[432, 433] and the peak incidence of Lyme borreliosis occurs between May and October.[251, 371, 405, 409, 422, 432, 434–436] Similar seasonality has been demonstrated historically in a retrospective study of museum ticks from Great Britain over the past 100 years, in which *B. burgdorferi* PCR–positive museum specimens of *I. ricinus* ticks were found mainly from May through October, the overall PCR positivity rate was 20%, and the nymphal positivity rate was 38%.[340] The seasonality was particularly well defined in the migratory seabird tick, *I. uriae*, because ticks of this species were found only from April through August, and the PCR positivity rate was 98%.[340] The frequency with which *I. uriae* bites humans is not known, but one of the British museum *I. uriae* was involved in a human bite.[340]

In Asia, the adult stage of *I. persulcatus*, the most common tick in the Lyme-endemic areas of China and Japan, feeds in May and June and commonly bites humans, but larvae and nymphs rarely bite humans. The *B. burgdorferi* infection rate of the adult ticks is high in endemic regions, and the seasonality of EM, which peaks in May and June, correlates with that of human *I. persulcatus* tick bites.[344, 351, 374, 437, 438] *I. ovatus* is also frequently found in Japan, and has been demonstrated to be infected with *B. japonicus*, but no human cases of Lyme disease have been associated with it[163, 374]; *B. burgdorferi* isolates from Japanese patients with EM have been strains transmitted by *I. persulcatus* ticks.[164, 374, 439]

The risk of transfusion-acquired Lyme borreliosis was zero in a large study of 149 recipients of 601 units of packed red blood cells, and 48 recipients of 371 units of platelets, in a Lyme-endemic area of Connecticut; one patient developed transfusion-acquired babesiosis during this study.[440]

In North America, seasonal peaks of other tickborne infections that share vectors with Lyme disease are similar to those of Lyme disease: HME peaks in May through July,[398] HGE in May through July and in October through December,[397, 398] and babesiosis in the summer.[394] In Europe, the seasonality of tickborne encephalitis (TBE) is similar to that of Lyme borreliosis, which shares tick vectors.[402]

Geographic Distribution of Tick Vectors

The focus here is on the vectors involved in human transmission. The *Ixodes ricinus* complex ticks are widely distributed in the northern hemisphere,[182] require an environment with high humidity and temperature between −10° C and 35° C, and are therefore not found at high elevations because they are susceptible to the desiccation that occurs in unprotected, high windy areas.[181, 336] *I. scapularis* inhabits heavily forested and brushy areas, particularly the brushy areas at junctions between cleared and forested areas,[336, 407] but it has also been found on well-manicured lawns in hyperendemic areas such as Westchester County, New York, at densities as high as one tick per square meter of lawn.[441] *I. pacificus* is found only at elevations less than 2100 feet in coastal California.[420] *I. ricinus* inhabits dense heterogeneous deciduous forests with dense undergrowth,[181] as well as pastures below 1000 meters of elevation, is rare between 1000 and 1500 meters, and is not found above 1500 meters of elevation.[167, 336, 352] There is uneven distribution of these ticks even within their geographic range as a result of local microniche differences in elevation, foliage, humidity, temperature, and host populations.[181]

The evolution of distinct tick species and their *B. burgdorferi* genospecies has resulted in unique geographic ranges of both ticks and *B. burgdorferi* genospecies.[7, 13, 54, 63, 74]

The geographic distribution of the northern *I. scapularis* includes the northeastern and upper midwestern United States from Maine to Virginia, from the Atlantic Coast to Minnesota and Iowa, and from southern Ontario along coastal Lake Erie through Illinois and Indiana; small numbers of *I. scapularis* have also been found in Canada as far north as 50 degrees North latitude in Ontario, and in all provinces from Manitoba east to the Gulf of St. Lawrence and the Atlantic coast; the southern *I. scapularis* is found in the Southeast from Virginia to Florida, from the Atlantic coast to Texas and Oklahoma, and from the Midwest to the Gulf Coast.[167, 182, 348, 419, 445, 447] These areas include most of the Atlantic and Gulf Coasts, the Mississippi Valley, and forested areas of Missouri, Arkansas, Louisiana, Oklahoma, and Texas; *I. scapularis* is not found west of the 100th meridian, which runs midway through Texas and beyond which annual rainfall decreases.[348]

The distribution of *I. pacificus* extends from British Columbia to Baja California, from the Pacific coast to the Cascade and Sierra Nevada Mountains, and from Nevada to the Wasatch Range in Utah; it also includes some pockets of higher humidity within arid regions in eastern Oregon, northwestern Arizona, southern Nevada and Utah, and Idaho.[167, 348, 419] *I. pacificus* is well established in localized areas of southern British Columbia around the Fraser Delta, the Gulf Islands, and Vancouver Island.[445] *Ixodes angustus*, also suspected to be a potential *B. burgdorferi* vector for humans in Washington State,[364] has a wide geographic range that overlaps with that of *I. pacificus* and extends along the Pacific from California to Alaska[336, 364]; *B. burgdorferi* has also been found in *I. angustus* in British Columbia. It is the most common tick in some parts of coastal Oregon.[364]

Several tick species involved in enzootic cycles also overlap geographically with human Lyme disease tick vectors but are rarely or never related to human Lyme disease transmission as they rarely bite humans.[348, 378] These include *I. neotomae*,[348, 378] *I. dentatus*,[100, 170, 348, 363] *I. cookei*,[129] *I. affinis*, and *I. minor*,[361] as well as *I. spinipalpis*[362] in North America, and *I. hexagonus*[182, 381] in Europe and Asia.

Although the status of *A. americanum* as a human vector of Lyme disease has not been proved, it has been suspected as a secondary vector in some mid-Atlantic, southeastern, and southern states[153–155, 158, 359, 360, 366–369]; it occurs from Rhode Island to Florida, and from the Atlantic Coast to central Texas.[73] A *Borrelia* identified as *B. burgdorferi* has been found in *A. americanum* in New Jersey, Missouri, Texas, Oklahoma, Virginia, North Carolina, and Alabama.[153–158, 386] Also, an uncultivable *Borrelia*, *Borrelia lonestarii*, which may be related to the

Lyme-like disease in the southern states,[73] was found in *A. americanum* from New York, New Jersey, Missouri, and North Carolina.

The geographic distribution of *I. ricinus* extends from Algeria, Tunisia, and Egypt in North Africa to 65 degrees North latitude in Europe to southern Norway, Sweden, and Finland, and from the United Kingdom to 50 to 55 degrees East longitude in Turkey, Iran, and Russia to the Caspian Sea west of the Ural Mountains.[11, 167, 181, 182, 336, 448] It also includes southern Italy, the Balkans, and subtropical Madeira Island. *I. ricinus* is the most common tick in Europe.[336] *I. ricinus* occurs in northern but not southern Spain.[90]

The distribution of *I. persulcatus* extends east from the Ural Mountains[448] in eastern Europe to Asia and Japan and, at its western margin, overlaps somewhat with that of *I. ricinus*[167, 344]; it extends south to include the Hokkaido and Nagano districts in northern Japan, but does not occur in southern Japan.[351] *I. persulcatus* was the predominant tick in the Lyme-endemic areas of northeastern (Heilongjiang, Jilin, Liaoning, and Hebei Provinces), north central (Inner Mongolia), and northwestern (Xinjiang Province) China,[344, 350, 437, 438, 449] and in the Lyme-endemic areas, Hokkaido and Nagano districts, and Saitama Prefecture of Japan.[163, 351, 450]

So far, no ticks of the *I. ricinus/persulcatus* complex have been found to occur in Australia.[375]

In South America, there are ixodid ticks but it is unknown whether they harbor *B. burgdorferi*[453]; there are no *Ixodes* ticks in Chile.[454]

I. ricinus is prevalent in northern Africa, including Tunisia,[455] but does not occur farther south. In most of Africa, the Middle East, Asia, South America, and Central America, there are ticks that transmit human non-Lyme borrelial relapsing fever.[342]

I. uriae has a large high-latitude bi- and circumpolar marine ecologic geographic distribution[13, 152, 165, 166]; migratory seabirds congregate to breed on subarctic and subantarctic islands and peninsulas; they make transequatorial migrations to overwinter in northern parts of the Atlantic and Pacific, and in southern waters around South America and South Africa.[165, 166] Migratory seabirds and their *I. uriae* ticks are thought to be involved in transhemispheric spread of *B. burgdorferi* to the southern hemisphere, and possibly to be involved in the occurrence of Lyme disease in the southern hemisphere in areas without known *I. ricinus* complex vector ticks, such as Australia and South Africa. *I. uriae* have occasionally been found to bite humans.[165, 340] Migratory birds are able to bring potentially *B. burgdorferi*–infected ticks into contact with humans in geographic areas in which they would otherwise have no tick contact.[182, 425]

Geographic Distribution of Lyme Borreliosis

GEOGRAPHIC DISTRIBUTION OF LYME DISEASE IN NORTH AMERICA

The earliest cases of Lyme disease in the United States were recognized retrospectively to have occurred in the small New England communities of Great Island, Massachusetts, in 1962[334] and in and around Lyme, Connecticut, in 1965.[335] The earliest recognized case of EM in the United States occurred in 1969 in the Upper Midwest, in north central Wisconsin,[333] and the earliest recognized case in the Pacific Northwest, which followed an *I. pacificus* tick bite,[343] was reported in 1978 from Sonoma County, California.

To monitor trends and determine endemic geographic areas, the CDC and the Council of State and Territorial Epidemiologists began a national Lyme disease surveillance program in 1982 and established Lyme disease as a nationally notifiable disease in 49 states and the District of Columbia in 1990.[3] In addition to the increased reporting of cases of Lyme disease since then, there has been a true increase in the incidence of Lyme disease because of spread of the *I. scapularis* tick vector and its large mammalian host, the white-tailed deer, into larger geographic areas. If nymphal tick infection rates are high, as in some endemic areas of the northeastern United States, small variations in the tick population can significantly change the risk of Lyme disease exposure, and this will be reflected in the annual incidence of Lyme disease cases.[459]

A comparison of Lyme disease cases reported to the CDC from 1982 through 1998 shows impressive increases in both the number of cases reported (see Fig. 11–3) and the number of states reporting cases (see Fig. 11–2).[460, 461] The original northeastern focus of endemic Lyme disease in Connecticut[15] and Massachusetts[334, 462] in the late 1970s progressively expanded[463] to the mid-Atlantic states, and by 1982 it included Rhode Island, New York,[464–466] and New Jersey[155, 467, 468]; by 1987, Ohio, Pennsylvania, Maryland,[469, 470] and Virginia[358]; by 1992, New Hampshire; and by 1998, it extended to Vermont.[4] The original upper midwestern focus in Wisconsin[271, 471–473] expanded to include Minnesota[272] by 1982. By 1987, cases of Lyme disease were reported from Texas,[382] and by 1992, from the majority of the southeastern,[359, 360, 474] south central,[369] and midwestern[366, 368, 473, 475, 476] states. In the northwestern states between 1982 and 1987, Lyme disease began to be reported from California, Oregon, and Washington State.[364] As of 1998, ten states—New York, Connecticut, New Jersey, Pennsylvania, Wisconsin, Rhode Island, Maryland, Massachusetts, California, and Minnesota—accounted for 90%, and the first four states accounted for 75%, of all cases of Lyme disease reported to the CDC from 1982 through 1998.[3, 461] Endemic areas have become established in many other states.

Although Lyme disease now has been reported from all states except Montana,[3, 4, 461] some states such as the Mountain states (Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, and Nevada), the Dakotas, Louisiana, Mississippi, South Carolina, Maine, Vermont, Hawaii, and Alaska reported very few or no cases in 1992, and most cases continue to be reported from the highly endemic areas of the northeastern, mid- and south Atlantic, and upper midwestern states. By region, in 1992 and 1998, there were approximately 5300 and 6900 cases of Lyme disease reported from the mid-Atlantic states, 2300 and 4500 from the northeastern

states, 1100 and 1165 from the north central states, 700 and 900 from the south Atlantic states (over 75% from the northern part of this area—Maryland, Delaware, and Virginia), 200 and 100 from the south central states, 300 and 200 from the Pacific states, and only 16 and 25 cases from the Mountain states. Cases reported from nonendemic areas but acquired in endemic areas may explain the reporting of some cases from nonendemic states. Variation in tick and reservoir host population density, application of more stringent case definitions, and Lyme disease educational programs may be related to decreases in incidence of cases in some areas in 1998 compared with 1992.

The existence of Lyme disease in southern United States has been controversial,[361, 477] although there is general agreement about the existence of a Lyme-like illness with erythema migrans in the South.[367, 368, 477] The presence of *B. burgdorferi* in *I. scapularis* and small mammals in the South has been established,[386, 477] but it has been suggested that genospecies of *B. burgdorferi* other than *sensu stricto* and tick vectors other than *I. scapularis*, such as *I. dentatus* or *A. americanum*, might be involved in enzootic cycles in nature and in transmission of this disease to humans.[153, 158, 359, 360, 366–368] This issue has been complicated by misdiagnosis, as was the case in Georgia in 1989 when more than 700 cases were suddenly reported in 1 year, the majority of which were later considered not to be Lyme disease.[461]

Yearly incidences of Lyme disease cases occurring per 100,000 population have been calculated for different geographic areas of the United States, and are designated as follows: low incidence, 10 cases per 100,000 population (0.01% annually); moderate, 100 cases per 100,000 (0.1% annually); high, 1000 cases per 100,000 (1% annually); and very high, 3000 cases per 100,000 (3% annually).[478] Very high, hyperendemic areas are Westchester County, New York, with a 2.6 to 3% annual incidence and a 17% cumulative incidence; Great Island, Massachusetts, with a 3% annual incidence and a 16% cumulative incidence; and Fire Island, New York, with a 1 to 3% annual incidence and a 7.5% cumulative incidence.[478]

In Canada, southern British Columbia (the Fraser Delta area, Vancouver Island, and the Gulf Islands) and Ontario (Long Point Peninsula and coastal areas of Lake Erie) are now considered Lyme-endemic areas,[376, 445, 479] with established tick vector populations (*I. pacificus* and *I. angustus* in British Columbia, and *I. scapularis* in Ontario)[376, 445]; there are limited focal, established populations of *I. scapularis* and *I. pacificus* in other areas of Canada at risk to become endemic foci if *B. burgdorferi* is introduced into these populations.[445] *I. pacificus* is established in southern British Columbia in the Fraser Delta area, the Gulf Islands, and Vancouver Island; *I. scapularis* is established in Ontario in coastal Lake Erie, and has also been reported in Manitoba, Quebec, Nova Scotia, New Brunswick, Newfoundland, and Prince Edward Island; its occasional appearance in other provinces has been thought to be due to introduction by migratory birds.[445] Between 1977 and 1989, 30 cases of Lyme disease were reported to the Canadian Laboratory Centre for Disease Control; Lyme disease is now notifiable in 8 of 12 provinces; between 1987 and 1997, 333 cases were reported, half acquired in Canada, mostly from southern Ontario (71% of autochthonous cases), British Columbia, Ontario, Quebec, Manitoba, and New Brunswick near Lyme-endemic areas in the United States.[479] In 1993, *B. burgdorferi* was found in *I. pacificus* and *I. angustus*, as well as deer mice, in British Columbia.[376] A serosurvey of residents of Alberta, Canada, in 1993 found no seropositivity by ELISA or Western blot assays, and a tick survey found *I. angustus* and *H. leporispalustris* but no *I. scapularis*[479]; in 1995, *B. burgdorferi* was isolated from an *H. leporispalustris* tick removed from a rabbit in Alberta, near the border with British Columbia, establishing its presence in Alberta.[479] In 1993, *B. burgdorferi* was found in *I. scapularis* from a dog in Ontario, at 50 degrees North latitude near the Manitoba border, just north of the endemic areas of Minnesota.[446]

EXPANSION OF LYME-ENDEMIC AREAS IN NORTH AMERICA

B. burgdorferi–infected ticks may be transported from Lyme-endemic areas into nonendemic areas, which may establish new Lyme-endemic foci.[165, 168, 169, 336, 408, 462, 490] Infected *I. ricinus* complex ticks (including *I. scapularis*) and infected *I. uriae* have been found on migratory birds and along migratory "flyways"; they may be transported into new areas by these birds as they travel between endemic and nonendemic areas, including counties, states, countries, continents, and even hemispheres.[13, 63, 157, 165, 167–169, 171, 376] Rodents, hunting dogs, household pets,[454] domestic animals, wide-ranging wild animals such as coyotes and foxes, and campers, hunters, and other people[13] traveling between endemic and nonendemic areas may also transport infected ticks from one area to another; deer hunters may transport deer or other game animals[63] with infected ticks still attached. If the newly arrived tick finds its necessary hosts, or if it arrives together with a population of its hosts, a new endemic focus of infected ticks and Lyme disease will be established.[460, 470, 492] *I. scapularis* and other *I. ricinus* complex ticks, along with the rabbit ticks *I. dentatus* and *H. leporispalustris*, are able to feed on birds as well as mammals,[157, 163, 167, 362] and could provide a bridging vector between hosts.[167]

In North America, the incidence of Lyme disease has been found to correlate with the population density and geographic distribution of *I. scapularis*[335, 442, 443, 490, 491] and white-tailed deer.[335] Because deer are the reproductive hosts of adult *I. scapularis* and they determine the success rate of tick mating, the population density of *I. scapularis* correlates with the population density of deer, and an *I. scapularis* focus may enlarge geographically as the geographic distribution of deer expands.[408] Even infrequent visits by deer to an area may be sufficient to sustain a small population of *I. scapularis*.[492]

