(in distal tibial and femoral metaphyses),[699] and rarely hematologic abnormalities.[711, 712]

Ophthalmologic manifestations of Lyme borreliosis may occur alone or in combination with other manifestations of Lyme borreliosis.[320, 702] These include cranial nerve palsies affecting extraocular movements[643]; conjunctivitis, nodular episcleritis, and keratitis[284, 325]; and orbital myositis,[703] optic neuritis,[704] retinitis, and panophthalmitis. The incidence of otologic complications, other than facial nerve palsy, is less than 12%; these include vestibular neuronitis, moderate hearing loss, tinnitus, otalgia, and temporomandibular joint pain.[284, 707]

Post-Lyme Syndromes

The post-Lyme syndrome (PLS), which includes persistence of fatigue and arthralgia for longer than 6 months after adequate antibiotic therapy of confirmed Lyme disease, has been reported to be associated with objective neuropsychiatric and neurocognitive abnormalities,[682, 683, 713, 714] and with delayed initial antibiotic therapy.[683, 714]

Fibromyalgia has been reported in 8 to 10% of patients with Lyme borreliosis, but it persisted after resolution of the symptoms of Lyme disease and was not considered to be related to active Lyme disease.[279, 715]

REINFECTION WITH *BORRELIA BURGDORFERI*

Reinfection rates as high as 5 to 21%, based on clinical histories, have been reported in some highly endemic areas in both North America and Europe.[522, 683, 714, 716] Reinfection with different strains of *B. burgdorferi* has been confirmed serologically and by culture[717, 718] in both North America and Europe; these patients developed seropositivity after the initial episode, but some became seronegative before the second episode and others remained seropositive between episodes. Serologic evaluation by IgG as well as IgM *B. burgdorferi* assays is recommended in patients suspected of having reinfection, as some have only an IgG response.[233]

CO-INFECTION WITH *BABESIA* OR *EHRLICHIA*

Babesiosis, caused by the protozoan *Babesia microti* in the United States, and *Babesia divergens* and *Babesia bovis* in Europe, is another tickborne infection of increasing prevalence and significance, which is co-vectored by the ticks that transmit Lyme borreliosis and human granulocytic ehrlichiosis and shares the same geographic distribution. There are two reports of infants with probable transplacental acquisition of babesiosis.[630]

HGE shares tick vectors and some geographic distribution with Lyme borreliosis. Co-infections with Lyme disease and ehrlichiosis are being increasingly reported, including one case in pregnancy,[632] and there is one report of probable transplacental transmission of HGE.[631]

Clinically symptomatic as well as asymptomatic past or recent co-infection with Lyme borreliosis and babesiosis[481–483] or ehrlichiosis[484] has been reported,[397, 400, 401, 481, 485–488, 498] although some seropositivity to more than one agent may be due to cross-reactivity. There is recent concern because of accumulating evidence for increased severity of Lyme disease in patients with concurrent babesiosis,[481] and it is uncertain if this occurs also with ehrlichiosis and Lyme borreliosis.

Insufficient data are available so far to determine the frequency of transplacental transmission of babesiosis or ehrlichiosis, or the optimal antibiotic therapy of either gestational or neonatal infection.

The possibility that co-infection with *B. burgdorferi* and tickborne encephalitis (TBE) may increase the severity of TBE has been raised.

Clinical Manifestations of Congenital Lyme Borreliosis

CONGENITAL AND GESTATIONAL LYME BORRELIOSIS

A review of the congenital and gestational Lyme borreliosis literature yielded 259 reported cases for which the outcome of the individual episode of gestational Lyme borreliosis was noted,* and addition of four of the author's cases brought the total to 263 cases. A total of 66 cases of the 263 were found that the author considers to represent an adverse event at least associated with an episode of gestational Lyme borreliosis,[25, 26, 28–48] including miscarriage, stillbirth, perinatal death, congenital anomalies, systemic illness, early-onset fulminant sepsis, and later-onset chronic progressive infection (Tables 11–8, 11–13, and 11–14). These 66 cases have been divided into logical groups (Table 11–15) based on an understanding of the pathophysiology and clinical course of Lyme borreliosis in older patients, and on inescapable similarities of Lyme borreliosis to syphilis. Many of the calculations of rates of adverse outcomes became apparent only when all of the available case information was compared, as each individual report of one or several cases represented too few cases from which to draw conclusions; in the larger, population-based studies or serologic surveys, individual outcomes of gestational Lyme disease were not provided for all patients, which made difficult the recognition of a small number of individual adverse outcomes associated with gestational Lyme disease. The reader is directed to additional information about these cases of congenital Lyme borreliosis, which are discussed in the individual sections of Pathology and Pathogenesis, Diagnosis and Differential Diagnosis, Therapy, Prevention, and Prognosis, in this chapter.

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

Several reports that involved serologic screening of

*See references 25–39, 42–48, 531, 536, 537, 622, 632, and 719–723.

TABLE 11–13
Frequency of Specific Adverse Outcomes[a] of 66 Pregnancies Complicated by Gestational Lyme Borreliosis (GLB) and Adverse Clinical Outcome

FETAL/NEONATAL ABNORMALITY	NO. WITH FINDING[b]	% WITH FINDING	REFERENCE
Cardiac	15/66	22.7%	
Myocardial dysfunction	5/66	7.6%	25, 31–33, 621
VSD	6/66	9.1%	33–35, 37, 48
PDA	3/66	4.5%	25, 33, 42, 621
Coarctation aorta	2/66	3.0%	25, 33, 34
ASD	2/66	3.0%	33, 34, 48
Other[d]	4/66	6.1%	25, 32, 33, 37, 46, 621
Neurologic	10/66	15.2%	
Developmental delay/mental abnormalities	5/66	7.6%	31, 36, 42, 44, 621
Hydrocephalus/macrocephaly	5/66	7.6%	31, 33, 37, 41
Hypotonia/lethargy	3/66	4.5%	32, 37, 621
Meningoencephalitis[e]	4/66	6.1%	31, 621
CNS lesions on scan[f]	2/66	3.0%	31, 621
Cortical blindness	1/66	1.5%	36
Hemiparesis	1/66	1.5%	621
Meningomyelocele	1/66	1.5%	33
Orthopedic	8/66	12.1%	
Syndactyly/clubfoot/metatarsus adductus	4/66	6.1%	29, 33, 36, 45
Arthritis/contractures	2/66	3.0%	31, 621
Long bone metaphyseal bands	2/66	3.0%	621
Pectus excavatum	1/66	1.5%	621
Vertebral defects	3/66	4.5%	33, 41, 45
Radial dysplasia	1/66	1.5%	45
Dermatologic	6/66	9.1%	
Rash	6/66	9.1%	31, 36, 43, 621
Ophthalmic	3/66	4.5%	
Blepharitis/exophthalmos	1/66	1.5%	31
Punctate retinal lesions	1/66	1.5%	621
Eso- /exotropia	1/66	1.5%	621
Genitourinary	7/66	10.6%	
Cryptorchidism	2/66	3.0%	42, 46
Hypospadias	1/66	1.5%	46
Inguinal hernia, bilateral	1/66	1.5%	621
Hydrocele	1/66	1.5%	46
Renal dysplasia	1/62	1.5%	45
Ureteral stenosis with hydronephrosis, bilateral	1/66	1.5%	48
Miscellaneous anomalies	8/66	12.1%	
Pilonidal dimple	2/66	3.0%	621
Sacral hemangioma with gluteal atrophy	1/66	1.5%	44
Facial/ear dysmorphia	1/66	1.5%	621
Simian crease, unilateral	1/66	1.5%	621
Absence of hemidiaphragm	1/66	1.5%	33
Omphalocele	1/66	1.5%	33
Laryngomalacia	1/66	1.5%	46
Tracheoesophageal fistula	1/66	1.5%	45
Imperforate anus	1/66	1.5%	45
Hypoplastic dental enamel/dental anomalies	3/66	4.5%	42

Table continued on opposite page

large populations of obstetric patients, but provided no information about the occurrence, treatment, or specific outcomes of any clinically symptomatic cases of gestational Lyme borreliosis, could not be used in evaluation of outcomes of gestational Lyme borreliosis; however, they provided data on seroprevalence in the obstetric patient population.[530, 724] In Germany, the seroprevalence of *B. burgdorferi*–specific IgM and IgG antibody was 0.8 and 7%, respectively, in 2600 patients in obstetric clinics, and pregnancy outcomes were considered the same in seropositive and seronegative groups of patients.[530] A large *B. burgdorferi* antibody serosurvey of 1039 preg-

TABLE 11–13
Frequency of Specific Adverse Outcomes[a] of 66 Pregnancies Complicated by Gestational Lyme Borreliosis (GLB) and Adverse Clinical Outcome *Continued*

FETAL/NEONATAL ABNORMALITY	NO. WITH FINDING[b]	% WITH FINDING	REFERENCE
Miscellaneous abnormalities			
Neonatal sepsis/DIC/respiratory distress	11/66	16.7%	25, 26, 33, 38, 39, 47, 48, 621
Hyperbilirubinemia	8/66	12.1%	36, 37, 41, 621
Growth retardation[g]	8/66	12.1%	31, 33–35, 37, 41, 47, 621
Hepatomegaly/splenomegaly	3/66	4.5%	31, 621
Adenopathy	4/66	6.1%	31, 43, 621
Recurrent fever	2/66	3.0%	43, 44
Recurrent infections	2/66	3.0%	31, 621
Dysphagia/GE reflux/aspiration	2/66	3.0%	31, 45
Meconium ileus	1/66	1.5%	621
Fetal/Neonatal demise	26/66	39.4%	
GLB prior to conception or first prenatal visit	10/66	15.2%	27, 32, 33
GLB in first trimester	5/66	7.6%	25, 29, 33–36, 38, 39, 42
GLB in second trimester	8/66	12.1%	33, 34
GLB in third trimester	0/66	0.0%	
GLB in unspecified trimester	2/66	3.0%	30, 33, 41, 46

