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11

Lyme Disease

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Introduction

Lyme disease, or Lyme borreliosis, is a tick-borne zoonosis of both children and adults caused by the spirochete *Borrelia burgdorferi*.[1,2] It has a worldwide geographic distribution and has been reported from over 40 countries and 6 continents, and the geographic distribution and number of cases reported continue to increase (Figs. 11–1 and 11–2). It is now the most common tick-borne infection in the United States,[3–5] where nearly 10,000 cases were reported to the Centers for Disease Control and Prevention (CDC) in 1992 (Fig. 11–3); in Europe; and possibly in the world.[6,7]

Lyme borreliosis is a fairly recently recognized infection,[8] although erythema migrans (EM), the characteristic skin lesion of early Lyme borreliosis, was first described in a Swedish woman in 1909 by Afzelius, who proposed that it was related to a zoonosis transmitted by a tick bite.[9] In 1975, Steere et al. recognized an outbreak of infectious arthritis and unusual rash similar to European EM in Old Lyme, Connecticut, proposed that transmission occurred via an arthropod vector and named the disease Lyme arthritis.[10] It was eventually found to be associated with Ixodid tick bites and later became known as Lyme disease when its multisystem involvement was recognized.

In 1981, Burgdorfer et al. discovered a new species of *Borrelia* in *Ixodes* ticks associated with Lyme disease, and this became known as *Borrelia burgdorferi*.[1,11] This spirochete was found to be the causative agent of North American Lyme disease[12] and of European EM,[13] as well as other European syndromes such as acrodermatitis chronica atrophicans,[14] Bannwarth's syndrome[15] and lymphadenosis benigna cutis,[16] and the entire disease complex is now known as Lyme borreliosis.

As worldwide reporting of Lyme borreliosis increases, a geographically defined "Lyme Belt" is emerging between 30 and 65 degrees north latitude in the Eastern Hemisphere and between 15 and 50 degrees north latitude in the Western Hemisphere, and there may also be a belt developing between 20 and 40 degrees south latitude in the Southern Hemisphere. This is reminiscent of the "Malaria Belt," which is defined by climactic conditions and the distribution of another major arthropod vector of human disease, the anopheles mosquito.

Lyme borreliosis is a multisystem infection that is emerging as a new "great imitator"[7] because of the diversity of its clinical presentations, which include early and late stages and dermatologic, cardiac, neurologic, arthritic and ocular manifestations.[17] The existence of congenital borreliosis was suspected because of clinical similarities between the two spirochetoses Lyme borreliosis and the classic "great imitator" syphilis,[18] and the well-known association of gestational syphilis with miscarriage, early congenital infection and late congenital infection.

Maternal-fetal transmission of *B. burgdorferi* was first reported in 1985 by Schlesinger et al.[19] As the number of reported cases of Lyme disease continue to increase, there have been increasing reports of gestational Lyme disease associated with adverse outcomes and suspected congenital Lyme borreliosis.[19–34] Although a homogeneous congenital Lyme borreliosis syndrome has not yet emerged, there are several features that are common among the 46 adverse outcomes of pregnancies complicated by gestational Lyme borreliosis reviewed in this chapter, including miscarriage during the first 20

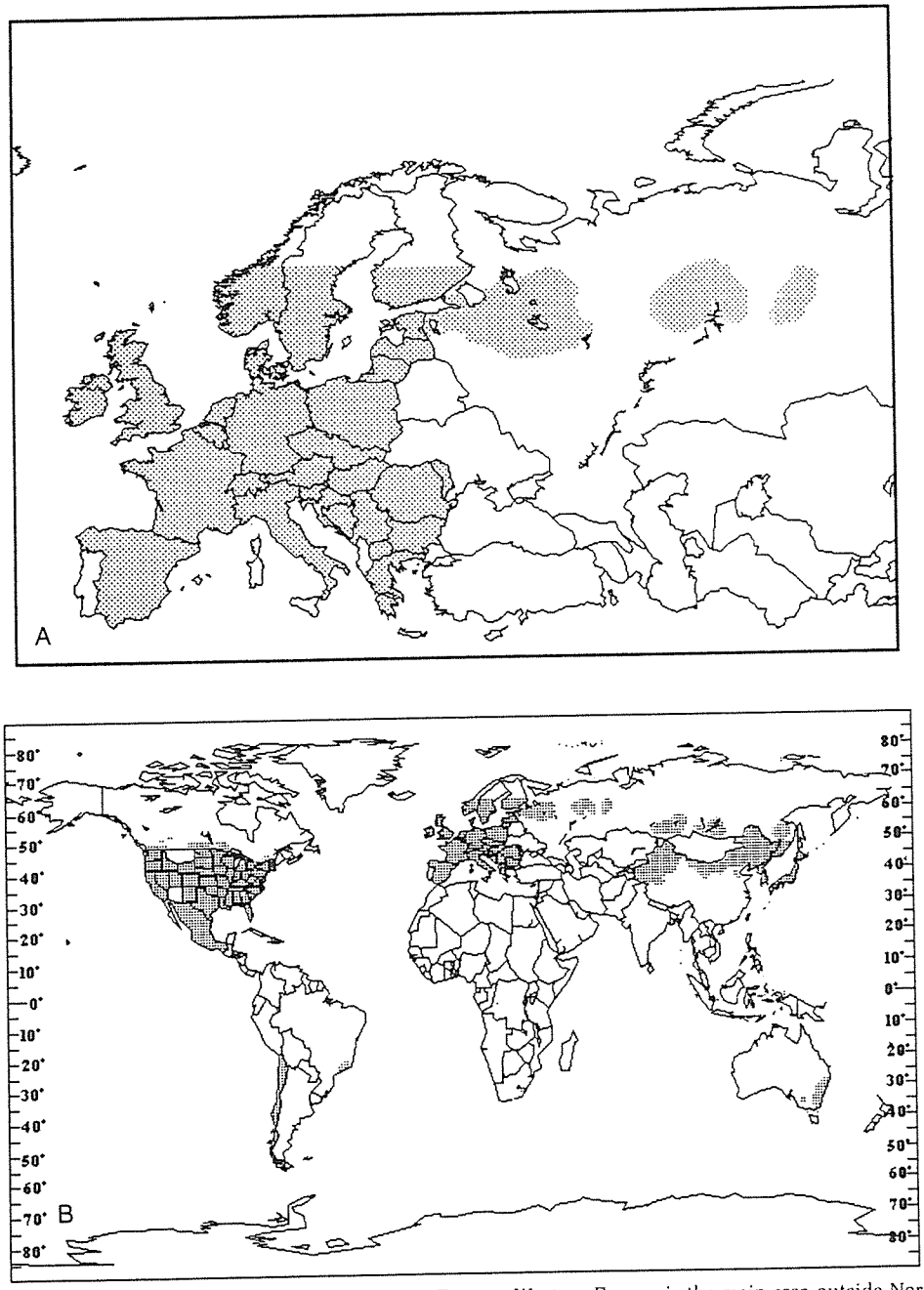

Figure 11–1. *A.* The geographic distribution of Lyme disease in Europe. Western Europe is the main area outside North America from which Lyme disease has been reported. This map shows European countries from which cases of Lyme disease have been reported either to the World Health Organization[231] or in the medical literature.[6, 7, 104, 106, 155, 170, 171, 197, 201, 233, 236, 237, 239–245, 247, 250–253] Reliable statistics on the incidence by country are not available, as reporting of cases is voluntary. The largest number of European cases have been reported from Austria, Germany, Switzerland and Czechoslovakia, and cases have also been reported from Belgium, Bulgaria, Denmark, Finland, France, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Sweden, United Kingdom, Romania, Russia (including Estonia and Moldavia), Spain and Yugoslavia. *B.* The worldwide geographic distribution of Lyme disease in temperate zone "Lyme Belts." In addition to North America and Europe, Lyme disease has also been reported from countries on four other continents and the Caribbean: Australia, Brazil, Chile, China, Honduras, Israel, Japan, Mexico, Puerto Rico and South Africa.[148–150, 152–154, 202–204, 254, 256–258, 260, 263, 264] Ixodid ticks infected with *Borrelia burgdorferi* are found in Korea, but no cases of Lyme disease have been reported yet.[265] One case of Lyme disease was reported in Argentina,[259] but it is not included in the map because the location of the case is not available. The geographic distribution of Lyme disease cases forms two belts, a 35-degree-wide northern temperate zone belt between 30 and 65 degrees north latitude in the Eastern Hemisphere, and another one slightly more southerly between 15 and 50 degrees north latitude in the Western Hemisphere, and these include the Asian, European and North American cases. In addition, the cases from Australia, South Africa and South America also appear to be clustered in a temperate zone belt between 20 and 40 degrees south latitude, but more cases are needed to determine if this is a true Southern Hemisphere " Lyme Belt."

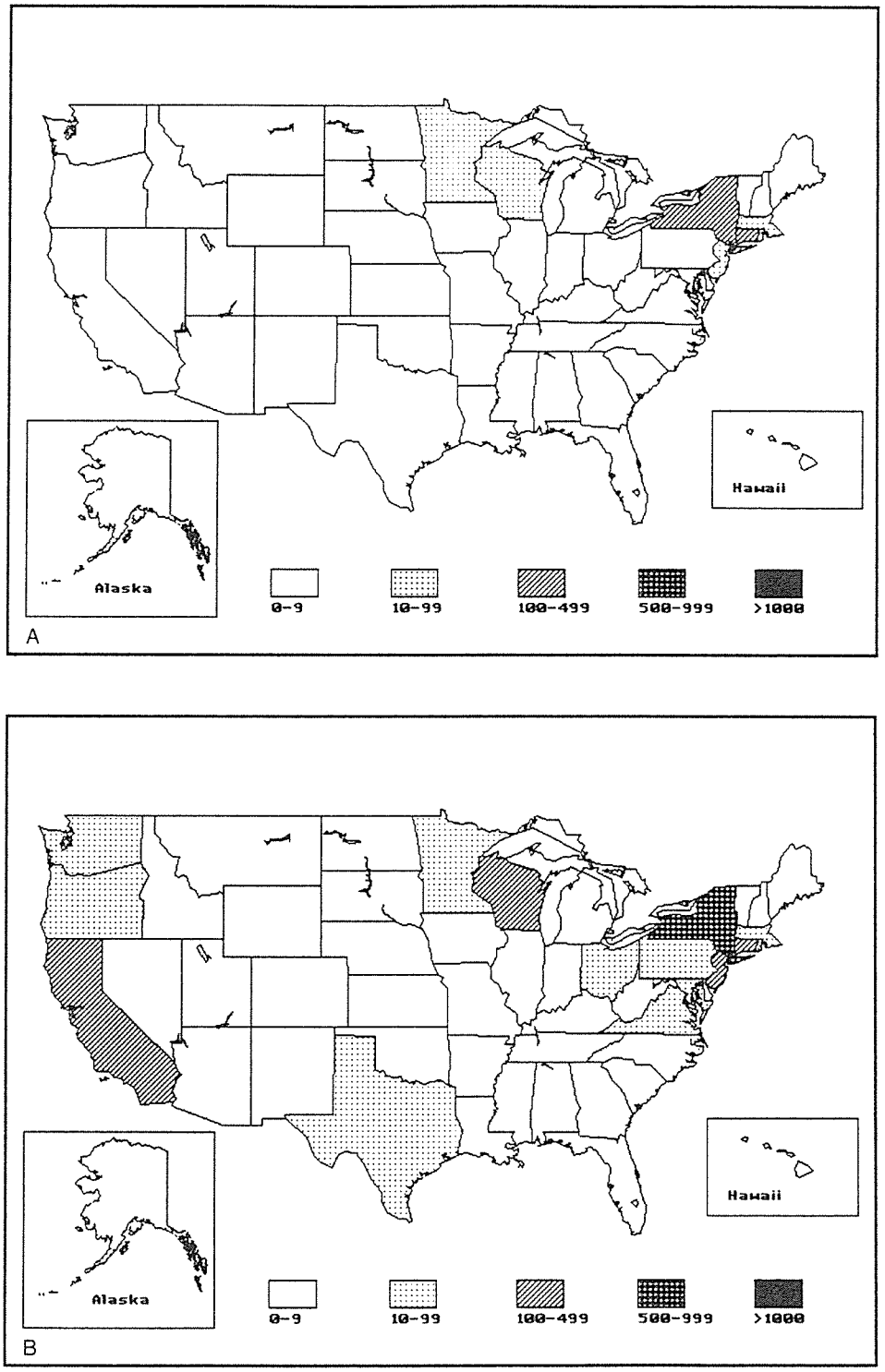

Figure 11–2. The increase in the number of cases and expansion of the geographic distribution of Lyme disease in the United States from 1982 through 1992. The number of cases of Lyme disease reported to the Centers for Disease Control and Prevention (CDC) by state health departments in *A*, 1982, *B*, 1987.

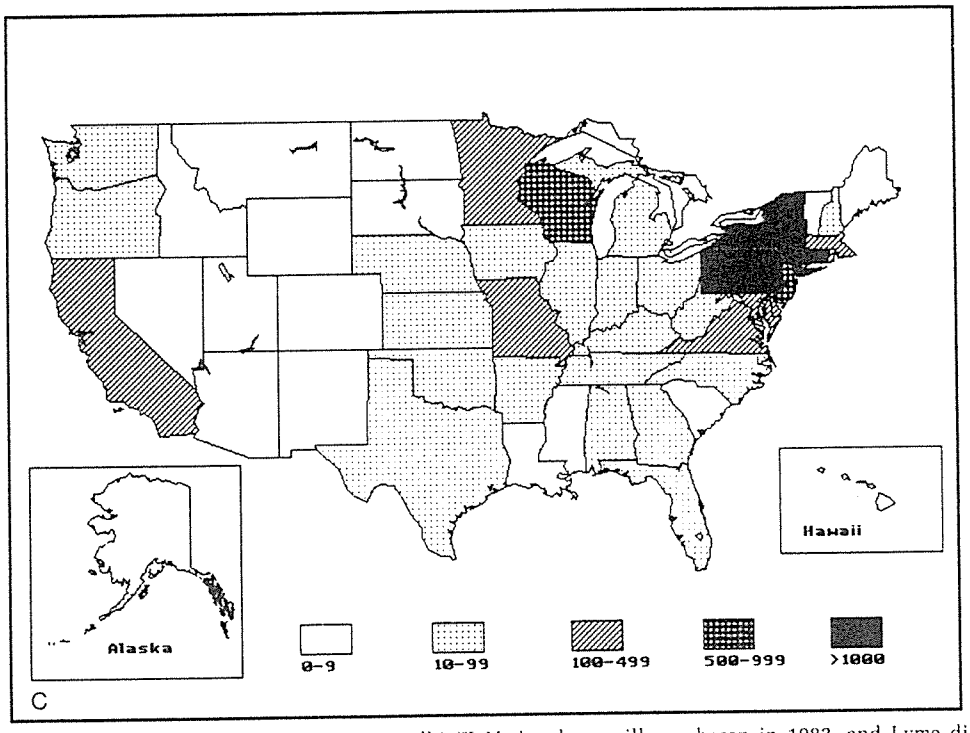

Figure 11–2 *Continued C.* 1992 (1992 data are provisional).[4, 205] National surveillance began in 1982, and Lyme disease became a notifiable disease in 1990.[4] A few cases of Lyme disease have also been reported from Canada, mostly from southern Ontario, which borders a Lyme endemic area of the northeastern United States.[226]

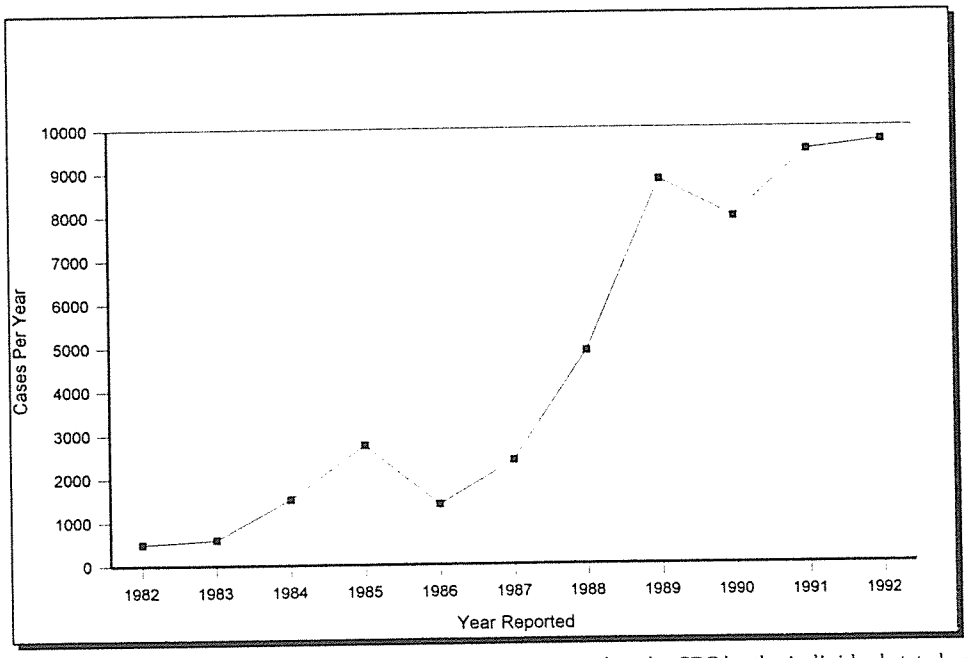

Figure 11–3. The number of cases of Lyme disease in the United States reported to the CDC by the individual state health departments has increased steadily from 1982 to 1992 (1992 data are provisional).[205] Lyme disease became a reportable disease in 1990.[4]

weeks of gestation with a high frequency of fetal cardiac abnormality, severe early congenital infection with fulminant neonatal sepsis and meningoencephalitis and a high frequency of cardiac abnormality, mild early congenital infection with growth retardation and mild cardiac abnormality, and late congenital infection with growth retardation, developmental delay, and neurologic, cutaneous, and skeletal involvement.

The Organism

Borrelia, *Leptospira* and *Treponema* are the three spirochetes that cause significant human infection, and all three have been reported to cause congenital infection. *Borrelia* organisms are arthropod-borne and infect birds, domestic and wild animals and humans. Several species of *Borrelia* cause systemic human borrelioses: *B. burgdorferi* is the tick-borne etiologic agent of Lyme borreliosis,[11, 35, 36] *B. recurrentis* is the agent of louse-borne relapsing fever[37] and *B. hermsii* and several related *Borrelia* species are the agents of tick-borne relapsing fever.[36, 37]

Borrelia burgdorferi as the Etiologic Agent of Lyme Borreliosis

In 1981, Burgdorfer and colleagues discovered (isolated) a new species of *Borrelia* in *Ixodes dammini* ticks from a Lyme endemic area in New York, demonstrated elevated antibody titers to this spirochete in convalescent sera of patients with Lyme disease and proposed that this spirochete was involved in the etiology of Lyme disease.[1, 35]

In 1982, Berger and colleagues demonstrated rare spirochetes, similar to the *I. dammini* spirochete, by Warthin-Starry silver stain in skin biopsy specimens of untreated but not treated patients with erythema migrans (EM) skin lesions and were able to isolate spirochetes from one specimen, thus supporting a spirochetal etiology for EM.[38, 39] In 1985, Berger and colleagues grew the *I. dammini* spirochete from several skin biopsy specimens of EM lesions[40] and thus confirmed this spirochete as the etiologic agent of North American EM.

In 1983, Steere and colleagues isolated the new spirochete, which was subsequently named *Borrelia burgdorferi*, from blood, spinal fluid and joint fluid of American Lyme disease patients and from *I. dammini* ticks in a Lyme endemic area of Connecticut and demonstrated serum IgM and IgG antibody titer increases directed against this spirochete in these patients.[12] Simultaneously in 1983, Benach and colleagues isolated the same spirochete from blood of patients with American Lyme disease and demonstrated similar seropositivity in these patients.[41] Both groups proposed the *I. dammini* spirochete as the etiologic agent of Lyme disease.[8, 12, 41] In the same year, Barbour and colleagues, including Burgdorfer, found (isolated) a new spirochete, similar to the *I. dammini* spirochete, in *Ixodes ricinus* ticks from an EM endemic area of Switzerland.[42]

Ryberg and colleagues, including Burgdorfer, in 1983 demonstrated significant levels of IgM and IgG serum antibodies against the North American Lyme disease spirochete in sera of European patients with lymphocytic meningoradiculitis (Bannwarth's syndrome) and proposed the Lyme disease spirochete as the etiologic agent of Bannwarth's syndrome.[15]

In 1984 and 1985, Asbrink, Hovmark and colleagues isolated the *I. ricinus* spirochete from skin biopsy specimens of European patients with EM,[13] acrodermatitis chronica atrophicans[13, 14] and lymphadenosis benigna cutis borrelial lymphocytoma[16] and demonstrated antibody titer elevations against this spirochete in these patients, and thus confirmed the spirochetal etiology of these European skin diseases. In 1987, de Koning and colleagues demonstrated spirochetes, morphologically consistent with *B. burgdorferi*, by Bosma-Steiner silver stain in European EM and lymphadenosis benigna cutis skin lesions, in synovia of patients with European Lyme arthritis and in spinal fluid of a patient with European Bannwarth's syndrome, and thus confirmed the spirochetal etiology of these additional European diseases.[43]

Morphology

Borrelia burgdorferi[1, 12, 42, 44–52] is a long (10 to 30 μm length), narrow (0.18 to 0.25 μm diameter), irregularly and loosely coiled, helical, motile, flexible spirochete with tapered ends and sheathed flagella. It is morphologically distinguishable from *Leptospira* by the lack of tight coiling and by the presence of many periplasmic flagella, from *Treponema* by the lack of cytoplasmic tubules, and from other *Borrelia* species by the presence of sheathed rather than unsheathed flagella, fewer flagella, tapered rather than sharply pointed ends, longer coiling wavelengths and a generally thinner shape.

It has an inner and outer cell membrane and four to eight flagella located subterminally in the periplasmic space between the inner and outer cell membranes. The trilaminar outer membrane structure is similar to but more fluid than that of gram-negative bacteria, and contains the embedded outer surface membrane lipoproteins and a lipopolysaccharide with weak endotoxin-like activity.

Molecular Biology

B. burgdorferi has several major antigens that can be separated by polyacrylamide gel electrophoresis and characterized antigenically by reactivity in Western blots with *B. burgdorferi*–specific polyclonal and monoclonal antibodies.[45, 46, 52–55]

The 100-kilodalton (kd) antigen p100 is genus- and species-specific[52] and cross-reacts minimally with other bacteria.[54] The constant molecular weight 60-kd common antigen p60 and the two antigens with molecular weights between 70 kd and 75 kd are heat shock proteins and cross-react broadly with other bacteria.[54] This 60-kd antigen is one of the two major proteins of the organism.[52, 55, 56]

The 41-kd flagellar antigen p41 is the other major protein of the organism[52, 55] and has a uniform molecular weight in all *B. burgdorferi* strains.[52] It has some cross-reactivity with other spirochetes, greater with other *Borrelia* species than with *Treponema* and *Leptospira*,[54] and has some spirochete-specific, some genus-specific and some species-specific epitopes.[54] *B. burgdorferi* has 100 per cent homology with the *I. dammini* and *I. ricinus* spirochetes, 59 per cent homology with *Borrelia hermsii*, 37 to 46 per cent homology with other *Borrelia* species and 2 per cent homology with *Leptospira* and *Treponema*.[51] A conserved area of DNA found in all *B. burgdorferi* strains has 70 per cent homology with *B. hermsii*.[57]

The smaller, variable-molecular-weight outer surface membrane lipoproteins, the 31- to 32-kd Osp A, the 33- to 36-kd Osp B and the 21- to 22-kd Osp C, of *B. burgdorferi* are species-specific and similar to the variable major proteins (VMP) of *Borrelia hermsii* and the other relapsing fever borreliae, and strain variation in the size or antigenicity of Osp B and possibly Osp A in culture has been occasionally found.[45, 46, 52, 55, 58, 59] These VMP proteins[45, 46, 59] are outer surface membrane lipoproteins encoded by linear DNA plasmids, define the relapsing fever serotype and show multiphasic antigenic variation during infection, in which the antigenicity of a VMP switches from one serotype to another every few days and allows the organism to repeatedly escape the immune response and produce the relapsing fever. It has been proposed that *B. burgdorferi* may show similar antigenic variation of Osp A, Osp B or Osp C during infection.[59]

Taxonomy

Borrelia burgdorferi,[47, 52] the etiologic agent of Lyme borreliosis, is a member of the order Spirochaetales, the family Spirochaetaceae, the genus *Borrelia* and the species *burgdorferi*. It was named *Borrelia burgdorferi* in 1984 when it was definitively established to be a new species.[11]

As more isolates of *B. burgdorferi* have been studied by various methods, including DNA restriction endonuclease analysis, polymerase chain reaction, ribosomal RNA sequencing, polyacrylamide gel electrophoresis, antigenic reactivity with monoclonal antibodies and ultrastructural studies, it has become clear that *B. burgdorferi* is a phenotypically and genotypically heterogeneous group.[61] Further subdivision into two additional species, *Borrelia garinii* and *Borrelia* group VS461, has been proposed on the basis of phenotypic and genotypic differences from *B. burgdorferi*.[52, 55, 61]

B. burgdorferi was initially divided into four phenotypes[53] and later into seven serotypes,[52, 55] serotypes 1 through 7, on the basis of antigenic diversity of Osp A as determined by reactivity with various monoclonal antibodies, and may possibly be further divided on the basis of antigenic diversity of other outer surface membrane antigens Osp B and Osp C. *B. burgdorferi* may also be divided into three subspecies—I (*B. burgdorferi* sensu stricto), II (*B. garinii*) and III (*Borrelia* group V S461)—based on DNA homology and ribosomal RNA restriction endonuclease pattern analysis.[52, 61] These three genotypes correspond to phenotypes based on major protein antigenicity, and within each group there is 76 to 100 per cent DNA homology, and only 46 to 74 per cent DNA homology between groups.[61]

There is clustering of isolates from different body sites, such as skin and spinal fluid, in certain groups based on antigenicity of Osp A and also of Osp B, as well as clustering of isolates from different geographic sites, such as North America and Europe.[52, 53, 55, 61] This clustering suggests the possibility of differences in pathogenicity and organotropism of strains of different phenotypes and genotypes, which may be related to consistent differences in clinical syndromes associated with these strains.[52, 55, 61] The similarity in Osp A phenotype of a few west central European strains and the North American strains raises the possibility that the *B. burgdorferi* originally introduced into the United States came from west central Europe.[53] The differences in DNA sequences for outer surface proteins of North American and European strains of *B. burgdorferi* suggest that these strains may have diverged long ago and may be pathogenically different.[57]

Isolation and Cultivation

B. burgdorferi lives in hosts such as vertebrates or hematophagous arthropods and is not found living free in the environment. In 1981, it was first isolated by Burgdorfer and colleagues from the midgut and

other tissues dissected from *Ixodes scapularis (dammini)* ticks from Shelter Island, a Lyme-endemic area of New York, and cloned to become the B31 strain of *B. burgdorferi*.[1] In 1983, Burgdorfer and colleagues also first isolated a similar spirochete from *Ixodes ricinus* ticks from the Seowald Forest, a Lyme-endemic area of Switzerland, and showed it to be morphologically and antigenically similar to the *I. dammini* spirochete.[42] Since then, it has been isolated from several species of ticks, vertebrate hosts and humans, and this is described in the section Epidemiology and Transmission.

B. burgdorferi is fastidious and microaerophilic and grows best in a liquid medium, modified Barbour-Stoenner-Kelly medium (BSK II), at 33° to 35° C.[42, 44] It has an 11- to 24-hour doubling time, which may be shortened to 11 to 12 hours under ideal conditions, but it may still take 3 weeks or longer to grow sufficiently in culture to become detectable.[12, 37, 44, 62]

Unlike other spirochetes, *B. burgdorferi* was also able to be grown in solid media, consisting of BSK II solidified with 1.3 per cent agarose, at 34° C in a candle jar.[50] It was found to produce colonies of several types, including a compact 0.43-mm round colony at the agarose surface, and three types of colonies that penetrated into the agarose, a 1.43-mm colony with a raised center surrounded by a diffuse ring, a colony composed of many small aggregations, and a diffuse 1.8-mm colony. It was also found to cause intense hemolysis on solid BSK II medium with horse blood.[63] More recently, *B. burgdorferi* has been found to have shorter doubling times of even 7 hours, when grown in solid media under strict anaerobic conditions and may be considered an obligate anaerobe.[64]

B. burgdorferi can be seen in cultures by dark-field or phase-contrast microscopy, stains with acridine orange, Giemsa, and silver stains such as Warthin-Starry or Dieterle[19] or Bosma-Steiner stain,[43] and can be demonstrated by immunofluorescence techniques utilizing *B. burgdorferi*–specific polyclonal or monoclonal antibodies.[65] It shows antigenic variation and loss of pathogenicity after 10 to 15 passages in culture and becomes noninfectious,[58] and this correlates with loss of plasmids.[45, 46, 51]

It is relatively easily isolated and grown from midgut and other tissues dissected from infected *Ixodes* ticks,[12, 37, 62] from which the isolation rate depends on the incidence of infection in the tick population, and from biopsy specimens of the leading edge of EM skin lesions, from which the isolation rate may be as high as 40 to 70 per cent under the best conditions.[13, 40] It has been isolated rarely from skin biopsy specimens of borrelial lymphocytoma and acrodermatitis chronica atrophicans, blood, synovium, spinal fluid, myocardium, placenta, fetal tissues or other tissues because the organism density is low[37] (see Diagnosis and Differential Diagnosis section).

The *B. burgdorferi*–specific polymerase chain reaction[66] (PCR) increases the sensitivity of detection of *B. burgdorferi* in body fluids and tissues. DNA sequences from the largest *B. burgdorferi* chromosome were used as the PCR target sequence because they were unique to *B. burgdorferi*, not present in other closely related *Borrelia* species or other spirochetes, and were highly conserved among *B. burgdorferi* strains.[66] PCR was used to demonstrate the spirochete in blood and skin biopsy specimens of patients with acute EM,[67, 68] in urine and spinal fluid of patients with neuroborreliosis of short duration[69] and in spinal fluid of patients with acute Lyme disease with or without neuroborreliosis.[70, 71]

Antibiotic Susceptibility

Isolates of *B. burgdorferi* from humans and ticks from different geographic areas, including the United States and Europe, have similar antimicrobial susceptibility patterns,[37, 62, 72–82] as shown in Table 11–1. *B. burgdorferi* antibiotic susceptibility can be assessed in vitro by comparison of the mean minimal inhibitory concentrations (MIC) and mean minimal bactericidal concentrations (MBC) for various antibiotics, and in vivo by comparison of the antibiotic dose required to cure 50 per cent of infected animals of their infection (CD_{50}).

B. burgdorferi was the most susceptible in vitro to the macrolides erythromycin, azithromycin, clarithromycin and roxythromycin (MIC, 0.01 to 0.06 μg/ml), and the second- and third-generation cephalosporins ceftriaxone, cefotaxime, cefuroxime and cefixime (MIC, 0.02 to 0.8 μg/ml). Isolates were also susceptible to the tetracyclines doxycycline, minocycline and tetracycline (MIC, 0.1 to 2.0 μg/ml); the penicillins amoxicillin, ampicillin, amoxicillin–clavulinic acid, mezlocillin and oxacillin (MIC, 0.03 to 4.0 μg/ml); imipenem (MIC, 0.25 μg/ml); and chloramphenicol (MIC, 2 μg/ml). The MIC value for penicillin (0.03 to 4 μg/ml) was poor and had a wide range. According to MIC values, the aminoglycosides, sulfonamides, metronidazole, rifampin and quinolones were not useful for *B. burgdorferi*.

For the various antibiotics, the in vitro MIC efficacy and the in vivo CD_{50} efficacy were in agreement except for penicillin and erythromycin. For erythromycin, evaluation of the CD_{50} showed that despite its excellent MIC, erythromycin was poorly active in vivo in the animal models. For penicillin, the poor in vivo efficacy may be due to strains of *B. burgdorferi* with high MIC values.

B. burgdorferi is killed slowly even by antibiotics to which it is sensitive, and prolonged exposure of

Table 11–1. IN VITRO AND IN VIVO ANTIMICROBIAL SUSCEPTIBILITIES OF *BORRELIA BURGDORFERI*

Antimicrobial Agent	Mean MIC[a] (μg/ml)	Mean MBC[b] (μg/ml)	Susceptibility[c] in Vitro	CD_{50}[d] (mg/kg/day)	Susceptibility in Vivo	References
Penicillin	0.03–4.0	0.5–8.75	MS-R	>320, >1975	R	37, 40, 62, 73, 76–78, 80, 82
Amoxicillin	0.5		S	50	S	73
Ampicillin	<0.25–0.47		S			62, 76
Augmentin	0.25		S	25	S	82
Mezlocillin	0.5		S			62
Oxacillin	1.0		S			82
Cefaclor	32–128	64–>256	MS			72
Cefalexin	16–32	32–>256	MS			72
Cefixime	0.8	0.8–1.6	S			72
Cefotaxime	0.12–0.45		S	50	S	62, 73, 80, 82
Ceftriaxone	0.02–0.06	0.02–3.8	S	50–240	S	37, 72, 73, 77, 78, 80, 82
Cefuroxime	0.06–0.18	0.25–0.75	S			72
Doxycycline	0.25–2.0	1.0–6.4	S			75, 76, 380
Minocycline	0.11–0.25	2.3	S			40, 76
Tetracycline	0.14–0.56	0.8–4.1	S	50–287	S	37, 62, 73, 76–78, 80, 82
Azithromycin	0.015		S	8	S	81
Clarithromycin	0.015		S	>50	R	81
Erythromycin	0.04–0.06	0.05–2.17	S	400–2353	R	37, 40, 62, 73, 76–78, 80–82
Roxythromycin	0.03		S	>50	R	81
Ciprofloxacin	2		MS			82
Ofloxacin	4		MS			82
Gentamicin	>16		R			62
Amikacin	>32		R			62
Chloramphenicol	2		S			62
Imipenem	0.25		S			82
Rifampin	>16		R			76

[a]MIC, minimal inhibitory concentration.
[b]MBC, minimal bactericidal concentration.
[c]S, susceptible to antimicrobial agent; MS, moderately susceptible to antimicrobial agent; R, resistant to antimicrobial agent.
[d]CD_{50}, dose of antimicrobial agent required to cure 50% of infected animals in animal model.

the spirochetes to the antibiotics is necessary to achieve adequate killing.[72, 78] In one study,[72] the length of time to kill 99 per cent of *B. burgdorferi* exposed to twice the MIC of antibiotic ranged from 72 hours for ceftriaxone and cefuroxime to 96 hours for cefixime. In another study,[78] the length of time to kill 99 per cent of *B. burgdorferi* was 72 hours for 0.1 μg/ml and 48 hours for 1.0 μg/ml of both penicillin and ceftriaxone, and 72 hours for 1.0 μg/ml of tetracycline. Low concentrations of tetracycline of 0.1 and 1.0 μg/ml allowed regrowth of organisms after prolonged incubation for 96 or more hours, but no such regrowth occurred with low concentrations of penicillin or ceftriaxone, or higher concentrations of tetracycline above 10 μg/ml.

The results of the animal model efficacy studies correlated better with clinical human patient results, since, for example, Steere and colleagues reported[83] that oral tetracycline was most effective, penicillin next most effective and erythromycin least effective for treatment of early Lyme disease. Several factors, in addition to the MIC of the antibiotic, play a role in determining whether an antibiotic will be clinically effective in elimination of *B. burgdorferi* infection, such as the duration of adequate serum, spinal fluid, intraocular, intrasynovial and tissue antibiotic concentrations; the efficacy of the host immune response; and potential sequestration of organisms in protected sites.

Interactions with the Immune System

T Lymphocyte Reactivity

B. burgdorferi antigen–triggered T cell activation occurs within a few days of the tick bite, develops prior to the antibody response, rises during infection, is initially directed against the 41-kd flagellar and the 31-kd Osp A antigens and is later also directed against additional outer surface membrane proteins, including the 20-kd Osp C, 31-kd Osp A and 34-kd Osp B, and the 60- to 66-kd heat shock protein antigens.[56, 84–90]

This response, measured by the *B. burgdorferi*–specific lymphocyte proliferative assay, is long last-

ing, may persist even in seronegative patients with Lyme borreliosis[84, 85] and may be greater in spinal fluid and synovial fluid than in peripheral blood in some patients with neurologic or arthritic manifestations of Lyme borreliosis.[91, 92] After successful antibiotic therapy of Lyme disease, the reactivity may decrease somewhat but is usually still detectable if the most sensitive assay methods are used.[84, 86–88, 90, 92]

Development of Serum Antibody

The antibody response to *B. burgdorferi* infection begins to develop a few days after the tick bite, after the T lymphocyte response,[89] and several differences exist between the response of North American and European patients. In both North American and European patients, the initial polyvalent antibody response to *B. burgdorferi* infection is directed primarily against the 41-kd flagellar antigen, while the late antibody response is more often directed primarily against the outer surface membrane proteins, 31-kd Osp A and 34-kd Osp B, in North American than in European patients.[52, 53, 93–96] In European but not North American patients, the early polyvalent antibody response may also be directed against the 18- to 23-kd outer surface protein Osp C.[52, 97]

The *B. burgdorferi*–specific IgM response develops in 1 to 3 weeks, peaks at 3 to 8 weeks and usually disappears after several months in uncomplicated treated patients but persists in the sicker patients with disseminated rather than localized infection, persistent infection and late chronic infection.[12, 60, 98–101] The initial specific IgM response is restricted to the 41-kd flagellar antigen,[60, 89, 99] while in patients with persistent or severe Lyme disease, it is directed against the 41-kd flagellar and the 83-kd antigens.[60, 98] In European patients, the initial IgM response may also be directed against the 18- to 23-kd Osp C antigens.[97] In patients with late Lyme disease, the IgM response is directed against the 41-kd flagellar and 34-kd Osp B antigens.[60] The IgM enzyme-linked immunosorbent assay (ELISA) antibody is higher in neuritis and arthritis patients with early Lyme disease than in patients with only EM.[98] In late chronic Lyme borreliosis, such as arthritis, neuroborreliosis and acrodermatitis chronica atrophicans, the specific IgM is often persistently positive by immunofluorescent assay (IFA), ELISA or Western blot assays.[12, 60, 87, 93, 95–98, 102–107]

The *B. burgdorferi*–specific IgG response develops at 3 to 8 weeks, peaks at 4 to 6 months and usually disappears after several months in uncomplicated treated patients, but may persist for years in persistent infection.[12, 60, 85, 98, 99] This response may be aborted by early antibiotic therapy.[85, 99] The initial IgG response is restricted to the 41-kd flagellar antigen and progressively expands against as many as 11 antigens: in persistent infection, the IgG response expands over months to years to include the 83-kd, 66-kd, 41-kd flagellar, 27-kd and 15-kd antigens; and in late infection to include the preceding plus the 75- and 60-kd heat shock proteins, 34-kd Osp B, 31-kd Osp A, 29-kd and 17-kd antigens.[60, 89] In addition, the European IgG response may include the 18- to 23-kd Osp C antigen.[97] This progressive expansion of the IgG antibody response develops regardless of whether the late manifestations are arthritic, neurologic or cardiac.[60] In late chronic Lyme borreliosis, such as arthritis, neuroborreliosis and acrodermatitis chronica atrophicans, the IgG is almost always positive by IFA, ELISA or Western blot assays.[12, 60, 87, 93, 95–98, 102–107]

The development of IgM and IgG antibody to new antigens months to years after onset of infection suggests the persistence of viable *B. burgdorferi* throughout the illness.[60] It has been proposed that the initial antibody response is restricted and later expands because the outer surface protein antigens may be slime covered or hidden intracellularly early in infection, and then are uncovered or exposed late in infection so that antibody to them can develop.[60]

Patients with neuroborreliosis usually have higher polyvalent *B. burgdorferi* antibody in spinal fluid than in serum,[96, 108, 109] and patients with arthritis usually have higher polyvalent specific antibody in synovial fluid than in serum.[110]

IgG1 and IgG3 subclass antibodies are primarily responsible for the antibody response to both early and late Lyme disease, regardless of whether the clinical manifestations are cutaneous, cardiac, neurologic or arthritic, and are the main sublasses that respond to protein antigens.[111] IgG2 subclass antibodies are responsible for some antibody responses in all stages of Lyme disease and are the main subclasses that respond to carbohydrate and lipopolysaccharide antigens.[111] IgG4 subclass antibodies react only minimally to Lyme disease.[111] The IgG1 response is directed against at least 12 *B. burgdorferi* antigens, the IgG3 response against 3 antigens, and the IgG2 and IgG4 responses against 2 antigens. The major immunogens of *B. burgdorferi* appear to be proteins rather than carbohydrates.

