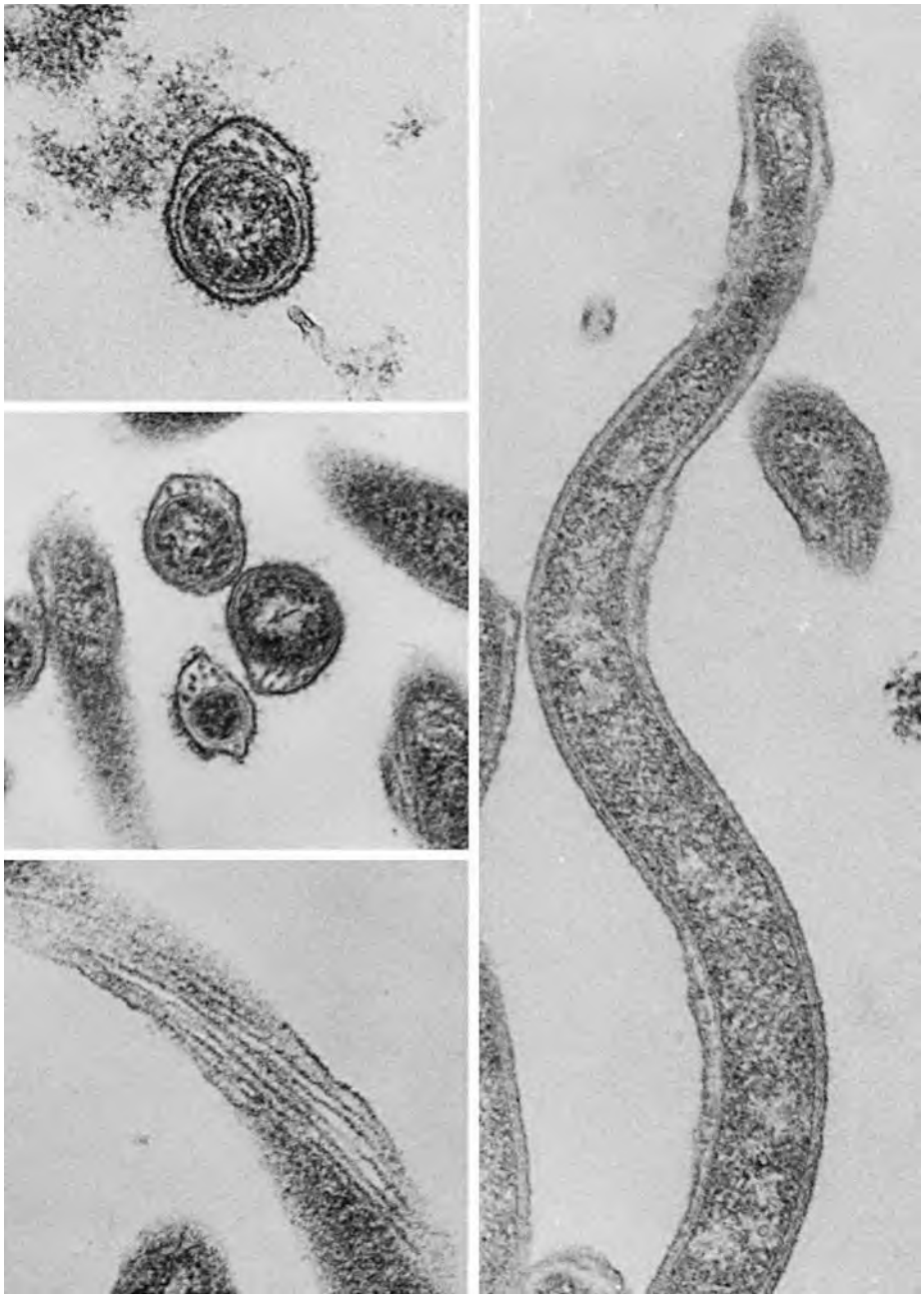

FIG. 241.1 Electron micrographs of *Borrelia burgdorferi.* The spirochetes have a transverse diameter of about 0.2 mm and 7–11 flagella, which are shown *(left)* in cross section in the upper and middle pictures and in tangential section in the lower picture. In longitudinal section *(right),* the organism has an apparent slime layer, an outer membrane, flagellae, a cell wall, and cytoplasmic constituents; its length is 11–39 mm (×40,000, except upper left [×60,000]). *(From Steere AC, Grodzicki RL, Kornblatt AN, et al. The spirochetal etiology of Lyme disease.* N Engl J Med. *1983;308:733–740. Copyright © 1983, Massachusetts Medical Society. All rights reserved.)*

called VlsE, undergoes extensive antigenic variation.[10] The organism has few proteins with biosynthetic activity and apparently depends on the host for much of its nutritional requirements.[8,9] The genome contains no homologues for systems that specialize in the secretion of toxins or other virulence factors. The only known virulence factors of *B. burgdorferi* are surface-exposed lipoproteins that allow the spirochete to attach to mammalian cells.

The genus *Borrelia* currently includes 20 closely related species known collectively as *Borrelia burgdorferi* sensu lato (*B. burgdorferi* in the general sense).[3,11] However, only three pathogenic species commonly cause Lyme borreliosis.[12] To date, all North American strains have belonged to the first group, *B. burgdorferi* sensu stricto (*B. burgdorferi* in the strict sense), hereafter called *B. burgdorferi.* All three groups have been found in Europe, but most isolates there have been group 2 *(Borrelia garinii)* and 3 *(Borrelia afzelii)* strains. Only the latter two groups have been found in Asia. These differences may well account for regional variations in the clinical picture of Lyme borreliosis. *B. burgdorferi* grows best at 33°C in a complex liquid medium called Barbour-Stoenner-Kelly (BSK) medium.[7]

Strains of *B. burgdorferi* have been subdivided according to several typing schemes, one based on sequence variation of OspC,[13] a second based on differences in the 16S-23S ribosomal RNA (rRNA) intergenic spacer (IGS) region (or RST [ribosomal RNA intergenic spacer type]),[14] and a third based on eight chromosomal housekeeping genes (multilocus typing).[15] Among *B. burgdorferi* strains in the northeastern United States, the genes encoding OspC or the IGS are in strong linkage disequilibrium, suggesting a clonal structure of strains in this geographic region.[16] From these typing systems, information is emerging concerning differential

pathogenicity of strains of *B. burgdorferi*.,[13,14] OspC type A (RST 1) strains, which account for 30% to 50% of infections in the northeastern United States, are particularly virulent. The OspC types of midwestern *B. burgdorferi* strains are more diverse than strains in the Northeast; OspC type H strains are most abundant (18%), and RST 1 strains account for only 3% of the infections there.[17] *B. burgdorferi* strains in the United States represent distinct genotypes from *B. burgdorferi* strains in Europe. However, the clinical features of *B. burgdorferi* infection in Europe appear similar to those for *B. afzelii* and *B. garinii* infection, the common *Borrelia* spp. in Europe, suggesting that strains within a particular regional environment accrue similar characteristics as other strains that share the same ecologic niche.[18]

VECTOR OF TRANSMISSION AND ANIMAL HOSTS

The vectors of Lyme borreliosis are closely related ixodid tick species that are part of the *Ixodes ricinus* complex (also called the *Ixodes persulcatus* complex).[19] In the northeastern and midwestern United States the deer tick, *Ixodes scapularis* (also called *Ixodes dammini;* Fig. 241.2), is the vector, and *Ixodes pacificus* is the vector in the West. In Europe the sheep tick, *Ixodes ricinus,* and in Asia, the taiga tick, *Ixodes persulcatus,* are the primary vectors.

Ixodid ticks have larval, nymphal, and adult stages, and they require a blood meal at each stage.[12] The peak questing periods for adult *I. scapularis* are spring and fall; for nymphs, May through July; and for larvae, August and September. In the northeastern United States, from Maine to North Carolina and in the north central states of Wisconsin and Minnesota, a highly efficient, horizontal cycle of *B. burgdorferi* transmission occurs among larval and nymphal *I. scapularis* ticks and certain rodents, particularly white-footed mice and chipmunks.[20] This cycle results in high rates of infection among rodents and nymphal ticks, and primarily nymphal tick bites cause many new human cases of Lyme disease during the late spring and summer months. White-tailed deer, which are not involved in the life cycle of the spirochete, are the preferred host of adult *I. scapularis*, and they seem to be critical for the survival of ticks.

The vector ecology of *B. burgdorferi* is different on the West Coast, where the frequency of Lyme disease is low. There, two intersecting cycles are necessary for the transmission of the disease,[21] one involving the dusky-footed wood rat and *Ixodes spinipalpus* (also called *Ixodes neotomae*) ticks, which do not bite humans and that maintain the cycle in nature, and the other involving wood rats and *I. pacificus* ticks, which are less often infected but do bite humans.