The deer populations in North America have changed dramatically over the past 400 years.[168, 394] Particularly since the 1970s, there has been a deer population explosion, and deer have regained their original widespread North American distribution as forests have replaced farmland and federal programs have protected deer. Hu-

man contact with deer has been increasing as residence or recreation in rural and suburban forested areas has become increasingly popular.[6, 7, 168, 336, 390, 394]

The expansion of the Lyme-endemic areas has been particularly impressive in New England, the mid-Atlantic states, and Wisconsin, where this has been extensively studied epidemiologically. In Ipswich, Massachusetts, the emergence of a new focal epidemic of Lyme disease was associated with a 35% Lyme disease attack rate overall for residents living near the deer-populated nature preserve considered to be the focus, and 66% for those living closest to the preserve.[462] Among permanent residents of Great Island, Massachusetts, the Lyme seropositivity rate was 8%, the history positivity rate was 16%, and the incidence of Lyme disease was 7% over a 2-year period.[334] Among middle and high school students in an endemic area of Connecticut, the physician-diagnosed Lyme disease history positivity and seropositivity rates were 7 and 3%, respectively; during the 1990–1992 tick season, 2% developed clinical physician-diagnosed Lyme disease and 1% experienced asymptomatic seroconversion.[493] The incidence of Lyme disease increased steadily between 1991 and 1996 from rates of 36 to 94 cases per 100,000 population annually overall for Connecticut, and from 340 to 450 cases per 100,000 annually for a hyperendemic 12-town area along the Connecticut River and the Atlantic Coast; the increase in the 12-town area was found to correlate with the abundance and *B. burgdorferi* infection rate of *I. scapularis* in this area; nymphal tick infection rates increased from 14 to 24% during this time in the 12-town area.[490]

In the mid-Atlantic United States, in New York and New Jersey, the geographic distribution of the *I. scapularis* tick vector has expanded annually outside of the original Long Island focus, and there has been a corresponding increase in both the number of counties reporting Lyme disease and the number of cases reported per county.[465, 494–497]

In Wisconsin, the Lyme-endemic area has expanded southward from the original northwestern region,[271, 416] and the seropositivity rate is 6 to 11%,[471, 473] which is similar to the 7% seropositive rate in Minnesota. In southern and southwestern United States, where the reported incidence of Lyme disease is low, seroprevalence studies have been less frequent; the rate of seropositivity was 23 to 26% in Texas,[382] and 0% in a nonendemic area of Arizona.[473] In western United States, the deer population is more stable than in eastern United States and in Europe, and apparent increases in Lyme disease may be related more to reporting than to actual increased incidence.[394]

Studies of the seroprevalence of antibody to *B. burgdorferi*, *Babesia microti*, *E. chaffeensis*, and the agent of HGE have been done in various geographic areas. In Wisconsin, the frequency of co-infection in patients with Lyme disease was 5.2% for HGE, 2.1% for *B. microti*, and 2.1% for both; the frequency of co-infection in patients with HGE was 5.3% for *B. burgdorferi*, 5.3% for *B. microti*, and 5.3% for both.[486] In Minnesota, one third of HGE patients had seropositivity to *B. burgdorferi*.[498] In Westchester County, New York, 22% of HGE patient sera were also seropositive for *B. burgdorferi*.[488] Twenty percent of patients from Minnesota, New York, New Jersey, and Connecticut with early Lyme disease had serologic evidence of previous or current HGE.[498] In Rhode Island and Connecticut, 11% of patients with Lyme disease were co-infected with *B. microti*, 72% of patients with babesiosis were co-infected with *B. burgdorferi*, and seroprevalence was 7% for *B. burgdorferi* compared with 5% for *B. microti*.[481] In Connecticut in 1994, the rates of co-infection with other tickborne infections in patients with serologically confirmed Lyme disease were 10% for HME, 7.5% for HGE, 7.5% for babesiosis, and 5% for more than two infections.[487] In eastern Long Island, 66% of Lyme disease sera were also positive for *B. microti* antibody, and 54% of babesiosis sera were positive for *B. burgdorferi* antibody.[485]

The earliest reported major inland focus of *I. scapularis* was on Long Point Peninsula, which extends into Lake Erie from the southern coast of Ontario.[394] Lyme disease is notifiable in 8 of 12 provinces in Canada, and its incidence has gradually increased from 30 cases reported to the Canadian Laboratory Centre for Disease Control between 1977 and 1989, predominantly from southern parts of the provinces Ontario and Manitoba (with single cases reported from the provinces of Alberta, British Columbia, and Quebec), to 333 cases (half acquired within Canada) between 1987 and 1997,[479] predominantly from the endemic areas in southern British Columbia, Vancouver Island, the Gulf Islands, Ontario along coastal Lake Erie, and other provinces such as Manitoba, Quebec, and New Brunswick, which are near Lyme-endemic areas of the United States. The presence of *B. burgdorferi* has been confirmed in ticks in the endemic provinces[376, 446] and Alberta,[479] but because of the existence of established vector tick populations in other parts of Canada, spread to these areas may occur if *B. burgdorferi* is introduced into these tick populations by dog and human travelers, or by migratory birds.[445]

Several studies have been done[442, 443, 491, 499] to try to develop predictors of geographic risk by using satellite photographs of vegetation, as well as data on *I. scapularis* population density and infection rate (acarologic index), deer population density, mouse reservoir population density, *B. burgdorferi* seroprevalence in resident dog populations, and human Lyme disease incidence; correlations have been found with vegetation, wetness, residence in less developed areas outside of towns, deer density, tick density, tick infection rates, mouse population density, dog seroprevalence rates, and even with the abundance of acorns. The abundance of acorns as a food source for white-footed mice determines their survival through the winter and resulting mouse population density; abundant acorns also attract deer, resulting in increased *I. scapularis* population density brought by the deer; the combination of increases in mouse, deer, and tick population densities is expected to increase the risk of Lyme disease acquisition about 2 years after a bumper crop of acorns.[500]

GEOGRAPHIC DISTRIBUTION OF LYME BORRELIOSIS IN EUROPE, ASIA, AND OTHER CONTINENTS

The true worldwide country-by-country incidence of Lyme borreliosis is impossible to determine because

only a few countries other than the United States have mandatory reporting of Lyme borreliosis, and because clinical and serologic criteria for definition and reporting of the disease vary in different countries.[11, 12, 501] Efforts are being made by the EUCALB to improve reporting and to standardize European case definitions.[8, 10, 502]

Lyme borreliosis has been reported from six continents—North and South America, Europe, Asia, northern Africa, and Australia—but the majority of cases have originated in North America, Central Europe, and Asia (see Fig. 11–1; Table 11–5).[4, 8–13, 504] The existence of indigenous Lyme borreliosis in South America[452, 453, 505, 506] and Australia is still uncertain.[391, 392]

In Europe, as of 1998, *B. burgdorferi sensu lato* had been isolated from either arthropod vectors, animal hosts, or human patients in the following European countries (Table 11–6): Austria, Belarus, Belgium, Croatia, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Great Britain, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Moldavia, the Netherlands, Norway, Poland, Portugal, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the Ukraine.[10, 54, 405] A large study by the EUCALB of over 2000 patients with Lyme borreliosis in 15 European countries during 12 months in 1994 found that the incidence of Lyme borreliosis per 100,000 population increased from western to eastern Europe, with higher incidences east of the Netherlands, France, and Italy.[10]

The number of European cases of Lyme borreliosis (LB) through 1998, since reporting has improved, has been estimated to be over 60,000 annually, based on *B. burgdorferi*–seropositive cases reported voluntarily to the World Health Organization (WHO) by Public Health Administrations of WHO European Region countries, and to the EUCALB by member countries, as well as cases reported in the medical literature through 1998.[9] Most of these cases were from central Europe (see Table 11–5).

In Asia, cases have been reported from China and Japan, as well as from eastern parts of Russia. In 1981, one case of EM was reported from Japan following an *Ixodes persulcatus* bite in the mountainous district of the Nagano Prefecture, across the Sea of Japan from Vladivostock, and as of 1998, 100 cases of Lyme disease had been reported, mainly from Hokkaido and Nagano Prefectures.[164, 374, 439] *I. persulcatus* is considered the major

TABLE 11–5
Incidence of Lyme Borreliosis (LB) in Europe, by Country[a]

RELATIVE RISK[b]	COUNTRY	LB/100,000 POPULATION PER YEAR	LB/YEAR	REGION
High	Austria	150	14,000	
	Slovenia	120	2000	Central
	Poland	120		
	Sweden	69	>2000	South, Southeast
	Bulgaria	50–55	3500	
Medium	Denmark[c]	50		
	Hungary	50	1000	
	Netherlands	43	6500	North, East, Coast
	Czech Republic	40	6300	
	Finland	40	2000	Southeast, Southwest, Aland Islands
	France	40	7200	Northwest, East
	Switzerland	30	2000	
	Germany	25	20,000	
	Italy	17		North, North Central
Low	Belgium	<5	50–100	East
	Yugoslavia (former)		400	
	Croatia		200	Northwest
	U.K.		200	South, Southwest England, Scottish Highlands
	Lithuania		350	
	U.S.S.R. (former)		6000–11,000	Kaliningrad, Leningrad, Kirov, Perm, Kurgan, Omsk, Tomsk, Khabarovsk, and Northwestern areas
Very low	Norway		<50	
	Ireland		<50	
	Spain		<50	North, Northeast
	Luxembourg		<100	
	Greece		~0	
	Romania		<100	

[a]Estimated or reported LB cases.
[b]LB/100,000 population/year: High: >50; Medium: 5–50; Low: <5; Very low: Only a few cases reported.
[c]As only neuroborreliosis is reported in Denmark, this is an underestimate of total LB cases in Denmark.
Data obtained from 9–12, 90, 162, 251, 268, 352, 370, 371, 402, 404, 405, 409, 432–434, 448, 501, 503, 504, 507, 511, 515, 517, 519, 525, 532, 534, 535, 539, 544–548, 550, 552, 621, and 881.

TABLE 11–6
Borrelia burgdorferi (Bb) Tick Infection Rates, by Country and Tick Species

COUNTRY	REGION	TICK SPECIES	% OF TICKS POSITIVE FOR *Bb*[a]
U.S.	Northeast and Mid-Atlantic	*I. scapularis*[b, c]	24–61
	Northeast	*I. dentatus*	32
	Mid-Atlantic	*A. americanum*	6–22
	Mid-Atlantic	*I. cookei*	22
	Upper Midwest	*I. scapularis*	38–40
	South and Southeast	*A. americanum*	4
	South	*I. scapularis*	0–3
	West	*I. neotomae*	15
	West	*I. spinipalpis*	50–66
	West and Pacific Northwest	*I. pacificus*	1–14
Austria		*I. ricinus*	4–40
Belgium		*I. ricinus*	10–50
Bulgaria		*I. ricinus*	17
Bulgaria		*D. marginatus*	4
China	North Inner Mongolia, Heilongjiang, Jilin, Liaoning, Hebei, Xinjiang	*I. persulcatus*	20–40
Croatia		*I. ricinus*	45
Czech Republic	South Moravia	*I. ricinus*	15–23
Finland	Coastal islands	*I. ricinus*	40
France		*I. ricinus*	7
Germany		*I. ricinus*	19–44
Germany		*I. hexagonus*	12
Ireland	National parks (greatest in South)	*I. ricinus*	4–27
Japan	North to Central (Hokkaido, Nagano)	*I. persulcatus*	7–22
Japan	North (Hokkaido)	*I. ovatus*	10
Japan	Central to South (Nagano, Fukushima)	*I. ovatus*	26–27
Lithuania		*I. ricinus*	10
Netherlands		*I. ricinus*	2–27
Poland		*I. ricinus*	10–23
Russia		*I. ricinus*	4–27
Russia		*I. persulcatus*[d]	30
Slovenia		*I. ricinus*	>40
Spain	La Rioja	*I. ricinus*	11
Sweden	North	*I. ricinus*	3
Sweden	Northern Baltic Islands	*I. ricinus*	8–19
Sweden	South and Liso Peninsula	*I. ricinus*	23–30
Switzerland		*I. ricinus*	10–50
U.K.		*I. ricinus*	8
Yugoslavia (former)		*I. ricinus*	29
—	Eastern Europe	*I. ricinus*	0–50
—	Eastern Europe	*I. persulcatus*	21–58
—	Subarctic islands	*I. ricinus*	5
—	Subarctic islands	*I. uriae*[e]	2–6

[a] *Bb* positivity determined by microscopy, polymerase chain reaction, immunofluorescence, or other assay. Tick infection rates of adult ticks are generally higher than those of nymphal ticks,[181] with the exception of *I. pacificus*.
[b] *I. scapularis* from Lyme-endemic areas contains a median of 1900 *Bb* per tick.[412]
[c] *I. scapularis* from some Lyme-endemic areas may also contain *Babesia microti* and/or the agent of human granulocytic ehrlichiosis, in addition to *Bb*.[395, 396, 497]
[d] Co-infection of ticks with *Bb* and tick-borne encephalitis virus may occur.[405]
[e] 98% of museum specimens of British *I. uriae* were positive for *Bb*.[340]
Data from references 1, 123, 154–157, 161, 162, 170, 180, 181, 336, 344, 350, 351, 356, 362, 371, 378, 387, 394, 395, 403, 405, 409, 410, 412, 416, 420, 422, 424, 438, 449, 497, 503, 508, 513–515, 517, 522, 528, 535, 540, 549, and 579.

vector and *I. ovatus* another potential vector,[164, 351, 357, 374] although human Lyme disease has not been associated with *B. burgdorferi* strains from *I. ovatus*.[163, 374]

Lyme disease was first recognized in China in 1985, and in 1990, 132 cases of EM were reported from Hailin County in the Heilongjiang Province of northeastern China,[12, 344] adjacent to the Vladivostock focus of Lyme borreliosis in southeastern Russia.[448] Since then, it has become the most common tickborne disease in China, and hundreds of additional cases have been recognized. It has been reported from ten provinces and two autonomous areas, predominantly from the northeastern and northwestern regions, including the Heilonjiang, Jilin, Liaoning, Hebei, Inner Mongolia, Xinjiang, and Mudanjiang provinces[344, 349, 350, 449, 554] and the Beijing area.[388] *I. persulcatus* is the vector in most of these areas, but

Haemaphysalis longicornis has also been identified as a vector in the Beijing area.[388]

In 1998, the first case of Lyme disease, serologically confirmed but not culture-confirmed, was reported from Taiwan; although several strains of *Borrelia* have been isolated from indigenous rodents, and *I. ovatus* and *I. granulatus* occur locally, the vector has not been identified.[451] *B. burgdorferi* has been isolated from *Ixodes* ticks and rodents in Korea; Korea would therefore be considered an endemic area.[555]

In Central and South America, rare cases, not culture-confirmed, have been reported from Mexico,[556] Chile,[557] Brazil,[558] Argentina,[559] Puerto Rico, and Honduras.[560] In Chile, a case of confirmed Lyme neuroborreliosis was not considered autochthonous, and was attributed to imported German hamsters.[454] There are no ixodid ticks in Chile, and a large study of Chilean patients with suspected Lyme disease could not confirm any cases by either culture or Western blot; ELISA seropositivity in 5 patients was attributed to cross-reactivity, possibly with non-Lyme *Borreliae*.[505] Thirty-three clinical Lyme disease cases, most with serologic confirmation (including Western blot confirmation), have been reported from Rio de Janeiro and the nearby Cotia/Itapevi region of Brazil,[452, 506, 558] where several species of ixodid ticks occur; seroprevalence in blood donors was 3% in a low-risk area and 6.7% in the Cotia area; *Borreliae* were isolated by culture from human, tick, and wild animal sources in the Cotia region, but PCR could not confirm identity with either *B. burgdorferi sensu stricto*, *B. garinii*, or *B. afzelii*. Three patients with serologically confirmed suspected Lyme disease were reported from Mato Grosso do Sul, Brazil.[506] In Argentina, one clinical case has been reported,[559] and no culture-confirmed cases have been reported; three farm workers with arthritis were found to be seropositive.[453] It is uncertain whether reports of Lyme disease from Haiti,[560] Jamaica,[560] Peru,[373] and India[561] were due to cross-reacting non-Lyme *Borrelia* species such as those that cause relapsing fever, or to Lyme borreliosis originally acquired in an endemic country outside the country of reporting.