There are similarities between the immune responses in Lyme disease and syphilis.[60] In both there is initial suppression of the antibody response, followed by a restricted antibody response to a few antigens, followed later by an expanded response to several antigens. In late infection, there may be persistence of the specific IgM response even after development of specific IgG antibody. In both, use of the flagellar antigen in assays increases the sensitivity of detection of specific IgM antibody in early infection.

Induction of Other Antibodies

The *B. burgdorferi*–specific IgM antibody rise during infection is also associated with polyclonal B lymphocyte activation that peaks 3 to 6 weeks after onset of infection and corresponds to the time of maximal total and *B. burgdorferi*–specific IgM antibody.[101, 112] This B cell hyperactivity leads to development of several antibodies that are not specific for *B. burgdorferi* and are directed against host tissues, such as rheumatoid factor,[89, 101, 112] antinuclear antibody,[89, 101] anti-cardiolipin antibody,[89, 101] antibody to neuronal axons[113] and antibodies to myelin basic proteins.[114] False-positive VDRL antibody,[89] cryoglobulins[89, 101] and circulating immune complexes[89, 101, 112] are also found during this time. In patients with Lyme arthritis, the circulating immune complexes disappear from serum in 3 months but increase in synovial fluid, while in patients with cardiac or neurologic involvement, the immune complexes persist in the serum.[110]

Low levels of induced rheumatoid factor are detectable in 32 per cent of Lyme patients by ELISA IgM and in 4 per cent by latex agglutination assays.[112] Serum IgM antibodies to neuronal axons were found in all patients with neuroborreliosis in one study,[113] and antibodies to myelin basic proteins were found in spinal fluid of 20 per cent of patients with neuroborreliosis in another study.[114] *B. burgdorferi*–specific oligoclonal bands were found in spinal fluid of 40 to 100 per cent of patients with neuroborreliosis.[108, 115–117]

Anti-tick saliva antibody (ATSA) develops following a tick bite in response to the bolus of tick saliva injected, peaks at 3 to 5 weeks, persists for weeks to months and subsequently decreases.[118] This antibody is a good biologic marker for tick exposure and may be useful in confirming tick exposure in seronegative patients with suspected Lyme borreliosis.

Failure to Develop Serum Antibody

Early antibiotic therapy may attenuate or eliminate the *B. burgdorferi*–specific antibody response.[12, 85–87, 99, 119–122] Normally, *B. burgdorferi* antigen triggers B lymphocyte as well as T lymphocyte responses, but if antigen is removed by early antibiotic therapy, the antigen-dependent T cell stimulation of B cell maturation does not occur, and the mature antibody response does not develop.[85] Thus, if antibiotic therapy is given prior to the development of the mature IgG antibody response, this response may be aborted even though the infection may not be fully eradicated, and the patient may be seronegative; if antibiotic therapy is given after the development of the mature IgG response, it may persist even after successful eradication of the infection.[99] The longer the Lyme disease persists prior to antibiotic therapy, the more *B. burgdorferi*–specific antibody bands develop by Western blot assay.[85, 86] Seropositivity or seronegativity alone are not always reliable indicators of cure.

Dattwyler and colleagues described several patients treated promptly for Lyme disease with oral antibiotic therapy who still developed chronic Lyme disease later, and were seronegative by ELISA or IFA assays.[86] Western blot assays showed only faint antibody to the 41-kd flagellar antigen and 66-kd antigen, and these were also found in the control patient sera, but all of these seronegative patients had vigorous *B. burgdorferi*–specific T lymphocyte reactivity, which was absent in control patients.

Development of Cerebrospinal Fluid Antibody

B. burgdorferi invades the central nervous system early in two thirds of patients with disseminated infection even in the absence of neurologic symptoms.[71] Patients who develop either acute or chronic neurologic involvement may have intrathecal production of specific IgG, IgM or IgA antibodies to *B. burgdorferi* demonstrable by IFA, ELISA (standard, antibody capture or immune-complex ELISA) or Western blot assays.[89, 96, 109, 114, 123]

The production of *B. burgdorferi*–specific intrathecal antibody confirms neuroborreliosis. Patients with late neuroborreliosis may be seronegative and still have intrathecal specific antibody production presumably because oral antibiotic therapy eradicates the majority of the organisms systemically, but may fail to achieve adequate MICs in the CSF and allow persistence of the organism in this privileged site.[85, 96]

There are some differences in intrathecal *B. burgdorferi* antibody between North American and European patients.[96, 109, 123] Polyclonal intrathecal *B. burgdorferi*–specific antibody was found in almost all North American patients with early Lyme meningitis, and in almost half of those with late central nervous system borreliosis, but not in those with late peripheral nervous system borreliosis. Polyclonal intrathecal *B. burgdorferi*–specific antibody was found in almost all European patients with either early or late neuroborreliosis. In one study of North American Lyme disease,[124] there was intrathecal *B. burgdorferi*–specific ELISA IgM in 100 per cent and IgG in 40 per cent of patients with meningitis, and ELISA IgM and IgG in 26 to 30 per cent of patients with encephalitis.

B. burgdorferi–specific CSF antibody was directed primarily against the 41-kd flagellar antigen, and also against the 33-kd and 17-kd antigens.[96, 108, 123] CSF ELISA antibody levels were higher than serum

antibody levels,[96, 109] but IFA antibody levels were higher in serum than CSF.[115]

Patients with lymphocytic meningoradiculitis (Bannwarth's syndrome) as the manifestation of neuroborreliosis also had intrathecal production of *B. burgdorferi*–specific IgG oligoclonal bands that developed within a few weeks and persisted long after therapy and recovery.[108, 115] In one study, all neuroborreliosis patients developed serum IgM antibody directed against normal human axons, patients with arthritis developed less reactivity and patients with only EM developed none.[113] Some patients who had intrathecal *B. burgdorferi* antibody positivity and chronic Lyme meningoencephalopathy also developed intrathecal antibody directed against myelin basic proteins.[114]

Interactions with Complement

B. burgdorferi activates the alternate and classic complement pathways but is still resistant to the nonspecific bactericidal activity of normal human serum. However, in the presence of *B. burgdorferi* immune serum, it is sensitive to serum and is killed via the classic pathway.[49]

Interactions with Phagocytes

Human peripheral blood polymorphonuclear and mononuclear phagocytes are able to phagocytose opsonized and non-opsonized *B. burgdorferi*.[125]

Persistence in Tissue

B. burgdorferi is able to persist in tissues for months to years, sometimes even after antibiotic therapy. This persistence often occurs in immunologically privileged sites and may occur even in the presence of seropositivity. *B. burgdorferi* has been isolated from Lyme arthritis joint fluid 3 months after antibiotic therapy[126] and 1 year after onset without therapy,[127] from EM skin lesions 2.5 and 3 months after therapy,[128] from acrodermatitis chronica atrophicans skin lesions 2.5 and 10 years after onset[13, 14] and from spinal fluid 3, 7.5, and 10 months after antibiotic therapy[128] and 2.5 months after onset without therapy.[129] The development of *B. burgdorferi*–specific IgM antibody responses to new spirochetal antigens late in the course of Lyme disease also indicates long-term persistence of live organisms in these patients.[60]

Correlation of Clinical Manifestations with HLA Type

Differences in HLA specificities may determine *B. burgdorferi* antigen binding and presentation to T cells and the composition of the T cell response, and may be related to susceptibility to infection.[130]

In one small study,[124] 83 per cent of patients with neuroborreliosis manifested by multifocal leukoencephalitis who responded well to antibiotic therapy were HLA DQw3 or DQw7 positive and DR4 negative, and patients who responded poorly or experienced relapse were DQw1 positive. In another study,[130] 89 per cent of patients with long duration (12 to 48 months) chronic Lyme arthritis were HLA DR2 or DR4 positive compared with 27 per cent of patients with short-duration Lyme arthritis, and HLA DR4 positivity but not DR2 positivity correlated with lack of response to antibiotic therapy. There has also been an association between Czechoslovakian meningopolyneuritis and HLA DR2 and DR4, Austrian acrodermatitis chronica atrophicans and HLA DR2 and late encephalomyelitis and DR2.[130]

Epidemiology and Transmission

The recognition of Lyme arthritis as an infectious disease, the discovery of its geographic clustering and association with Ixodid tick bites, the discovery of the new spirochete *Borrelia burgdorferi* in Ixodid ticks, the development of diagnostic assays based on *B. burgdorferi*, the confirmation of *B. burgdorferi* as the etiologic agent of Lyme borreliosis, the recognition of a wide variety of large and small animal hosts and reservoirs and the development of therapeutic antibiotic regimens are all parts of a fascinating saga of creative curiosity, persistence and cooperation between the people in the Lyme-endemic communities and the clinical and laboratory investigators.[8, 35, 36] The subsequent recognition that several unusual European diseases of previously unknown etiology were also caused by *B. burgdorferi* and related strains transmitted by European and Asian *Ixodes* ticks completed a remarkable saga.

Historical Review

In 1909, Afzelius described a migrating annular skin lesion in a Swedish woman at the site of an *Ixodes ricinus* sheep tick bite, called it erythema chronicum migrans (ECM) and proposed that it was a zoonosis transmitted by a tick from an animal reservoir to humans.[9, 35] ECM became a well-recognized European disease thought initially to be caused by either a tick-associated toxin or infectious agent.[35]

Another European disease, acrodermatitis chronica atrophicans (ACA), which had first been described by Buchwald in 1883 in Germany, was noted

to frequently be preceded by ECM and was named ACA Herxheimer by Herxheimer and Hartman in 1902.[35] In 1922, Garin and Boujadoux described cutaneous lesions and paralysis following a tick bite and suspected a spirochetal etiology,[131] and in 1944, Bannworth described chronic lymphocytic meningitis following European ECM, and this became known as Garin-Boujadoux-Bannwarth syndrome, or simply Bannwarth's syndrome.[35, 132]

In 1948, Lennhoff reported spirochetes in ECM skin biopsy specimens,[35, 133] but this finding could not be confirmed by others and was essentially forgotten. By 1949, there were suggestions in Europe that penicillin therapy was beneficial in ECM,[35, 134] and between 1948 and 1957 Hollstrom found that most European ECM cleared within 2 weeks after intramuscular penicillin therapy.[38, 134] In 1949, Thyresson successfully treated patients with ACA with penicillin, and in 1952, Gruneberg considered spirochetes as possible etiologic agents.[14]

In 1955, Binder and colleagues, in Europe, transplanted skin biopsy specimens from the rim of an ECM lesion from a patient to three scientist-volunteers who then developed ECM lesions within 3 weeks, and also transplanted a specimen from the skin lesion of one of these volunteers to the two other volunteers and to a fourth volunteer who all developed ECM skin lesions that responded to penicillin therapy.[35, 135] They thus established that ECM was caused by a penicillin-susceptible infectious agent transmitted by the *Ixodes ricinus* tick,[35] but the etiologic agent was still not known. In 1955, Gotz transmitted ACA from patient to patient by transplantation of ACA skin biopsy specimens[14] and thus confirmed ACA as an infectious disease. Both ECM and ACA became well-known European skin diseases.

The first report in the medical literature of North American erythema migrans (EM), as ECM was eventually called, was from Wisconsin in 1970 by Scrimenti,[136] although retrospective studies have found that it existed in small foci in New England as early as 1962 and 1965.[137, 138]

The recognition of Lyme arthritis as a distinct disease came in 1975, when two mothers from the small village of Old Lyme, Connecticut, brought the existence of an epidemic of children diagnosed as having juvenile rheumatoid arthritis to the attention of the state health department and the Yale Rheumatology Clinic. Steere and colleagues investigated and recognized an outbreak of infectious arthritis, noted that many patients had an unusual rash similar to European EM, proposed that transmission occurred via an arthropod vector and named the disease Lyme arthritis.[10] By 1980, it became known as Lyme disease because meningoencephalitis and myocarditis were also recognized as part of the disease.[8]

Many patients with Lyme disease remembered a preceding tick bite and one patient saved the tick, which was identified in 1977 as *Ixodes scapularis*,[2] a tick related to the *Ixodes ricinis* tick associated with European ECM. In 1979, this tick was classified as a new species, *Ixodes dammini*,[138, 139] but later in 1993, it was reclassified as *I. scapularis*.[140] Between 1977 and 1979, the geographic prevalence of Lyme disease was found to correlate with the presence of *I.dammini* ticks,[2, 138, 141] but the etiologic agent was still not known.

Serologic and culture studies of Lyme disease patients for many infectious agents, including viruses, rickettsiae, *Mycoplasma* and others, was unrevealing.[142] In 1980, Steere and colleagues[143] reported that penicillin or tetracycline therapy shortened the duration of the EM and reduced the severity and frequency of subsequent arthritis. They concluded that antibiotic therapy was useful and that the disease was caused by a penicillin-sensitive bacterium such as a spirochete.

Eventually, in 1981, a new spirochete was accidentally discovered by Burgdorfer in *I. dammini* ticks collected for a rickettsial study from Shelter Island, New York, a highly Lyme-endemic focus.[1, 35] This spirochete was shown to be able to induce EM lesions in rabbits, and convalescent sera from Lyme patients reacted with it in immunofluorescence assays.[1, 35] In 1983, two groups of investigators, Steere and colleagues[12] and Benach and colleagues,[41] isolated the same spirochete from patients with Lyme disease, found specific antibody titers against this spirochete in convalescent sera of Lyme disease patients and concluded that the *I. dammini* spirochete was the etiologic agent of Lyme disease. In 1984, it was named *B. burgdorferi* when it was confirmed to be a new species.[11]

In 1983, Barbour, Burgdorfer and colleagues isolated a spirochete similar to the *I. dammini* spirochete from *Ixodes ricinus* ticks.[42] Between 1983 and 1986, this spirochete, which was indistinguishable from *B. burgdorferi*, was also confirmed by several investigators to be the etiologic agent of European ECM,[13] European ACA,[13, 14] European Bannwarth's syndrome[15, 129] and European borrelial lymphocytoma[16] by demonstration of a serologic response to this spirochete in sera from patients with these diseases, and by its successful isolation from clinical samples.

The first case of congenitally transmitted Lyme borreliosis was described by Schlesinger and colleagues in 1985 following gestational Lyme disease acquired in Wisconsin.[19] Since then, several additional cases have been reported, and it has become

clear that gestational Lyme borreliosis carries a low but concerning risk of congenital infection.

The incidence of Lyme borreliosis has continued to increase in North America since it was initially recognized, and it is now the most common tick-borne infection in North America,[5] Europe and possibly the world.[6, 7]

Tick (and Other Arthropod) Vectors

Epidemiologic studies indicated that Lyme borreliosis is caused by *B. burgdorferi* transmitted from animals to humans by Ixodid ticks that are members of the *Ixodes ricinus* complex,[139, 144] and that this transmission occurs during tick feeding because of either tick salivation or regurgitation of organisms.[145, 146] Ticks that have been associated with this transmission are the deer tick *Ixodes dammini/scapularis* in the northeastern and upper midwestern United States,[5, 138, 141] the western black-legged tick *Ixodes pacificus* in the western United States,[2, 138, 141, 147] the sheep tick *Ixodes ricinus* in Europe,[6, 42] the *Ixodes persulcatus* tick in Asia[148, 149] and the *Ixodes holocyclus* tick in Australia.[150]

In 1979, the northern *Ixodes scapularis* tick initially associated with North American Lyme disease was considered to be morphologically different from the southern *Ixodes scapularis* and was placed in a separate species, *Ixodes dammini*.[138, 139, 151] However, in 1993, on the basis of mating experiments, DNA homology, chromosomes, morphology and life cycle, it was determined to be the same as *I. scapularis* and has now been reclassified as *I. scapularis* because this name preceded the name *I. dammini*.[140] In this chapter, the name *I. dammini* or *I. dammini/scapularis* is used to indicate the northern *I. scapularis* tick, and the name *I. scapularis* refers to the southern tick. The interface of the northern and southern ticks occurs in Maryland and Virginia.[151]

In 1981, Burgdorfer and colleagues isolated a new spirochete from 61 per cent of *I. dammini/scapularis* ticks from Shelter Island, New York, a Lyme endemic area,[1] and later also found *B. burgdorferi* in 1 to 2 per cent of *I. pacificus* from the western United States, and in 29 per cent of *I. ricinis* from western Europe.[35, 42] *B. burgdorferi* has also been isolated from 20 to 45 per cent of *I. persulcatus* ticks from Lyme-endemic provinces in China[148, 152, 153] and from 7 to 22 per cent of *I. persulcatus* ticks from Lyme-endemic areas of Japan.[154]

B. burgdorferi is often found in nymphal and adult stages of *Ixodes dammini/scapularis, pacificus* and *ricinus*, but rarely in unfed larvae, because infection is acquired by larva by feeding on *B. burgdorferi*–infected animal reservoirs, is passed transstadially (between stages) from larvae to nymphs to adults and is rarely passed transovarially from infected female ticks to less than 1 per cent of eggs and larvae.[12, 144, 155–159] However, since occasional female ticks may produce progeny with high infection rates, rare transovarial transmission may be important for establishment of new endemic foci of Lyme disease in instances in which an infected tick is transported by birds or other methods into a new previously nonendemic area.

In the United States, most Lyme disease transmission is due to the *I. dammini/scapularis* and *I. pacificus* tick vectors, but several other species of ticks have been thought to be vectors in some geographic areas, particularly in areas where *I. dammini* is not prevalent[5]: the Lone Star tick *Amblyomma americanum* in New Jersey,[160] North and South Carolina,[161, 162] Kentucky,[163] Alabama[164] and Texas[165]; *Dermacentor variabilis* in Kentucky[163]; *Ixodes scapularis* in Georgia[166], Virginia[167] North Carolina and South Carolina[161, 162]; *Ixodes cookei* in West Virginia[168]; *Ixodes dentatus* in West Virginia[168]; and *Amblyomma angustus* in Washington State.[169] There have been occasional reports of suspected Lyme borreliosis transmission by other hematophagous arthropods such as mosquitoes[170] and tabanid flies (deer and horse flies) in North America and Europe.[171, 172] The *Ixodes affinis* and *Ixodes pararicinus* ticks from Peru are also members of the *Ixodes ricinus* complex and are considered potential vectors of *B. burgdorferi*.[173] Figure 11–4 shows different stages of three common North American ticks: *I. dammini/scapularis, A. americanum*, and *D. variabilis*.

In addition to *Ixodes dammini, pacificus, ricinus* and *persulcatus* ticks,[139] *B. burgdorferi* has also been isolated from ticks of other *Ixodes* species and of four additional genera (Table 11–2), including the Lone Star tick *Amblyomma americanum*[139, 157, 160, 164, 174–178]; the Gulf Coast tick *Amblyomma maculatum*[178]; the dog tick *Dermacentor variabilis*[139, 160, 174, 175, 179, 180]; the rabbit tick *Dermacentor parumapertus*[176]; *Ixodes cookei*[175, 177]; the rabbit tick *Ixodes dentatus*[139]; the woodrat tick *Ixodes neotomae*[139]; the hedgehog tick *Ixodes hexagonus*[139]; the Asian ticks *Ixodes ovatus*,[154] *Ixodes granulatus*[153] and *Ixodes rangtangensis*[153]; the dog tick *Rhipicephalus sanguineus*[139, 176]; the rabbit tick *Haemaphysalis leporispalustris*[139]; and the Asian ticks *Haemaphysalis concinna*,[153] *Haemaphysalis bispinosa*[153] and *Haemaphysalis longicornis*.[153] It has also been isolated from the cat flea *Ctenocephalides felis* in Texas,[176, 178] and from tabanid flies and mosquitoes (Table 11–2).[139, 157, 160, 176, 179]

In order for a tick to be vector competent for *B. burgdorferi*, it must be able to become and remain infected and transmit the infection to a host. *Ixodes*

Figure 11–4. Common species of ticks. *Ixodes ricinus* complex ticks are vectors of transmission of the Lyme disease spirochete, *Borrelia burgdorferi*, to humans. *A. Ixodes dammini/scapularis* (northern species) adult female. *B.* Adult male. *C.* Nymph. The North American deer tick *Ixodes dammini* (the same species as the black-legged tick *Ixodes scapularis*) is the vector in the northeastern and north central, and possibly in southeastern and south central, United States. Other *Ixodes* ticks are similar in appearance, such as the western black-legged tick *Ixodes pacificus* (the vector in the northwestern United States), the European wood or sheep tick *Ixodes ricinus* (the vector in Europe) and the taiga tick *Ixodes persulcatus* (the vector in Eurasia). Some non-*Ixodes* ticks have been suspected but not proven to be associated with transmission of the Lyme disease spirochete to humans: *(D) Amblyomma americanum* adult female. *(E)* adult male, *(F)* nymph and *(G)* larva. The Lone Star tick *A. americanum* may be a vector in the southeastern and south central United States. *H. Dermacentor variabilis* adult female. *I.* adult male. The American dog tick *Dermacentor variabilis* and the Rocky Mountain wood tick *Dermacentor andersoni* may be occasional vectors and are similar in appearance.

dammini/scapularis, pacificus, ricinus and *persulcatus* are efficient and competent *B. burgdorferi* vectors,[139, 181] but *I. cookei, A. americanum* and *D. variabilis* are not efficient vectors and do not pass the spirochete transstadially.[139, 174, 177–179, 180] In one study in southeastern Connecticut, the tabanid flies had rates of infection of 4 to 9 per cent, and because they feed many times during a feeding period and fly over a wide range, they may be important as minor vectors of *B. burgdorferi*.[179] Mosquitoes are probably not vector-competent for *B. burgdorferi*, as the spirochete survived only for 6 days in the gastrointestinal tract of mosquitoes.[179]

Tick Vector Life Cycles and Reservoir Animal Hosts

The *Ixodes ricinus* complex ticks are all three-host ticks with a 2- to 3-year life cycle, and each of the three stages of the tick feeds once (Table 11–3): larvae feed on small rodents, reptiles and birds; nymphs feed on small or medium-sized mammals; and adults feed on large mammals.[139, 144, 151, 158, 181–184] Eggs laid by infected adult female ticks usually hatch into uninfected larvae, as the rate of transovarial transmission of the spirochete is very low,[12, 144, 155–159] and larvae acquire the spirochete by feeding

Table 11–2. ARTHROPOD SPECIES FROM WHICH *BORRELIA BURGDORFERI* HAS BEEN ISOLATED

Species	Common Name	Vector Competence for *B. burgdorferi*
Ixodes dammini/scapularis	Deer tick	Efficient
Ixodes pacificus	Western black-legged tick	Efficient
Ixodes ricinus	Sheep tick	Efficient
Ixodes persulcatus	Taiga tick	Efficient
Ixodes dentatus	Rabbit tick	Efficient
Ixodes neotomae	Woodrat tick	Efficient
Ixodes cookei		Efficient
Ixodes hexagonus	Hedgehog tick	Poor
Ixodes ovatus		?
Ixodes granulatus		?
Ixodes rangtangensis		?
		?
Amblyomma americanum	Lone Star tick	Poor
Amblyomma maculatum	Gulf Coast tick	?
Dermacentor variabilis	Dog tick	Poor
Dermacentor parumapertus	Rabbit tick	?
Dermacentor albipictus	Winter tick	?
Rhipicephalus sanguineus	Dog tick	?
Haemaphysalis leporispalustris	Rabbit tick	?
Haemaphysalis concinna		?
Haemaphysalis bispinosa		?
Haemaphysalis longicornis		?
Ctenocephalides felis	Cat flea	?
Tabanid flies	Deer and horse flies	?
	Mosquitoes	Poor

on *B. burgdorferi* spirochetemic competent reservoir hosts. The infection is maintained in the larvae through the transstadial molt and is passed from the larval to the nymphal stage. The infected nymphs transmit the infection to reservoir-competent hosts by feeding, maintain the infection through the transstadial molt and pass it to the adult stage of the tick, which then mates while feeding on a large mammalian host.

In order for *B. burgdorferi* infection to be maintained in nature, there must be horizontal transmission of infection from infected nymphs to a competent reservoir host to larvae, which requires that nymphs feed prior to larvae on the same reservoir-competent host. The white-footed mouse, *Peromyscus leucopus*, and other *Peromyscus* species mice are reservoir-competent for *B. burgdorferi*, are easily infected by a single infected tick bite, develop persistent spirochetemia, are able to infect feeding ticks and are almost universally infected in endemic areas.[185, 186] Humans are accidental hosts of all stages of *I. dammini/scapularis* and *I. ricinus*, and of the adult ticks of *I. pacificus*.

The life cycle of *I. dammini/scapularis* has been the most extensively studied.[139, 144, 151, 157, 181–184] Eggs laid on the ground in the spring hatch into larvae in the mid to late summer. In the late summer, larvae become infected with *B. burgdorferi* by feeding for 3 to 5 days on small rodents such as the white-footed mouse, which are reservoirs for *B. burgdorferi* infec-

Table 11–3. PREFERRED HOSTS FOR DIFFERENT STAGES OF *IXODES RICINUS* COMPLEX TICKS THAT TRANSMIT *LYME BORRELIOSIS* TO HUMANS[a, b]

Tick	Larval and Nymphal Stages	Adult Stage	Total No. Hosts
I. dammini/ scapularis	White-footed mouse, *Peromyscus leucopus*	White-tailed deer, *Odocoileus virginianus*	80
I. pacificus	Fence lizard, *Sceloporus occidentalis*	Black-tailed deer, *Odocoileus hemionus columbianus*	80
I. ricinus	Woodmouse, *Apodemus sylvaticus* and *flavicolus*	Deer, *Capreolus capreolus*	317
	Vole, *Clethrionomys glareolus*	Canids, cattle, hares, sheep	
I. persulcatus	?	Deer, canids, cattle, hares	241

[a]Data from references 139, 144, 183, 187, 188, 190 and 191.
[b]Humans are incidental hosts of all stages of the ticks.

tion, and the fed larvae then fall to the ground. The infection persists in the larvae through the winter and through the transstadial molt the following spring into the nymphal stage. The nymphs are voracious and feed in the spring and early summer (May and June) for 4 to 7 days on a variety of hosts, including small rodents such as the white-footed mouse, birds, wild and domestic animals and occasionally humans, and the fed nymphs fall to the ground. Because transovarial passage of *B. burgdorferi* infection is rare, horizontal transmission is necessary to maintain the tick infection, and occurs because infected nymphs feed earlier in the season on the same hosts as the larvae and infect the hosts, which then infect the larvae. The nymphs molt into adults by late summer or fall, and the spirochete is passed transstadially to the adult form. The adults quest on vegetation, especially at edges between lawns and forests,[139] for mid to large mammalian hosts, such as white-tailed deer, in the fall, winter and following spring, and mate while the females are feeding on these hosts. Because tick mating occurs on these large mammalian hosts, particularly deer, these hosts are needed for tick survival but not for maintenance of the *B. burgdorferi* infection.[186] The females then feed for 8 to 11 days, fall to the ground, lay eggs in the spring and die, and the eggs hatch in 45 to 53 days into larvae in the summer.

The preferred small rodent host of *I. dammini/scapularis* is the white-footed mouse, *Peromyscus leucopus*, which is also the primary reservoir of *B. burgdorferi* infection in nature,[144, 151, 186] and the preferred large mammal host is the white-tailed deer, *Odocoileus virginianus*, which is the host of the reproductive stage of the tick,[151, 184] but larvae and nymphs have been found attached to 80 different species of mammals and birds, and adult ticks to 13 species of medium to large mammals.[139, 141, 144, 183, 187] The mice remain chronically spirochetemic but asymptomatic.[185] The deer are occasionally spirochetemic with *B. burgdorferi* but are also asymptomatic.[182, 184, 187, 188] The deer are responsible for the geographic expansion of Lyme endemic areas because the infected *I. dammini* adult females overwinter and mate on the deer, and the deer travel widely. The geographic distribution of North American Lyme disease and *I. dammini* correlates with that of the white-tailed deer.[184] The meadow vole *Microtus pennsylvanicus* is less important as a secondary small mammal reservoir host of *I. dammini*.[183] In areas where the enzootic *I.dammini*–white footed mouse cycle of maintenance of *B. burgdorferi* infection is inefficient or does not occur, the infection may be maintained by a parallel cycle involving the cottontail rabbit, *Sylvilagus floridanus*, the rabbit tick *Ixodes dentatus* and *I. dammini*.[188, 189]

Ixodes pacificus[139, 144, 190, 191] has a life cycle similar to that of *I. dammini* but with some differences in hosts and reservoirs. There are some differences between the life cycles of European *I. ricinus* and North American *I. dammini* ticks[139, 144, 183, 188]: *I. ricinus* has a 2- to 3-year life cycle, less coherent seasonal activity and a broader host range than *I. dammini*. *I. ricinus* occurs in geographic areas even in the absence of deer because it can use cattle as well as deer as the large mammalian host.[183] The geographic distribution of Lyme borreliosis in Europe correlates with the geographic distribution of *I. ricinus* ticks[6] and of deer,[183] as in North America. *I. persulcatus*[144, 188] has a similar life cycle but a greater host range, which includes 241 different species of mammals, birds and reptiles, although deer, canids, cattle and hares are particularly important hosts.[148] The geographic distribution of Lyme disease in China, Japan and eastern Russia correlates with that of *I. persulcatus*.

Seasonality of Human Tick Bites/ Transmission of *B. burgdorferi* Infection

Humans acquire Lyme borreliosis by being used as the incidental host of a *B. burgdorferi*–infected tick. Table 11–4 shows the seasonality of human

Table 11–4. SEASONAL RISK OF HUMAN TICK BITES AND DEVELOPMENT OF LYME BORRELIOSIS (LB[a])

Geographic Location	*B. burgdorferi* Tick Vector	Months of Tick Feeding Activity, by Stage			Most Common Months of Onset of LB
		Larvae	*Nymphs*	*Adults*	
North America Northeast, Atlantic, Midwest	*I. dammini/scapularis*	July–Sept.	May–June[b]	Oct.–May	May–Sept. (peak June–July)
Pacific Northwest	*I. pacificus*	Mar.–June	Mar.–June	Nov.–May[b]	Jan.–May
Europe	*I. ricinus*	Mar.–Nov.	Mar.–Nov.	Mar.–Nov[b]	May–Oct.
Asia	*I. persulcatus*			May–June[b]	May–June

[a]Data from references 3, 17, 101, 106, 139, 148, 167, 171, 193, 197, 206, 209, 211, 213–216, 274 and 318.
[b]Stage responsible for most *B. burgdorferi* transmission to humans.

tick bites and the time of onset of Lyme borreliosis by geographic region.

In North America, humans are incidental hosts of all stages of *I. dammini/scapularis*[141] and are usually infected by voracious host-seeking *I. dammini* nymphs during the spring and early summer in May and June, and the peak incidence of Lyme disease occurs 1 month later in June and July.[139, 193] Epidemiologic studies have found the tick infectivity rate increases from less than 1 per cent of larvae, to 45 to 74 per cent of nymphs, to 57 to 87 per cent of adult ticks.[186] Because the nymphs are so small, and because the tick injects saliva containing anti-inflammatory, analgesic, antihemostatic and immunosuppressive components while feeding,[183] the bites are not painful and often go unnoticed long enough to allow *B. burgdorferi* transmission, which usually takes 2 days.[194, 195] Human infection is less often caused by adult female *I. dammini*, which feed in late fall through early winter from October through May, with a peak in October, even though *B. burgdorferi* infection rates are higher than for nymphs, because the adults are larger and more easily detected and removed before transmission of *B. burgdorferi* infection occurs.[139, 194, 195]

The *I. dammini/scapularis* tick takes a long time to feed, and during a 5-day feeding period, the female tick ingests 3.5 ml of blood and injects or regurgitates 2.5 ml of fluid secretions into the host.[118] The blood meal triggers multiplication of the *B. burgdorferi* associated with the tick's gastrointestinal tract, which may disseminate to the hemolymph by the third day of feeding, and which may then spread to the host either by injection of *B. burgdorferi*–containing tick saliva or regurgitation of *B. burgdorferi*–containing tick gut contents into the dermal feeding cavity created by the tick.[145, 146] These immunosuppressive salivary secretions result in host-specific immune evasion by the tick that modifies the tick attachment site so that *B. burgdorferi* deposited in the skin may be in an immunologically privileged site and may be protected against attack by the host immune system.[183]

In the Pacific Northwest, humans are frequently bitten by the adult stage of *I. pacificus*, which feeds from November to May, but not the larvae or nymphs, which feed from March through June,[139] and the peak onset of Lyme disease occurs from January through May.[3] Because the incidence of *B. burgdorferi* infection of *I. pacificus* is much lower than that of the northeastern *I. dammini/scapularis*, the rate of human infection following *I. pacificus* bites is also lower.[191, 192]

In Europe, humans are incidental hosts for all stages of the I. ricinus tick, which is the most common tick in Europe,[139] the most frequent cause of human tick bites in Central Europe[196] and the main vector for *B. burgdorferi* transmission to humans in Europe.[139] Ticks feed from March through November, and the peak incidence of Lyme borreliosis occurs between May and October.[106, 171, 197]

In Asia, the adult stage of *I. persulcatus*, the most common tick in the Lyme endemic area in China, feeds in May and June and commonly bites humans, while 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.[148]

Geographic Distribution of the Tick Vectors

The *Ixodes ricinus* complex ticks require an environment with high humidity and are therefore not found at high elevations because they are susceptible to the desiccation that occurs in unprotected high windy areas.[139] *I. dammini* inhabits heavily forested and brushy areas, particularly the brushy areas at junctions between cleared and forested areas,[139, 182, 198] but 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.[199] The range of *I. dammini* in New Jersey correlates with elevation, and it occurs predominately below 600 feet of elevation in the inner and outer coastal plains and not the highlands.[200] *I. pacificus* is found only at elevations less than 2100 feet in coastal California.[191] *I. ricinus* inhabits dense deciduous forests with dense undergrowth, as well as pastures below 1000 meters of elevation, and is rare between 1000 to 1500 meters and not found above 1500 meters of elevation.[139, 144, 155] There is uneven distribution of these ticks even within their geographic range as a result of local differences in elevation, foliage, humidity, temperature and host populations.

The geographic distribution of the northern *I. dammini/scapularis* includes the Northeast from Maine to Virginia, from the Atlantic coast to the Mississippi River, and into Minnesota and southern Ontario; the southern *I. scapularis* is found in the Southeast from Virginia to Florida, from the Atlantic coast to Texas and Oklahoma, and north from Texas to the Midwest.[144, 190]

Another tick, *Ixodes angustus*, has been suspected to be a *B. burgdorferi* vector for humans in Washington State,[169] and it has a wide range that extends along the Pacific from California to Alaska.[139]

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, and there is a single pocket in Idaho.[144, 190]

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 to Turkey, Iran and Russia to the Caspian Sea west of the Ural Mountains.[6, 139, 144, 201] It also includes southern Italy and the Balkans. *I. ricinus* is the most common tick in Europe.[139]

The distribution of *I. persulcatus* extends east from the Ural Mountains[201] from eastern Europe to Asia to Japan and overlaps somewhat with that of *I. ricinus*.[144, 148, 149] *I. persulcatus* was the predominant tick in the Lyme endemic areas in northeastern (Heilongjiang Province) and northwestern (Xinjiang Province) China.[148, 153, 202]

I. holocyclus is the most common tick in the Lyme endemic area Hunter Valley and New South Wales coast of Australia and is suspected to be the vector of this newly recognized Lyme endemic area.[150, 203, 204]

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[137] and in and around Lyme, Connecticut, in 1965.[138] The earliest recognized case of EM in the United States occurred in 1969 in the upper Midwest, in north central Wisconsin,[136] and the earliest recognized case in the Pacific Northwest was reported in 1978 from Sonoma County, California, and followed an *I. pacificus* tick bite.[147]

In order 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.[4] In addition to the increased reporting of cases of Lyme disease since then, there has also been a true increase in incidence of Lyme disease because of spread of the *I. dammini* tick vector and its large mammalian host, the white-tailed deer, into larger geographic areas.

A comparison of Lyme disease cases reported to the CDC at 5-year intervals from 1982 through 1992 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).[3–5, 205, 206] The original northeastern focus of endemic Lyme disease in Connecticut[10, 207] and Massachusetts[137, 208] in the late 1970s progressively expanded[209] to the mid Atlantic states and by 1982 included Rhode Island, New York[210–213] and New Jersey[160, 214, 215]; by 1987, included Ohio, Pennsylvania, Maryland[216, 217] and Virginia[167]; and by 1992, included New Hampshire. The original upper midwestern focus in Wisconsin[119, 136, 218–220] expanded to include Minnesota[121] by 1982. By 1987, cases of Lyme disease were reported from Texas[176] and by 1992 from the majority of the southeastern,[161, 162, 166, 221] south central,[165] and midwestern[163, 222–225] states. In the northwestern states, between 1982 and 1987 Lyme disease began to be reported from California, Oregon and Washington State.[169]

Although Lyme disease has now been reported from all states except Montana,[4, 205] 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 in the northeastern, mid and south Atlantic, and upper midwestern states. By region, there were approximately 5800 cases of Lyme disease reported from the mid and south Atlantic states in 1992, 2300 from the northeastern states, 1100 from the north central states, 200 from the south central states, 300 from the Pacific states and only 16 cases from the Mountain States.