In the southeastern United States, immature *I. scapularis* ticks feed primarily on lizards rather than rodents, and lizards are not susceptible to *B. burgdorferi* infection. Therefore *B. burgdorferi* infection occurs rarely in that part of the country. Instead, in the southern United States, in the mid-Atlantic states, and now moving into northeastern states, a rash resembling erythema migrans, called southern tick-associated rash illness (STARI), has been associated with the bite of the Lone Star tick *(Amblyomma americanum).*[22] Although a novel *Borrelia* spp. called *Borrelia lonestari* has been found in these ticks, it is not clear that they are the cause of the disease. STARI may be accompanied by nonspecific systemic symptoms, but it is not known to cause chronic infection (see Chapter 298 for further details).

In Europe there is still debate about the preferred animal hosts of *I. ricinus*. These ticks feed on more than 300 animal species, including small mammals, birds, and reptiles.[23] Because the *Borrelia* species differ in their resistance to complement-mediated killing, small rodents are important reservoirs for *B. afzelii,* whereas birds are strongly associated with *B. garinii.*[24]

EPIDEMIOLOGY

Since surveillance was begun by the Centers for Disease Control and Prevention (CDC) in 1992, the number of reported cases of Lyme disease has increased dramatically in the United States. Currently, more than 30,000 cases have been reported yearly, making Lyme disease the most common vector-borne infection in the United States.[3] Moreover, the CDC estimates that the actual number of cases is closer to 300,000 annually.[25] The disorder occurs primarily in three distinct foci: in the Northeast from Maine to North Carolina; in the Midwest in Wisconsin, Minnesota, and Michigan; and in the West, primarily in northern California. The infection has now spread to Canada. Lyme borreliosis also occurs in temperate regions of the Northern Hemisphere in Europe and Asia. There, the highest reported frequencies of the infection are in middle Europe, particularly in Germany, Austria, Slovenia, and also in Sweden.[26]

During the past 40 years the infection in the United States has continued to spread, particularly in the Northeast. It has caused focal outbreaks in some coastal areas, and it now affects suburban locations near Boston, New York, Philadelphia, Baltimore, and Washington—the most heavily populated parts of the country.[27] Within these areas the occurrence of Lyme disease is highly focal. In Connecticut, which has one of the highest reported frequencies of Lyme disease in the United States, cases have been noted in all parts of the state, but most of the cases are still clustered in two counties in the southeastern part of the state, where the original epidemiologic investigation took place in the town of Lyme. In a large, 2-year vaccine trial, the yearly incidence of the disease in such highly endemic areas was greater than 1 per 100 participants.[28]

Why did Lyme disease emerge in the northeastern United States during the latter part of the 20th century?[12] The infection has probably been in North America for thousands of years, but ecologic conditions were altered during the European colonization of North America. Woodlands were cleared for farming, and deer were hunted practically to extinction. However, during the 20th century, farmland reverted to woodland, deer proliferated, white-footed mice and other rodents were plentiful, and the deer tick thrived. Soil moisture and land cover, as found near rivers and along the coast, were favorable for tick survival. Moreover, these areas became heavily populated with both humans and deer, as more rural wooded areas became wooded suburbs in which deer were without predators and hunting was prohibited. Finally, the spread of a particularly virulent spirochetal strain, *B. burgdorferi* OspC type A, may have contributed to the rise in the incidence of the infection.[29]

PATHOGENESIS

To maintain its complex enzootic cycle, *B. burgdorferi* must adapt to two markedly different environments: the tick and the mammalian or avian host. The spirochete survives in a dormant state in the nymphal tick midgut during the fall, winter, and spring, where it expresses primarily OspA and certain other proteins.[30] When the tick feeds during the late spring or summer, these proteins are downregulated, and another set of proteins, including OspC, is upregulated.[31,32] OspC binds mammalian plasminogen and its activators present in the blood meal, which facilitates spreading of the organism in the tick.[33] In addition, within

FIG. 241.2 The deer tick, *Ixodes scapularis,* is the primary vector of Lyme disease in the United States. The nymph stage is most frequently implicated. For comparison, the dog tick, *Dermacentor variabilis,* is shown, but this tick does not transmit Lyme disease. Shown actual size. *(Courtesy Massachusetts Department of Public Health Division and the Cape Cod Cooperative Extension.)*

the tick salivary gland, OspC binds a tick salivary gland protein (Salp 15), and coating of the spirochete in this tick protein is essential for initial immune evasion in the mammalian host.[34] The spirochete, which has few proteins with biosynthetic activity,[8] appears to meet its nutritional requirements by infection of a mammalian or avian host.

After injection of *B. burgdorferi* by the tick (and a clinical incubation period of 3–32 days), the spirochete usually first multiplies locally in the skin at the site of the tick bite. In most patients immune cells first encounter *B. burgdorferi* at this site. Dendritic cells isolated from the dermis readily engulf *B. burgdorferi* in vitro.[35] During the initial infection *B. burgdorferi* induces potent proinflammatory and compensatory antiinflammatory responses in cells in EM lesions,[36,37] and *B. burgdorferi*–stimulated peripheral blood mononuclear cells (PBMCs) produce primarily proinflammatory cytokines, particularly interferon (IFN)-γ.[38] Thus both innate and adaptive cellular elements are mobilized to fight the infection.

Within days to weeks, *B. burgdorferi* strains in the United States often disseminate to many distant anatomic sites. During this period the spirochete has been recovered from blood and cerebrospinal fluid (CSF),[6,7,39] and it has been seen in small numbers in specimens of myocardium, retina, muscle, bone, spleen, liver, meninges, and brain.[40] To disseminate, *B. burgdorferi* adheres to integrins, proteoglycans, or glycoproteins on host cells or tissue matrices. As in the tick, spreading through the skin and other tissue matrixes may be facilitated by the binding of plasminogen and its activators to the surface of the spirochete.[33] During dissemination, a 66-kilodalton (kDa) spirochetal protein binds the platelet-specific integrin $\alpha_{IIb}\beta_3$ and the vitronectin receptor ($\alpha_v\beta_5$).[41] A 26-kDa glycosaminoglycan binding protein binds heparan sulfate and dermatan sulfate,[42] which are expressed on endothelial cells. A 47-kDa fibronectin-binding protein (BBK32) binds fibronectin,[43] a ubiquitous extracellular matrix protein. Finally, decorin-binding proteins A and B (DbpA and DbpB) of the spirochete bind decorin,[44] a proteoglycan on the surface of collagen, which may explain the alignment of spirochetes with collagen fibrils in the extracellular matrix in the heart, nervous system, or joints.[40]

All affected tissues show an infiltration of lymphocytes and plasma cells.[40] Some degree of vascular damage, including mild vasculitis or hypervascular occlusion, may be seen in multiple sites, suggesting that spirochetes may have been in or around blood vessels. Although *B. burgdorferi* has been identified inside cultured cells in vitro, it has not been seen in intracellular locations in histologic sections of infected tissues from patients with Lyme disease.

Despite an active immune response, *B. burgdorferi* may survive during dissemination by changing or minimizing antigenic expression of surface proteins and by inhibiting certain critical host immune responses. Two linear plasmids (lps) seem to be essential, including lp25, which encodes a nicotinamidase,[45] and lp28-1, which encodes the VlsE lipoprotein,[10] the protein that undergoes extensive antigenic variation.[46] In addition, the spirochete has a number of highly homologous, differentially expressed lipoproteins, including OspE/F paralogs, which further contribute to antigenic diversity.[47] Finally, *B. afzelii* and, to a lesser degree, *B. burgdorferi* have complement regulator-acquiring surface proteins that bind complement factor H and factor H–like protein 1.[48,49] These complement factors inactivate C3b, which protects the organism from complement-mediated killing.