[a]Underestimate of incidence of findings, as autopsies not done on all fetal deaths.
[b]Number with finding/total number.
[c]Author's patients.
[d]Endocardial fibroelastosis, aortic stenosis, left superior vena cava, multiple congenital heart defects, aortic thrombosis, or arrhythmia.
[e]Chronic meningitis, or CSF pleocytosis/elevated protein.
[f]Cortical atrophy on CT or white matter lesions on MRI.
[g]Intrauterine or postnatal.
ASD = atrial septal defect; CNS = central nervous system; DIC = disseminated intravascular coagulation; GE = gastroesophageal; GLB = gestational Lyme borreliosis; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

nant women in the Perm area of Russia from 1992 to 1994 found a 5.5% seropositivity rate (57 of 1039) and noted that their data indicated that Lyme borreliosis is a serious risk factor for miscarriage and perinatal death, but provided no information on individual outcomes of gestational Lyme borreliosis.[724] Some reports note the occurrence of adverse effects of gestational Lyme borreliosis such as stillbirth and congenital defects but provide no details.[725]

In 1989, Nadal and associates[37] reported a large serosurvey of 1416 mothers and their infants at the time of delivery, from 1986 to 1987, in a Lyme-endemic area of Switzerland, and found a *B. burgdorferi*–specific seropositivity rate of 0.85% (12 of 1416) in maternal sera. Of the seropositive mothers, one had a history of first-trimester tick bite and Lyme borreliosis and her infant had a congenital ventricular septal defect (VSD); five mothers had histories of pre-gestational Lyme borreliosis, one had a history of pre-gestational tick bite, and five were asymptomatic; 6 of their infants had minor problems that resolved.

Bracero and colleagues,[47] in a serosurvey of pregnant women at the first prenatal visit in an endemic area of New York from 1988 to 1989, found a seropositivity rate of 1.1% (7 of 638), and noted non–statistically significant but interesting differences in the pregnancy outcomes of seropositive and seronegative women: The frequencies of low birth weight, birth size small for gestational age, and Apgar less than 7 were 28.6, 14.3, and 14.3% for seropositive women, and 16.4, 2.6, and 5.2% for seronegative women.

In 1993, Strobino and co-workers[45] reported a prospective *B. burgdorferi* serosurvey of 2000 pregnant women from areas of high and low Lyme endemicity in New York, from 1988 to 1990, at the first prenatal visit and at delivery; pregnancy outcomes were available for 96%. Eleven patients were seropositive at the first visit (rate 0.7%); only one patient seroconverted by delivery, and this patient had an untreated second-trimester flu-like illness and delivered a normal infant; the seropositive mothers delivered live-born infants, one with gastroesophageal reflux, one with metatarsus adductus, and one with multiple major anomalies. Fifteen developed Lyme disease during the pregnancy, but the specific outcomes of these pregnancies were not provided. They concluded that gestational Lyme disease or *B. burgdorferi* exposure was not associated with an overall increase in fetal death, prematurity, or congenital malformations, but noted that the incidence of cardiac defects was two times higher in infants born to mothers in high versus low endemicity areas, and that there was an association of minor malformations with a history of maternal tick bite less than 3 years before conception. The frequencies of total, major, and minor malformations in the infants born to these mothers were 24, 7, and 17% for those with a history of previous Lyme disease at any time; 19, 3 to 7, and 15 to 16% for those with a history of tick bite within 3 years; 16, 5, and 10% for those with no history of previous Lyme disease; and 15, 5, and 10% for those with no history of tick bite. They qualified their conclusions by noting that the miscarriage rate in this study was 8%, which is lower than the usual rate of

TABLE 11–14
Outcomes of 263 Pregnancies Complicated by Lyme Borreliosis (LB)[a]

TRIMESTER OF LB[b]	ANTIBIOTIC THERAPY OF LB[c]	NO. PATIENTS	NO. FETAL DEATHS[d]	NO. NEONATAL DEATHS[e]	NO. LIVEBORN, ILL, OR ABNORMAL[f]	NO. LIVEBORN, NORMAL	NO. TOTAL ADVERSE OUTCOMES[g, h]	NO. TOTAL NORMAL OUTCOMES[h]
≤1[i]	yes	57[j]	4	1	5	47	10 (17.5%)	47 (82.5%)
	no	11	4	2	2	3	8 (72.7%)	3 (27.3%)
	unknown	6	3	2	1	0	6 (100.0%)	0 (0.0%)
	Total	74	11	5	8	50	**24 (32.4%)**	**50 (67.6%)**
2	yes	56	0	0	9	47	9 (16.1%)	47 (83.9%)
	no	6	4	0	0	2	4 (66.7%)	2 (33.3%)
	unknown	6	4	0	0	2	4 (66.7%)	2 (33.3%)
	Total	68	8	0	9	51	**17 (25.0%)**	**51 (75.0%)**
3	yes	32	0	0	3	29	3 (9.4%)	29 (90.6%)
	no	6	0	0	3	3	3 (50.0%)	3 (50.0%)
	unknown	0	0	0	0	0	0 (0.0%)	0 (0.0%)
	Total	38	0	0	6	32	**6 (15.8%)**	**32 (84.2%)**
Unknown	yes	12	0	0	1	11	1 (8.3%)	11 (91.7%)
	no	7	1	0	4	2	5 (71.4%)	2 (28.6%)
	unknown	64[k]	0	1	12	51[k]	13 (20.3%)	51 (79.7%)
	Total	83	1	1	17	64	**18 (21.7%)**	**64 (77.1%)**
Total	yes	157	4	1	18	134	**23 (14.6%)**	**134 (85.4%)**
	no	30	9	2	9	10	**20 (66.7%)**	**10 (33.3%)**
	unknown	76	7	3	13	53	**23 (30.3%)**	**53 (69.7%)**
	Total	263	20	6	40	197	**66 (25.1%)**	**197 (74.9%)**

[a]Data from cases reported in references 25–39, 41–48, 531, 536, 537, 621, 622, 632, 719–723.
[b]LB either by clinical history or positive *Borrelia burgdorferi* assay.
[c]Antibiotic therapy given for the episode of LB.
[d]Miscarriages or stillbirths.
[e]Four neonatal deaths occurred before 2 days of age, and one at 8 days.
[f]Includes nonfatal congenital anomalies, growth retardation, developmental delay, and neonatal illness (see Table 11–8).
[g]Includes miscarriages, stillbirths, neonatal deaths, illness, or abnormality.
[h]Percentage of total in treatment category is included despite small numbers in some categories.
[i]Trimester ≤1 indicates LB in first trimester, or prior to conception or first prenatal care visit.
[j]2 of 23 patients in one group in this category were not treated with antibiotics but, as specific outcomes were not separated out from their group, these were placed in the treated group and considered as Live Born, Normal, for use in this table to avoid overestimation of adverse outcome risk.
[k]Unspecified outcome for two pregnancies was considered as Live Born, Normal, for use in this table.

TABLE 11–15
Clinical Manifestations of Congenital Lyme Borreliosis (CLB)[a]

Fetal Death[b]
30% (9/30) risk after untreated GLB[c]
2.5% (4/157) risk after treated GLB
8% (20/263) risk after any GLB (9/20+)[d]
Most (75%, 15/20) occur at ≤20 weeks of gestation (range, 8–40 weeks) and may present with
  High frequency of
    Cardiac anomaly/abnormality (40%, 4/9, of fetal deaths after untreated GLB; 0%, 0/4, of fetal deaths after treated GLB)
Most occur after first- or second-trimester GLB (95%, 19/20), with variable interval between GLB and fetal demise.

Early Congenital, Severe
20% (6/30) risk after untreated GLB
4% (6/157) risk after treated GLB
6% (16/263) risk after any GLB (7/16+)[e]
Present in first week of life with acute suspected sepsis
  High frequency of
    Mortality (36%, 6/16)
    Cardiac anomaly or abnormality (56%, 9/16, overall; 85%, 5/6, in fatal cases)
    Respiratory distress (50%, 8/16)
    Prematurity (50.0%, 8/16, most ≤5 wks premature)
  May also have
    Intrauterine growth retardation
    Skeletal anomaly/abnormality/metaphyseal bands
    Neurologic abnormality/meningoencephalitis
    Fever
    Hepatosplenomegaly
    Hyperbilirubinemia
    Adenopathy
    Rash
    Lethargy/meningoencephalitis
    Miscellaneous anomalies
Most occur after first- or second-trimester GLB (63%, 10/16, overall; 100%, 10/10, when trimester of GLB is known).

Early Congenital, Mild
10% (3/30) risk after untreated GLB
4% (6/157) risk after treated GLB
8% (22/263) risk after any GLB
Present in first 2 weeks of life with mild illness
  Moderate frequency of
    Hyperbilirubinemia (32%, 7/22)
  May also have
    Genitourinary anomaly/abnormality
    Skeletal anomaly
    Cardiac abnormality/anomaly
    Rash
    Neurologic abnormality/meningoencephalitis/hypotonia
    Prematurity (all ≤4 weeks premature)
    Suspected sepsis
    Intrauterine growth retardation
    Adenopathy
    Miscellaneous anomalies
Most occur after first- or second-trimester GLB (41%, 9/22, overall; 90%, 9/10, when trimester of GLB is known).

Late Congenital
7% (2/30) risk after untreated GLB
4% (7/157) risk after treated GLB
4% (10/263) risk after any GLB (1/10+)[f]
Risk is a minimum estimate as long-term follow-up unavailable for most patients. 70% (7/10) of cases of late CLB occurred after treated GLB.
Present after 2 weeks of life, usually within first 2 years, with subacute illness
  High frequency of
    Developmental delay/meningoencephalitis (50%, 5/10)
  Moderate frequency of
    Genitourinary anomaly/abnormality (30%, 3/10)
  May also have
    Skeletal abnormality/metaphyseal bands
    Rash
    Prematurity
    Adenopathy
    Hepatosplenomegaly
    Fever
    Growth retardation/failure to thrive
    Miscellaneous anomalies
Potential progression to chronic neurologic, cardiac, skeletal, cutaneous, ocular involvement should be considered.
Most occur after second- or third-trimester GLB (60%, 6/10, overall; 86%, 6/7, when trimester of GLB is known).

