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Lyme disease, or Lyme borreliosis, is a tickborne zoonosis of both children and adults caused by the spirochete Borrelia burgdorferi. It has a worldwide geographic distribution and has been reported from more than 40 countries and 6 continents; the geographic distribution and number of cases reported continue to increase (Figs. 11-1 and 11-2). It is now the most common tickborne infection in the United States, where 16,800 cases were reported to the Centers for Disease Control and Prevention (CDC) in 1998 (Fig. 11-3); in Europe, where 2100 cases were reported to the European Union Concerted Action of Risk Assessment in Lyme Borreliosis (EUCALIB) in 1994, and more than 60,000 cases were estimated to occur annually as of 1998; and possibly in the world. Lyme borreliosis is a fairly recently recognized infection, although erythema migrans (EM), the characteristic skin lesion of early Lyme borreliosis, was first described in a Swedish woman in 1909 by Afdellis, who proposed that it was related to a zoonosis transmitted by a tick bite. In 1975, Steere and associates recognized an outbreak of infectious arthritis and unusual rash similar to European EM in Old Lyme, Connecticut; they proposed that transmission occurred via an arthropod vector and named the disease Lyme arthritis. Eventually, it was found to be associated with ixodid tick bites and later, when its multisystem involvement was recognized, became known as Lyme disease.

In 1981, Burgdorfer and colleagues discovered a new species of Borrelia in Ixodes ticks associated with Lyme disease, and this became known as Borrelia burgdorferi. This spirochete was found to be the causative agent of North American Lyme disease and of European EM, as well as other European syndromes such as acrodermatitis chronic atrophicans (ACA), Banwarth's syndrome, and lymphadenitis benigna cutis; 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 23 and 50 degrees North latitude in the Western Hemisphere; there may also be a belt developing between 30 and 40 degrees South latitude in the Eastern Hemisphere. This is reminiscent of the "Malaria Belt," which has been defined by climatic conditions and the distribution of another major arthropod vector of human disease, the Anopheles mosquito.
LYME DISEASE

COUNTRIES IN EUROPE FROM WHICH LYME DISEASE HAS BEEN REPORTED

FIGURE 11–1 A, The geographic distribution of Lyme borreliosis in Europe. Europe is the main area outside North America from which Lyme borreliosis has been reported. This map shows European countries from which cases of Lyme borreliosis have been reported either to the World Health Organization,201 to the European Union Concerted Action on Risk Assessment in Lyme Borreliosis,202 or in the medical literature.203 Reliable statistics on incidence by country are not available, as reporting of cases is voluntary in most countries. The highest incidences (either 1000–20,000 cases/country or 15–140 cases/100,000 population annually) of European Lyme borreliosis have been reported from Austria, Slovenia, Poland, Sweden, Bulgaria, Denmark, Hungary, the Netherlands, Finland, the Czech Republic, Switzerland, Germany, Italy, and France; lower incidences (either <500 cases/country, or <5 cases/100,000 population annually) have been reported from Belgium, Croatia, Estonia, Greece, Ireland, Latvia, Lithuania, Luxembourg, Moldavia, Norway, Romania, Russia, Spain, the United Kingdom, and the former Yugoslavia.

Illustration continued on following page

Lyme borreliosis is a multisystem infection that initially emerged as a new “great imitator” because of the diversity of its clinical presentations, which comprise both early and late stages and include dermatologic, cardiac, neurologic, arthritic, and ocular manifestations.21 However, more than 20 years since its recognition as a new disease,14 the spectrum of its clinical manifestations has been extensively characterized, resulting in gradual loss of this reputation.24 The existence of congenital borreliosis was suspected because of clinical similarities between the two spirochetes Lyme borreliosis and the classic “great imitator” syphilis,99 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 and co-workers.25 As the number of reported cases of Lyme disease continues to increase, there have been increasing reports of gestational Lyme disease associated with adverse outcomes and suspected congenital Lyme borreliosis.26–60 Although a homogeneous congenital Lyme borreliosis syndrome has not yet emerged, there are several features that are common among the 66 adverse outcomes of pregnancies complicated by gestational Lyme borreliosis reviewed later in this chapter (including miscarriage during the
first 20 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, dental, and skeletal involvement).

THE ORGANISM

*Borrelia* organisms are arthropod-borne spirochetes that infect birds, domestic and wild animals, and humans.\(^\text{39,37}\) It is now recognized that *B. burgdorferi* is a phenotypically and genotypically heterogeneous genospecies complex, and the name has been modified to *Borrelia burgdorferi sensu lato* to reflect this. There are several genospecies of *Borrelia burgdorferi sensu lato*: *Borrelia burgdorferi sensu stricto*, *Borrelia andersonii*, *Borrelia garinii*, *Borrelia afzelii*, *Borrelia valaisiana*, *Borrelia lusitaniae*, *Borrelia japonica*, *Borrelia turicata*, and several genetically distinct genomic groups that have not yet achieved genospecies status.\(^\text{31-71, 86-84}\) *B. burgdorferi sensu stricto*, *garinii*, and *afzelii* have been associated with human Lyme borreliosis;\(^\text{39}\) *B. valaisiana* DNA has been found in EM lesions of two patients by polymerase chain reaction (PCR);\(^\text{32}\) and strains similar to strain 25015 in
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 1998. 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, and (C) 1998. National surveillance began in 1982, and Lyme disease became a notifiable disease in 1990. Cases of Lyme disease have also been reported to the Canadian Laboratory Centre for Disease Control (LCDC), mostly from southern areas that border Lyme-endemic areas of the northeastern, upper midwestern, and northwestern United States. Illustration continued on following page
genomic group DN127 occasionally have been associated with Lyme disease.83, 85 The other genospecies are involved in enzootic cycles of maintenance of *B. burgdorferi* in nature, but have not yet been isolated from patients with Lyme borreliosis.55, 56 There is a newly described uncultivable *Borrelia* species, *Borrelia lonestarii*, which has been found in the Lone Star tick, *Amblyomma americanum*, and may be associated with Lyme-like disease in the southern United States.73 Certain genospecies have been associated more frequently with certain clinical manifestations.16, 74-76 *B. lonestarii* and a new species, *Borrelia miyamotoi*, may be more closely related to the relapsing fever *borreliae* than to *B. burgdorferi sensu lato*.75, 77

**Borrelia burgdorferi** as the Etiologic Agent of Lyme Borreliosis

In 1981, Burgdorfer and associates discovered (isolated) a new species of *Borrelia* in *Ixodes dammini* (later renamed *Ixodes scapularis*) 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, 17

In 1982, Berger and colleagues demonstrated rare spirochetes, similar to the *I. dammini* (scapularis) spirochete, by Warthin-Starry silver stain in skin biopsy specimens of untreated patients with EM skin lesions; they were able to isolate spirochetes from one specimen, thus supporting a spirochetal etiology for EM.29 In 1985, Berger and co-workers grew the *I. dammini* (scapularis) spirochete from several skin biopsy specimens of EM lesions26 and thus confirmed this spirochete as the etiologic agent of North American EM.

In 1983, Steere and associates 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* (scapularis) ticks in a Lyme-endemic area of Connecticut; they
demonstrated serum IgM and IgG antibody titer increases in these patients directed against this spirochete. Simultaneously in 1983, Benach and colleagues isolated the same spirochete from the blood of patients with American Lyme disease and demonstrated similar seropositivity in these patients. Both groups proposed the *I. dammini* (scapularis) spirochete as the etiologic agent of Lyme disease. In the same year, Barbour and co-workers, including Burgdorfer, isolated a new spirochete, similar to the *I. dammini* (scapularis) spirochete, from *Ixodes ricinus* ticks from an EM-endemic area of Switzerland.

Ryberg and associates, 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); they proposed the Lyme disease spirochete as the etiologic agent of Bannwarth's syndrome.

In 1984 and 1985, Asbrink, Hovmark, and colleagues isolated the *I. ricinus* spirochete from skin biopsy specimens of European patients with EM, chronic atrophic tonsillar lesions, and lymphadenosis benigna cutis; antibody titer elevations against this spirochete were demonstrated in these patients, thus confirming the spirochetal etiology of these European skin diseases. In 1987, de Koning and co-workers demonstrated spirochetes, morphologically consistent with *B. burgdorferi*, 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.

Some genospecies, such as *B. burgdorferi sensu stricto*, *garinii*, and *afzelii*, have been associated with human Lyme borreliosis, and others, such as *B. japonica*, only with tick vectors and reservoir hosts but not yet with human disease. A *vaalwaisana* DNA has been found in EM lesions of two patients by PCR; *B. burgdorferi sensu lato* isolates similar to strain 25015 of group DN127 were found in the cerebrospinal fluid (CSF) and EM of nine Slovenian patients; and *B. burgdorferi* genospecies DN127 was isolated from one patient with borrelial lymphocytoma. There is clustering of genospecies from patients with different clinical manifestations, such as EM, ACA, neuroborreliosis, arthritis, and carditis, which suggests the possibility of differences in pathogenicity and organotropism of strains of different phenotypes and genotypes, which may be related to differences in clinical syndromes associated with these strains.

In North America, where ACA does not occur, *B. burgdorferi sensu stricto* is the only agent of human Lyme disease, and is associated with all North American manifestations of Lyme disease, EM, neuroborreliosis, arthritis, and carditis. In Europe, ACA is associated predominantly with *B. afzelii*, and occasionally with *garinii* or *sensu stricto*; EM with all three genospecies (*B. burgdorferi sensu stricto*, *garinii*, *afzelii*); neuroborreliosis predominantly but not exclusively with *B. garinii*; arthritis predominantly with *sensu stricto* and sometimes with *garinii*; and carditis with *sensu stricto* and occasionally with *garinii*.

Within genospecies, there may be strains that are more pathogenic than others, as may be involved in the clustering of strains isolated from European patients with disseminated Lyme borreliosis in one sub-branch of *B. garinii*, the clustering of *B. garinii* strains associated with adult neuroborreliosis in Osp A serotype 4, and the clustering of *garinii* associated with pediatric neuroborreliosis in Osp A serotype 6.

A large study by the EUCLAB, of over 2000 patients with Lyme borreliosis in 15 European countries during 12 months in 1994, found that the incidence of Lyme borreliosis per 100,000 population increased from Western to Eastern Europe, with higher incidences east of the Netherlands, France, and Italy.

**Morphology**

*Borrelia burgdorferi* is a long (10 to 30 micrometers in length), narrow (0.18 to 0.25 micrometer in diameter), irregularly and loosely coiled, helical, motile, flexible spirochete with tapered ends and sheathed flagellae.

It has an inner and an outer cell membrane and four to eight flagella, located in the periplasmic space between the inner and outer trilaminar cell membranes. These membranes, which are inserted at each end and extend toward the middle of the spirochete, allow it to move efficiently through viscous solutions and presumably enhance its ability to disseminate in body tissues. The trilaminar outer membrane structure is similar to, but more fluid than, that of gram-negative bacteria, and it contains the embedded outer surface membrane lipoproteins and a lipopolysaccharide with weak endotoxin-like activity. The flexible cell wall is located just outside the cytoplasmic membrane. In addition to the typical *B. burgdorferi* morphology, morphologic variants have been found in tissue biopsies.