In northern Africa, 21 cases of serologically confirmed Lyme disease, with arthritis, lymphocytic meningitis, facial palsy, or pericarditis, were reported from Tunisia in 1998.[455] In South Africa, rare cases of Lyme disease[456, 562] have been reported, four potential tick vectors occur, and at least one has been found to be competent for *B. burgdorferi*.[456] From the rest of Africa, only sporadic cases have been reported, without culture confirmation, and several serosurveys have been done; it is uncertain whether these represent locally or non–locally acquired Lyme borreliosis, infection with other *Borreliae* producing Lyme-like illness, or cross-reacting infection with other prevalent bacteria. In southeastern Africa, a serosurvey in Zimbabwe found ELISA seropositivity rates of 1.6 to 5% in blood donors and healthy villagers, and 0% in dogs, cattle, and horses, and concluded that Lyme borreliosis was absent there[458]; a case of serologically confirmed probable Lyme disease with EM at a tick bite site from an autochthonous tick bite in Mozambique was reported in 1993,[563] but a serosurvey in Mozambique, reported in 1997, attributed 11% ELISA positivity in febrile patients to serologic cross-reactivity with leptospira, *Borrelia crocidurae*, and syphilis[564]; a serosurvey in Tanzania found very high ELISA seropositivity rates in blood donors, pregnant women, and arthritis and syphilis patients (30 to 55%) and noted that Lyme-like illness and tick bites occur, but that the seropositivity probably represents cross-reactions with leptospira, relapsing fever, and syphilis, which are prevelent.[565] A serosurvey of rural residents in Mali found no seropositivity by ELISA, but a survey of patients with neurologic disease identified six patients who were seropositive by both ELISA and Western blot; no ixodes ticks occur in Mali, and the authors conclude that *B. burgdorferi* does not exist in Mali, but that other cross-reacting *Borreliae*, such as *B. crocidurae*, transmitted by the soft tick *Alectorobius sonraai*, which causes tickborne meningoencephalitis in nearby Senegal, might cause a Lyme-like illness.[457]

From the Middle East, two serologically confirmed (IFA, ELISA, and/or Western blot), but not culture-confirmed, cases have been reported from Israel,[566, 567] but none has occurred in the absence of previous travel to known endemic areas. *B. burgdorferi* IFA and Western blot seropositivity of uncertain etiology have been reported from Fayoum, Egypt, and four ELISA serologically confirmed, but not culture-confirmed, cases have been reported from Alexandria, Egypt[568]; no information about travel to endemic areas was given. *I. ricinus* ticks have been found on migratory birds resting in Egypt during their fall migration from Europe and Asia to Africa.[376]

In southeastern Australia, between 1982 and 1986, nine cases of erythema migrans–like rashes were reported from the Hunter Valley and the New South Wales coast near Sydney; this area was initially considered a possible newly recognized endemic area.[391] In 1994, a case of ACA was reported in an Australian resident who had immigrated from Europe 25 years earlier, but it could not be considered an autochthonous case.[569] In 1998, the first case of an Australian patient with *B. garinii* culture–positive Lyme borreliosis (erythema migrans–like rash) associated with a locally acquired tick bite (from the New South Wales coastal area near Sydney) was reported[303]; however, because this patient had traveled to European endemic areas 17 months earlier, it could not be definitely proven that the case was acquired in Australia. Proof of Lyme endemicity will require additional culture-confirmed, locally acquired cases without previous travel to endemic areas.[391–392]

In the northern hemisphere, the Lyme borreliosis endemic and hyperendemic areas of Europe and Asia cluster in a definite band, which could be called the "Lyme Belt" (see Fig. 11–1); it is located approximately between 30 degrees North latitude and the Arctic Circle at 65 degrees North latitude (65° N). This region includes the majority of cases from Central Europe, Scandinavia, the former USSR, China, Japan, and northern Africa (Tunisia and Alexandria, Egypt). Israel is also located within this belt. In the western part of the northern hemisphere, the "Lyme Belt" extends from approximately 15° N to 50° N and includes the endemic areas of the United States and southern Canada, as well

as the cases from Mexico and the Caribbean. In the southern hemisphere, the cluster of Lyme or Lyme-like cases from southeastern Australia and Rio de Janeiro, Brazil, the cases from South Africa and Mozambique, and the *B. burgdorferi* seropositivity noted near Buenos Aires, Argentina, are all between 10 degrees South latitude (10° S) and approximately 40° S, but insufficient cases have been reported from the southern hemisphere to determine whether there is a similar southern hemisphere "Lyme belt." The presence of the migratory bird *B. burgdorferi* tick vector, *I. uriae*, has been demonstrated in the Falkland Islands at 51° S; the presence of this vector and *B. burgdorferi* has been demonstrated in Crozet Island at 46° S and in Campbell Island, New Zealand, between 45° S and 55° S in the southern hemisphere, placing the southern margin of the range of *B. burgdorferi* at least to the subantarctic region,[165] although no human Lyme disease cases have been reported from these islands.

EXPANSION OF LYME-ENDEMIC AREAS IN EUROPE, ASIA, AND OTHER CONTINENTS

In Europe, the geographic distribution of Lyme borreliosis correlates with the distribution of *I. ricinus*[9, 125] and the distribution of the deer population, and the number of deer has increased dramatically, as in North America.[144] Deer were initially abundant in Central Europe, but in the 1940s during and after World War II, deer were used for food and forests for fuel, resulting in almost complete destruction of the deer population and partial deforestation of the region. In the 1960s, regrowth of forests and return of deer began, and there has since been a deer population explosion, which has coincided with the increase in Lyme borreliosis in Central Europe. *B. burgdorferi* has been found in museum specimens of European ticks from the late nineteenth century.[340]

Several seroepidemiologic studies have reported the rates of *B. burgdorferi* seropositivity in the general population in Europe and Asia (Table 11–7).

The existence of Lyme borreliosis in South America is uncertain, although its presence has been suspected. A 2% seropositivity rate was reported in agricultural workers in Peru, but this may be due to cross-reacting relapsing fever *Borrelia* organisms[373]; seropositive farmers with arthritis have been reported from Argentina,[453] and 7% seropositivity was reported in residents of Cotia, Brazil, which is suspected to be an endemic area.[452]

Lyme disease has been reported from northern Africa, where *I. ricinus* is prevalent, including Tunisia[455] and Egypt,[568] but its presence in the rest of Africa is uncertain, although suspected. An 11% seropositivity rate found in patients with nonspecific febrile illness in Mozambique, Africa, was considered due to cross-reactions with leptospirosis, non-Lyme borrelial relapsing fever, and syphilis.[564] However, one serologically confirmed case of Lyme disease with EM acquired from a Mozambique tick has been reported,[563] and its presence is suspected in South Africa.[456]

TABLE 11–7
Borrelia burgdorferi (Bb) Seropositivity Rates in Europe and Asia, by Country

COUNTRY	% OF PERSONS SEROPOSITIVE	
	General Population	High-Risk Population[a]
Austria	4–8	
Bulgaria		15–35 (forest workers, animal farmers)
China	1–12	26–53 (forest workers and rural northeastern residents)
Croatia	7	
Finland	3–6	12 (military recruits in Southwestern archipelago)
France		18–26 (forest workers)
Germany	5	18–34 (forest workers)
Greece	1	
Hungary	2–5	
Italy	0–13	8–18 (forest workers)
Ireland	5–15	
Japan	1	6–20 (forest workers)
Lithuania	4	14–32 (forest/field workers, veterinarians)
Netherlands	2–17	15 (hunters, military recruits)
Poland	19–24	50–71 (outdoor workers)
Russia	9	
Spain	3–13	31 (forest workers, farmers, cattle raisers)
Sweden	2–9	26–30 (Liso peninsula/Aspo Island residents)
Switzerland	4–6	19–60 (orienteers, sportsmen, forest workers, rural residents)
U.K./England	0–4	14–55 (forest workers, farmers, game keepers)
U.K./Scotland		16–27 (nature conservancy workers, Highlands residents)
Yugoslavia (former)	5	

[a]Persons with high frequencies of occupational, recreational, or residential exposure to tick-infested *Bb*-endemic geographic areas within these countries. Seropositivity rates increased with age and length of exposure in several longitudinal studies.

Data from references 162, 305, 344, 349, 388, 405, 406, 409, 437, 438, 450, 504, 508–510, 512, 514, 516, 517, 521–524, 526, 527, 529, 532, 533, 538, 539, 541–543, 548, 549, 551, 553, 554, 570, 571, and 573.

Lyme Borreliosis in Travelers to Endemic Areas

There are increasing reports of Lyme borreliosis in individuals who have acquired the infection during travel, often international, to Lyme-endemic areas in the recent or remote past.[9, 75, 454, 482, 569, 574–576] This may explain some of the cases that have been reported from areas such as Australia, which lack either the necessary tick vectors or *B. burgdorferi*.[303, 392, 566, 567] In Canada, where the incidence of Lyme disease is relatively low, half of all cases reported to the Laboratory Centre for Disease Control were acquired outside of Canada.[429] Pets that travel from endemic to nonendemic areas could be potential vehicles of transfer of infected ticks to their owners.[454]

Presentation with Lyme borreliosis in a nonendemic region may increase the risk of delayed diagnosis because the clinical presentations, although easily recognized by physicians in the endemic area, may be unrecognized by physicians in the nonendemic area who have little experience with the infection, or with its possibly different clinical manifestations in the area of acquisition.[482]

Travelers from nonendemic areas who engage in outdoor activities such as hiking, mountaineering, orienteering, or camping in endemic areas are at increased risk as they may be unaware of the local risk of tickborne infections, including the higher risk in hyperendemic areas, and may be less likely to use appropriate precautions, to recognize a tick bite, or to recognize early symptoms of infection. Vacationers, even when residing in endemic areas and knowledgeable about Lyme disease, are less likely to engage in tick-avoidance behaviors while on vacation.[577]

Borrelia burgdorferi Tick Infection Rates

In the United States, rates of *B. burgdorferi* infection of *I. scapularis* and *I. pacificus* in North America, and of *I. ricinus* and *I. persulcatus* in Europe and Asia, vary with geographic region, elevation, season, and stage of the tick, and are highest in the hyperendemic areas during early summer.[181, 411] *I. ricinus* infection rates were noted to increase significantly from Western to Eastern Europe.[181]

The distribution of the different genospecies of *B. burgdorferi sensu lato* in *I. ricinus* complex ticks varies with the global geographic location, and is more fully characterized in the northern hemisphere than the southern hemisphere. In Central Europe, the diversity is greatest, with four genospecies—*B. burgdorferi sensu stricto*, *B. garinii*, *B. afzelii*, and *B. valaisiana*—found in ticks.[53, 74] At the far western margin, in North America, only *B. burgdorferi sensu stricto* is indigenous.[53] At the far eastern margin of the range of its geographic distribution, in far eastern Russia and Japan, *B. burgdorferi sensu stricto* is absent but *B. garinii*, *B. afzelii*, and *B. japonica* are found[67, 69, 74, 163, 164]; in Japan, *B. tanukii* and *B. turdae* are also found.[58, 68] At the far northern, subarctic edge of the range in the northern hemisphere, only *B. garinii* has been found.[13, 152, 165] Co-infection of ticks with more than one genospecies has been reported from areas in which several genospecies occur.[74, 84, 160]

Borrelia burgdorferi Reservoir Animal Infection Rates

North American epidemiologic studies indicate that the white-footed mouse, *Peromyscus leucopus*, is reservoir-competent for *B. burgdorferi*[580] and is in fact the most important reservoir for *B. burgdorferi* infection in nature,[167, 182] and that the white-tailed deer *Odocoileus virginianus* is the reproductive host of the *I. scapularis* tick vector and is necessary for the maintenance of the tick, but not the spirochete, in nature.[411]

In the northeastern part of the United States, the enzootic cycle that maintains *B. burgdorferi* infection in nature is the white-footed mouse–*I. scapularis* cycle. The mice are reservoir-competent for *B. burgdorferi*[336, 378, 578, 580] because they have a high rate of infection, remain spirochetemic and highly infectious for all stages of *I. scapularis* ticks throughout the tick feeding season, do not develop immunity to the tick vector and therefore do not reject the tick, and serve as the reservoir of *B. burgdorferi* that infects the next cycle of ticks and results in high tick infection rates.

The white-footed mouse is the most important reservoir for *B. burgdorferi* infection in nature, and it maintains the horizontal transmission of infection from nymphal to larval ticks. Because ticks are already infected with *B. burgdorferi* before deer attachment, the white-tailed deer does not appear to be important for transmission and maintenance of *B. burgdorferi* infection in nature, although they are important for maintenance and geographic dissemination of the tick.[167]

B. burgdorferi has been isolated from the blood of asymptomatic, wild, white-footed mice and white-tailed deer from the Lyme-endemic coastal islands of northeastern United States.[413, 578] The geographic distribution of infected mice has been noted to correlate with the areas of Lyme endemicity.[384] Mice were found to be chronically spirochetemic in nature during the spring, summer, and fall,[578] and were spirochetemic and infectious for ticks for more than 200 days after experimental infection with *B. burgdorferi*.[580] Deer were heavily infested by adult but not immature *I. scapularis* during the winter, suggesting that deer were important wintertime hosts for adult *I. scapularis*.[578] Although the deer were spirochetemic during summer, fall, and winter, and may be reservoirs for *B. burgdorferi*,[578] they are not major reservoirs for maintenance of *B. burgdorferi* in nature because they host mainly adult ticks that have a very low rate of transovarial transmission of the spirochete.[154, 167, 354]

In northwestern United States, the *I. pacificus* tick transmits Lyme borreliosis to humans, but the enzootic transmission cycle is different from that in northeastern United States.[378, 420] Because the preferred host of immature *Ixodes pacificus* is the fence lizard, which is not a competent reservoir for *B. burgdorferi*, the infection rate of *I. pacificus* is low (1 to 2%) and the *I. pacificus*–*Peromyscus* mouse cycle is unable to maintain transmission of the *B. burgdorferi* infection in nature; this is

accomplished instead by *Ixodes neotomae*, a non–*ricinus* complex tick that has a 15% infection rate, and the dusky-footed woodrat, *Neotoma fuscipes*. *I. neotomae* and *I. pacificus* are both competent vectors for *B. burgdorferi*, but *I. neotomae* rarely bites humans and is needed only for maintenance of *B. burgdorferi* infection in the woodrat reservoir, which remains spirochetemic and is able to infect feeding ticks. *I. pacificus* nymphs and adult ticks are commonly associated with human tick bites, and they are needed to transfer infection from the woodrat to humans. These two ticks and the woodrat have the same geographic distribution, which extends from Oregon to Southern California and into the Sierra Nevada foothills, from sea level to 2100 meters elevation, where Lyme disease is endemic. The infection rate in woodrats in California was 44% and in *I. neotomae* was 15%.[378]

In some geographic areas of North America, other mammalian reservoir-tick cycles in addition to or instead of the mouse–*I. scapularis* cycle may contribute to maintenance of *B. burgdorferi* infection in nature, such as the cottontail rabbit–*I. dentatus* cycle in Nantucket[170] and New York,[100] the Norway rat–*I. scapularis* cycle on Monhegan Island, Maine (where no mice occur),[415] the *Peromyscus maniculatus*–*I. scapularis* cycle on Isle au Haut, Maine (where no *P. leucopus* occur),[414] the chipmunk–*I. scapularis* cycle in Wisconsin and Illinois,[416, 417] the squirrel–*I. scapularis* cycle in Connecticut and Wisconsin,[416] the woodrat–*I. neotomae* cycle in California,[378] the Mexican woodrat–*I. spinipalpis* cycle in Colorado,[362] the meadow vole–*I. scapularis* cycle in the Northeast,[168] and the cotton mouse–*Peromyscus gossypinus* cycle on Sapelo Island, Georgia.[361] The *B. burgdorferi* infection rate in some of these reservoir hosts may be as high as 90 to 100%, depending on the host species and geographic location. Seroepidemiologic studies found the rates of *B. burgdorferi* seropositivity in wild and domestic host animals in various geographic areas of the United States to be 10 to 100% in the northeastern states,[154, 169, 578] 5 to 60% in Wisconsin,[169, 416] 11% in North Carolina,[169] and 14 to 99% in Texas.[169, 382]

In Europe, in addition to the woodmouse–and yellow-necked mouse–*I. ricinus* cycle, which is considered to maintain *B. burgdorferi* infection in nature, other cycles such as the edible dormouse *Glis glis*–*I. ricinus* cycle in Germany,[581] the hedgehog–*I. hexagonus* cycle in Germany,[336] and the mouse–*I. trianguliceps* cycle in Central Europe[168] may be important. In a highly Lyme-endemic area of Germany, the edible dormouse is the preferred host of *I. ricinus*, even though the woodmouse and yellow-necked mouse are abundant, and it is considered more important in amplification of the human Lyme disease risk because these mice have a peridomestic rather than sylvan habitat.[581]

In Japan, the *I. persulcatus*–rodent (woodmouse and vole) and *I. persulcatus*–migratory bird enzootic cycles are responsible for maintenance of the *B. burgdorferi* infection in nature; *B. burgdorferi* has been isolated from woodmice[163] and voles,[68, 163] and from larval ticks that fed on migratory birds of the genera *Emberiza* and *Turdus*.[163]

B. burgdorferi infection has been demonstrated in 24 different species of mammals and birds.[167] It has even been found in migratory European seabirds, which may play a role both in transhemispheric transfer of infection and in maintenance of *B. garinii* in enzootic cycles of remote high-latitude northern and southern hemisphere islands and peninsulas.[165]

Serosurveys for the presence of *B. burgdorferi* antibody in sentinel animals such as white-tailed deer,[154, 578, 582] which usually have a travel range of less than 10 kilometers, and cattle[583] are useful in the definition of geographic areas of *I. scapularis* occurrence and *B. burgdorferi* endemicity.

PATHOLOGY AND PATHOGENESIS

Immunopathogenesis

Tissue damage or dysfunction is the result of either direct tissue invasion by *B. burgdorferi* or the immunopathologic immune response to the infection.[148, 149, 151, 204–207] Infection elicits a sequence of immunologic, B and T lymphocyte, and other cellular responses in activated antigen-presenting cells, and in various host tissues and organs, as is discussed in the section on Interactions with the Immune System, earlier in this chapter. These responses are the reaction to either live *B. burgdorferi*, degenerated dead organisms, degraded antigens, or even membrane-bound blebs (containing *B. burgdorferi* antigens on their surfaces and DNA fragments inside),[102, 103, 215] and they result in characteristic histopathologic findings.