[a]Data from Tables 11–8, 11–13, and 11–14, summaries of 66 adverse outcomes of gestational Lyme borreliosis.
[b]Miscarriages (including one induced abortion with congenital anomalies) or stillbirths. This represents a minimum estimate, as many of the published reports included patients enrolled only at the first prenatal visit or at delivery, and therefore did not include early miscarriage data.
[c]GLB-gestational Lyme borreliosis; treated/untreated refers to gestational antibiotic therapy.
[d]9 positive for borreliae in tissue samples.
[e]7 positive for borreliae in tissue samples.
[f]1 positive for borreliae in tissue samples.

10 to 15%; however, they indicated that enrollment at the first prenatal visit would have missed miscarriages that occurred before that visit. They also noted that if *B. burgdorferi* were to have very specific fetal teratogenic effects, if the period of fetal susceptibility to such effects were narrow, and if successful antibiotic therapy were to decrease the risk of such teratogenesis, a much larger study would be needed to determine a teratogenic effect.

In 1995, Williams and associates,[46] from the same group, reported a large cord blood serosurvey of 2500 infants in a Lyme-endemic and 2500 in a nonendemic area from 1986 to 1988 in New York; clinical information regarding congenital malformations was available for 95% of endemic and 97% of nonendemic area infants. Maternal *B. burgdorferi* exposure was 5 to 10 times higher in mothers from endemic than from nonendemic areas, and infants from endemic areas had a (significantly higher) 13% incidence of congenital cardiac defects and murmurs compared with a 5% incidence in those from nonendemic areas; there was no increase in the incidence of other malformations. Of cardiac malformations, VSD was the most common in both endemic and nonendemic infants; other defects in the endemic infants included tetralogy of Fallot, atrial septal defect, patent

ductus arteriosus, pulmonic stenosis, cyanotic congenital heart disease, multiple cardiac defects, hypoplastic right heart, and dextrocardia. Among endemic area infants, major malformations occurred in 17, 9, and 5% of infants born after gestational Lyme disease, pre-gestational Lyme disease, and gestational tick bite, compared with 3% born after neither maternal Lyme disease nor tick bite. Six infants, all from the endemic area, had histories of antibiotic-treated gestational Lyme disease, and one had had hypospadias. The authors note that late developmental sequelae would not be detected by this study owing to absence of long-term follow-up, and that a larger study would be needed to address the question of cardiac teratogenicity.

Two retrospective studies assessed the possible association of late neurologic or cardiac sequelae in infants with histories of gestational Lyme disease exposure.[727, 728] Gerber and Zalneraitis[727] surveyed 162 of 176 listed pediatric neurologists in Lyme-endemic areas of the northeastern and upper midwestern United States, as well as a random subset of adult neurologists in Connecticut, from 1989 to 1990, for possible cases of congenital Lyme disease in their practices. Only three children with a diagnosis of congenital Lyme disease were found, but the clinical histories were not considered by the study authors to meet criteria for gestational Lyme disease, and they concluded that one of the following is true: (1) congenital Lyme disease with neurologic sequelae is very rare; (2) it may involve sequelae not recognized as related; (3) the association of sequelae with congenital Lyme disease may be underrecognized because the association between the child's neurologic disorder and maternal Lyme disease was not made; or (4) neurologic sequelae could be too subtle to result in pediatric neurology consultation. Additionally, they note that the incidence of gestational Lyme disease is low in these areas because pregnant women commonly avoid tick exposure, because women with recent Lyme disease commonly delay pregnancy until after full recovery, because antibiotic prophylaxis of gestational tick bites by obstetricians in these areas is routine, and because prompt antibiotic therapy of gestational Lyme disease occurs. They note that a larger study would be needed to determine any association between subtle neurologic sequelae and congenital Lyme disease.

Strobino and colleagues[728] conducted a retrospective case-control study of 796 children who were followed by pediatric cardiologists for congenital cardiac anomalies (and 705 controls evaluated by those cardiologists for possible cardiac disease and found to have none), from 1985 to 1995, in a Lyme-endemic area in New York; they found no association of the occurrence of congenital cardiac anomalies with histories of maternal gestational or pre-gestational Lyme disease or tick bite, based on maternal retrospective questionnaires. Only four patients in each group had histories of maternal Lyme disease within 3 months before or during the pregnancies with these patients. Because the enrollment population included only children with congenital cardiac anomalies who survived to be referred to pediatric cardiologists, no conclusions could be made regarding any association of gestational or pre-gestational Lyme disease with cardiac anomalies that might have resulted in miscarriage, stillbirth, or early infant death.

Sigal suggests that because organogenesis is complete by the end of the second trimester, the risk of congenital anomaly should be very low in the late second and third trimesters.[729] It is generally agreed that the incidence of adverse outcomes of gestational Lyme borreliosis is low,[435, 530, 729–732] probably because of prompt antibiotic therapy for early gestational Lyme borreliosis, particularly when it presents with its easily recognized and most common manifestation, erythema migrans. Shapiro suggests that the existence of congenital Lyme borreliosis has not been ruled out, but it must be very rare.[733]

REVIEW OF 66 CASES OF ADVERSE OUTCOMES OF GESTATIONAL LYME BORRELIOSIS

Table 11–8 lists 66 individual cases of adverse outcomes of gestational Lyme borreliosis. Only five groups—Schlesinger and co-workers,[25] MacDonald,[33–35] Lavoie and associates,[32] Weber and colleagues,[38, 39] and Hercogova and co-workers[41]—have had any success in demonstrating spirochetes in either fetal autopsy or placental tissues, and only Trevisan and associates have confirmed spirochetes in a tissue biopsy.[43] Only one infant was found to be seropositive for *B. burgdorferi* antibody (patient 24), and this was transient; therefore, this does not appear to be a sensitive method of diagnosis, and reliance on seropositivity leads to misdiagnosis of the majority of congenitally infected infants. The poor protection provided by short courses of oral antibiotic therapy against the development of serious adverse complications of gestational Lyme borreliosis is evident from this table; this is discussed in detail in the section on Therapy.

Of the 20 fetal deaths among the 66 patients with adverse outcomes after gestational Lyme borreliosis, 95% (19 of 20) of the fetal deaths occurred after first- or second-trimester infection, 75% (15 of 20) of these fetal deaths occurred before 20 weeks of gestational age, and the incidence of cardiac anomaly or abnormality in fetal deaths after untreated and treated gestational Lyme borreliosis was 40% (4 of 9) and 0% (0 of 4), respectively. Information from fetal autopsies was available only for fetuses over 25 weeks' gestation, and all three stillborn infants and the 25-week miscarried fetus had significant cardiac anomalies.

Of the 16 infants with an early severe presentation among the 66 patients with adverse outcomes after gestational Lyme borreliosis, 100% (10 of 10) in whom the trimester of gestational Lyme disease was known occurred after first- or second-trimester infection; the incidence of cardiac anomaly or abnormality was 56% (9 of 16) overall and 85% (5 of 6) in fatal cases.

Currently, it is uncertain whether or not *B. burgdorferi* is teratogenic, although there is an indication that there may be, as noted earlier, an increased risk of congenital cardiac malformations after first- and early second-trimester gestational Lyme borreliosis, which is decreased by antibiotic therapy for the gestational episode. It is also possible that *B. burgdorferi* gestational infection with

transplacental dissemination could cause fetal pathology simply by causing Lyme borreliosis with the same manifestations (cutaneous, musculoskeletal, neurologic, neuropsychiatric, neurocognitive, and urologic) that it produces in children and adult patients, which could explain some of the adverse events noted in Table 11–8.

It is likely that prompt and adequate antibiotic therapy of gestational Lyme borreliosis may attenuate its potential adverse fetal effects, and may shift the clinical manifestations away from the more severe presentations such as miscarriages, stillbirths, perinatal deaths, and cardiac anomalies. This could result in higher infant survival rates, with an increased incidence of presentation with late sequelae, which would be expected to exhibit features similar to those of late Lyme borreliosis as described in the section Clinical Manifestations. It is also likely that neonates or infants with undiagnosed congenitally acquired *B. burgdorferi* infection who have received antibiotic therapy for bacterial culture–negative presumed sepsis may not be seropositive for *B. burgdorferi* antibody because of attenuation or prevention of seroconversion by early antibiotic therapy. If the antibiotic therapy has been inadequate to eliminate *B. burgdorferi* infection, these infants may present the dilemma of seronegative late Lyme borreliosis.

It is anticipated that more infants and fetuses with complications related to gestational Lyme borreliosis will be diagnosed in the future as the diagnosis is more frequently considered; it eventually will be possible to better describe the various clinical manifestations of congenital Lyme borreliosis. Large-scale prospective studies of sufficient numbers of patients with gestational Lyme borreliosis, with follow-up to determine the pregnancy outcome of each enrolled patient; *B. burgdorferi*–specific evaluation of any fetal or neonatal demise; and long-term follow-up of each infant born to determine the occurrence of possible early and late sequelae are needed.

FREQUENCY OF SPECIFIC ADVERSE OUTCOMES OF GESTATIONAL LYME BORRELIOSIS

Table 11–13 shows the frequency of occurrence of various types of fetal or neonatal adverse outcomes after gestational Lyme borreliosis.

The 23% incidence of cardiac malformation is strikingly high and includes significant abnormalities such as ventricular septal defect, coarctation of the aorta, and myocardial dysfunction, as well as less severe abnormalities such as patent ductus arteriosus and atrial septal defect; it is reminiscent of the ability of the spirochete to cause carditis, including cardiomyopathy and pancarditis, in older patients.

The 15% incidence of neurologic abnormalities is also high, and includes meningoencephalitis, hydrocephalus, and developmental delay; this would also be consistent with the neurotropic nature of the infection in older patients. One infant (patient 24) had focal parenchymal brain lesions with increased T_2 signal demonstrated by MRI scan that were similar to those reported in the literature in adult patients with chronic meningoencephalomyelitis.

The incidence of orthopedic abnormalities was 12%, but there were some unique features of this involvement, including 4 patients of the 66 with syndactyly or clubfoot, 2 with significant joint contractures, and 2 with a new finding of transverse metaphyseal bands.

