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

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

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

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

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

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

PULMONARY

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

CARDIAC

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

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

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

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

NEUROLOGIC

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

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

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

MUSCULOSKELETAL

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

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

GENITOURINARY

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

INFANTILE MULTISYSTEM INFLAMMATORY DISEASE

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

PLACENTA

The placental histopathology associated with gestational Lyme borreliosis has been reported only occasionally.[31–36, 590, 622, 623] Some of the placentas described were associated with normal fetal and neonatal outcomes; others were associated with infants with congenital Lyme borreliosis (included in Table 11–14 in the section Clinical Manifestations).

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

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

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

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

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

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

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

Other Congenital Borrelial Infections

RELAPSING FEVER

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

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

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

CLINICAL MANIFESTATIONS

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

Case Definition and Classification of Stages of Lyme Borreliosis

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

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

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

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

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

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

Erythema migrans

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

or

Borrelial lymphocytoma

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

or

Acrodermatitis chronica atrophicans

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

or

Early neuroborreliosis

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

or

Chronic neuroborreliosis

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

or

Lyme arthritis

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

or

Lyme carditis

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

[a]Adapted from Stanek, G, et al. European Union Concerted Action on Risk Assessment in Lyme Borreliosis: Clinical case definitions for Lyme Borreliosis. Wien Klin Wochenschr 108:741–747, 1996[502] and Cimmino, M, et al. European Lyme Borreliosis Clinical Spectrum. Zentralbl Bakteriol 287:248–252, 1998.[8]
[b]*Borrelia burgdorferi* may also be isolated from patient specimen.
[c]*Bb* = *Borrelia burgdorferi*.

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

Incidence of Lyme Borreliosis in Women of Childbearing Age

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

Clinical Manifestations of Gestational and Nongestational Lyme Borreliosis

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

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

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

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

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

[a]Adapted from Rahn DW, Felz MW. Lyme disease update. Current approach to early, disseminated, and late disease. Postgrad Med 103:51, 1998,[633] and Asbrink E, Hovmark A. Comments on the course and classification of Lyme borreliosis. Scand J Infect Dis Suppl 77:41, 1991.[634]