Both innate and adaptive immune responses are required for optimal control of spirochetal dissemination. Membrane lipoproteins are mitogenic for B cells.[50] The specific immunoglobulin M (IgM) response is often associated with polyclonal activation of B cells, including elevated total serum IgM levels,[51] circulating immune complexes,[52] and cryoglobulins.[51] In murine *B. burgdorferi* infection, CD1d presentation of monogalactosyl diacylglycerol (MgalD, BbGL-II) to natural killer T cells may be important in the early innate immune response, possibly as an initial source of IFN-γ.[53] CD1d-deficient mice do not control the infection as well as their wild-type counterparts.[54]

In the human infection the adaptive IgG response develops gradually over weeks to months to an increasing array of spirochetal proteins[55] and two borrelial glycolipids.[56] Using protein arrays that expressed approximately 1200 or more *B. burgdorferi* proteins, antibody responses were detected to a total of more than 100 proteins in a population of patients with early or late Lyme disease, particularly plasmid-encoded outer-surface lipoproteins.[57] Spirochetal killing seems to be accomplished primarily by bactericidal B-cell responses,[58] which promote spirochetal killing by complement fixation and opsonization.[59] As shown in mice, the primary purpose of *B. burgdorferi*–specific $CD4^+$ Th1 cells, which secrete mainly IFN-γ, is to prime T-cell–dependent, B-cell responses.[60] *B. burgdorferi*–specific $CD8^+$ T cells and NK cells are other important sources of IFN-γ.[61,62] In patients with EM a dichotomy was noted between Th1 and Th17 responses. High Th1-associated responses correlated with more effective immune-mediated spirochetal killing, whereas high Th17-associated immune responses correlated with post-Lyme symptoms.[63]

In the enzootic infection *B. burgdorferi* spirochetes must survive this immune assault for only the summer months before returning to the larval ticks to begin the cycle again the next year. In contrast, infection of humans is a dead-end event for the spirochete. Within several weeks to months, innate and adaptive immune mechanisms, even without antibiotic treatment, control widely disseminated infection, and generalized systemic symptoms wane.[1] However, without antibiotic therapy, spirochetes may survive in localized niches for several more years. *B. burgdorferi*, the sole cause of the infection in the United States, may cause persistent arthritis or, in rare cases, a subtle encephalopathy or polyneuropathy accompanied by minimal, if any, systemic symptoms.[1] Patients with Lyme arthritis have high antibody responses to many spirochetal proteins that are suggestive of hyperimmunization due to recurrent waves of spirochetal growth.[55] Even without antibiotic treatment, the number of patients who continue to have attacks of arthritis decreases by about 10% to 20% each year, and few patients have had attacks for longer than 5 years.[64] Thus immune mechanisms seem to succeed eventually in the eradication of *B. burgdorferi* from selected niches, including the joints or nervous system.

CLINICAL CHARACTERISTICS

As with other spirochetal infections, human Lyme borreliosis generally occurs in stages, with remissions and exacerbations and different clinical manifestations at each stage.[4] Early infection consists of stage 1 (localized EM), followed within days or weeks by stage 2 (disseminated infection). Late infection, or stage 3 (persistent infection), usually begins months to years after the disease onset, sometimes following long periods of latent infection. In an individual patient, however, the infection is highly variable, ranging from brief involvement in only one system to chronic, multisystem involvement of the skin, nerves, or joints. In the United States about 10% of individuals have asymptomatic *B. burgdorferi* infection and seem to cure the infection without antibiotic therapy.[65]

Early Infection: Stage 1 (Localized Infection)

In about 70% to 80% of patients EM develops at the site of the tick bite (Fig. 241.3A and Table 241.1).[66,67] However, because of the small size of nymphal *I. scapularis*, most patients do not remember the tick bite. During the first several days the lesion often has a homogeneous red appearance.[68] In addition, the centers of early lesions sometimes become intensely erythematous and indurated, vesicular, or necrotic. As the area of redness around the center expands, most lesions continue to have bright-red outer borders (usually flat, but occasionally raised) and partial central clearing. In some instances migrating lesions remain an even, intense red; several red rings are found within the outside one; or the central area turns blue before it clears. Although the lesion can be located anywhere, the thigh, groin, and axilla are particularly common sites. If EM is on the head, only a linear streak might be seen to emerge from the hairline. The lesion is hot to the touch, and patients often describe it as burning or occasionally itching or painful.

In Europe EM is often an indolent, localized infection, whereas in the United States, the lesion is associated with more intense inflammation and signs and symptoms that suggest dissemination of the spirochete.[1] In one US study spirochetes were cultured from plasma samples in 50% of patients with EM.[69] In a recent study the EM skin lesions of *B. burgdorferi*–infected US patients expanded faster, were associated with more symptoms, and had higher messenger RNA levels of

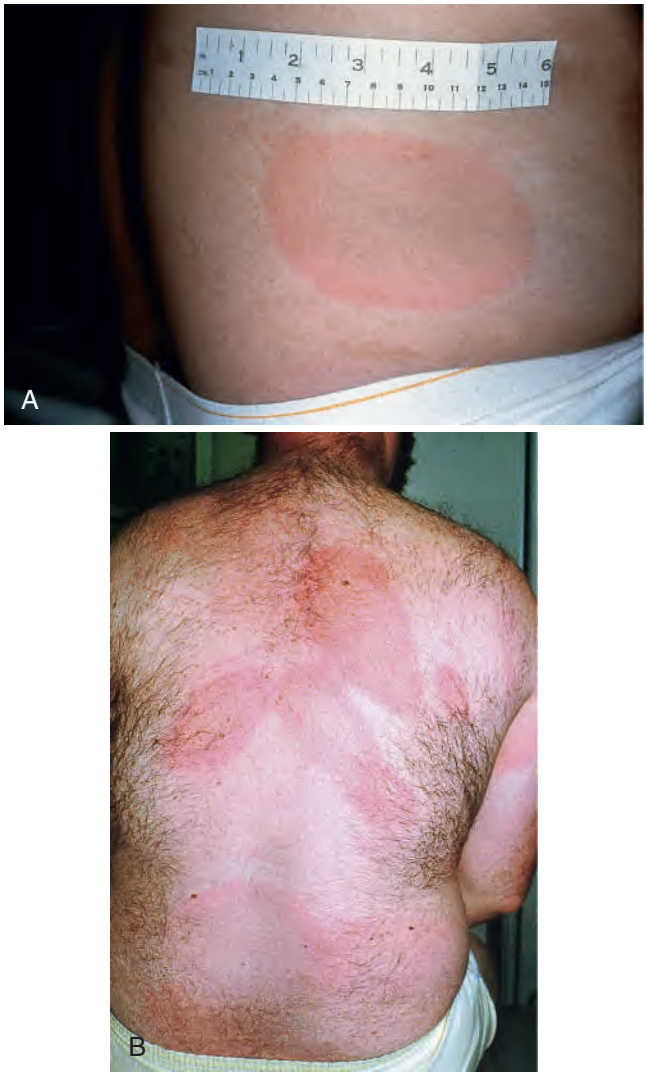

FIG. 241.3 (A) An early erythema migrans skin lesion is seen 4 days after detection. (B) Four days after the onset of the initial skin lesion, secondary lesions have appeared, and several of their borders have merged. *(From Steere AC, Bartenhagen NH, Cratt JE, et al. The early clinical manifestations of Lyme disease.* Ann Intern Med. *1983;99:76–82.)*

macrophage-associated chemokines and cytokines than did EM lesions of *B. afzelii*–infected Austrian patients.[70]

Early Infection: Stage 2 (Disseminated Infection)

Within several days to weeks of the onset of the initial EM lesion, patients, particularly in the United States, may develop multiple annular secondary skin lesions (see Fig. 241.3B and Table 241.1),[1,67] a sign of hematogenous dissemination. Although their appearance is similar to that of the initial lesions, they are generally smaller, migrate less, and lack indurated centers; they are not associated with previous tick bites. Individual lesions sometimes appear and fade at different times, and their borders sometimes merge. During this period some patients develop malar rash, conjunctivitis, or, rarely, diffuse urticaria. EM and secondary lesions usually fade within 3 to 4 weeks (range, 1 day–14 months).

EM is often accompanied by malaise and fatigue, headache, fever and chills, generalized achiness, and regional lymphadenopathy.[1,67] In about 18% of patients[66] these symptoms are the presenting picture of the infection.[71] In addition, patients sometimes have evidence of meningeal irritation with episodic attacks of excruciating headache and neck pain, mild encephalopathy with difficulty with mentation, migratory musculoskeletal pain, hepatitis, generalized lymphadenopathy or splenomegaly, sore throat, or rarely, nonproductive cough.[67] A few patients have had microscopic hematuria, sometimes with mild proteinuria (dipstick). During the first days of illness headache and neck stiffness are not associated with a spinal fluid pleocytosis or objective neurologic deficit. Except for fatigue and lethargy, which are often constant, the early signs and symptoms are typically intermittent and changing. For example, a patient might experience predominantly headache and a stiff neck for several days. After a few days of improvement, musculoskeletal pain might begin.

After several weeks to months, about 15% of untreated patients in the United States develop frank neurologic abnormalities, including meningitis, encephalitis, cranial neuritis (including bilateral facial palsy), motor and sensory radiculoneuritis, mononeuritis multiplex, cerebellar ataxia or myelitis—alone or in various combinations.[72] The usual pattern consists of fluctuating symptoms of meningitis with superimposed cranial (particularly facial palsy) or peripheral radiculoneuropathy.