**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 polyvalent and monoclonal antibodies. The 83- to 100-kilodalton (kd) antigen p83/100 is *Borrelia* genus-specific, cross reacts minimally with other bacteria, is associated with either the flagella or the periplasmic cylinder, and is a chromosomally encoded immunodominant antigen of *B. burgdorferi sensu lato*, which has minor homology with the muscle and cytoskeletal proteins myosin and troponin, and contains an amino acid sequence that is a common cell recognition signal of integrins and may be involved in spirochetal attachment to cells. The constant-molecular weight, major immunodominant 60-kd common antigen HSP60, and the 70-kd antigen HSP70 are heat shock proteins that function as flagellin chaperones, are encoded by chromosomal genes, and cross react broadly with other bacteria. The 35-kd protein, a *B.
B. burgdorferi sensu lato—specific lipoprotein encoded by a chromosomal gene, is expressed early in human infection and is an important immunodominant marker for early human infection. There are several other significant antigens, including the 39-kd molecular weight protein, some encoded by chromosomal and some by plasmid genes.

The 41-kd flagellar antigen p41 is the other major protein of the organism; it has a uniform molecular weight in all B. burgdorferi strains. is encoded by a highly conserved gene (with 96–97% sequence homology between strains) located on the main chromosome, and is the antigen most often recognized in Lyme borreliosis patient sera. B. burgdorferi flagellin has an epitope that shares amino acid homology with the N-terminal amino acid sequences of human chaperonin, a 60-kd heat shock protein, and has some cross-reactivity with other spirochetes.

B. burgdorferi has several major outer surface lipoproteins—Osp A, Osp B, Osp C, Osp D, Osp E, and pG—that are encoded by plasmids. The 18-kd EppA protein (exported plasmid protein A) is thought to be either an outer membrane or a secreted protein. Osp A has the least variability and the greatest homology (77–83%) of the three major B. burgdorferi genospecies; Osp B has high variability; and Osp C has the highest variability and exhibits polymorphism of its amino acid sequences and Osp C–encoding gene sequences. Osp C is expressed early in infection, and, despite this heterogeneity, the three major genospecies have common as well as genospecies-specific Osp C immunogenic epitopes recognized by patient sera. Osp A has an immunodominant epitope that shares amino acid sequence homology and encoding DNA sequence homology with human leukocyte function-associated antigen-1 (LFA-1), which is a candidate arthritogenic autoantigen that may be involved in the immunopathogenesis of Lyme arthritis.

The smaller, variable-molecular-weight outer surface membrane lipoproteins of B. burgdorferi are species-specific, and antigenic modulation, variation in size, antigenicity, and expression of these outer surface proteins have been found. In 1998, Kawabata and associates reported that B. burgdorferi sensu stricto strain 297 has VMP-like proteins coded by VMP-like sequences (Vls) located in multiple copies on the 20 kilobase pair plasmid. In 1997, Zhang and colleagues described a system in B. burgdorferi sensu stricto strain B31 that produces extensive antigenic variability in a surface lipoprotein. B. burgdorferi Vls is expressed in patients with Lyme borreliosis, and the system of antigenic variability may enhance evasion of the host immune response.

B. burgdorferi also has nonprotein antigens, composed of lipid–carbohydrate–, and phosphorus-containing compounds, which react with Lyme disease patient sera but are of unknown significance.

The genome of B. burgdorferi has been sequenced. B. burgdorferi sensu stricto strain B31 has a large linear chromosome of 910,725 base pairs (about 900 kbp) and at least 17 plasmids (10 linear plasmids ranging in size from 17 to 56 kbp, and 7 circular plasmids ranging from 9 to 32 kbp) with a combined total of 533,000 base pairs (about 500 kbp) of double-stranded DNA with an average G plus C content of 28.6%. The linear chromosome has been sequenced and contains 853 genes that encode proteins needed for DNA replication, transcription, translation, energy metabolism, and solute transport, but not for cellular biosynthesis. Eleven of the plasmids (ranging from about 9 to 54 kbp in size), containing 450 genes, have been sequenced. The functions of most of these genes are unknown, but they may be involved in antigenic variation and immune evasion; some, such as the 53- to 58-kbp linear plasmid in B. burgdorferi sensu stricto, garvini, and afzellii, and the 90- to 105-kbp linear plasmid in B. japonica, encode outer surface proteins A and B. Others, such as the 26- to 27-kbp circular plasmid, encode Osp C. Fifty-nine percent of the chromosomal genes have known biologic roles, 12% match genes in other organisms with unknown roles, and 29% are new genes; these percentages for plasmid genes are 16, 26, and 38, respectively.

Almost all of the membrane proteins of B. burgdorferi are lipoproteins, and 8% of its genes encode 105 putative lipoproteins, which is a much greater percentage than occurs with most other bacteria; six percent of the genes encode proteins involved in spirochetal motility and chemotaxis.

Although North American and European B. burgdorferi sensu stricto isolates tend to cluster into separate subbranches by DNA analysis, there are genetic similarities between some isolates from the two continents, suggesting some previous interchange of strains between the two continents.

Among the different genospecies, there are differences in the number, size, and sequences of the linear and circular plasmids, as well as their presence or absence, which correlate with the expression of the outer surface proteins they encode. The Osp A- and Osp B-encoding linear plasmid is present in all B. burgdorferi sensu lato genospecies (although some individual isolates may lack the Osp B gene, and this plasmid may be lost in culture). Almost all North American and European strains express Osp A and it shows the least antigenic variability between genospecies; Osp A serotyping has been used to divide B. burgdorferi sensu lato into different phenotypes, which correlate with different genotypes by Osp A gene sequencing. The Osp C gene is located on a 26-kbp circular plasmid that is present in all genospecies, but its expression, both qualitatively and quantitatively, is variable; most European strains express Osp C, but Osp C has been found to be cryptic in North American strains, where it is expressed only in strains that have lost all plasmids other than the Osp C-encoding and Osp AB-encoding plasmids. The Osp D gene is highly conserved and is present in 24, 30, and 90%, respectively, of isolates of B. burgdorferi sensu stricto, afzellii, and garvini; its encoding plasmid has significant size variability, ranging from 36 to 40 kbp, and contains varying numbers of copies of a 17-kbp repeating sequence bordering a variable region with evidence of homologous recombinational events. The Osp E and Osp F genes are located in tandem on the
45-kbp linear plasmid. The pG gene is located on a 48-kbp linear plasmid that has some sequence homology to the Osp EF gene and is detectable in most strains of B. burgdorferi sensu stricto and B. afzelii, but not in B. garinii or B. japonica. There is p83/100 gene heterogeneity in B. garinii, but not in either B. burgdorferi sensu stricto or B. afzelii; B. garinii strains could be separated into two major subtypes on the basis of p83/100 gene sequence variation, one corresponding to Osp A serotype 4 and the other to serotypes 3, 5, 6, and 7. The EppA protein gene is located on the 9-kbp circular plasmid, and loss of this plasmid has been associated with loss of virulence during passage of B. burgdorferi in culture.

It has been proposed that the high level of variability of Osp C and D and the existence of a VMP-like system may be involved in immune evasion by B. burgdorferi. Evasion of the immune response by a B. burgdorferi strain expressing a truncated Osp B also raised this as a possible immune escape mechanism. Differential gene expression, which has been found in B. burgdorferi, has also been suspected to be involved in infectivity, invasion, and dissemination, and in evasion of the host immune response to the infection; it may also have a role in differential organotropism. Abundant Osp A and Osp B, and no Osp C, are expressed by B. burgdorferi in unfed tick midguts. The beginning of tick feeding and the arrival of the blood meal in the tick midgut trigger downregulation of Osp A and B, and upregulation of Osp C expression of B. burgdorferi in the engorged tick midgut. Although Osp A and B are not expressed initially after infection, they are eventually expressed, in particular in patients with chronic Lyme arthritis. Although Osp E and Osp F are expressed by B. burgdorferi in ticks and in the mammalian host, it appears that the Osp E and F homologues, the Erp proteins (Osp EF-related proteins), form a gene group that is differentially expressed at different stages of the spirochete’s life cycle; the Osp E homologue, p21, which has 70% amino acid homology with Osp E, and the Osp F homologues, pG, bb210, and bb211, are expressed only in the mammalian host and not in the spirochete in culture or in ticks.

Expression of p21 does not occur even in engorged ticks, only in the mammalian host; antibody to p21 is found in 28 to 33% of patients with early or late Lyme disease, including Lyme arthritis, indicating its expression during Lyme disease. Confirmation of differential gene expression during Lyme disease was first reported in 1998, when p35 (the 35-kd protein) and p37 (the 37-kd protein) messenger RNA (mRNA), but not Osp A mRNA, was found in EM skin biopsies and Lyme arthritis synovium, consistent with upregulation of p35 and p37 and the downregulation of Osp A. The protein EppA (exported plasmid protein A) is downregulated at the transcriptional level in cultured B. burgdorferi, is expressed only in the mammalian host, and is associated with virulent strains of B. burgdorferi. Temperature increases, as occur with ingestion of the blood meal by the tick, and even increases in culture temperature from 23°C to 35°C, induce downregulation of Osp A expression, and upregulation of Osp C, Osp E, Osp F, and of the Osp EF homologues, the Erp proteins. As Osp A is downregulated and disappears, the spirochete becomes resistant to antibody against Osp A; this is important in vaccine development, as is discussed in the section Prevention: Vaccine Development.

B. burgdorferi produces none of its own proteolytic enzymes. It acquires a host-derived activated proteolytic complex consisting of plasmin, plasminogen, and aurokinase-type plasminogen activator, which arrives at the tick midgut in the blood meal, binds to Osp A while it is still expressed, and coats the spirochete; this complex is presumably able to dissolve extracellular matrix, facilitate dissemination of the spirochete to the tick salivary glands for transmission to the host, and then enhance spirochete dissemination in host tissues, where the host-derived antigens cause the spirochete to be invisible immunologically to the host. Surface antigens of B. burgdorferi, particularly Osp A, are also involved in binding of the spirochete to collagen fibers, vascular endothelium, and other cells, including antigen-presenting cells, and in triggering a variety of events in host cells, ranging from expression of adhesion molecules to production of cytokines and other factors involved in the immunopathogenesis of the infection, as is discussed in the section Pathology and Pathogenesis.

Some antigens of B. burgdorferi have epitopes that share homology and cross react with host epitopes, leading to molecular mimicry, such as B. burgdorferi Osp A and human leukocyte function-associated antigen-1 (LFA-1), and possibly p83/100 and the human muscle and cytoskeletal proteins myosin and troponin. B. burgdorferi flagellin, and human axonal heat shock protein 60. This is discussed further in the sections Pathology and Pathogenesis, and Interactions with the Immune System: Correlation of Clinical Manifestations with HLA Type.

Taxonomy

Borrelia burgdorferi, the etiologic agent of Lyme borreliosis, is a member of the order Spirochaetales, the family Spirochaetaceae, the genus Borrelia, and the species B. burgdorferi. Borreliae are more closely related genetically to Spirochaeta than to Treponema, and all borreliae are transmitted by arthropods.

B. burgdorferi was initially divided into four phenotypes, and later into eight serotypes on the basis of antigenic diversity of Osp A as determined by reactivity with various monoclonal antibodies and by Osp A gene sequencing. It was also initially divided into three genotype subspecies, based on DNA homology and ribosomal RNA restriction endonuclease pattern analysis, and corresponding to phenotypes based on major protein antigenicity, with 76 to 100% DNA homology within groups, and 46 to 74% between groups.