Lyme disease is not a notifiable disease in Canada, and only 30 cases of Lyme disease were reported to the Canadian Laboratory Center for Disease Control between 1977 and 1989.[226] These were predominantly from southern parts of the provinces of Ontario and Manitoba, which border Lyme endemic areas of the United States, and there were single cases reported from the provinces of Alberta, British Columbia and Quebec.

Expansion of Lyme Endemic Areas in North America

B. burgdorferi–infected ticks may be transported from Lyme endemic areas into nonendemic areas and establish new Lyme endemic foci.[139, 183, 184, 188, 208] Infected *I. dammini* ticks have been found on migratory birds and along migratory "flyways," and may be transported into new areas by these birds as they travel between endemic and nonendemic areas, between counties, states, countries and even continents.[144, 175, 183, 188, 227] Rodents, hunting dogs, household pets, domestic animals, wide-ranging wild animals such as coyotes and foxes, and campers,

hunters and other people traveling between endemic and nonendemic areas may also transport infected ticks from one area to another, and deer hunters may transport deer with infected ticks still attached. If the newly arrived tick finds its necessary hosts, a new endemic focus of infected ticks and Lyme disease will be established.[5]

In North America, the incidence of Lyme disease has been found to correlate with the population density and geographic distribution of *I. dammini* and white-tailed deer.[138] Because deer are the reproductive host of adult *I. dammini* and determine the success rate of tick mating, the population density of *I. dammini* correlates with the population density of deer, and an *I. dammini* focus may enlarge geographically as the geographic distribution of the deer expands.[184]

The deer populations in North America have changed dramatically over the past 400 years.[183] Before 1600, deer were abundant and extended into all the heavily forested areas of the northeast, Atlantic coastal and midwestern states, but decreased dramatically as deer were killed by Native Americans and colonists and forest was cleared to develop farmland. By about 1930, the deer populations in the United States had been decimated and were limited to a few small isolated sites such as the northeastern coastal islands (Naushon, Gardiner and Shelter Islands), Long Point, Ontario, and northeastern Wisconsin. Since the 1930s, and particularly since the 1970s, there has been a deer population explosion and deer have regained their original widespread North American distribution as farmland has been replaced by forest and by suburban residential woodlots.[139, 181, 183]

I. dammini/scapularis was first reported in Naushon Island, Massachusetts, in 1926. It spread to Cape Cod, Massachusetts, and eastern Long Island, New York, by the 1950s; to Rhode Island by the 1960s; to northern Wisconsin by 1968; and to New Jersey, Nantucket and Martha's Vineyard by the mid-1970s.[181] *B. burgdorferi* was found by the polymerase chain reaction technique in preserved museum specimens of *I. dammini/scapularis* ticks collected between 1924 and 1951 from eastern Long Island, New York, many years before the first cases of Lyme disease occurred in Lyme, Connecticut, and it has been proposed that this is the original area into which *B. burgdorferi* was introduced, possibly from Europe.[228]

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 per cent Lyme disease attack rate overall for residents living near the deer-populated nature preserve considered to be the focus, and 66 per cent for those living the closest to the preserve.[208] In permanent residents of Great Island, Massachusetts, the Lyme seropositivity rate was 8 per cent, the history positivity rate was 16 per cent and the incidence of Lyme disease was 7 per cent over a 2-year period.[137]

In New York, the geographic distribution of the *I. dammini* 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 in New York State reporting Lyme disease and the number of cases reported per county.[212] In Fire Island, New York, the Lyme seropositivity rate was 8.5 per cent, the Lyme history positivity rate was 5.5 per cent and the incidence of Lyme disease was 1.5 per cent in 4 months[210]; in Westchester County, New York, the seropositivity rate was 6.1 per cent, the history positivity rate was 2.7 per cent and the incidence of Lyme disease was 2.6 per cent in 5 months.[210] In Wisconsin, the Lyme endemic area has expanded southward from the original northwestern region,[119, 229] and the seropositivity rate is 6 to 11 per cent,[218, 220] which is similar to the 7 per cent seropositive rate in Minnesota.[230] The rate of seropositivity was 23 to 26 per cent in Texas.[176] The seropositivity rate was 0 per cent in a nonendemic area of Arizona.[220]

B. burgdorferi may be introduced and become established in the midst of nonendemic areas. A small pocket of Lyme hyperendemicity in an inner city park in Baltimore in the midst of a Lyme-free area was discovered when a zookeeper acquired Lyme disease in the park, and *I. dammini*– and *B. burgdorferi*–infected wild rodents were found in the park.[217] There is an isolated small pocket of Lyme endemicity in the Wasatch area of Utah southeast of Salt Lake City.[206]

Geographic Distribution of Lyme Borreliosis in Europe and Asia

The true worldwide country-by-country incidence of Lyme borreliosis is impossible to determine because there is no mandatory worldwide reporting of Lyme borreliosis, and no standardization of clinical or serologic criteria for definition and reporting of the disease in different countries.[6, 7, 231] Only an estimation of the incidence of Lyme borreliosis by country is possible, based on *B. burgdorferi* seropositive cases reported voluntarily to the World Health Organization (WHO) by Public Health Administrations of WHO European Region countries as of 1989,[231] and cases reported in the medical literature through 1992.

Lyme borreliosis has been reported from six continents—North and South America, Europe, Asia,

Africa and Australia—but the majority of cases have originated in North America and Central Europe (see Fig. 11–1).[6, 7]

In Europe, over 1000 cases per country have been reported from Austria,[6, 7, 106, 231] Germany,[6, 7, 102, 196, 231–234] Switzerland[6, 7, 155, 231, 235] and Czechoslovakia[6, 104, 231]; 500 to 1000 cases have been reported from Sweden[6, 7, 197, 231, 236]; 100 to 500 cases per country have been reported from the former Yugoslavia,[231] the former USSR,[6, 201, 231] Denmark,[6, 7, 231, 237] Scotland,[6, 238–240] Belgium,[6, 171, 231] France,[6, 7, 231, 241] Italy,[6, 231, 242] Bulgaria[243] and Lithuania[244]; less than 100 cases per country have been reported from Norway,[6, 231] the Netherlands,[6, 231, 245, 246] Luxembourg,[171, 231] Hungary,[170, 231] Poland[247] and the United Kingdom[7, 240, 248, 249]; and rare cases or asymptomatic seropositives have been reported from Finland,[6, 250] Ireland,[240, 251] Spain,[6, 252] Greece,[253] Romania[6] and Israel.[254]

Rare cases have been reported from South Africa,[255] Mexico,[256] Chile,[257] Brazil,[258] Argentina,[259] Puerto Rico and Honduras.[260] It is uncertain whether reports of Lyme disease from Haiti,[260] Jamaica,[260] Peru,[173] Egypt[261] and India[262] 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 Asia, cases have been reported from China and Japan as well as eastern parts of Russia. In 1981, one case of EM was reported from Japan[149] following an *Ixodes persulcatus* bite from the mountainous district of the Nagano Prefecture, across the Sea of Japan from Vladivostock. Since then, over 40 cases of Lyme disease have been reported from Japan. *I. persulcatus* is considered the major vector and *I. ovatus* another potential vector.[154, 263]

In 1990, 132 cases of EM were reported from Hailin County in the Heilongjiang Province in northeastern China,[7, 148] adjacent to the Vladivostock focus of Lyme borreliosis in southeastern Russia.[201] Since then, over 100 additional cases have been reported from China, predominately from the northeastern and northwestern regions, including the Heilonjiang, Jilin, Liaoning, Hebei, Nei Monggol, Xinjiang and Mudanjiang provinces.[148, 152, 153, 202, 264] *I. persulcatus* is the vector. *B. burgdorferi* has been isolated from *Ixodes* ticks and rodents in Korea, and Korea would therefore be considered an endemic area.[265]

Between 1982 and 1986, nine cases of EM were reported from the Hunter Valley and the New South Wales coast of southeastern Australia near Sydney, and this appears to be a newly recognized endemic area.[6, 7, 150, 203, 204]

The Lyme borreliosis endemic and hyperendemic areas in Europe and Asia cluster in a definite band, which could be called the "Lyme Belt" (see Fig. 11–1), located approximately between 30 degrees north latitude and the Arctic Circle at 65 degrees north latitude. This region includes the majority of cases from Central Europe, Scandinavia, the former USSR, China and Japan. In the Western Hemisphere, the "Lyme Belt" extends from approximately 15 degrees north latitude to 50 degrees north latitude and includes the endemic areas in the United States and southern Canada, as well as the cases from Mexico and the Caribbean. The cluster of cases from southeastern Australia, Rio de Janeiro, Brazil, and the case from South Africa are just south of the Tropic of Capricorn between 30 degrees and 40 degrees south latitude, but insufficient cases have been reported from the Southern hemisphere to determine whether there is a similar Southern hemisphere "Lyme Belt."

Expansion of Lyme Endemic Areas in Europe and Asia

In Europe, the geographic distribution of Lyme borreliosis correlates with the distribution of *I. ricinus*[6, 155] and the distribution of the deer population, and deer have recently increased dramatically as in North America.[183] 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.

Several seroepidemiologic studies have reported the rates of *B. burgdorferi* seropositivity in the general population in Europe and Asia: 4 to 6 per cent in Switzerland,[235] 5 to 16 per cent in Germany,[206, 234] 0 to 4 per cent in Italy,[242] 3 per cent in England,[249] 5 to 15 per cent in Ireland,[251] 6 per cent in Spain[252] and 2 to 9 per cent in Sweden.[236] The seropositivity rate is much higher in individuals exposed frequently to ticks in endemic regions, and may be as high as 19 to 26 per cent in Swiss orienteers and sportsmen[235, 266]; 15 per cent in Dutch hunters[246]; 15 to 18 per cent in Bulgarian forest workers and animal farmers[243]; 14 to 55 per cent in English farmers, forest workers and game keepers[248, 249]; 16 per cent in Scottish nature conservancy workers[238]; 27 per cent in one area of the Scottish Highlands[239]; 31 per cent in farmers, forest workers and cattle raisers from northern Spain[252]; 34 per cent in German Bavarian forest workers[232]; and 26 per cent in residents of the Liso peninsula in southeastern Sweden.[236]

A Lyme disease incidence of 6 to 8 per cent and a seropositivity rate of 6 per cent has been reported for forestry workers and rural inhabitants of northeastern China,[148, 152, 264] and a Lyme disease incidence

of 1 to 4.5 per cent has been noted in the Xingjiang Province in northwestern China.[264] A 2 per cent seropositivity rate was reported in agricultural workers in Peru, but this is probably due to cross-reacting relapsing fever *Borrelia* organisms.[173]

B. burgdorferi *Tick Infection Rates*

In the United States, rates of *B. burgdorferi* infection of *I. dammini/scapularis* and *I. pacificus* vary with geographic region, elevation, season and stage of the tick and are highest in the hyperendemic areas during the early summer.[186] Infection rates have been reported for *I. dammini/scapularis* from many areas and range from 27 to 67 per cent in the northeastern and mid Atlantic coastal islands,[1, 35, 267, 268] 11 to 100 per cent in the northeastern and mid Atlantic mainland[12, 36, 157, 179, 186, 188, 193, 199, 208] and 39 per cent in the upper Midwest.[229] Infection rates were 1 to 2 per cent for *I. pacificus* in the Pacific Northwest,[35, 191] 0 to 59 per cent for *Amblyomma americanum* in the mid Atlantic states[157, 160] and less than 1 per cent for *I. scapularis* in the mid Atlantic states.[157]

In Europe, Asia and other areas of the world, *B. burgdorferi* infection rates of *I. ricinus* and *I. persulcatus* ticks also vary with season, elevation and stage of the tick, as well as geographic region, and there may be wide differences in tick infection rates between different areas. Infection rates for *I. ricinus* have been reported to be 4 to 40 per cent in Austria,[139] 17 to 36 per cent in Switzerland,[35, 156, 155] 13 to 33 per cent in Germany,[55, 102, 196] 10 to 50 per cent in Belgium,[171] 30 per cent in the Liso peninsula of Sweden,[236] 2 to 14 per cent in the Netherlands,[246] 11 per cent in Spain[252] and 8 per cent in the United Kingdom and Ireland.[240] Rates for *I. persulcatus* were 20 to 45 per cent from Lyme endemic areas such as the Heilongjiang, Jilin, Liaoning, Nei Monggol, Hebei and Xinjiang Provinces in China,[148, 153, 202] and 7 to 22 per cent in Japan.[154] Infection rates were 10 to 27 per cent for *I. ovatus* from Japan.[154] Infection rates for *I. hexagonus* were 12 per cent from Germany.[139]

B. burgdorferi *Reservoir Animal Infection Rates*

North American epidemiologic studies indicate that the white-footed mouse, *Peromyscus leucopus*, is reservoir-competent for *B. burgdorferi*[269] and is in fact the most important reservoir for *B. burgdorferi* infection in nature,[144] and that the white-tailed deer *Odocoileus virginianus* is the reproductive host of the *I. dammini/scapularis* tick vector and is necessary for the maintenance of the tick but not the spirochete in nature.[186]

In the northeastern United States, the enzootic cycle that maintains *B. burgdorferi* infection in nature is the white-footed mouse–*I. dammini/scapularis* cycle. The mice are reservoir-competent for *B. burgdorferi*[139, 192, 267, 269] because they have a high rate of infection, remain spirochetemic and highly infectious for all stages of *I. dammini* 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.

In an epidemiologic study of *I. dammini/scapularis* ticks and small mammalian reservoirs collected in a Lyme endemic region in coastal Massachusetts,[144] the white-footed mouse was the most frequent animal captured in traps, *B. burgdorferi* infection of the mice was universal, almost all of the larvae or nymphs collected were found attached to mice and the *B. burgdorferi* tick infection rate correlated with the frequency of mouse attachment. It was concluded that the white-footed mouse is the most important reservoir for *B. burgdorferi* infection in nature and maintains the horizontal transmission of the infection from nymphal to larval ticks. Because ticks were already infected with *B. burgdorferi* prior to deer attachment, the white-tailed deer did not appear to be important for transmission and maintenance of *B. burgdorferi* infection in nature.

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 the northeastern United States.[187, 267] The geographic distribution of infected mice correlated with the areas of Lyme endemicity.[174] Mice were found to be chronically spirochetemic in nature during the spring, summer and fall[267] and were spirochetemic and infectious for ticks for over 200 days after experimental infection with *B. burgdorferi*.[269] Deer were heavily infested by adult but not immature *I. dammini* during the winter, suggesting that deer were important wintertime hosts for adult *I. dammini*.[267] Although the deer were spirochetemic during summer, fall and winter, and may be reservoirs for *B. burgdorferi*,[267] 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.[144, 157, 158]

In the northwestern United States, the *I. pacificus* tick transmits Lyme borreliosis to humans, but the enzootic transmission cycle is different from that in the northeastern United States.[191, 192] 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 per cent) 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 per cent infection rate, and the dusky-footed woodrat, *Neotoma fuscipes*. *I. neotomae* and *I. pacificus* are both competent vectors for *B. burgdorferi*, but *I. neotomae* does not bite humans and is needed only for maintenance of *B. burgdorferi* infection in the woodrat reservoir. *I. pacificus* larvae and nymphs rarely bite humans, but the adults commonly do and 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.

In some geographic areas of North America, other mammalian reservoir-tick cycles in addition to the mouse–*I. dammini* cycle may also contribute to maintenance of the *B. burgdorferi* infection in nature, such as the cottontail rabbit–*I. dentatus* cycle in Nantucket,[189] the chipmunk–*I. dammini* cycle in Wisconsin,[229] the squirrel–*I. dammini* cycle in Connecticut and Wisconsin,[229] the woodrat–*I. neotomae* cycle in California[192] and the meadow vole–*I. dammini* cycle in the Northeast.[183] In Europe, in addition to the mouse–*I. ricinus* cycle, which is considered to maintain the *B. burgdorferi* infection in nature, other cycles such as the hedgehog–*I. hexagonus* cycle in Germany[139] and the mouse–*I. trianguliceps* cycle in Central Europe[183] may be secondarily important.

B. burgdorferi infection has been demonstrated in 24 different species of mammals and birds.[144] Seroepidemiologic studies found the rates of *B. burgdorferi* seropositivity in wild and domestic animals in various geographic areas of the United States to be 10 to 100 per cent in the northeastern states,[157, 188, 267] 5 to 60 per cent in Wisconsin,[188, 229] 11 per cent in North Carolina[188] and 14 to 99 per cent in Texas.[176, 188]

Pathology and Pathogenesis

Borrelia burgdorferi is the etiologic agent of Lyme borreliosis, which is a multisystem infection, and includes EM, borrelial lymphocytoma, acrodermatitis chronica atrophicans, Bannwarth's syndrome (meningopolyneuritis) and other manifestations of neuroborreliosis, and Lyme disease. Infection elicits a sequence of immunologic, B and T cell, responses in the infected individual, in response to either live *B. burgdorferi* or degenerated organisms, and results in characteristic histopathologic findings. The responding B cells differentiate into plasma cells and produce perivascular lymphoplasmacytic infiltrations and hypercellular vascular occlusive damage in many involved tissues but primarily in the skin and soft tissues, heart, synovium, reticuloendothelial system and peripheral nervous system. The responding T cells form the major inflammatory infiltrations in the central nervous system.[270]

B. burgdorferi enters the skin through the bite of an infected tick and produces a "tick papule" at the bite site. Within several days to 7 weeks, the organism produces a local skin lesion, EM, and also enters the skin vasculature and disseminates hematogenously throughout the body to the skin, where it produces secondary EM lesions, and to the organs and reticuloendothelial system, where it produces a generalized flu-like illness with fever, headache, myalgias, arthralgias, conjunctivitis, pharyngitis, adenopathy, tender hepatosplenomegaly, pneumonitis and orchitis.[270, 271] After the initial hematogenous dissemination, about 4 to 9 weeks after infection, cardiac or neurologic involvement may occur, including myocarditis, meningoencephalitis, cranial nerve paresis, stupor and personality changes.[271] Months to years after infection, chronic manifestations of *B. burgdorferi* infection may develop as a result of persistence of *B. burgdorferi* in various organs, especially the skin, eye, joints and nervous system.[271]

Small numbers of *B. burgdorferi* may be visualized in some infected tissue samples, particularly skin biopsy specimens, by silver staining (Warthin-Starry, Dieterle or Bosma-Steiner) or by staining with polyclonal or monoclonal *B. burgdorferi*–specific antibody, or isolated in culture, as discussed in the Diagnosis section of this chapter. Organisms are most easily found in early infection, but persistence of live *B. burgdorferi* for as long as 10 years after infection has also been demonstrated.[13]

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 description of the pathology of the placenta and congenitally infected fetus or infant.

Lyme Borreliosis: Pregnant and Nonpregnant

Cutaneous

A "tick papule" develops at the tick bite site and consists of an ulcerated papule of partially denuded hyperplastic epithelium above a lymphocytic, plasmacytic, macrophage and mast cell inflammatory infiltrate.[270] 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, and the mouthparts have rows of "teeth" called denticles, which become embedded in the skin and the cement.[272] *B. burgdorferi* spirochetes have been detected in skin surrounding the bite site in animal models at this stage[273] but not in humans.[270]

Erythema migrans (EM)[38, 39, 43, 68, 101, 142, 270, 271, 274] occurs during early infection as either single (localized) or multiple (disseminated) skin lesions. The central part of the skin lesion contains upper and deep dermal perivascular and interstitial mononuclear cell infiltration (lymphocytes, histiocytes, plasma cells and mast cells) and upper dermal edema, telangiectasia, fibrin deposition and nuclear fragments. The epidermis is usually normal but may have mild acanthosis, spongiosis, parakeratosis, hyperkeratosis, edema, hemosiderin deposits or focal inflammatory infiltrates at the dermal-epidermal junction, or even intraepidermal vesiculation and necrosis. The lesion center may contain eosinophils in the dermal infiltrate as a reaction to the tick bite. The peripheral part of the EM lesions contains upper and mid dermal perivascular mononuclear cell infiltration (lymphocytes, plasma cells, histiocytes, and mast cells or neutrophils), and the epidermis is normal. 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 upper dermis or at dermal-epidermal junction and occasionally in epidermal or follicular epithelium. The secondary EM lesions of disseminated infection have the same perivascular infiltrate as found in primary EM lesions, and spirochetes have also been demonstrated in these lesions.

The histopathology of septal panniculitis, which manifests as erythema nodosum following EM, consists of sparse dermal and patchy subcutaneous adipose tissue perivascular lymphohistiocytic infiltration.[275]

Borrelial lymphocytoma (BL),[16, 18, 43, 270, 271, 276, 277] also known as lymphadenosis benigna cutis or B cell pseudolymphoma, occurs during early infection as either single (solitaria) or multiple (dispersa) skin lesions, usually occurring on the ear lobe or areola, 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, 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)[270, 271, 277, 278] 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 shows epidermal loss of rete ridges, a dense patchy or interstitial mononuclear (lymphocytic, plasmacytic, macrophage and mast cell) infiltration of the dermis and subcutaneous fat around and between blood vessels and skin appendages, panniculitis, prominent dilated dermal blood vessels, endothelial proliferation and telangiectasia. This progresses to eventual epidermal atrophy, with liquefaction degeneration with scattered dermal lymph-filled vacuoles near the dermal-epidermal junction and degeneration of elastin and collagen. The histopathology of ulnar fibrous nodules of the elbows, which are associated with ACA, shows soft tissue deposits of collagen, perivascular infiltrations of plasma cells and macrophages and occluded blood vessels. Spirochetes can be found in these nodules and in ACA skin lesions.

Localized scleroderma, eosinophilic fasciitis and lichen sclerosus et atrophicus,[270, 271] three additional cutaneous manifestations of chronic *B. burgdorferi* infection, have been described histopathologically. Skin lesions similar clinically and pathologically to those of localized scleroderma consist of dermal perivascular lymphoplasmacytic infiltration and dermal thickening due to increased collagen extending into the fatty subcutaneous tissue. Skin lesions similar to those of Shulman's disease (eosinophilic fasciitis) consist of localized nonmobile areas of skin firmness consisting of perivascular lymphoplasmacytic infiltrations in the deep dermis, subcutaneous tissue and muscle, and increased mast cells, eosinophils and macrophages in fascia. Skin lesions similar to those of lichen sclerosus et atrophicus consist of upper dermal edema and amorphous collagen deposition, mid-dermal lymphocytic infiltration and deep dermal endarteritis obliterans. Lesions similar in appearance to granuloma annulare, and having the same histopathology, have been found to be associated with *B. burgdorferi*.

Reticuloendothelial

Splenitis,[270, 271, 279] hepatitis[270, 280, 281] and lymphadenitis[270, 271, 282] 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, and 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.

Interstitial pneumonitis[270] with mononuclear cell (macrophages, tissue histiocytes and lymphocytes) infiltration of irregular alveolar spaces, and with rare spirochetes in the lung, has been described in one patient.

Cardiac

Cardiac involvement[270, 271, 283–286] 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) band-like endocardial infiltration, myocardial infiltration and occasionally pericardial infiltration, and vascular changes suggestive of early obliterative vasculopathy. There may even be myocardial cell degeneration and fibrosis and fibrinous pericarditis, and spirochetes may be seen in endocardium and myocardium near interstitial infiltrations and in intramyocardial vessels.

Spirochetes have also been demonstrated in endomyocardial biopsy specimens of patients with chronic dilated cardiomyopathy, an unusual form of late chronic infection, in the endomysial space and in myocardial cells.

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.[43, 116, 270, 271, 287–291]

During meningitis or meningoencephalitis in early disseminated infection, there may be an elevated CSF protein and a CSF pleocytosis as a result of immature B cells and plasma cells, and *B. burgdorferi* can occasionally be isolated from CSF. There are only occasional reports of central nervous system pathology from either brain biopsies or from autopsies of fatal cases, and these show scattered perivascular mononuclear (lymphocytic and plasmacytic) cell infiltrates, occasional focal increase in microglial cells, mild spongiform changes in cerebral cortex and band-like lymphocytic and plasmacytic infiltrate in leptomeninges. Rare spirochetes may be seen in brain tissue.

Cranial nerve paresis (cranial neuritis) histopathology consists of lymphocytic and plasmacytic cell infiltrations of autonomic ganglia and nerves, with perivascular cuffing and with inflammatory cell infiltrate and thickening of perineural blood vessels.

Meningoradiculoneuritis, also known as Bannwarth's syndrome, Garin-Bujadoux-Bannwarth syndrome or meningopolyneuritis, occurs in early disseminated Lyme disease and is more common in Europe than the United States. The histopathology[288, 289] consists of marked perivascular lymphocytic (T helper) and plasmacytic infiltration around endoneural capillaries, thrombosis of epineural vasa vasorum and axonal degeneration, consistent with a local immune reaction to the triggering spirochete and resulting angiopathic-ischemic nerve damage. In the spinal cord, there is segmental perivascular infiltration of meninges and white and gray matter. In the spinal ganglia and dorsal nerve roots, there is parenchymal perivascular infiltration. In the peripheral nerves, there is perivascular infiltration around the epi-, peri- and endoneural vessels; slight diffuse endoneural infiltration; axonal degeneration; slight myelin degeneration; segmental decrease in myelinated and unmyelinated fibers; and wallerian degeneration. After successful antibiotic therapy of Bannwarth's syndrome, no perivascular infiltrations are found, but there is still mild proliferation of endoneural tissue. Demonstration of spirochetes in CSF is very unusual, but rare organisms were seen in CSF from one patient with Bannwarth's syndrome.[43]

The peripheral neuropathy of late chronic borreliosis[270, 271, 292] 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 in acute meningoradiculoneuritis but is more severe, and consists of perivascular lymphocytic and plasmacytic infiltration of small and medium epineural vessels and epineural soft tissue, with vessel lumen obliteration. In severe neuropathy, there is also axonal degeneration with disseminated demyelination and loss of large myelinated fibers that correlates with severe mononuclear cell

infiltration and cuffing of epineural and endoneural vessels and degeneration of perineural cells, and suggests an ischemic etiology of the neuropathy. Spirochetes have not been demonstrated in these biopsy specimens.

Acute focal encephalitis[116, 290, 291] with focal contrast-enhancing central nervous system lesions may develop during either early disseminated or late chronic infection. The histopathology of brain biopsy 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 loss of myelinated fibers similar to an acute demyelinating process. Rare spirochetes are seen. The brain biopsy histopathology of progressive nonfocal encephalitis shows microglial cell foci and no perivascular cuffing, and few spirochetes.

Musculoskeletal

Myositis,[270, 271, 293] especially of proximal muscles, may occur in early disseminated infection. The histopathology consists of tightly packed perivascular lymphocytic, plasmacytic and macrophage infiltrations; muscle fiber atrophy; and minimal muscle fiber swelling, similar to the histopathology of polymyositis and dermatomyositis, and rare spirochetes may be found in the interstitium and overlying muscle fibers.

Arthritis[43, 65, 142, 270, 294–297] may be a manifestation of either early or late chronic infection. In early infection, spirochetes have been found in a biopsy specimen of a metaphyseal bone lesion. Synovial histopathology in Lyme arthritis ranges from mild to severe and 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 (B and T lymphocyte, plasmacyte, macrophage and mast cell) infiltration, often forming synovial nodules histologically similar to lymphoid follicles but without well-defined germinal centers; subsynovial vascular proliferation; endarteritis obliterans as a result of vessel lining hypercellularity; 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. The characteristic "onion-skinning" of endarteritis obliterans plus prominent synovial fibrin deposition in a Lyme endemic area is therefore very suggestive of Lyme arthritis.

The histopathology of the chronic arthritis associated with ACA[278] shows degenerative arthritis, joint capsule atrophy, bony atrophy and cortical thickening.

Lyme Borreliosis: Fetus and Newborn

Although there have been a relatively small number (only 46) of cases of congenital Lyme borreliosis reported,[19, 21, 23–32, 34] there are several reports of the pathologic findings. There are 11 descriptions of pathologic or culture findings in gestational Lyme disease placentas, 19 descriptions of fetal or neonatal pathologic findings 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 colleagues,[19] MacDonald and colleagues,[27–29] Lavoie and colleagues[26] and Weber and colleagues.[32, 33]

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, following 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.

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.

Cutaneous

There are no reports of 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, Table 11–8).[25]

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, Table 11–8) and in the spleen and bone marrow of one 35-week slightly premature infant (patient 1) with severe fatal early congenital Lyme borreliosis after first-trimester gestational Lyme disease.[19, 27–29, 32, 33] The spirochetes were seen in the lumen of a large 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), without definite histories of gestational Lyme disease.[27, 28] The histopathology of a lymph node biopsy of a patient with infantile multisystem inflammatory disease considered to have congenital Lyme borreliosis (patient 40) showed acute lymphadenitis with follicle hyperplasia.[25]

Pulmonary

Histopathologic examinatiion 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, Table 11–8).[32, 33]

Cardiac

Cardiac histopathology has been reported for 11 infants or fetuses with congenital Lyme borreliosis. Major cardiac malformations were found in 9 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 four term or near-term infants with congenital Lyme borreliosis (three fatal and one nonfatal) following first-trimester gestational Lyme disease during the period of cardiac organogenesis (patients 1, 2, 6 and 27, Table 11–8),[19, 27–29, 31] and *B. burgdorferi* spirochetes were found by IFA in the myocardium of two of these infants (patients 1 and 2).[27–29] The malformations consisted of aortic coarctation, endocardial fibroelastosis, persistent left superior vena cava, patent ductus arteriosis and aortic stenosis in one 35-week slightly premature infant (patient 1), and ventriculoseptal defects in three term infants (patients 2, 6 and 27).[19, 27–29]

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),[27] and the other had myocardial dysfunction but no malformation, following gestational Lyme disease of unspecified trimester (patient 21).[26]

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, 4 and 11)[27, 28] and in one 34-week infant with nonfatal congenital Lyme borreliosis after second-trimester gestational Lyme disease (patient 24), and consisted of an atrial septal defect (patient 3), aortic coarctation (patient 4), ventriculoseptal defect (patient 11) and patent ductus arteriosus (patient 24).

Neurologic

Neuropathology has been described in six fetuses or infants with fatal congenital Lyme borreliosis, and spirochetes were found in brain tissue of five of these and in unspecified fetal tissue in the sixth, by 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, Table 11–8),[27–29, 32, 33] in the frontal cerebral cortex of another term infant after gestational Lyme disease of unspecified trimester (patient 21)[26] and in the brain of a 16-week miscarried fetus with no history of gestational Lyme disease (patient 9).[27]

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, and consisted of small perivenous hemorrhages with aggregates of leukocytes in the pons, small infratentorial hemorrhages, cerebral edema and congestion, but no significant inflammation.[32, 33] One term infant had hydrocephalus and spirochetes in unspecified fetal tissue following probable first-trimester infection (patient 6),[27] and one 17-week miscarried fetus had hydrocephalus and *B. burgdorferi* in fetal brain tissue (patient 8).[27]

MacDonald described spirochetes consistent with *B. burgdorferi* retrospectively in autopsy sections of brain from 2 of 10 infants studied who died of sud-

den infant death syndrome in a highly Lyme endemic area, and there was no inflammation in the tissues containing the spirochetes.[27]

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, Table 11–8),[27] and absent left hemidiaphragm in the other (patient 7),[27] and 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),[23, 30] and inguinal hernias and pectus excavatum were found in a 37-week infant who survived following first-trimester gestational Lyme disease (patient 25).

Renal

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 (patients 2 and 22, Table 11–8)[27–29, 32, 33] and one 35-week premature infant (patient 1)[19] born after first-trimester gestational Lyme disease, and two fetuses miscarried or stillborn at 12 weeks (patient 10)[27] and 23 weeks (patient 4),[27, 28] with no definite history of gestational Lyme disease. Spirochetes were also found in the neonatal adrenal in one of the term infants (patient 2).

Infantile Multisystem Inflammatory Disease

Although the etiology of neonatal or infantile multisystem inflammatory disease, 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.[25] The histopathology[298, 299] 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 only occasionally reported.[27–30, 270, 300] Some of the placentas described were associated with normal fetal and neonatal outcomes, while others were associated with infants with congenital Lyme borreliosis included in Table 11–8 in the section Clinical Manifestations.

MacDonald and colleagues[27–29] described seven placentas associated with gestational Lyme borreliosis. Spirochetes were grown from one placenta and 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 rare plasma cells in placental villi of one placenta, and this lack of inflammation despite the presence of spirochetes was remarkable. Spirochetes were demonstrated in placentas of two women with 15-week and 19-week miscarriages with no history of gestational Lyme disease (cases 3 and 5, Table 11–8), one woman with a term stillbirth after untreated first-trimester gestational Lyme disease (case 2), two women with term or near-term infants with severe early congenital Lyme disease with no history of gestational Lyme disease (cases 12 and 13) and one woman with treated second-trimester and untreated third-trimester Lyme disease who delivered a normal term infant treated after delivery with antibiotics. A term placenta, from a gestation complicated by second-trimester Lyme disease treated with intravenous antibiotic therapy, had no spirochetes detectable.

Markowitz and colleagues[30] 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 (case 14), but found no spirochetes by either culture or IFA. Duray and Steere[270] reported that in maternal gestational Lyme disease, the placental chorionic villi had increased Hofbauer's cells as in syphilitic placentitis. Mikkelsen and Palle[300] reported a normal placenta following last-trimester treated gestational Lyme disease.

Placental histopathology of two of the author's 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 (case 23); and focal chorionic villus 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 (case 24).

The histopathology of one placenta associated with neonatal multisystem inflammatory disease[301] showed thickened thrombotic vessels and subchorionic and intrachorionic calcification, and is of interest because 1 of 14 patients with this syndrome was considered to have congenital Lyme borreliosis.[25]

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 need to be studied histologically, with silver and *B. burgdorferi*–specific IFA stains, and possibly with PCR and culture, in order for a definitive description of placental pathology in gestational Lyme borreliosis to emerge.

Congenital Relapsing Fever

The other human borrelioses, tick-borne and louse-borne gestational relapsing fever, caused by *B. hermsii, B. duttonii* and related *Borrelia* strains, may also result in congenital infection[302–312] and have been described more extensively than congenital Lyme borreliosis. In one large series of African tick-borne gestational relapsing fever, the overall fetal mortality rate was 30 per cent and the perinatal mortality rate was 15 per cent.[307] Several other reports, including some from the United States, describe the typical clinical presentation of congenital relapsing fever as onset, within 3 days post partum, of fever, hypotonia, hepatosplenomegaly, thrombocytopenia, anemia, hemorrhagic rash, respiratory distress, fulminant sepsis or meningitis and spirochetemia with relapsing fever *Borrelia* species. Some of these infants recovered with prompt parenteral penicillin or ampicillin, but in others the spirochetal sepsis was too far advanced and death occurred despite antibiotic therapy. The highest risk for adverse fetal or perinatal outcome is with peripartum or last-trimester maternal gestational relapsing fever with spirochetemia.

The placental histopathology in congenital relapsing fever has only rarely been reported[309–311] and consists of abundant spirochetes seen in placental villous capillaries, on the fetal side of the circulation, and in the umbilical vessels. The histopathology of the congenitally infected fetus has also rarely been reported[305, 312] 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's cells in the liver and hemorrhagic lesions in the skin, subepicardium and brain. Abundant spirochetes have been found in spleen, liver and brain.

Congenital Leptospirosis

There are only rare reports of the histopathology of congenitial leptospirosis, another human spirochetosis. A 5-month stillborn fetus was delivered after maternal leptospirosis at 5 months of gestation, and pathologic examination showed disseminated hemorrhages in fetal skin, muscles and organs, and leptospirae were isolated from fetal liver and kidney and maternal blood.[313] A term infant with hepatomegaly, scleral hemorrhages and fever, born after 39-week gestational leptospirosis, was successfully treated with intravenous penicillin, and leptospirae were isolated from amniotic fluid, placenta and cord blood.[313] A spontaneous fetal death occurred after 30-week gestational leptospirosis, but the fetal tissues were macerated and no specific histopathologic lesions and no leptospirae were found.[314]

Clinical Manifestations

Lyme borreliosis is a multisystem infection with a variety of clinical manifestations that may change with time as the infection progresses, and may be modified by antibiotic therapy and by patients' 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.[51, 315]

Case Definition and Classification of Stages of Lyme Borreliosis

The case definition of Lyme borreliosis used by the CDC[316] for epidemiologic purposes in order to follow the geographic spread of the infection in the United States is given in Table 11–5, but it is not intended for use in patient care situations.

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

Table 11–5. LYME DISEASE: CDC CASE DEFINITION FOR PUBLIC HEALTH SURVEILLANCE PURPOSES[a]

Erythema migrans
or
One or more late manifestations without other etiology:
1. Musculoskeletal:
   Recurrent brief monoarticular or pauciarticular arthritis, +/− chronic arthritis
2. Neurologic:
   Lymphocytic meningitis, 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, sometimes associated with myocarditis

plus

Isolation of *B. burgdorferi* from patient specimen
or
Diagnostic levels of *B. burgdorferi* IgM or IgG antibodies in serum or CSF
or
Significant change in levels of *B. burgdorferi* IgM or IgG antibodies in acute and convalescent sera

[a]Adapted from Centers for Disease Control. M.M.W.R. 39(RR13):1, 1990.

stages according to different clinical manifestations has been more recently agreed upon by many European and North American clinicians[317] and consists of division of the infection into early localized, early disseminated and late chronic Lyme borreliosis (Table 11–6). 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 manifestatons of systemic spread of the spirochete such as neurologic, arthritic, cardiac or other organ involvement. Late Lyme borreliosis consists of cutaneous, neurologic or arthritic manifestations persisting either constantly or intermittently for at least 6 to 12 months.

Table 11–6. CLINICAL CLASSIFICATION OF LYME BORRELIOSIS (LB)[a]

Early localized LB	Solitary erythema migrans or *Borrelia* lymphocytoma +/− regional lymphadenopathy or minor constitutional symptoms
Early disseminated LB	Multiple erythema migrans or early neurologic, arthritic, cardiac or other organ involvement
Late chronic LB	Acrodermatitis chronica atrophicans or persisting/remitting neurologic, arthritic or other organ involvement for over 6–12 months

[a]Adapted from Asbrink, E. and Hovmark, A. Comments on the course and classification of Lyme borreliosis. Scand. J. Infect. Dis. Suppl. 77:41, 1991.

Incidence of Lyme Borreliosis in Women of Childbearing Age

It is estimated that between 7 and 20 per cent of patients with North American Lyme borreliosis and 18 to 20 per cent 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[3, 101, 119, 121, 161, 162, 166, 206, 209, 211, 213–216, 218, 318] and Europe[148, 171, 237] that note the ages and sex of the patients. Lyme borreliosis may affect all ages of patients, from the infant to the elderly, but the majority of cases occur in patients less than 40 years of age. In large studies by the CDC of over 4500 patients, the highest incidence was in patients below 15 years and between 24 and 44 years old.[3] The percentage of female patients with Lyme borreliosis acquired in different states of the United States usually ranges from 44 to 51 per cent, but it may be as low as 22 to 36 per cent in some groups studied. In the largest studies by the CDC between 1982 and 1992, women comprised 44 per cent of the total patients reported in 1982 and 51 per cent of those reported in 1987 and 1992.[3, 4, 206] The percentage of female patients in several European studies was slightly higher than in the United States and ranged between 40 and 60 per cent.