The incidence of genitourinary abnormalities was 11%; these included cryptorchidism, inguinal hernia, hydrocele, hypospadias, renal dysplasia, and ureteral stenosis with hydronephrosis.

The incidence of maculopapular erythematous rash was 9%, which would be consistent with disseminated spirochetosis, and many of these rashes increased or developed during the first few days of antibiotic therapy and resembled Jarisch-Herxheimer reactions. The one infant (case 25) with chronic distal extremity rash that resolved after prolonged antibiotic therapy raises the possibility that this was similar to the rash of secondary syphilis or disseminated Lyme borreliosis in older patients.

Among the miscellaneous abnormalities reported were three patients (4.5%) with dental anomalies, including two with hypoplastic enamel and one with structural anomalies.

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

Congenital Lyme borreliosis presenting as manifestations that are not specific for *B. burgdorferi*, such as the 17% incidence of presentation as fulminant early sepsis, the 12% presentation with hyperbilirubinemia, and the 12% presentation with growth retardation, may be missed unless careful maternal gestational and pre-gestational histories are obtained.

Thirty percent (20 of 66) of the total number of adverse outcomes were miscarriages (including one aborted fetus with congenital anomalies), 9% (6 of 66) were neonatal deaths, and 39% (26 of 66) were either fetal or neonatal deaths.

FREQUENCY OF ADVERSE OUTCOMES OF 263 CASES OF GESTATIONAL LYME BORRELIOSIS

Table 11–14 shows the fetal and neonatal mortality rates, and the total fetal and neonatal adverse outcome rates divided by trimester and according to whether or not gestational antibiotic therapy was given. Those considered treated or untreated were patients in whom antibiotic therapy was specifically reported as having been specifically given or not given to the individual patient, and those considered as having unknown treatment were those in whom statements about treatment could not be correlated with the individual patient.

Effect of Trimester of Infection

Lyme borreliosis in the first trimester carried an overall 32% (24 of 74 patients) risk of adverse outcome. In the second trimester, the risk was 25% (17 of 68); in the

third trimester, it was 16% (6 of 38); in gestational Lyme borreliosis with trimester unspecified, it was 22% (18 of 83); the overall risk in all trimesters was 25% (66 of 263).

Effect of Gestational Antibiotic Therapy

Gestational antibiotic therapy had a protective effect against adverse fetal or neonatal outcome, and the overall adverse outcome risk after treatment in all trimesters was 15% (23 of 157); after no treatment in all trimesters, it was 67% (20 of 30). This protective effect was apparent in all trimesters: 18 compared with 73% in the first trimester, 16 compared with 67% in the second trimester, and 9 compared with 50% in the third trimester.

Rate of Miscarriage and Stillbirth

The overall risk of miscarriage for any trimester of infection was 7.6% (20 of 263 patients). Antibiotic therapy showed a protective effect, with a rate of 2.5% (4 of 157) fetal loss after treated gestational Lyme borreliosis, compared with 30% (9 of 30) without antibiotic therapy.

Rate of Neonatal Death

The overall risk of neonatal death for any trimester of infection was 2% (6 of 263 patients); the rate was less than 1% (1 of 157) with antibiotic therapy, and 7% (2 of 30) without antibiotic therapy, for gestational Lyme borreliosis.

Rate of Neonatal Illness

The risk of nonfatal neonatal illness for any trimester of infection was 15% (40 of 263 patients); the risk was 11% (18 of 157) with antibiotic therapy compared with 30% (9 of 30) without antibiotic therapy for the gestational Lyme borreliosis episode.

Description of Congenital Lyme Borreliosis

Table 11–15 lists the incidence, time of presentation, and clinical manifestations of the various adverse outcomes associated with gestational Lyme borreliosis, including miscarriage, early severe congenital Lyme borreliosis, early mild congenital Lyme borreliosis, and late chronic congenital Lyme borreliosis.

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

ASYMPTOMATIC INFANT WITH GESTATIONAL LYME BORRELIOSIS EXPOSURE

CLINICAL CASE

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

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

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

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

Placenta. No pathologic testing was performed on either placenta.

Infant 1. The baby, who was delivered by cesarean section 2 days after onset of the maternal Bell's palsy at 38 weeks of gestation, was considered normal at birth. However, he was hospitalized at 5.5 months of age for fever, irritability, lethargy, full fontanelle, and the possibility of culture-negative (bacterial and viral) sepsis or meningitis (normal spinal fluid); responded clinically to intravenous cefotaxime over 3 days; and developed a maculopapular rash on the second day of the cefotaxime treatment that resolved despite continuation of the cefotaxime. He was treated by his pediatrician with oral amoxicillin several times during his first 2 years of life for upper respiratory infections. When the mother's Lyme borreliosis was diagnosed 2 years after the birth of this infant, he was tested and found to have no antibodies to *B. burgdorferi*; he has remained normal at 2.8-year follow-up.

Infant 2. A second baby born to this mother in

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

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

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

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

MILD EARLY CONGENITAL LYME BORRELIOSIS

CLINICAL CASE (patient 23 in Table 11–8)

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

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

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

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

After the result of the proliferative assay was obtained, the infant was treated with intravenous ceftriaxone 100 mg/kg daily for 2 weeks and developed an intensely erythematous generalized maculopapular rash on the sixth day of treatment, which resolved despite continuation of the antibiotic. The inguinal adenopathy resolved by the end of the antibiotic therapy; the infant remained clinically well at 15 months, and by verbal report continued to be well at almost 6 years of age. ■

CLINICAL CASE (case 26 in Table 11–8)

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

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

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

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

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

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

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

These cases illustrate the importance of prompt and aggressive antibiotic therapy for gestational Lyme borreliosis. In one of these cases, the intravenous ceftriaxone had to be discontinued because of severe diarrhea and therapy was completed with high-dose penicillin; in the other case, the mother was treated with prolonged oral cefuroxime axetil through the time of delivery. Longer courses of intravenous antibiotic therapy have been more effective in the treatment of other manifestations of Lyme borreliosis. Recommendations for optimal antibiotic therapy of gestational Lyme borreliosis, for mild symptoms of congenital Lyme borreliosis such as inguinal adenopathy and mild lethargy as well as for the more obvious symptoms of severe congenital Lyme borreliosis are discussed in the section on gestationally exposed newborn infants; also, recommendations are made to begin antibiotic therapy promptly after birth to prevent later clinical sequelae. ■

SEVERE EARLY CONGENITAL LYME BORRELIOSIS

CLINICAL CASE (patient 24 in Table 11–8)

Mother. A 34-year-old woman had a tick bite between mid-April and late May 1987 at 6.5 to 12.5 weeks' gestation; she was treated with oral amoxicillin 250 mg three times daily for 10 to 14 days for sinusitis and flulike symptoms at 5 to 7 weeks', and at 20 to 22 weeks' gestation. A routine fetal sonogram performed at 17 weeks was normal, but another done at 24 weeks because of decreased amniotic fluid showed marked intrauterine growth retardation. Fetal blood sampling at 24.5 weeks showed normal chromosomes and no evidence of intrauterine viral infection; the infant was

delivered by cesarean section at 34 weeks' gestation. The mother remained clinically well following delivery and was seronegative for polyvalent EIA *B. burgdorferi* antibody at 1 week, 9 months, and 10 months after delivery; she was also negative by the *B. burgdorferi* LPA at 9 and 10 months.

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

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

This infant was initially considered to have culture-negative bacterial sepsis and was treated with intravenous ampicillin and gentamicin for 6 days, but failed to improve and continued to require platelet transfusions and intensive cardiovascular support. Because of the maternal gestational history of tick bite, the possibility of congenital Lyme borreliosis was raised, and intravenous ceftriaxone (100 mg/kg per day) was added on the seventh day and continued for 1 week; within 24 hours, the platelet count stabilized, the pressors were able to be discontinued, and the infant began to recover. Spinal fluid on the sixth day showed an elevated protein but no pleocytosis. The dense sclerotic transverse metaphyseal bands present in all of the long bones during the first week gradually resolved during ceftriaxone therapy. Extensive evaluation for bacterial and viral causes of this fulminant sepsis was unrevealing; neither did the infant have detectable polyvalent EIA *B. burgdorferi* antibody. The infant was eventually discharged from the hospital at 2 months of age in good condition.

By 9 months, she demonstrated growth retardation, mild developmental delay, mild lower extremity spasticity, and persistently small head circumference; the possibility of congenital Lyme borreliosis was reconsidered. At 9 but not at 10 months, she was found to have polyvalent EIA *B. burgdorferi* antibody; at 9 and 10 months, she had a positive *B. burgdorferi* in vitro LPA; and between 9 and 10 months, further evaluation included a normal spinal fluid with no detectable *B. burgdorferi* antibody, a normal electrocardiogram, normal complete blood count, slightly elevated liver enzymes, and MRI scan of the brain that showed left parietal parenchymal lesions of increased T_2 signal. She was treated with intravenous ceftriaxone (75 mg/kg daily) for 3 weeks for neuroborreliosis. She subsequently improved and exhibited normal growth and development at follow-up at 2.5 years of age.