Adhesion of *B. burgdorferi* to different host tissues and cells may be involved in tropism for various tissues and organs, and in the pathogenesis of the manifestations of Lyme disease in various organs.[150, 204, 297, 298, 585–587] Several different strains of all three genospecies, *B. burgdorferi sensu stricto*, *B. garinii*, and *B. afzelii*, bind to at least one of three mammalian cell integrins, $\alpha_{IIb}\beta_3$ (the fibrinogen receptor located on platelets), $\alpha_V\beta_3$ (the vitronectin receptor located on platelets, osteoclasts, smooth muscle, endothelial cells, and some lymphocytes), and $\alpha_5\beta_1$ (the fibronectin receptor located on epithelial cells, endothelial cells, fibroblasts, lymphocytes, and platelets); each strain has a distinct integrin recognition pattern.[585]

B. burgdorferi, Osp A, and even *B. burgdorferi* membrane blebs induce T lymphocyte proliferation in immune individuals,[208, 209, 211–213] and some groups have reported a nonspecific T lymphocyte proliferative effect, even in nonimmune individuals.[217] T lymphocyte populations in peripheral blood, synovial fluid, and CSF of patients with Lyme borreliosis are mainly of the type 1 helper (Th1) subset.[205, 214, 393] The responding T lymphocytes form inflammatory infiltrations in the synovium,[323, 370, 372, 393] central nervous system,[295, 592] and other tissues.

B. burgdorferi, Osp A, and membrane blebs also induce polyclonal B lymphocyte stimulation in immune and even in nonimmune individuals.[215, 216] The responding B lymphocytes differentiate into plasma cells and produce perivascular lymphoplasmacytic infiltrations and hypercellular vascular occlusive damage, resembling syphilitic endarteritis obliterans, in many involved tissues but primarily in the skin and soft tissues, heart, synovium, reticuloendothelial system, and peripheral nervous sys-

tem. *B. burgdorferi* also induces macrophage production of cytokines (IL-6 and TNF-α)[216] and nitric oxide,[216, 296] as well as peripheral blood mononuclear cell production of IL-10.[217] The histopathology of Lyme borreliosis includes inflammatory infiltrates consisting of neutrophils, lymphocytes, plasma cells, and macrophages.

Changes in the expression of *B. burgdorferi* outer surface proteins (such as the downregulation of Osp A and B expression and the upregulation of Osp C, E, and F) and in Erp protein expression that occur either during tick feeding, with transmission of the spirochete to the bite site, or after entry of the spirochete into the mammalian host are important in the pathogenesis of the infection.[119, 121, 127, 128, 138–142] *B. burgdorferi* does not produce proteolytic enzymes, but its outer surface protein A is able to bind host blood meal–derived plasmin, plasminogen, and urokinase-type plasminogen activator, creating a host-derived bioactive surface protease, which is involved in dissemination of *B. burgdorferi* from the tick midgut to the tick salivary glands for transmission, and which is necessary for spirochetemia in mice after tick-transmitted infection.[146] It also presumably digests extracellular matrix and facilitates spirochetal spread in the skin after inoculation by the tick. Because of these bound host-derived enzymes, the spirochete is invisible to, and able to evade, the host immune response, in a mechanism referred to as "stealth pathogenesis."[144–146] This may explain the paradox of the ability of *B. burgdorferi* to persist in skin or other tissues for long periods of time with only minimal mononuclear cell infiltration, despite eliciting a strong immune response that, in vitro, is capable of killing it.

B. burgdorferi is introduced into the deep dermis via the bite of an infected tick, which produces a "tick papule" at the bite site. The spirochete induces expression of adhesion molecules by endothelial cells, which facilitate the spirochete's ability to cross endothelial cell layers and extravasate into tissues; this also leads to recruitment of inflammatory cells to areas of spirochetal infection.[145] Within several days to a few weeks, the organism migrates centrifugally in the skin, produces a local skin lesion (EM), and also enters the skin vasculature and disseminates hematogenously[280, 591] throughout the body to the skin, where it may produce secondary EM lesions, and to the organs and reticuloendothelial system, where it may produce a generalized flulike illness with fever, headache, myalgias, arthralgias, conjunctivitis, pharyngitis, adenopathy, tender hepatosplenomegaly, pneumonitis, and orchitis.[145, 393, 592] Some of the nonspecific symptoms occuring during infection, such as myalgia, arthralgia, fatigue, malaise, and fever, may be due to spirochetal triggering of host cell cytokine release.[151] Four to nine weeks after the initial hematogenous dissemination, spirochetal invasion of heart, central nervous system (CNS), and presumably peripheral nervous system may occur, producing myocarditis, meningoencephalitis, cranial nerve paresis, stupor, and personality changes.[588, 592] Months to years after infection, late manifestations of *B. burgdorferi* infection may develop as a result of the initial dissemination of *B. burgdorferi* to various organs, especially the skin, eye, joints, and nervous system.[592]

The manifestations of acute Lyme borreliosis are related to direct spirochetal invasion of the involved tissues and the resulting local immunohistopathologic response, and they are generally responsive to antibiotic therapy. The manifestations of late disease, if not previously treated with adequate antibiotic therapy, may be related to a combination of persistence of infection and the host immunohistopathologic response; these may respond to antibiotic therapy if the presence of active ongoing infection is the essential trigger of the pathologic response. The manifestations of late chronic disease, if resistant to repeated courses of antibiotic therapy considered adequate by current standards, are considered related to previous damage or to ongoing autoimmune immunopathologic responses induced by the initial infection.

Immunopathologic mechanisms, based on autoimmunity and molecular mimicry, may be involved in the pathogenesis of Lyme peripheral neuropathy and chronic Lyme arthritis, even after elimination of active *B. burgdorferi* infection.[126, 151, 204, 256, 323, 587, 589] An epitope of flagellin that cross reacts with an epitope at the N-terminal end of human axonal HSP 60 may be involved in the immunopathogenesis of peripheral nerve damage.[113, 151, 265] An arthritogenic epitope of Osp A, which cross reacts and shares homology with an epitope of human leukocyte function–associated antigen-1 (LFA-1), is a candidate autoantigen for chronic treatment-resistant Lyme arthritis in patients with HLA-DR4 specificity.[126, 323, 593] The phenomenon of epitope spreading, in which T cells initially recognize a single immunodominant epitope, and then progressively recognize an increasing number of nearby epitopes, could play a role in the immunopathogenesis of Lyme arthritis, if an arthritogenic epitope is eventually recognized, which results in overcoming of self-tolerance.[323]

Small numbers of *B. burgdorferi* may be visualized in some infected tissue samples, particularly skin biopsy specimens. Organisms are most easily found in early infection, but persistence of live *B. burgdorferi* for several years after onset of infection has also been demonstrated.[19, 200, 284, 304, 306, 594] *B. burgdorferi* PCR has also demonstrated *B. burgdorferi* DNA in tissue samples and body fluids but does not confirm the presence of viable spirochetes, as PCR will detect even *B. burgdorferi* DNA fragments in cystic blebs arising from spirochetal outpouchings.[102, 103, 186]

The histopathology of the various manifestations of Lyme borreliosis has been extensively studied, but only sparse data are available on the histopathology of congenital Lyme borreliosis. This section includes a description of the pathology of Lyme borreliosis by organ system, followed by a discussion on the pathology of the placenta and the congenitally infected fetus or infant.

Lyme Borreliosis in Pregnant and Nonpregnant Women

CUTANEOUS

A "tick papule" develops at the tick bite site, which consists of an ulcerated papule of partially denuded hyperplastic epithelium above a lymphocytic, plasmacytic,

macrophage, and mast cell inflammatory infiltrate.[590] During an ixodid (hard) tick bite, the tick's salivary glands secrete a latex-like material that hardens to a tough tissue-like material and cements the mouthparts to the skin; the mouthparts have rows of "teeth" called *denticles*, which become embedded in the skin and the cement.[880] *B. burgdorferi* spirochetes have been detected in skin surrounding the bite site.

Erythema migrans (EM)[82, 148, 338, 592, 596, 597] occurs during early infection as either single (localized) or multiple (disseminated) skin lesions. The skin lesion contains upper and deep dermal perivascular and interstitial mononuclear cell infiltration. Spirochetes are found most often in the peripheral advancing edge of the EM lesion in areas with plasma cell infiltration, around and in small vessels, in collagen fibers, in the upper dermis, or at the dermal-epidermal junction.

Borrelial lymphocytoma (BL),[82, 592, 597] also known as lymphadenosis benigna cutis or B cell pseudolymphoma, occurs during early infection as either single (solitaria) or multiple (dispersa) skin lesions, usually on the earlobe or areola, and more often in Europe than the United States. The histopathology consists of hyperplastic and crowded, well-defined lymphoid follicles composed of dense, diffuse polyclonal lymphocytic (polyclonal B cells, helper T cells, or suppressor T cells), plasmacytic, macrophage, and occasionally eosinophilic infiltration in the dermis or subcutaneous tissue (sometimes with formation of germinal centers) that is similar in appearance to tonsillar tissue. Spirochetes are found in the subepidermal zone, in and around small blood vessels, and in collagen fibers in areas of inflammatory infiltration.

Acrodermatitis chronica atrophicans (ACA)[148, 592, 600–602] occurs during late chronic infection as either unilateral or symmetrical bilateral distal extremity skin lesions, more often in Europe than in the United States. The histopathology in the infiltrative phase shows epidermal loss of rete ridges, a subepidermal bandlike infiltrate, a dense patchy or interstitial mononuclear infiltration of the dermis and subcutaneous fat around and between blood vessels and skin appendages, a small fibrotic zone between the epidermis and the infiltrate, panniculitis, prominent dilated dermal blood vessels, endothelial proliferation, telangiectasia, and disappearance of elastin fibers; this progresses to eventual epidermal atrophy. Spirochetes can be found easily in these nodules and sparsely in ACA skin lesions.

RETICULOENDOTHELIAL

Splenitis,[590, 592, 604] hepatitis,[590, 605] and lymphadenitis[590, 592, 606] may occur during early infection.

Lymphadenopathy occurs in early infection, and lymph node histopathology ranges from perifollicular mononuclear cell (lymphocytic, plasmacytic, macrophage, and occasionally eosinophilic) infiltration and follicular hypertrophy, to focal necrotizing microabscesses with thrombosed capillaries; rare spirochetes may be seen.

Splenomegaly occurs in early infection, and splenic histopathology ranges from perifollicular lymphoplasmacytic infiltration with prominent germinal centers, to necrotizing splenitis with patchy subcapsular inflammation and suppuration, inflammation and acute central necrosis of splenic follicles, occasional destruction of blood vessels, and the presence of many spirochetes.

Hepatomegaly and hepatitis may occur in early infection and may be either transient or severe. Histopathology ranges from mild granulomatous hepatitis or lymphocytic portal triaditis to severe hepatocellular damage with ballooned hepatocytes, fat microvesicles, mononuclear (including plasmacytic) and granulocytic sinusoidal infiltration, Kupffer cell hyperplasia, marked hepatocyte mitotic activity, and sparse spirochetes in the hepatic sinusoids and parenchyma.

CARDIAC

Cardiac involvement[590, 592, 607] in early disseminated infection consists of tachycardia, varying degrees of heart block, or myocarditis. Histopathologic examination of endomyocardial biopsy (or autopsy) specimens shows perivascular and interstitial mononuclear cell (lymphocytic, plasmacytic, and macrophage) bandlike endocardial infiltration, myocardial infiltration, and occasionally pericardial infiltration, as well as vascular changes suggestive of early obliterative vasculopathy. Spirochetes may be seen in endocardium and myocardium near interstitial infiltrations and in intramyocardial vessels.[308]

NEUROLOGIC

The meningoencephalitis and meningoradiculoneuritis of early infection, which include meningitis, encephalopathy, psychoneurosis, cranial neuritis, radiculoneuritis, and the triad of cranial neuritis–meningitis–radiculoneuritis (Bannwarth's syndrome), have a common basic histopathology consisting of lymphoplasmacytic infiltration around epineural blood vessels,[82, 311, 590, 592, 609–611] which suggests vasculitis as a major pathophysiologic mechanism in neuroborreliosis. Rare spirochetes may be seen in brain tissue. Demonstration of spirochetes in CSF is very unusual.

The peripheral neuropathy of late chronic borreliosis[590, 592, 612] is more common in Europe than in the United States and is often associated with ACA. The histopathology of chronic peripheral neuropathy is similar to that of acute meningoradiculoneuritis but is more severe. Spirochetes have not been demonstrated in these biopsy specimens.

Acute focal encephalitis[267, 311, 610] with focal contrast-enhancing central nervous system lesions may develop during either early disseminated or late chronic infection. The histopathology of brain biopsy or autopsy specimens shows sharply demarcated areas of lymphocytic (and occasionally eosinophilic) perivascular cuffing, increased cellularity as a result of foamy macrophages and astrocytes, spongiform change with reactive astrocytes, and areas of necrosis and subcortical and periventricular loss of myelinated fibers, similar to an acute demyelinating process; only rare spirochetes are seen.

The pathogenesis of neuroborreliosis probably in-

volves a small number of spirochetes, adhering to oligodendroglia in neural tissue, which elicit an intense local inflammatory immune response that produces the actual tissue damage; molecular mimicry may also be involved, as *B. burgdorferi* and axonal proteins have cross-reactive epitopes.[113, 151, 265]

Vasculitis is one of the major mechanisms involved in the pathogenesis of central nervous system neuroborreliosis.[311]

MUSCULOSKELETAL

Myositis,[592, 614–616] especially of proximal muscles, may occur in early disseminated infection, and localized myositis may occur adjacent to areas of cutaneous, articular, or neuropathic involvement.

Arthritis[82, 177, 205, 590, 618, 620] may be a manifestation of either early or late chronic infection. Histopathology consists of hypertrophy and hyperplasia of synovial lining cells; deposition of fibrin and neutrophils on synovial surfaces and villous stroma; synovial villous hypertrophy; diffuse or perivascular subsynovial mononuclear cell infiltration; subsynovial vascular proliferation; endarteritis obliterans; and even synovial pannus formation and cartilage erosion. Rare spirochetes are found in areas of heavy perivascular and subsynovial inflammatory infiltration but not in synovial fluid. The small number of spirochetes present is similar to tertiary syphilis or tuberculoid leprosy, in which a small number of organisms elicit an intense immunologic response.

The synovial histopathology of Lyme arthritis and other chronic inflammatory arthritides, including rheumatoid arthritis, is similar, but endarteritis obliterans is seen only in Lyme arthritis and syphilis, and not in other non-Lyme arthritis synovial biopsy specimens. There has also been evidence of active vascular injury consistent with repeated microvascular injuries, probably occurring with each episode of arthritis.[620]

The histopathology of the chronic arthritis associated with ACA[600] shows degenerative arthritis, joint capsule atrophy, bony atrophy, and cortical thickening.

Lyme Borreliosis in the Fetus and Newborn Infant

Although there have been a relatively small number (only 66) of reported cases that could be considered congenital Lyme borreliosis,[25, 27, 29–38, 41–48, 621] there are several reports of the pathologic findings. There are 13 descriptions of pathologic or culture findings in gestational Lyme disease placentas or decidua,[33–36, 41, 690, 622, 623] 19 descriptions of fetal or neonatal pathologic findings in congenital Lyme borreliosis, 2 descriptions of skin biopsies in congenital Lyme borreliosis, and 2 descriptions of brain pathologic and culture findings in sudden infant death syndrome of suspected Lyme borrelial etiology. Spirochetes have been found by culture, silver stain, or *B. burgdorferi*–specific IFA in autopsied organs (liver, spleen, bone marrow, heart, brain, kidney) of congenitally infected fetuses and neonates by Schlesinger and associates,[25] MacDonald and colleagues,[33–35] Lavoie and co-workers,[32] and Weber and associates,[38, 39] as well as in the skin biopsy of a congenitally infected infant by Trevisan and colleagues.[43]

It is striking that many of the late stillbirths and perinatal deaths occurred in infants with cardiac abnormalities and generalized spirochetosis involving the kidneys, reticuloendothelial system, and central nervous system, after first-trimester gestational Lyme disease, and that most of the miscarriages studied pathologically occurred late, between 15 and 25 weeks. The lack of inflammatory findings even when spirochetes were present has been remarkable, and could be related to the immunopathogenetic features of *B. burgdorferi* infection, in which the spirochete is able to spread and persist in tissues without eliciting a prominent host immune response (discussion of this is in the sections Pathology and Pathogenesis: Immunopathogenesis, and The Organism: Interactions with the Immune System: Evasion of Host Defenses and Persistence in Tissue).

Although relatively few cases of congenital Lyme borreliosis have been studied pathologically, comparisons with congenital syphilis may be appropriate, particularly as congenital syphilis causes late abortion, stillbirth, and early perinatal death, and the histopathology shows perivascular and interstitial inflammation, including endarteritis obliterans, of the reticuloendothelial system, nervous system, skeletal system, and placenta.

The histopathologic findings of patients with congenital Lyme borreliosis listed in Table 11–8 in the section Clinical Manifestations are described by organ system in Table 11–9.