On examination such patients usually have neck stiffness only on extreme flexion; Kernig and Brudzinski signs are not present. Facial palsy may occur alone,[73] and in rare instances, it may be the presenting manifestation of the disease. In children the optic nerve may be affected by inflammation or increased intracranial pressure, which may lead to blindness.[1] In Europe the most common neurologic manifestation is Bannwarth syndrome, which consists of neuritic pain, lymphocytic pleocytosis without headache, and sometimes cranial neuritis.[1]

In patients with meningitis, CSF typically has a lymphocytic pleocytosis of about 100 cells/mm,[4] often with an elevated protein but a normal glucose level.[72] Specific IgG, IgM, or IgA antibody to the spirochete is produced intrathecally,[74] and *B. burgdorferi*–specific oligoclonal bands may be present. Electrophysiologic studies of affected extremities suggest primarily axonal nerve involvement.[75] Histologically, the lesions show axonal nerve injury with perivascular infiltration of lymphocytes and plasmocytes around epineural blood vessels. Stage 2 neurologic abnormalities usually last for weeks or months, but they may recur or become chronic.

Within several weeks after the onset of illness, about 5% of untreated patients develop cardiac involvement.[76] The most common abnormality is fluctuating degrees of atrioventricular block (first-degree, Wenckebach, or complete heart block). However, some patients have evidence of more diffuse cardiac involvement, including electrocardiographic changes or a gallium scan, compatible with acute myopericarditis, radionuclide evidence of mild left ventricular dysfunction, or, rarely, cardiomegaly. No patients have had heart murmurs. The duration of cardiac involvement is usually brief (3 days–6 weeks), and the insertion of a permanent pacemaker is usually considered unnecessary.[77] However, fatal cases have been reported.[78,79] In Europe *B. burgdorferi* has been isolated from endomyocardial biopsy samples from several patients with chronic dilated cardiomyopathy.[80] However, this complication has not been observed in the United States.[81]

During this stage migratory musculoskeletal pain is common in joints, tendons, bursae, muscle, or bones.[1] In addition, a few patients have been described with osteomyelitis, myositis, panniculitis, or fasciitis. Conjunctivitis is the most common eye abnormality in Lyme disease, but deeper tissues in the eye may be affected as well.[1,82] There are case reports of iritis, followed by panophthalmitis, choroiditis with exudative retinal detachments, or interstitial keratitis, similar to that seen in syphilis. In Europe *Borrelia* lymphocytoma, a subacute skin lesion, typically on the ear or breast, may occur during this period.[83] These lesions have dense infiltrates of B cells, which often form follicular structures, sometimes with the appearance of germinal centers. *Borrelia* lymphocytomas usually last for months but may persist for 1 year or longer.

Late Infection: Stage 3 (Persistent Infection)

Months after the onset of the illness, within the context of strong cellular and humoral immune responses to *B. burgdorferi,* about 60% of patients in the northeastern United States begin to experience intermittent attacks of joint swelling and pain, primarily in large joints, especially the knee, usually one or two joints at a time (see Table 241.1).[1,64] However, both large and small joints may be affected. Joint fluid white blood cell counts range from 500 to 110,000 cells/mm,[4] most of which, in patients with

TABLE 241.1 Manifestations of Lyme Disease by Stage

	EARLY INFECTION		LATE INFECTION
System[b]	**Localized Stage 1**	**Disseminated Stage 2**	**Persistent Stage 3**
Skin	Erythema migrans	Secondary annular lesions Malar rash Diffuse erythema or urticaria Evanescent lesions Lymphocytoma	Acrodermatitis chronica atrophicans Localized scleroderma-like lesions
Musculoskeletal		Migratory pain in joints, tendons, bursae, muscle, bone Brief arthritis attacks Myositis[c] Osteomyelitis[c] Panniculitis[c]	Prolonged arthritis attacks Chronic arthritis Peripheral enthesopathy Periostitis or joint subluxations below acrodermatitis
Neurologic		Meningitis Cranial neuritis, facial palsy Motor or sensory radiculoneuritis Subtle encephalitis Mononeuritis multiplex Pseudotumor cerebri Myelitis[c] Cerebellar ataxia[c]	Chronic encephalomyelitis Spastic paraparesis Ataxic gait Subtle mental disorders Chronic axonal polyradiculopathy
Lymphatic	Regional lymphadenopathy	Regional or generalized lymphadenopathy Splenomegaly	
Heart		Atrioventricular nodal block Myopericarditis Pancarditis	
Eyes		Conjunctivitis Iritis[c] Choroiditis[c] Retinal hemorrhage or detachment[c] Panophthalmitis[c]	Keratitis
Liver		Mild or recurrent hepatitis	
Respiratory		Nonexudative sore throat Nonproductive cough	
Kidney		Microscopic hematuria or proteinuria	
Genitourinary		Orchitis[c]	
Constitutional systems	Minor	Severe malaise and fatigue	Fatigue

[a]The staging system provides a guideline for the expected timing of the different manifestations of the illness, but this may vary in an individual case.
[b]The systems are listed from the most to the least commonly affected.
[c]Because the inclusion of these manifestations is based on one or a few cases, they should be considered possible but not proven manifestations of Lyme disease.
From Steere AC. Lyme disease. N Engl J Med. *1989;321:586–596. Copyright © 1989, Massachusetts Medical Society. All rights reserved.*

high white blood cell counts, are polymorphonuclear leukocytes. Although the total number of patients who continue to have recurrent attacks of arthritis decreases by about 10% to 20% each year, attacks of knee swelling sometimes become longer during the second or third year of illness, sometimes lasting 1 year or longer. However, even in untreated patients, intermittent or persistent arthritis usually resolves completely within several years.

Although most patients with either intermittent or persistent arthritis respond to oral or intravenous (IV) antibiotic treatment, a small percentage of patients have persistent joint inflammation in a knee for months or even several years after 1 to 2 months or longer of oral antibiotics and 1 month or longer of IV antibiotics. This illness is defined as postinfectious, antibiotic-refractory Lyme arthritis.[84] In these patients the synovial lesion, which is similar to that seen in other forms of chronic inflammatory arthritis, including rheumatoid arthritis, shows synovial cell hyperplasia; vascular proliferation; an infiltration of mononuclear cells, particularly T cells; and upregulation of adhesion molecules.[85] In some patients obliterative microvascular lesions are seen, which appears to be a unique feature of Lyme synovitis.[86]

Antibiotic-refractory Lyme arthritis, which has been noted primarily in the northeastern United States, is associated with a high frequency of infection with highly inflammatory RST 1 strains.[87] However, persistent synovitis in the postantibiotic period is not thought to result from persistent infection. The results of polymerase chain reaction (PCR) testing are usually negative in synovial fluid after antibiotic therapy, and both culture and PCR results have been uniformly negative in synovial tissue obtained at synovectomy more than 1 year after the conclusion of antibiotic treatment.[88] This suggests that joint inflammation may continue in some patients after the near or total eradication of live spirochetes from the joint with antibiotic therapy. In MyD88$^{-/-}$ mice, which have a high pathogen load, spirochetal antigens are retained near cartilage surfaces after antibiotic therapy, and patellae homogenates from these mice induce macrophages to secrete tumor necrosis factor (TNF)-α.[89] However, patients with either antibiotic-responsive or antibiotic-refractory Lyme arthritis have low pathogen loads during the infection.[88] Moreover, in human patients with refractory arthritis, T-cell and B-cell responses to *B. burgdorferi* decline after antibiotic treatment,[90,91] whereas the levels of inflammatory cytokines in synovial fluid often increase,[92] suggesting that *B. burgdorferi* antigens are not the sole driver of postinfectious immune responses.