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

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

The initial clinical presentation of this infant resembles the description by Lampert[31] of the infant with infantile multisystem inflammatory syndrome who was later found to have chronic Lyme borreliosis, as well as the description of some reported infants who had fulminant early congenital Lyme sepsis,[26, 32, 33, 38, 39] although this infant did not have the severe cardiac malformations found in some of these patients. ■

LATE CONGENITAL LYME BORRELIOSIS

CLINICAL CASE (patient 25 in Table 11–8)

Mother. A 35-year-old mother of five children visited a tick-infested farm with her entire family for 2 weeks every summer from 1988 through 1990, and she and several family members had occasional tick bites during this time. During the first 6 weeks of her next pregnancy, between mid-March and late April 1990, she developed a flulike illness that progressed to pneumonia and was associated with unusually large nonpruritic, nontender, vesiculobullous, and even purulent round or oval skin lesions on her legs. She was treated with almost continuous antibiotic therapy for the first 10 weeks of gestation, initially oral erythromycin (333 mg three times daily) for 7 weeks; followed by cefaclor (250 mg three times daily) for 3 days, intravenous cefuroxime (750 mg three times daily) for 4 days, and oral cephalexin (500 mg four times daily) for 2 weeks; and then oral cefixime (100 mg daily) for 10 days at 12 to 13 weeks. The large erythematous skin lesions intermittently reappeared during the second and third trimesters, and she

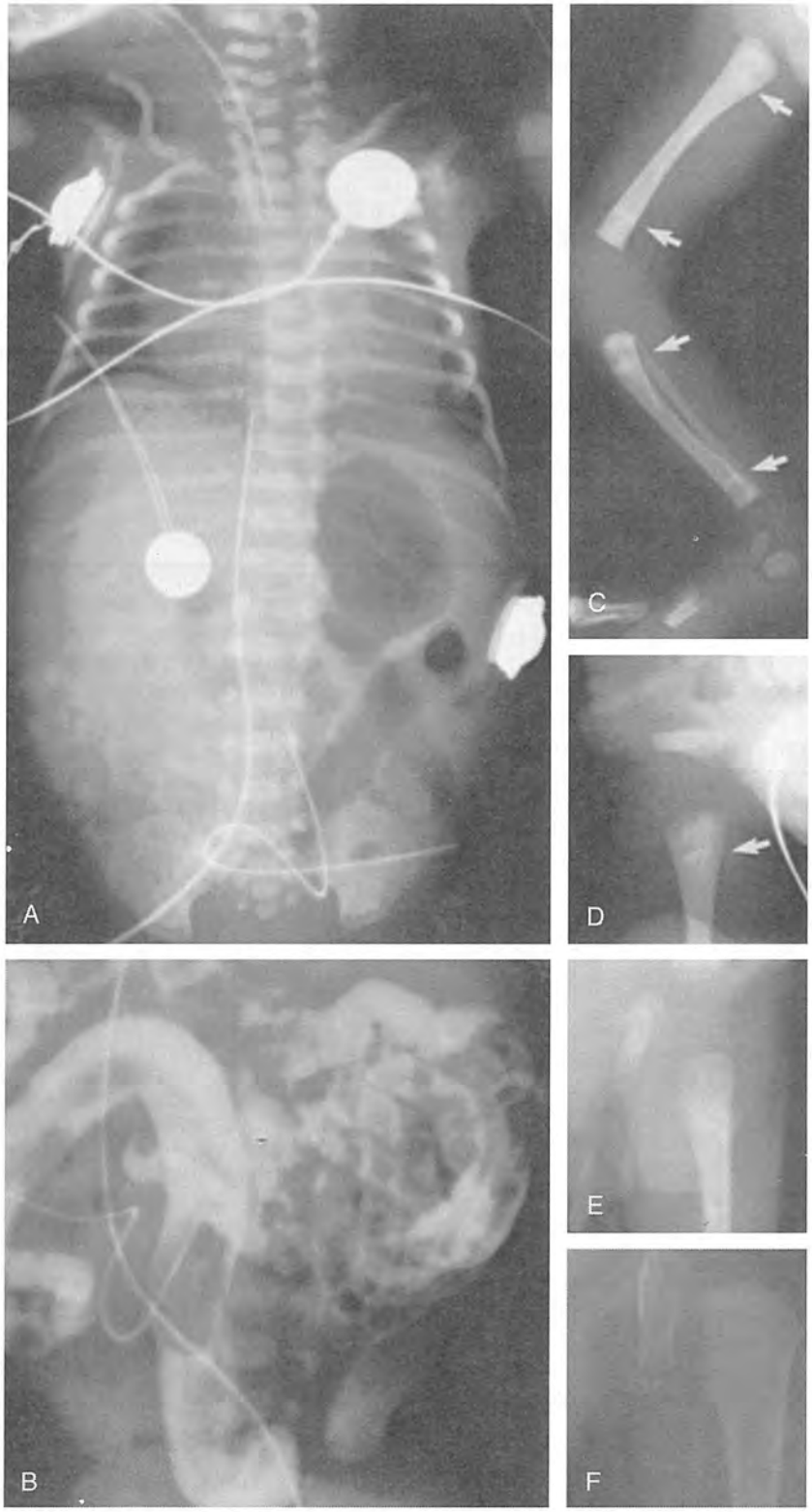

FIGURE 11–9 Congenital Lyme disease. An infant presented at birth with thrombocytopenia, cardiomyopathy, meconium ileus equivalent, and intrauterine growth retardation. *A,* Chest and abdominal radiograph at 1 day of age show cardiomegaly and mottled increased density in the right lower quadrant from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

developed progressive arthralgias and arthritis of her hips, knees, and lower back; by the time of delivery, in December 1990, she was unable to walk without stooping over. The skin lesions, polyarthralgias, and polyarthritis recurred after delivery and continued intermittently for 4 months post partum; she also noted headaches, fatigue, and short-term memory lapses.

In March 1991, the history of this maternal gestational illness and tick exposure was discovered on routine questioning during hospitalization of the then 3-month-old infant for severe failure to thrive. As part of the evaluation of the infant for possible congenital infection, maternal blood was sent and found to be seropositive for polyvalent EIA *B. burgdorferi* antibody. Figure 11–5*D* shows one of the mother's recurrent skin lesions, and a skin biopsy of this lesion showed the superficial and deep dermal perivascular lymphocytic inflammatory infiltrates commonly seen in erythema migrans lesions, but no spirochetes were seen.

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

Placenta. No placental pathologic examination was performed.

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

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

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

The child received a total of 7 weeks of intravenous ceftriaxone (100 mg/kg daily) between 2.5 and 7 months and showed dramatic improvement in neurologic function. When initial attempts were made to use a less aggressive and shorter course of intravenous ceftriaxone, he experienced relapse with evidence of loss of developmental milestones; finally, after a total of 7 weeks of intravenous ceftriaxone followed by a 1-year course of oral amoxicillin (40 mg/kg daily) from 7 months to 19 months of age, he remained clinically well and continued to progress to essentially normal neurologic status by 3 years of age. He had gradual resolution of the scaly erythematous maculopapular abdominal and distal extremity rash by the completion of the ceftriaxone therapy. He gradually improved neurologically, regained lost developmental milestones, and resolved the majority of his focal neurologic findings, including the subtle right hemiparesis, mild proximal hypotonia, and distal hyperreflexia, by 2 years of age. At follow-up at 3 years of age, he remained well, was at an appropriate developmental level, and was slowly learning to take food by mouth. At 8 years of age, he had reached an almost age-appropriate developmental and intellectual level, but developed regression of reading, spelling, and vocabulary skills, a seizure disorder, and episodic unilateral knee and ankle arthritis, with no additional *B. burgdorferi* exposure; the arthritis and deterioration of language skills responded to intravenous ceftriaxone therapy. At 9 years of age, he has regained almost all of the lost language skills, but exhibits delayed dentition and structural dental anomalies.

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

Comments. This mother-infant pair illustrates the ability of *B. burgdorferi* to cause severe progressive neurologic deficits consistent with chronic

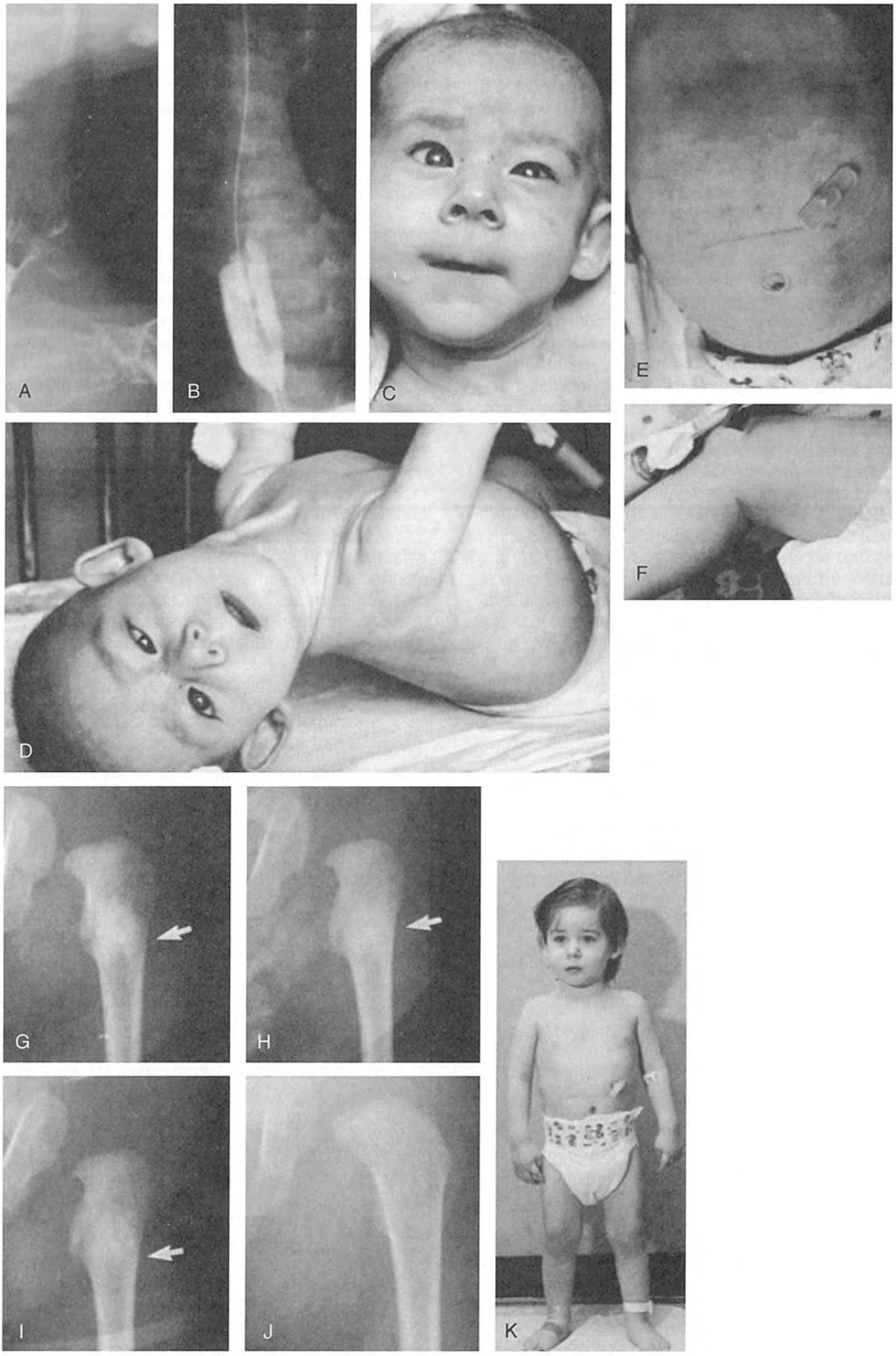

FIGURE 11–10 *See legend on opposite page*

neuroborreliosis, and the failure of oral erythromycin and oral cephalosporins to prevent these complications. However, the prolonged first-trimester courses of oral antibiotics may have sufficiently stabilized the gestational spirochetal infection to allow the pregnancy to be carried almost to term. Although there were several dysmorphic features in this infant, the significance of the cupped ears is unclear, as there were two other siblings with slightly "lop" ears.