CUTANEOUS

There are no reports on the histopathology of the skin of fatal cases of early congenital Lyme disease, but skin biopsy of a patient with infantile multisystem inflammatory disease who was considered to have congenital Lyme disease showed vasculitis with stromal edema and marked eosinophilia (patient 40, see Table 11–8).[31] Biopsy of a skin lesion of a 9-year-old child with congenital Lyme borreliosis (patient 51, see Table 11–8), with a history of recurrent multiple EM lesions since 3 weeks of age, showed a normal epidermis; superficial and deep perivascular, periadnexal, and interstitial lymphocytic infiltrates with sparse plasma cells and some neutrophils; and numerous *Borreliae* by Warthin-Starry silver stain visible in the epidermis and dermis; *B. burgdorferi* PCR of the biopsy material was positive.[43]

RETICULOENDOTHELIAL

Spirochetes have been found in liver, spleen, or bone marrow of six fetuses or infants with congenital Lyme borreliosis in the absence of inflammation, necrosis, or granuloma formation. Spirochetes were seen by silver stain, *B. burgdorferi*–specific IFA stain, or culture in the livers of two term infants (patients 2 and 22, see Table 11–8) and in the spleen and bone marrow of one 35-week, slightly premature infant (patient 1, see Table 11–8) with severe fatal early congenital Lyme borreliosis after first-trimester gestational Lyme disease.[25, 33–35, 38, 39] The spirochetes were seen in the lumen of a large

Text continued on page 561

TABLE 11–8
Congenital Lyme Borreliosis: 66 Adverse Outcomes of Pregnancies Complicated by Lyme Borreliosis (LB)

	MATERNAL GESTATIONAL				FETAL/NEONATAL				
PATIENT NO.	Trimester of LB	Clinical History[b]	Antibiotic Therapy No. Days[c]	LB Serology[d]	Gestational Age (wk)	Weight (g)	Antibiotic Therapy No. Days[c]	LB Serology[d]	Tissue *Borrelia*[f]
1	1	EM,Fl,Ar	–	+	35	3000	–		+H,S,K,BM
2	1	EM,Ar	–	+	40	2500			+L,H,K,AB
3	≤2	Tx	–	–	19	514			+L,P
4	≤2	Tx,Ar	–	–	23	490			+L,K
5	≤2	O	–	–	15	85			+L,P
6	≤1	VB	NA[a]	NA	39	2250	NA		+F
7	NA	O	NA	NA	40	1950	NA		+F
8	≤2	VB	NA	–	17	30			+B
9	≤2	VB	NA	–	16	150			+B
10	≤1	O	NA	NA	12	294			+K
11	≤2	Ar	–	–	25	NA			+F
12	NA	O	–	NA	~40	3746	+ IV		+P
13	NA	Tx	–	NA	37	2157	+ IVPN, IVMT		+P
14	1	EM,Ar	+ PO PN 10 d	+	20	NA			–
15	1	BP,Ar	–	NA	36	2100	NA		
16	2	EM,Ar	+ PO ER 10 d PO PN 10 d	NA	NA	NA	NA		
17	2	EM	+ PO PN 10 d	NA	40	NA	NA	–	
18	3	EM,Me	–	NA	40	NA	+ IVPN 10 d		
19	1	LB	+	+	13	NA			–
20	1	LB	+	+	NA	NA	NA		
21	≤1	Ar	–	–	~40	NA	NA		+B,H
22	1	EM	+ PO PN 7 d	+	40	3400	NA		+L,B
23	1	EM,Fl	+ IV CTX 2 d, PO PN 12 d	+(+LPA[e])	40	3461	+ IVCTX 14 d	–(+LPA)[e]	
24	2	Fl	+ PO AM 10 d	–(–LPA[e])	34	1050	+ IVAM 6 d, IVCTX 7 d	+(+LPA)[e]	
25	1	EM,Pn,Ar	+ PO ER 10 d, IV CFX 5 d, PO CFC/CEP/ CFM 39 d	+(+LPA[e])	37	3490	+ IVAM 5 d, IVCFT/CTX 3 d	–(+LPA)[e]	
26	2	EM,Ar	+ PO ER 10 d, PO CFM 49 d	–(+LPA[e])	40	3461	+ IVCTX 28 d	–(+LPA)[e]	
27	1	EM,Ar	–	+	NA	NA	NA	–	
28	NA	NA	NA	+	NA	NA	NA	–	
29	NA	NA	NA	+	NA	NA	NA	–	
30	NA	NA	NA	+	NA	NA	NA	–	
31	NA	NA	NA	+	NA	NA	NA	–	
32	NA	NA	NA	+	NA	NA	NA	–	
33	NA	NA	NA	+	NA	NA	NA	–	

[a]NA, information not available.

[b]O = unremarkable; EM = erythema migrans; FI = flulike illness; Ar = arthralgia/arthritis; BP = Bell's palsy; Me = meningoencephalitis; Cr = cranial neuritis; Ra = radiculitis; HA = headache; LB = Lyme borreliosis, unspecified; Pn = pneumonia; Tx = toxemia; VB = vaginal bleed.

[c]PO = oral; IV = intravenous; PN = penicillin; ER = erythromycin; CTX = ceftriaxone; CFX = cefuroxime; CFC = cefaclor; CEP = cephalexin; CFM = cefixime; CFT = cefotaxime; CDX = cefadroxil; MT = metronidazole; AM = ampicillin; NA = not available (use of antibiotic therapy could not be definitively established for the individual patient, although in some reports, some patients in the group may have been treated).

[d]*Borrelia burgdorferi* antibody detected either by IFA (immunofluorescence assay), ELISA (enzyme-linked immunosorbent assay), or WB (Western immunoblot).

[e]LPA = in vitro lymphocyte proliferative assay for *B. burgdorferi*.

[f]*Borrelia* detected in tissue samples by IFA, silver stain, culture, or PCR (polymerase chain reaction); H = heart; S = spleen; K = kidney; BM = bone marrow; L = liver; A = adrenal; B = brain; Sk = skin; P = placenta; F = fetal tissue unspecified; D = decidua.

[g]CoA = coarctation aorta; EFE = endocardial fibroelastosis; AS = aortic stenosis; LSVC = left superior vena cava; PDA = patent ductus arteriosus; VSD = ventricular septal defect; ASD = atrial septal defect; RD = respiratory distress; IUGR = intrauterine growth retardation; GR = growth retardation; DD = developmental delay; GER = gastroesophageal reflux; TEF = tracheoesophageal fistula; BIH = bilateral inguinal hernia.

[h]21 of 23 (91.3%) of patients with LB in this subgroup received antibiotic therapy, but individual outcomes of the two untreated pregnancies were not specifically identified.

CLINICAL OUTCOME[a]	REFERENCE
CoA, EFE, AS, LSVC, PDA, cardiac dysfunction, RD, death 39 hours	25, 33
IUGR, VSD, stillbirth	33–35
ASD, stillbirth	33, 34
CoA, stillbirth	33, 34
Miscarriage	33, 34
VSD, hydrocephalus, omphalocele, clubfoot, meningomyelocele, RD, death 4 hours	33
IUGR, absent hemidiaphragm, RD, cardiac dysfunction, VSD, death 30 min	33
Hydrocephalus, miscarriage	33
Miscarriage	33
Miscarriage	33
VSD, miscarriage	33
R/O sepsis, RD	33
R/O sepsis, RD, hypoglycemia, fever	33
Miscarriage	36
Prematurity, hyperbilirubinemia	36
Syndactyly	36
DD, cortical blindness	28, 36
Rash, hyperbilirubinemia	36
Miscarriage	29
Syndactyly	29
Cardiac dysfunction, aortic thrombosis, lethargy, hypertension, acidosis, death 8 days	32
RD, death 23 hours	38, 39
Rash, adenopathy	621
IUGR, cardiomyopathy, PDA, R/O sepsis, RD, rash, adenopathy, hepatomegaly, hyperbilirubinemia, meconium ileus, metaphyseal bands, joint contractures, R/O encephalitis	621
R/O sepsis, rash, hepatomegaly, hyperbilirubinemia, metaphyseal bands, pectus excavatum, R/O encephalitis, hypotonia, hemiparesis, eso/exotropia, dysphagia, GER, BIH, facial/ear dysmorphia, unilateral simian crease, GR, DD, dental anomalies	621
Hyperbilirubinemia, retinal lesions, R/O meningoencephalitis	621
VSD	37
Hyperbilirubinemia	37
Hyperbilirubinemia	37
Hypotonia	37
IUGR	37
Macrocephaly	37
Supraventricular extrasystoles	37

Table continued on following page

TABLE 11–8
Congenital Lyme Borreliosis: 66 Adverse Outcomes of Pregnancies Complicated by Lyme Borreliosis (LB) *Continued*

	MATERNAL GESTATIONAL				FETAL/NEONATAL				
PATIENT NO.	Trimester of LB	Clinical History[b]	Antibiotic Therapy No. Days[c]	LB Serology[d]	Gestational Age (wk)	Weight (g)	Antibiotic Therapy No. Days[c]	LB Serology[d]	Tissue *Borrelia*[f]
34	≤1	NA	–	+	11	NA			
35	≤1	NA	+	+	9	NA			
36	≤1	NA	–	+	9	NA			
37	≤1	NA	NA	+	10	NA			
38	≤1	NA	–	+	10	NA			
39	≤1	NA	NA	+	8	NA			
40	NA	NA	NA	NA	37	2150	NA	+	
41	NA	O	–	+	NA	NA			
42	≤1	LB	NA[h]	NA	NA	NA	NA	–	
43	≤1	LB	NA[h]	NA	NA	NA	NA	–	
44	NA	LB	+	NA	NA	NA	NA	–	
45	NA	O	NA	NA	NA	NA	NA	+	
46	2	EM,Ar	+	+	33	1450	NA	–	–
47	NA	NA	NA	+	NA	NA	NA	+	
48	NA	NA	NA	+	NA	NA	NA	+	
49	NA	NA	NA	+	NA	NA	NA	+	
50	NA	O	–	+	39	NA	–	–	+Sk
51	1	EM	NA	–	40	3160	–	–	
52	2	EM	+ IV PNx14 d	–	40	2700	–	NA	
53	2	EM	+ IV PNx14 d	–	40	3500	–	–	
54	3	EM,FI	+ IV PNx14 d	+	40	3650	–	+	
55	2	EM	+ IV PNx14 d	+	40	2920	–	–	
56	NA	EM,FI,Ar, Cr,Ra	–	+	NA	NA	NA	+	
57	≤2	O	–	+	28	1030	NA		
58	NA	O	–	+	37	2125	NA		
59	2	EM	+ IV CTXx14 d	NA	26	840	NA		
60	2	EM,Ar	+ IV CTXx14 d	NA	36	2940	NA		
61	3	persistent EM	+ PO CDXx14 d, IV CTXx13 d	NA	40	NA	NA		
62	1	EM,FI,HA, Ar	+ IV CTXx14 d	–	9	NA	NA		
63	NA	EM	NA						
64	NA	EM	NA						
65	≤2	EM	NA	+	15	NA			+D
66	≤2	EM	NA	+	18	NA			

CLINICAL OUTCOME[a]	REFERENCE
Miscarriage	27
Miscarriage	27
Miscarriage	27
Miscarriage	27
Miscarriage	27
Miscarriage	27
Cardiac hypertrophy, fever, rash, adenopathy, hepatosplenomegaly, chronic arthritis, chronic meningoencephalitis, macrocephaly, exophthalmos, blepharitis, GR, DD	31
Miscarriage	30
Neonatal death, multiple congenital cardiac defects	46
Hydrocele, laryngomalacia	46
Hypospadias	46
Cryptorchidism	46
RD, anemia	26
Metatarsus adductus	45
GER	45
Multiple major anomalies (vertebral defects, radial dysplasia, imperforate anus, TEF, renal dysplasia)	45
Chronic relapsing multiple annular erythema, fever, generalized lymphadenopathy	43
PDA at 1 year	41, 42
Cryptorchidism	42
Hypoplastic dental enamel	41, 42
Hypoplastic dental enamel	41, 42
DD	42
Huge sacral hemangioma, gluteal atrophy, general weakness, recurrent fever, minor mental abnormalities	44
Preterm, acute chorioamnionitis and funisitis, 5 min Apgar 7 (+ *Staphylococcus aureus* on fetal placental surface)	47
IUGR, 5 min Apgar 5 (+ maternal drug abuse)	47
RD	48
RD, pneumothorax, ASD, VSD	48
Bilateral ureteral stenosis and hydronephrosis	48
Missed abortion	48
Hyperbilirubinemia	41
Hypotrophic infant	41
Fetal death at 15 weeks	41
Induced abortion; hydrocephalus and spina bifida	41

TABLE 11–9
Clinical Symptoms of Lyme Borreliosis, by Organ System Involved

SITE	CLINICAL DIAGNOSIS	SYMPTOMS
Systemic	Dissemination of spirochetes	Fever, sore throat, conjunctival injection, malaise, fatigue, myalgias, arthralgias, headache, meningismus, generalized adenopathy
Skin	Erythema migrans (single or multiple)	Expanding erythematous bull's-eye, or diffuse maculopapular rash
	Borrelial lymphocytoma (single or multiple)	Bluish nodule on earlobe or areola
	Acrodermatitis chronica atrophicans	Violaceous doughy distal extremity rash, later atrophic skin overlying subluxed joint with associated peripheral neuropathy and chronic arthritis
	Septal panniculitis	Skin lesions resembling erythema nodosum
Heart	Fluctuating heart block	Syncope, dizziness, chest pain, palpitations
	Myopericarditis, pancarditis	Arrhythmia, chest pain, acute heart failure
	Chronic cardiomyopathy	Chronic heart failure
Nervous system	Meningitis (acute or chronic)	Headache, meningismus
	Cranial and peripheral neuropathy (acute or chronic) and Bannwarth's syndrome (meningopolyneuritis)	Facial palsy (Bell's), other cranial nerve palsy, paresthesia/hyperesthesia, paresis, radicular pain, carpal tunnel syndrome
	Encephalopathy (acute or chronic)	Disturbance of sleep, mood, memory, or personality; neuropsychiatric disorders, including psychosis, schizophrenia, paranoia, depression, anorexia
	Multifocal encephalomyelitis (acute or chronic)	Spastic paraparesis, hemiparesis, ataxia, aphasia, apraxia, dementia, focal neurologic deficits, meningovasculitis, leukoencephalitis, mononeuritis multiplex, cerebellar ataxia, Guillain-Barré, transverse myelitis
Musculoskeletal system	Arthralgia/arthritis	Intermittent monarticular or oligoarticular asymmetrical migratory joint pain, with swelling and warmth, but no erythema; may become chronic with joint space narrowing, bone cysts, cartilage loss, bone erosion
	Ruptured Baker's cyst	Sudden popliteal pain and swelling
	Temporomandibular joint arthritis	Temporomandibular joint syndrome
	Myositis	Muscle pain, swelling
Reticuloendothelial system	Lymphadenitis (regional or generalized)	Lymphadenopathy
	Hepatitis	Tender hepatomegaly, elevated hepatocellular enzymes
	Splenitis	Tender splenomegaly
Genitourinary system	Bladder neuropathy	Urinary retention, hydronephrosis
Eye	Conjunctivitis, interstitial keratitis, nodular episcleritis, panophthalmitis, uveitis, pars planitis, iridocyclitis, choroiditis, vitritis, retinitis, cranial and peripheral nerve palsies, pseudotumor cerebri, papilledema, optic neuritis/atrophy, orbital myositis	Conjunctival injection, visual disturbances, ocular pain, decreased vision/blindness, Horner's syndrome, Argyll Robertson pupil, extraocular muscle paresis
Ear	Auditory neuritis	Otalgia; tinnitus; acute, intermittent, or progressive neuronal hearing loss

hepatic vein in one case. *B. burgdorferi* was also found by IFA in the livers of three fetuses miscarried at 15, 19, and 23 weeks, respectively (patients 5, 3, and 4, see Table 11–8), without definite histories of gestational Lyme disease.[33, 34] The histopathology of a lymph node biopsy of a patient with infantile multisystem inflammatory disease considered to have congenital Lyme borreliosis (patient 40, see Table 11–8) showed acute lymphadenitis with follicle hyperplasia.[31]

PULMONARY

Histopathologic examination of the lungs in one term baby with severe fatal early congenital Lyme borreliosis after first-trimester gestational Lyme disease showed microscopic edema and extreme congestion but no inflammation, and no spirochetes were seen (patient 22, see Table 11–8).[38, 39]

CARDIAC

Cardiac histopathology has been reported for 11 infants or fetuses with congenital Lyme borreliosis. Major cardiac malformations were found in 12 infants, and spirochetes were found in the heart in 3, and in other or unspecified fetal tissues in 4 of these cases, in the absence of associated inflammatory findings.

Major cardiac malformations were seen in seven term or near-term infants with congenital Lyme borreliosis (four fatal and three nonfatal) following first-trimester, or in one case, early second-trimester (15 to 19 weeks) gestational Lyme disease during the period of cardiac organogenesis (patients 1, 2, 6, 27, 42, 51, and 60, see Table 11–8),[25, 33–35, 37, 42, 46, 48] and *B. burgdorferi* spirochetes were found by IFA in the myocardium of two of these infants (patients 1 and 2).[33–35] The malformations consisted of aortic coarctation, endocardial fibroelastosis, persistent left superior vena cava, patent ductus arteriosus, and aortic stenosis in one 35-week, slightly premature infant (patient 1)[25, 33]; ventriculoseptal defects in three term infants (patients 2, 6, and 27)[33–35, 37]; a persistent patent ductus arteriosus in one term infant (patient 51)[41, 42]; atrial and ventricular septal defects in a 36-week, slightly premature infant (patient 60)[48]; and multiple unspecified fatal congenital cardiac defects in another infant (patient 42).[40, 46]

Spirochetes were found in either the myocardium or unspecified tissue of two additional term babies who died of early congenital Lyme borreliosis. One had a large ventriculoseptal defect and no known history of gestational Lyme disease (patient 7),[33] and the other had myocardial dysfunction but no malformation, following gestational Lyme disease of unspecified trimester (patient 21).[32]

Cardiac malformations were also found in three fetuses miscarried at 15, 23, and 25 weeks, respectively, with congenital Lyme borreliosis but no definite history of gestational Lyme disease (patients 3 and 4),[33, 34] although one mother had arthritis (patient 11),[33] and in one 34-week infant with nonfatal congenital Lyme borreliosis after second-trimester gestational Lyme disease (patient 24)[621]; these consisted of an atrial septal defect (patient 3), aortic coarctation (patient 4), a ventriculoseptal defect (patient 11), and patent ductus arteriosus (patient 24).