As more isolates of B. burgdorferi have been studied by various methods, it has become clear that B. burgdorferi has phenotypic and genotypic heterogeneity. On the basis of phenotypic and genotypic differences from

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*See references 13, 51–66, 68, 70, 100, 105, 115, 117, 123, and 884.
B. burgdorferi sensu stricto and from each other, further subdivision into additional subbranches was done, dendrograms of genetic relatedness were constructed, and some of the subbranches were designated as new genospecies—Borrelia garinii (formerly 20047), B. afzelii (formerly VS461), B. andersonii (includes former groups 21038 and 21123), B. valaisiana (formerly VS116 and M19), B. lusitaniae (formerly PotiB2), B. japonica (formerly HO14), B. tanukii (formerly Hk301), B. turdus (formerly Ya501), and B. miyamotoi (formerly HT31). There is also a genomic group DN127, which includes strain CA55 and sometimes strain 25015, and which is distinct from the other genospecies.

In 1998, isolation of an unusual strain of B. burgdorferi sensu lato was reported from Ixodes dentatus and A. americanum in southeastern Missouri, which is similar to strains isolated from I. dentatus in New York and Georgia, but different from B. burgdorferi sensu stricto. Also, an uncultivable borrelia, Borrelia lonetarii, was found in A. americanum from New York, New Jersey, Missouri, and North Carolina, which may be related to the Lyme-like disease in the southern states. A borrelia identified as B. burgdorferi has been found in A. americanum in New Jersey, Missouri, Texas, Oklahoma, Virginia, North Carolina, and Alabama.

There is clustering of B. burgdorferi genospecies from different geographic areas, as such as North America, Europe, Asia, and the circumpolar arctic and subantarctic regions, and from different tick vectors. B. garinii, afzelii, sensu stricto, valaisiana, and lusitaniae accounted for 39.7%, 15.9%, and 6.6% of B. burgdorferi sensu lato genospecies isolated from arthropod vectors, animal hosts, and human patients in Europe. B. burgdorferi sensu stricto is found in I. scapularis and I. pacificus in North America, and group CA55 in Ixodes neomexicanus in the western United States. B. bissetii is found in I. pacificus and group 25015 in I. scapularis from New York. B. bissetii represents the only strain other than sensu stricto to be present in both Europe and North America. Four genospecies—B. burgdorferi sensu stricto, B. afzelii, B. garinii, and B. valaisiana—are found in I. ricinus in central Europe. Human coinfections and I. ricinus co-infections with different genospecies have been reported. B. afzelii and B. garinii have been found in Ixodes persulcatus in eastern Europe and in Asia, including Japan, and B. burgdorferi sensu stricto has not been found. B. japonica is found in Ixodes ovatus in Japan, and B. garinii, and no other genospecies, is found in Ixodes uriae and I. ricinus in the far northern subarctic latitudes, and in I. uriae in the far southern subantarctic latitudes; genetically heterogeneous B. burgdorferi sensu stricto, B. garinii, and B. afzelii occur in migratory passerine (perching) birds in Sweden.

Hypotheses about the phylogenetic origins and historical patterns of global migration of the different B. burgdorferi genospecies have been developed, based on genetic analysis of the different strains. Initially, it was thought that there was greater diversity of genospecies in Europe, with B. garinii, afzelii, and sensu stricto, and in Asia, with B. garinii, afzelii, and japonica, than in North America, where only B. burgdorferi sensu stricto was thought to occur; this led to hypotheses that B. burgdorferi was introduced into North America from Europe, possibly by migratory birds or small mammalian hosts of infected ticks. The initial genetic studies were done mainly on isolates from the restricted hyperendemic areas of the Northeast and Upper Midwest; later, when isolates from the South and West were studied, more genetic heterogeneity was found, raising the reverse hypothesis—that introduction was from North America into Europe. 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, or that North American strains were introduced into Europe. 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.

B. burgdorferi is clonal, and widespread genetic exchange between chromosomal genes is thought not to occur. The order of occurrence of genes is the same across different genospecies, and there is no evidence of chromosomal rearrangements since the evolutionary divergence of the different genospecies from a common ancestor. Genetic exchange between plasmid genes, such as the Osp A and Osp B linear plasmid genes, has been found but is thought to be rare; there is evidence of exchange with other plasmid genes, such as the Osp D—encoding plasmid, which suggests that B. afzelii and garinii are closely related and that B. burgdorferi sensu stricto only recently acquired the Osp D gene.

There are differences in vector competence of I. ricinus and I. scapularis for the three genospecies of B. burgdorferi sensu lato, which correlates with the known geographic association of these vectors and genospecies. Acquisition of infection by I. scapularis was 83% to 90%, 87%, 10%, and 3% by I. ricinus in 83% to 90%, 87%, 10%, and 3%, respectively. Other genospecies are associated with some tick species and have not been found in others.

There is clustering of B. burgdorferi genospecies from different reservoir host species and some host species, which may act as biologic filters.

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 associates from the midgut and other tissues dissected from Ixodes scapularis (dannmini) ticks from Shelter Island, a Lyme-endemic area of New York, and was cloned to become the B31 strain of B. burgdorferi. In 1983, Burgdorfer and colleagues also first isolated a similar spirochete from Ixodes ricinus ticks from the Geo-
wald Forest, a Lyme-endemic area of Switzerland, and showed it to be morphologically and antigenically similar to the *I. dammini* spirochete.88 Since then, it has been isolated from several species of ticks, vertebrate hosts, and humans; 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 35°C to 37°C. 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 by microscopy.86, 87, 91, 174 However, the use of *B. burgdorferi*-specific PCR has shortened the time for detection in culture media.174 It can also grow anaerobically, and has even been grown aerobically in the presence of 1 to 5% carbon dioxide.90

Unlike other spirochetes, *B. burgdorferi* can be grown in solid media.97 It has been 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.97 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 it may be considered an obligate anaerobe.176

*B. burgdorferi* can be seen in cultures by dark-field or phase-contrast microscopy. It stains with acidic orange, Giemsa, and silver stains such as Warthin-Starkey or Biomer's or Bosma-Steiner stain,99 and can be identified with immunofluorescence techniques using *B. burgdorferi*-specific polyclonal or monoclonal antibodies175 or *B. burgdorferi*-specific PCR.175

Transformation of *B. burgdorferi* from typical motile spirochetes to immotile cystic spheroplast L-forms occurs when *B. burgdorferi* is grown in culture in the presence of antibodies, *B. burgdorferi*-specific antibody, or normal CSF.102 The conversion to spheroplast forms may be related to the ability of the spirochete to persist in tissues without elimination by the host immune response.

*B. burgdorferi* shows antigenic variation and loss of pathogenicity after 10 to 15 passages in culture, and becomes noninfectious; this correlates with loss of plasmids.129, 131, 134, 178, 882 Loss of several outer surface proteins and their encoding plasmid genes, including Osp B, C, and D, with passage has been noted; there is a suggestion that linear plasmid of 24.7 kb (1p24.7) is required for infectivity of *B. burgdorferi* sensu stricto, garinii, and afzelii, and that 1p38 (which encodes Osp D) is not required. Loss of 1p27.5 may increase infectivity, but correlation of individual plasmids with infectivity has been inconsistent.173, 135, 178 High-passage strains of *B. burgdorferi* have also been found to decrease both invasiveness and cytopathic killing of B and T lymphocytes.179

*B. burgdorferi* is relatively easily isolated and grown from midgut and other tissues dissected from infected *Ixodes* ticks,80, 74, 174, 180, 181 from which the isolation rate depends on the incidence of infection within the tick population (see section Epidemiology and Transmission: *B. burgdorferi* Tick Infection Rates); from blood and organ cultures of infected reservoir–competent host animals80, 182 (see section Epidemiology and Transmission: *B. burgdorferi* Reservoir Animal Infection Rates); and from biopsy specimens of the leading edge of EM skin lesions, from which the isolation rate is usually 28 to 86% (it may be higher in disseminated infection).153, 194 It has been isolated occasionally from blood, CSF, and ACA skin biopsy specimens, and rarely from borrelial lymphocytoma skin biopsies, synovium and synovial fluid, myocardium and heart valves, the iris, ligamentous tissue, placenta, fetal tissues, or other tissues because the organism density is low90 (see section Diagnosis and Differential Diagnosis: Diagnostic Tests: Culture).

The *B. burgdorferi*-specific PCR has increased the sensitivity of detection of *B. burgdorferi* in body fluids and tissues by using DNA target sequences that are unique to *B. burgdorferi*, are not present in other closely related *Borrelia* species or other spirochetes, and are highly conserved among *B. burgdorferi* strains. PCR has been used to demonstrate the spirochetes in EM, ACA, and borrelial lymphocytoma skin biopsy specimens; serum, plasma, and bone marrow; CSF, brain biopsy, sural nerve biopsy, and vitreous fluid; synovial fluid and membrane; urine; breast milk; placental tissue; and various animal hosts and tick vectors (see section Diagnosis and Differential Diagnosis: Diagnostic Tests: Polymerase Chain Reaction).

**Antibiotic Susceptibility**

Isolates of *B. burgdorferi* from humans and ticks from different geographic areas, including the United States and Europe, generally have similar antimicrobial susceptibility patterns,50, 173, 198–199, 192, 194–198 as is shown in Table 11-1. *B. burgdorferi* antibiotic susceptibility can be assessed in vitro by comparison of the minimal inhibitory concentrations (either mean MIC or MFC 50%) and the minimal bactericidal concentrations (either mean MBC or MBC 50%) for various antibiotics, and in vivo by comparison of the antibiotic dose required to cure 50% of infected animals of their infection (CD90). However, there is one report196 of lower doxycycline MIC values for cutaneous isolates than for CSF isolates.

*B. burgdorferi* was the most susceptible in vitro to the macrolides erythromycin, azithromycin, clarithromycin, and roxithromycin (MIC, 0.01 to 0.17 μg/ml); the penicillins penicillin, amoxicillin, ampicillin, amoxicillin-clavulanic acid, mezlocillin, azlocillin, and oxacillin (MIC, 0.02 to 1.1 μg/ml); the second- and third-generation cephalosporins ceftriaxone, cefotaxime, cefuroxime, cefixime, and ceftizoxime (MIC, 0.02 to 0.8 μg/ml); and the tetracyclines doxycycline, minocycline, and tetracycline (MIC, <0.13 to 0.79 μg/ml). Isolates were also susceptible to imipenem (MIC, 0.12 μg/ml) and chloramphenicol (MIC, 2 μg/ml). The mean MIC (or MFC 50%) value for penicillin was 0.02 to 1.1 μg/ml, but the range was wide (up to 8 μg/ml). According to MIC values, the aminoglycosides, sulfonamides, metronida-
### TABLE 11-1