The neurologic recovery of this patient during the prolonged course of antibiotic therapy and the near-normalization of his developmental level by 3 years of age lend support for such prolonged therapy until it appears that maximum recovery of neurologic function has occurred. The later development of arthritis, seizure disorder, and deterioration of language skills with no additional *B. burgdorferi* exposure, and improvement after antibiotic therapy are suggestive of a relapse of Lyme disease, and provide support for the use of additional antibiotic therapy for such relapses. The infant reported by Markowitz and colleagues who was normal at birth and later developed cortical blindness may represent this type of clinical manifestation of congenital Lyme borreliosis.[36] ■

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The demand for diagnostic testing for Lyme disease is great, particularly in Lyme-hyperendemic areas.[734–737]

False-positive serologic results for Lyme disease may occur because of cross-reactivity with other bacteria, particularly other spirochetes (Table 11–16); because of intra- or interlaboratory variability of assay results[529, 738, 739, 741]; or because of cross-reactivity seen in other diseases, including autoimmune disorders[224, 233, 236, 252, 742, 743] such as systemic lupus erythematosus, rheumatoid arthritis, and Reiter's disease; peridontal disease[245]; viral infections[233, 744–746] such as Epstein-Barr Virus (EBV), varicella-zoster Virus (VZV), and parvovirus B19; and non-Lyme meningoencephalitis or other neurologic diseases.[223, 233] Another problem is that seropositivity in residents of Lyme-endemic areas reflects the frequency of seropositivity of the area and may be unrelated to clinical illness.[254] Because ehrlichiosis and babesiosis occur in the same geographic distribution as Lyme borreliosis, and share many of the same tick vectors, seropositivity for these agents may reflect true exposure rather than cross-reactivity with *B. burgdorferi*[481–484, 486]; however, some cross-reactivity may be due to a heat shock protein of *B. burgdorferi* and the agent of human granulocytic ehrlichiosis (HGE) that shares amino acid sequence homology. Cross-reactivity is greatest, even by Western blot assay, between relapsing fever *Borreliae* and *B. burgdorferi*, which are usually distinguishable clinically, and are vectored by different tick species that do not share the same habitat niches; however, the geographic distribution of the tick vectors may overlap in some areas of the south central and southwestern United States.[477] Recognition that cross-reactivity may produce false-positive *B. burgdorferi* seroprevalence data in non–Lyme-endemic countries without known tick vectors is important.

False-negative serologic results may occur either because the sample was obtained early in the course of the Lyme disease before development of detectable *B. burgdorferi* immune responses,[222, 254] because early antibiotic therapy eliminated or blunted the *B. burgdorferi* immune response,[208, 209, 218, 232, 233, 254, 271, 272, 275] because of intra- or interlaboratory variability of assay results,[529, 738, 739, 741] because of regional antigenic strain variability, or because a low-level true-positive result is masked by cross-reacting antibody that necessitates a high "cut-off" for positivity.[739] Some patients reinfected with *B. burgdorferi* may have only an IgG response, and seropositivity may not be detected if only IgM assays are done in early reinfection.[233]

The practical ability to confirm or exclude Lyme disease by diagnostic assays remains a complicated and controversial problem. Continued development and clinical correlation of new diagnostic assays using increasingly sophisticated molecular biologic tools have improved diagnostic sensitivity and specificity, but the diagnosis of Lyme disease cannot be either made or excluded solely on the basis of these assays. Lyme disease must remain a clinical diagnosis, based on clinical and epidemiologic history, physical findings, and laboratory data other than *B. burgdorferi* serologic tests; the serologic test results may be considered either supportive or nonsupportive of the diagnosis, according to accepted guidelines.[238, 254, 478, 633, 748–750]

Diagnostic Tests

Diagnostic tests for Lyme disease are divided into several categories and are listed in Table 11–16. Practical problems with these tests are low sensitivity or low specificity, wide intra- and interlaboratory variability of the most common commercially available antibody de-

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

TABLE 11–16
Cross-Reactivity Between *Borrelia burgdorferi* and Other Spirochetes, *Babesia*, and *Ehrlichia*

	% OF PRIMARY DISEASE SERA WITH POSITIVE RESULT BY DIAGNOSTIC TEST									
							Babesiosis[c]		Ehrlichiosis[d]	
DIAGNOSTIC TEST	Lyme	Syphilis	Yaws, Pinta	Borrelial Relapsing Fever[a]	*Borrelia coriaceae*[b]	Leptospirosis	*B.m.*	WA1	HGE	HME
Bb IFA[e]		13–61	28–40	50	63	0–14			36	2
Bb ELISA[f]		20–100	40–43	45–100[g]		0–23	0	0	0–86[h]	0
ELISA-AC		0–4				5				
Bb WB[i]		0–50		64–100[g]		5–17	0	0	23–90[h]	0
WB (stringent)		0–9								
FTA-Abs[j]	6–43									
MHA-TP[k]	0									
RPR[l]	0									
VDRL[m]	0									
TP WB[n]	0–67									
Other borreliae[o], IFA	54–85									
Leptospira MA[p]	0									
B. microti IFA	0	0						0	0	0
B. microti ELISA	0									
B. microti WB	0									
WA1	0									<10
HGE IFA	0–6	0		0			0	0		0
HGE ELISA	4–26	0		0						0
HGE WB	4–13	0		0						0
HME IFA	0	0					0	3	11–56	
HME WB									0	

[a]*B. hermsii* and *B. recurrentis*, as well as many other borreliae, are the major causes of relapsing fever.
[b]*B. coriaceae* is endemic in soft ticks in California but rarely causes human illness.
[c]*B.m.* = *Babesia microti*; WA1 = *Babesia* species WA1.
[d]HGE = human granulocytic ehrlichiosis; HME = human monocytic ehrlichiosis.
[e]*Bb* IFA = *B. burgdorferi* immunofluorescence assay.
[f]ELISA = enzyme-linked immunosorbent assay; ELISA-AC = antibody capture ELISA.
[g]This represents only two patients in one group of two.
[h]Some of these results may represent past or current co-infection rather than cross-reactivity.
[i]WB = Western blot, results from all references listed; WB (stringent) = results from references 233–236, using stringent criteria for positivity.
[j]FTA-Abs = fluorescent treponemal antibody absorption test.
[k]MHA-TP = microhemagglutination assay for antibodies to *Treponema pallidum*.
[l]RPR = rapid plasma reagin test.
[m]VDRL = Venereal Disease Research Laboratory test.
[n]TP WB = *Treponema pallidum* WB.
[o]Other borreliae, IFA = immunofluorescence assay for other borreliae, including *B. hermsii*, a major cause of relapsing fever, and *B. coriaceae*.
[p]MA = microhemagglutination assay for antibodies to *Leptospira*.
Data obtained from references 20, 112, 233–236, 245, 401, 485, 487, 488, 498, 621, 746, 747, 757, 758, and 762.

tection tests,[529, 738, 739, 741, 750] and lack of availability of some of the better research laboratory tests.

CULTURE

The organism grows best in liquid Barbour-Stoenner-Kelly medium II (BSK II)[81, 91] at 35° C, usually takes 2 to 6 weeks to grow, is usually detected by dark-field examination of culture medium every 1 to 2 weeks, and is confirmed as *B. burgdorferi* by IFA with *B. burgdorferi*–specific monoclonal or other antibody, or by *B. burgdorferi*–specific PCR.[175] Use of PCR analysis to detect *B. burgdorferi* growth in culture fluids has produced more rapid detection of positive cultures, with detection of 95% of positive cultures 2 weeks after inoculation, compared with 70% by microscopic examination.[175] Culture is the "gold standard" for confirmation of Lyme disease, but disadvantages of culture are that generally it is not available outside of research institutions, it is cumbersome and time-consuming and is often positive only very early in untreated infection, and the overall yield is quite low.

Under optimal conditions, isolation rates from biopsies of active untreated EM skin lesions usually range from 28 to 86%[19, 79, 175, 183, 184] ACA lesions from 10 to 26%[19, 20, 436]; rates are much lower from other sites. Isolation rates from antibiotic-treated or partially treated EM lesions are 0 to 8%,[175, 183, 436] from normal-appearing skin after spontaneous resolution of EM lesions 8%,[436] and from partially treated ACA lesions 0%.[436] Berger and associates achieved an isolation rate of 86% by biopsy inside the peripheral border of the lesion,[183] and 57% by biopsy of perilesional skin just outside the peripheral border; the isolation rate was higher in EM from disseminated infection (88%), than from localized infection (71%); it was 100% in untreated disseminated infection.[183]

The rate of isolation of *B. burgdorferi* from blood

cultures has usually been 1 to 6%[80, 591, 751] in Lyme borreliosis even though hematogenous dissemination occurs clinically. In 1998, Wormser and colleagues[591] found that by using 3 ml of serum instead of 3 ml of whole blood, and inoculating samples within 3 hours of collection, positive cultures were detectable in 2.7 rather than 7.7 weeks, and positive cultures could be obtained in 20% of untreated early EM patients with solitary EM, 50% of untreated early multiple EM patients, and 25% overall of untreated early EM patients. Culturing a larger volume of serum by obtaining six simultaneously drawn 3-ml serum samples increased the yield, especially in patients with solitary EM. Patients with multiple EM had more positive blood cultures than those with single EM, indicating a higher level of spirochetemia. Goodman and co-workers[280] found higher rates of both culture and PCR positivity from plasma than from whole blood, and of PCR positivity from plasma than from serum, indicating possible concentration of spirochetes in plasma.