NEUROLOGIC

Neuropathology has been described in seven fetuses or infants with fatal congenital Lyme borreliosis, and spirochetes were found in the brain tissue of five of these and in unspecified fetal tissue in one, using silver staining, IFA staining, or culture, without evidence of inflammation even in areas where spirochetes were found. *B. burgdorferi* was found in the brain parenchyma, meninges, or subarachnoid space in two term infants after first-trimester gestational Lyme disease (patients 2 and 22),[33–35, 38, 39] in the frontal cerebral cortex of another term infant after gestational Lyme disease of unspecified trimester (patient 21),[32] and in the brain of a 16-week miscarried fetus with no history of gestational Lyme disease (patient 9).[33]

Three infants had either structural or histopathologic abnormalities. Patient 22 had minor histopathologic findings that could have been related to either the congenital infection or birth trauma; these consisted of small perivenous hemorrhages with aggregates of leukocytes in the pons, small infratentorial hemorrhages, and cerebral edema and congestion, with no significant inflammation.[38, 39] One term infant had hydrocephalus and spirochetes in unspecified fetal tissue following probable first-trimester infection (patient 6),[33] one 17-week miscarried fetus had hydrocephalus and *B. burgdorferi* in fetal brain tissue (patient 8),[33] and one 18-week fetus had hydrocephalus and spina bifida.[41]

MacDonald retrospectively described spirochetes consistent with *B. burgdorferi* in autopsy sections of brain from 2 of 10 infants who died of sudden infant death syndrome in a highly Lyme-endemic area; there was no inflammation in the tissues containing the spirochetes.[33]

MUSCULOSKELETAL

Musculoskeletal abnormalities have been found in five term or near-term infants with congenital Lyme borreliosis. Abnormalities in two term infants with fatal congenital Lyme borreliosis but no definite history of gestational Lyme disease consisted of clubfoot, spina bifida with meningomyelocele, and omphalocele in one (patient 6),[33] and absent left hemidiaphragm in the other (patient 7)[33]; spirochetes were seen in unspecified fetal tissues. In addition, syndactyly has been reported in two term infants who survived after first- or second-trimester gestational Lyme disease (patients 16 and 20)[29, 36]; metatarsus adductus (patient 47)[45] and multiple major anomalies, including vertebral defects and radial dysplasia (patient 49),[45] have been reported in infants of seropositive mothers without histories of previous Lyme disease.[45] An infant (patient 56),[44] born after severe gestational Lyme disease (trimester unspecified but of long duration, with progression from EM to arthritis and neuroborreliosis), had a sacral hemangioma, gluteal atrophy, and general weakness; another infant (patient 25),[621] born after prolonged gestational Lyme disease (first-

trimester EM with progression to arthritis), had pectus excavatum and hypotonia. Another (patient 24),[621] born after early second-trimester infection, had joint contractures.

GENITOURINARY

Renal histopathology has been reported in five fetuses or infants with fatal congenital Lyme borreliosis. Spirochetes were found by silver staining, IFA staining, or culture (without inflammation) in the kidney in all five, including two term infants (patients 2 and 22)[33–35, 38, 39] and one 35-week premature infant (patient 1),[25] born after first-trimester gestational Lyme disease, as well as two fetuses who were miscarried or stillborn at 12 weeks (patient 10)[33] and 23 weeks (patient 4),[33, 34] with no definite history of gestational Lyme disease. Spirochetes were also found in the neonatal adrenal in one of the term infants (patient 2). Renal dysplasia was reported in an infant (patient 49) with other major congenital anomalies, born to a seropositive asymptomatic mother. Inguinal hernias were found in a 37-week infant who survived following first-trimester gestational Lyme disease (patient 25).[621] Bilateral ureteral stenosis and hydronephrosis were reported in an infant (patient 61)[48] after third-trimester gestational Lyme borreliosis with persistent EM. Cryptorchidism was found in two infants (patients 45 and 52)[42, 46]—one born after second-trimester gestational Lyme disease, and the other to an asymptomatic seropositive mother. Hypospadias was found in one infant (patient 44),[46] born after gestational Lyme disease of unspecified trimester, and hydrocele was found in another (patient 43),[46] born after first-trimester Lyme disease.

INFANTILE MULTISYSTEM INFLAMMATORY DISEASE

Although the etiology of neonatal or infantile multisystem inflammatory disease[624] (a persistent inflammation of skin, synovia, lymph nodes, eyes, and the central nervous system) is unclear, 1 of 14 reported patients with this syndrome has been considered most likely to have congenital Lyme disease.[31] The histopathology[625] of skin, lymph nodes, and synovia has been reported in several of these patients and consists of chronic perivascular granulocytic, mast cell, and especially eosinophilic, inflammatory infiltration of skin, lymph nodes, synovia, and muscle, and granulocytic (including eosinophilic) meningeal inflammation. Muscle atrophy associated with the inflammatory infiltration has also been seen.

PLACENTA

The placental histopathology associated with gestational Lyme borreliosis has been reported only occasionally.[33–36, 590, 622, 623] Some of the placentas described were associated with normal fetal and neonatal outcomes; others were associated with infants with congenital Lyme borreliosis (included in Table 11–14 in the section Clinical Manifestations).

MacDonald and colleagues[33–35] described seven placentas associated with gestational Lyme borreliosis. Spirochetes were grown from one placenta and were seen by silver staining or identified as *B. burgdorferi* by IFA staining in placental tissues or villi from six placentas, in the absence of inflammation or other placental abnormalities (except for rare plasma cells in the placental villi of one placenta); this lack of inflammation despite the presence of spirochetes was remarkable. Spirochetes were demonstrated in the placentas of two women with 15-week and 19-week miscarriages with no history of gestational Lyme disease (patients 3 and 5, see Table 11–8), in one woman with a term stillbirth after untreated first-trimester gestational Lyme disease (patient 2, see Table 11–8), in two women with term or near-term infants with severe early congenital Lyme disease with no history of gestational Lyme disease (patients 12 and 13, see Table 11–8), and in one woman with treated second-trimester and untreated third-trimester Lyme disease who delivered a normal term infant, who was treated with antibiotics after delivery. A term placenta, from a gestation complicated by second-trimester Lyme disease and treated with intravenous antibiotic therapy, had no spirochetes detectable.

Markowitz and colleagues[36] described a placenta with hypoperfusion, immaturity, syncytial and cytotrophoblastic features, and autolytic membrane changes (but no inflammation or nodularity), associated with a 20-week miscarriage following first-trimester–treated gestational Lyme disease (patient 14, see Table 11–8), but found no spirochetes by either culture or IFA. Duray and Steere[590] reported that in maternal gestational Lyme disease, the placental chorionic villi had increased Hofbauer cells as in syphilitic placentitis. Mikkelsen and Palle[622] reported a normal placenta following last-trimester–treated gestational Lyme disease.

Placental histopathology of two of my cases of congenital Lyme borreliosis consisted of focal acute chorioamnionitis, focal calcification, marked congestion, and a 2.5-cm subchorionic nodular infarct in one term placenta following first-trimester–treated Lyme disease (patient 23, see Table 11–8), as well as focal chorionic villous edema, chronic fibrosing villitis, fibrin deposition between villi, syncytial knots, and marked congestion in the other 34-week placenta following second-trimester–treated gestational Lyme disease (patient 24, see Table 11–8).

The histopathology of one placenta associated with neonatal multisystem inflammatory disease[626] showed thickened thrombotic vessels and subchorionic and intrachorionic calcification; this is of interest because 1 of 14 patients with this syndrome was considered to have congenital Lyme borreliosis.[31]

Hercogova and colleagues[41] reported that *Borrelia*-like spirochetes, visualized by staining with specific monoclonal antibody against *B. burgdorferi* flagellin, were found in a placenta evaluated after an intrauterine fetal death at 15 weeks in a pregnancy complicated by EM, but no description of the histopathology was given. Figueroa and colleagues[623] reported that spirochetes were demonstrated in the villi and intervillous maternal space in 3 of 60 placentas of asymptomatic *B. burgdorferi* ELISA–seropositive/equivocal, syphilis-negative women;

spirochetes in two of these placentas were identified as *B. burgdorferi* by PCR, and identification was not done in the other. There was no correlation of pregnancy outcome with presence or absence of these spirochetes, and no information was given regarding any antibiotic therapy; therefore, the significance of this observation is uncertain.

Thus, in the small number of gestational Lyme borreliosis placentas described, rare spirochetes may be found, and the histopathology may be either normal or abnormal. The focal chronic fibrosing villitis, nodular subchorionic infarcts, focal calcification, fibrin deposition between chorionic villi, syncytial and trophoblastic features, and the suggestion of perivascular lymphoplasmacytic infiltrations are reminiscent of the pathology of syphilitic placentitis, just as the basic histopathologic lesion of Lyme disease, lymphoplasmacytic perivascular infiltration with vasculopathic damage, shows similarities with syphilis. A larger number of placentas must be studied histologically, using silver and *B. burgdorferi*–specific IFA stains, and possibly with PCR and culture, before a definitive description of placental pathology in gestational Lyme borreliosis is to emerge.

Other Congenital Borrelial Infections

RELAPSING FEVER

The other human borrelioses, tickborne and louseborne gestational relapsing fever, caused by *B. hermsii*, *B. duttonii*, and related *Borrelia* strains, may also result in congenital infection[627, 628] and have been described more extensively than congenital Lyme borreliosis.

The placental histopathology in congenital relapsing fever has only rarely been reported[627] and consists of abundant spirochetes seen in placental villous capillaries, both on the fetal side of the circulation and in the umbilical vessels. The histopathology of the congenitally infected fetus has also rarely been reported[628] and shows mononuclear and occasional neutrophil inflammatory infiltration of the meninges, miliary splenic lesions consisting of liquefaction necrosis of the white pulp, hypertrophy of Kupffer cells in the liver, and hemorrhagic lesions in the skin, subepicardium, and brain. Abundant spirochetes have been found in spleen, liver, and brain.

Leptospirosis, although not tickborne or borrelial, is another nonsyphilitic spirochetosis capable of causing occasional congenital infection with some similarities to Lyme borreliosis. Sixteen cases, many with fetal and placental histopathology, are summarized in an excellent review.[629]

CLINICAL MANIFESTATIONS

Lyme borreliosis is a multisystem infection with a variety of clinical manifestations that may change with time as the infection progresses; these may be modified by antibiotic therapy and by patient immune responses. It has many similarities to another human spirochetosis—syphilis—because of its ability to persist in body tissues for long periods of time, its association with both early and late stages of infection, including neuroborreliosis, and its ability to produce a wide range of symptoms.[98, 206, 290]

Case Definition and Classification of Stages of Lyme Borreliosis

The case definitions of Lyme borreliosis used by the CDC[633] for epidemiologic purposes to follow the geographic spread of the infection in the United States are given in Table 11–10; although they were not initially intended for use in patient care situations, they have proven useful in standardizing criteria for the disease. Clinical case definitions of the main presentations of European Lyme borreliosis were developed by the European Union Concerted Action of Risk Assessment in Lyme Borreliosis (EUCALB)[8, 502] by consensus agreement of representatives from many European countries, to standardize criteria for reporting of Lyme borreliosis, to facilitate clinical management of Lyme borreliosis, and to more fully define the broad spectrum of the disease in different European countries (Table 11–11).

TABLE 11–10
CDC Lyme Disease Case Definition for Public Health Surveillance Purposes[a]

ERYTHEMA MIGRANS
Single primary red macule or papule, expanding for days to weeks to large round lesion ≥5 cm diameter (physician-confirmed), +/− central clearing, +/− secondary lesions, +/− systemic symptoms (fever, fatigue, headache, mild neck stiffness, arthralgia, myalgia)
plus
Known exposure ≤30 days before onset to an endemic area (in which ≥2 confirmed cases have been acquired, or in which *B. burgdorferi*–infected tick vectors are established)
or
One or more late manifestations without other etiology:
1. Musculoskeletal —Recurrent brief episodes of monarticular or pauciarticular arthritis with objective joint swelling, +/− chronic arthritis
2. Neurologic —Lymphocytic meningitis, facial palsy, other cranial neuritis, radiculoneuropathy, encephalomyelitis (confirmed by CSF *B. burgdorferi* antibody > serum *B. burgdorferi* antibody)
3. Cardiovascular —Acute second- or third-degree atrioventricular conduction defects, lasting days to weeks, +/− myocarditis
plus
Laboratory confirmation by either:
1. Isolation of *B. burgdorferi* from patient specimen
2. Diagnostic levels of *B. burgdorferi* IgM or IgG antibodies in serum or CSF (initial ELISA or IFA screen followed by Western blot of positive or equivocal results)

CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; IFA = immunofluorescence assay.

[a]Adapted from Centers for Disease Control. MMWR 46(RR):20–21, 1997.[633]

TABLE 11–11
EUCALB Lyme Borreliosis Clinical Case Definitions[a]

Erythema migrans

Macule or papule, expanding for days to weeks to a red or blue-red patch, usually but not always ≥5 cm diameter, +/− central clearing, +/− secondary lesions, +/− systemic symptoms of fever, fatigue, headache, mild neck stiffness, arthralgia, myalgia (laboratory confirmation not required)[b]

or

Borrelial lymphocytoma

Blue-red painless nodule or plaque, usually on earlobe/pinna, nipples, or scrotum (confirmed by diagnostic change of *Bb*[c] serum antibody)[b]

or

Acrodermatitis chronica atrophicans

Chronic red or blue-red lesion, +/− initial doughy swelling, eventual atrophy, usually on extensor surface of distal extremity, +/− induration over bony prominences (confirmed by high *Bb* serum IgG antibody)[b]

or

Early neuroborreliosis

Painful meningoradiculoneuritis (Garin-Bujardoux-Bannwarth syndrome), lymphocytic meningitis, facial palsy, other cranial neuritis (confirmed by cerebrospinal fluid (CSF) lymphocytic pleocytosis and CSF *Bb* antibody >serum *Bb* antibody)[b]

or

Chronic neuroborreliosis

Chronic encephalitis, encephalomyelitis, meningoencephalitis, radiculomyelitis (confirmed by CSF lymphocytic pleocytosis and CSF *Bb* antibody >serum *Bb* antibody and diagnostic *Bb* serum IgG antibody)[b]

or

Lyme arthritis

Recurrent brief episodes of monarticular or pauciarticular arthritis with objective joint swelling, +/− chronic arthritis (confirmed by high *Bb* serum IgG antibody)[b]

or

Lyme carditis

Acute second- or third-degree atrioventricular conduction defects, lasting days to weeks, +/− myocarditis or pericarditis (confirmed by diagnostic change in *Bb* serum IgG antibody)[b]

[a]Adapted from Stanek, G, et al. European Union Concerted Action on Risk Assessment in Lyme Borreliosis: Clinical case definitions for Lyme Borreliosis. Wien Klin Wochenschr 108:741–747, 1996[502] and Cimmino, M, et al. European Lyme Borreliosis Clinical Spectrum. Zentralbl Bakteriol 287:248–252, 1998.[*]

[b]*Borrelia burgdorferi* may also be isolated from patient specimen.

[c]*Bb* = *Borrelia burgdorferi*.

Initial classification of Lyme borreliosis as stage 1, 2, or 3 proved to be confusing because the stages did not necessarily develop sequentially. A more useful clinical classification of the infection into three stages according to different clinical manifestations has been agreed upon by many European and North American clinicians and consists of division of the infection into early localized, early disseminated, and late chronic Lyme borreliosis[8, 24, 502, 633–635] (Table 11–12). Early localized Lyme borreliosis includes solitary EM and solitary borrelial lymphocytoma, without significant constitutional symptoms, although mild regional adenopathy and mild constitutional symptoms may be present. Early disseminated Lyme borreliosis includes multiple EM and multiple borrelial lymphocytomas, as well as other manifestations of systemic spread of the spirochete such as neurologic, arthritic, cardiac, or other organ involvement. Early Lyme borreliosis has also been clearly shown to present occasionally as a flulike illness[636] without the pathognomonic erythema migrans lesion; it is characterized by fever, fatigue, and headache, and sometimes by neck pain, anorexia, and arthralgia, lasting 5 to 21 days if untreated. Late Lyme borreliosis consists of cutaneous, neurologic, or arthritic manifestations that persist either constantly or intermittently for at least 6 to 12 months.