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 will 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 11–7.

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 stage of the infection, and this is discussed in the section Therapy. Because decisions regarding antibiotic therapy of infants

Table 11–7. 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
	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 monoarticular 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
Eye	Conjunctivitis, interstitial keratitis, nodular episcleritis, 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

with gestational Lyme exposure will depend on the adequacy of prior 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 European and North American Lyme borreliosis. About half of patients with Lyme borreliosis recall a preceding tick bite, but the range is 21 to 75 per cent, and bites are reported slightly more often in North American than in European patients.[12, 51, 104, 106, 121, 155, 161, 163, 171, 197, 206, 209, 211, 213–216, 218, 226, 233, 241, 319] EM is reported in 45 to 85 per cent of patients with Lyme borreliosis from both continents.[33, 51, 101, 104, 106, 137, 155, 161, 163, 171, 209, 211, 213, 215, 216, 218, 226, 233, 241, 242, 320, 319]

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 1 to 4 weeks, with a range of 1 day to 4 months,[33, 121, 197, 214, 274] 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 over 40 to 65 cm[33, 142, 274, 319] 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 but may be homogeneous 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.[33, 142, 274, 277] Some lesions have recurred over as long as 1 year,[277] and these probably represent hematogenous spread (Fig. 11–5*D*).

While solitary EM with only very mild associated flu-like symptoms is considered early localized infection, the development of significant systemic symptoms of fever, pharyngitis, regional or generalized adenopathy, conjunctivitis, malaise, fatigue, myalgias, arthralgias, headache and meningismus, either alone or associated with either single or multiple EM, occurs in about half of patients and indicates systemic hematogenous spread of the spirochete and is considered early disseminated infection.[142, 143, 197, 251, 319]

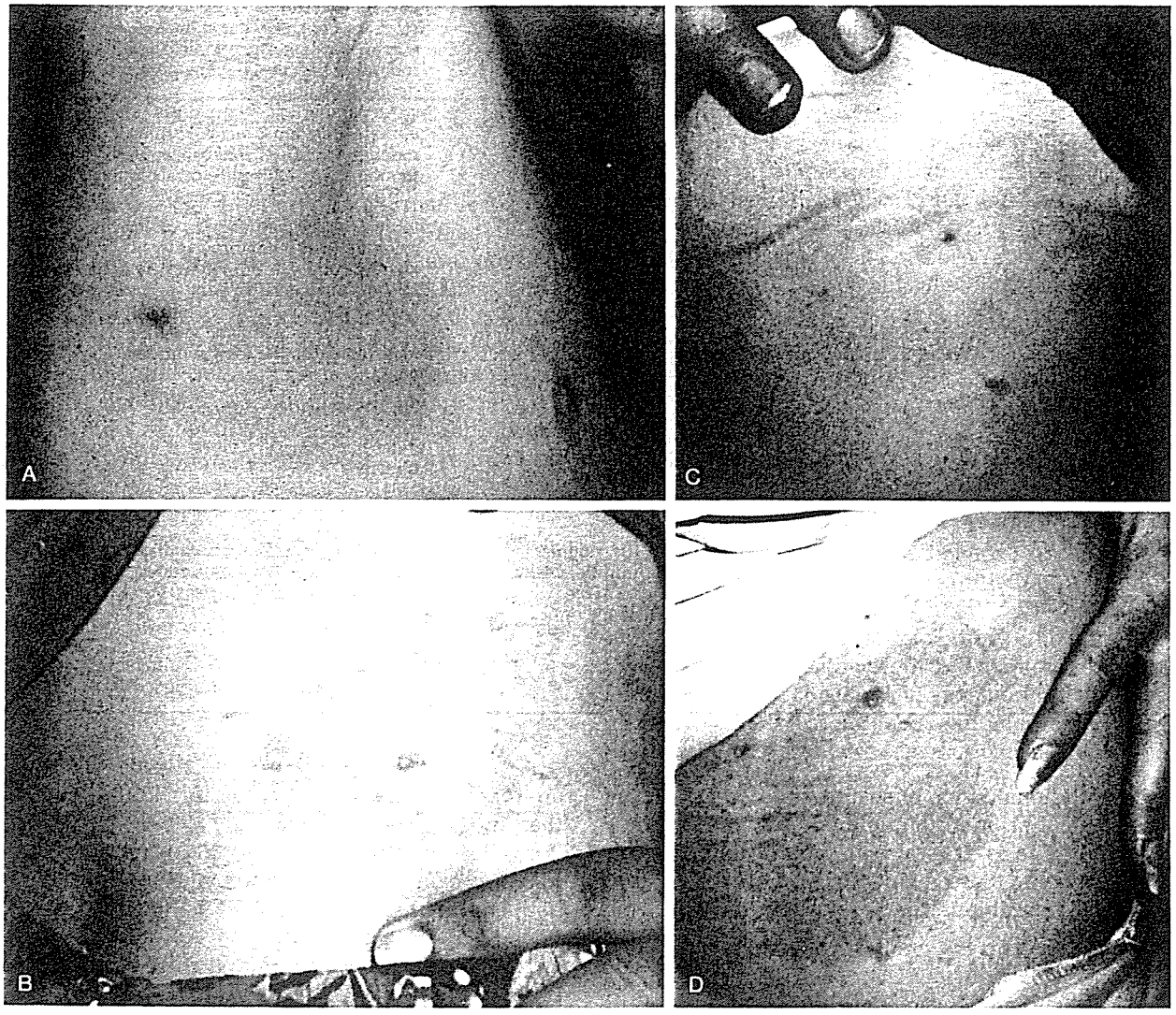

Figure 11–5. The pathognomonic skin lesion of Lyme disease, the "bull's-eye" or erythema migrans (EM) lesion. *A* to *C*. EM lesion of early Lyme disease, which is a large, expanding, round or oval, smooth or stippled, erythematous annular rash with central clearing located around a central or eccentric 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 (case 25 in Table 11–8).

Multiple EM (Fig. 11–6) indicates early disseminated Lyme borreliosis with hematogenous spread and occurs in 17 to 50 per cent of North American patients[101, 143, 206, 209, 274, 319] with EM, and in only 4 to 10 per cent of European patients[33, 197, 201] with EM. The skin lesions are smaller than the initial EM lesion and presumably arise from hematogenous spread.[206, 214] A maculopapular rash rather (Fig. 11–7) than multiple EM lesions has been reported in some patients, including 3 per cent of European patients with Lyme borreliosis in one large study, and also indicates early disseminated infection.

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.

Borrelial Lymphocytoma

Borrelial lymphocytoma, a B cell pseudolymphoma, is also called lymphadenosis benigna cutis and occurs in 1 to 5 per cent of European patients with Lyme borreliosis,[33, 104, 106, 197, 233, 242] usually less than 10 months after onset of infection, and has also been reported in a young woman from Wisconsin.[321] It presents as a bluish-red tumor-like or nodular swelling of the earlobe in children, or of the nipple or areola in older patients, and may occur either at the site of a prior tick bite or at a distant site. Lymphocytoma solitaria, a single lesion, is considered to be early localized Lyme borreliosis, while lymphocytoma dispersa, multiple lesions, represents disseminated infection.[16, 231, 276, 277, 322]

Arthritis

Approximately 20 per cent of patients with Lyme borreliosis present with arthritis or arthralgia with-

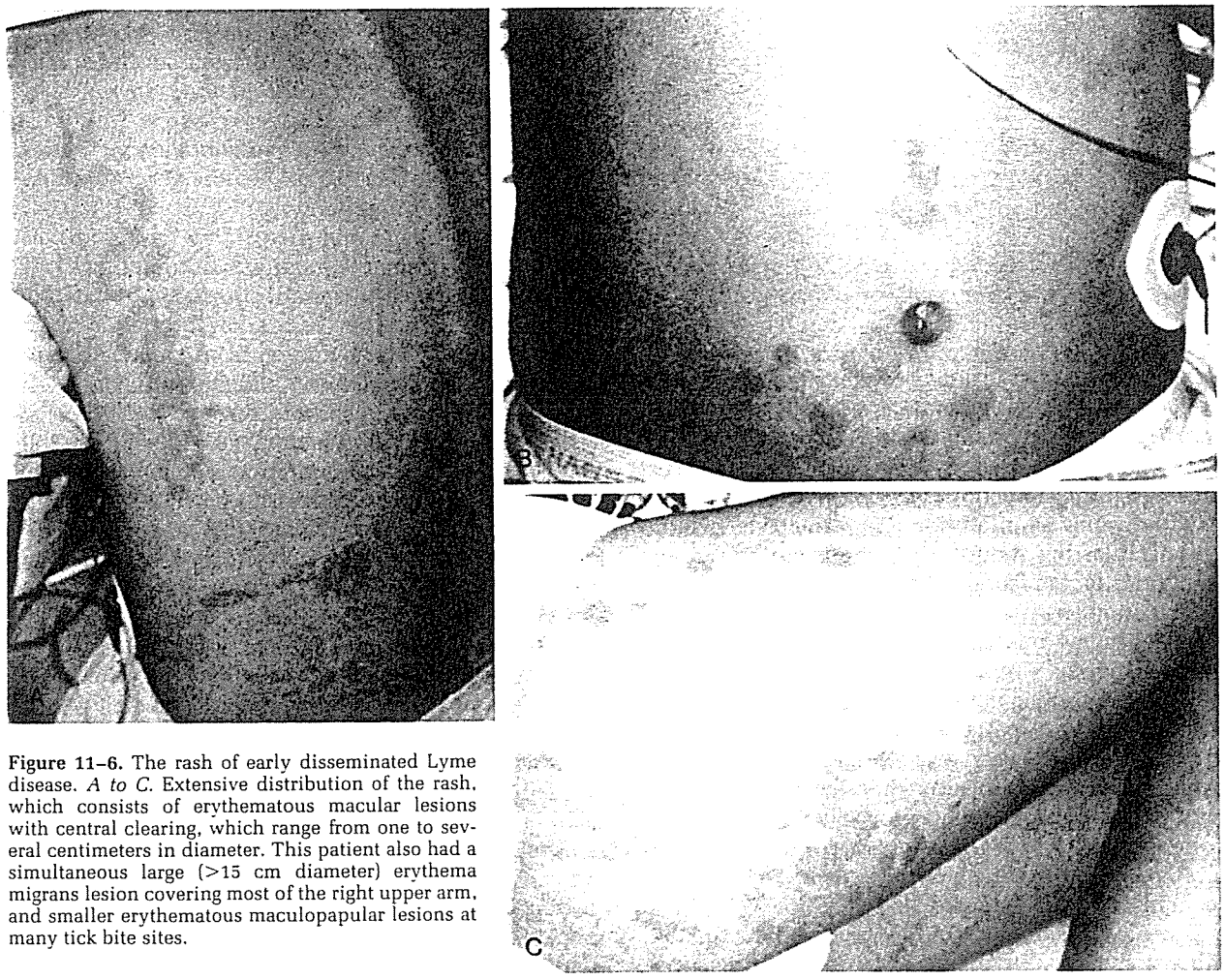

Figure 11–6. The rash of early disseminated Lyme disease. *A to C.* Extensive distribution of the rash, which consists of erythematous macular lesions with central clearing, which range from one to several centimeters in diameter. This patient also had a simultaneous large (>15 cm diameter) erythema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

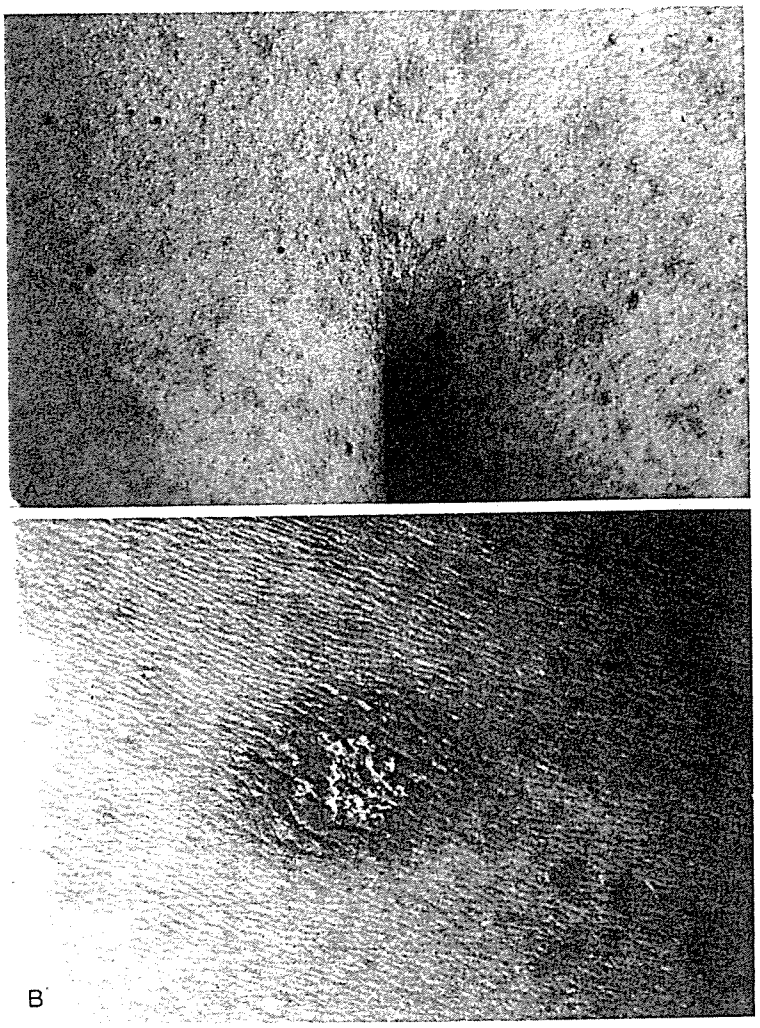

Figure 11–7. The rash of early disseminated Lyme disease. Dense erythematous maculopapular rash on the chest *(A)* and an erythematous oval expanding erythema migrans lesion on the buttock *(B)* in a first-trimester pregnant woman (case 23 in Table 11–8).

out preceding skin lesions.[211] Eighty per cent of untreated patients with Lyme borreliosis develop arthralgias within 2 months, and 40 to 60 per cent develop arthritis, usually 4 to 6 weeks to 2 years after the initial infection.[33, 142, 318, 323, 324] The arthritis usually begins as intermittent asymmetrical arthralgias each lasting about 1 week, and then progresses to intermittent episodes of monoarticular or oligoarticular frank arthritis, especially of the large joints, which become markedly swollen, hot and tender, but not red.[10, 142] The development of Baker's cysts that may rupture is not infrequent.[142, 320, 323] About 10 to 20 per cent of patients with arthritis experience spontaneous resolution each year, about 10 per cent eventually progress to severe destructive chronic arthritis with longer episodes of arthritis by the second or third year, and about 2 per cent develop joint space narrowing, bone cysts, cartilage loss, osteopenia and erosive bone disease.[320, 323, 324]

The most common joint involved is the knee, but other commonly involved joints include the wrist, elbow, shoulder, ankle, hip and temporomandibular joint, and even the heel and fingers.[206, 209, 320] 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.[142, 323] Sedimentation rates are mildly elevated.

It was initially thought that Lyme arthritis was found only in North American patients with Lyme borreliosis, but once it was recognized, it was subsequently also found in European patients, although not as frequently as in North America.[7, 33, 106, 155, 171, 197, 233, 241, 242, 320, 324]

Neuroborreliosis

About 4 per cent of patients with Lyme borreliosis present with neurologic symptoms without any preceding skin lesions,[211] and approximately 5 to 17 per cent of untreated patients develop neurologic abnormalities, usually 2 to 4 weeks to several months after

the initial infection.[33, 231] 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 assays for *B. burgdorferi* DNA.[71] Chronic peripheral nervous system manifestations develop a median of 16 months, and chronic central nervous system manifestations a median of 26 months after initial infection.[325]

It was initially thought that neuroborreliosis was primarily a European and not a North American manifestation of Lyme borreliosis, but it is now recognized to occur in North America as well.[326] The reported incidence of neuroborreliosis is higher in Europe than in North America, and within Europe, it is higher in the northern European countries (Netherlands, Sweden and Norway) than in the southern, central, and eastern European countries.[6, 7, 231, 242] 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.[242]

Patients with Lyme borreliosis may develop either central or peripheral nervous system involvement at any stage of the infection.[117, 315, 326, 325] 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),[116, 117, 124, 315, 325, 326] cranial neuropathy (including Bell's palsy),[117, 326–328] peripheral neuropathy[117, 325, 326, 329, 330] and painful meningopolyneuritis with peripheral extremity paresis (Bannwarth's syndrome),[124, 266, 326, 331, 332] neuropsychiatric disorders[333] and transverse myelitis, acute focal meningoencephalitis, Guillain-Barré syndrome, acute cerebellar ataxia, mononeuritis multiplex or chorea.[323, 334]

Acute lymphocytic meningitis may occur as a manifestation of early disseminated Lyme borreliosis. Spinal fluid of patients with acute neuroborreliosis shows a lymphocytic pleocytosis of approximately 100 to 200 cells per mm^3; slightly elevated protein, normal glucose and sometimes oligoclonal bands; and intrathecal production of *B. burgdorferi*–specific antibody.[117]

One of the more common neurologic manifestations of 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 per cent of patients with Lyme borreliosis within 4 weeks of EM.[327, 328] However, since Bell's palsy may also be the initial presentation, without preceding history of tick bite or EM, the possibility of Lyme borreliosis should be considered as a potential etiology for idiopathic Bell's palsies.

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,[124, 266, 331, 332] also known as Garin-Bujadoux-Bannwarth syndrome, tick-borne meningopolyneuritis, meningoradiculoneuritis, or lymphocytic meningoradiculitis, is more common in European patients and consists of intense radicular pain with paresthesias or hyperesthesias; asymmetrical polyneuritis, often with unilateral or bilateral facial palsy; and lymphocytic meningitis, which develops within a few weeks after the initial EM and lasts approximately 3 to 5 months.

Manifestations of late neuroborreliosis include progressive encephalomyelitis with cranial and peripheral neuropathies, myelitis, meningitis and encephalitis[315]; limb paresthesias, carpal tunnel syndrome, painful radiculopathy, Bell's palsy and disseminated multifocal patchy axonal neuropathy similar to mononeuritis multiplex[329]; and progressive encephalomyelitis with spastic paraparesis, bladder dysfunction, ataxia, cranial nerve deficits and dementia.[51] Chronic encephalopathy and leukoencephalitis have also been reported.[325] Spinal fluids of patients with chronic neuroborreliosis show slight lymphocytic pleocytosis of approximately 150 cells per mm^3, slightly elevated protein and usually *B. burgdorferi*–specific intrathecal antibody production.[325, 326]

There are several reports of unusual manifestations of neuroborreliosis, including presentation with acute papilledema and pseudotumor cerebri,[335, 336] presentation as a brain-stem tumor,[290] presentation with acute meningovasculitis and basilar artery occlusion[337] and presentations with acute par-

aparesis or hemiparesis[124, 338] and global aphasia and apraxia.[339] Urinary retention has also been reported because of involvement of the innervation of the bladder.[340]

Neuropsychiatric disorders such as psychosis, schizophrenia, paranoia, depression, anorexia nervosa, dementia and personality changes have been reported.[333] Disturbances of sleep, mood and memory have been reported and are considered symptoms of mild encephalopathy.[333, 341]

Electroneurogram and electromyogram evaluation may be useful in assessment of the severity of and response to antibiotic therapy of paresis and peripheral neuropathy.

Magnetic resonance imaging (MRI) of the brain may be useful in evaluation of chronic neuroborreliosis and has demonstrated periventricular brain lesions with hyperintense T2 signal in two patients with chronic neuroborreliosis consisting of chronic encephalopathy and leukoencephalitis,[325] frontal and parietal lobe subcortical white matter lesions with hyperintense T2 signal suggestive of demyelination or perivascular inflammation in 6 patients with central nervous system neuroborreliosis,[342] multiple 2.5-cm brain parenchymal white matter lesions with ring-like enhancement with gadolinium contrast suggestive of demyelination or inflammation in a patient with central nervous system neuroborreliosis,[291] a pontine mass lesion and two smaller brain parenchymal lesions with hyperintense T2 signal and gadolinium enhancement in a patient with neuroborreliosis who presented with signs of a mass lesion[290] and multifocal hyperintense T2 signal lesions in the white and occasionally the gray matter of the brain in 26 patients with either acute or indolent multifocal encephalomyelitis.[124]

Carditis

About 2 to 8 per cent of patients with Lyme borreliosis present with carditis initially and 6 to 8 per cent develop it if untreated, usually within 2 to 4 weeks but up to 3 months after the initial infection.[33, 142, 323, 343, 344] Although this complication was initially thought to occur only in North American patients, it has now been reported, with the same rate, from Europe as well.[7, 345]

The most common finding is mild transient fluctuating atrioventricular block, but complete heart block may also occur and may manifest as syncopal episodes, dizziness, chest pain, palpitations and fatigue,[343–345] but myopericarditis,[344] mild left ventricular dysfunction,[344] ventricular tachycardia,[286] chronic dilated cardiomyopathy[285] and even fatal pancarditis[283] have also been reported.[284, 343–345] The carditis usually resolves spontaneously within 3 days to 6 weeks,[344] but more rapidly if treated. Electrocardiograms show atrioventricular block, T wave flattening or inversion and interventricular conduction defects and occasional premature ventricular contractions.

Acrodermatitis Chronica Atrophicans

Acrodermatitis chronica atrophicans (ACA) is a late chronic cutaneous manifestation of Lyme borreliosis and occurs in 2 to 16 per cent of European patients with Lyme borreliosis,[33, 104, 106, 155, 233, 242, 320] 6 months to 10 years after initial infection.[278] While this is rare in North America and is more common in the elderly, it has been reported in both a child and a young woman in the United States.[346, 347] 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 prior EM lesion, followed by the atrophic phase, which produces atrophic skin changes in the previously affected areas of skin.[18, 231, 277, 278, 292] Patients may have periarticular manifestations such as bursitis, Achilles tendonitis and epicondylitis, and juxta-articular fibrotic nodules.[18] Two thirds of patients with ACA have associated peripheral neuropathies, and 20 per cent have deformities of the joints underlying the ACA lesions, including subluxation and degenerative arthritis.[278, 292] In Europe, 5 to 10 per cent of patients with ACA eventually develop scleroderma-like skin lesions.[277]

Other Organ Involvement in Disseminated Infection

During the dissemination phase of the infection, there have also been reports of hepatitis,[101, 280, 348] necrotizing splenitis,[279] eosinophilic lymphadenitis,[282] myositis[293] and panniculitis resembling erythema nodosum.[275]

Several ophthalmologic manifestations of Lyme borreliosis have been reported, including severe panophthalmitis with iridocyclitis, choroiditis, vitritis and retinitis and resulting blindness[349]; conjunctivitis, interstitial keratitis and nodular episcleritis[335, 350]; orbital myositis and periostitis[350]; optic neuritis, papilledema, pseudotumor cerebri and optic atrophy[350, 351]; and cranial nerve palsies affecting extraocular movements, Horner's syndrome and Argyll Robertson–like pupil.[350]

The incidence of otologic complications, other than facial nerve palsy, is less than 12 per cent and includes moderate hearing loss, tinnitus, otalgia and temporomandibular joint pain.[352]

Symptoms consistent with fibromyalgia have been reported in 8 per cent of patients with Lyme borre-

liosis in one small study, but these symptoms persisted after antibiotic therapy resulted in resolution of the symptoms of Lyme disease and were not considered to be related to Lyme disease.[353, 354]

Clinical Manifestations of Congenital Lyme Disease

A review of the congenital and gestational Lyme borreliosis literature yielded 157 cases reported for which the outcome of the episode of gestational Lyme borreliosis was noted, and addition of four of the author's cases brought the total to 161 cases. A total of 46 cases of adverse outcomes of these 161 cases of gestational Lyme borreliosis were found, including miscarriage, stillbirth, perinatal death, congenital anomalies, systemic illness, early-onset fulminant or mild sepsis and later-onset chronic progressive infection.

In some of these reports, the gestational trimester of onset of the Lyme borreliosis, the clinical manifestation of the Lyme borreliosis, the gestational antibiotic therapy, the *B. burgdorferi* serologic status of the mother and details about the specific type of fetal or neonatal abnormality that may have occurred, including specific malformations, birth weight, prematurity, serologic status of the infant, trimester of miscarriage, antibiotic therapy of the infant and placental and autopsy pathologic information, are indicated, while in others this information is missing.

The reader is directed to additional information about these cases of congenital Lyme borreliosis discussed in the individual sections of Pathology and Pathogenesis, Diagnosis and Differential Diagnosis, Therapy, Prevention and Prognosis in this chapter.

It is anticipated that more infants and fetuses with complications related to gestational Lyme borreliosis will be diagnosed in the future as the diagnosis is more frequently considered, and it will eventually be possible to better describe the various clinical manifestations of congenital Lyme borreliosis. In this section, the 46 available cases that the author considers to represent an adverse event at least associated with an episode of gestational Lyme borreliosis have been divided into logical groups based on an understanding of the pathophysiology and clinical course of Lyme borreliosis in older patients, and on inescapable similarities of Lyme borreliosis to syphilis. Many of the calculations of rates of adverse outcomes became apparent only when all of the available case information was compared, as each individual report of one or several cases represented too few cases from which to draw conclusions.

Review of 46 Cases of Adverse Outcomes of 161 Cases of Gestational Lyme Borreliosis

Table 11–8 lists the individual cases of adverse outcomes of the 161 cases of gestational Lyme borreliosis found. Only four groups—Schlesinger and colleagues,[19] MacDonald,[27–29] Lavoie and colleagues[26] and Weber and colleagues[32, 33]—have had any success in demonstrating spirochetes in either fetal autopsy or placental tissues. Only one infant was found to be seropositive for *B. burgdorferi* antibody (case 24), and this was transient, so that this does not appear to be a sensitive method of diagnosis, and reliance on seropositivity will lead to misdiagnosis of the majority of congenitally infected infants. The poor protection provided by short courses of oral antibiotic therapy against development of serious adverse complications of gestational Lyme borreliosis is evident from this table, and is discussed in detail in the section on Therapy.

Frequency of Specific Adverse Outcomes of Gestational Lyme Borreliosis

Table 11–9 shows the frequency of occurrence of various types of fetal or neonatal adverse outcomes after gestational Lyme borreliosis.

The 24 per cent incidence of cardiac malformation is strikingly high and includes significant abnormalities such as ventricular septal defect and myocardial dysfunction, which is reminiscent of the ability of the spirochete to cause carditis, including cardiomyopathy and pancarditis, in older patients.

The 20 per cent incidence of neurologic abnormalities is also high, and would also be consistent with the neurotropic nature of the infection in older patients. One infant (case 24) had focal parenchymal brain lesions with increased T2 signal demonstrated by MRI scan that were similar to those reported in the literature in adult patients with chronic meningoencephalomyelitis. Nonspecific neurologic abnormalities may not be easily recognized as manifestations of neuroborreliosis.[33a]

The incidence of orthopedic abnormalities was 13 per cent, but there were some unique features of this involvement, including 3 patients with syndactyly or clubfoot, 2 with significant joint contractures and 2 with a new finding of transverse metaphyseal bands.

Several infants were reported to have a maculopapular erythematous rash, which would be consistent with disseminated spirochetosis, and many of these rashes increased or developed during the first

Table 11–8. CONGENITAL LYME BORRELIOSIS: 46 ADVERSE OUTCOMES OF PREGNANCIES COMPLICATED BY LYME BORRELIOSIS (LB)

	Maternal Gestational				Fetal/Neonatal				
Patient No.	*Trimester of LB*	*Clinical History*[a]	*Antibiotic Number of Days*[c]	*LB Serology*[d]	*Gestational Age (wk)*	*Weight (g)*	*Antibiotic Number of Days*[c]	*LB Serology*[d]	*Tissue Borrelia*[f]
1	1	EM,Fl, Ar	–	+	35	3,000	–		+ H,S,K, BM
2	1	EM,Ar	–	+	40	2,500			+ L,H,K,A, B
3	≤2	Tx	–	–	19	514			+ L,P
4	≤2	Tx,Ar	–	–	23	490			+ L,K
5	≤2	0	–	–	15	85			+ L,P
6	≤1	VB	NA[e]	NA	39	2,250	NA		+ F
7	NA	0	NA	NA	40	1,950	NA		+ F
8	≤2	VB	NA	–	17	30			+ B
9	≤2	VB	NA	–	16	150			+ B
10	≤1	0	NA	NA	12	294			+ K
11	≤2	Ar	–	–	25	NA			+ F
12	NA	0	–	NA	~40	3,746	+ iv		+ P
13	NA	Tx	–	NA	37	2,157	+ ivPN, ivMT		+ P
14	1	EM,Ar	+ poPN 10d	+	20	NA			
15	1	BP,Ar	–	NA	36	2,100	NA		
16	2	EM,Ar	+ poER 10d, poPn 10d	NA	NA	NA	NA		
17	2	EM	+ poPN 10d	NA	40	NA	NA	–	
18	3	EM,Me	–	NA	40	NA	+ ivPN 10d		
19	1	LB	+	+	13	NA			–
20	1	LB	+	+	NA	NA	NA		
21	≤1	AR	–	–	~40	NA	NA		+ B,H
22	1	EM	+ poPN 7d	+	40	3,400	NA		+ L,B
23	1	EM,Fl	+ ivCTX 2d, poPN 12d	+ (+ LPA[g])	40	3,461	+ ivCTX 14d	– (+ LPA)[g]	
24	2	Fl	+ poAM 10d	– (+ LPA[g])	34	1,050	+ ivAM 6d, ivCTX 7d	+ (+ LPA)[g]	
25	1	EM,Pn,Ar	+ poER 10d, ivCFX 5d, poCFC/CEP/CFM 39d	+ (+ LPA[g])	37	3,490	+ ivAM 5d, ivCFT/CTX 3d	– (+ LPA)[g]	
26	2	EM,Ar	+ poER 10d, poCFM 49d	– (+ LPA[g])	40	3,461	+ ivCTX28d	– (+ LPA)[g]	
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	–	
34	≤1	NA	–	+	11	NA			
35	≤1	NA	+ (≤IT)	+	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	2,150	NA	+	
41	NA	0	–	+	NA	NA			
42	NA	LB	NA	NA	NA	NA	NA	–	
43	NA	LB	NA	NA	NA	NA	NA	–	
44	NA	LB	NA	NA	NA	NA	NA	–	
45	NA	0	NA	NA	NA	NA	NA	+	
46	2	EM,Ar	+	+	33	1,450	NA	–	–

[a]NA, information not available.
[b]0, unremarkable; EM, erythema migrans; Fl, flu-like illness; Ar, arthralgia/arthritis; BP, Bell's palsy; Me, meningoencephalitis; 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; MT, metronidazole; AM, ampicillin.
[d]*Borrelia burgdorferi* antibody detected either by IFA (immunofluorescence assay) or ELISA (enzyme-linked immunosorbent assay).
[e]LPA, in-vitro lymphocyte proliferative assay for *B. burgdorferi*.
[f]*Borrelia* detected in tissue samples by IFA, silver stain or culture; H, heart; S, spleen; K, kidney; BM, marrow; L, liver; A, adrenal; B, brain; P, placenta; F, fetal tissue unspecified.
[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; BIH, bilateral inguinal hernia.

Table 11–8. CONGENITAL LYME BORRELIOSIS: 46 ADVERSE OUTCOMES OF PREGNANCIES COMPLICATED BY LYME BORRELIOSIS (LB) *Continued*

Clinical Outcome[a]	Reference
CoA, EFE, AS, LSVC, PDA, cardiac dysfunction, RD, death 39 hours	19, 27
IUGR, VSD, stillbirth	27–29
ASD, stillbirth	27, 28
CoA, stillbirth	27, 28
Miscarriage	27, 28
VSD, hydrocephalus, omphalocele, clubfoot, meningomyelocele, RD, death 4 hours	27
IUGR, absent hemidiaphragm, RD, cardiac dysfunction, death 30 min	27
Hydrocephalus, miscarriage	27
Miscarriage	27
Miscarriage	27
VSD, miscarriage	27
R/O sepsis, RD	27
R/O sepsis, RD, hypoglycemia, fever	27
Miscarriage	30
Prematurity , hyperbilirubinemia	30
Syndactyly	30
DD, cortical blindness	22, 30
Rash, hyperbilirubinemia	30
Miscarriage	23
Syndactyly	23
Cardiac dysfunction, aortic thrombosis, lethargy, hypertension, acidosis, death 8 days	26
RD, death 23 hours	32, 33
Rash, adenopathy	Author's patient
IUGR, cardiomyopathy, PDA, R/O sepsis, RD, rash, adenopathy, hepatomegaly, hyperbilirubinemia, meconium ileus, metaphyseal bands, joint contractures, R/O encephalitis	Author's patient
R/O sepsis, rash, hepatomegaly, hyperbilirubinemia, metaphyseal bands, pectus excavatum, R/O encephalitis, hemiparesis, eso/exotropia, dysphagia, GER, BIH, dysmorphic, unilateral simian crease, GR, DD	Author's patient
Hyperbilirubinemia, retinal lesions, R/O meningoencephalitis	Author's patient
VSD	31
Hyperbilirubinemia	31
Hyperbilirubinemia	31
Hypotonia	31
IUGR	31
Macrocephaly	31
Supraventricular extrasystoles	31
Miscarriage	21
Miscarriage	21
Miscarriage	21
Miscarriage	21
Miscarriage	21
Miscarriage	21
Cardiomegaly, rash, adenopathy, hepatosplenomegaly, chronic arthritis, chronic meningoencephalitis, exophthalmos, blepharitis, GR, DD	25
Miscarriage	24
Malformation, unspecified	34
Malformation, unspecified	34
Malformation, unspecified	34
Malformation, unspecified	34
RD, anemia	20

Table 11–9. FREQUENCY OF SPECIFIC ADVERSE OUTCOMES[a] OF 46 PREGNANCIES COMPLICATED BY GESTATIONAL LYME BORRELIOSIS (GLB) AND ADVERSE CLINICAL OUTCOME

Fetal/Neonatal Abnormality	No. with Finding[b]	% with Finding	Reference
Cardiac	11/46	23.9	
Myocardial dysfunction	5/46	10.9	19, 25–27, 131
VSD	4/46	8.7	27–29, 31
Coarctation aorta	2/46	4.3	19, 27, 28
ASD	1/46	2.2	27, 28
Other [c]	4/46	8.7	19, 26, 27, 31, 131
Neurologic	9/46	19.6	
Developmental delay	4/46	8.7	25, 30, 131
Hydrocephalus/macrocephaly	4/46	8.7	25, 27, 31
Hypotonia/lethargy	3/46	6.5	26, 131
Meningoencephalitis[d]	3/46	6.5	25, 131
CNS lesions on scan[e]	2/46	4.3	25, 131
Cortical blindness	1/46	2.2	30
Hemiparesis	1/46	2.2	131
Meningomyelocele	1/46	2.2	27
Orthopedic	6/46	13.0	
Syndactyly/clubfoot	3/46	6.5	23, 27, 30
Arthritis/contractures	2/46	4.3	25, 131
Long bone metaphyseal bands	2/46	4.3	131
Dermatologic			
Rash	5/46	10.9	25, 30, 131
Ophthalmic	3/46	10.9	
Blepharitis/exophthalmos	1/46	2.2	25
Punctate retinal lesions	1/46	2.2	131
Eso/exotropia	1/46	2.2	131
Miscellaneous anomalies	8/46	17.4	
Malformation, unspecified	4/46	8.7	34
Pilonidal dimple	2/46	4.3	131
Facial/ear dysmorphia	1/46	2.2	131
Simian crease, unilateral	1/46	2.2	131
Inguinal hernia, bilateral	1/46	2.2	131
Omphalocele	1/46	2.2	27
Miscellaneous abnormalities			
Neonatal sepsis/DIC/respiratory distress	9/46	19.6	19, 20, 27, 32, 131
Hyperbilirubinemia	7/46	15.2	30, 31, 131
Growth retardation[f]	6/46	13.0	25, 27–29, 31, 131
Hepatomegaly/splenomegaly	3/46	6.5	25, 131
Adenopathy	3/46	6.5	25, 131
Recurrent infections	2/46	4.3	25, 131
Dysphagia, GE reflux, aspiration	1/46	2.2	131
Meconium ileus	1/46	2.2	131
Fetal/Neonatal demise:	22/46	47.8	
After first trimester GLB	14/46	30.4	19, 21, 23, 26, 27, 30, 32
After second trimester GLB	6/46	13.0	27
After third trimester GLB	0/46	0.0	
After unspecified trimester GLB	2/46	4.3	24

[a]Underestimate of incidence of findings, as autopsies not done on all fetal deaths.
[b]Number with finding/total number.
[c]Endocardial fibroelastosis, aortic stenosis, left superior vena cava, patent ductus arteriosus, aortic thrombosis, or arrhythmia.
[d]Chronic meningitis, or CSF pleocytosis/elevated protein.
[e]Cortical atrophy on CT or white matter lesions on MRI.
[f]Intrauterine or postnatal.

few days of antibiotic therapy and resembled Jarisch-Herxheimer reactions. The one infant (case 25) with chronic distal extremity rash that resolved after prolonged antibiotic therapy raises the possibility that this was similar to the rash of secondary syphilis or disseminated Lyme borreliosis in older patients.

Hepatosplenomegaly and inguinal adenopathy were also seen in several patients and probably represent disseminated spirochetal infection, as these findings resolved with antibiotic therapy.

Congenital Lyme borreliosis presenting as manifestations that are not specific for *B. burgdorferi*, such as the 20 per cent incidence of presentation as fulminant early sepsis, the 15 per cent presentation with hyperbilirubinemia and the 13 per cent presentation with growth retardation, may be missed unless careful maternal gestational and pregestational histories are obtained. One study noted an approximately double incidence of jaundice and low birth weight in Lyme-seropositive compared with Lyme-seronegative newborns.[33b]

Thirty-seven per cent of the total number of adverse outcomes were miscarriages or fetal deaths, 11 per cent were neonatal deaths and 48 per cent were either fetal or neonatal deaths (Tables 11–9 and 11–10). Williams and colleagues[336] also noted an approximately double incidence of low birth weight and jaundice in Lyme-seropositive newborns.

Frequency of Adverse Outcomes of 161 Cases of Gestational Lyme Borreliosis

Table 11–10 shows the fetal and neonatal mortality rates, and total fetal and neonatal adverse outcome rates divided by trimester and according to whether or not gestational antibiotic therapy was given.

Effect of Trimester of Infection. Lyme borreliosis in the first trimester carried an overall 63 per cent risk of adverse outcome. In the second trimester the risk was 38 per cent, in the third trimester it was 10 per cent; the overall risk in all trimesters was 29 per cent.

Effect of Gestational Antibiotic Therapy. Gestational antibiotic therapy had a protective effect against adverse fetal or neonatal outcome, and the overall adverse outcome risk after treatment in all trimesters was 25 per cent and after no treatment in all trimesters it was 75 per cent.