In Vitro and In Vivo Antimicrobial Susceptibilities of *Borrelia burgdorferi*

<table>
<thead>
<tr>
<th>ANTIMICROBIAL AGENT</th>
<th>MEAN(^a) (RANGE(^b)) MIC (µg/ml)</th>
<th>MEAN(^b) (RANGE(^c)) MBC (µg/ml)</th>
<th>SUSCEPTIBILITY(^d) IN VITRO</th>
<th>CD(_{50})(^e) (mg/kg/day)</th>
<th>SUSCEPTIBILITY IN VIVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>0.02-1.0 (0.003-8)</td>
<td>1.08-8.7 (0.1-50)</td>
<td>S-MS-R</td>
<td>&gt;320-&gt;1975</td>
<td>R</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>&lt;0.03-0.25 (&lt;0.03-1)</td>
<td>0.06-1.9 (&lt;0.03-3.2)</td>
<td>S</td>
<td>50</td>
<td>S</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>&lt;0.25-0.47 (&lt;0.25-1)</td>
<td>S</td>
<td>25</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Amox/clav(^a)</td>
<td>0.12 (0.12-5)</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Mezlocillin</td>
<td>0.5 (0.25-1)</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Oxacillin</td>
<td>0.3 (0.25-2)</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Cefclar</td>
<td>(23-128)</td>
<td>(64-&gt;256)</td>
<td>MS</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>(11-128)</td>
<td>(32-&gt;128)</td>
<td>MS</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Cefalexin</td>
<td>(16-32)</td>
<td>(32-&gt;256)</td>
<td>MS</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Cefixime</td>
<td>0.8 (0.8)</td>
<td>(0.8-1.6)</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&lt;0.03-0.45 (&lt;0.03-1)</td>
<td>&lt;0.03-0.17 (&lt;0.03-0.8)</td>
<td>S</td>
<td>50</td>
<td>S</td>
</tr>
<tr>
<td>Cefotizoxime</td>
<td>0.125 (0.06-5)</td>
<td>0.5 (0.25-1)</td>
<td>S</td>
<td>50-240</td>
<td>S</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.02-0.06 (0.06-1)</td>
<td>0.04-3.8 (0.02-50)</td>
<td>S</td>
<td>50-240</td>
<td>S</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>(0.06-0.5)</td>
<td>(0.25-0.75)</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>0.125 (0.1-2)</td>
<td>0.71 (0.2-6.4)</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
<td>&lt;0.13 (&lt;0.13-0.25)</td>
<td>2.3</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.14-0.79 (0.01-2)</td>
<td>0.8 (0.8-6)</td>
<td>S</td>
<td>50-287</td>
<td>S</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.01-0.017 (0.003-0.03)</td>
<td>0.13 (0.06-0.25)</td>
<td>S</td>
<td>S</td>
<td>8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.01 (0.003-0.06)</td>
<td>(0.06-0.25)</td>
<td>S</td>
<td>S</td>
<td>50-&gt;80</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.03-0.15 (0.07-1)</td>
<td>0.05-2.17 (0.04-10)</td>
<td>S</td>
<td>50-240</td>
<td>S</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>0.02-1.05 (0.02-1.6)</td>
<td>1.1 (0.02-1.6)</td>
<td>S</td>
<td>50-240</td>
<td>S</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1.25-5</td>
<td>2-10 (0.5-10)</td>
<td>S</td>
<td>S</td>
<td>400-2353</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>20-5.8</td>
<td>2-10 (0.5-10)</td>
<td>S</td>
<td>S</td>
<td>400-2353</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;16</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Amikacin</td>
<td>&gt;32</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Chloramphenicol</td>
<td>2-10</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Imipenem</td>
<td>0.12 (0.06-1)</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<td>Trimethoprim</td>
<td>&gt;256</td>
<td>S</td>
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</table>

\(^a\)MIC = minimal inhibitory concentration (either mean MIC or MIC 50%).

\(^b\)MIC Range, minimum and maximum MIC values reported.

\(^c\)MBC = minimal bactericidal concentration (either mean MBC or MBC 50%).

\(^d\)MBC Range, minimum and maximum MBC values reported.

\(^e\)S = susceptible to antimicrobial agent; MS = modestly susceptible to antimicrobial agent; R = resistant to antimicrobial agent.

\(^f\)CD\(_{50}\) = dose of antimicrobial agent required to cure 50% of infected animals in animal model.

\(^g\)Amox/clav = amoxicillin-clavulanic acid.

Data obtained from references 50, 79, 174, 188, 189, 191, 192, 194-200, and 621.

zole, rifampin, and quinolones were not useful for *B. burgdorferi*. Although *B. burgdorferi* is resistant to co-trimoxazole in vitro, a minor synergistic decrease in the roxithromycin MIC from 0.031 to 0.015 µg/ml and a significant decrease in spirochetal mortality were reported to occur in combination with co-trimoxazole.\(^{199}\)

For the various antibiotics, the in vitro MIC efficacy and the in vivo CD\(_{50}\) efficacy were in agreement except for penicillin, erythromycin, clarithromycin, and roxithromycin. For erythromycin, clarithromycin, and roxithromycin, evaluation of the CD\(_{50}\) showed that despite excellent MIC values, they were 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 the spirochetes to the antibiotics is necessary to achieve adequate killing.\(^{188, 192, 200}\) In one study,\(^{188}\) the length of time required to kill 99% of *B. burgdorferi* exposed to twice the MIC of antibiotic ranged from 72 hours for ceftriaxone and cefuroxime to 96 hours for cefoxime. In another study,\(^{192}\) the length of time needed to kill 99% 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 (0.1 and 1.0 µg/ml) allowed regrowth of organisms after prolonged incubation for 96 hours or longer, but no such regrowth occurred with low concentrations of penicillin or ceftriaxone, or higher concentrations of tetracycline (above 10 µg/ml). In one study,\(^{200}\) some differences in the kinetics of killing of different *B. burgdorferi* strains by different antibiotics were found after 48 hours, but all strains were effectively killed by antibiotics to which they were susceptible after 72 hours.

Results of the animal model efficacy studies show better correlation for some antibiotics than others with
clinical human patient results. For example, Steere and colleagues reported\(^{209}\) that, of the oral antibiotics, tetracycline was most effective, penicillin was next most effective, and erythromycin was least effective for treatment of early Lyme disease. Clarithromycin\(^{210}\) and azithromycin\(^{211, 205}\) have been found to be equally or almost equally as efficacious as amoxicillin and doxycycline in the treatment of EM. Several factors, in addition to the MIC of the antibiotic, play a role in determining whether an antibiotic will be clinically effective in the elimination of \(B. burgdorferi\) infection; these include the duration of adequate serum, spinal fluid, intraocular, intrasynovial, and tissue antibiotic concentrations; the efficacy of the host immune response; and the potential sequestration of organisms in protected sites.

**Interactions with the Immune System**

\(B. burgdorferi\) infection triggers a sequence of immunologic and other cellular events that are involved in the local and systemic dissemination of the infection, the immunopathogenesis of the various manifestations of the infection, and the host elimination of the infection, as well as in the ability of the spirochete to evade host defenses.\(^ {186, 149, 151, 206-207}\) A discussion of the immunopathogenesis of Lyme borreliosis is provided in the section Pathology and Pathogenesis.

**T Lymhocyte Reactivity**

\(B. burgdorferi\) antigen–triggered T cell activation occurs within a few days of the tick bite, develops before the B cell antibody response, rises during infection, is directed initially against the 41-kd flagellar and the 31-kd Osp A antigens, and is directed later against additional outer surface membrane proteins.\(^ {209, 209, 211, 212}\) \(B. burgdorferi\) spirochetes, Osps A, and Osp B have been reported to induce specific proliferation in T lymphocytes from Lyme disease patients\(^ {213, 214}\); the response is predominantly due to CD4+ and CD8+ T lymphocytes,\(^ {215}\) and there is also a response due to CD56+ NK (natural killer) cells.\(^ {213}\) \(B. burgdorferi\), Osp A, Osp B, and even Osp-containing membrane blebs have been found to possess nonspecific B lymphocyte proliferative activity.\(^ {215, 216}\) However, \(B. burgdorferi\)–induced nonspecific T lymphocyte or mononuclear cell proliferation has been found by some\(^ {211}\) and not by others.\(^ {211}\)

\(B. burgdorferi\) antigen–specific T lymphocyte reactivity, measured by the \(B. burgdorferi\)–specific lymphokine proliferative assay, is long lasting, and may persist even in seronegative patients with Lyme borreliosis.\(^ {208, 214, 210, 210}\) The lymphoproliferative response may be greater in spinal fluid and synovial fluid than in peripheral blood in some patients with neurologic or arthritic manifestations of Lyme borreliosis.\(^ {215, 220, 221}\) There is \(B. burgdorferi\)–specific synovial fluid T lymphocyte production of Th1-type cytokines interferon-gamma (IFN-\(\gamma\)) and tumor necrosis factor-alpha (TNF-\(\alpha\)).\(^ {201}\) There is peripheral blood and intrathecal \(B. burgdorferi\)–specific T lymphocyte production of the Th1-type cytokine IFN-\(\gamma\), as well as specific B lymphocyte production of IgG antibody, all of which persist for several months after clinical recovery from treated neuroborreliosis.\(^ {214}\) 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.\(^ {208-210, 212, 213}\).

**Development of Serum Antibody**

The antibody response to \(B. burgdorferi\) infection begins to develop a few days after the tick bite, after the development of the T lymphocyte response.\(^ {211}\) and there are several studies of the temporal evolution of serum IgG and IgM antibody responses to the infection in North American\(^ {222, 226, 212}\) and European\(^ {227, 228}\) patients. \(B. burgdorferi\) sensu stricto is the only major genospecies causing Lyme disease in North America; all three of the major genospecies, \(B. burgdorferi\) sensu stricto, \(B. garinii\), and \(B. afzelii\), cause Lyme borreliosis in Europe, resulting in some differences between the antibody responses of North American and European patients. Because of these differences, distinct criteria for Western blot positivity for each of the three genospecies in European patient sera, and for \(B. burgdorferi\) sensu stricto in North American patient sera, have been recommended.\(^ {235, 234, 237, 238}\) In both North American and European patients, the initial polyvalent antibody response to \(B. burgdorferi\) infection is directed primarily against the 24-40-kd Osp C,\(^ {235, 233, 239, 240}\) and the 41-kd flagellar antigen. The early response to the 39-kd antigen is more common in North American than European patients,\(^ {233, 237}\) and the late antibody response is more often directed primarily against the outer surface membrane proteins, that is, the 31-kd and 34-kd Osp B, in North American than in European patients.\(^ {234, 237, 241, 242}\)

The \(B. burgdorferi\)–specific IgM response develops in 1 to 2 weeks, peaks at 2 to 8 weeks, and usually disappears after several months in uncomplicated treated patients but may persist in patients with disseminated rather than localized infection, patients with persistent infection, some with late chronic infection,\(^ {18, 222, 226, 240, 245}\) patients with initially delayed antibiotic therapy (even after clinical recovery),\(^ {226, 246}\) and some patients with promptly and successfully treated EM and neuroborreliosis.\(^ {226, 227, 235}\) Although comparisons of the temporal evolution of antibodies detectable by Western blots to individual \(B. burgdorferi\) antigens are often difficult because of lack of standardization of band and molecular weight nomenclature, a general pattern of progressive expansion of the antibody repertoire after infection emerges. There is general agreement that the initial specific IgM response is made to the 24-kd Osp C antigen and to the 41-kd flagellar antigen. Several investigators describe early development of IgM antibody and other antigens as well. After recovery, Western blot IgM antibody reactivity to several antigens declines after 1 month and usually disappears after several months. IgM reactivity to the 24-kd Osp C and 41-kd flagellin may persist,\(^ {256, 240, 247, 248}\) and is even still detectable in 38% of patients with successfully treated EM 1 year later.\(^ {256}\) IgM antibody to Osp C is detectable in 54% of patients with chronic arthritis for months to years, and in 20% of those with chronic neuroborreliosis.\(^ {240}\) However, in a follow-up study of resolved pediatric Lyme arthritis,
only 5% had any IgM Western blot reactivity at a mean of 10 months after treatment, and this was only to the 41-kd flagellar antigen. In very early infection, in both North American and European patients, IgM antibody to Osp A may be bound in immune complexes, and may be detectable only when these are dissociated. The acute IgM response during EM in North American patients who progress to severe persistent Lyme disease includes the 83-kd and 34-kd antigens, and these responses persist into chronic disease. In North American patients, the IgM Osp C antibody response is greatest in patients with EM and meningitis, early in the course of infection, and decreases to low levels in those who develop chronic neuroborreliosis.