B. burgdorferi has been successfully grown from skin biopsy specimens of EM,[18, 79, 183, 184, 432] BL,[22] cutaneous B cell lymphoma,[647] ACA,[20, 436] and tick bite site skin biopsies,[307, 752] and of blood,[80, 591] CSF,[95] iris,[284] synovium or joint fluid,[200] ligamentous tissue,[304] bone,[699] myocardium,[607] and placental and fetal tissues.[32–35]

SILVER AND IMMUNOFLUORESCENT STAINS

B. burgdorferi spirochetes may be visualized by Dieterle,[16] Warthin-Starry,[33–35, 79] or Bosma-Steiner[94] silver staining, or by *B. burgdorferi*–specific immunohistochemical monoclonal or polyclonal antibody staining of tissue, or immuno-electron microscopy of blood or CSF.[620] The Bosma-Steiner modification of the Warthin-Starry stain has resulted in much improved sensitivity for demonstration of *B. burgdorferi*.[94]

B. burgdorferi has a characteristic morphology by silver staining that is distinct from that of other spirochetes and even other *Borrelia* species; they are sharply demarcated, short or long, coiled, undulating, or elongated straight forms, of equal thickness, with no irregularities or granularity, and they are found sparsely in tissues, in the superficial dermal papillae, often between collagen fibers, or in vessel walls.[597] *B. burgdorferi* spirochetes have also been found in the endomysial space in a myocardial biopsy by silver staining.[308] Its morphologic appearance may vary in different tissues and with the serologic status of the patient.

The specificity of immunohistochemical staining, including immunogold silver staining, is greater than that of silver staining alone. The sensitivity of detection of *B. burgdorferi* by staining ranges from 25 to 100%.

Spirochetes have been demonstrated in multiple tissues.*

DARK-FIELD EXAMINATION

Dark-field microscopy is not a sensitive method for visualization of *B. burgdorferi* because the number of organisms in infected tissues is very small and the yield is essentially zero, with occasional rare exceptions.[18]

POLYMERASE CHAIN REACTION

PCR is generally considered more sensitive than either culture or special stains for detection of *B. burgdorferi* in multiple tissues or body fluids; it is much faster than culture, providing results in a few days rather than the several weeks required for culture detection of *B. burgdorferi*.[185–187, 317] The sensitivity of PCR for detection of *B. burgdorferi* is highest in fresh or fresh-frozen specimens,[187] but PCR, using short DNA segments to detect DNA degraded by fixation, has even detected *B. burgdorferi* DNA extracted from 67% of de-paraffinized formalin-fixed, paraffin-embedded EM skin biopsies.[753]

Different PCR target gene sequences have been used to detect *B. burgdorferi*.[187] Use of sequences for the 41-kd flagellar antigen and 34-kd Osp B in PCR improved the sensitivity of detection of *B. burgdorferi* in CSF to 67% of patients with very early disseminated Lyme disease, even when CSF *B. burgdorferi* antibody was still negative.[282] Use of an Osp A gene sequence and use of a *B. burgdorferi* RNA polymerase gene sequence detected *B. burgdorferi* DNA in serum and plasma, respectively, of early Lyme disease patients, even before seropositivity developed.[280, 281]

In a comparative study that used a sequence from the *B. burgdorferi* RNA polymerase C gene, PCR was more sensitive than culture for detection of spirochetemia.[280] Other studies, however, have achieved higher culture positivity but did not directly compare PCR.[591]

The *B. burgdorferi* PCR is 100% specific if performed in a reliable laboratory without cross-contamination because the DNA target sequences are selected specifically for lack of cross-reactivity with other spirochetes.[143, 185, 753] These sequences are not present in other closely related *Borrelia* species or other spirochetes, and they are highly conserved among *B. burgdorferi* strains. PCR is generally considered to be useful in the detection of small numbers of *B. burgdorferi* in tissue or body fluid samples,[280–282, 591, 755] is particularly useful in the diagnosis of very early Lyme disease before standard serologic assays become positive,[280, 281] and may be more sensitive and less cumbersome than culture, but its use is limited to research facilities. Although reports of *B. burgdorferi* CSF, plasma, synovial fluid, or skin biopsy, or of urine PCR positivity converting to negativity after antibiotic therapy of neuroborreliosis,[287, 309–311] arthritis,[312, 314] EM,[316, 754] ACA,[143, 316] and BL,[754] suggest a correlation of PCR positivity with active infection, the role of PCR in decisions about antibiotic therapy has not been definitively established[186, 187, 324]; a positive *B. burgdorferi* PCR indicates presence of *B. burgdorferi* antigens; this may be due to either past or present *B. burgdorferi* infection, but it provides no information on organism viability or persistence of active infection because it detects even degraded DNA or residual DNA fragments present inside membrane bound blebs[102, 103] produced by *B. burgdorferi*.[186, 187] PCR has often been noted to have increased sensitivity for the detection of *B. burgdorferi* in clinical specimens obtained from patients after a few

*See references 25, 32–35, 38, 41, 43, 82, 267, 596, 597, 605, 607, 617, 618, 620, 623, and 695.

days of antibiotic therapy, which possibly is related to the release of spirochetal antigens into body fluids as spirochetes are killed by antibiotic therapy.[187]

IMMUNOFLUORESCENT ASSAY

Immunofluorescent assay (IFA) uses fluorescein-tagged antihuman immunoglobulin to detect serum, CSF, or synovial fluid IgG, IgM, or IgA antibody binding specifically to whole *B. burgdorferi* fixed on a slide.[1, 10]

The range of sensitivity of the polyvalent IFA is 13 to 100% in early Lyme disease, and 64 to 100% in late Lyme disease. With IFA, IgM antibody is detectable earlier in infection than IgG antibody; thus, it is more sensitive in the diagnosis of early Lyme disease, and it generally disappears by convalescence except in patients with persistently active Lyme disease. Under ideal circumstances, IFA may detect *B. burgdorferi*–specific IgM antibody in 100% of patients with early culture-positive erythema migrans on the day of presentation.[756] The specificity of Lyme IFA is low in patients with other spirochetal infections because of cross-reactivity between *B. burgdorferi* and other spirochetes, especially syphilis, but it is good in rapid plasma reagin (RPR)-negative patients (see Table 11–16). Major disadvantages of the IFA—subjective test reading, the need for highly trained personnel for test performance, lack of test automation, and unsuitability for high volume use—have resulted in its replacement by the ELISA in most laboratories.[250, 252, 750]

ENZYME-LINKED IMMUNOSORBENT ASSAY

The standard indirect enzyme-linked immunosorbent assay (ELISA) uses enzyme-tagged antihuman immunoglobulin to detect serum, CSF, or synovial fluid IgG, IgM, or IgA antibody binding specifically to either whole disrupted (sonicated) *B. burgdorferi* or specific *B. burgdorferi* components (antigens) bound to multi-well ELISA plates.[224, 252]

The ELISA is 13 to 92% sensitive in early Lyme disease and 89 to 100% sensitive in late Lyme disease. IgM antibody is detectable earlier in infection than IgG, and it generally decreases during convalescence except in patients with persistently active infection, although ELISA IgM antibody positivity has been found even in some successfully treated patients.[244]

The ELISA is more efficient and reproducible than the IFA.[224, 252] Comparisons of IFA and ELISA generally have shown that ELISA is also more sensitive and specific than IFA,[98, 224] although some reports have found them to be comparable.[250, 252] In RPR-negative patients, the sensitivity of IFA and ELISA is high for detection of late Lyme disease, when *B. burgdorferi* antibody levels are high, but lower for detection of early Lyme disease, when there is a high false-negative rate because of the combination of low *B. burgdorferi* antibody in the first few weeks and high background as a result of cross-reactive antibody.[222]

Cross-reactivity in both ELISA and IFA assays occurs between *B. burgdorferi* and other spirochetes (see Table 11–16). Because of the high cross-reactivity with syphilis, it is essential that an RPR test be performed on all Lyme-positive sera to exclude syphilis (as RPR does not cross react and should be negative in Lyme disease.[252] Only a low rate of cross-reactivity occurs with *Leptospira*[252, 746, 758] and *Rickettsia*.[252, 758] Cross-reactivity with *B. coriacea* may lead to confusion, as this infection is endemic in *Ornithodoros coriaceus* ticks in California's Mendocino County, and humans are an occasional host for this tick.

Other causes of false-positive Lyme ELISA or IFA results are normal spirochetal oral flora,[245] viral infections such as varicella-zoster virus (VZV), Epstein-Barr virus (EBV), or parvovirus,[18, 74, 224, 746] other bacterial infections such as subacute bacterial endocarditis,[745] and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and Reiter's disease.[224, 252, 743] Lyme Western blot appears to be more useful than ELISA for evaluation of Lyme serologic status in patients with certain of the illnesses listed here. The significant problem of false Lyme seropositivity by ELISA or IFA testing should serve as a reminder that serologic data should be judiciously interpreted in the context of both the clinical illness and epidemiologic data.