Multiple host factors are also thought to be important in antibiotic-refractory Lyme arthritis. Along with spirochetal factors, these host factors may lead to excessive inflammation, immune dysregulation, and infection-induced, site-specific autoimmunity. Patients with refractory arthritis who are homozygous for a specific Toll-like receptor 1 polymorphism (1805GG), particularly when infected with RST 1 strains of *B. burgdorferi*, have significantly higher levels of proinflammatory cytokines in synovial fluid, including TNF-α and IFN-γ, compared with the levels in patients with antibiotic-responsive arthritis.[93] Moreover, in patients with refractory arthritis, the CD4$^+$ CD25 high T-cell population often has lower frequencies of T-regulatory cells, higher expression of

activation coreceptors, and less effective inhibition of proinflammatory cytokines than this cell population in patients with antibiotic-responsive arthritis.[94]

Furthermore, the greatest known risk factors for antibiotic-refractory Lyme arthritis are specific human leukocyte antigen (HLA)-DR alleles, which are risk factors for many autoimmune diseases. In antibiotic-refractory arthritis the alleles that are increased in frequency (such as the DRB1*0101 and 0401 alleles) encode HLA-DR molecules that bind and present an epitope of *B. burgdorferi* outer-surface protein A ($OspA_{165–173}$).[95] OspA presentation by the DRB1*0401 molecule appears to stimulate a particularly strong Th1 response,[96] which may contribute to excessive joint inflammation. However, an immune response to OspA is commonly found only in patients with Lyme arthritis in the United States, where arthritis is a more frequent manifestation of the disease than in other locations.[97] In support of the hypothesis that autoimmune phenomena may play a role in persistent arthritis after antibiotic therapy, four autoantigens have now been identified: endothelial cell growth factor (ECGF), matrix metalloproteinase-10 (MMP-10), apolipoprotein B-100 (apoB-100), and annexin A2, which are targets of T-cell and B-cell responses in a subset of patients with antibiotic-refractory arthritis.[98–101] Autoantibodies to ECGF correlate with the presence of obliterative microvascular lesions in synovial tissue in these patients.[86] However, within months to several years, the adaptive immune response to autoantigens, in the absence of live spirochetes, seems to eventually regain homeostasis, and the arthritis resolves.

In rare instances, along with or after episodes of Lyme arthritis, patients may develop chronic neurologic manifestations of the disorder.[1,102] In both the United States and Europe a chronic axonal polyneuropathy may develop, manifested primarily as spinal radicular pain or distal paresthesias. Even though sensory symptoms are often localized, electrophysiologic testing frequently shows a diffuse axonal polyneuropathy affecting both proximal and distal nerve segments.[75] In Europe *B. garinii* may cause chronic encephalomyelitis, characterized by spastic paraparesis, ataxia, cognitive impairment, bladder dysfunction, and cranial neuropathy, particularly of the seventh or eighth cranial nerve, accompanied by intrathecal antibody production of IgG antibody to *B. burgdorferi*.[1]

In the United States a mild, late neurologic syndrome has been reported, called Lyme encephalopathy, manifested primarily by subtle cognitive disturbances.[102] Although there are no inflammatory changes in CSF, intrathecal antibody production to the spirochete can often be demonstrated. Neither neuropsychological tests of memory nor single-photon emission computed tomography scanning of the brain has sufficient specificity to be helpful in diagnosis. Acrodermatitis chronica atrophicans, which sometimes follows years after EM, has been observed primarily in Europe and Asia in association with *B. afzelii* infection.[83] Acrodermatitis chronica atrophicans begins with red violaceous lesions that become sclerotic or atrophic. These lesions, which may be the presenting manifestation of the disease, may last for many years, and *B. burgdorferi* has been cultured from such lesions as many as 10 years after their onset.

POST–LYME DISEASE SYMPTOMS OR SYNDROME

The term "post-Lyme symptoms" probably consists of more than one syndrome, and the pathogenetic mechanisms that account for these symptoms may not be the same in all patients. At one end of the spectrum, one or a few subjective symptoms, such as malaise and fatigue or minor joint symptoms, may persist for several months after antibiotic treatment of EM.[103] At the far end of the spectrum, patients may have disabling joint and muscle pain, neurocognitive difficulties, incapacitating fatigue, and sleep disorder for years after Lyme disease.[104] This syndrome is similar to or indistinguishable from chronic fatigue syndrome or fibromyalgia, which is thought to be a centralized pain syndrome.[105] Patients with these conditions do not have evidence of joint inflammation; they have normal neurologic test results; and they may have a greater degree of anxiety and depression than unaffected persons.[106] In contrast, late well-recognized manifestations of Lyme disease, including arthritis, encephalopathy, or neuropathy, are usually associated with minimal systemic symptoms. A subset of patients with Lyme disease who develop post–Lyme disease symptoms after erythema migrans have elevated interleukin-23 levels.[107] There is currently no evidence that persistent subjective symptoms after recommended courses of antibiotic therapy for Lyme disease are caused by active *B. bergdorferi* infection.[108]

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.[108] In such patients the term chronic Lyme disease, which is equated with chronic *B. burgdorferi* infection, is a misnomer, and the use of prolonged antibiotic treatment has not been shown to be beneficial and may lead to substantial cost and serious harm.[109] Patients should be counseled that the proposed therapies have never been proven to be effective and can carry significant side effects, including fatalities.

CONGENITAL INFECTION

In the mid-1980s the transplacental transmission of *B. burgdorferi* was reported in two infants whose mothers had Lyme borreliosis during the first trimester of pregnancy.[1] Both infants died during the first week of life. In both, spirochetes were seen in various fetal tissues stained with the Dieterle silver stain, but cultures and serologic testing were not performed. However, in subsequent prospective studies, no cases of congenital infection have been linked to the Lyme disease spirochete.[110]

COINFECTION

I. scapularis ticks transmit not only *B. burgdorferi,* the Lyme disease agent, but also other infectious agents. These include *Babesia microti* (a red blood cell parasite)[111]; *Anaplasma phagocytophilum* (formerly referred to as "the agent of human granulocytic ehrlichiosis")[111,112]; *Borrelia miyamotoi,* which is more closely related to relapsing fever *Borrelia* than *B. burgdorferi*[112,113]; *Borrelia mayonii* and *Ehrlichia* sp. Wisconsin,[113,114] which are newly recognized species that occur in the upper midwestern United States; and Powassan (deer tick) encephalitis virus,[115,116] which is closely related to European tick-borne encephalitis virus. Babesiosis, anaplasmosis, and *B. miyamotoi* may each cause nonspecific systemic symptoms during summer, and *B. miyamotoi* may cause meningoencephalitis in immunocompromised patients.[117] However, neither *A. phagocytophilum, B. microti*, nor *B. miyamotoi*, is known to cause chronic infection, as with untreated *B. burgdorferi* infection. Fatal cases of infection with deer tick encephalitis virus have been described.[116]

In Europe and Asia *I. ricinus* and *I. persulcatus* ticks, the vectors of *B. burgdorferi* (sensu lato), also transmit tick-borne encephalitis virus.

LABORATORY DIAGNOSIS

Culture of *B. burgdorferi* from patient specimens in BSK medium permits definitive diagnosis. However, positive cultures have been obtained mainly early in the illness, primarily from biopsies of EM lesions,[28] less often from plasma samples,[69] and only occasionally from CSF samples in patients with meningitis. Later in the infection, PCR testing is greatly superior to culture in the detection of *B. burgdorferi* in joint fluid.[88] *B. burgdorferi* has not been isolated from the CSF of patients with chronic neuroborreliosis, and *B. burgdorferi* DNA has been detected in CSF samples in only a small number of such patients.[118]

Because of limited utility of microbiologic techniques, diagnosis is usually based on the recognition of a characteristic clinical picture, exposure in an endemic area, and, except in those with EM, a positive antibody response to *B. burgdorferi*.[119] For serologic testing in the United States, the CDC currently recommends a two-test approach in which samples are first tested by enzyme-linked immunosorbent assay (ELISA), and those with equivocal or positive results are tested by Western blotting (Fig. 241.4).[120] These tests are usually performed with *B. burgdorferi* sonicates, most often obtained from strain B31, an RST 1 strain.

According to the CDC criteria,[119] 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 the 23- and 41-kDa bands may still be a false-positive result. An IgG blot is considered positive if 5 of the following 10 bands are present: 18, 23, 28, 30, 39, 41, 45, 58, 66,