Incidence of Lyme Borreliosis in Women of Childbearing Age

It is estimated that between 7 and 20% of patients with North American Lyme borreliosis and 18 to 34% of patients with European Lyme borreliosis are women 20 to 49 years old, and therefore in the major childbearing years. This is based on data from reports of patients with Lyme borreliosis from various geographic areas in the United States* and Europe[162, 344, 371] that note the age and sex of the patients. Lyme borreliosis may affect patients of all ages, from the infant to the elderly, but the majority of cases occur in patients younger than 40 years of age. In large studies by the CDC of over 4500 patients, the highest incidence was in those younger than 15 years and between 24 and 44 years old. The percentage of female patients with Lyme borreliosis acquired in different states of the United States usually ranges from 44 to 51%, but it may be as low as 22 to 36% in some groups studied. The percentage of female patients in several European studies was slightly higher than in the United States and ranged between 40 and 63%.

Clinical Manifestations of Gestational and Nongestational Lyme Borreliosis

Initial consideration of the diagnosis of congenital Lyme borreliosis and therefore initiation of prompt antibiotic therapy of the congenitally infected infant usually depend on suspicion or confirmation of Lyme borreliosis in the mother. Therefore, in order for infants with congenital Lyme borreliosis to be recognized, it is essential for clinicians caring for newborns and infants to become familiar with the various manifestations of Lyme borreliosis in the adult, as well as in the congenitally infected infant. The symptoms of Lyme borreliosis in pregnant women are the same as those in nonpregnant patients, and the clinical manifestations of Lyme borreliosis are shown in Table 11–9.

Diagnostic tests and differential diagnosis of both gestational and congenital Lyme borreliosis are discussed in the section Diagnosis and Differential Diagnosis. All stages of Lyme borreliosis respond to antibiotic therapy, but it is important to select therapy appropriate for the

[*]See references 243, 271, 272, 359, 360, 460, 463, 464, 466–469, 471, and 637.

TABLE 11–12
Clinical Classification of Lyme Borreliosis (LB)[a]

Early localized LB (≤1 month after bite by infected tick)	Solitary erythema migrans or Borrelia lymphocytoma +/− regional lymphadenopathy or minor constitutional symptoms (fatigue, malaise, lethargy, headache, myalgia, arthralgia)
Early disseminated LB (days to months after bite by infected tick)	Multiple erythema migrans or early neurologic (lymphocytic meningitis; cranial neuritis; radiculoneuritis; encephalitis), musculoskeletal (migratory arthralgia; myalgia; polyarthritis), cardiac (myocarditis; brief atrioventricular block), or other organ involvement (ophthalmic, hepatic, renal, etc.). Lymphocytoma is sometimes considered disseminated LB
Late chronic LB (months to years after bite by infected tick)	Acrodermatitis chronica atrophicans or persisting/remitting neurologic (chronic encephalitis; chronic neuropathy), musculoskeletal (migratory polyarthritis; chronic arthritis), or other organ involvement for over 6–12 months

[a]Adapted from Rahn DW, Felz MW. Lyme disease update. Current approach to early, disseminated, and late disease. Postgrad Med 103:51, 1998,[611] and Asbrink E, Hovmark A. Comments on the course and classification of Lyme borreliosis. Scand J Infect Dis Suppl 77:41, 1991.[634]

stage of the infection, and this is discussed in the section Therapy. Because decisions regarding antibiotic therapy of infants with gestational Lyme exposure depend on the adequacy of previous antibiotic therapy of the mother's Lyme borreliosis, it is also important for the clinician managing these infants to be familiar with recommended antibiotic therapy for adults with Lyme borreliosis.

ERYTHEMA MIGRANS

The EM skin lesion is common in both Eurasian and North American Lyme borreliosis. About half of patients with Lyme borreliosis recall a preceding tick bite, but the range is 21 to 80%. EM is reported in 45 to 87% of patients with Lyme borreliosis from Eurasia and North America.*

The spirochete is transmitted to the skin by the bite of a *B. burgdorferi*–infected tick, and a small papule develops at the bite site. After an average interval of 10 days (1 to 4 weeks), with a range of 1 day to 4 months,[434, 467, 596, 640] the skin lesion of EM develops as an initially erythematous patch at the bite site that slowly expands over a period of several days to several weeks and may reach a diameter of 40 to 73 cm[338, 596, 638, 640] before spontaneously resolving, unless antibiotic therapy interrupts the course and causes more rapid resolution of the lesion.

EM (Fig. 11–5*A* to *C*) is usually erythematous but may be purplish or brownish; is usually round but may be elongated or triangular; is usually smooth but may be stippled, bumpy, or even vesicular, necrotic, hemorrhagic, crusty, or scaly; usually shows central clearing as it expands (if duration is longer than 3 weeks) but may be homogeneous (if duration is short) or have secondary concentric annuli ("bull's-eye" appearance) in the center; and is usually asymptomatic but may be associated with minimal pruritus, burning, dysesthesia, and regional adenopathy.[338, 502, 596, 599, 640] Some lesions have recurred over as long as 1 year,[599] and these probably represent hematogenous spread (Fig. 11–5*D*). In China, EM lesions are usually indurated, less often show annular erythema, and sometimes have central necrosis or vesiculation.[438]

*See references 2, 98, 251, 334, 352, 374, 432, 434, 437, 460, 463, 471, 511, 546, 638, and 640.

Although solitary EM with only very mild associated flulike symptoms is considered early localized infection, the development of significant systemic symptoms of fatigue, arthralgia, myalgia, headache, fever, chills, meningismus, anorexia, dysesthesia, dizziness, nausea, vomiting, difficulty concentrating, pharyngitis, regional or generalized adenopathy, conjunctivitis, and malaise, either alone or associated with single or multiple EM, occurs in about half to two thirds of patients, indicates systemic hematogenous spread of the spirochete, and is considered early disseminated infection.[338, 434, 502, 638, 640, 642]

Multiple EM (Fig. 11–6) indicates early disseminated Lyme borreliosis with hematogenous spread and occurs in 13 to 50% of North American patients[232, 243, 463, 596, 638, 640, 643] with EM, 23% of Russian patients with EM,[546] only 4 to 10% of other European patients[434, 448] with EM, and is becoming less common owing to prompt diagnosis and antibiotic therapy of solitary EM before dissemination occurs.[639, 640] The skin lesions are smaller than the initial EM lesion and presumably arise from hematogenous spread.[460, 467] A maculopapular rash (Fig. 11–7) rather than multiple EM lesions has been reported in some patients, and also indicates early disseminated infection. Presentation of Lyme disease as multiple erythema multiforme lesions has also been reported.[277]

Dissemination of infection may lead to severe complications of early infection of various organs, such as meningitis, myocarditis, hepatitis, myositis, and arthritis. Dissemination to organs without successful eradication of infection by antibiotic therapy may lead to late chronic manifestations of infection such as acrodermatitis chronica atrophicans, chronic neuroborreliosis, and chronic Lyme arthritis.

Seropositivity correlates with the duration of EM; usually, one third of patients with EM are seropositive at presentation, and 88% are seropositive during the first month after EM, using the standard polyvalent ELISA assay.[640]

BORRELIAL LYMPHOCYTOMA

Borrelial lymphocytoma (BL),[22, 434, 502, 644–646, 865] a B cell pseudolymphoma, is also called lymphadenosis cutis benigna, and is reported predominantly from Europe, where it occurs in 1 to 5% of European patients with

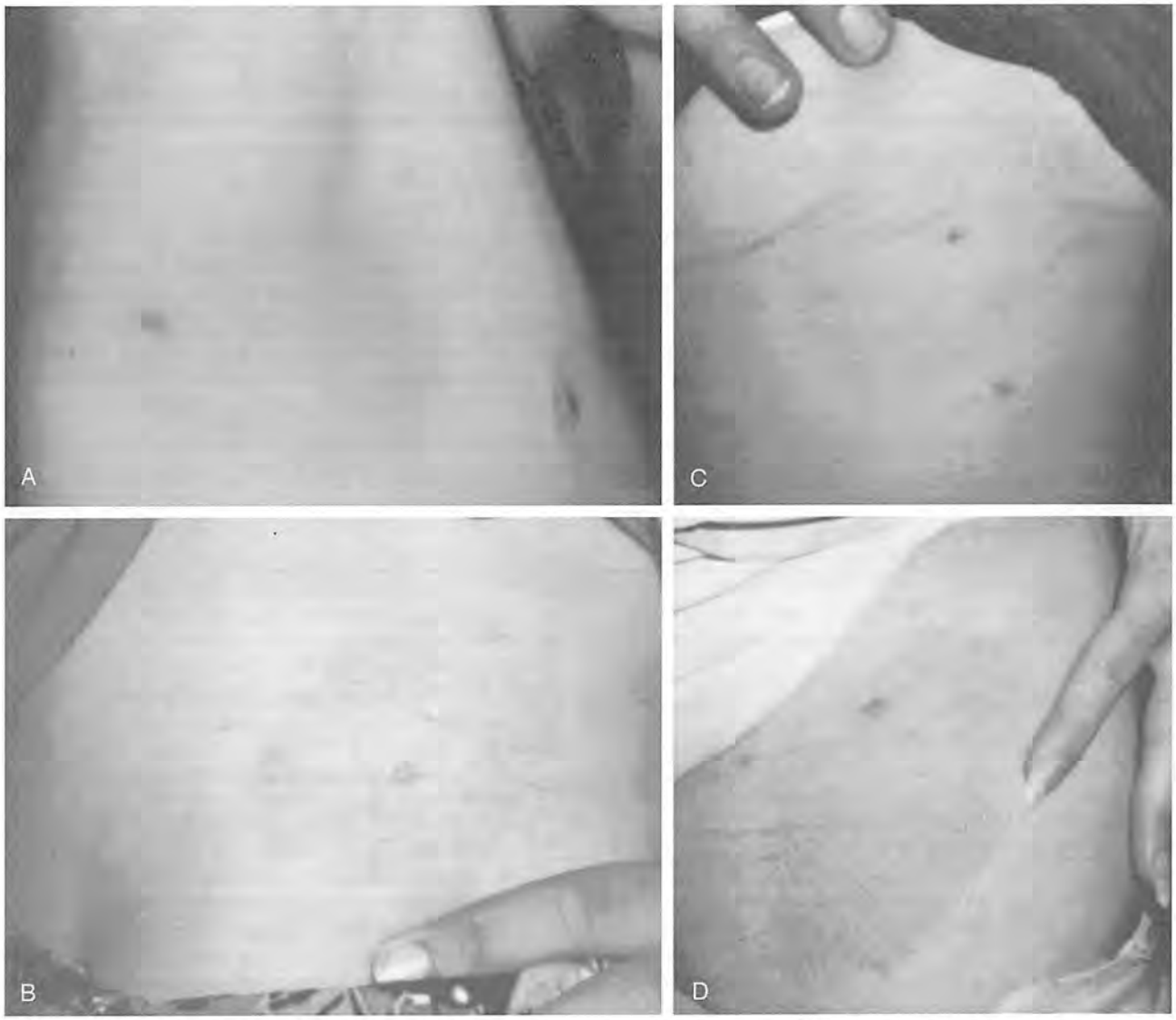

FIGURE 11–5 The pathognomonic skin lesion of Lyme disease, the "bull's-eye" or erythema migrans (EM) lesion. *A* to *C*, EM lesion of early Lyme disease, which is a large, expanding, round or oval, smooth or stippled, erythematous annular rash with central clearing located around a central or eccentric erythematous papule at a tick bite site. *D*, EM lesion of late Lyme disease, which is similar in appearance but develops around an erythematous papule that arises from hematogenous spread and not at a tick bite site. This photograph was taken 4 months post partum and shows an EM lesion on the thigh of a woman who had similar lesions since the first trimester of pregnancy (patient 25 in Table 11–8).

Lyme borreliosis, either at the time of EM or within 10 months after onset of infection, although it has also been reported from Wisconsin[257] and China.[438] It presents as a bluish red, tumor-like or nodular swelling, 1 to 5 cm in diameter, more often occurring in children, usually of the earlobe, nipple, or areola (less often of the nose, scrotum, or other sites), with minimal or no local symptoms such as pruritus or tenderness; two thirds have regional lymphadenopathy, and half have constitutional symptoms. A history of tick bite 4 to 6 weeks previously is reported in 40 to 80% of patients, and a history of previous or concomitant EM in 50 to 70%.[22, 644] The BL usually occurs at the site of the EM lesion if EM is present, but it may also occur at a distant site; if untreated, it may last weeks to months. One third of patients are seropositive for specific IgM antibody, and one half to three quarters for specific IgG at presentation.[22, 644, 646] Antibiotic therapy usually results in full resolution within 3 to 8 weeks of initiation of therapy.[22, 644, 646] Lymphocytoma solitaria, a single lesion, is considered to be early localized Lyme borreliosis; lymphocytoma dispersa (multiple lesions) represents disseminated infection.[22, 501, 599, 644, 645] A true B cell cutaneous lymphoma, of low-grade malignancy, has also been associated occasionally with *B. burgdorferi*–induced ACA.[647]

ARTHRITIS

In the early years after recognition of Lyme disease, and before routine use of antibiotic therapy for its treatment, approximately 20% of patients with Lyme borreliosis presented with arthritis or arthralgia without preceding

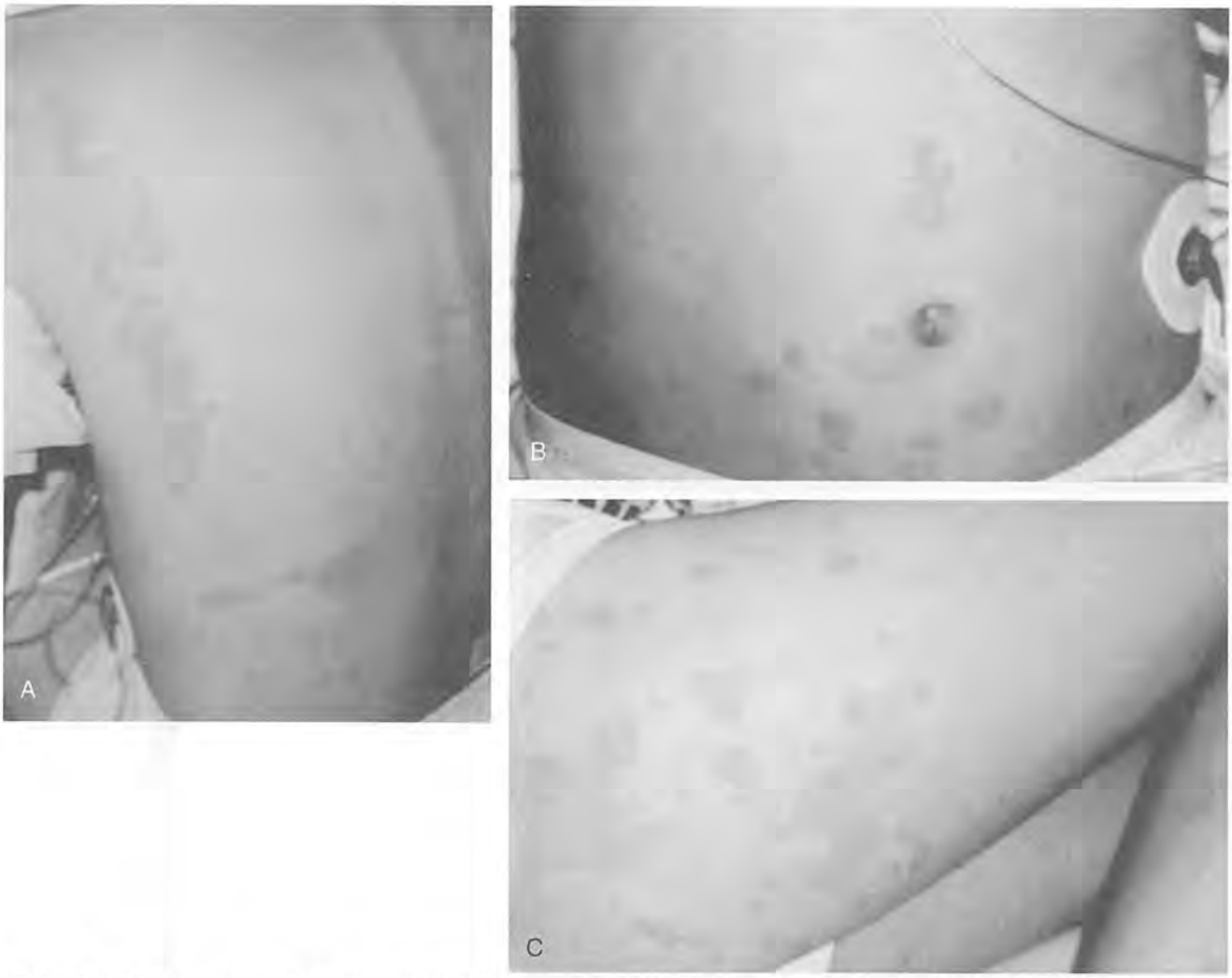

FIGURE 11–6 The rash of early disseminated Lyme disease. *A* to *C*, Extensive distribution of the rash, which consists of erythematous macular lesions with central clearing that range from one to several centimeters in diameter. This patient also had a simultaneous large (>15 cm in diameter) erythema migrans lesion covering most of the right upper arm, and smaller erythematous maculopapular lesions at many tick bite sites.