Rate of Miscarriage and Stillbirth. The overall risk of fetal death for any trimester of infection was 17 of 161 patients (11 per cent).

Rate of Neonatal Death. The overall risk of neonatal death for any trimester of infection was 5 of 161 patients (3 per cent).

Rate of Neonatal Illness. The risk of nonfatal neonatal illness or abnormality for any trimester of infection was 24 of 161 patients (15 per cent).

Rate of Normal Outcome. The overall rate of normal outcome for any trimester of infection was 115 of 161 patients (71 per cent). Several authors have reported normal infants born after antibiotic-treated gestational Lyme borreliosis,[23, 27, 30, 300, 381, 386, 395–398] after untreated gestational Lyme borreliosis[30, 396] or after gestational Lyme borreliosis in which antibiotic therapy was not specified[21, 31, 33, 34, 34a, 396] (Table 11–10).

Description of Congenital Lyme Borreliosis Syndrome

Table 11–11 lists the incidence of, the time of presentation and the clinical manifestations of the various adverse outcomes associated with gesta-

Table 11–10. OUTCOMES OF 161 PREGNANCIES COMPLICATED BY LYME BORRELIOSIS (LB)[a]

Trimester of LB[b]	Antibiotic Therapy of LB[c]	No. Patients	No. Fetal Deaths[d]	No. Neonatal Deaths[e]	No. Live Born, Ill or Abnormal[f]	No. Live Born, Normal	No. Total Adverse Outcomes[g]	No. Total Normal Outcomes[h]
1	Yes	17	4*	1	3	9	8 (47.1%)	9 (52.9%)
	No	10	4	2	2	2	8 (80.0%)	2 (20.0%)
	Unknown	3	2	1	0	0	3 (100.0%)	0 (0.0%)
	Total	30	10	4	5	11	**19 (63.3%)**	**11 (36.7%)**
2	Yes	22	0	0	5	17	5 (22.7%)	17 (77.3%)
	No	5	4	0	0	1	4 (80.0%)	1 (20.0%)
	Unknown	2	2	0	0	0	2 (100.0%)	0 (0.0%)
	Total	29	6	0	5	18	**11 (37.9%)**	**18 (62.1%)**
3	Yes	8	0	0	0	8	0 (0.0%)	8 (100.0%)
	No	2	0	0	1	1	1 (50.0%)	1 (50.0%)
	Total	10	0	0	1	9	**1 (10.0%)**	**9 (90.0%)**
Unknown	Yes	6	0	0	0	6	0 (0.0%)	6 (100.0%)
	No	3	0	0	2	1	2 (66.7%)	1 (33.3%)
	Unknown	83	1	1	11	70	13 (15.7%)	70 (84.3%)
	Total	92	1	1	13	77	**15 (16.3%)**	**77 (83.7%)**
Total	Yes	53	4	1	8	40	**13 (24.5%)**	**40 (75.5%)**
	No	20	8	2	5	5	**15 (75.0%)**	**5 (25.0%)**
	Unknown	88	5	2	11	60	**18 (20.5%)**	**70 (79.5%)**
	Total	**161**	**17**	**5**	**24**	**115**	**46 (28.6%)**	**115 (71.4%)**

[a]Data from cases reported in references 19–34, 131, 300, 381, 386, 396–398.
[b]LB either by clinical history or positive *Borrelia burgdorferi* assay.
[c]Antibiotic therapy given for the episode of gestational LB except in one case* in which antibiotic may have been given either in or prior to first trimester.
[d]Miscarriages or stillbirths.
[e]Four neonatal deaths occurred before 2 days of age, and one at 8 days.
[f]Includes nonfatal congenital anomalies, growth retardation, developmental delay and neonatal illness (see Table 11–8).
[g]Includes miscarriages, stillbirths, neonatal deaths, illness or abnormality.
[h]Percentage of total in treatment category is included despite small numbers in some categories.

Table 11–11. CLINICAL MANIFESTATIONS OF CONGENITAL LYME BORRELIOSIS SYNDROMES[a]

Miscarriage
40% (8/20) risk after untreated GLB[b]
8% (4/53) risk after treated GLB
11% (17/161) risk after any GLB
~80% occur at <20 weeks gestation (range 8–40 weeks), after first- or second-trimester gestational LB, with variable interval between GLB and fetal demise; high frequency (23%, 4/17) of cardiac abnormality or anomaly
Early Congenital, Severe
20% (4/20) risk after untreated GLB
8% (4/53) risk after treated GLB
6% (10/161) risk after any GLB
Present in first week of life with R/O sepsis (fulminant or routine) and any of the following:
Intrauterine growth retardation
Cardiomyopathy, cardiac abnormality or anomaly (55%, 5/9)
Respiratory distress
Hepatosplenomegaly
Hyperbilirubinemia
Adenopathy
Rash
Lethargy, meningoencephalitis
Metaphyseal bands, bony involvement
Other organ involvement (ocular, dysmorphia, other anomalies)
Early Congenital, Mild
10% (2/20) risk after untreated GLB
8% (4/53) risk after treated GLB
11% (17/161) risk after any GLB
Present in first 2 weeks of life with any of the following:
Intrauterine growth retardation
Prematurity
Mild cardiac abnormality (arrhythmia, VSD)
Hyperbilirubinemia
Adenopathy
Rash
Hypotonia
Minor anomalies (syndactyly, macrocephaly)
Late Congenital
2–3% (4/161) risk is a minimum estimate as long-term follow-up unavailable for most patients
Present after 2 weeks of life, usually in first year, with any of the following:
Growth retardation and failure to thrive
Developmental delay
Hepatosplenomegaly
Adenopathy
Rash
Lethargy
Meningoencephalitis
Metaphyseal bands, bony involvement
Other organ involvement (ocular, other anomalies)
May progress to chronic neurologic, cardiac, bone, cutaneous, ocular involvement

[a]Adapted from Tables 11–8 to 11–10, summaries of 46 adverse outcomes of gestational Lyme borreliosis.
[b]GLB, gestational Lyme borreliosis.

tional Lyme borreliosis, including miscarriage, early severe congenital Lyme borreliosis, early mild congenital Lyme borreliosis and late chronic congenital Lyme borreliosis.

Clinical case reports of mother-infant pairs who illustrate these various manifestations of congenital Lyme borreliosis are presented in the following sections.

Asymptomatic Infant with Gestational Lyme Borreliosis Exposure

CLINICAL CASE (previously unpublished)

Mother. A 26-year-old woman developed acute onset of hypertension of 160/140 and severe left facial pain, paresthesia and paralysis in the thirty-eighth week of her third pregnancy in mid-March 1991, and because of the hypertension had a cesarean section for delivery of the infant 2 days later. A diagnosis of idiopathic Bell's palsy was made, and she was treated with prednisone, 40 to 60 mg daily for less than 1 week. She had partial return of motor function after 6 months, but still had residual discomfort, paresthesias and mild to moderate left facial motor deficits 2 years later.

In 1992, during her next pregnancy, she was treated with oral cephalexin for a first-trimester urinary tract infection and gave birth at term to a second infant in October 1992.

In April 1993, during routine questioning about maternal gestational history because of hospitalization of her then 2-year-old child for gastroenteritis, she reported that ever since the Bell's palsy she had persistent severe daily headaches; neck aches; intermittent left conjunctivitis; migratory polyarthralgias of the wrists, elbows, knees and hips; infrequent 10- to 20-cm diameter round erythematous rashes on her legs that spontaneously resolved; fatigue; and short-term memory deficits. She was an avid hiker and had an over-10-year history of multiple tick bites to her scalp, ears and neck, and reported that many of these ticks had become fully engorged before removal. In April 1993, she was found to have specific *B. burgdorferi* antibody by polyvalent EIA and IgM Western blot assays.

She was initially treated with oral cefuroxime axetil (because of a history of penicillin allergy) for 6 weeks, had a mild Jarisch-Herxheimer reaction on the second day, had resolution of fatigue and headache and improvement in the residual Bell's palsy symptoms by the end of therapy, but experienced relapse within 1 week of completion of the oral cefuroxime with fatigue, headache, left eye conjunctivitis and left facial weakness (see Fig. 11–8). She had a lumbar puncture (spinal fluid *B. burgdorferi* antibody negative, and spinal fluid normal); was treated with 3.5 weeks of intravenous ceftriaxone; had resolution of fatigue, headache and conjunctivitis and marked improvement of the left facial weakness by the end of therapy; and remained well at 6-month follow-up.

Placenta. No pathologic testing was performed on either placenta.

Infant 1. The baby, delivered by cesarean section 2 days after onset of the maternal Bell's palsy at 38 weeks of gestation, was considered normal at birth. However, he was hospitalized at 5.5 months of age for fever, irritability, lethargy, full fontanel and the possibility of culture-negative (bacterial and viral) sepsis or meningitis (normal

spinal fluid); responded clinically to intravenous cefotaxime for 3 days; and developed a maculopapular rash on the second day of the cefotaxime that resolved despite continuation of the cefotaxime. He was treated with oral amoxicillin several times during his first 2 years of life for upper respiratory infections by his pediatrician. When the mother's Lyme borreliosis was diagnosed 2 years after the birth of this infant, he was tested and found to have no antibodies to *B. burgdorferi*, and he has remained normal at 2.8 year follow-up.

Infant 2. A second baby born to this mother in October 1992 after a term pregnancy was also normal at birth. At 7.5 months of age, this infant was treated by his pediatrician with oral amoxicillin–clavulinic acid for an upper respiratory infection and developed an erythematous maculopapular rash on the fourth day, which resolved despite continuation of the antibiotic. When the mother's Lyme borreliosis was diagnosed, he was tested and found to be seronegative for *B. burgdorferi* antibodies, and he has remained normal at 1.3 year follow-up.

Comments. This mother gave birth to two infants before the diagnosis of Lyme borreliosis during the gestation for the first infant was made retrospectively 2 years later, on routine questioning to obtain a gestational history because of hospitalization of one of the infants for an unrelated illness (bacterial gastroenteritis). Her *B. burgdorferi* seropositivity, Jarisch-Herxheimer reaction (refer to discussion of Jarisch-Herxheimer reaction in section Therapy) after initiation of antibiotic therapy and impressive clinical response to antibiotic therapy all support the diagnosis of chronic Lyme borreliosis in this patient, although it was made retrospectively.

Fortunately, both infants were normal at birth and remained so, but both had erythematous maculopapular rashes, possibly reminiscent of Jarisch-Herxheimer reactions, between 5.5 and 7.5 months of age within the first few days of either intravenous third-generation cephalosporin or oral amoxicillin therapy, given in one case for an episode of "rule out sepsis and meningitis" with negative viral and bacterial cultures, and in the other case for an upper respiratory infection. It is not known whether either of these infants ever acquired the spirochete gestationally, as both infants were *B. burgdorferi* seronegative, and have not yet been tested by the in vitro lymphocyte proliferative assay (LPA), which may be more sensitive in detection of congenital Lyme borreliosis.

This mother-infant group illustrates the possibility that infants born after untreated gestational Lyme borreliosis may be normal. Possible explanations for this could be that transplacental spread of the spirochete is variable; that spirochetemia may not yet have occurred at the time the first infant was delivered, which was within 2 days of onset of the Bell's palsy; that the oral cephalosporin therapy during the first trimester of gestation of the second infant may have partially treated the Lyme borreliosis sufficiently to prevent transplacental spread to the fetus; or that if transplacental spread of infection occurred in either of these two infants, the courses of antibiotic therapy given by the pediatrician for other illnesses during the first year of life may have been beneficial in prevention of symptomatic congenital Lyme borreliosis.

Mild Early Congenital Lyme Borreliosis

CLINICAL CASE (case 23 in Table 11–8, previously unpublished)

Mother. A 38-year-old woman visited a lake for 4 days in mid-April 1987, and the day after returning home found and removed an engorged tick attached to her groin. A 1-cm indurated erythematous patch had developed at the bite site and resolved a few days after she applied topical Neosporin ointment. She conceived in mid-May 1987, developed a mild flu-like illness 1 week later at 3 weeks of gestational age, developed an asymptomatic rash on her trunk at 4 weeks and presented at 4.5 weeks with low-grade fever, a dense erythematous maculopapular rash of her trunk and proximal extremities (see Fig. 11–7*A*), and two larger (1- to 2-cm) erythematous patches with central clearing (see Fig. 11–7*B*).

She was referred for infectious disease evaluation for suspected rubella, but because of the appearance of the rash and the history of the tick bite, the diagnosis of Lyme borreliosis was considered; she was treated immediately at 4.5 weeks' gestation with intravenous ceftriaxone 2 g daily and had improvement in the rash after 2 days, but developed severe watery diarrhea, which necessitated a change to penicillin 500 mg four times daily for the remainder of the 2-week course. The rash resolved completely after 8 days, and she remained well throughout the rest of the pregnancy, except for mild toxemia in the last trimester, and delivered a term infant by cesarean section because of nonprogression of labor. Maternal polyvalent ELISA serum antibody to *B. burgdorferi* was initially negative at presentation at 4.5 weeks' gestation, became positive at 5.5 weeks, remained positive through 12 weeks and was negative at delivery. The in vitro LPA for *B. burgdorferi* was positive at 16 weeks' gestation, at delivery and at 1 month post partum, but the level decreased with time. She has remained well after 6.5 years by verbal follow-up.

Placenta. Focal chorioamnionitis and subchorionic nodules were found (refer to discussion of placental pathology in section Pathology and Pathogenesis).

Infant. The infant was normal at birth except for a sacral dimple and 0.5-cm bilateral inguinal adenopathy of initially unclear significance (case 23 in Table 11–8). The child weighed 3461 g and had a normal pediatric ophthalmology examination, brain-stem auditory evoked response evaluation, head ultrasound, electrocardiogram, chest and long bone x-rays and complete blood count. Spinal fluid had 3 mononuclear cells, protein 53 mg/dl, glucose 37 mg/dl, and both blood and spinal fluid were negative for polyvalent EIA *B. burgdorferi* antibody. The in vitro LPA for *B. burgdorferi* was positive on both cord blood and on infant blood at 1 month of age but was lower at 1 month.

After the result of the *B. burgdorferi* LPA was obtained, the infant was treated with intravenous ceftriaxone 100 mg/kg daily for 2 weeks and developed an intensely erythematous generalized maculopapular rash on the sixth day of treatment, which resolved despite continuation of the antibiotic. The inguinal adenopathy resolved by the end of the antibiotic therapy, and the infant remained

clinically well at 15 months, and by verbal report continues to be well at almost 6 years of age.

CLINICAL CASE (case 26 in Table 11–8, previously unpublished)

Mother. In early April 1989, a 29-year-old woman in the seventeenth week of pregnancy camped in a wooded area frequented by deer and had several small tick bites, including one that was deeply embedded in her scalp. At 18 weeks of gestation, she developed a 10 × 5 cm diameter erythematous oval "bull's-eye" rash that lasted 3 weeks and then spontaneously resolved, on her thigh at one of the tick bite sites. Between 20 and 28 weeks of gestation, she experienced low-grade fever, myalgias, fatigue, stiff neck, dizziness, photophobia and migratory polyarthralgias, especially of the knees, and between 23 and 26 weeks had recurrence of the rash.

At 28 weeks, she took oral erythromycin 250 mg four times daily for 10 days and her symptoms resolved. She then heard about Lyme disease, obtained and began oral cefuroxime axetil 1 g twice daily from 33 weeks to the time of delivery and remained well except for mild knee arthralgias. She reported that her urine had been positive for Lyme antigen at a commercial laboratory at 32 weeks.

At delivery, maternal blood was negative for polyvalent EIA *B. burgdorferi* antibody, but blood obtained 1 day post partum was positive by the *B. burgdorferi* in vitro LPA. After delivery, because of recurrence of headache, photophobia, flu-like symptoms and knee arthralgias, she was treated with oral doxycycline 100 mg twice daily for 1 month, improved within 24 hours and recovered by the end of therapy. Long-term follow-up information is unavailable.

Infant. The infant was normal at birth except for diffuse small retinal hemorrhages with white centers; weighed 3461 g; and had a normal brain-stem auditory evoked response evaluation, electrocardiogram, two-dimensional echocardiogram, complete blood count and liver enzyme panel. Cord blood, and infant's blood on the first day, and at 2.5 weeks and at 7 weeks were all seronegative for polyvalent EIA *B. burgdorferi* antibody, but blood from the first day was positive by the in vitro LPA for *B. burgdorferi.*

By 2.5 weeks, the infant had become somewhat listless and slept more than expected, and spinal fluid showed a slight lymphocytic pleocytosis, slightly elevated protein and normal glucose, MRI scan of the brain was normal, complete blood count was normal, liver enzymes were normal, there was slight hyperbilirubinemia, but the retinal lesions had spontaneously resolved. The infant was treated at 2.5 weeks with intravenous ceftriaxone 75 mg/kg daily for 4 weeks, developed a "pale spell" on the second day of therapy and became more active and alert after 3 days of therapy and was completely well by completion of antibiotic therapy. A repeat lumbar puncture was performed at the end of the antibiotic therapy but was traumatic, and long-term follow-up is unavailable.

Comments. The preceding two mothers both had gestational erythema migrans with systemic symptoms, both were treated with antibiotic therapy during pregnancy and both delivered infants who were clinically normal at birth except for minor manifestations of early congenital Lyme borreliosis. The infant born to the mother with gestational Lyme borreliosis treated within 2 weeks of onset had only inguinal adenopathy, rash and a sacral dimple (dimple is of unclear significance), while the one born to the mother with symptoms of gestational Lyme borreliosis persisting for 10 weeks before antibiotic therapy had evidence of mild neurologic symptoms, transient retinal lesions, mild lymphocytic meningitis and mild hyperbilirubinemia. Both infants had episodes resembling Jarisch-Herxheimer reactions shortly after initiation of ceftriaxone therapy at 2 weeks of age, and had resolution of their manifestations of early congenital Lyme borreliosis by the end of antibiotic therapy.

These mother-infant groups illustrate the observation that infants with congenital Lyme borreliosis and mothers who have been treated with antibiotics for gestational Lyme borreliosis may be seronegative by antibody assays or in the peripartum period, and may be positive by the *B. burgdorferi*–specific LPA.

These cases illustrate the importance of prompt and aggressive antibiotic therapy for gestational Lyme borreliosis. In one of these mothers the intravenous ceftriaxone was discontinued because of severe diarrhea and therapy was completed with high-dose penicillin, and in the other the mother was treated with prolonged oral cefuroxime axetil through the time of delivery. These courses of antibiotic therapy attenuated but did not prevent congenital infection. Longer courses of intravenous antibiotic therapy have been more effective in treatment of other manifestations of Lyme borreliosis. Recommendations for optimal antibiotic therapy of gestational Lyme borreliosis are discussed in the section on therapy. It is recommended that gestationally exposed newborn infants be evaluated for mild symptoms of congenital Lyme borreliosis such as inguinal adenopathy and mild lethargy as well as for the more obvious symptoms of severe congenital Lyme borreliosis, and that antibiotic therapy be started promptly after birth in order to prevent later clinical sequelae.

Severe Early Congenital Lyme Borreliosis

CLINICAL CASE (case 24 in Table 11–8, previously unpublished)

Mother. A 34-year-old woman had a tick bite between mid-April and late May 1987 at 6.5 to 12.5 weeks of gestation; she was treated with oral amoxicillin 250 mg three times daily for 10 to 14 days for sinusitis and flu-like symptoms at 5 to 7 weeks and at 20 to 22 weeks of gestation. A routine fetal sonogram performed at 17 weeks was normal, but another done at 24 weeks because of decreased amniotic fluid showed marked intrauterine growth retardation. Fetal blood sampling at 24.5 weeks showed normal chromosomes and no evidence of intrauterine viral infection, and the infant was delivered by cesarean section at 34 weeks of gestation. The mother remained clinically well following delivery and was seronegative for polyvalent EIA *B. burgdorferi* antibody 1 week, 9 months and 10 months after delivery, and was also negative by the *B. burgdorferi* LPA at 9 and 10 months.

Placenta. Pathologic evaluation showed chronic fibrosing villitis, described in the section on the placenta in Pathology and Pathogenesis.

Infant. The infant was small for gestational age (1050 g, 34 weeks); had a low Apgar score; a "blueberry muffin" rash and profound thrombocytopenia that required platelet transfusions; hepatomegaly and hyperbilirubinemia; meconium ileus that required enemas; severe dilated cardiomyopathy with biventricular dysfunction and low voltage on electrocardiogram that required intensive cardiopulmonary support with intubation, mechanical ventilation and pressors; and a transient patent ductus arteriosus. Several additional abnormalities were also noted, including a pilonidal dimple, flexion contractures of the large joints (hips, knees and elbows), longitudinal striations and dense sclerotic transverse metaphyseal bands of the long bones, a large forehead and split sutures, a full fontanel and bilateral inguinal adenopathy. Head ultrasound showed diffuse punctate increased parenchymal echogenicity, skull x-rays showed no calcifications, liver enzymes were normal, brain-stem auditory evoked response evaluation was normal, and ophthalmologic examination was normal. Figure 11–9 shows the meconium ileus, cardiomegaly and sclerotic metaphyseal bands of this patient.

This infant was initially considered to have culture-negative bacterial sepsis and was treated with intravenous ampicillin and gentamicin for 6 days, but failed to improve and continued to require platelet transfusions and intensive cardiovascular support. Because of the maternal gestational history of tick bite, the possibility of congenital Lyme borreliosis was raised and intravenous ceftriaxone (100 mg/kg per day) was added on the seventh day and continued for 1 week, and within 24 hours the platelet count stabilized, the pressors were able to be discontinued and the infant began to recover. Spinal fluid on the sixth day showed an elevated protein but no pleocytosis. The dense sclerotic transverse metaphyseal bands present in all of the long bones during the first week gradually resolved during the ceftriaxone therapy. Extensive evaluation for bacterial and viral causes of this fulminant sepsis was unrevealing, and the infant was seronegative for polyvalent EIA *B. burgdorferi* antibody. The infant was eventually discharged from the hospital at 2 months of age in good condition.

By 9 months, she had growth retardation, mild developmental delay, mild lower extremity spasticity and persistently small head circumference, and the possibility of congenital Lyme borreliosis was reconsidered. At 9 but not at 10 months she was found to have polyvalent EIA *B. burgdorferi* antibody, at 9 and 10 months she had a positive *B. burgdorferi* in vitro LPA, and between 9 and 10 months further evaluation included a normal spinal fluid with no *B. burgdorferi* antibody detectable, a normal electrocardiogram, normal complete blood count, slightly elevated liver enzymes and MRI scan of the brain that showed left parietal parenchymal lesions of increased T2 signal. She was treated with intravenous ceftriaxone (75 mg/kg daily) for 3 weeks for neuroborreliosis. She subsequently improved and had normal growth and development at follow-up at 2.5 years of age.

Comments. This mother-infant pair illustrates the presentation of severe early congenital Lyme borreliosis as fulminant neonatal sepsis, the need to consider Lyme borreliosis in the differential diagnosis of culture-negative sepsis and the need to include optimal intravenous antibiotic therapy for Lyme borreliosis, such as third-generation cephalosporins, if Lyme disease is considered. This case also indicates the failure of short oral courses of antibiotic therapy in prevention of severe congenital Lyme borreliosis and the need for more aggressive antibiotic therapy of gestational Lyme disease.

The unusual finding of the sclerotic transverse metaphyseal bands in the long bones that faded during the ceftriaxone therapy in this infant and in one other infant (case 25 in Table 11–8) with congenital Lyme borreliosis may eventually prove to be a useful diagnostic finding in severe congenital Lyme borreliosis.

The initial clinical presentation of this infant resembles the description by Lampert[25] of the infant with the infantile multisystem inflammatory syndrome who was later found to have chronic Lyme borreliosis, as well as the description of some of the reported infants who had fulminant early congenital Lyme sepsis,[20, 26, 27, 32, 33] although this infant did not have the severe cardiac malformations found in some of these patients.

Late Congenital Lyme Borreliosis

CLINICAL CASE (case 25 in Table 11–8, previously unpublished)

Mother. A 35-year-old mother of five children visited a tick-infested farm with her entire family for 2 weeks every summer from 1988 through 1990, and she and several family members had occasional tick bites during this time. During the first 6 weeks of her next pregnancy, between mid-March and late April 1990, she developed a flu-like illness that progressed to pneumonia and was associated with unusually large nonpruritic, nontender, vesiculobullous and even purulent round or oval skin lesions on her legs. She was treated with almost continuous antibiotic therapy for the first 10 weeks of gestation, initially oral erythromycin (333 mg three times daily) for 7 weeks, followed by cefaclor (250 mg three times daily) for 3 days, intravenous cefuroxime (750 mg three times daily) for 4 days and oral cephalexin (500 mg four times daily) for 2 weeks, and then with oral cefixime (100 mg daily) for 10 days at 12 to 13 weeks. The large erythematous skin lesions intermittently reappeared during the second and third trimesters, and she developed progressive arthralgias and arthritis of her hips, knees and lower back, and by the time of delivery, in December 1990, she was unable to walk without stooping over. The skin lesions, polyarthralgias and polyarthritis recurred after delivery and continued intermittently for 4 months post partum, and she also noted headaches, fatigue and short-term memory lapses.

In March 1991, the history of this maternal gestational illness and tick exposure was discovered on routine questioning during hospitalization of the then 3-month-old infant for severe failure to thrive. As part of the evaluation of the infant for possible congenital infection, maternal blood was sent and found to be seropositive for polyvalent EIA *B. burgdorferi* antibody. Figure 11–5*D* shows one of the mother's recurrent skin lesions, and a skin biopsy of

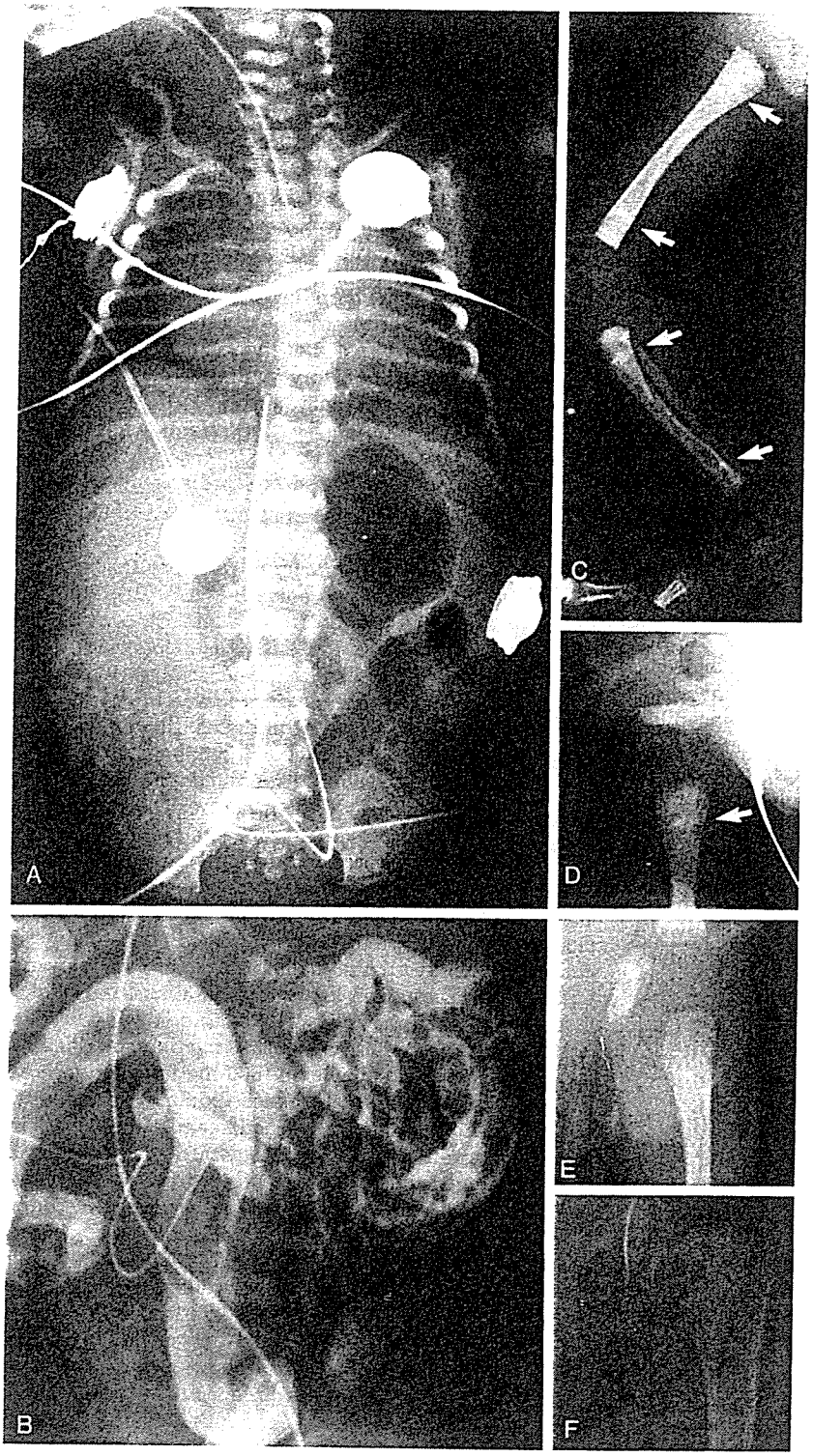

Figure 11–9. Congenital Lyme disease. An infant presented at birth with thrombocytopenia, cardiomyopathy, meconium ileus equivalent and intrauterine growth retardation. *A.* Chest and abdominal radiograph at 1 day of age shows cardiomegaly and mottled increased density in the right lower quadrant from inspissated meconium. *B.* Lower GI study at 1 day of age demonstrates impacted meconium in the distal ileum. Bone radiographs show *(C)* sclerotic transverse metaphyseal bands at birth *(arrows)*, *(D)* fading metaphyseal bands after antibiotic therapy for 5 days *(arrow)*, *(E)* further fading of the metaphyseal bands after antibiotic therapy for 16 days and *(F)* resolution of the metaphyseal bands by 7 months (case 24 in Table 11–8).

this lesion showed the superficial and deep dermal perivascular lymphocytic inflammatory infiltrates commonly seen in erythema migrans lesions, but no spirochetes were seen.

She was treated with oral doxycycline 100 mg twice daily and had initial improvement of the lesions, was changed to intravenous ceftriaxone 1 week later because of subsequent intensification of the skin lesions and recurrence of fever and arthralgias, and was changed back to oral doxycycline after 3 days of ceftriaxone because of development of a generalized erythematous nonpruritic maculopapular rash that was considered an allergic reaction by her physicians. The headache, memory loss, fatigue and skin lesions resolved after 6 weeks of doxycycline, but the right hip arthritis and the polyarthralgias persisted, and 1.5 years later she developed chronic palpebral conjunctivitis and distal paresthesias of her hands and was treated with several weeks of intravenous ceftriaxone with good clinical improvement.

Placenta. No placental pathologic examination was performed.

Infant. The infant was born after 37 weeks' gestation, had birth weight of 3490 g and was considered normal at birth, but developed neonatal hyperbilirubinemia and nursed poorly. He was treated with intravenous ampicillin and a third-generation cephalosporin for suspected sepsis and urinary tract infection at 1 week of age, and developed a generalized erythematous maculopapular rash thought to be an allergic reaction. Bilateral inguinal hernias were repaired at 1 month of age, and he received a short course of oral cefaclor (Ceclor) for otitis media at 2 months of age.

His very experienced mother noted that he became increasingly limp and listless, held his head and neck to the right, slept almost all day and fed poorly. He presented at 2.5 months of age for infectious diseases evaluation to look for possible congenital infection because of severe failure to thrive, developmental delay, growth retardation and gastroesophageal reflux with recurrent vomiting and recurrent aspiration pneumonias, and was found to have hepatomegaly, erythematous abdominal and distal extremity rough maculopapular rash, lethargy, marked proximal hypotonia, distal hyperreflexia and hypertonia, a moderate right hemiparesis, jitteriness, alternating exotropia and some dysmorphic features consisting of cupped ears, upturned nose, small chin, a unilateral simian crease and pectus excavatum. The collecting system was slightly dilated and the kidneys slightly small, there were dense transverse metaphyseal bands in the long bones, an MRI scan of the brain was normal, brain-stem auditory evoked response evaluation was normal, spinal fluid was unremarkable and chromosome analysis was normal. He underwent fundoplication and feeding gastrotomy because of inability to swallow without aspiration, and the exotropia was surgically corrected.

Evaluation for possible congenital infection was initially unrevealing, and the spinal fluid and serum were both negative for polyvalent EIA antibody to *B. burgdorferi*. However, because of the presence of metaphyseal bands, which were reminiscent of those in an earlier infant with congenital Lyme borreliosis, the maternal gestational history and the maternal Lyme seropositivity, the diagnosis of late congenital Lyme borreliosis was considered and both the infant and mother were found to have positive responses in the *B. burgdorferi* in vitro LPA.

The child received a total of 7 weeks of intravenous ceftriaxone (100 mg/kg daily) between 2.5 and 7 months and showed gradual improvement in neurologic function and resolved the rash. When attempts were initially made to use a less aggressive and shorter course of intravenous ceftriaxone, he experienced relapse with evidence of loss of developmental milestones. Finally after a total of 7 weeks of intravenous ceftriaxone followed by a 1-year course of oral amoxicillin (40 mg/kg daily) from 7 months to 19 months of age, he regained lost developmental milestones and resolved the majority of his focal neurologic findings, including the subtle right hemiparesis, mild proximal hypotonia and distal hyperreflexia. At follow-up at 3 years of age, he remains well, is at an appropriate developmental level and is slowly learning to take food by mouth.

Figure 11–10*A* to *J* shows the gastroesophageal reflux, aspiration, strabismus, facial dysmorphia, severe hypotonia, rash and metaphyseal bands in the first few months of life; Figure 11–10*K* shows the patient at 2 years of age.

Comments. This mother-infant pair illustrates the ability of *B. burgdorferi* to cause severe progressive neurologic deficits consistent with chronic neuroborreliosis, and the failure of oral erythromycin and oral cephalosporins to prevent these complications. However, the prolonged first-trimester courses of oral antibiotics may have stabilized the gestational spirochetal infection sufficiently to allow the pregnancy to be carried almost to term. Although there were several dysmorphic features in this infant, the significance of the cupped ears is unclear, as there were two other siblings with slightly "lop" ears.

The neurologic recovery of this patient during the prolonged course of antibiotic therapy and the near normalization of his developmental level by 3 years of age lend support for such prolonged therapy until it appears that maximum recovery of neurologic function has occurred.

The infant reported by Markowitz and colleagues (case 17, Table 11–8) who was normal at birth and later developed cortical blindness and the infant reported by Lampert (case 40) with infantile multisystem inflammatory syndrome may represent this type of clinical manifestation of congenital Lyme borreliosis.[30]

Diagnosis and Differential Diagnosis

The demand for diagnostic testing for Lyme disease is great: in New Jersey residents alone, in 1988, 90,000 Lyme serologic tests were performed at a total estimated cost of $3.5 million.[355] A true estimate of the annual cost of serologic testing for Lyme disease in the entire United States is unavailable. The demand for Lyme serologic testing continues to increase, but the sensitivity and specificity of diagnostic assays currently available to the clinician are not ideal.

The practical ability to diagnose Lyme disease by

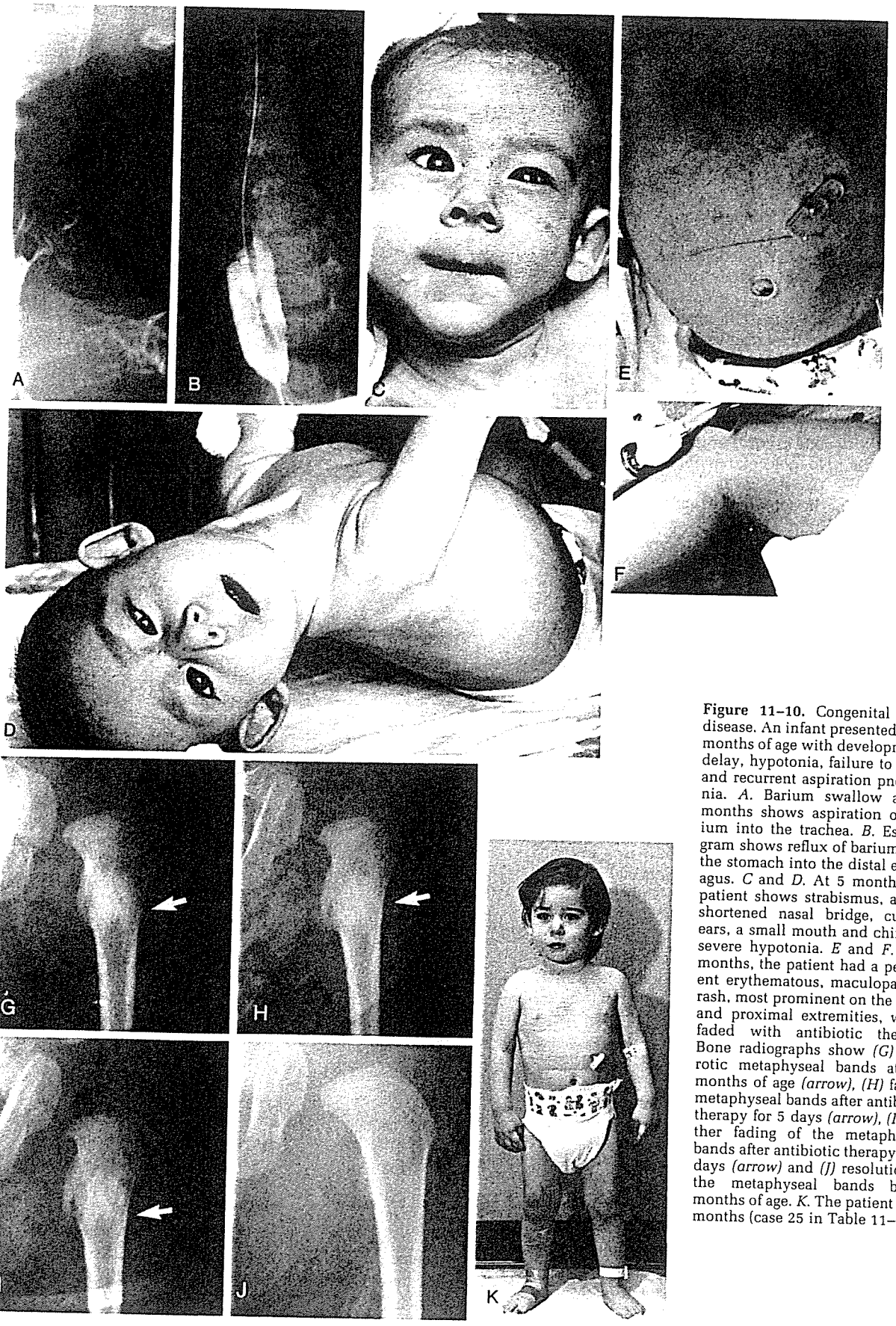

Figure 11–10. Congenital Lyme disease. An infant presented at 2½ months of age with developmental delay, hypotonia, failure to thrive and recurrent aspiration pneumonia. *A.* Barium swallow at 2½ months shows aspiration of barium into the trachea. *B.* Esophagram shows reflux of barium from the stomach into the distal esophagus. *C* and *D.* At 5 months, the patient shows strabismus, a foreshortened nasal bridge, cupped ears, a small mouth and chin and severe hypotonia. *E* and *F.* At 5 months, the patient had a persistent erythematous, maculopapular rash, most prominent on the trunk and proximal extremities, which faded with antibiotic therapy. Bone radiographs show *(G)* sclerotic metaphyseal bands at 2½ months of age *(arrow), (H)* fading metaphyseal bands after antibiotic therapy for 5 days *(arrow), (I)* further fading of the metaphyseal bands after antibiotic therapy for 6 days *(arrow)* and *(J)* resolution of the metaphyseal bands by 5 months of age. *K.* The patient at 25 months (case 25 in Table 11–8).

diagnostic assays remains a complicated and controversial problem. Despite the continued development of new diagnostic assays utilizing increasingly sophisticated molecular biologic tools, the diagnosis of Lyme disease cannot be either made or excluded solely on the basis of these assays: Lyme disease must remain a clinical diagnosis, and the test results may be considered either supportive or nonsupportive of the diagnosis.