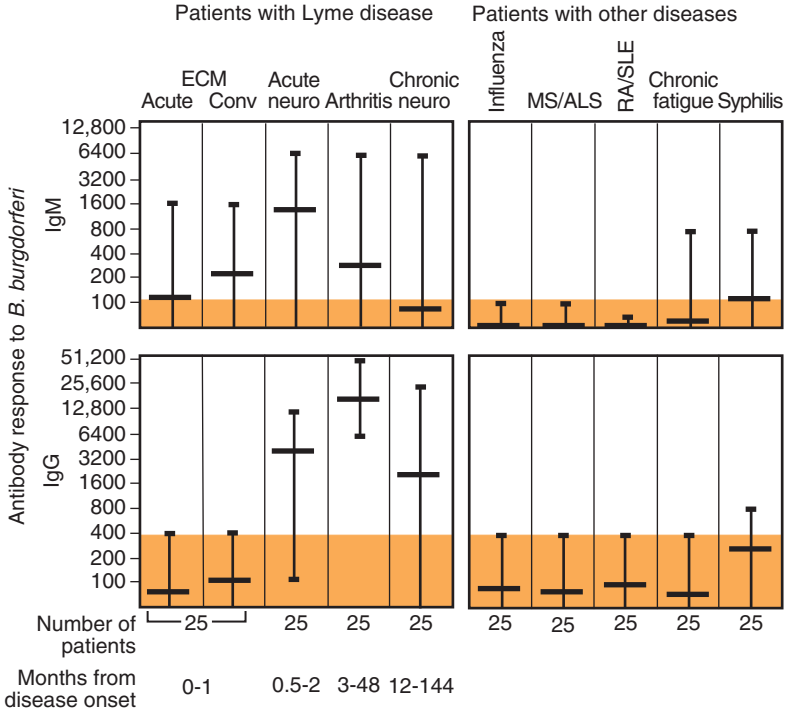

FIG. 241.4 Antibody titers to *Borrelia burgdorferi* by enzyme-linked immunosorbent assay in patients with various manifestations of Lyme disease and in control subjects. Horizontal bars = mean; vertical bars = range; orange hatched area = normal range. Normal range was derived from sera from 50 healthy control subjects. *Acute neuro,* Meningitis; *ALS,* amyotrophic lateral sclerosis; *chronic neuro,* encephalopathy or polyneuropathy; *Conv,* convalescent phase; *ECM,* erythema chronicum migrans; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *MS,* multiple sclerosis; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus. *(From Dressler F, Whalen JA, Reinhardt BN, et al. Western blotting in the serodiagnosis of Lyme disease.* J Infect Dis. *1993;167:392–400.)*

and 93 kDa (Fig. 241.5). Approximately half of the normal population has IgG reactivity with the 41-kDa flagellar antigen of the spirochete, and this response, by itself, has no diagnostic significance. In Europe no single set of criteria for immunoblot interpretation gives high levels of sensitivity and specificity in all countries.[121]

Serodiagnosis is insensitive during the first several weeks of infection. During this period approximately 30% of patients with EM in the United States have positive responses in acute phase samples, usually of the IgM isotype, but by convalescence 2 to 4 weeks later, about 65% to 75% have seroreactivity, even after antibiotic treatment.[122,123] In patients with classic EM (a large erythema with a bull's eye center, partial central clearing, and a redder outer border), serologic testing is not necessary. However, in patients with less characteristic EM, serologic testing may be helpful. However, it is often necessary to test both acute and convalescent serum samples at the conclusion of 2 to 3 weeks of antibiotic therapy to have reasonable serologic sensitivity. Because these tests are usually performed with an RST 1 strain, the sensitivity of Western blotting may be somewhat lower when the patient is infected with an RST 2 or 3 strain.[14] After 4 to 8 weeks, patients with active infection have positive IgG antibody responses, regardless of the RST of the strain causing the infection. In persons with illness for longer than 4 to 8 weeks, a positive IgM test alone is likely to be a false-positive result, and thus a positive IgM response should not be used to support the diagnosis after the first 2 months of infection.

In patients with acute neuroborreliosis, especially those with meningitis, intrathecal production of IgM, IgG, or IgA antibody to *B. burgdorferi* may often be demonstrated. However, an additional step must be taken to account for the fact that IgG antibody can diffuse across the blood-brain barrier. One method involves dilution of serum and CSF samples according to the total IgG concentrations in these fluids prior to ELISA determinations.[124] Another method, antibody capture enzyme immunoassay, compares the proportion of total-to-specific antibody in both serum and CSF.[74] CSF testing is not a part of the CDC case definition for neuroborreliosis because intrathecal antibody production can be demonstrated primarily in patients with meningitis and not reliably in those with other neurologic manifestations of the disorder or in those with chronic neuroborreliosis.

After antibiotic treatment, antibody titers decline, but IgG and even IgM responses may persist for many years after treatment.[11] However, the Western blot, a nonquantitative test, does not change much after treatment or the number of positive bands decreases very slowly. Thus even a positive IgM response cannot be interpreted as showing recent infection or reinfection unless the appropriate clinical picture is present. In a large vaccine trial in the United States, *B. burgdorferi* caused asymptomatic infection in about 10% of infected patients.[65] In seroprevalence surveys in Europe, more than half of the subjects who were seropositive by ELISA did not remember symptoms of Lyme borreliosis.[125] If patients with past or asymptomatic infection have symptoms caused by another illness, the danger is that the symptoms may be attributed incorrectly to Lyme disease.

The most promising second-generation serologic test is an IgG ELISA that uses a 26-mer peptide of the sixth invariant region of the VlsE lipoprotein of *B. burgdorferi,* called the C6 peptide ELISA.[122,123,126] Similar results were obtained with this test and the standard two-test approach of sonicate IgM and IgG ELISA and Western blot. The principal advantage of the C6 peptide ELISA is the early IgG response, and therefore an IgM test is not necessary. However, the C6 ELISA is not quite as specific as sonicate Western blot.

For this reason, an alternative two-tier test strategy has been proposed that uses two enzyme immunoassays—a sonicate ELISA followed by an IgG VlsE C6 peptide enzyme immunoassay.[127,128] This method eliminates the need for IgM testing; it has nearly comparable sensitivity to the VlsE C6 peptide ELISA alone, and it has better specificity than the C6 ELISA, comparable with that of the conventional two-tiered sonicate ELISA and Western blot assays. The most valuable use for this test is to support the diagnosis of early Lyme disease. Moreover, the information provided to the clinician is straightforward; the patient is either seropositive or seronegative. However, a two-test approach that includes Western blot remains valuable for assessing more complex