In North America, the CDC criteria for a positive IgM Western immunoblot are the presence of two of the following three bands in early disease: 24-kd Osp C, 39-kd Bmp A, and 41-kd Fla. In Europe, proposed criteria for IgM Western blot positivity include the following: for B. burgdorferi sensu stricto IgM, at least one of 39, Osp C, and 17a or a strong 41; for B. afzelii IgM, at least one of 39, Osp C, and 17 or a strong 41; and for B. garinii IgM, at least one of 39 and Osp C or a strong 41.

A delay in initial antibiotic therapy appears to be associated with increased dissemination, with development of higher polyvalent enzyme-linked immunosorbent assay (ELISA) titers and greater numbers of Western blot IgM bands, and with persistence of IgM positivity even after clinically successful treatment. However, prompt antibiotic treatment of early Lyme disease appears to be associated with disappearance of IgM positivity within several months. Longer disease duration is associated with a higher incidence of IgM seropositivity. The IgM ELISA antibody is higher in neuritis and arthritis patients with early Lyme disease than in patients with only EM. In late chronic Lyme borreliosis, such as arthritis, neuroborreliosis, and sometimes even in acrodermatitis chronica atrophicans, the specific IgM is often persistently positive by immunofluorescent assay (IFA), ELISA, or Western blot assays.

The B. burgdorferi–specific IgG response develops at 2 to 8 weeks, peaks at 4 to 6 months, and in uncomplicated treated patients, usually gradually declines and sometimes eventually disappears after several months, but it may persist for years in persistent infection, sometimes even after successful antibiotic therapy. Delays in initial antibiotic therapy are associated with a higher incidence of dissemination, progression to later stages of infection, strongly positive IgG responses, higher polyvalent ELISA antibody titers, and increased numbers of IgG Western blot bands. In one study, the number of Western blot bands reacting with serum IgG antibody decreased after successful treatment of pediatric Lyme arthritis, and no new ones appeared. As is the case for IgM Western blot bands, direct comparison of IgG bands from different studies is not always possible. However, general patterns of the temporal evolution of the IgG antibody response to infection emerge. The initial IgG response is made to the 41-kd flagellar and the 24-kd Osp C antigens; it progressively expands to include additional antigens, such as the 26-kd Osp E, and eventually, within the first month after successful treatment, it includes many additional antigens.

In very early infection, in both European and North American patients, IgG antibody to Osp A is often present in immune complexes, but may be detectable only if these are dissociated. In persistent infection, the IgG response expands over months to years. In late European Lyme borreliosis, IgG antibody is almost always directed toward the 41-kd flagellin, and the 58-kd and 83/100-kd antigens. Although the Western blot antibody patterns may differ with various late manifestations.

In North America, the CDC criteria for a positive IgG Western immunoblot are the presence of five of the ten most common bands after the first few weeks of disease. The proposed criteria for IgG Western blot positivity in Europe can be seen in reference 237.

The development of IgM and IgG antibody to new antigens months to years after onset of infection suggests either the persistence of viable B. burgdorferi throughout the illness, or reinfection. There are varying opinions regarding the significance of positive IgM antibody in Lyme disease of more than 1 month's duration, but there is agreement that a diagnosis of active Lyme disease should not be made on this basis alone.

Patients with neuroborreliosis usually have higher polyvalent B. burgdorferi antibody in spinal fluid than in serum, and some may have spinal fluid antibody in the absence of serum antibody. Patients with arthritis usually have higher polyvalent specific antibody in synovial fluid than in serum.

Highly specific antibody capable of killing B. burgdorferi in culture and of passively protecting mice against experimental B. burgdorferi challenge develops during infection and quantitatively increases with increasing severity and duration of the infection. In one study, the seroprotective and borreliocidal activity occurring in patient sera from late but not early Lyme borreliosis correlated with the presence of reactivity to Osp A and Osp B. Borreliocidal antibody is seroprotective against the homologous strain, and sometimes against heterologous strains.

**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. This B cell hyperactivity leads to the development of several antibodies that are not specific for B. burgdorferi and are directed against host tissues, such as rheumatoid factor, antinuclear antibody, anti-cardiolipin antibody, and antibody to fibrinectin-binding protein.
antibody to neuronal axons,\textsuperscript{151, 265} antibodies to myelin basic proteins,\textsuperscript{266} and antibody to neurofilament proteins\textsuperscript{246} and oligoclonal bands.\textsuperscript{258, 267, 268} False-positive Venereal Disease Research Laboratory (VDRL) antibody,\textsuperscript{11, 211, 234} cryoglobulins,\textsuperscript{211, 234} and circulating immune complexes \textsuperscript{211, 234, 260} 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; in patients with cardiac or neurologic involvement, the immune complexes persist in the serum.\textsuperscript{262, 269}

Induced low levels of rheumatoid factor are detectable in 32% of Lyme patients by ELISA IgM and in 4% by latex agglutination assay.\textsuperscript{264} Serum IgM antibodies to neuronal axons were found in all patients with neuroborreliosis in one study;\textsuperscript{211} autoantibodies were found in the spinal fluid of 20% of patients with neuroborreliosis in another study.\textsuperscript{246} *B. burgdorferi*–specific oligoclonal bands were found in the spinal fluid of 40 to 100% of patients with neuroborreliosis.\textsuperscript{258, 267}

Anti–tick saliva antibody (ATS) develops after a tick bite in response to the holus of tick saliva injected, peaks at 3 to 5 weeks, persists for weeks to months, and subsequently decreases.\textsuperscript{270} 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.\textsuperscript{18, 208, 209, 218, 225, 235, 237} 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.\textsuperscript{253} Thus, if antibiotic therapy is given before 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, the antibody response may eventually decrease, disappear, or persist, even after successful eradication of the infection.\textsuperscript{274–277} The longer the Lyme disease persists before antibiotic therapy is begun, the more *B. burgdorferi*–specific antibody bands develop by Western blot assay.\textsuperscript{208, 225, 248} Persistent *B. burgdorferi* infection may also occur in sequestered sites such as the central nervous system, inducing local CSF but not systemic antibody responses. Seronegative patients usually still have detectable T lymphocyte proliferative responses.\textsuperscript{208, 216, 218, 219, 269, 277, 278} Seropositivity or seronegativity alone is not always a reliable indicator of cure.

Steere and colleagues\textsuperscript{272} reported the incidence of true seronegative Lyme disease to be 4% in a large study of 180 patients with confirmed North American Lyme disease; they noted that all were EM history–positive, 75% had *B. burgdorferi*–specific T lymphocyte reactivity, and manifestations were usually neurologic or musculoskeletal. In seronegative patients, clinical manifestations were attenuated compared with those in seropositive patients; in seronegative patients with symptoms of significant arthritis, the term *seronegative Lyme arthritis* is contradictory, as the *B. burgdorferi* antibody response is considered to be involved in the pathogenesis of the arthritis, and these patients are unlikely to have Lyme disease.

In some patients, apparent seronegativity is due to testing by standard ELISA and Western blot assays, which detect free antibody, and specific antibody may be detected by using methods that dissociate immune complexes, antibody.\textsuperscript{276}

Failure to develop *B. burgdorferi* serum antibody in patients with confirmed Lyme borreliosis may be due to serologic testing done very early after onset of infection, during the spirochetal phase, before the development of even a very early antibody response. Thirty-five to 100% of early Lyme borreliosis patients with *B. burgdorferi* detectable in plasma or serum by PCR were seronegative,\textsuperscript{280, 281} and 53% of seronegative Lyme borreliosis patients had *B. burgdorferi* DNA detectable in serum by PCR, compared with none of the seropositive patients.\textsuperscript{281}

**DEVELOPMENT OF CEREBROSPINAL FLUID ANTIBODY**

*B. burgdorferi* invasion of the central nervous system (CNS) occurs early in two thirds of patients with disseminated infection even in the absence of neurologic symptoms; this has been reported from both North America\textsuperscript{282, 283} and Europe.\textsuperscript{284} 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 assay.\textsuperscript{285}

Intrathecal production of *B. burgdorferi*–specific 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 organisms systemically, but it may fail to achieve adequate MICs in the CSF, thus allowing persistence of the organism in this privileged site.\textsuperscript{281} Some patients with early neuroborreliosis may also have specific intrathecal antibody production, as has been observed with *B. burgdorferi* IgM antibody, without seropositivity.\textsuperscript{253, 260, 261} Early in CNS invasion, *B. burgdorferi*–specific CSF antibody may be located in immune complexes, which are not detected by free antibody assays.\textsuperscript{280}

There are some differences in intrathecal *B. burgdorferi* antibody between North American and European patients.\textsuperscript{259, 260, 263} 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,\textsuperscript{282} there was intrathecal

\footnote{See references 211, 253, 259, 260, 265, 267, 268, 283, and 285–292.}
B. burgdorferi-specific ELISA IgM in 100% and IgG in 40% of patients with meningitis, as well as ELISA IgM and IgG in 26 to 30% of patients with encephalitis; in another study of North American early and late neuroborreliosis, intrathecal free antibody detectable by ELISA was found in 48% and specific immune complex-associated IgG and IgM antibody in 43%.293

B. burgdorferi-specific CSF antibody was directed primarily against the 41-kd flagellar antigen, and also against the 33-kd Osp A and 17-kd antigens.293, 294, 295, 296 CSF ELISA antibody levels were higher than serum antibody levels,297 but IFA antibody levels were higher in serum than in CSF.

INTERACTIONS WITH COMPLEMENT

B. burgdorferi activates the alternate and classic complement pathways but is 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.298 Host-specific differential transmission of different B. burgdorferi sensu lato genospecies by ticks has been found to correlate with the differential susceptibility of the genospecies to bacteriolysis by serum complement, including via the alternate pathway, of the different host species.299

INTERACTIONS WITH PHAGOCYTES

Peripheral blood polymorphonuclear and mononuclear phagocytes and macrophages are able to phagocyte opsonized and nonopsonized B. burgdorferi.300 B. burgdorferi binds to polymorphonuclear phagocytes via integrin $\alpha_\text{M}$/$\beta_2$, the CR3 complement receptor, during nonimmune phagocytosis.