False-positive serologic results for Lyme disease may occur because of cross-reactions with other bacteria, particularly other spirochetes,[107] in the assays or because of intra- or inter-laboratory variability of assay results. False-negative serologic results may occur either because the sample was obtained early in the course of the Lyme disease before development of detectable *B. burgdorferi* immune responses, because early antibiotic therapy eliminated or blunted the *B. burgdorferi* immune response,[86, 87, 119–122] because of regional antigenic strain variability, because a low-level true-positive result is masked by cross-reacting antibody that necessitates a high "cut-off" for positivity or because of intra- or inter-laboratory variability. Another problem is that seropositivity in residents of Lyme endemic areas reflects the frequency of seropositivity of the area and may be unrelated to clinical illness.

Diagnostic Tests

Diagnostic tests for Lyme disease are divided into several categories and are listed in Table 11–12: culture and special stains for whole *B. burgdorferi*, antibody assays for whole *B. burgdorferi* or individual antigens, lymphocyte proliferative assays for whole *B. burgdorferi* or individual antigens and PCR assays for detection of specific *B. burgdorferi* DNA sequences. Practical problems with these tests are low sensitivity or low specificity, wide intra- and inter-laboratory variability of the most common commercially available antibody detection tests[355–361] and lack of availability of some of the better research laboratory tests.

Culture

B. burgdorferi was first isolated from biopsy specimens or body fluids of patients with Lyme disease in 1983.[12, 14, 41] The organism grows best in liquid Barbour-Stoenner-Kelly medium II (BSK II) at 35° C,[42, 44] usually takes 2 to 6 weeks to grow, is detected by dark-field examination of culture medium every 1 to 2 weeks and is confirmed as *B. burgdorferi* by IFA with *B. burgdorferi*–specific antibody. Culture is the "gold standard" for confirmation of Lyme disease, but disadvantages of this are that it is not generally available outside of research institutions, is cumbersome and time-consuming and is often positive only very early in untreated infection, and the overall yield is quite low. Under optimal conditions, isolation rates from EM skin lesions are 40 to 70 per cent[13, 40] and are much lower for other sites. The isolation rate from EM lesions by the two-needle intradermal lavage method is 29 per cent.[362]

B. burgdorferi has been successfuly grown from skin biopsy specimens of EM,[12, 13, 38, 40, 68, 128, 363] borrelial lymphocytoma[16] and acrodermatitis chronica atrophicans[13, 14]; from blood[12, 41, 122, 363, 364]; from CSF[48, 128, 129, 363, 365–367]; from synovium or joint fluid[126, 127]; from myocardium[285]; from placenta[27]; and from fetal liver,[27–29] kidney[27] and brain.[26]

Silver and Immunofluorescent Stains

Spirochetes were first demonstrated in EM skin biopsy specimens in 1982 by Warthin-Starry silver staining.[39] *B. burgdorferi* spirochetes may be visualized by Dieterle,[19] Warthin-Starry[27–29, 38, 39] or Bosma-Steiner[43] silver staining or by *B. burgdorferi*–specific monoclonal or polyclonal antibody[27–29, 65] staining of tissue. The Bosma-Steiner modification of the Warthin-Starry stain includes pretreatment of the sample with amylase to reduce mucoid material surrounding the spirochetes, which blocks silver impregnation of the spirochetes, and has resulted in much improved sensitivity for demonstration of *B. burgdorferi*.[43]

B. burgdorferi has a characteristic morphology by silver staining, which is distinct from other spirochetes and even other *Borrelia* species, but the specificity of IFA staining is greater because the use of *B. burgdorferi*–specific monoclonal or polyclonal antibody allows definite confirmation of the spirochetes as *B. burgdorferi*. The sensitivity of detection of *B. burgdorferi* by staining ranges from 25 to 100 per cent and is greatest in skin biopsy specimens of EM lesions (29 to 100 per cent),[38, 43, 274] borrelial lymphocytoma lesions (100 per cent)[43] and synovia of joints with chronic Lyme arthritis (25 to 100 per cent),[43, 65, 295] but it is low in other samples.

Spirochetes have been demonstrated in skin biopsy specimens of EM,[38, 39, 43, 274] borrelial lymphocytoma[43, 276] and acrodermatitis chronica atrophicans[346, 347]; brain biopsy specimens[116, 291]; placental or fetal tissues[19, 26–29, 32]; myocardial biopsy specimens[283, 285, 286]; muscle,[293] spleen,[279] liver,[281] bone[294] and synovial[43, 65, 295] biopsy specimens; and one CSF sample.[43]

Dark-field Examination

Although it is possible to visualize spirochetes by dark-field microscopy in the blood in relapsing fe-

Table 11–12. LABORATORY DIAGNOSIS OF LYME BORRELIOSIS (LB)

Assay for *B. burgdorferi* (Bb)	*B. burgdorferi* Component Detected by Assay	Time Course of Positive Result (% Patients with Positive Assay Result During Different Stages of LB)			Assay Specificity for *B. burgdorferi*[a]	Assay Commercially Available	Reference
		Early Localized LB	*Early Disseminated LB*	*Late Chronic LB*			
Culture of biopsy (bx) or fluid	Whole Bb, live	2–73% EM[b] bx low % BL[c] bx 2–6% blood 11–100% CSF[d]		10% ACA[e] bx low% Snv[f] bx low % CSF	+ + + +	No	12–14, 16, 18, 38, 40, 41, 48, 68, 102, 116, 122, 126–129, 197, 363–367
Silver stain or FA stain[g] of biopsy	Whole spirochetes	29–100% EM bx 100% BL bx		low % ACA bx 25–100% Synv bx	+ + + +	No	38, 43, 65, 274, 295, 346, 347
PCR[h]	Bb DNA sequences	75% EM bx acute (ac) 40% serum ac 38–67% CSF ac 90% urine ac			+ + + +	No	67–71
IFA[i]: IgG	Whole Bb	25–58% ac 58–100% convalescent (cv)		80–100%	+ + +	Yes	1, 12, 33, 87, 102, 105, 322
IFA: IGM	Whole Bb	20–94% ac 0–14% cv		64–80%	+ + +	Yes	12, 33, 102, 105, 322
IFA: Polyvalent IgG + IgM	Whole Bb	13–100% ac 53–100% cv		94–100%	+ + +	Yes	14, 105–107, 213, 278, 319, 322, 368
ELISA[j]: IgG	Whole Bb	0–35% ac 10–100% cv		41–100%	+ + +	Yes	16, 93–98, 116, 122, 315
	Flagellin	0% ac 36–88% cv		75–100%	+ + +	No	93–96
	Osp A[k]			42%	+ + + +	No	93
	Osp B[l]			42%	+ + + +	No	93
ELISA: IgM	Whole Bb	9–92% ac 23–60% cv		36%	+ + +	Yes	93–98, 122
	Flagellin	18–45% ac 45–75% cv		68%	+ + +	No	93–96
ELISA: Polyvalent IgG + IgM	Whole Bb	13–56% ac 57–92% cv		89–100%	+ + +	Yes	71, 94, 97, 104–107, 116, 368
	Flagellin	13–21% ac 63–100% cv			+ + +	No	368
ELISA-AC[m]: IgG	Whole Bb	0% ac 13–63% cv			+ + +	No	368
ELISA-AC IgM	Whole Bb	25–71% ac 75–100% cv			+ + +	No	368
ELISA-AC: Polyvalent IgG + IgM	Whole Bb	25–71% ac 93–100% cv			+ + +	No	368
ELISA-IC[n]: IgG	Whole Bb	30–100%		95–100%	+ + +	No	373
Western blot[o]: IgG	Whole Bb	17–25% ac 13–64% cv		91–92%	+ + + +	Yes	99, 103, 368
	41-kd flagellin	0% ac 25% cv	%	83–100%	+ + +		60, 93, 373
	31-kd Osp A	0–20%		100%	+ + + +		60, 373
	34-kd Osp B	0%		100%	+ + + +		60, 93
	18–23 kd Osp C[p]		~50%				97
	83 kd		83% cv				60
	75 kd	0%		100%	+ + + +		60
	66 kd		83% cv				60
	60 kd	0%		100%			60
	29 kd	0%		100%			60
	27 kd		50% cv				60
	17 kd	0%		80%			60
	15 kd		50% cv				60
Western blot: IgM	Whole Bb	33–87% ac 50–69% cv			+ + +	Yes	93, 103, 251
	41-kd flagellin	33–50% ac 83% cv	100% cv	33–40%	+ + +		60, 93
	31-kd Osp A	0%		0%	+ + + +		60, 93
	34-kd Osp B	0%		20–33%	+ + + +		60, 93
	18–23 kd Osp C	~50%					97
	83 kd	33% cv	50% cv				60
Western blot: Polyvalent IgG + IgM	Whole Bb	53–88% ac 73–92% cv		100%	+ + + +	Yes	94, 97, 371
LPA[q]:	Whole Bb, sonicated	0%		45–100%	+ + +	No	90, 92, 116, 120
	Whole Bb, live	50–91%		82–100%	+ + +	No	84, 86–88
	66-kd protein			36%		No	90
	58-kd protein			14%		No	90
	41-kd flagellin	82%		21–68%	+ + +	No	87, 90
	31-kd Osp A	82%		29–76%	+ + + +	No	87, 90
	34-kd Osp B			14%	+ + + +	No	90
	20-kd Osp C			29%		No	90

Table 11–12. LABORATORY DIAGNOSIS OF LYME BORRELIOSIS (LB) *Continued*

Assay for *B. burgdorferi* (Bb)	*B. burgdorferi* Component Detected by Assay	Time Course of Positive Result (% Patients with Positive Assay Result During Different Stages of LB)			Assay Specificity for *B. burgdorferi*[a]	Assay Commercially Available	Reference
		Early Localized LB	*Early Disseminated LB*	*Late Chronic LB*			
			Laboratory Diagnosis of Neuroborreliosis				
ELISA: IgG	Whole Bb or flagellin		63–100% CSF				96, 315
ELISA: IgM	Whole Bb or flagellin		84–88% CSF				96
ELISA: Polyvalent	Whole Bb	0% CSF	53–100 CSF				71, 115, 116, 124, 124a
ELISA-AC: Polyvalent	Whole Bb		42–100% CSF				69, 109
ELISA-IC: Polyvalent	Whole Bb		38% CSF				123
IFA:	Whole Bb		92% CSF		+ + +	Yes	124a
Western blot:	Whole Bb		92% CSF		+ + +	Yes	124a
LPA:	Whole Bb, sonicated		100% CSF		+ + +	No	116

[a]Estimation of specificity is given for RPR-negative sera (see Table 11–13).
[b]EM, erythema migrans skin lesion.
[c]BL, borrelial lymphocytoma skin lesion.
[d]CSF, cerebrospinal fluid.
[e]ACA, acrodermatitis chronicum atrophicans skin lesion.
[f]Synv, synovial.
[g]Warthin-Starry, Bosma-Steiner or Dieterle silver stains, or *B. burgdorferi*–specific polyclonal or monoclonal FA (fluorescent antibody) stains.
[h]PCR, polymerase chain reaction.
[i]IFA, immunofluorescence assay.
[j]ELISA, enzyme-linked immunosorbent assay.
[k]Osp A, outer surface protein A.
[l]Osp B, outer surface protein B.
[m]ELISA-AC, ELISA–antibody capture.
[n]ELISA-IC, ELISA–immune complex.
[o]Western blot: kd, kilodalton size of individual *B. burgdorferi* antigens.
[p]Osp C, outer surface protein C (in European strains).
[q]LPA, lymphocyte proliferative assay.

ver, and in skin transudates in syphilis, it is not a sensitive method for visualization of *B. burgdorferi* because the number of organisms in infected tissues is very small and the yield is essentially zero, with occasional rare exceptions (Steere found spirochetes in one skin biopsy specimen by dark-field microscopy).[12]

Polymerase Chain Reaction (PCR)

PCR is more sensitive than either culture or special stains for detection of *B. burgdorferi* in patient tissues or fluids. In 1989, the *B. burgdorferi* PCR assay utilized the technique of amplification of unique *B. burgdorferi* target DNA sequences to detect the presence of very small amounts of *B. burgdorferi* DNA (a few organisms per cell) in the presence of large amounts of cellular DNA.[66] Utilization of sequences for *B. burgdorferi* 41-kd flagellar antigen and 34-kd Osp B in PCR improved the sensitivity of detection of *B. burgdorferi* in CSF to 67 per cent of patients with very early disseminated Lyme disease even when CSF *B. burgdorferi* antibody was still negative.[71] Overall sensitivity is 38 to 90 per cent in early Lyme disease.

The *B. burgdorferi* PCR is 100 per cent specific because the DNA target sequences are selected specifically for lack of cross-reactivity with other spirochetes.[66, 69] These sequences are not present in other closely related *Borrelia* species or other spirochetes and are highly conserved among *B. burgdorferi* strains. PCR is generally considered to be useful in detection of small numbers of *B. burgdorferi* in tissue samples, is particularly useful in diagnosis of very early Lyme disease before standard serologic assays become positive and may be more sensitive and less cumbersome than culture, but its use is limited to research facilities.

B. burgdorferi has been demonstrated by PCR in EM skin biopsy specimens,[68] serum,[67] CSF[69–71] and urine[69] in early Lyme disease.

Immunofluorescent Assay (IFA)

The first diagnostic serologic assay for Lyme disease was the immunofluorescent assay used by Burgdorfer et al. in 1982 to confirm the new *Ixodes dammini* spirochete as the causative agent of Lyme disease.[1, 12] IFA utilizes fluorescein-tagged anti-human immunoglobulin to detect serum, CSF or synovial fluid IgG, IgM or IgA antibody binding specifically to whole *B. burgdorferi* fixed on a slide.

The range of sensitivity of the Lyme polyvalent IFA is 13 to 100 per cent in early Lyme disease and 64 to 100 per cent in late Lyme disease. IgM antibody is detectable earlier in infection than IgG antibody by the IFA and is therefore more sensitive in diagnosis of early Lyme disease, and generally disappears by convalescence except in patients with persistently active Lyme disease. The specificity of the Lyme IFA is low in patients with other spirochetal infections because of cross-reactivity between *B.*

Table 11–13. CROSS-REACTIVITY BETWEEN *B. BURGDORFERI* AND OTHER SPIROCHETES

Primary Disease	% of Sera with Positive Result									Reference
	Lyme IFA[a]	*Lyme ELISA*[b]	*Lyme WB*[c]	*FTA-Abs*[d]	*RPR*[e]	*VDRL*[f]	*MHA-TP*[g]	*IFA Other Borreliae*[h]	*MA Leptospira*[i]	
Syphilis	13–61	20–77	0–46							94, 107, 368–371
Yaws, pinta	28–40	40–43								107, 370
Relapsing fever *borrelia*[j]	50	45								370
Borrelia coriaceae[k]	63									359
Leptospirosis[l]	0–14	0								107, 370
Lyme				6–43	0	0	0	54–85	0	14, 107, 359, 369, 370

[a]IFA, immunofluorescence assay.
[b]ELISA, enzyme-linked immunosorbent assay.
[c]WB, Western blot.
[d]FTA-Abs, fluorescent treponemal antibody absorption test.
[e]RPR, rapid plasma reagin test.
[f]VDRL, Venereal Disease Research Laboratory test.
[g]MHA-TP, microhemagglutination assay for antibodies to *Treponema pallidum*.
[h]IFA, immunofluorescence assay for other borreliae, including *B. hermsii*, a major cause of relapsing fever, and *B. coriaceae*.
[i]MA, microhemagglutination assay for antibodies to *Leptospira*.
[j]*B. hermsii* and *B. recurrentis*, as well as many other borreliae, are the major causes of relapsing fever.
[k]*B. coriaceae* is endemic in soft ticks in California but rarely causes human illness.[359]
[l]*Leptospira interrogans* is the major cause of leptospirosis.

burgdorferi and other spirochetes, especially syphilis but is good in rapid plasma reagin (RPR)–negative patients (Table 11–13).

Enzyme-Linked Immunosorbent Assay (ELISA)

The ELISA technique was successfully applied to the serodiagnosis of Lyme disease in 1984.[98, 107] It utilizes enzyme-tagged anti-human immunoglobulin to detect serum, CSF or synovial fluid IgG, IgM or IgA antibody binding specifically to either whole disrupted (sonicated) *B. burgdorferi* or specific *B. burgdorferi* components (antigens) bound to multiwell ELISA plates.

The Lyme ELISA is 13 to 92 per cent sensitive in early Lyme disease and 89 to 100 per cent sensitive in late Lyme disease. IgM antibody is detectable earlier in infection than IgG and decreases later during convalescence except in patients with persistently active infection.

The Lyme ELISA is more efficient and reproducible than the Lyme IFA.[98, 107] Comparisons of IFA and ELISA have generally shown that ELISA is also more sensitive and specific than IFA,[51, 98] although some reports found them to be comparable.[105, 107] In RPR-negative patients, the sensitivity of IFA and ELISA is high for detection of late Lyme disease, when *B. burgdorferi* antibody levels are high, but lower for detection of early Lyme disease, when there is a high false-negative rate because of the combination of low *B. burgdorferi* antibody in the first few weeks and high background as a result of cross-reactive antibody.[60]

Cross-reactivity in both the ELISA and IFA assays occurs between *B. burgdorferi* and other spirochetes (see Table 11–13), specifically with the treponemes syphilis, yaws and pinta,[94, 107, 368–371] and with other *Borrelia* species, such as *B. hermsii, B. recurrentis, B. duttonii* and *B. coriaceae*,[359, 370] but is removed or decreased by absorption with the cross-reacting spirochete.[98] Because of the high cross-reactivity with syphilis, it is essential to perform an RPR test on all Lyme-positive sera in order to exclude syphilis, as RPR does not cross-react and should be negative in Lyme disease.[107] Only a low rate of cross-reactivity occurs with *Leptospira*[107, 370] and *Rickettsia*.[107, 370] Cross-reactivity with *B. coriaceae* may lead to confusion, as this infection is endemic in *Ornithodoros coriaceus* ticks in California's Mendocino County and humans are an occasional host for this tick.[359]

Other causes of false-positive Lyme ELISA or IFA results are normal spirochetal oral flora,[94] viral infections such as varicella-zoster virus (VZV) or Epstein-Barr virus (EBV),[12, 98] and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and Reiter's disease.[12, 60, 98, 107, 372] False Lyme IgM IFA positivity of 15 per cent has been reported in patients with acute EBV mononucleosis.[12, 98] IgM rheumatoid factor can result in false-positive Lyme IgM by ELISA but not by Western blot, in the presence of IgG Lyme antibody.[372] The false-positive rate in patients with non-Lyme meningoencephalitis was 2 to 11 per cent for IgM and IgG ELISA or Western blot.[97, 371]

The specificity of the standard Lyme ELISA was increased by utilizing components of the organism such as the 31-kd outer surface protein A (Osp A),

34-kd outer surface protein B (Osp B), the 41-kd flagellar antigen or the 41-G highly immunogenic portion of the flagellar antigen as ELISA target antigens.[93–96] The flagellar antigen has little or no strain variation, and has less cross-reactivity with syphilis than the standard whole *B. burgdorferi* ELISA: the false-positive rate is 40 per cent in secondary syphilis serum and 0 per cent in neurosyphilis CSF.[96] However, because of cross-reactivity of the 41-kd flagellar antigen with other *Borrelia* species, it is not completely specific for *B. burgdorferi*.

Antibody Capture ELISA (ELISA-AC)

In 1988, another modification of the ELISA, the antibody capture ELISA,[368] increased the sensitivity of detection of IgM and IgG in early Lyme disease so that diagnosis of Lyme disease could be confirmed in most acute patients and in almost all convalescent patients. The false-positivity rate was 3 to 6 per cent overall, 0 per cent for healthy controls, 13 per cent for patients with acute EBV mononucleosis, 8 per cent for patients with Rocky Mountain spotted fever and 29 per cent for syphilis patients.

Immune-Complex ELISA (ELISA-IC)

In 1990, the sensitivity of the ELISA for detection of the *B. burgdorferi* IgG antibody response in early Lyme disease was further increased by utilizing a polyethylene glycol (PEG) precipitation method to dissociate the antibody sequestered in circulating immune complexes (IC) before performing the ELISA.[373] With this PEG-ELISA IC assay, IgG antibody to the 41-kd flagellar antigen was detected in 100 per cent of patients with early Lyme disease with EM, 30 per cent of patients with early Lyme disease without EM and 95 per cent of patients with late Lyme disease, and IgG antibody to a 30-kd (probable Osp A) antigen was detected in 20 per cent of early Lyme disease patients. The false-positive rate was 0 per cent. *B. burgdorferi* antibody sequestered in immune complexes was found in both seropositive and seronegative patients with Lyme disease. This assay is specific and sensitive and less cumbersome than the lymphocyte proliferative assay, and could therefore be used for evaluation of seronegative Lyme patients.

Western Blot (Immunoblot)

The technique of immunoblotting was used to demonstrate antibody directed against many individual *B. burgdorferi* antigens in 1983,[103] and was subsequently used to improve the sensitivity and specificity of serologic assays for Lyme disease.[60, 93, 94, 97, 368, 371, 374] This method detects serum, CSF or synovial fluid IgG or IgM antibodies to individual *B. burgdorferi* protein antigens that have been separated into bands by gel electrophoresis and bound to paper. The pattern of antibody to these specific *B. burgdorferi* antigens, demonstrated by the pattern of bands seen in the Western blot assay, is characteristic of Lyme disease and differs slightly in sera of patients from the United States and Europe.

In the United States, the IgM antibody response in early Lyme disease is directed against the 41-kd antigen, in persistent Lyme disease against the 41-kd flagellar and 83-kd antigens and in late Lyme disease against the 41-kd flagellar and 34-kd Osp B antigens. The IgG antibody response in early infection is directed against the 41-kd flagellar antigen; in persistent infection against the 83-kd, 66-kd, 41-kd flagellar, 27-kd and 15-kd antigens; and in late infection against the preceding plus the 75-kd and 60-kd heat shock protein, 34-kd Osp B, 31-kd Osp A, 29-kd and 17-kd antigens.[60] In Europe, one pattern of bands that is highly specific for Lyme disease has antibody directed against the 18- to 23-kd Osp C, 39-kd, 41-kd flagellar, 72-kd and 84-kd antigens.[97]

Western blot is useful for identification of false-positive Lyme ELISA results, but one problem is variability in the definition of Western blot positivity. Some laboratories require a positive result to have four bands and define an equivocal result as one to three bands, while others use two or more bands as positive and one as equivocal.[60, 374] Some are more specific and define a positive result as a 41-kd flagellar band plus one or more 18- to 23-kd Osp C bands.[97] Development of a quantitative Western blot that utilizes densitometer readings of the bands has allowed more objectivity in interpretation of bands.[371]

The Lyme Western blot is generally considered more sensitive and more specific than ELISA or IFA, particularly for diagnosis of early Lyme disease, especially in the first 2 to 4 weeks when IFA and ELISA antibody responses are low.[94, 97, 368, 371] Sensitivity of the polyvalent Western blot is 53 to 92 per cent in early Lyme disease and 100 per cent in late chronic Lyme disease. False-positives occur because of cross-reactivity of the *B. burgdorferi* 41-kd flagellar antigen and other spirochetes, and because of cross-reactivity of other *B. burgdorferi* antigens with syphilis.[371] Cross-reactivity with other spirochetes and the presence of low levels of positivity in control sera from endemic areas make it difficult to estimate the true incidence of false-positive Western blot assays, but it is considered to be low.[97]

Patients who are seropositive by both ELISA and Western blot usually have a strong clinical history of Lyme disease[371, 374] and improve clinically with

antibiotic therapy,[374] but over 90 per cent of patients with only positive ELISA and negative Western blot usually have some other inflammatory or rheumatologic disease instead of Lyme disease[371, 374] and do not improve with antibiotic treatment. Most (93 per cent) European neuroborreliosis patients who were seropositive by Lyme ELISA were also seropositive by Western blot.[97]

Lymphocyte Proliferative Assay (LPA)

The LPA was used in 1985 to 1986 to demonstrate specific T cell reactivity with *B. burgdorferi*.[84, 91, 92] The assay determines specific reactivity of viable peripheral blood, CSF or synovial fluid lymphocytes to whole *B. burgdorferi*, whole disrupted (sonicated) *B. burgdorferi* or individual *B. burgdorferi* antigens incubated with these lymphocytes in vitro.[84, 86–88, 90–92, 116, 120, 375]

The development of the T cell response to Lyme disease precedes the antibody response, and the LPA may be positive in IFA and ELISA seronegative patients with early Lyme disease.[84, 85] In early Lyme disease the LPA T cell reactivity is directed primarily against the 31-kd Osp A and the 41-kd flagellar antigen,[87] while in late Lyme disease it is directed against the 20-kd Osp C, 31-kd Osp A, 41-kd flagellar and 60- to 66-kd heat shock protein antigens.[56, 90] After successful antibiotic therapy of Lyme disease, there may be some decrease in the level of LPA positivity.[88, 92]

The LPA may be positive in other patients who are IFA and ELISA seronegative as a result of prompt antibiotic therapy of early Lyme disease because early therapy may prevent or attenuate the *B. burgdorferi*–specific antibody response[85–88, 119–122] but not prevent the development of the T cell response. The LPA was positive in all of 40 chronic Lyme disease patients in six studies who were IFA and ELISA seronegative because of early antibiotic therapy.[85–88, 120] These IFA- and ELISA-negative sera usually have small amounts of IgM and IgG antibody that reacts with the 41-kd antigen in Western blots.[85]

The use of whole intact *B. burgdorferi* rather than disrupted (sonicated) organisms has increased the sensitivity of LPA in some reports[85–87] but not in others.[120] In some patients, CSF[91] and synovial fluid[92] lymphocytes are more reactive in the LPA than peripheral blood lymphocytes, and therefore sensitivity may be increased by using these fluids.

The sensitivity of LPA is 50 to 91 per cent in early Lyme disease, and 82 to 100 per cent in late Lyme disease. Cross-reactions occur with other spirochetes, and the LPA positivity rate in healthy controls is 0 to 5 per cent[88, 120] and in patients with non-Lyme inflammatory diseases is 5 to 10 per cent.[88, 120]

Although the LPA is more sensitive than antibody assays in certain patients, it requires use of live lymphocytes and whole *B. burgdorferi* and is available only in research laboratories. The LPA should therefore be reserved only for diagnosis of Lyme disease in seronegative patients with good clinical objective evidence of Lyme disease, or for babies with potential congenital Lyme disease.

Laboratory Variability in Lyme Antibody Assays

One of the major problems with laboratory diagnosis of Lyme disease is the wide intra-laboratory and inter-laboratory variability of results both in the United States[355–360] and in Europe.[361] Several comparisons in which standard case defined sera were sent simultaneously to different commercial, hospital, state and national reference or research laboratories for Lyme ELISA or IFA serologic testing demonstrated that the percentage of laboratories that reported concordant results ranged from 10 to 90 per cent, and the reproducibility of results within the same laboratory ranged from 27 to 96 per cent. Agreement among laboratories was greatest for sera with high positive titers to *B. burgdorferi*, and least for sera with low positive titers. Sensitivity, specificity and reproducibility were greatest among research laboratories that prepared their own reagents for the assays and least among commercial laboratories utilizing commercially available kits. Manufacturers of the commercially available kits had greater sensitivity, specificity and reproducibility than commercial laboratories utilizing the same kits.

The wide variation in results may be due to differences in strains of *B. burgdorferi* used for preparation of the diagnostic kits, differences in the methods of kit preparation, differences in definitions of negative and positive results, geographic differences in the incidence of background Lyme seropositivity and differences in quality control within individual laboratories. Better standardization of commercially available assays for Lyme disease is needed, because the more specific, sensitive and reproducible research laboratory tests are not generally available.

Recommendations for Diagnostic Testing

The ELISA test, either polyvalent or IgM or IgG, is the most widely available assay for serodiagnosis of patients and is preferred over the IFA, but it is ad-

visable to confirm positives with the Western blot assay. The antibody capture ELISA may have increased sensitivity and specificity but is not as widely available. The lymphocyte proliferative assay is useful for diagnosis of seronegative patients with suspected Lyme borreliosis but is not generally available commercially. Biopsies of involved tissues for histopathology, culture, PCR or silver or IFA staining are usually best reserved for special clinical circumstances when serologic diagnosis is insufficient.

Any pregnant woman who develops an illness consistent with Lyme borreliosis (see section Clinical Manifestations) should have serologic confirmation if possible. Because specific IgM seropositivity may be transient and because development of specific IgG seropositivity may be prevented by early antibiotic therapy, it is recommended that immediate acute serum and several convalescent sera be collected at approximately 2-week intervals over a period of approximately 8 weeks and at delivery. The initial acute and early convalescent sera should be sent for polyvalent or IgM and IgG Lyme ELISA testing, and the remaining convalescent sera may be sent if no confirmation is obtained with the first sera. Western blot confirmation of seropositivity is recommended. It is advisable to save aliquots of these sera for possible further testing with more sensitive assays in the future if necessary. While it is not recommended that biopsies of involved tissues be routinely performed in pregnancy, this could be done for diagnostic confirmation if clinically indicated.

Any infant with possible congenital Lyme borreliosis should have serologic confirmation by ELISA and Western blot, on paired maternal and cord blood at delivery, and on the infant's blood and CSF after birth. If the index of suspicion is high for congenital Lyme borreliosis and the serologic assays are negative, the LPA should be performed (at a research center), as it appears to be more sensitive than serologic testing for confirmation of Lyme borreliosis in congenitally infected patients. Histopathology, culture, PCR and silver and IFA stains of biopsy specimens of involved tissues, such as skin, may be useful in diagnosis.

A full histopathologic evaluation is recommended of any placenta, miscarriage, stillbirth or perinatal death from a pregnancy complicated by Lyme borreliosis. In addition, Bosma-Steiner or Warthin-Starry silver stains and, if possible, *B. burgdorferi*–specific IFA stains, culture and PCR of the brain, heart, lungs, kidneys, liver, spleen, lymph nodes, bone marrow and any histologically abnormal tissues are recommended. The physician may wish to contact a center engaged in Lyme research for help in processing of these samples. The author has agreed to be available, by pre-arrangement, for performance of the LPA on infants suspected of having congenital Lyme borreliosis: Tessa Gardner, M.D., 314-388-6155).

Differential Diagnosis of Lyme Borreliosis

The differential diagnosis of Lyme borreliosis (Table 11–14), including gestational Lyme borreliosis, is extensive and depends on the particular stage and manifestation of infection, as described in the section Clinical Manifestations. Because Lyme borreliosis may manifest with symptoms relating to almost any organ system, a pregnant woman with Lyme disease may seek medical care from physicians in diverse medical or surgical specialties, including infectious diseases specialists, internists, family practitioners, obstetricians, dermatologists, cardiologists, neurologists, neurosurgeons, ophthalmologists, otolaryngologists, dentists or oral surgeons, psychiatrists, urologists, gastroenterologists, rheumatologists, orthopedic surgeons and general surgeons. Familiarity with the various clinical manifestations of Lyme borreliosis and a careful clinical history, including history of tick bite or exposure to endemic areas, is necessary to allow correct diagnosis, especially when the clinical presentation is unusual. If the initial diagnosis of gestational Lyme borreliosis is not made, the neonatologist, pediatrician or family practitioner may be presented with either a miscarriage, stillbirth or congenitally infected infant and may need to make a retrospective diagnosis of maternal gestational Lyme borreliosis.

The characteristic rash of EM is usually easily recognized but may be misdiagnosed if it is vesicular, necrotic or otherwise unusual in appearance. Usually a careful clinical history of the rash will lead to the correct diagnosis, which may be confirmed by serologic testing, by biopsy or by response to antibiotic therapy. Borrelial lymphocytoma is less widely recognized in the United States than in Europe and may therefore be mistaken for cellulitis or cutaneous malignancy, but a careful clinical history and serologic or biopsy confirmation will usually lead to the correct diagnosis. A common error is to misdiagnose the initial presentation of ACA, a swollen painful bluish-red leg, as circulatory insufficiency, even in Europe where ACA is prevalent.

The flu-like illness associated with early Lyme borreliosis may be indistinguishable from that caused by other generalized infections or inflammatory illnesses, such as viral infections, connective

Table 11–14. DIFFERENTIAL DIAGNOSIS OF LYME BORRELIOSIS[a] (LB)

Disease	Rash	Flu-like Illness	Musculoskeletal Symptoms	Cardiac Symptoms	Neurologic Symptoms	Reference
Granuloma annulare	+					274
Ringworm	+					277
Cellulitis	+					68, 277, 323
Impetigo	+					68
Contact dermatitis	+					68
Tick/insect bite reaction	+					68, 277
Cutaneous malignancy	+					277, 322
Circulatory insufficiency[b]	+					277
Brown recluse spider bite	+	+				405
Serum sickness	+	+	+			101, 323
Erythema nodosum	+					274, 275, 277
Erythema multiforme	+	+	+			101, 323
Henoch-Schönlein purpura	+					274
JRA/RA[c]	+	+	+	+		296, 323, 324
Lupus	+	+	+		+	101, 277
Dermatomyositis	+	+	+			277
Scleroderma	+				+	18, 274
Reiter's syndrome			+			323, 324
Fibromyalgia		+	+		+	354
Inflammatory bowel disease		+	+			
Rheumatic fever	+	+	+	+	+	101, 344, 375a
Bacterial endocarditis		+	+	+		375b
Acute myocarditis		+		+		284, 344
Chronic cardiomyopathy				+		285
Syphilis	+		+	+	+	315, 375c
Relapsing fever		+				375d
Sarcoidosis		+			+	89, 277
Mycoplasma pneumoniae infection	+	+	+	+	+	
Epstein-Barr virus mono	+	+	+	+	+	101, 323, 324
Cytomegalovirus mono	+	+	+	+	+	
Echo/coxsackie infection	+	+	+	+	+	344
Rubella	+	+	+		+	
Rubeola	+	+	+		+	
Hepatitis B	+	+	+			101, 323, 348
Mumps		+	+	+	+	344
Influenza		+	+	+		344
Adenoviral infection	+	+	+	+	+	344
Fifth's disease		+	+	+		375e
Arboviral infection		+			+	375f
Herpes simplex	+	+			+	68
Zoster	+	+	+		+	142
Gonococcal arthritis			+	+		323
Yersinia arthritis			+	+		344
Septic arthritis			+			294
Gout			+			318
Temporomandibular joint disorder			+			375g
Vertebral disk herniation			+		+	117, 375h
Aseptic meningitis	+	+			+	101, 323, 333, 366
Idiopathic cranial/peripheral neuropathy					+	117, 327, 328, 330
Behçet's disease	+	+	+		+	89
Mollaret's meningitis		+			+	89
Multiple sclerosis		+			+	124, 287, 291, 323, 333
Amyotrophic lateral sclerosis					+	89, 333
Guillain-Barré syndrome		+			+	323, 333
Seizure disorder					+	315, 333
Stroke, paresis, cerebral vasculitis, focal encephalitis					+	124, 291, 315, 333, 337–339
Dementia					+	168, 485
Brain tumor					+	290
Meningeal lymphoma					+	117
Psychosis					+	333
Schizophrenia					+	333
Anorexia nervosa					+	333
Cryptococcal meningitis					+	
Severe pain syndrome[d]					+	117

[a]Diseases that, on clinical presentation, could either be misdiagnosed instead of LB, or that could be misdiagnosed as LB.
[b]Acrodermatitis chronica atrophicans may be confused with circulatory insufficiency of the extremities.
[c]Juvenile rheumatoid arthritis, rheumatoid arthritis.
[d]Severe radicular pain may be confused with gastric ulcer, cholelithiasis, renal calculi, myocardial infarction, zoster or herniated vertebral disk.

tissue disorders and drug hypersensitivity reactions. The correct diagnosis can usually be made by clinical history, confirmation of Lyme seropositivity and, when necessary, serologic exclusion of the other causes.

The cardiac manifestations of Lyme disease may initially be misdiagnosed as acute or chronic viral myocarditis or even myocardial infarction because of the presence of arrhythmias and myocardial dysfunction, and establishment of the correct diagnosis is based on Lyme seropositivity and exclusion of the other causes by appropriate testing. Rheumatic fever and bacterial endocarditis may also be confused initially with Lyme carditis but are usually excluded because of Lyme seropositivity and because of valvular involvement, which is absent in Lyme carditis. In addition, complete heart block is more characteristic of Lyme disease than of rheumatic fever or bacterial endocarditis.

When the presenting symptoms are neurologic, without antecedent EM, the diagnosis of Lyme borreliosis may be difficult to make. In acute neuroborreliosis, cranial nerve palsies, such as Bell's palsy, Horner's syndrome or Argyll Robinson pupil, may be misdiagnosed as idiopathic rather than Lyme related. Radiculitis, one presentation of neuroborreliosis, may produce localized pain severe enough to be initially mistaken for an acute abdominal emergency, cholecystitis or cholelithiasis, ulcer, nephrolithiasis, vertebral disk herniation, myocardial infarction or zoster, but these may usually be excluded by the absence of the expected abnormalities by appropriate radiographic, sonographic or other diagnostic tests, and by Lyme seropositivity. The central nervous system manifestations of neuroborreliosis may initially be mistaken for viral meningoencephalitis, stroke, multiple sclerosis, brain tumors or even dementia or psychiatric disorders, but the correct diagnosis can usually be established by serologic testing for Lyme borreliosis and by appropriate testing to exclude the other diagnoses. When the presentation mimics brain tumor, a biopsy is indicated, and if Lyme borreliosis is in the differential diagnosis, the specimen should be sent for *B. burgdorferi* culture and staining as well as for histopathologic examination.