skin lesions.[464] Since antibiotic treatment of EM has become routine, with the resulting decrease in progression to late sequelae such as arthritis, 75 to 82% of patients with Lyme arthritis in the United States present with negative histories of EM.[274, 324, 648] Eighty percent of untreated North American patients with Lyme borreliosis develop arthralgias within 2 months, and 40 to 60% develop arthritis, usually 4 to 6 weeks to 2 years after the initial infection.[325, 338, 637, 648, 651, 652] The arthritis usually begins as intermittent asymmetrical arthralgias, each lasting about 1 week, and then progresses to intermittent episodes of monarticular or oligoarticular frank arthritis, especially of the large joints, which become markedly swollen, hot, and tender, but not red.[15, 338] The development of Baker's cysts that may rupture is not infrequent,[338, 641] and quadriceps femoris muscle atrophy resulting in knee instability and patellofemoral syndrome with joint dysfunction and pain is an uncommon but characteristic sequela of North American chronic Lyme arthritis.[206, 325] About 10 to 20% of patients with arthritis experience spontaneous resolution each year, about 10% eventually progress to severe destructive chronic arthritis with longer episodes of arthritis by the second or third year, and about 2% develop joint space narrowing, bone cysts, cartilage loss, osteopenia, and erosive bone disease.[641, 651]

The most common joint involved is the knee, but other commonly involved joints include the wrist, elbow, shoulder, ankle, hip, temporomandibular joint, and even the heel and fingers.[460, 463, 641, 652] Synovial fluid shows 500 to 100,000 white blood cells per mm^3, usually with a predominance of polymorphonuclear leukocytes, and an elevated protein of 5 g/dl.[324, 338, 648, 649, 653] Sedimentation rates are mildly elevated. Most patients with Lyme arthritis have *B. burgdorferi* IgG antibody, and particularly Osp A antibody in chronic Lyme arthritis, detectable by ELISA and Western blot, and *B. burgdorferi* DNA may often be detectable in synovial fluid by PCR.[312, 314, 652] Persistent *B. burgdorferi* PCR positivity in synovial fluid correlates with active infection[312, 314] and

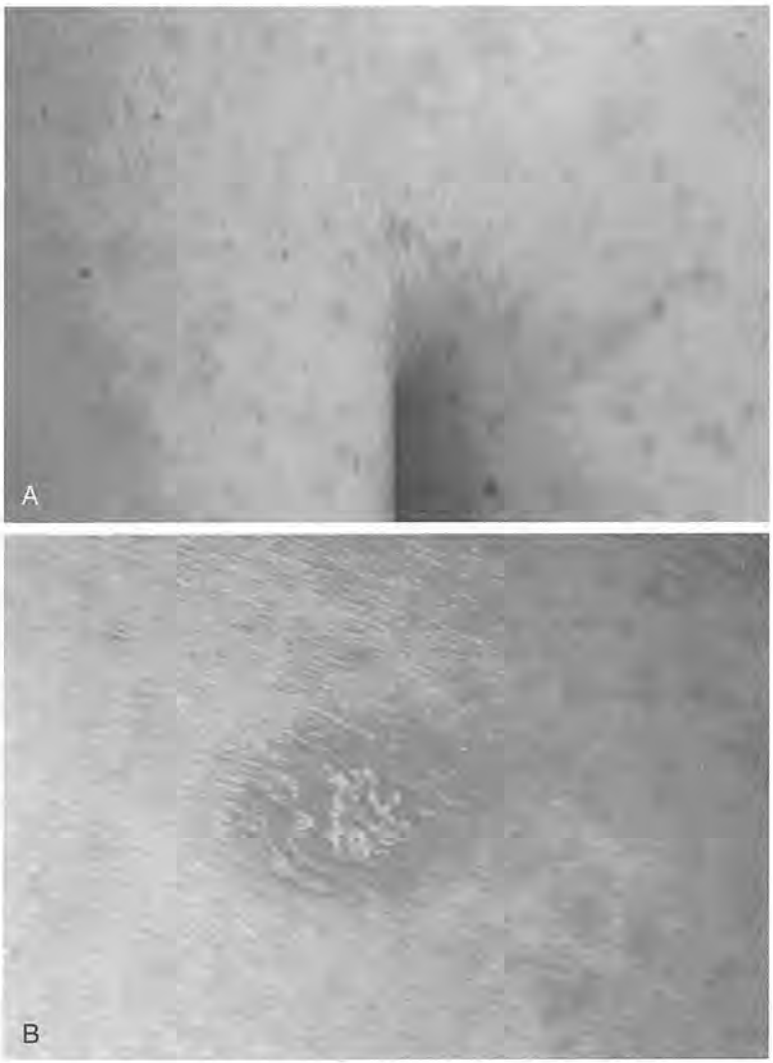

FIGURE 11–7 The rash of early disseminated Lyme disease. Dense erythematous maculopapular rash on the chest *(A)* and an erythematous oval expanding erythema migrans lesion on the buttock *(B)* in a first-trimester pregnant woman (patient 23 in Table 11–8).

indicates a need for antibiotic therapy; PCR negativity in chronic Lyme arthritis is consistent with an immunopathologic process likely to be antibiotic-unresponsive.[312]

It was initially thought that Lyme arthritis was found only in North American patients with Lyme borreliosis; however, once it was recognized, it was subsequently also found in European[39, 502, 511, 546, 649, 650, 652] and Asian patients.[374, 438]

NEUROBORRELIOSIS

Before the routine use of antibiotic therapy for early Lyme disease, about 4% of patients with Lyme borreliosis presented with neurologic symptoms without any preceding skin lesions.[464] Because routine antibiotic therapy of early Lyme borreliosis has become standard, especially when associated with the pathognomonic EM lesion, fewer patients with neuroborreliosis present with a history of EM; 10 to 64% of patients with neuroborreliosis report a history of EM, and 10 to 65% a history of tick bite.[268, 289, 290, 310, 404, 435] Approximately 5 to 17% of untreated patients develop neurologic abnormalities, usually 2 to 4 weeks to several months after the initial infection.[268, 325] Two thirds of patients with early disseminated Lyme borreliosis even without symptoms of central nervous system involvement had evidence of spread of the spirochete to the central nervous system by PCR assay for *B. burgdorferi* DNA.[282] Chronic peripheral nervous system manifestations develop over a median of 16 months, and chronic central nervous system manifestations over a median of 26 months after initial infection.[655]

It was initially thought that neuroborreliosis was primarily a European* manifestation of Lyme borreliosis, but it is now recognized to occur in North America and Asia as well.[288, 291, 292, 437] The reported incidence of neuroborreliosis is higher in Europe than in North America, and there is a suggestion that it is higher in the northern European countries, particularly Scandinavia, than in the southern, central, and eastern European countries.[11, 12, 501, 532] Involvement of the peripheral nervous system is more frequent than that of the central

*See references 90, 162, 268, 290, 404, 435, 502, 511, 516, 546, and 550.

nervous system[265]; the incidence of central nervous system infection may be higher in North America than Europe, and the incidence of peripheral neuropathy may be higher in Europe,[268, 532] although severe and even fatal central nervous system neuroborreliosis has been reported from Europe.[311]

Patients with Lyme borreliosis may develop either central or peripheral nervous system involvement at any stage of the infection.[265, 286–292, 435, 655–657] The early neurologic syndromes (meningitis, cranial neuropathy, and radiculoneuropathy) usually develop a median of 1 month after EM, the chronic peripheral nervous system syndromes (polyradiculopathies) develop over a median of 16 months, and the central nervous system syndromes (encephalopathy and leukoencephalitis) a median of 26 months after EM.[291] The diversity of clinical manifestations is great and includes central nervous system infection (including acute or chronic lymphocytic meningitis, acute or chronic mild encephalopathy, and acute multifocal or chronic progressive multifocal encephalomyelitis),[267, 286, 292, 311, 516, 655, 657] cranial neuropathy (including Bell's palsy),[90, 659, 660] peripheral neuropathy,[291, 656, 662] and painful meningopolyneuritis with peripheral extremity paresis (Bannwarth's syndrome),[516, 572] neuropsychiatric disorders,[663–665] transverse myelitis,[668, 669] acute focal meningoencephalitis, Guillain-Barré syndrome,[265, 289, 530] acute cerebellar ataxia,[261, 311, 530] and chorea.[90] Peripheral nervous system manifestations are grouped under the designation of mononeuropathy multiplex, with perivascular inflammation and axonal loss.[265]

Acute lymphocytic meningitis may occur as a manifestation of early disseminated Lyme borreliosis, with or without radiculitis or cranial neuritis[290–292, 657, 658]; it occurs in up to 15% of patients with other manifestations of Lyme borreliosis.[657] Spinal fluid of patients with acute neuroborreliosis shows a lymphocytic pleocytosis of approximately 100 to 250 cells per mm^3; slightly elevated protein, normal glucose, and sometimes oligoclonal bands; and intrathecal production of *B. burgdorferi*–specific antibody.[260, 265, 268, 287, 290–292] In some patients with neuroborreliosis, particularly those with very early infection, spinal fluid *B. burgdorferi* antigen-detection methods such as PCR[282, 309] or antigen capture ELISA[283] may be positive before the development of specific intrathecal antibody, and even without evidence of inflammation.[283]

One of the more common neurologic manifestations of early Lyme disease in both North American and European patients is cranial neuropathy, especially unilateral (Fig. 11–8) or bilateral Bell's palsy, which develops in about 10% of patients with Lyme borreliosis, and in 50 to 75% of patients with early neuroborreliosis, within 4 weeks of EM.[659, 660] Because Bell's palsy may also be the initial presentation, without preceding tick bite or EM, the possibility of Lyme borreliosis should be considered as a potential etiology for idiopathic Bell's palsies in Lyme-endemic areas.[661] Sixth nerve palsy is reported in 1 to 2% of pediatric neuroborreliosis patients in North America[289] and Europe.[435] In a large study of North American pediatric Lyme facial palsy patients, the incidence of CSF pleocytosis, increased CSF protein, intrathecal specific antibody, and neuroborreliosis was 55, 45, 82, and 92%, respectively.[289, 661] In patients with isolated cranial neuropathy, CSF evaluation for pleocytosis, *B. burgdorferi* antibody, and PCR, is helpful in determining the presence of CNS spread, as this has therapeutic implications.[291, 654, 657, 661]

FIGURE 11–8 Bell's palsy. Persistence of residual left facial weakness 2½ years after the onset of last-trimester gestational Bell's palsy in a young woman who was later diagnosed as having Lyme disease (clinical case described in asymptomatic infant with gestational Lyme exposure).

Bannwarth's syndrome,[502, 572] also known as Garin-Boujadoux-Bannwarth syndrome, tickborne meningopolyneuritis, meningoradiculoneuritis, or lymphocytic meningoradiculitis, occurs in 10 to 15% of patients with North American Lyme borreliosis,[265] is the most common manifestation of European neuroborreliosis, and occurs in 75% of patients with European neuroborreliosis[288, 290]; it occurs infrequently in pediatric neuroborreliosis,[289, 435] with a reported incidence of 4% in a large European study[435] and 1% in a large North American study.[289] Symptoms and signs consist of intense radicular pain with paresthesias or hyperesthesias, progressing to asymmetrical polyneuritis, with sensory loss, weakness, or hyporeflexia, often with cranial nerve palsy (particularly unilateral or bilateral facial palsy), and sometimes with transverse myelitis and lymphocytic meningitis that develops within a few days to weeks after the initial EM or tick bite and lasts approximately 3 to 5 months if untreated. Manifestations of progressive peripheral nervous system involvement (mononeuritis multiplex) are cranial neuropathy, radiculoneuropathy, brachial or lumbosacral plexopathy, distal axonopathy, acute disseminated neuropathy (Guillain-Barré–like), and motor neuropathy.[265] Most patients with Lyme radiculoneuritis are *B. burgdorferi*–seropositive and have CSF pleocytosis and specific CSF *B. burgdorferi* antibody, some have CSF culture or PCR positivity, and some (European patients) have CSF oligoclonal bands.[290–292]

Manifestations of late parenchymal central nervous system and spinal cord neuroborreliosis include progressive encephalomyelitis,[265, 292, 657] with cranial and peripheral neuropathies, myelitis, meningitis, and multifocal encephalitis[265, 286, 311]; spastic paraparesis or quadriparesis,

bladder dysfunction, ataxia, cranial nerve deficits, and dementia[98, 311]; seizures[311, 325]; and chronic encephalopathy and leukoencephalitis.[655] The incidence of Lyme encephalomyelitis is estimated to be 0.1% of cases of untreated Lyme borreliosis[265, 292, 657]; most patients have intrathecal *B. burgdorferi* antibody, some (European patients) have oligoclonal bands, and some have CSF PCR positivity.[290, 657] Late neuroborreliosis manifestations may also include distal limb paresthesias, carpal tunnel syndrome, painful radiculopathy, Bell's palsy, and disseminated multifocal patchy axonal neuropathy similar to mononeuritis multiplex.[289] Spinal fluids of patients with chronic neuroborreliosis show slight lymphocytic pleocytosis of approximately 150 to 200 cells per mm^3, slightly elevated protein, and usually *B. burgdorferi*–specific intrathecal antibody production.[290, 655, 656] Spinal fluid and lesion brain biopsy[311] may also be positive for *B burgdorferi*–specific antigen by PCR.[287, 309, 311]

Neuropsychiatric disorders have been reported.[664, 665, 682–684] Encephalopathy, or neurocognitive dysfunction, particularly subjective perception of memory deficits, may occur during or after Lyme borreliosis, with and even without evidence of invasive inflammatory neurologic infection; it was initially thought to occur only in North American patients, but is now recognized in European patients as well.[265, 681]

Magnetic resonance imaging (MRI) of the brain may be useful in evaluation of central nervous system neuroborreliosis,[311, 610, 671, 672, 685] including meningitis, encephalitis, acute or indolent multifocal encephalitis, chronic neuroborreliosis with encephalopathy and leukoencephalitis, and even facial palsy, as well as other manifestations of Lyme borreliosis that may also involve the central nervous system,[679] including neuro-ophthalmic manifestations; it has demonstrated focal nodular areas or large patchy areas of hyperintense T_2 signal in deep or periventricular white matter, sometimes with ringlike enhancement with gadolinium contrast suggestive of demyelination, perivascular inflammation, or even pontine, frontal, or parietal mass lesions, and occasionally lesions in cortical or subcortical gray matter. MRI imaging has also demonstrated T_2 hyperintense areas with gadolinium contrast enhancement of the nerve roots and cauda equina in Bannwarth's syndrome.[680]

Functional brain imaging, by single photon emission computed tomography (SPECT) or positron emission tomography (PET), may be useful in determination of whether there are objective abnormalities in patients with subjective neuropsychiatric complaints in late Lyme encephalopathy; in some of these patients, including some with normal brain MRI imaging,[666, 667] it has demonstrated multifocal areas of diminished perfusion in the cortex and subcortical white matter, including the frontal white matter, basal ganglia, and medial cortex.

CARDITIS

About 2 to 8% of patients with North American Lyme borreliosis present with carditis initially and 4 to 10% develop it if untreated, usually within 2 to 4 weeks but up to 3 months after the initial infection.[325, 643, 686–688] Although Lyme carditis was initially thought to occur only in North American patients, it has now been reported, with a lower rate of 0.3 to 4%, from Europe as well,[10, 435, 502, 516, 546, 689] and has also been occasionally reported in Asia.[374, 438]

The most common findings are conduction disturbances,[689–986] including mild transient fluctuating first- and second-degree atrioventricular block, Wenckebach periodicity, intraventricular conduction disturbances, and bundle branch block, but complete heart block may also occur and may manifest as syncopal episodes, seizure-like episodes, dizziness, chest pain, and fatigue,[686, 687, 689, 890] although other manifestations also have been reported.[607, 691–693] Electrocardiograms commonly show atrioventricular block or other conduction defects, ST changes, T wave flattening or inversion, intraventricular conduction defects, or occasional premature ventricular contractions. Because carditis is usually a complication of early Lyme borreliosis, specific *B. burgdorferi* antibody is not always detectable at the time of presentation, but it develops later.

The prognosis of acute Lyme carditis is usually good, and it usually resolves spontaneously within 3 days to 6 weeks.[687]

ACRODERMATITIS CHRONICA ATROPHICANS

ACA is a late chronic cutaneous manifestation of Lyme borreliosis that occurs in 2 to 16% of European patients with Lyme borreliosis,[39, 251, 352, 404, 502, 525, 532, 546, 641] 6 months to 10 years after initial infection.[600] Although this is rare in North America, is more common in the elderly, and is rare in childhood, it has been reported in both a child and two young women in the United States,[695] and occasionally in European children.[435, 530] Progression of erythema migrans skin lesions to ACA skin lesions in the same patient over time has been demonstrated.[696] There is an initial inflammatory phase that manifests as insidious onset of bluish red discoloration and doughy induration of the skin on the distal extremities at the site of a previous EM lesion, followed by the atrophic phase, which produces atrophic skin changes in the previously affected areas of skin.[501, 599, 600, 612] Patients may have periarticular bursitis, Achilles tendinitis and epicondylitis, juxta-articular fibrotic nodules, peripheral neuropathies, and joint deformities, including subluxation and degenerative arthritis.[600, 612, 670, 697] Most patients with ACA are seropositive by IgG antibody assay and by the lymphocyte proliferative assay.[219] Antibiotic therapy has resulted in improvement of the inflammatory component but not the permanent atrophic component of ACA.

OTHER ORGAN INVOLVEMENT IN DISSEMINATED INFECTION

During the dissemination phase of the infection, there have also been reports of hepatitis,[243, 698] necrotizing splenitis,[604] eosinophilic lymphadenitis,[606] localized or generalized myositis,[616, 617] eosinophilic fasciitis,[603] panniculitis resembling erythema nodosum,[598] tenosynovitis with ligament involvement,[304] multifocal osteomyelitis