B. burgdorferi stimulates human endothelial cells to express the neutrophil adhesion molecule, E-selectin, and the neutrophil chemoattractant agent, interleukin-8 (IL-8), both of which are probably involved in recruitment of neutrophils to sites of B. burgdorferi-induced inflammation, and in transmigration of neutrophils across the endothelium.301, 302 Whole B. burgdorferi spirochetes were demonstrated to be strong inducers, equivalent to or more potent than lipopolysaccharide (LPS), of chemoattractant cytokine production by human monocytes, including MIP-1$\alpha$ (macrophage inflammatory protein-1$\alpha$), MCP-1 (monocyte chemoattractant protein-1), and RANTES (regulated upon activation, normal T cell expressed and secreted), which attract monocytes and lymphocytes, and IL-8 (interleukin-8) and GRO-$\alpha$ (melanoma growth–stimulatory activity), which attract neutrophils and contribute to tissue inflammation and damage.298

Recombinant lipitated, but not unlipidated, B. burgdorferi Osp A, even in minute amounts, is a potent human neutrophil activator that induces neutrophil responses similar to those induced by bacterial LPS. Neutrophils are the main cell type in Lyme arthritic joints; they are involved both in maintaining an inflammatory response and in the destruction of opsonized B. burgdorferi, presumably via a combination of reactive oxygen intermediates and lysosomal products, including the proteolytic enzyme elastase.300 Elastase has been demonstrated to be the main borrelial factor in human neutrophils.300

A possible additional mechanism by which the spirochete might evade borrelialicid antibody and temporarily persist in a protected niche is by invasion and killing of both B and T lymphocytes.173

EVAISON OF HOST DEFENSES AND PERSESTENCE IN TISSUE

B. burgdorferi has the unusual, but fortunately uncommon, ability to evade the host immune response and persist in tissues for months to years, sometimes even after antibiotic therapy, and sometimes even after intravenous antibiotic therapy. An unusual persistence is usually either in immunologically privileged sites inaccessible to host defenses, after local or systemic steroid therapy, after initially delayed or inadequate antibiotic therapy, or in patients with risk factors such as HLA-DR4 specificity, and may occur in the presence or absence of seropositivity.302, 303

B. burgdorferi has been isolated, months to several years after oral or intravenous (IV) antibiotic therapy, from CSF294, 302, synovial fluid304, 305, EM skin lesions306, 307, 308, 309, 310, mitral valve tissue309; ligamentous tissue310; and iris biopsy tissue.304 It has also been isolated, 1 month to 10 years after onset, without preceding antibiotic therapy, from CSF;303 synovial fluid305, 307, 309, 311; brain;311 synovial fluid and membrane312, 313, 314, ACA skin biopsy;315 and serum, blood, plasma, and bone marrow.316, 317 Persistence for 1 month to 10 years without antibiotic therapy has also been demonstrated by PCR or antigen-detection methods in CSF and ACA skin biopsy.316, 317, 318 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.318

Differential gene expression of B. burgdorferi antigens, which results in variation in antigenicity of the spirochete during different stages of infection, is thought to be involved in evasion of the immune response.120, 121, 122 It has been proposed that the spirochete may be able to evade the host immune response while still inducing the inflammatory pathology characteristic of the various manifestations of Lyme disease. Differential expression of surface lipoproteins during various stages of infection allows the spirochete to vary its antigenic310, 314, 315, 316, 317, 318, 142 while maintaining its ability to activate cells because the lipid moiety of the lipoproteins is responsible for cell activation.147 The use of the host's own fibrinolytic enzymes for invasion, while eliciting minimal immunologic response by the host, is an immunologically silent method of invasion called "stealth pathogenesis,"148 which may exp-

*See references 19, 20, 206, 209, 281, 283, 284, 287, 302–308, and 311–318.
plain the long-term persistence of *B. burgdorferi* in host tissues with only minimal mononuclear cell infiltration. *B. burgdorferi* invasion of epidermal dendritic Langerhans' cells induces downregulation of major histocompatibility class II (MHC II) molecules on this major antigen-presenting cell, and may result in inability of Langerhans' cells to eliminate the spirochete and long-term *B. burgdorferi* persistence in the skin.148

The immunosuppressive and immunomodulatory properties of *B. burgdorferi* may also be involved in its ability to evade the host immune response. The addition of *B. burgdorferi* to lymphocyte proliferative assays reduces the proliferative responses of human peripheral blood lymphocytes to concanavalin A and phytohemagglutinin. It has been proposed that this immunosuppressive effect may allow the spirochete to rapidly disseminate from the skin inoculation site and persist in the host; it could also explain the better efficacy of prompt antibiotic therapy in elimination of the spirochete.217

Another mechanism by which the spirochete might evade porphyrinoid antibody is by entering a protected niche such as an intracellular or other environment that is inaccessible to either a porphyrinoid immune response or antibiotic therapy. Proposed potential sites for such persistence include the central nervous system, the eye, and the joints.170, 220, 321 Temporarily, persistence in a protected niche occurs by invasion of B and T lymphocytes. *B. burgdorferi* persistence in ligamentous tissue, the iris, synovium, and the central nervous system may also represent the use of a protected niche.

Several antigens of *B. burgdorferi* have portions that share amino acid homology with human cellular proteins; molecular mimicry may also be involved in immune evasion.113, 126, 151, 204, 205, 256, 265, 323

**CORRELATION OF CLINICAL MANIFESTATIONS WITH HLA TYPE**

Differences in HLA specificities may determine *B. burgdorferi* antigen binding and presentation to T cells and the presentation of the T cell response, and may be related to susceptibility to infection.256

Several studies by Steere and colleagues and others reported that HLA-DR4 specificity and Osp A or Osp B IgG seropositivity are associated with chronic antibiotic-resistant Lyme arthritis but not with EM or acute or chronic neuroborreliosis.356, 312, 324, 425 Long-duration chronic Lyme arthritis patients had high frequencies of HLA-DR4 or -DR2 positivity (89%) compared with those with short-duration Lyme arthritis (27%), and HLA-DR4 positivity but not -DR2 positivity correlated with lack of response to antibiotic therapy.

Correlation of HLA specificity with outcome of antibiotic therapy of Lyme arthritis is discussed in the section Therapy: Predictors of Antibiotic Therapy Cure.

**EPIDEMIOLOGY AND TRANSMISSION**


**Historical Review**

In 1909, Azabiel 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.16 ECM became a well-recognized European disease thought initially to be caused by either a tick-associated toxin or an infectious agent.17

Another European disease, acrodynia chronica atrophicans (ACA), which had first been described by Buchwald in 1883 in Germany, was noted to be preceded frequently by ECM and was named ACA by Herxheimer by Herxheimer and Hartman in 1902. In 1922, Garin and Boujadoux described cutaneous lesions and paralysis after a tick bite and suspected a spirochetal etiology,328 and in 1944, Banwarth described chronic lymphocytic meningitis after European ECM; this became known as Garin-Boujadoux-Banwarth syndrome, or simply Banwarth's syndrome.17, 329

In 1948, Lennhoff reported spirochetes in ECM skin biopsy specimens,17, 330 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,17, 331 and between 1948 and 1957, Hultstrom found that most European ECM cleared within 2 weeks after intramuscular penicillin therapy.78, 311 In 1949, Thyresson successfully treated patients with ACA with penicillin, and in 1952, Gruneberg considered spirochetes as possible etiologic agents.20

In 1955, Binder and associates, 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. They established that ECM was caused by a penicillin-susceptible infectious agent transmitted by the *Ixodes ricinus* tick.17 In 1955, Gotz transmitted ACA from patient to patient by transplantation of ACA skin biopsy specimens 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 Scrimmings,231 although retrospective studies have found that it existed in small foci in New England as early as 1962 and 1965.334, 335

The recognition of Lyme arthritis as a distinct disease came in 1975, when two mothers from the small village of OId 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. By 1980, it became known as Lyme disease because meningoencephalitis and myocarditis were also recognized as part of the disease.

In 1980, Steere and co-workers found that penicillin or tetracycline therapy shortened the duration of 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.

In 1981, a new spirochete was accidentally discovered by Burgdorfer in I. dammini ticks (now renamed I. scapularis) collected for a rickettsial study from Shelter Island, New York, a highly Lyme-endemic focus. It induced EM lesions in rabbits, and convalescent sera from Lyme patients reacted with it. In 1983, two groups of investigators, Steere and associates and Benach and colleagues, 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.

In 1983, Barbour, Burgdorfer, and co-workers isolated a spirochete similar to the I. dammini spirochete from Ixodes ricinus ticks; it was indistinguishable from B. burgdorferi and was also confirmed to be the etiologic agent of European ECM, European ACA, European Bannwarth’s syndrome, and European borreliotic lymphocytoma.

The recent application of new molecular biologic techniques such as the polymerase chain reaction (PCR) to the historical study of B. burgdorferi in museum specimens of ticks and animals has made it possible to retrospectively document its presence in Europe in museum tick specimens as early as 1882 to 1897, and in North America in museum mouse specimens as early as 1894. This dates the presence of the spirochete in Europe to the times of the earliest clinical descriptions of Lyme borreliosis.

The first case of congenitally transmitted Lyme borreliosis was described by Schlesinger and associates in 1985 after gestational Lyme disease acquired in Wisconsin. Since then, several additional cases have been reported, and it has become clear that gestational Lyme borreliosis carries a low but serious risk of congenital infection.

Tick (and Other Arthropod) Vectors

Epidemiologic studies have indicated that Lyme borreliosis is caused by B. burgdorferi sensu lato transmitted from animals to humans by ixodid ticks that are members of the Ixodes ricinus complex, and that this transmission occurs during tick feeding because of either tick salivation or regurgitation of organisms. Ticks that are members of the I. ricinus complex and have been associated with human Lyme borreliosis transmission are the deer tick Ixodes dammini/scapularis in the northeastern and upper midwestern United States, the black-legged tick Ixodes pacificus in the western United States, the sheep tick Ixodes ricinus in Europe, and the Ixodes persulcatus tick in Asia. Other ticks that are not members of the I. ricinus complex are also associated with enzootic B. burgdorferi cycles, but either are not or are rarely involved in human Lyme borreliosis transmission and may be involved in bridging between separate enzootic cycles. (In this chapter, the name I. scapularis is used to indicate both northern and southern ticks.)

B. burgdorferi is often found in nymphal and adult stages of Ixodes scapularis, pacificus, ricinus, and persulcatus, but rarely in unfed larvae, because infection is acquired by larval feeding on B. burgdorferi–infected animal reservoirs, is passed transstadially (between stages) from larva to nymph to adult, and is rarely passed transovarially from infected female ticks to less than 1% of eggs and larvae. However, because 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. Partially fed larval ticks (in which feeding on infected hosts was interrupted) are able to transmit B. burgdorferi during refeeding, which may explain some larval positivity.

In North America, most Lyme disease transmission is due to northern I. scapularis and I. pacificus tick vectors, which frequently bite humans, but several other species of ticks have been thought to be vectors in some geographic areas, particularly in areas where northern I. scapularis and I. pacificus are not prevalent, the southern I. scapularis has been considered a Lyme disease vector in parts of the southern United States, and in the western United States, I. neotomae and Ixodes spinipalpis are involved in B. burgdorferi enzootic cycles, and I. pacificus serves as a bridge vector to man; in the eastern United States, I. denticulus and Ixodes minor are also involved in B. burgdorferi enzootic cycles, and I. scapularis may be involved as a bridge vector. Although infrequent, human bites have been documented for I. spinipalpis and I. denticulatus, and for other two ticks that are not members of the subgenus Ixodes—Ixodes angustus and Ixodes cookei; rare cases of possible EM have been reported after human bites by I. angustus in Washington state and I. cookei in West Virginia.