The musculoskeletal manifestations of Lyme borreliosis, particularly Lyme arthritis, may initially be confused with rheumatoid arthritis and occasionally with septic arthritis, but the diagnosis of Lyme disease may usually be made by clinical history, by negative rheumatoid factor and negative joint fluid cultures and by Lyme seropositivity, as most Lyme arthritis patients are seropositive at presentation. There may be slight increases in rheumatoid factor during Lyme arthritis, but these should be transient.

Other spirochetal infections, such as leptospirosis, relapsing fever and syphilis, may result in false seropositivity for Lyme disease (see Table 11–13) but can usually be distinguished from Lyme disease clinically and epidemiologically.

Table 11–15. DIFFERENTIAL DIAGNOSIS OF CONGENITAL LYME BORRELIOSIS (CLB)[a]

Early CLB	Late CLB
Acute bacterial sepsis/ meningoencephalitis	Subacute bacterial sepsis/ meningoencephalitis
Congenital viral sepsis/ meningoencephalitis	Congenital viral sepsis/ meningoencephalitis
Enterovirus	Enterovirus
Cytomegalovirus	Cytomegalovirus
Herpes simplex	Herpes simplex
Rubella	Rubella
Hepatitis A/B/C	Hepatitis A/B/C
? Parvovirus or other	? Parvovirus or other
Congenital toxoplasmosis	Congenital toxoplasmosis
Congenital syphilis, early onset	Congenital syphilis, late onset
Congenital leptospirosis	Failure to thrive due to noninfectious etiologies
Congenital relapsing fever	Congenital hypotonia
Idiopathic congenital heart disease	Idiopathic congenital heart disease
	Immunodeficiency and recurrent infections
	Infantile multisystem inflammatory disease
	Sudden infant death syndrome

[a]Diseases that, on clinical presentation, could either be misdiagnosed instead of CLB, or that could be misdiagnosed as CLB.

Differential Diagnosis of Congenital Lyme Borreliosis

The differential diagnosis of congenital Lyme borreliosis (Table 11–15) includes bacterial and viral sepsis and meningoencephalitis, toxoplasmosis, syphilis, leptospirosis, relapsing fever, idiopathic congenital heart disease, immunodeficiency and recurrent infections, infantile multisystem inflammatory disease and even sudden infant death syndrome. Early congenital Lyme borreliosis may be misdiagnosed as acute fulminant sepsis and meningoencephalitis or severe congenital heart disease, because of its similar presentation. Late congenital Lyme borreliosis may manifest with symptoms of a more chronic congenital infection, such as failure to thrive, hypotonia or recurrent infections.

The diagnosis of congenital Lyme borreliosis may be made in infants with these presentations by obtaining a history of maternal gestational illness compatible with Lyme disease (see above section on differential diagnosis), by serologic confirmation of maternal Lyme disease, by exclusion of the other causes by serologic and/or culture evaluation of the infant and, if possible, by serologic or lymphocyte

proliferative assay confirmation of *B. burgdorferi* infection of the infant. If placental tissue is available, histopathology, culture and special stains for *B. burgdorferi* spirochetes may confirm the diagnosis. Because of histopathologic similarities between congenital and placental Lyme borreliosis and syphilis, it is advisable to rule out syphilis serologically in patients with suspected Lyme disease.

Congenital Lyme disease should also be considered as a possible cause of infantile multisystem inflammatory disease, a chronic progressive inflammatory disease of so far undetermined etiology, with cutaneous, neurologic, ophthalmologic, lymphoreticular and joint involvement, particularly as one of these patients was considered to have congenital Lyme disease.[299] Lyme borreliosis also appears to be involved in some instances of sudden infant death syndrome and should therefore be considered in infants with missed sudden infant death syndrome.[27]

Therapy

Antibiotic therapy has been used for treatment of Lyme borreliosis since 1951 when Hollstrom found that penicillin cured the skin lesions of European EM.[134] Between 1977 and 1979, following the initial description of North American Lyme disease and EM by Steere and colleagues,[10] it was unclear whether antibiotic therapy was beneficial in Lyme disease. However, because of the similarities between Lyme disease and European EM, the improvement of European EM with penicillin therapy and the suspicion that the etiology of both was spirochetal, trials of antibiotic therapy for Lyme disease were conducted between 1977 and 1983 by Steere and colleagues, and a definite response to antibiotic therapy of the cutaneous, arthritic and neurologic manifestations was found.[83, 143, 376] Since then, further antibiotic therapy trials have been performed to determine the optimal antibiotic, route of administration and duration of therapy, in order to maximize the immediate cure rate and reduce the incidence of major late complications such as meningoencephalitis, myocarditis and arthritis.

Early Antibiotic Therapy Efficacy Trials

Early antibiotic therapy trials by Steere and colleagues[83, 143] between 1976 and 1981 demonstrated that low-dose short (7- to 10-day) courses of oral penicillin or tetracycline for treatment of EM led to more rapid resolution of EM than erythromycin. Tetracycline prevented development of major late manifestations, while penicillin decreased this incidence to 8 per cent and erythromycin to 14 per cent.[83] Penicillin decreased the incidence of later development of Lyme arthritis from 74 per cent to 35 per cent and shortened the duration of Lyme arthritis from 17 weeks to 4 weeks when it occurred, but it did not affect the incidence of later cardiac (4 per cent) or neurologic (14 per cent) involvement.[83, 143] The severity of the minor late systemic symptoms of headache and musculoskeletal pain correlated with the severity of the initial presentation.

Further trials by the same group in 1983[297, 376] showed that high-dose intravenous penicillin (20 million units daily for 10 days) was effective for treatment of chronic Lyme arthritis and acute Lyme meningitis. This course of high-dose penicillin cured 55 per cent of patients with chronic Lyme arthritis. For patients with Lyme meningitis, it reduced the mean duration of meningeal symptoms from 29 weeks to 1 week and led to resolution of headache, meningismus and radicular pain within 7 to 10 days and resolution of cranial and peripheral neuropathies within 8 weeks, but 25 per cent of patients still had persistent arthralgias, musculoskeletal pain and fatigue.

The possibility was raised that penicillin treatment failures,[40, 297, 376] with progression of early EM to later complications, could be due to failure to eradicate spirochetes in the central nervous system or synovia or other immunologically protected sites, either because of the short penicillin half-life, the relatively high and variable penicillin MIC of *B. burgdorferi* (see Table 11–1) or the failure to achieve and maintain spinal fluid or synovial fluid levels above the MIC of the spirochete. Inadequate antibiotic therapy may be due to inappropriate choice of antibiotic, route, dose or duration of therapy.

It was proposed that cephalosporins with longer half-lives, lower MICs and greater penetration into the central nervous system or synovia than penicillin might achieve better cure rates than penicillin. Because ceftriaxone and cefotaxime have long half-lives, achieve sustained high serum and spinal fluid levels and have a low MIC for *B. burgdorferi*, clinical efficacy trials of these antibiotics were performed.

Ceftriaxone was found to be more effective than penicillin by Dattwyler and colleagues[377, 378] from 1986 to 1987 in treatment of refractory patients with late chronic Lyme disease, including arthritis and peripheral neuropathy of over 1 year duration. Intravenous ceftriaxone (1 or 2 g twice daily for 14 days) cured approximately 90 per cent of patients, even those treated after failing to respond to high-dose intravenous penicillin, compared with a 50 per cent cure rate in patients treated with high-dose intravenous penicillin (24 million units daily for 10 days). Hassler and colleagues in 1990[379] also reported that

intravenous cefotaxime (2 g three times daily for 10 days) achieved 88 per cent cure/partial remission rates, while intravenous penicillin (20 million units daily for 10 days) achieved 61 per cent cure/partial remission rates for treatment of late European Lyme borreliosis, including patients with oligoarthritis, peripheral neuropathies, radicular pain, ACA and borrelial lymphocytoma. They proposed that the success with cefotaxime was related to high tissue antibiotic concentrations above the MIC of *B. burgdorferi* during the entire dose interval and excellent CSF penetration, and that high sustained levels above the MIC are needed because of reduced tissue permeability that may occur in late Lyme borreliosis as a result of the microangiopathic changes in the synovia and nervous system.

In addition, if antibiotic therapy of the initial early Lyme disease has been inadequate for eradication of the spirochete but has been given promptly enough to attenuate or eliminate the *B. burgdorferi* antibody response,[12, 85–87, 99, 120–122] seronegative late chronic Lyme borreliosis may develop.[85, 86] Longer (14-day) intravenous courses of ceftriaxone or high-dose penicillin were found by Dattwyler and colleagues in 1988 to be equally efficacious in treatment of seronegative and seropositive chronic Lyme disease in patients who had developed this despite oral penicillin, tetracycline or erythromycin treatment of the initial EM.[86]

Because the rates of cure for late chronic Lyme borreliosis even with high-dose intravenous cefotaxime or ceftriaxone therapy were still not 100 per cent, and because *B. burgdorferi* was still cultured from skin biopsy specimens and spinal fluid of a few patients with chronic Lyme disease 3 to 7.5 months after 10- to 14-day treatment courses with high-dose intravenous penicillin or ceftriaxone, or oral penicillin or doxycycline,[128, 334] the question was raised of whether longer courses of therapy were indicated.

Achievement of Serum and CSF Antibiotic Levels Above the *B. burgdorferi* Minimal Inhibitory Concentration

European and North American *B. burgdorferi* isolates from patients as well as from ticks have all been found to have similar antibiotic susceptibility patterns (see Table 11–1), so that recommendations regarding antibiotic therapy are applicable to all geographic areas from which Lyme borreliosis has been reported.

Comparisons of antibiotic activity against *B. burgdorferi* by in vitro MIC studies found erythromycin to be more active than penicillin, amoxicillin, amoxicillin–clavulanic acid, doxycycline and tetracycline,[76, 82] but by in vivo animal efficacy studies the opposite was found, and erythromycin was much less active than penicillin, amoxicillin, amoxicillin–clavulanic acid or tetracycline.[82] The early comparisons of clinical efficacy of various antibiotics in treatment of Lyme disease demonstrated that tetracycline was best, penicillin next best and erythromycin worst,[83] and these results correlated with efficacy studies in animal models. The cephalosporins ceftriaxone, cefotaxime, cefuroxime and cefixime all had good activity against *B. burgdorferi* by both in vitro MIC and by in vivo animal model efficacy studies.[72, 82]

In 1988, Luft and colleagues found that *B. burgdorferi* is killed slowly by antibiotics and requires prolonged blood levels above the MIC of the organism for cure.[78] The mean MIC of the organism for penicillin is 0.3 to 4.0 μg/ml, for tetracycline is 0.14 to 0.56 μg/ml and for ceftriaxone is 0.02 to 0.06 μg/ml (see Table 11–1). Seventy-two hours of exposure to 0.1 μg/ml of penicillin, forty-eight hours of exposure to 1.0 μg/ml of penicillin or seventy-two hours of exposure to 1.0 μg/ml of tetracycline is required to achieve 99 per cent killing of the spirochetes. Increasing the concentration of either penicillin or ceftriaxone above the MIC does not result in any faster killing of the organism, while the rate of killing with tetracycline is dose-dependent. Peak antibiotic levels achieved after 250 mg and 500 mg of oral tetracycline were 2 and 4 μg/ml, respectively, in the serum and 0.2 to 0.4 and 0.4 to 0.8 μg/ml, respectively, in the spinal fluid, and after 250 mg and 500 mg of oral phenoxymethylpenicillin were 2 to 3 and 3 to 5 μg/ml, respectively, in the serum and undetectable in the spinal fluid.[78] Luft and colleagues[78] conclude that these data suggest the possible need for longer than 10 days of high-dose antibiotic therapy to kill *B. burgdorferi* in the spinal fluid.

In 1989, Dotevall and Hagberg[75] found that mean spinal fluid doxyxycline concentrations of 0.6 μg/ml after 100 mg of doxycycline orally twice a day and 1.1 μg/ml after 200 mg orally twice a day were achieved after 5 to 8 days of antibiotic therapy. They concluded that the higher doxycycline dose achieved CSF concentrations above the MIC in 90 per cent of patients and could potentially be used for treatment of early neuroborreliosis. In 1988, a small clinical trial by Dotevall and colleagues[74] found oral or intravenous doxycycline 100 mg twice daily for 10 to 20 days effective in mild neuroborreliosis.

In 1991, Philipson[80] demonstrated prolonged serum levels significantly above the MIC and minimal bactericidal concentration (MBC) of *B. burgdor-*

feri after intravenous doses of cefotaxime, ceftriaxone and doxycycline, but not penicillin. Mean 4-hour serum peak level after 2 g of cefotaxime was 200 μg/ml compared with an MIC of 0.12 μg/ml, after 1 g of ceftriaxone was over 200 μg/ml compared with an MIC of 0.03 to 0.06 μg/ml, after 200 mg of doxycycline was 5 to 10 μg/ml compared with an MIC of 0.25 to 2.0 μg/ml and after 3 g of penicillin was 3 μg/ml compared with an MIC of 0.25 to 3.0 μg/ml.

Also in 1991, Pfister and colleagues[334] reported achievement of spinal fluid levels above the MIC of *B. burgdorferi* with either ceftriaxone 2 g intravenously every 24 hours or cefotaxime 2 g intravenously every 8 hours, and achieved an overall 63 per cent cure rate of European neuroborreliosis with 10 days of antibiotic therapy. However, 37 per cent of treated patients were still symptomatic 8 months later, and *B. burgdorferi* was still cultured from spinal fluid of one patient 7.5 months after antibiotic therapy, and this raised the question of whether longer courses of therapy are indicated.

Doxycycline, cefotaxime or ceftriaxone is preferable to penicillin for therapy of Lyme borreliosis because their longer half-lives allow maintenance of tissue antibiotic concentrations above the MIC for *B. burgdorferi* during the entire course of therapy.

Jarisch-Herxheimer Reaction and Other Antibiotic Therapy Side Effects

Symptoms of the Jarisch-Herxheimer reaction, which may occur in 7 to 50 per cent of patients treated with antibiotics for Lyme borreliosis, are most likely due to release of endotoxin during lysis of the spirochetes caused by initiation of antibiotic therapy.[380] Typical symptoms initially consist of vasoconstriction with hypertension, pallor and chills in the first 6 to 18 hours, followed by vasodilation with hypotension, headache, flushing and exacerbation of arthralgias, myalgias, rash and fever for 24 to 48 hours.[379] Development of the Jarisch-Herxheimer reaction is more common if the Lyme borreliosis is severe,[83] disseminated[381] or chronic,[379] presumably because the spirochetal burden is high. The incidence of occurrence of a Jarisch-Herxheimer[380] reaction within 24 hours after initiation of antibiotic therapy of Lyme borreliosis is 10 to 50 per cent with penicillin or amoxicillin,[83, 376, 379, 381, 382] 0 to 16 per cent with tetracycline,[83, 381] 8 per cent with doxycycline,[382, 383] 7 per cent with erythromycin[83] and 22 to 40 per cent with cefuroxime, cefotaxime or ceftriaxone.[378, 379, 383, 384] Development of a Jarisch-Herxheimer reaction may be considered evidence of a response to antibiotic therapy. Symptoms may be prevented if desired by prophylactic treatment with 80 mg of triamcinolone acetonide intravenously 30 minutes before starting antibiotic therapy.[379]

It is important to recognize this reaction, including the increased rash that may occur, as a Jarisch-Herxheimer reaction rather than an allergic reaction to the antibiotic, in order to prevent unnecessary discontinuation of the antibiotic therapy.

Other common side effects of antibiotic therapy include photosensitivity with tetracycline and doxycycline; *Clostridium difficile* enteritis with broad-spectrum cephalosporins, tetracycline or doxycycline, more frequent with 4 g daily of ceftriaxone than with 2 g daily[378]; hypersensitivity rash with any antibiotic; gastrointestinal intolerance with tetracycline, doxycycline or erythromycin; and reversible biliary sludging or pseudolithiasis with high-dose ceftriaxone. Patients should be cautioned to use sunscreen to avoid sunburn while taking tetracycline or doxycycline. If diarrhea develops, a *C. difficile* toxin assay should be sent and the patient appropriately treated with either oral metronidazole or vancomycin. If rash develops, it is important to distinguish a hypersensitivity reaction from either a Jarisch-Herxheimer reaction or the rash of disseminated Lyme borreliosis. Gastrointestinal intolerance of antibiotics may be relieved by taking the medication with food. Ceftriaxone-associated biliary sludging is less common if lower doses of 2 g rather than 4 g daily for adults are used, but occurs even in children with the doses recommended for treatment of Lyme disease.[385] If symptomatic biliary pseudolithiasis develops, it should be evaluated by ultrasound, and cefotaxime should be substituted for the ceftriaxone.

Review of Antibiotic Therapy of Nongestational Lyme Borreliosis

This section reviews antibiotic therapy trials for nongestational Lyme borreliosis, and doses listed here are adult doses. Current recommendations are summarized in Tables 11–16 and 11–17 and are discussed in the section Recommendations for Antibiotic Therapy of Gestational, Nongestational, and Congenital Lyme Borreliosis.

Erythema Migrans

Data from several large antibiotic therapy trials between 1981 and 1992 indicate that prompt antibiotic therapy of early EM results in cure rates of 76 to 92 per cent with oral penicillin (1 to 2 g daily for 10 to 12 days),[83, 384] 87 to 95 per cent with oral amoxicillin plus probenecid (500 mg of each three times daily for 10 to 21 days),[79, 382] 88 to 95 per cent with oral doxycycline (100 mg twice daily for 10 to 21 days),[79, 382, 383] 93 per cent with oral cefuroxime axetil

(500 mg twice daily for 20 days),[383] and 95 per cent with oral azithromycin (500 mg first, then 250 mg daily for 4 days),[79] but that more severe early disseminated infection requires more aggressive antibiotic therapy such as parenteral ceftriaxone. A short (5-day) course of intramuscular ceftriaxone (1 g daily) was more efficacious than a longer (12-day) course of high-dose oral penicillin for treatment of severe early disseminated European EM, as it achieved an 85 per cent cure rate compared with 76 per cent for penicillin and reduced the incidence of subsequent late manifestations of Lyme borreliosis.[384]

Between 1981 and 1987, Berger[381, 386] treated over 300 patients with early North American EM with oral antibiotic therapy, including penicillin (1 to 2 g daily for 10 to 30 days), tetracycline (1 to 2 g daily for 10 to 30 days), amoxicillin and probenecid (500 mg three times daily for 15 to 30 days), or doxycycline (100 mg three times daily for 15 to 30 days), and reported a 98 to 100 per cent cure rate for those with early localized Lyme disease and a 77 to 79 per cent cure rate for those with early disseminated Lyme disease. Most of those who experienced relapse after initial oral antibiotic therapy for disseminated infection were cured by further oral or intravenous antibiotic therapy, but some developed late manifestations.

In 1990, Dattwyler and colleagues reported comparable efficacy of amoxicillin plus probenecid (500 mg of each three times daily) and doxycycline (100 mg twice daily) for 21 days for treatment of early EM.[382] The rate of full recovery without minor late symptoms was 94 per cent for doxycycline and 87 per cent for amoxicillin/probenecid, and both regimens gave 100 per cent prevention of major late complications of meningoencephalitis, myocarditis or arthritis.

In 1992, Nadelman and colleagues[383] treated EM with oral cefuroxime axetil (500 mg twice daily) or doxycycline (100 mg twice daily) for 20 days and achieved a 93 per cent cure rate with cefuroxime and an 88 per cent cure rate with doxycycline with no late Lyme disease at 12-month follow-up with either regimen.

Also in 1992, Massarotti and colleagues[79] found equal efficacy of oral azithromycin for 5 days, amoxicillin and probenecid for 10 days and doxycycline for 10 days for treatment of early EM and achieved cure rates of 95 per cent. Antibiotic susceptibility data suggest superiority of azithromycin to erythromycin,[81] and the high tissue levels achieved with azithromycin may make it more effective clinically than erythromycin,[79] but at the time of this publication, these macrolide antibiotics should not be considered first-line drugs for the treatment of Lyme borreliosis.

Lyme Arthritis

Antibiotic therapy of chronic Lyme arthritis results in cure rates of 35 per cent with intramuscular benzathine penicillin (2.4 million units weekly for 3 weeks),[297] 28 to 55 per cent with intravenous penicillin (20 to 24 million units daily for 10 days),[297, 378, 379] 92 to 100 per cent with intravenous ceftriaxone (1 to 2 g daily for 14 days),[377, 378] and 81 per cent with intravenous cefotaxime (2 g three times daily for 10 days).[379]

Because several studies have found that intra-articular or systemic steroid therapy of patients with Lyme disease is associated with lack of response to antibiotic therapy, including intravenous penicillin and ceftriaxone treatment of late Lyme arthritis, steroid therapy is not currently recommended in initial treatment of Lyme arthritis.[297, 376, 378] Restriction of weight bearing is recommended during the acute inflammatory phase of Lyme arthritis.[387]

In 1990, Caperton reported that 47 per cent of *B. burgdorferi* seropositive patients with chronic non-Lyme inflammatory arthritis, including rheumatoid arthritis, responded to intravenous ceftriaxone (2 g daily for 14 days), and this suggested the presence of an occult bacterial infection underlying their arthritis.[388]

Schoen and colleagues[389] reported that arthroscopic synovectomy in patients with chronic Lyme arthritis who had failed to respond to appropriate antibiotic therapy or intra-articular steroids resulted in an 80 per cent cure of the inflammatory arthritis within approximately 1 month, and full or partial functional recovery occurred in 65 per cent. For management of chronic Lyme arthritis, these investigators recommend first prolonged oral antibiotic therapy, then intravenous antibiotic therapy if this fails, then intra-articular steroid injections if antibiotic therapy fails and then arthroscopic synovectomy if these measures fail, and prefer synovectomy to hydroxychloroquine sulfate (Plaquenil) or gold therapy. They postulate that the persistent inflammatory arthritis is a synovitis that may be due either to persistent *B. burgdorferi* spirochetes or to antigens in the synovia, and that removal of this source of immunologic stimulation results in cure.

Lyme Carditis

In 1980, Steere and colleagues[344] reported that high-degree heart block due to Lyme borreliosis responded rapidly to prednisone therapy but that a major disadvantage of this therapy was persistence of neurologic or joint involvement for several months. Most patients with complete heart block required temporary pacemaker placement for less than 1 week; complete heart block usually resolved

within 24 to 48 hours of initiation of prednisone therapy, and full resolution of the carditis occurred within 1 to 2 weeks.[344]

By 1991, since these initial cases were reported, it became apparent that antibiotic therapy was beneficial for other manifestations of Lyme borreliosis, and that there was some benefit also for treatment of Lyme carditis.[284–286, 345] A 94 per cent recovery rate was reported for 105 North American and European patients with Lyme carditis treated with various therapies including penicillin, tetracycline, third-generation cephalosporins, steroids and nonsteroidal anti-inflammatory agents.[345] A temporary pacemaker was required in 28 per cent of these patients.[345] In 1992, Rubin and colleagues[343] reported that prompt antibiotic therapy of early Lyme borreliosis successfully treated a patient who presented with carditis initially and may have prevented the later development of carditis in others.

Current recommendations for treatment of Lyme carditis are intravenous ceftriaxone or high-dose penicillin for serious carditis, although oral antibiotic therapy may be acceptable for mild carditis such as first-degree heart block (see Table 11–16). Systemic steroid therapy (1 to 2 mg/kg per day prednisone) may also be indicated for severe carditis if unresponsive to initial antibiotic therapy,[51, 284, 344, 345, 390] and temporary pacemaker placement may be needed for complete heart block.[51, 284, 345]

Neuroborreliosis

Clinical trials of antibiotic therapy of neuroborreliosis have reported cure rates of 66 to 75 per cent with intravenous penicillin (20 to 24 million units daily) for 10 days,[378, 379] 100 per cent with intravenous penicillin (400,000 to 500,000 units/kg daily) for 14 days,[391] 63 to 67 per cent with intravenous ceftriaxone (2 g daily) for 10 days,[325, 330, 334] 76 to 100 per cent with intravenous ceftriaxone (2 to 4 g or 75 to 93 mg/kg daily) for 14 days[325, 330, 377, 378, 391] and 60 to 90 per cent with intravenous cefotaxime (2 g daily) for 10 days.[334, 379] In small trials of oral doxycycline (100 to 200 mg twice daily for 10 to 20 days) for treatment of mild European neuroborreliosis, all patients improved clinically.[74, 75] Problems with comparison of cure rates among different studies include differences in antibiotic doses and durations of therapy and differences in lengths of time after therapy at which cure is assessed, so that the most valid conclusions may be drawn from comparisons of antibiotic therapies in the same study.

Although most studies have found ceftriaxone and cefotaxime superior to penicillin for treatment of neuroborreliosis,[377–379] in 1991 Mullegger and colleagues[391] reported that intravenous high-dose ceftriaxone (75 to 93 mg/kg per day) and penicillin (400,000 to 500,000 units/kg per day) for 14 days were equally efficacious in treatment of children with European neuroborreliosis, including meningitis and cranial neuropathy, and that all children had full recovery by 5 to 130 days after start of antibiotic therapy. The increased efficacy of penicillin in this study compared with the lower penicillin efficacy found in earlier clinical comparisons may have been due to the higher doses of penicillin and the longer duration of therapy used.

Data from additional clinical studies also suggest that longer courses of antibiotic therapy are more efficacious for treatment of neuroborreliosis. Between 1990 and 1992, Logigian and colleagues[325, 330] reported that treatment of patients with chronic Lyme peripheral neuropathy with intravenous ceftriaxone (2 g daily) for 10 days cured 63 per cent and transiently improved 22 per cent of patients, while a longer (2-week) course cured 76 per cent and a 4-week course is being evaluated.

There are also reports of patients with acute Lyme meningoencephalitis that was apparently clinically resistant to high-dose intravenous penicillin but that responded to intravenous cefotaxime (2 g three times daily for 10 days)[392] or chloramphenicol (1 g four times daily for 10 days).[393]

In 1991, Hassler and colleagues reported that late European Lyme arthritis refractory to repeated courses of high-dose intravenous third-generation cephalosporins (2 weeks of cefotaxime and 3 weeks of ceftriaxone) was reported to respond to intravenous cefotaxime (2 to 4 g three times daily) for 1 to 2 days per week for 6 to 10 weeks.[394] The rationale for this regimen was that since *B. burgdorferi* has a 7- to 33-hour doubling time, and not all organisms are in division during antibiotic therapy, use of an antibiotic pulse would eventually catch every organism in division at a time during which it would be susceptible to antibiotic killing.

In 1992, Luft and colleagues[71] demonstrated that *B. burgdorferi* invades the central nervous system (CNS) early in Lyme disease even in the absence of CNS symptoms, when they detected *B. burgdorferi* by PCR in CSF of 67 per cent of patients with early disseminated Lyme borreliosis and 67 per cent of patients with isolated cranial neuritis. This has significant therapeutic implications and lends support to the concept that maintenance of high spinal fluid antibiotic levels during treatment of disseminated Lyme borreliosis is essential in order to eradicate the spirochete in the CNS, where it is in a relatively protected environment. These authors recommend that antibiotic therapy for disseminated Lyme disease, with or without cranial neuritis, be selected to achieve high spinal fluid levels and suggest high-dose oral amoxicillin/probenecid or doxycycline, or preferably intravenous ceftriaxone.

Correlation Between Antibiotic Therapy and Outcome of Gestational and Congenital Lyme Borreliosis

Table 11–10 shows the frequency of adverse outcomes of 161 pregnancies complicated by Lyme borreliosis reported in the literature, including four of the author's cases. Although there are relatively small numbers of patients in each trimester who were either treated or not treated with antibiotic therapy, the overall adverse outcome rate for all trimesters was 75 per cent for untreated and 25 per cent for treated gestational Lyme borreliosis. This protective effect of antibiotic therapy was seen in each trimester, so that the incidence of adverse outcomes of pregnancy decreased from 80 per cent to 47 per cent for first-trimester Lyme borreliosis, from 80 per cent to 23 per cent for second-trimester infection and from 50 per cent to 0 per cent for third-trimester infection. However, the adverse outcome rate for untreated third-trimester infection is less reliable, as only one case fell into this category.

Antibiotic therapy for gestational Lyme borreliosis may be successful, partially successful or unsuccessful at prevention of congenital Lyme borreliosis, and probably depends on the choice, dose, route of administration and duration of antibiotic therapy, as well as the trimester of the gestational Lyme borreliosis and the duration of infection prior to initiation of antibiotic therapy.

There are several reports of antibiotic therapy of gestational Lyme borreliosis that was associated with normal outcomes of the pregnancies,[27, 300, 381, 386, 395–398] and most of these "successful" antibiotic regimens consisted of either prolonged oral penicillin for 3 to 4 weeks or intravenous penicillin or cephalosporin antibiotics. In 1986 and 1988, Berger[381, 386, 395] reported on four patients with 12-, 14-, 22- and 24-week gestational Lyme borreliosis treated promptly within 4 to 10 days of onset of early localized EM with oral penicillin (500 mg four times daily) for 3 to 4 weeks who all delivered normal infants. In 1987, Mikkelson and Palle[300] reported on a patient with third-trimester gestational EM who was treated with phenoxymethyl penicillin (3 million units daily) for 10 days and who delivered a normal infant. In 1987, Cieszelski and colleagues[23] reported on 15 women treated for gestational Lyme borreliosis with unspecified antibiotic courses who all delivered normal infants. In 1989, MacDonald[27] reported on a patient with second-trimester gestational EM and neuroborreliosis who was treated with intravenous penicillin for 10 days and delivered a normal infant with no evidence of spirochetes in the placenta and another patient with second-trimester EM who was treated with oral penicillin for 15 days, then developed carditis, and delivered a normal infant with borreliae isolated from the placenta. This infant was treated at delivery with oral penicillin and probenecid and remained well. In 1990, Luger[396] noted six patients with gestational Lyme borreliosis, including two with EM, two with carditis, and one with facial palsy and temporomandibular arthritis, at least three of whom were treated with unspecified regimens of intravenous antibiotics, who all delivered normal infants. Also in 1990, Stiernstedt[398] reported on three patients with gestational Lyme borreliosis who were all treated with antibiotic therapy and who all delivered normal infants: one with localized EM was treated with oral penicillin of unspecified duration, one with disseminated EM was treated with intravenous penicillin for 4 days and then with oral penicillin for 10 days and one with neuroborreliosis was treated with intravenous cefuroxime for 14 days. In 1991, Schutzer[397] and colleagues noted a patient with 27-week gestational EM treated within 3 days with intravenous ceftriaxone (2 g daily) for 3 weeks who delivered a normal infant.

There are also several reports of antibiotic therapy for gestational Lyme borreliosis that did not prevent adverse fetal outcomes,[20–23, 30, 32, 33] and most of these "unsuccessful" antibiotic regimens consisted of short (7- to 10-day) courses of oral penicillin or erythromycin or unspecified oral antibiotics. In 1986 and 1988, Weber and colleagues[32, 33] reported on a patient with first-trimester gestational EM treated with oral penicillin (3 million units daily) for 1 week who delivered an infant (case 22 in Table 11–8) with severe fatal early congenital Lyme borreliosis. In 1986, Markowitz and colleagues[30] and the CDC[22] reported on three patients with gestational EM treated with oral antibiotic therapy who had adverse fetal outcomes: one patient with 6-week gestational EM with associated headache, stiff neck and arthritis was treated with oral penicillin for 10 days and had a fetal death at 20 weeks (case 14 in Table 11–8); one patient with 20-week gestational EM associated with headache, stiff neck and arthralgia was treated with oral erythromycin for 10 days and then with oral penicillin of unspecified duration at 27 weeks and delivered an infant with syndactyly (case 16 in Table 11–8); and one patient with 27-week gestational EM treated with oral penicillin for 10 days delivered an infant who developed cortical blindness and developmental delay (case 17 in Table 11–8). In 1987, Cieszelski and colleagues[23] reported on two patients with first-trimester gestational Lyme borreliosis treated with unspecified antibiotics: one patient with 4-week gestational infection had a miscarriage at 13 weeks (case 19 in Table 11–8), and the other with 7-week gestational infection delivered an infant with syndactyly (case

20 in Table 11–8). In 1988, Carlomagno and colleagues[21] noted a *B. burgdorferi* seropositive patient who had a tick bite; she was treated with unspecified antibiotic therapy prior to pregnancy and had a miscarriage at 9 weeks of gestation (case 35 in Table 11–8).

If the episode of maternal gestational Lyme borreliosis is untreated and if the fetus survives and is born alive, prompt antibiotic therapy is beneficial. There are reports of three infants born with early congenital Lyme borreliosis after undiagnosed and/or untreated gestational Lyme borreliosis who responded to prompt antibiotic therapy at birth.[22, 27, 30] In 1986, Markowitz and colleagues[30] reported on an infant with mild early illness following untreated gestational Lyme borreliosis 1 week before delivery who recovered after 10 days of intravenous penicillin (case 18 in Table 11–8). In 1989, MacDonald[27] reported on an infant with severe early congenital infection after an unremarkable gestation who recovered after treatment with unspecified intravenous antibiotic therapy (case 12 in Table 11–8), and another infant with severe early congenital infection after a toxemic gestation who recovered after being treated with intravenous penicillin (case 13 in Table 11–8).

Antibiotic therapy for gestational Lyme disease may still attenuate the severity of congenital Lyme borrelioisis even if it does not prevent it completely. MacDonald[27] has described one infant and the author has described four additional infants born after antibiotic-treated gestational Lyme borreliosis who had evidence of symptomatic congenital Lyme borreliosis and who responded to intravenous antibiotic therapy either in the neonatal period or during the first year of life (cases 23, 24, 25 and 26 in Table 11–8).

One mother had 4-week gestational disseminated EM treated within 4 days with intravenous ceftriaxone (2 g daily) for 2 days followed by oral penicillin (500 mg four times daily) for 12 days and delivered an infant with very mild early congenital Lyme borreliosis (case 23 in Table 11–8), who recovered with a 2-week course of intravenous ceftriaxone (100 mg/kg per day).

A second mother had flu-like illnesses at 5 weeks and 20 weeks of gestation, was treated with amoxicillin (250 mg three times daily) for 10 to 14 days each time and delivered an infant with severe early congenital Lyme borrelioisis (case 24 in Table 11–8); the child initially failed to improve but did not further deteriorate with intravenous ampicillin (100 mg/kg per day) for 6 days, and recovered when intravenous ceftriaxone (100 mg/kg per day) was added for the next 7 days. This infant required retreatment with intravenous ceftriaxone (75 mg/kg daily for 3 weeks) at 10 months for neuroborreliosis and subsequently remained well.

A third mother had intermittent disseminated EM with flu-like symptoms and polyarthralgias; was treated with almost continuous antibiotic therapy for the first 10 weeks of gestation, initially erythromycin (333 mg three times daily) for about 7 weeks, followed by cefaclor (250 mg three times daily) for 3 days, intravenous cefuroxime (750 mg three times daily) for 4 days, oral cephalexin (500 mg four times daily) for 2 weeks and then with oral cefixime (100 mg daily) for 10 days at 12 to 13 weeks; and delivered an infant with moderate early congenital Lyme borreliosis (case 25 in Table 11–8) who responded to intravenous antibiotic therapy for 6 days (including ampicillin for 5 days and ceftriaxone/cefotaxime for 3 days). This infant later presented with late chronic congenital Lyme borreliosis that required retreatment with a total of 7 weeks of intravenous ceftriaxone (100 mg/kg daily) between 2.5 and 7 months, and prolonged oral antibiotic therapy with amoxicillin (40 mg/kg daily) for 1 year from 7 to 19 months of age. Each time a less aggressive course of either oral cefaclor (Ceclor) or a shorter course of intravenous ceftriaxone was given, a relapse consisting of loss of developmental milestones occurred, but finally after a total of 7 weeks of intravenous ceftriaxone followed by a 1-year course of oral amoxicillin, the infant remained clinically well and continued to progress to essentially normal neurologic status by 3 years of age.

A fourth mother had second- and third-trimester EM associated with flu-like illness, polyarthralgias, stiff neck and dizziness and was treated with oral erythromycin (250 mg four times daily) for 10 days at about 28 weeks, followed by oral cefuroxime axetil (2 g daily) from 33 weeks through delivery, and delivered an infant with mild early Lyme borreliosis (case 26 in Table 11–8) who recovered with intravenous ceftriaxone (75 mg/kg daily) for 4 weeks. Two of these infants (cases 25 and 26) had episodes resembling Jarisch-Herxheimer reactions within 2 to 5 days of the start of the initial antibiotic therapy.

MacDonald[27] reported on an infant whose placenta grew spirochetes following second-trimester gestational EM treated with oral penicillin (500 mg four times daily) for 15 days and untreated gestational EM 2 weeks before delivery, who was well at birth, was treated promptly with oral penicillin and probenecid and who remained well.

Review of Antibiotic Therapy of Gestational Lyme Borreliosis

Because there has previously been uncertainty about the true incidence of fetal risk associated with

gestational Lyme borreliosis, there has been great diversity among recommendations for management of gestational tick bites and gestational Lyme borreliosis, and there are four basic approaches recommended in the medical literature. Prenatal screening for Lyme seropositivity to detect and treat seropositives with evidence of active Lyme borreliosis is recommended by some investigators.[21, 73, 399] Some recommend antibiotic prophylaxis of all *Ixodes* tick bites because of evidence that this is successful in prevention of development of Lyme borreliosis following the bite of an infected tick, and because of concern that early dissemination to the placenta and fetus may occur before initiation of antibiotic therapy if Lyme borreliosis does develop.[89, 399–401] Others recommend antibiotic therapy of gestational Lyme borreliosis determined by the clinical stage of the infection, which usually consists of oral antibiotic therapy for early localized infection and intravenous antibiotic therapy for early disseminated or late infection, because of their impression that the actual risk of development of congenital Lyme borreliosis is exceedingly low, and that there is no need for more aggressive treatment of gestational Lyme borreliosis.[21, 30, 73, 390, 398–403] Yet other investigators recommend intravenous antibiotic therapy for all cases of gestational Lyme borreliosis because of concern that there is a significant potential risk to the fetus, which is not yet fully appreciated, following any gestational Lyme borreliosis infection, and an impression that high-dose intravenous antibiotic therapy is more successful at achieving antibiotic levels above the MIC of the spirochete on both the maternal and the fetal sides of the placenta.[32, 89, 99] Others recommend consideration of parenteral antibiotic therapy for some patients with gestational Lyme borreliosis, particularly first- or early second-trimester or disseminated gestational Lyme borreliosis.[17, 387, 404]

Some reports favor prenatal screening: Carlomagno and colleagues[21] and Cryan and Wright[73] recommended prenatal screening for *B. burgdorferi* seropositivity, and treatment of all seropositive patients, even those with asymptomatic gestational *B. burgdorferi* seropositivity, with oral or intramuscular penicillin or with intravenous ceftriaxone. Williams and Strobino[399] also recommended prenatal screening but recommended antibiotic treament only for those with evidence of active infection.

Some reports favor antibiotic prophylaxis of gestational *B. burgdorferi* vector tick bites: Edly[401] recommended prophylaxis for bites only in the first half of pregnancy during the period of maximum susceptibility to teratogens, while Williams and Strobino,[399] Ostrov and Athreya[89] and the American College of Obstetricians and Gynecologists[400] recommended prophylaxis of all gestational bites in endemic areas. When specified, the most commonly recommended prophylactic regimens consisted of oral amoxicillin 500 mg three times daily or oral penicillin 500 mg four times daily for 3 weeks.