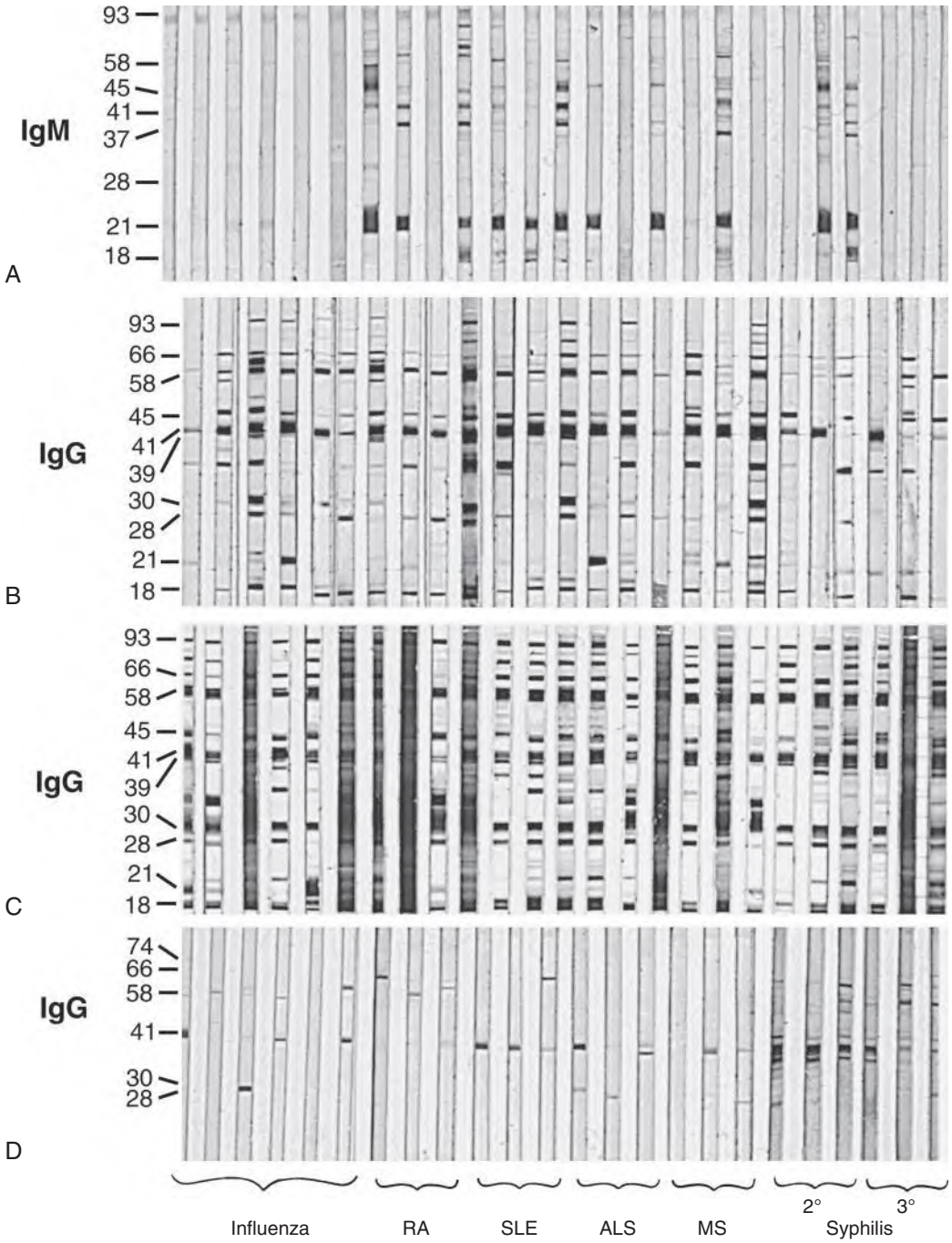

FIG. 241.5 Western blots. (A) Acute-phase sera from 25 patients with erythema migrans. (B) 25 patients with Lyme meningitis or facial palsy. (C) 25 patients with Lyme arthritis. (D) 24 representative patients (controls) who had influenza vaccinations, rheumatoid arthritis *(RA),* systemic lupus erythematosus *(SLE),* amyotrophic lateral sclerosis *(ALS),* multiple sclerosis *(MS),* or secondary or tertiary syphilis. Molecular masses (kDa) are at left. *(From Dressler F, Whalen JA, Reinhardt BN, et al. Western blotting in the serodiagnosis of Lyme disease.* J Infect Dis. *1993;167:392–400.)*

cases because the blot can provide information about the duration of the infection or whether reinfection has occurred. As with the sonicate tests, the response to the VlsE peptide may persist for months or years after successful antibiotic treatment; therefore persistence of the anti-VlsE antibody response cannot be equated with spirochetal persistence in Lyme disease.[122]

Can the infection acquired in Europe be detected with standard two-tiered serologic testing, using assays designed for use in the United States? European assays outperformed analogous US assays in a conventional two-tiered testing algorithm. However, a VlsE C6 peptide ELISA used as a stand-alone test or in the second tier of a two-tiered algorithm performed comparably with conventional two-tiered testing using European assays and can be used for evaluation of any patient, regardless of travel history.[129]

DIFFERENTIAL DIAGNOSIS

Early in its course, a small, homogeneous EM lesion may resemble the red papule of an uninfected tick bite. If an erythema expands rapidly after a tick bite, it is more likely an allergic reaction to tick saliva than an EM lesion, which expands slowly (≈1 cm/day). Patients with secondary annular EM lesions may be thought to have erythema multiforme, but Lyme disease is not associated with blistering, mucosal lesions, or involvement of the palms and soles. Facial palsy caused by *B. burgdorferi* differs from that associated with herpes simplex type 1 virus (Bell palsy)

or varicella-zoster virus (Ramsey-Hunt syndrome) by its seasonal onset (usually June through September), frequent association with EM, and positive IgM and IgG antibody responses to *B. burgdorferi*. Lyme arthritis is most like reactive arthritis or peripheral spondyloarthropathy in an adult or the pauciarticular form of juvenile idiopathic arthritis in a child. Patients with Lyme arthritis usually have high *Borrelia*-specific IgG antibody titers by ELISA, with responses to many spirochetal proteins by Western blot.

The most common mistake is to confuse chronic fatigue syndrome or fibromyalgia with chronic Lyme disease. Although subjective pain or fatigue symptoms may follow Lyme disease, the active infection usually affects one system at a time, and the patient has objective measures of involvement in that system. Moreover, in late disease, systemic symptoms are usually minimal, if present at all.

THERAPY

Evidence-based treatment recommendations for Lyme disease have been presented by the Infectious Diseases Society of America.[130] In brief, the various manifestations of Lyme disease can usually be treated with oral antibiotic therapy, except for patients with certain, objective neurologic abnormalities and occasional patients with Lyme arthritis who may require IV therapy for successful treatment of the infection (Table 241.2). For early localized or disseminated infection, doxycycline for 14 to 21 days is recommended in persons age 8 years or older, except for pregnant women. An advantage of doxycycline is its efficacy against *A. phagocytophilum*, a possible coinfecting agent. Amoxicillin, the second-choice alternative, should be used in children or pregnant women. In case of allergy cefuroxime axetil is a third-choice alternative. Erythromycin or its cogeners, which are fourth-choice alternatives, are recommended only for patients who are unable to take doxycycline, amoxicillin, or cefuroxime axetil. Approximately 15% of patients with disseminated infection experience a Jarisch-Herxheimer–like reaction during the first 24 hours of therapy. In vitro, *B. burgdorferi* is sensitive to tetracycline, penicillin, erythromycin, and their congeners and to third-generation cephalosporins, but it is resistant to rifampin, ciprofloxacin, and the aminoglycoside antibiotics.[130,131]

In multicenter studies of patients with EM, similar results were obtained with doxycycline, amoxicillin, and cefuroxime axetil, and more than 90% of patients had satisfactory outcomes.[132,133] Although some patients had subjective symptoms after treatment, objective evidence of persistent infection or relapse was rare, and re-treatment was usually not necessary. In a recent study 10 days of doxycycline therapy was as effective as 20 days of treatment in the majority of patients with EM, and adding one 2-g dose of parenteral ceftriaxone to the beginning of a 10-day course of doxycycline did not enhance therapeutic efficacy.[134] IV ceftriaxone, although effective, was not superior to oral agents in patients with EM in the absence of objective neurologic involvement.[135] In contrast with second- and third-generation cephalosporin antibiotics, first-generation cephalosporins, such as cephalexin, were ineffective.

For patients with objective neurologic abnormalities, 2- to 4-week courses of IV ceftriaxone are most commonly given.[102,136] Parenteral therapy with cefotaxime or penicillin G may be a satisfactory alternative. In Europe oral doxycycline gave equivalent results to IV therapy in both children and adults with acute neuroborreliosis.[137,138] Although not tested systematically in the United States, oral doxycycline is being used more for this purpose in the United States, particularly in patients who have facial palsy alone or other more localized involvement of the nervous system. With antibiotic treatment the signs and symptoms of acute neuroborreliosis usually resolve within weeks, but those of chronic neuroborreliosis improve slowly over a period of months. Objective evidence of relapse is rare after a 4-week course of therapy. In patients with high-degree atrioventricular nodal block, IV therapy for at least part of the course and cardiac monitoring are recommended, but insertion of a permanent pacemaker is not necessary.

Either oral or IV regimens are usually effective for the treatment of Lyme arthritis.[136,139] Oral therapy is easier to administer; it is associated with fewer side effects, and it is considerably less expensive. Therefore the recommendation is to treat with oral doxycycline or amoxicillin for 30 days.[139] In those with minimal or no response, IV therapy for 2 to 4 weeks is recommended, although improvement does not often begin until the third or fourth week of therapy. Despite treatment with either oral or IV antibiotic therapy, a small percentage of patients in the United States have persistent joint inflammation for months or even several years after 2 months or longer of oral antibiotics or 1 month or longer of IV antibiotics, termed postinfectious, antibiotic-refractory Lyme arthritis.[84] If patients have persistent arthritis despite this treatment, such patients may be treated with nonsteroidal anti-inflammatory agents, disease-modifying antirheumatic drugs, or arthroscopic synovectomy.[84]

TABLE 241.2 Treatment Regimens for Lyme Disease

	EARLY INFECTION (LOCAL OR DISSEMINATED)
Adults	Doxycycline, 100 mg orally twice a day for 14–21 days Amoxicillin, 500 mg orally three times a day for 14–21 days *Alternatives in case of doxycycline or amoxicillin allergy:* Cefuroxime axetil, 500 mg orally twice a day for 14–21 days Erythromycin, 250 mg orally four times a day for 14–21 days
Children (age 8 years or younger)	Amoxicillin, 250 mg orally three times a day or 20 mg/kg/day in divided doses for 14–21 days *Alternatives in case of penicillin allergy:* Cefuroxime axetil, 125 mg orally twice a day for 14–21 days Erythromycin, 250 mg orally three times a day or 30 mg/kg/day in divided doses for 14–21 days
Arthritis (intermittent or persistent)	Doxycycline, 100 mg orally twice a day for 30–60 days Amoxicillin, 500 mg orally four times a day for 30–60 days *or* Ceftriaxone, 2 g IV once a day for 14–28 days Penicillin G, 20 million U IV in four divided doses daily for 14–28 days
Neurologic abnormalities (early or late)	Ceftriaxone, 2 g IV once a day for 14–28 days. Penicillin G, 20 million U IV in four divided doses daily for 14–28 days *Alternative in case of ceftriaxone or penicillin allergy:* Doxycycline, 100 mg orally three times a day for 14–28 days[b]
Facial palsy alone	Oral regimens may be adequate
Cardiac abnormalities First-degree AV block (P-R interval >0.3 s) High-degree AV block	Oral regimens, as for early infection Ceftriaxone, 2 g IV once a day for 14–21 days[c] Penicillin G, 20 million U IV in four divided doses daily for 28 days[c]

[a]Treatment failures have occurred with any of the regimens given, and a second course of therapy may be necessary.
[b]In the author's experience, this regimen is ineffective for the treatment of late neurologic abnormalities of Lyme disease.
[c]Once the patient has stabilized, the course may be completed with oral therapy.
AV, Atrioventricular; *IV,* intravenous.