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

ERYTHEMA MIGRANS

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

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

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

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

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

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

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

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

BORRELIAL LYMPHOCYTOMA

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

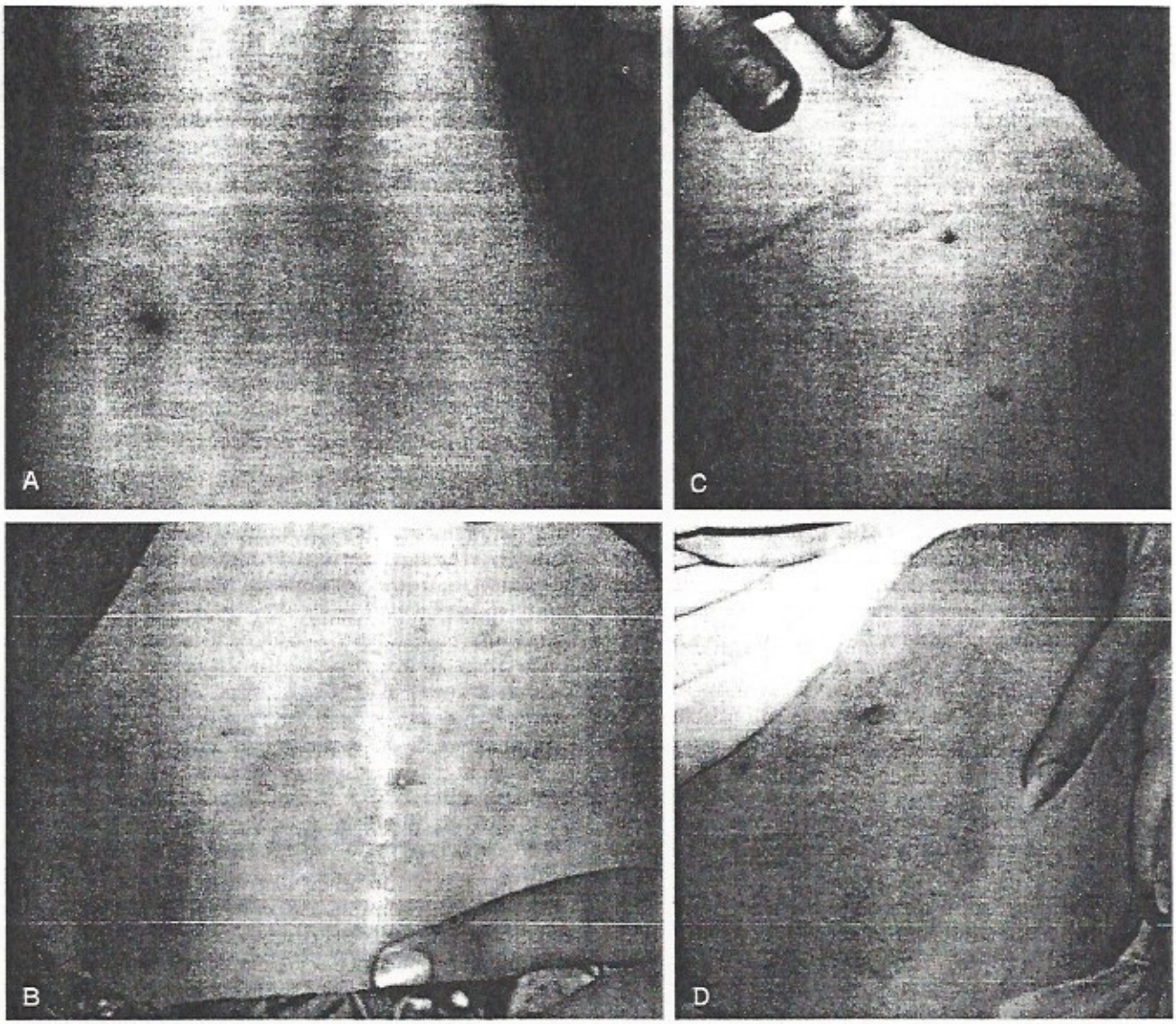

FIGURE 11–5 The pathognomonic skin lesion of Lyme disease, the "bull's-eye" or erythema migrans (EM) lesion. *A* to *C*, EM lesion of early Lyme disease, which is a large, expanding, round or oval, smooth or stippled, erythematous annular rash with central clearing located around a central or eccentric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

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

ARTHRITIS

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

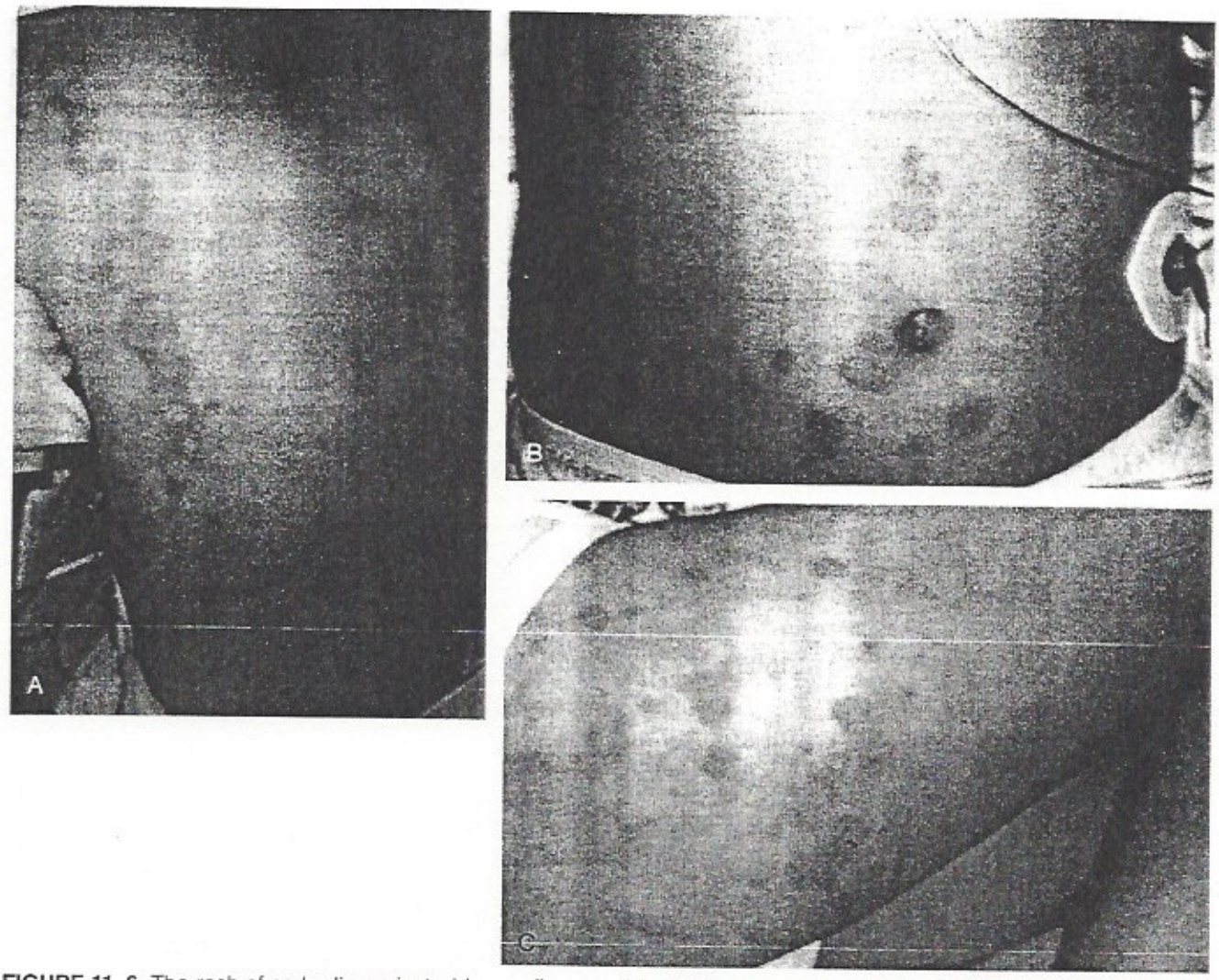

FIGURE 11–6 The rash of early disseminated Lyme disease. *A* to *C*, Extensive distribution of the rash, which consists of erythematous macular lesions with central clearing that range from one to several centimeters in diameter. This patient also had a simultaneous large (>15 cm in diameter) erythema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

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

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