Other reports favor antibiotic therapy of gestational Lyme disease based on guidelines for nonpregnant patients with no special modifications for pregnancy other than not using doxycycline or probenecid: Markowitz and colleagues favor oral penicillin (500 mg four times daily for 10 to 20 days) for early infection and consideration of intravenous penicillin for late infection.[30] Stiernstedt[398] and Williams and Strobino[399] suggested oral penicillin or amoxicillin for 2 to 3 weeks for localized EM, and intravenous penicillin or cephalosporin therapy for 2 to 3 weeks for disseminated EM or neuroborreliosis. Carlomagno and colleagues,[21] Cartter and colleagues,[402] Smith and colleagues[390] and the American Academy of Pediatrics[403] recommended treatment for gestational Lyme borreliosis but made no special modifications in the recommendations for more aggressive therapy of gestational infection.

There are investigators who favor more aggressive therapy for gestational Lyme disease: The National Institute of Arthritis and Musculoskeletal and Skin Disease and the National Institute of Allergy and Infectious Disease[387] recommended consideration of intravenous antibiotic therapy for first-trimester gestational Lyme borreliosis, and routine therapy according to guidelines for the clinical stage of disease for other trimesters. Podolsky[17] suggests intravenous ceftriaxone may provide greater protection of the fetus than oral penicillin. MacDonald and colleagues,[29] Weber and colleagues[32] and Ostrov and Athreya[89] favor intravenous penicillin therapy (20 million units daily for 10 to 14 days) and possibly intravenous ceftriaxone (2 to 4 g daily for 10 to 14 days)[89] for all gestational Lyme borreliosis cases. Dattwyler and colleagues[99] recommend antibiotic therapy of gestational Lyme borreliosis to achieve eradication of spirochetes on both the maternal and fetal sides of the placenta and imply that this is best accomplished by high-dose intravenous therapy. Rahn and Malawista[404] recommend intravenous penicillin (20 million units daily) for 14 to 21 days for all cases of gestational Lyme borreliosis except single localized EM with no associated systemic symptoms, for which they recommend oral amoxicillin (500 mg three times daily) for 21 days.

Recommendations for Antibiotic Therapy of Gestational, Nongestational and Congenital Lyme Borreliosis

Tables 11–16 and 11–17 show antibiotic regimens recommended for different stages of Lyme borre-

Table 11–16. TREATMENT OF LYME BORRELIOSIS

Clinical Classification	Adult, Nonpregnant	Child Noncongenitally Infected[a]	Adult, Pregnant[b]
Early localized (erythema migrans; borrelial lymphocytoma) *or* Early disseminated, mild (multiple erythema migrans; Bell's palsy; mild arthritis; mild cardiac or other organ involvement)	Doxycycline 100 mg po BID × 10–30 d *or* Amoxicillin + probenecid 500 mg each po TID–QID × 10–30 d *or* Cefuroxime axetil 500 mg po BID × 10–30d *or* Erythromycin[c] 250 mg po TID × 10–30 d	Amoxicillin + probenecid 50 mg/kg/day each po TID × 10–30 d *or* Cefuroxime axetil 40 mg/kg/day po BID × 10–30 d *or* Erythromycin[c] 30 mg/kg/day po TID × 10–30 d	Ceftriaxone 2 g iv QD × 14 d *or* Penicillin G 4 million units iv Q4hr × 14 d *or* Ampicillin 2 g iv Q6hr × 14 d
Early disseminated, serious (severe arthritis[d]; severe neurologic[e], cardiac, or other organ involvement) *or* Chronic disseminated (chronic arthritis[d]; chronic meningitis, encephalitis, peripheral neuropathy[e]; chronic other organ involvement; ≥ 6–12 months)	Ceftriaxone 2 g iv QD × 14–30 d *or* Penicillin G[f] 4 million units iv Q4hr × 14–30 d	Ceftriaxone 100 mg/kg/day iv BID × 14–30 d *or* Penicillin G[f] 300,000 units/kg/day iv Q4hr × 14–30 d	Ceftriaxone 2 g iv QD × 14–30 d *or* Penicillin G 4 million units iv Q4hr × 14–30 d *or* Ampicillin 2 g iv Q6hr × 14–30 d

Recommendations for children and nonpregnant adults are adapted from references 51, 404 and 404a, and recommendations for pregnant women are based on limited data from Table 11–8 of adverse outcomes of gestational Lyme borreliosis following oral antibiotic therapy. Lengths of therapy are not well established. The author prefers consideration of the higher and longer dosages and lengths of therapy.

[a]Doxycycline should not be used in children under 9 years of age, and dosages of other antibiotics should not exceed adult dosages.

[b]Doxycycline should not be used in pregnant or lactating women. The author prefers to recommend intravenous therapy, but if this is not feasible, oral therapy with amoxicillin, cefuroxime axetil or erythromycin as for nonpregnant patients could be used for a prolonged period ranging from 2 weeks to the duration of pregnancy. Erythromycin should be discontinued 1 week prior to delivery to avoid neonatal hyperbilirubinemia.

[c]Erythromycin is less effective but may be used in penicillin-, cephalosporin- or tetracycline-allergic patients. Azithromycin (500 mg once po, then 250 mg po QD × 4 d) may be an alternative,[79] but no data are available on its use in pregnancy.

[d]Possible alternative for arthritis: doxycycline 100 mg po BID × 30 d, or amoxicillin + probenecid 500 mg each po TID–QID × 30 d.

[e]Possible alternative for neurologic: cefotaxime 2 g iv Q8hr × 14–30 d, doxycycline 100 mg po or iv Q12hr × 14–30 d,[74] or chloramphenicol 1 g iv Q6hr × 14–30 d.[193]

[f]Ampicillin (2 g iv or 200 mg/kg/day iv Q6hr × 14–30 d) may be an alternative.

liosis, which have been developed based on the literature and the author's experience and include specific recommendations for gestational and congenital Lyme borreliosis.

It should be emphasized that the best time to treat Lyme borreliosis successfully is at the onset of the early infection, as treatment of late chronic infection is more difficult and has a higher failure rate. The goal of antibiotic therapy should ideally be eradication of the spirochete from all sites, including potentially immunologically privileged sites such as the eye, the joints, the central nervous system and, in pregnancy, the fetal side of the placenta. The lengths of therapy are not well established, and because of concern regarding the need to maintain serum, synovial fluid and spinal fluid levels above the MIC of the spirochete, the author prefers to recommend the longer (4-week) durations of antibiotic therapy. There are no current recommendations regarding whether prolongation of oral antibiotic therapy for several months is beneficial, although this could be considered in individual unique clinical situations. However, an open mind must be maintained regarding any recommendations for antibiotic therapy for Lyme borreliosis because recommendations will most likely require modification as additional data on clinical efficacy trials become available.

For treatment of nongestational and noncongenital early localized or mild disseminated Lyme borreliosis (Table 11–16), 10- to 30-day courses of oral doxycycline (100 mg twice daily) or oral amoxicillin and probenecid (each at 500 mg three times daily, or 50 mg/kg per day for children) are the regimens of choice, but doxycycline should not be used either in pregnant or lactating women or in children under 9 years of age. Oral cefuroxime axetil (500 mg twice daily, or 40 mg/kg per day for children) or oral erythromycin (250 mg three times daily, or 30 mg/kg per day for children) are alternatives. Because erythromycin has been associated with frequent treatment failures, its use should be reserved for patients in whom no other acceptable therapy is possible. It is possible that azithromycin may prove to be more efficacious than erythromycin in the future, and may be a good alternative for penicillin or cephalosporin allergic patients, but further therapeutic efficacy data are needed.

For treatment of gestational early localized or mild

Table 11–17. TREATMENT OF CONGENITAL LYME BORRELIOSIS (CLB)[a]

Clinical Classification of CLB	Age at Time of Antibiotic Therapy		
	Neonate, <1 Week	*Neonate, 1–4 Weeks*	*Infant >4 Weeks*
Gestational LB exposure: Asymptomatic at birth, born to adequately treated mother[b]	None *or* Amoxicillin 40 mg/kg/day po TID × 10–30 d	None *or* Amoxicillin 50 mg/kg/day po TID × 10–30 d	None *or* Amoxicillin 50 mg/kg/day po TID × 10–30 d
Gestational LB exposure: Asymptomatic at birth, born to inadequately treated mother[c] *or* Early CLB: Symptomatic in first 2 weeks[c]	Ceftriaxone 50 mg/kg/day iv/im Q24hr × 14–30 d *or* Cefotaxime 100 mg/kg/day iv/im Q12 hr × 14–30 d	Ceftriaxone[d] 75 mg/kg/day iv/im Q24hr × 14–30 d *or* Cefotaxime[e] 150 mg/kg/day iv/im Q8hr × 14–30 d	Ceftriaxone 100 mg/kg/day iv/im Q12hr × 14–30 d *or* Cefotaxime 150 mg/kg/day iv/im Q8hr × 14–30 d
Late CLB: Symptomatic after first 2 weeks[c]		Ceftriaxone 75 mg/kg/day iv/im Q24hr × 14–42 d[f] *or* Cefotaxime 150 mg/kg/day iv/im Q8hr × 14–42 d[f]	Ceftriaxone 100 mg/kg/day iv/im Q12hr × 14–42 d[f] *or* Cefotaxime 150 mg/kg/day iv/im Q8hr × 14–42 d[f]

Recommendations are based on limited data, and lengths of therapy are not well established.
[a]Different age appropriate doses are shown, but treatment is recommended as soon as possible after birth.
[b]Because there is a wide range in what is considered adequate therapy, the alternative of oral amoxicillin therapy to be given pending further evaluation of the neonate for CLB is offered.
[c]Because ceftriaxone should not be used if hyperbilirubinemia is present, cefotaxime is offered as an alternative although clinical experience in therapy of Lyme borreliosis is not as extensive as with ceftriaxone.
[d]Ceftriaxone dose 50 mg/kg/day iv/im Q24hr if weight <2000 g.
[e]Cefotaxime dose 100 mg/kg/day iv/im Q12hr if weight <1200 g.
[f]Prolonged oral amoxicillin (40 mg/kg/day) after the course of iv antibiotic therapy may be considered depending on the clinical course of the infant.

disseminated Lyme borreliosis (Table 11–16), intravenous antibiotic therapy is preferred because of the failure of oral antibiotic therapy to reliably prevent the development of congenital Lyme borreliosis, including miscarriage, stillbirth and early or late congenital infection. The drugs of choice are ceftriaxone (2 g daily) and penicillin (24 million units daily) for 2 weeks. If antibiotic-induced gastroenteritis develops because of the ceftriaxone, either a change to penicillin or treatment of the diarrhea with oral vancomycin is indicated. The use of erythromycin for treatment of gestational Lyme borreliosis is to be discouraged unless no other options are possible, as it has been associated with failure to prevent congenital infection, but if used, it should probably be continued throughout the pregnancy until the week before delivery, when it should be discontinued to avoid neonatal hyperbilirubinemia. Although intravenous antibiotic therapy is preferable, if this is impossible, reasonable oral alternatives would be amoxicillin (500 mg four times daily) or possibly cefuroxime axetil (500 mg twice daily) for 3 to 4 weeks, and consideration should be given to continuation of treatment for the duration of pregnancy.

For treatment of severe gestational and nongestational early disseminated or chronic disseminated Lyme borreliosis (Table 11–16), 14- to 30-day courses of intravenous antibiotic therapy with either ceftriaxone 2 g (or 100 mg/kg per day for children) daily or penicillin 24 million units (or 300,000 units/kg per day for children) daily given every 4 hours are the regimens of choice. Current evidence supports ceftriaxone, or possibly cefotaxime, as the first-choice drug, as clinical efficacy has been greater than with penicillin, although there is less difference in efficacy when longer durations of antibiotic therapy are used. Although intravenous therapy is preferable, if this is impossible, alternatives include amoxicillin (500 mg three to four times daily) or cefuroxime axetil (500 mg three times daily, or 40 mg/kg daily for children) for 30 days or, for nonpregnant and nonlactating patients over 9 years of age, oral doxycycline 100 mg twice daily for 30 days. Although chloramphenicol was found to be effective, its general use cannot be advocated unless no other antibiotic alternatives are possible, and it should not be used in pregnant or lactating women.

Treatment of congenital Lyme borreliosis is summarized in Table 11–17, and antibiotic dosages and intervals vary according to the age of the infant to be treated. For treatment of asymptomatic infants born to mothers who had adequate treatment of their

pregestational or gestational Lyme borreliosis, no antibiotic therapy is necessary, although if there is any question of adequacy of maternal treament, the infant could be treated with oral amoxicillin for 10 to 30 days. If maternal Lyme borreliosis was inadequately treated, even an infant who is asymptomatic at birth may be at risk for congenital Lyme infection, and prompt antibiotic therapy should be started at birth with either intravenous cefotaxime or ceftriaxone for 2 to 4 weeks. If the infant is already symptomatic at birth, this indicates more severe infection, and prompt antibiotic therapy is essential and may be life-saving, and the longer duration of 4 weeks may be preferable because of concern regarding the risk of late chronic Lyme borreliosis with its associated developmental and neurologic deterioration. For the infant who either presents with or later develops signs of late congenital infection, intravenous therapy with ceftriaxone or cefotaxime for 4 to 6 weeks is recommended, and the longer duration is favored by the author.

Intravenous ceftriaxone or cefotaxime is preferred to penicillin for treatment of congenital Lyme borreliosis because of lower *B. burgdorferi* MICs, higher cure rates of late chronic Lyme borreliosis in older patients[377, 378] and some reports of possible clinical resistance of neuroborreliosis to penicillin therapy.[392, 393] If intravenous penicillin or ampicillin has been used rather than ceftriaxone or cefotaxime for initial therapy of congenital Lyme borreliosis because of treatment of an initially different diagnosis, and if there is no clinical improvement, the possibility of clinical resistance to penicillin should be considered and the patient should be changed to intravenous ceftriaxone or cefotaxime. This was done in one infant with severe early congenital infection (case 24 in Table 11–8) and resulted in dramatic clinical improvement.

If clinical relapse occurs after initial treatment of either gestational or congenital Lyme borreliosis, retreatment with a more aggressive antibiotic regimen such as a longer course of intravenous ceftriaxone or cefotaxime is indicated. Prolonged oral antibiotic therapy following this retreatment should be considered for either the duration of the pregnancy in gestational infection or, in the case of congenitally infected infants, until growth, developmental and neurologic assessment indicates maximal clinical improvement has been achieved.

Clinical studies of antibiotic prophylaxis for tick bites are discussed in the section on prophylaxis, and recommendations are given in Table 11–18. The author prefers to recommend gestational antibiotic prophylaxis of *B. burgdorferi* vector tick bites in endemic areas because of the established success of antibiotic therapy in prevention of Lyme borreliosis, and because some cases of congenital Lyme borreliosis have occurred in the absence of clinical symptoms of gestational Lyme borreliosis. Oral amoxicillin 500 mg three times daily for 10 days would be the first choice, and possible alternatives include cefuroxime axetil 500 mg twice daily or erythromycin 500 mg four times daily for 10 days. Antibiotic prophylaxis for tick bites of infants and children with histories of prior congenital Lyme borreliosis is also recommended because of concern that reinfection with *B. burgdorferi* may lead to unusual, possibly immunologically mediated, manifestations of infection. Antibiotic prophylaxis of tick bites of nonpregnant and noncongenitally infected individuals may be considered if the estimated risk of acquisition of Lyme borreliosis from the bite exceeds 1 per cent.

In general, with antibiotic therapy of early localized Lyme borreliosis, EM skin lesions begin to improve within 2 to 3 days and resolve within a week, and the mild associated flu-like symptoms improve within a few days and resolve within a few weeks. With antibiotic therapy of early disseminated Lyme borreliosis, the EM lesions also resolve within a week, and the flu-like symptoms and arthralgias improve within a few days but may take 6 to 8 months to resolve. Improvement is generally gradual in patients with chronic borreliosis who responded to antibiotic therapy. Subjective improvement usually becomes noticeable several weeks after start of antibiotic therapy, and objective improvement is seen months later.[86, 377, 378] Symptoms of arthritis improve within a few weeks and resolve by 3 months, and symptoms of neuroborreliosis, including neuropathies, show initial improvement within a few weeks but may take as long as 24 months to resolve.

Clinical relapses or treatment failures after therapy of any patients with Lyme borreliosis with established antibiotic therapy regimens should be retreated with longer, more aggressive regimens.

Empirical intravenous antibiotic therapy of patients with fatigue syndromes without convincing clinical and epidemiologic evidence of Lyme borreliosis is not advocated, whether or not they are Lyme seropositive.

Predictors of Antibiotic Therapy Cure

Cure rates following antibiotic therapy of Lyme borreliosis are generally highest for early localized, next highest for early disseminated and lowest for late chronic infection.

Reduction of *B. burgdorferi* antibody titers has been reported following successful antibiotic therapy,[379] but Lyme seropositivity or seronegativity is not always a reliable indicator of antibiotic cure.[99] Patients may be seronegative even though inade-

Table 11–18. ANTIBIOTIC PROPHYLAXIS OF *BORRELIA BURGDORFERI* VECTOR TICK BITES IN LYME ENDEMIC AREAS

Clinical Situation		Antibiotic Prophylaxis Recommended
Tick bite, pregnant woman	Asymptomatic	Yes, amoxicillin 500 mg po TID × 10–21 d[a,b]
	Symptomatic	No, full antibiotic therapy for active Lyme borreliosis instead, according to clinical stage of the infection
Tick bite, infant or child with history of congenital Lyme borreliosis	Asymptomatic	Yes, amoxicillin 50 mg/kg/day po TID × 10 d[c]
	Symptomatic	No, full antibiotic therapy for active Lyme borreliosis instead, according to clinical stage of the infection
Tick bite, nonpregnant and noncongenitally infected person	Asymptomatic	Possibly, if estimated risk of development of Lyme borreliosis is over 1%
	Symptomatic	No, full antibiotic therapy for active Lyme borreliosis instead, according to clinical stage

Data from references 89, 399, 400, 401, 425, 427 and 428.
[a]Possible alternatives are cefuroxime axetil 500 mg po BID × 10 d or erythromycin 500 mg po QID × 10 d, but the efficiency of these for prophylaxis has not been tested in large clinical trials.
[b]American College of Obstetricians and Gynecologists recommends 21 days.
[c]Possible alternatives are cefuroxime axetil 40 mg/kg/day po BID × 10 d or erythromycin 30 mg/kg/day po TID × 10 d.

quate antibiotic therapy may have failed to eradicate the infection because early antibiotic therapy aborts the development of the mature IgG antibody response to *B. burgdorferi* infection. Patients may be seropositive even though antibiotic therapy has successfully eradicated the infection if the antibiotic therapy was given later in infection, after the development of the mature IgG antibody has already developed. However, persistence of *B. burgdorferi*–specific IgM antibody beyond the first few weeks after onset of infection appears to correlate with increased severity and dissemination of the initial Lyme borreliosis and with the development of late complications such as meningoencephalitis, carditis or arthritis and could indicate the need for more aggressive antibiotic therapy.

Intra-articular or systemic steroid therapy of Lyme disease has been associated with an increased risk of dissemination, development of chronic complications such as persistent arthritis and meningitis and lack of responsiveness to antibiotic therapy, including high-dose penicillin or ceftriaxone.[124, 297, 376, 378, 405] The routine use of steroid therapy in the initial treatment of Lyme borreliosis is discouraged, except in patients with severe inflammatory processes such as severe carditis and arrhythmias unresponsive to initial antibiotic therapy, severe destructive encephalomyelitis with cerebral edema unresponsive to high-dose intravenous antibiotic therapy or severe arthritis refractory to high-dose intravenous antibiotic therapy.

Certain HLA types have been associated with late Lyme complications and with poor antibiotic therapy response, and others with good antibiotic therapy response. In 1990, Steere and colleagues[130] reported that 89 per cent of patients with long-duration chronic Lyme arthritis were HLA DR2 or DR4 positive compared with 27 per cent of patients with short-duration Lyme arthritis, and that HLA DR4 positivity but not DR2 positivity correlated with lack of response to antibiotic therapy. In another study in 1991, Halperin and colleagues[124] reported that 83 per cent of patients with disseminated Lyme multifocal leukoencephalomyelitis who responded well to antibiotic therapy were HLA DQw3 or DQw7 positive and DR4 negative, and patients who responded poorly or relapsed were DQw1 positive. An association has also been reported between HLA DR2 and DR4 positivity and Czechoslovakian meningopolyneuritis, and between DR2 and Austrian ACA and late encephalomyelitis.[130]

Prevention

Methods to reduce the risk of development of Lyme borreliosis include attempts at reducing the population density, geographic distribution and incidence of *B. burgdorferi* infection of the tick vectors and their animal hosts; development of animal and possibly human *B. burgdorferi* vaccines; use of personal protective clothing and other methods to reduce the risk of tick bite; and use of prophylactic antibiotic therapy for tick bites in endemic areas.

Tick Vector and Animal Reservoir/ Host Control Measures

The large mammalian hosts of the adult *Ixodes ricinus* complex ticks determine the geographic distribution and population density of the larval and adult stages of the tick vectors, while the small mammalian or other small reservoir hosts of *B. burgdorferi* determine the infection rate in the tick population.[182, 184, 406] In hyperendemic areas, almost all of the nymphs and reservoir mice may be infected.[406]

When deer are the only large mammalian host, as in hyperendemic coastal islands of the northeastern United States, elimination or reduction of the deer population results in reduction of the *I. dammini/scapularis* tick population and of the incidence of Lyme disease.[182, 406] When domestic animals such as cattle or sheep are the only large mammalian host, as in some endemic areas in Europe, pasture rotation results in reduction in the *I. ricinus* tick population and is more effective than acaricides.[182, 406]

Because ticks inhabit humid areas of dense vegetation, tick populations may be reduced by habitat control measures.[182, 198, 406] Methods such as springtime burning and mowing of brushy areas in the northeastern United States reduce the questing nymph population and therefore the subsequent adult tick population by 70 to 88 per cent for approximately 1 year, but the effects of such drastic measures on the risk of human Lyme disease are not known. Mowing of lawns reduces the adult tick population by 70 per cent but does not eliminate nymphal ticks in hyperendemic areas. Removal of leaf litter, underbrush and shrubs from the edges between lawns and forests, use of fences or dry border material between lawns and forests and use of deer-proof fencing have had some success in reducing tick populations if these measures are continued.

Chemical control of the tick population has been attempted using acaricides applied to small mammalian reservoirs, large mammalian hosts or the environment.[182, 198, 406] Acaricide treatment of deer was unsuccessful in reducing the number of ticks feeding on deer.[406] Acaricide applied to mice by distribution of permethrin-treated rodent nest materials in early spring killed the nymphs and in midsummer killed the larvae and led to a reduction in the tick population and rate of tick infection with *B. burgdorferi*, and an 82 per cent reduction in the incidence of Lyme disease.[406] This approach was successful in some areas because no other competent reservoirs were endemic and no other mouse bedding source was available.

Various acaricides, such as carbaryl, chlorpyrifos, diazinon, and cyfluthrin, have been applied to the environment in high-risk residential areas for immediate 97 to 100 per cent reduction of the *Ixodes* tick populations within 3 days, but these measures kill primarily the adult ticks exposed to the acaricide while questing on vegetation and not the larvae or nymphs, only temporarily reduce the tick population for up to 1 year and are most useful for treatment of well-maintained lawns and not for wooded areas.[182, 198, 406] Biologic tick attractants, such as *Ixodes* species pheromones, may be useful in the future to attract ticks to acaricide-containing traps.[182]

Biologic control of ticks has been attempted by introduction of a wasp species that lays eggs in *I. dammini* larvae into two northeastern coastal islands, but this was unsuccessful in one island and only reduced the *I. dammini* population by 50 per cent in the other.[182, 406]

The combination of annual environmental acaricide application in the fall and spring for adult tick control, provision of acaricide-treated rodent nest material in late spring and midsummer for nymphal and larval tick control and deer management methods for overall reduction of tick population density appears to achieve the best reduction in human risk of acquisition of Lyme disease in endemic areas of North America.[198]

Vaccine Development

Lyme disease is a major worldwide public health problem, and fear of acquisition of Lyme borreliosis has interfered with outdoor activities and led to loss of real estate value in hyperendemic regions.[419] Pets and domestic animals in endemic areas have also been affected by *B. burgdorferi* infection: dogs have developed arthritis,[410, 419] horses have developed arthritis and uveitis[417, 420] and cattle have developed arthritis and spontaneous abortion.[417] There is intense interest in development of a vaccine for both humans and domestic and household animals.[421]

Because elimination or reduction of animal reservoirs such as the white-footed mouse or deer is impractical, and elimination or reduction of the tick vectors by the environmental use of acaricides has been only minimally successful, the most promising way to control Lyme disease appears to be development of vaccines for wildlife, domestic animals and humans. The availability of various animal models of Lyme disease has made it possible to begin to do this.

Potential vaccine candidates are inactivated whole *B. burgdorferi* and various subunit antigens such as Osp A, Osp B and flagellin. Antibodies to flagellin develop early in human Lyme disease, and antibodies to Osp A and B develop later. Osp A is a major human vaccine candidate because there is almost complete DNA homology among North American and European strains and because both passive and oral or parenteral active immunization of mice with this has been successful in achieving protection against challenge infection.[413, 414, 422, 423] In addition, an unexpected finding in these mouse studies was destruction of infectious *B. burgdorferi* in infected ticks that fed on immunized mice, presumably because the ingestion of the antibody-containing blood meal inactivated the gut-associated spirochetes.[414]

A canine *B. burgdorferi* bactericin vaccine has been released by the U.S. Department of Agricul-

ture,[411] and additional vaccines for household and domestic animals are being developed. Many veterinarians in Lyme endemic areas recommend vaccination of dogs.

The use of an oral vaccine, such as purified Osp A, in the food supplies of reservoir animals such as mice and deer could potentially immunize these reservoirs, and the antibodies induced in these animals could potentially eradicate the spirochetes in the vector tick population that feeds on these reservoirs.[414, 421]

Although development of a human Lyme vaccine would be desirable, there are several unusual features of Lyme borreliosis that make caution important.[419] There may be genetically determined differences in immune response to *B. burgdorferi* infection, such as HLA differences, that may be involved in the pathogenesis of the clinical manifestations. There may be cross-reactivity of *B. burgdorferi* antibodies against human tissues such as synovia, heart, muscle and axons, and any human vaccine candidate should not induce cross-reactive antibodies to human tissues. Jarisch-Herxheimer reaction may release spirochetal products and trigger a severe inflammatory reaction. The duration of protective immunity may be short, and booster immunizations may be necessary.

Animal Models

Animal models of Lyme borreliosis have been of value in evaluation of vaccine efficacy. There are several animal models of *B. burgdorferi* infection: EM in rabbits[273]; arthritis in rats[407] and dogs[410]; and asymptomatic disseminated infection in gerbils[408] and hamsters.[37, 77, 409] The hamster model has been useful for active and passive immunization studies, and the dog model[410] has been used to develop a canine Lyme disease vaccine. Dogs immunized with whole inactivated *B. burgdorferi* developed neutralizing antibody, and immunoblot antibody directed against Osp A and B, and were protected against experimental infection, while unvaccinated dogs developed arthritis, fever and spirochetemia after challenge.[411]

B. burgdorferi also causes arthritis and carditis in mice,[412] and this model has been useful for testing potential vaccine candidates, including Osp A, Osp B and flagellin.[413] In this model, Osp A appeared to induce the major protective antibody,[413] which even resulted in destruction of the *B. burgdorferi* in vector ticks fed on the immunized mice, probably because of ingestion of neutralizing antibody by the ticks during feeding.[414]

No transplacental transmission has been found in the mouse[415] or rat[416] models, but *B. burgdorferi* causes arthritis and spontaneous abortion in horses and cows, and transplacental infection has been demonstrated in one aborted calf and one newborn calf.[417] A closely related species, *Borrelia coriaceae*, transmitted by the soft tick *Ornithodoros coriaceus*, has been suspected to be the cause of epizootic bovine abortion in California.[418]

Methods for Individual Protection Against Tick Bites

One of the most important methods of protection against development of Lyme borreliosis is avoidance of exposure to tick-infested endemic areas during the seasons of maximal tick feeding activity,[17, 182, 406] and this is strongly recommended during pregnancy, but if such exposure is unavoidable, as is the case with individuals who live in endemic areas, there are additional precautions that are recommended.

It is best to remain on trails and avoid tall grass and brushy areas. Hats and light-colored, long-sleeved, long-legged, smooth fabric clothing, with pants tucked into socks and shirts tucked into pants, will reduce the risk of tick attachment. Clothing, shoes and socks, but not skin, may be sprayed with chemical tick repellents, such as *N*-diethyl-toluamide (deet) or permethrin, that discourage ticks from adhering to clothing. Tick repellents containing 0.5 per cent permethrin are 100 per cent protective, and mosquito repellents containing 30 per cent deet are 92 per cent protective against all stages of Lyme disease vector ticks.[424] However, these may be toxic or teratogenic and there is concern regarding their use in pregnant women, and one report urges use of deet in pregnancy only if clearly indicated.[399]

Prompt and proper tick removal reduces the risk of transmission of the spirochete because *B. burgdorferi* is transmitted most often on the third day of feeding.[145, 146, 406] Frequent inspection every few hours for tick attachment and immediate tick removal are recommended during exposure to tick-infested areas.[182, 406] Shower, shampoo and total body tick checks are recommended on return from tick-infested areas, and also 1 to 2 days later, as small nymphal or larval ticks may be detected more easily after they engorge. Clothing worn into tick-infested endemic areas should be placed into sealed plastic bags until washed in hot water, and cars and camping equipment should be inspected for ticks that may be seeking hosts.

Needham[272] evaluated several methods of removal of both hard (Ixodid) and soft (Argasid) ticks and found that the best method for complete removal of the tick intact was to grasp it near the skin surface with forceps or protected fingers and pull steadily

upward without squeezing, puncturing or crushing the tick, and without twisting or jerking so that the mouth parts do not break off. It is important to also remove the latex-like cement secreted by the tick around the attachment site. The bite site should be disinfected afterwards, and the tick disposed of in alcohol or saved in an airtight container with a moist cotton-tipped swab if analysis for presence of *B. burgdorferi* is desired. The tick may continue to salivate for several minutes after removal, so care must be taken to avoid direct contact with this potentially infectious fluid.

The body site location of any tick bite should be noted, the site observed for 1 month and prompt antibiotic therapy instituted if any evidence of EM or other illness consistent with Lyme borreliosis develops. In some geographic areas, and particularly for tick bites in pregnancy, antibiotic prophylaxis is indicated and is reviewed in the following section.

It is advisable to keep pets away from endemic tick-infested areas if possible, but if this is unavoidable, they should be checked for ticks and the ticks removed before allowing the pets into the home. Gloves and tweezers should always be used for removal of ticks from pets.

Antibiotic Prophylaxis of Tick Bites in Pregnant and Nonpregnant Patients

For nonpregnant patients, there is controversy over whether antibiotic prophylaxis is indicated for tick bites in Lyme endemic areas, and the risks and benefits of both prophylaxis and no prophylaxis should be weighed. Several reports discuss the pros and cons of prophylaxis.[425–428] For pregnant patients, many groups,[89, 399, 401] including the American College of Obstetricians and Gynecologists,[400] recommend antibiotic prophylaxis, while others recommend against it.[73, 402]

A practical approach taken by many physicians practicing in Lyme endemic areas of North America is to either routinely recommend penicillin prophylaxis during the entire tick feeding season for residents of hyperendemic communities, or institute antibiotic therapy at the first sign of either a Lyme vector tick bite or any illness potentially consistent with Lyme disease; a more conservative approach recommended by many researchers studying the epidemiology of the disease is to treat the infection if it develops.[406, 426]

In a small double-blind placebo-controlled trial of penicillin prophylaxis of *I. dammini* tick bites, excluding pregnant women, in a Lyme endemic area of Connecticut in 1989, Costello, Steere and colleagues[425] reported development of Lyme disease in 1 of 29 untreated patients and none of 27 treated patients, but also noted that the rate of complications from prophylaxis equaled the rate of acquisition of Lyme disease in unprophylaxed patients. They concluded that the study population was too small to allow general recommendations to be made.

In 1992, Shapiro and colleagues[428] reported a large double-blind placebo-controlled study of amoxicillin prophylaxis of *I. dammini* tick bites in a Lyme endemic area of Connecticut, excluding pregnant women, and found that 2 of 173 untreated and none of 192 treated patients developed Lyme disease, and there was no asymptomatic seroconversion within the 1-year follow-up period. The risk of development of Lyme disease after an unprophylaxed bite by a tick confirmed to be infected was 4 to 8 per cent, and 0 per cent after a prophylaxed bite. However, because they found no asymptomatic seroconversion, these investigators recommended against routine tick bite prophylaxis and preferred to treat only when Lyme disease developed.

In 1992, Magid and colleagues[427] used a statistical method, decision analysis, to estimate the cost effectiveness of doxycycline prophylaxis of *B. burgdorferi* vector tick bites in Lyme endemic areas, excluding children and pregnant and lactating women, and recommended empirical antibiotic prophylaxis of bites in areas where the risk of acquiring Lyme disease after a bite is greater than 3.6 per cent, and consideration of prophylaxis if the risk is over 1 per cent. Because the risk of acqusition of *B. burgdorferi* infection following a bite by a definitely infected tick is approximately 10 per cent, prophylaxis is recommended in areas where the tick infection rate is 10 per cent or greater, such as after *I. dammini/scapularis* bites in the northeastern, mid Atlantic and upper midwestern states, where the tick infection rate is high, but not in the Pacific Northwest, where the *I. pacificus* tick infection rate is only 1 to 2 per cent.

Data regarding risk of infection after single tick bites suggest that it is reasonable to use antibiotic prophylaxis for single tick bites if the chance of development of Lyme disease is over 1 per cent in nonpregnant individuals (see Table 11–18). There are several factors that should be considered in making this decision. The risk of development of Lyme borreliosis increases if the species of tick is a known *B. burgdorferi* vector *(I. dammini/scapularis, pacificus, ricinus, persulcatus)*, if it is a nymphal or adult rather than a larval tick, if the *B. burgdorferi* infection rate in the endemic tick vector population is over 10 per cent, if the duration of tick attachment prior to removal is over 48 to 72 hours or if the tick is engorged and if the method of tick removal used was likely to have caused injection of tick contents into the bite site. In addition, if the likelihood of good patient follow-up is low, and therefore ade-

quate treatment of Lyme disease, if it were to develop, would be impossible, it is advisable to use antibiotic prophylaxis for the bite at the time the patient seeks medical attention. If patient anxiety is high, and if there are significant concerns about the potential risk of development of late chronic Lyme borreliosis without the initial EM lesion, it would also be reasonable to use prophylaxis.

In pregnant women, antibiotic prophylaxis of all *B. burgdorferi* vector tick bites in known endemic areas is indicated (see Table 11–18) because of the potential risk of congenital Lyme borreliosis following maternal gestational Lyme borreliosis. In lactating women, antibiotic prophylaxis is also recommended because insufficient data are so far available regarding the potential risk of transmission to the infant by nursing. The antibiotic regimen of choice is amoxicillin 500 mg by mouth three times daily for at least 10 days, and acute and convalescent sera are indicated if there is any suspicion that asymptomatic infection has occurred following the bite. In penicillin allergic patients, Ceftin 500 mg orally twice a day (if the patient has no cross-reacting hypersensitivity) or erythromycin 500 mg orally four times daily for at least 10 days may be used. Doxycycline or tetracycline should not be used in pregnant or lactating women.

No data exist regarding whether antibiotic therapy should be given for tick bite prophylaxis of congenitally infected infants or children because so few of these infants have been recognized. Because some of the chronic complications of Lyme borreliosis may be immunologicaly mediated and the immune response of congenitally infected infants to future *B. burgdorferi* infection is unknown, the author currently favors use of antibiotic prophylaxis, although these recommendations may change as further data become available (see Table 11–18).

Prognosis

Data indicate that the prognosis of gestational Lyme borreliosis is good if the infection is promptly recognized and treated aggressively with antibiotic therapy aimed at crossing the placental barrier. The prognosis is unknown in gestational Lyme borreliosis that lacks the typical history of tick bite followed by EM or other symptoms that lead to its recognition, and it is uncertain how many episodes of gestational toxemia, spontaneous miscarriage, spontaneous abortion, stillbirth, culture-negative neonatal sepsis, failure to thrive, congenital heart disease or sudden infant death syndrome may be due to unrecognized gestational Lyme borreliosis. Determination of the true risk to the fetus and infant of maternal gestational Lyme disease will require better diagnosis of Lyme disease in the affected fetuses, placentas and infants.

The prognosis for immediate survival of infants who present with fulminant early congenital Lyme borreliosis depends on the recognition of the disease and institution of prompt aggressive intravenous antibiotic therapy appropriate for *B. burgdorferi* sepsis, as discussed in the section Therapy. It should be stressed that maximal supportive management alone, including supportive measures for management of severe septic shock and respiratory distress, without appropriate antibiotic therapy is not sufficient and may result in death of the infant.

The prognosis of infants who present with late congenital Lyme borreliosis depends on the extent of the cardiac, neurologic or other damage already present at the time of diagnosis and institution of appropriate antibiotic therapy. It is the author's opinion that aggressive intravenous antibiotic therapy initially, followed by prolonged oral antibiotic therapy, as discussed in the section Therapy, should at least prevent further clinical deterioration and may even lead to eventual improvement in any reversible damage.

Because long-term chronicity of Lyme borreliosis with persistence of spirochetes in immunologically protected sites has been reported in older patients, because it is not known whether fetally acquired *B. burgdorferi* infection may result in similar persistence of the organism in some immunologically protected site and because the effect of this fetally acquired infection on the way a congenitally infected infant will respond to future *B. burgdorferi* infection is unknown, any evidence of clinical deterioration, particularly in growth and development, hearing or neurologic status, should be closely re-evaluated for the possible relation to *B. burgdorferi* relapse or reinfection. If the deterioration is considered to be due to *B. burgdorferi* infection, aggressive antibiotic therapy should be instituted in order to prevent future clinical deterioration, as reviewed in the sections Diagnosis and Differential Diagnosis, and Therapy.

Because there are insufficient data to allow prognostic predictions of long-term outcome of infants treated for early or late congenital Lyme borreliosis, close follow-up is required for these infants and should include at least pediatric neurology, ophthalmology, otolaryngology and infectious disease evaluations. Other specialties such as pediatric cardiology, cardiac surgery, gastroenterology, orthopedics or rheumatology may be indicated, depending on the extent of involvement of these systems.

The index of suspicion should be high that any illness consistent with the late chronic manifestations of Lyme borreliosis reported in older patients may also theoretically occur in the congenitally in-

fected infant. It will continue to be most important to recognize, treat and evaluate infants with suspected congenital Lyme borreliosis in order for a more complete description of the syndrome to evolve.

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