Other ticks in North America commonly biting humans are the dog tick Dermacentor variabilis, and the Pacific Coast tick Dermacentor occidentalis. D. variabilis in Kentucky has been considered a possible secondary human Lyme disease vector. The Lone Star tick Amblyomma americanum, which is the most common tick biting humans in the southeastern and south central United States, has been considered a potentially important alternate human vector in New Jersey, southeastern Missouri, North and South Carolina, Kentucky, Alabama, and Texas. B. burgdorferi sensu lato and Borrelia lonestari, a noncultivable Borrelia possibly related to Lyme-like disease in
the South, have been found in A. americanum, H. leporis-palustris and Dermacentor variabilis rarely bite hu-
man,\textsuperscript{335} There have been occasional reports of suspected
Lyme borreliosis transmission by other hematophagous
arthropods such as mosquitoes\textsuperscript{376} and tabanid flies (deer
and horseflies) in North America and Europe.\textsuperscript{371, 372} Figure
11–4 shows different stages of three common North
American ticks: I. scapularis, A. americanum, and D. vari-
abilis.
In South America, the Ixodes affinis and Ixodes pararici-
nus ticks from Peru are also members of the Ixodes ricinus
complex and are considered potential vectors of B.
burgdorferi.\textsuperscript{373} In Asia, although the Ixodes sounts tick in
Japan frequently bites humans and has been found to
harbor B. japonicus, this has not been found to be associ-
ated with human Lyme borreliosis.\textsuperscript{365, 374} The Ixodes boro-
cyclus tick in Australia is the tick most often biting hu-
man, but it has not been found to harbor B.
burgdorferi.\textsuperscript{375}
In addition to Ixodes scapularis, pacificus, ricinus, and
persulcatus ticks,\textsuperscript{336} B. burgdorferi has been isolated from
ticks of other Ixodes species and of four additional genera
(Table 11–2).
For a tick to be vector-competent for B. burgdorferi,
it must be able to become and remain infected, pass the
infection transstadially, and transmit the infection to a
host. Ixodes scapularis, pacificus, ricinus, persulcatus, delta-
ris, neotomae, and hexagonus are efficient and competent
B. burgdorferi vectors,\textsuperscript{178, 336, 335, 337, 365, 378, 399} and I.
uriae,\textsuperscript{365, 366} and I. spinipalpis\textsuperscript{365} are probably efficient and
competent vectors.
It has been recognized that there are significant differ-
<table>
<thead>
<tr>
<th>SPECIES</th>
<th>GEOGRAPHIC LOCATION</th>
<th>COMMON NAME</th>
<th>Bb SENSU LATO GENOSPECIES ISOLATED</th>
<th>VECTOR COMPETENCE FOR B. BURGDORFERI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amblyomma americanum</td>
<td>N. America</td>
<td>Lone Star tick</td>
<td>B.b.s.t., B.b.s.l., B. lonestarii</td>
<td>Poor</td>
</tr>
<tr>
<td>Amblyomma maculatum</td>
<td>N. America</td>
<td>Gulf Coast tick</td>
<td>B.b.</td>
<td>?</td>
</tr>
<tr>
<td>Dermacentor variabilis</td>
<td>N. America</td>
<td>Dog tick</td>
<td>B.b.</td>
<td>?</td>
</tr>
<tr>
<td>Dermacentor albipictus</td>
<td>N. America</td>
<td>Pacific Coast tick</td>
<td>B.b.</td>
<td>Poor</td>
</tr>
<tr>
<td>Dermacentor occidentalis</td>
<td>N. America</td>
<td>Rabbit tick</td>
<td>B.b.</td>
<td>?</td>
</tr>
<tr>
<td>Dermacentor parumapertus</td>
<td>N. America</td>
<td></td>
<td>B.b.</td>
<td>?</td>
</tr>
<tr>
<td>Rhipicephalus sanguineus</td>
<td>N. America</td>
<td>Dog tick</td>
<td>B.b.</td>
<td>?</td>
</tr>
<tr>
<td>Haemaphysius leporipalpis</td>
<td>Europe</td>
<td>Rabbit tick</td>
<td>B.b.</td>
<td>?</td>
</tr>
<tr>
<td>Haemaphysius punctata</td>
<td>Europe</td>
<td></td>
<td>B.b.</td>
<td>?</td>
</tr>
<tr>
<td>Haemaphysius concinna</td>
<td>Asia</td>
<td></td>
<td>B.b.s.l.</td>
<td>?</td>
</tr>
<tr>
<td>Haemaphysius bispinosa</td>
<td>Asia</td>
<td></td>
<td>B.b.s.l.</td>
<td>?</td>
</tr>
<tr>
<td>Haemaphysius longicornis</td>
<td>Asia</td>
<td></td>
<td>B.b.s.l.</td>
<td>?</td>
</tr>
<tr>
<td>Genomphalites felix</td>
<td>N. America</td>
<td>Cat flea</td>
<td>B.b.</td>
<td>?</td>
</tr>
<tr>
<td>Chrysops and Hybomitra spp.</td>
<td>N. America, Europe</td>
<td>Tibetan (Deer and horse) flies</td>
<td>B.b.</td>
<td>Poor</td>
</tr>
<tr>
<td>Aedes spp. and Culex spp.</td>
<td>N. America, Europe</td>
<td>Mosquitoes</td>
<td>B.b.</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Data obtained from references 33, 59, 61, 64-70, 73, 74, 77, 100, 153-158, 165-166, 170, 180, 336, 344, 350, 351, 353, 362, 365, 376-381, 382-389, 405, 412, 420, 438, 449, 621, 878, 884, and additional references noted in text.

In North America, *I. scapularis* has also been reported to be the vector of the agents of human babesiosis, *Babesia microti*, and of the agent of human granulocytic ehrlichiosis (HGE) (which is closely related to *Ehrlichia equi/phagocytophila*); presumably, *I. pacificus* in the western United States and *I. ricinus* in Europe.

In North America, *I. scapularis* and *I. ricinus* for different genospecies of *B. burgdorferi*, and even for different strains within the same genospecies, which may be related to differential susceptibility to bacteriolysis of various *B. burgdorferi* genospecies by complement of different host species.

In North America, *I. scapularis* has also been reported to be the vector of the agent of human babesiosis, *Babesia microti*, and of the agent of human granulocytic ehrlichiosis (HGE) (which is closely related to *Ehrlichia equi/phagocytophila*); presumably, *I. pacificus* in the western United States and *I. ricinus* in Europe.
act in the same capacity. In North America, *Amblyomma americanum* is the vector of the agent of human monocytic ehrlichiosis (HME), *Ehrlichia chaffeensis* (initially incorrectly reported as *Ehrlichia canis*), and has also been considered a possible secondary vector of *B. burgdorferi*; the European vector of HME is not known. The vector of the *Babesia* species piroplasm WA1, which causes human infection in California, is not known. Co-infections of ticks with *B. burgdorferi* and *Ehrlichia* or *Babesia* have been reported.

**Enzootic Cycles: 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. Eggs laid by infected adult female ticks usually hatch into unfed larvae, as the rate of transovarian transmission of the spirochete is very low, and larvae acquire the spirochete by feeding on *B. burgdorferi* spirochete-competent reservoir hosts. The infection is maintained in the larvae through the transstadial molt and is passed from the larva 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. The prevalence of *B. burgdorferi* infection in a tick population is determined by the frequency of feeding of larvae and nymphs on infected reservoir-competent hosts. The infection rate in adult ticks is higher than in nymphal ticks. Larval ticks have been found to acquire *B. burgdorferi* even after only partial feeding.

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 before 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. Humans are accidental hosts of all stages of *I. scapularis* and *I. ricinus*, and of the adult ticks of *I. pacificus*, *I. persulcatus*, and *I. ocatus*. Some animal hosts of *I. ricinus* complex ticks, such as North American cats, birds, feral lizards, and European blackbirds, have a zoonotic effect, and decrease the force of *B. burgdorferi* transmission by eliminating infectious spirochetes within feeding ticks, thus removing these ticks from the enzootic cycle.

The life cycle of *I. scapularis* has been the most extensively studied. Eggs laid on the ground in the spring hatch into larvae in mid- to late summer. In late summer, July and August, larvae become

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**TABLE 11-3**

**Preferred Hosts for Different Stages of *Ixodes ricinus* Complex Ticks That Transmit Lyme Borreliosis to Humans**

<table>
<thead>
<tr>
<th>TICK</th>
<th>LARVAL AND NYMPHAL STAGES</th>
<th>ADULT STAGE</th>
<th>TOTAL NO. HOSTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mammal</td>
</tr>
<tr>
<td>(southern U.S.)</td>
<td>Lizards and skinks</td>
<td>White-tailed deer, <em>Odocoileus virginianus</em></td>
<td>39</td>
</tr>
<tr>
<td><em>I. pacificus</em></td>
<td>Cotton mouse, <em>Peromyscus gossypinus</em></td>
<td>Black-tailed deer, <em>Odocoileus hemionus columbianus</em></td>
<td>54</td>
</tr>
<tr>
<td><em>I. ricinus</em></td>
<td>Fence lizard, <em>Sceloporus occidentalis</em></td>
<td>Deer, <em>Capreolus capreolus</em></td>
<td>89</td>
</tr>
</tbody>
</table>

*Data from references 162, 164, 167-169, 182, 336, 348, 378, 413, and 419-421.

Human hosts are generally not known. Infection rates of all stages of the ticks.
infected with *B. burgdorferi* by feeding for 3 to 5 days on small rodents such as the white-footed mouse, which are amplifying reservoirs for *B. burgdorferi* infection; the fed larvae then fall to the ground. The infection persists in the larvae throughout 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, June, and early July) 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; 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 it 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 for vegetation, especially at edges between lawns and forests, and for medium-sized to large mammalian hosts, such as white-tailed deer, in the fall (mid-October through November), warm days in winter, and the following spring (April and early May); they mate while the females are feeding on these hosts. Questing adult field-collected infected ticks contain a median of 1500 to 1900 spirochetes per tick. 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. The females then feed for 8 to 11 days, fall to the ground, lay eggs in the spring, and die; the eggs hatch in 45 to 53 days into larvae in the summer. The prevalence of *B. burgdorferi* infection increases from the nymphal to the adult stage because the ticks feed on amplifying reservoir–competent hosts.

In northeastern and upper midwestern North America, the preferred small rodent host of *I. scapularis* is the white-footed mouse, *Peromyscus leucopus*, which is also the primary reservoir of *B. burgdorferi* infection in nature, and the preferred large mammal host is the white-tailed deer, *Odocoileus virginianus*, which is the host of the reproductive stage of the tick, however, larvae and nymphs have been found attached to 80 different species of mammals and birds, but not reptiles, and adult ticks to 13 species of medium-sized to large mammals, and the mice remain chronically spirochetal but asymptomatic. The deer are occasionally spirochetal with *B. burgdorferi* but are also asymptomatic. The deer are responsible for the geographic expansion of Lyme–endemic areas because the infected *I. scapularis* adult females overwinter and mate on the deer, and the deer travel widely but are not considered reservoirs for *B. burgdorferi* maintenance in nature. The geographic distribution of North American Lyme disease and *I. scapularis* correlates with that of the white-tailed deer.

Other reservoir–competent small mammal hosts may be involved in the maintenance of *B. burgdorferi* infection in nature in certain geographic areas, and at times in which the population of the usual reservoir host, the white-footed mouse, is low or absent. The deer mouse, *Peromyscus maniculatus*, has been shown to be a competent reservoir host for *I. scapularis* on an offshore island in Maine with no resident *P. leucopus*, and may also be an important alternate reservoir host in the northern forests of Maine.

The eastern chipmunk, *Tamias striatus*, is an important reservoir–competent alternate host for immature *I. scapularis*, which can feed on either mice or chipmunks in hardwood forests of the Upper Midwest, including Wisconsin and northwestern Illinois; the meadow vole *Microtus pennsylvanicus* is a secondary, less important, small mammal reservoir host of *I. scapularis* in some areas of eastern North America.

A parallel cycle involving the cotton tail rabbit, *Sylvilagus floridanus*, *I. scapularis*, and the rabbit tick *Ixodes dentatus* occurs either in areas where the enzootic *I. scapularis*–white-footed mouse cycle of maintenance of *B. burgdorferi* infection is inefficient or does not occur, or in areas such as Nantucket Island, Massachusetts, and some parts of the northeastern United States where the *I. scapularis*–mouse cycle occurs but the *I. dentatus*–rabbit cycle functions as an independent complementary cycle. The *I. dentatus*–rabbit cycle is silent with respect to human Lyme disease as *I. dentatus* rarely bites humans; *I. scapularis* rarely feeds on rabbits, but may be important in the spread of *B. burgdorferi* to new geographic areas because immature *I. dentatus* also feeds on birds.