After appropriately treated Lyme disease, approximately 10% of patients (although the percentage is highly variable in different studies) continue to have subjective symptoms, primarily musculoskeletal pain, neurocognitive difficulties, or fatigue, in some instances, for years.[103,130] Among such patients, five double-blind, placebo-controlled trials failed to show a benefit from additional courses of antibiotic treatment.[140,141,142] In the largest of these studies, patients with post–Lyme disease syndrome received IV ceftriaxone for 30 days, followed by oral doxycycline for 60 days or IV and oral placebo preparations for the same duration. However, there were no significant differences between the groups in the percentage of patients who felt that their symptoms had improved, worsened, or remained the same.[140] However, there was considerable evidence of adverse effects from antibiotic therapy or the IV catheter, including catheter-induced sepsis, pulmonary embolus, anemia, or allergic reactions.[140,141,142] Moreover, prolonged IV antibiotic therapy for unsubstantiated Lyme disease has resulted in biliary complications, *Clostridioides difficile* (formerly *Clostridium difficile*)–associated colitis, autoimmune hemolytic anemia, granulocytopenia, septic shock, vertebral osteomyelitis, paraspinal abscess, and in several instances, death.[109,130] Patients with post–Lyme disease syndrome are best treated symptomatically rather than with prolonged courses of antibiotic therapy.

Although it has not been studied systematically, patients with asymptomatic infection are often given a course of oral antibiotics. Because the risk of maternal-fetal transmission seems to be low, standard therapy for the stage and manifestation of the illness may be sufficient for pregnant patients, except that doxycycline should be avoided.[130] Reinfection may occur in patients who are treated with antibiotics for EM, an early disease manifestation.[143] However, the author has not observed reinfection in a patient with the expanded immune response associated with Lyme arthritis.

PREVENTION

When possible, people should avoid tick-infested areas.[144] If not, insecticides containing DEET (*N,N*-diethyl-meta-toluamide) or permethrin effectively deter ticks, but permethrin can be applied only on clothing, and DEET, although generally safe, can cause serious side effects when excessive amounts are applied directly to the skin.[144] Therefore insecticides may be valuable for the occasional hike in the woods but are less helpful for people living in endemic areas who have daily tick exposures. After exposure in tick-infested areas, tick checks are important. Immature *I. scapularis* ticks usually stay within a few inches of the ground; they often transfer to the lower extremities of the host and attach to moist parts of the body, such as the groin or axillae. In small children they may also be found on the head and neck, which are unusual sites for tick attachment in adults. Because 24 to 72 hours of tick attachment is necessary before transmission of the spirochete occurs, removal of a tick within 24 hours of attachment is usually sufficient to prevent Lyme disease. However, if an engorged nymphal *I. scapularis* tick is found, a single, 200-mg dose of doxycycline usually prevents Lyme disease when given within 72 hours after the tick bite occurs.[130,145]

Environmental control of ticks over widespread areas is difficult.[144] Methods that may be helpful include application of acaricides, landscaping to provide desiccating barriers between tick-infested areas and lawns, and in some settings, removal or exclusion of deer. New methods of tick control, including host-targeted acaricides against rodents and deer, are being developed and may provide help in the future. A commercial Lyme disease vaccine consisting of recombinant OspA with adjuvant was marketed in 1999,[28] but it was withdrawn in 2002. A second-generation OspA vaccine for Lyme disease has been tested in Europe.[146,147] Although a vaccine for Lyme disease is not available now, previous experience proved that vaccination is feasible for the prevention of this infection.

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The complete reference list is available online at Expert Consult.

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242 Anaerobic Infections: General Concepts

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SHORT VIEW SUMMARY

Definition
- An anaerobe is an organism that requires reduced oxygen for growth, failing to grow on the surface of solid media in 10% carbon dioxide in air.
- Anaerobes that commonly cause human infections (*Bacteroides, Prevotella*, and *Fusobacterium* spp.) are generally aerotolerant.

Epidemiology
- Anaerobic bacteria are the predominant forms of life in the human body.
- Anaerobes are dominant commensals in mucosal surfaces, such as the oral cavity and the gastrointestinal (GI) and female genital tracts.
- Infections involving anaerobes are often polymicrobial and usually result from the disruption of mucosal surfaces by surgery, trauma, tumors, or ischemia and the subsequent infiltration of resident microbiota.
- Commensal anaerobes have been implicated as crucial mediators of several physiologic, metabolic, and immunologic functions in the mammalian host.

Microbiology
- Despite the number of anaerobic species represented in the normal human microbiota, relatively few are involved in human infections.
- Among the anaerobic gram-negative bacilli, the *Bacteroides fragilis* group is most commonly isolated from human infections.
- Other important gram-negative bacilli involved in human infections include *Prevotella, Porphyromonas*, and *Fusobacteria* spp.

Diagnosis
- Because of their fastidious nature, anaerobes are difficult to isolate and therefore are often overlooked.
- Their isolation requires appropriate methods for collection, transport, and cultivation of specimens.

Clinical Setting
- Anaerobic bacteria generally cause endogenous infections after the breakdown of mucosal barriers and the leakage of indigenous aerobic and anaerobic microbiota into normally sterile sites.
- Infections that are likely to involve anaerobes as important pathogens include oral and dental infections; brain abscess; human and animal bites; aspiration pneumonia and lung abscess; peritonitis after a perforated viscus; infections of the female genital tract, infections after surgeries involving the GI, oral, or female genital tract; and necrotizing infections of soft tissues and muscles.
- The hallmark of infection caused by anaerobic bacteria, mostly gram-negative bacilli, is abscess formation.

Therapy
- Successful therapy for anaerobic infections generally involves the administration of appropriate antimicrobial agents combined with surgical management or percutaneous drainage.
- The antibiotics used to treat anaerobic infections should be active against both aerobic and anaerobic organisms because many of these infections are of mixed etiology. Antibiotic regimens are usually selected empirically on the basis of the type of infection.
- Antibiotic susceptibility testing of anaerobic bacteria is rarely performed in clinical laboratories.
- The antibiotics with the greatest activity against nearly all anaerobic bacteria include carbapenems, β-lactam/β-lactamase inhibitor combinations, metronidazole, and chloramphenicol.
- Antibiotic resistance is increasingly reported among anaerobic bacteria. The major changes have involved the activity of clindamycin, cephamycins, and moxifloxacin against *B. fragilis* and related strains.

Anaerobic bacteria are a major component of the normal human microbiota (formerly termed the *normal flora*) residing on mucous membranes and predominate in many infectious processes, particularly those arising from mucosal sites. These organisms generally cause disease after the breakdown of mucosal barriers and the leakage of indigenous flora into normally sterile sites. The predominance of anaerobes in certain clinical syndromes can be attributed to the large numbers of these organisms residing on mucous membranes, the elaboration of a variety of virulence factors, the ability of some anaerobic species to resist oxygenated microenvironments, synergy with other bacteria, and resistance to certain antibiotics.

Clinicians have become more aware in the past few decades of the types of infections caused by anaerobic bacteria. However, difficulty in handling specimens in which anaerobes may be important and technical difficulties in cultivating and identifying these organisms in clinical microbiology laboratories continue to lead to many cases in which the anaerobic etiology of an infectious process remains unproven. The importance of anaerobes in certain infections is further enhanced by the failure to provide appropriate antibiotic coverage for anaerobes in mixed aerobic/anaerobic infections and an increase in the number of anaerobes that have become resistant to antimicrobial agents. These various factors combine to make it crucial to understand the types of infections in which anaerobes can play a role, to use appropriate microbiologic tools to identify the organisms in clinical specimens, and to choose the most appropriate treatment, including antibiotics and surgical drainage or débridement of the infected site.

This chapter focuses on infections caused by nonsporulating anaerobic bacteria and does not include the clostridial infections and syndromes (see Chapters 243 to 246).

DEFINITION OF AN ANAEROBE

An anaerobe is an organism that requires reduced oxygen for growth and fails to grow on the surface of solid media in 10% carbon dioxide (CO_2) in air. In contrast, facultative organisms can grow in the presence