In some parts of North America, *B. burgdorferi* is present in areas that are not endemic for human Lyme disease because *B. burgdorferi* is maintained in nature by enzootic cycles that produce endemic foci that are silent with respect to human transmission of Lyme disease. One such cycle is the *I. spinipalpis*–*Mexican woodrat* cycle in Colorado; this tick has a broad host range, including rodents, rabbits, and ground-dwelling birds, but humans are rarely bitten because questing ticks are found only in woodrat nests; therefore, this cycle does not contribute to transmission of human Lyme disease.

In the southern United States, the enzootic cycles that maintain *B. burgdorferi* in nature have been described, are more complex and less efficient than those in the North, and result in lower *B. burgdorferi* tick infection rates. The most common reservoir hosts for maintenance of *B. burgdorferi* infection in nature are the cotton mouse, *Peromyscus gossypinus*, and the cotton rat, *Sigmodon hispidus*; however, the life cycle of southern *I. scapularis* is less synchronized, so that nymphal feeding does not always precede larval feeding, thereby reducing the acquisition of infection by feeding larvae. The southern *I. scapularis* is able to feed on 33 species of hosts, including mammals, birds, and reptiles, but the preferred hosts for immature *I. scapularis* are lizards and skinks (which are incompetent hosts incapable of maintaining and amplifying *B. burgdorferi* infection); the large mammal hosts for adult *I. scapularis* are white- and black-tailed deer, *Odocoileus virginianus* or *bemius columbianus*. Reptiles exert a zooprophylactic effect on Lyme disease transmission, with a decrease in transmission in areas where reptiles predominate: South of the 38 degrees North latitude boundary, which runs from Virginia through Missouri, reptiles make up over 10% of the total *I. scapularis* hosts available (reptile index is greater than 10), and questing...
ticks are significantly diverted away from reservoir-competent amplifying hosts, such as the cotton mouse and the cotton rat, leading to lower tick infection rates. B. burgdorferi in Missouri, and probably in Georgia, appears to be maintained in a cotton tail rabbit-I. densatus enzootic cycle, and I. scapularis and possibly A. americanum have been proposed as bridge vectors from rabbits to humans. I. cookei has been reported to bite humans in West Virginia, where it is considered a possible human Lyme disease vector; its immature forms feed on small and medium-sized carnivores, and its adults only on medium-sized carnivores. I. affinis may enhance enzootic I. scapularis—cotton mouse/rat cycles, and I. minor may be involved in parallel enzootic cycles with the eastern woodrat, Neotoma floridana, or birds; these cycles maintain B. burgdorferi infection in nature in Georgia and South Carolina.

Ixodes pacificus, in the far western United States, has a life cycle similar to that of I. scapularis but with some differences in hosts, reservoirs, and seasonality of feeding. Although I. pacificus is able to feed on a wide variety of hosts, including 80 different species of mammals, birds, and reptiles, its immature stages feed preferentially on lizards, which are not competent B. burgdorferi reservoirs and cannot infect feeding ticks; its larval feeding peaks before nymphal feeding, leading to the relatively low tick infection rates reported for adult ticks. The black-tailed deer, Odocoileus hemionus columbianus, is the host of the adult tick, which feeds mostly in fall and winter, and to a lesser degree of the immature stages; in one study, all three stages were present simultaneously on deer. B. burgdorferi infection is maintained in nature by a parallel enzootic cycle involving the competent reservoir host, the dusky-footed woodrat Neotoma fuscipes, and a non-I. ricinus complex tick, I. neotoma (now I. spinipalpis), which rarely bites humans. I. pacificus is responsible for human transmission and acts as a bridging vector between the I. neotoma—woodrat cycle and man. In 1995, in California, the nymphal tick infection rate was found to be 14%, compared with the adult rate of 4%, and the possibility of a borrelioidal factor in lizard hosts was raised.

There are some differences between the life cycles of European I. ricinus and North American I. scapularis ticks. I. ricinus has a 2- to 3-year life cycle (occasionally, 5 to 6 years in far northern latitudes), less coherent seasonal activity, and all three tick stages have feeding activity at the same time, particularly from mid-May to early July; it has a broader host range, which includes 237 to 317 species of mammals, birds, and reptiles. I. ricinus abundance correlates with that of deer, but I. ricinus occurs in some geographic areas even in the absence of deer because it can use cattle as well as deer as the large mammalian host. The geographic distribution of Lyme borreliosis in Europe correlates with the geographic distribution of I. ricinus ticks, particularly the distribution of B. burgdorferi-infected ticks, and even more with the distribution of highly infected ticks and of deer, as in North America. The hedgehog Erinaceus europaeus—I. hexagonus cycle is involved in maintenance of B. burgdorferi infection in nature in Europe and Asia, but I. hexagonus rarely bites humans and is not considered important in the transmission of human Lyme disease. In some areas, such as an urban park in Magdeburg, Germany, Norway rats, Rattus norvegicus, and I. ricinus are involved in maintenance of B. burgdorferi in nature in a cycle that occurs in addition to the mouse cycle.

I. persulcatus is responsible for human Lyme disease transmission in Asia; it has a similar life cycle to I. ricinus but a greater host range, which includes 212 to 241 different species of mammals, birds, and reptiles, although deer, canids, cattle, and hares are particularly important hosts. The life cycle is usually 2 to 3 years, but in extreme northern latitudes it may be 5 to 6 years. The geographic distribution of Lyme disease and the genospecies of B. burgdorferi isolated from human Lyme disease patients in China, Japan, and eastern Russia correlate with the geographic distribution of, and genospecies isolated from, I. persulcatus. There appear to be two separate enzootic cycles involving larvae and nymphs in Japan—the I. persulcatus—rodent cycle involving mainly the woodmouse (and sometimes the vole), and the I. persulcatus—bird cycle; adult ticks feed mainly on large animals.

I. holocyclus, the most common tick in Australia, is not competent for B. burgdorferi. So far, no competent vector or reservoir host has been identified in Australia. The mammalian hosts of B. burgdorferi in the northern hemisphere are all placental animals, and none of these are present in Australia, where the small mammals are mostly marsupial.

A migratory seabird—I. uriae enzootic cycle has been described in high-latitude subarctic and subantarctic circumpolar areas, in which the seabirds maintain B. burgdorferi (B. garinii) infection in nature without the involvement of mammalian hosts. The geographic distributions of I. uriae and I. ricinus overlap on islands in the Bzhonian Gulf at the northern end of the Baltic Sea, and bridging may occur between the two enzootic cycles. It has been proposed that the migratory seabird is the reservoir for B. burgdorferi in the southern hemisphere, is responsible for the transhemispheric and global spread of B. burgdorferi, and may be important for the spread of Lyme disease to Australia and South Africa.

In addition to I. uriae, other ixodid ticks, including the human Lyme disease vectors, I. ricinus, I. scapularis, I. pacificus, and I. persulcatus, and the rabbit-feeding ticks, I. dentatus, I. spinipalpis, and H. leporispalustris, are able to feed on birds as alternate hosts in addition to mammalian hosts; therefore, they presumably have an opportunity to be transported by migratory birds to new geographic areas.

The potential epidemiologic impact of migratory birds as transporters of infected ticks is great because in estimated 100 million birds migrate into Sweden each spring, carrying 6.8 million new ticks, 1.8 million of which carry B. burgdorferi; also, 4.7 million ticks, 1.3 million of which harbor B. burgdorferi, are transported out of Sweden toward the South every fall.

Small mammals, including mice and rabbits, and their
ticks may be important in establishment and maintenance of new cryptic B. burgdorferi endemic foci in nature by providing reservoir–competent hosts for infected ticks carried to new sites by migratory birds. 170, 171

Seasonality of Human Tick Bites/Transmission of Borrelia 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 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. scapularis, 137 and in the Northeast and Upper Midwest, they are usually infected by voracious host-seeking I. scapularis nymphs during the spring and early summer (in May and June); the peak incidence of Lyme disease with erythema migrans occurs 1 month later during June and July. 330, 428 In mid-Atlantic states such as Maryland, the onset of most cases of Lyme disease is from May through September. 409 Epidemiologic studies have found that the tick infectivity rate increases from less than 1% of larvae, to 20 to 74% of nymphs, to 57 to 87% of adult ticks. 411 Nymphs are responsible for transmission of almost 90% of cases of Lyme disease. 441 Because the nymphs are so small, and because the tick injects saliva containing anti-inflammatory, analgesic, antihemostatic, and immunosuppressive components while feeding, 413 the bites are not painful and often go unnoticed long enough to allow B. burgdorferi transmission, which usually takes 2 to 3 days. 415 However, there are rare European reports of transmission after less than 24 hours 130, 411 and within 2 hours. 411 Human infection is less often caused by adult female I. scapularis, which feeds in late fall through early winter (from October through May), with a peak in October, even though B. burgdorferi infection rates among adults are higher than for nymphs, because the adults are larger and more easily detected and can be removed before transmission of B. burgdorferi infection occurs. 136, 430

The I. scapularis tick takes a long time to feed; 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. 29 The blood meal triggers multiplication of the B. burgdorferi associated with the tick's gastrointesinal tract, which disseminate to the hemolymph by the third day of feeding and then spread to the host either by injection of B. burgdorferi–containing tick saliva or by regurgitation of B. burgdorferi–containing tick gut contents into the dermal feeding cavity created by the tick. 341, 342 These immunosuppressive salivary secretions and other factors related to the spirochete and its acquisition of host extracellular matrix digestive enzymes 344 result in host-specific immune evasion by the tick, which 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. 348

In the Pacific Northwest, along the Pacific Coast, humans are also incidental hosts of both the adult and immature stages of I. pacificus, which is one of the most common ticks biting humans 29, 420; it is responsible for 59% of human tick bites 186 (66% of bites by adult ticks, and 44% by nymphs). The incidence of B. burgdorferi infection in nymphal ticks is much higher than in adult ticks, possibly because of the zoonoprophylactic effect of the reptile hosts of the immature stages. 186 The peak onset of Lyme disease with EM (March through August) corresponds to the nymphal feeding season (March through September), rather than to the adult tick feeding season (October through June, with peaks in December and March). 186 Because the incidence of B. burgdorferi infection of I. pacificus is lower than that of the northeastern I. scapularis, the rate of human infection following I. pacificus bites is also lower. 29, 420

In Europe, humans are incidental hosts for all stages of the I. ricinus tick—which is the most common tick in Europe, 350 the most frequent cause of human tick bites in Central Europe, and the main vector for B. burgdorferi transmission to humans in Europe. 341, 346 The feeding activities of the three stages of I. ricinus overlap throughout Europe, especially from April through July, 409, 422,

<table>
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<th>GEOGRAPHIC LOCATION</th>
<th>B. BURGDORFERI TICK VECTOR</th>
<th>MONTHS OF TICK FEEDING ACTIVITY, BY STAGE</th>
<th>MOST COMMON MONTHS OF ONSET OF LB</th>
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<td>Asia</td>
<td>I. persulatus</td>
<td>Mar.–Nov.</td>
<td>May–June</td>
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*Nymphal ticks feeding during this time are responsible for most B. burgdorferi transmission to humans.

*Adult ticks feeding during this time are responsible for most B. burgdorferi transmission to humans.