The sensitivity and specificity of the standard whole-cell ELISA sometimes have been increased by using either purified or recombinant components of the organism such as outer surface membrane lipoproteins,[124, 239, 241, 245] the 41-kd flagellar antigen[241, 242, 746] combinations of recombinant Osp C with a recombinant flagellin fragment,[125] or synthetic, non–cross-reactive, immunodominant peptide sequences of the flagellar antigen as antigens. Some Lyme disease patient sera may react with individual antigens present in whole-cell antigen preparations but not with recombinant preparations of the same antigens, possibly because the immunogenic epitopes are presented differently in the recombinant antigens.[108, 124] *B. burgdorferi* loses Osp C during repeated passage in culture; these strains are often used to produce antigens for ELISA assays, which do not detect the early IgM antibody response that is mainly directed toward Osp C. The use of either recombinant Osp C or Osp C–positive strains in ELISA assays has increased the sensitivity of detection of specific IgM antibody in early Lyme disease.[239]

ANTIBODY CAPTURE ELISA, IMMUNE-COMPLEX ELISA, AND ANTIBODY CAPTURE IMMUNE-COMPLEX BIOTINYLATED ELISA

The antibody capture ELISA (ELISA-AC),[757] which reduces competition between IgG and IgM for the same antigenic sites in the assay and false positivity due to rheumatoid factor, increased the sensitivity of detection of IgM and IgG in early Lyme disease so that diagnosis could be confirmed in 67% of acute patient sera and in 93% of convalescent sera. The IgM ELISA-AC was particularly useful in disseminated disease, where the rate of positivity was 71 to 100% and 93 to 100%, respectively, of acute and convalescent sera, compared with 25% and 75%, respectively, in localized Lyme disease. The ELISA-AC assay with flagellar antigen, using the biotin–avidin peroxidase method for demonstration

of IgM, increased the sensitivity and specificity of detection of IgM antibody compared with the standard indirect IgM ELISA with flagellar antigen.[746]

The sensitivity of the ELISA for detection of IgG antibody in early Lyme disease was increased by using a polyethylene glycol (PEG) precipitation method to dissociate the antibody sequestered in circulating immune complexes (IC) before performing the ELISA.[278] This PEG ELISA-IC assay detected IgG antibody in 100% of patients with histories of recent erythema migrans who were seronegative by the standard ELISA assay, and 95% of patients with seropositive Lyme disease; the false positivity rate was zero.

The antibody capture immune-complex biotinylated ELISA (EMIBA)[756] was able to detect specific IgM seropositivity in culture-positive EM patients, as early as the day of lesion biopsy in 100% of disseminated EM patients and in 73% of localized EM patients, including some who were IgM-seronegative by standard IgM or polyvalent ELISA, IgM Western blot, IgM IFA, and IgM ELISA-AC. For localized EM patients, the rate of IgM seropositivity was 36% by the ELISA-AC assay for free serum antibody, 55% by the EMIBA assay with whole *B. burgdorferi* antigen, and 73% with the addition of the flagellar peptide. The false positivity rate was zero. The EMIBA assay is specific and sensitive, particularly for serologic confirmation of early disseminated EM. It is less cumbersome than the lymphocyte proliferative assay and may be useful in the evaluation of seronegative Lyme patients, but it is not widely available.

WESTERN BLOT (IMMUNOBLOT)

This method detects serum, CSF, or synovial fluid IgG or IgM antibodies to many of the over 30 individual *B. burgdorferi* protein antigens,[120, 223, 232, 241, 249, 742] including major outer surface proteins, flagellar antigen, and heat shock proteins. The pattern of antibody to these specific *B. burgdorferi* antigens, demonstrated by the pattern of bands seen in the Western blot assay, is characteristic of Lyme disease and shows temporal evolution with initial expansion of the antibody repertoire and increasing disease duration.[222, 232–234]

The Western blot test is currently recommended as the second test in a two-step serologic testing algorithm, in which ELISA or IFA is used as the highly sensitive initial test, and positive or equivocal ELISA or IFA results are then evaluated by a highly specific Western blot test to exclude false positivity.[236, 478, 748] The Western blot is generally considered more sensitive and more specific than ELISA or IFA, but because of its complexity, it has been plagued by lack of standardization. Efforts are under way to reduce interlaboratory variability in the definition of Western blot positivity.[225, 254, 741, 749, 766]

CDC criteria for positive Western blots[238] are based on studies by Dressler and associates[234] and Engstrom and colleagues.[233] 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. For a positive IgG Western immunoblot, five of the ten most common bands must be present after the first few weeks of disease: 18-kd, 21-kd Osp C, 28-kd, 30-kd, 39-kd Bmp A, 41-kd Fla, 45-kd, 58-kd, 66-kd, and 93-kd bands. A dissenting opinion[759] regarding the CDC criteria[238] for Western blot positivity recommends inclusion of IgG antibody to 31-kd Osp A and 34-kd Osp B in the criteria because of concern that serologic confirmation in some patients would not be possible without these inclusions.

Although European criteria for Western blot positivity have not been officially standardized,[738] in 1997, Hauser and co-workers[237] proposed such criteria, based on extensive studies of over 500 European sera (from patients with early and late Lyme borreliosis and controls) tested in IgG and IgM Western blots prepared with antigens from the three major European genospecies: *B. burgdorferi sensu stricto*, *B. afzelii*, and *B. garinii*. The proposed criteria for positivity, with over 96% specificities, are: for *sensu stricto* IgG, at least one band of molecular weight 83/100, 58, 56, Osp C, 21, and 17a, and for IgM, at least one of 39, Osp C, and 17a or a strong 41; for *afzelii* IgG, at least two bands of 83/100, 58, 43, 39, 30, Osp C, 21, 17, and 14, and for IgM, at least one of 39, Osp C, and 17 or a strong 41; and for *garinii* IgG, at least one of 83/100, 39, Osp C, 21, and 17b, and for IgM, at least one of 39 and Osp C or a strong 41-kd band.

Because of *B. burgdorferi* strain variability, both between genospecies and within genospecies, the molecular weights of several *B. burgdorferi* protein antigens may vary, and some antigens may be variably expressed, resulting in apparent differences in antibody patterns if different strains are used as antigen sources in preparation of Western blots[108, 529]; use of monoclonal antibodies for identification of the protein bands is important for Western blot standardization to allow comparisons between different laboratories.[232, 233, 237]

The Western blot reactivity pattern differs slightly in sera of patients infected with different strains and genospecies of *B. burgdorferi sensu lato* from the United States, Europe, and Asia,[237, 760, 761] and, because of antigenic heterogeneity, differs slightly to moderately in sera reacting in Western blots prepared with different strains and genospecies.[108, 231, 257, 529, 760, 761] Lyme borreliosis patient sera are usually more reactive in Western blot assays prepared with strains homologous to the infecting strains or from the same endemic area.[760, 761] In Europe, where the three major *B. burgdorferi* genospecies all cause Lyme borreliosis, because of the more frequent association of certain clinical manifestations with some genospecies than with others, sera of patients with different clinical manifestations may show different reactivity patterns in Western blots prepared with the different genospecies.[257]

In early Lyme disease, when ELISA and IFA antibody responses are low, Western blot may be more sensitive and specific, particularly during the first 4 weeks of illness.[223, 232, 233, 236, 757] Sera from early Lyme disease of less than 1 week's duration were positive in 79% by Western blot, compared with 71% by the two-step test using ELISA as the initial test followed by Western blot testing only of positives by ELISA.[236] Sensitivity of the polyvalent Western blot is 53 to 92% in early Lyme disease and 100% in late chronic Lyme disease. Use

Text continued on page 594

TABLE 11–17
Laboratory Diagnosis of Lyme Borreliosis (LB)

ASSAY FOR *B. BURGDORFERI* (*Bb*)	*B. BURGDORFERI* COMPONENT DETECTED BY OR USED IN ASSAY	TIME COURSE OF POSITIVE RESULT (% PATIENTS WITH POSITIVE ASSAY RESULT DURING DIFFERENT STAGES OF LB)				ASSAY SPECIFICITY FOR *B. BURGDORFERI*[a]	ASSAY COMMERCIALLY AVAILABLE
		Early Localized LB		Early Disseminated LB	Late LB		
Culture of biopsy (bx) or fluid	Whole *Bb*, live	46–71% ac	2–92% EM[b] bx low % BL[b] bx 1–6% whole blood 5% plasma ac	71–88% ac	10–26% ACA[c] bx low % Snv[c] bx low % CSF[f]	++++	no
		20% ac	25% serum ac 6–100% CSF	50% ac			
Silver stain or FA stain[g] of biopsy	Whole spirochetes		29–100% EM bx 100% BL bx		low % ACA bx 25–100% Snv bx	++++	no
PCR[h]	*Bb* DNA sequences	25% ac	25–80% EM bx ac 7% whole blood ac	79% ac	16–71% ACA bx 80–85% Snv fluid[i]	++++	no
		9% ac	18% plasma ac 40–59% serum ac 45–90% urine ac	30% ac	100% Snv bx[j]		
IFA[j] IgG	Whole *Bb*		25–58% ac 58–100% cv[k]		80–100%	+++	yes
IFA IgM	Whole *Bb*	42–55% ac	20–94% ac 0–14% cv	100% ac	64–80%	+++	yes
IFA Polyvalent (IgG + IgM)	Whole *Bb*		13–100% ac 53–100% cv		94–100%	+++	yes
ELISA[k] IgG	Whole *Bb*	19% ac 28–50% cv	0–35% ac 8–100% cv 8% late cv	34–79% ac 60–62% cv	41–100% Ar[l] 90–92% NB[m] 90% ACA	+++	yes
	p83/100		14%	37%	86–100% Ar, NB, ACA	++++	no
	Flagellin	21% ac	0–31% ac 26–88% cv 37–46% late cv	55–70% ac 81% cv 63–100% late cv	68–100% Ar 95% ACA	+++	no
	Osp A[n]				42% Ar	++++	no
	Osp B[n]				42% Ar	++++	no
	Osp C[n]	31% ac 44% cv	33% ac 49% cv	34% ac 51% cv 65% NB	84% Ar 36% NB	+++	no
ELISA IgM	Whole *Bb*	9–58% ac 21–67% cv	9–92% ac 23–100% cv 12% late cv	34–89% ac 35–44% cv	36–64% Ar 10% ACA	+++	yes
	p83/100		7%	0%	12% Ar 100% NB 5% ACA	++++	no
	Flagellin	38% ac	18–50% ac 41–100% cv 23–44% late cv	43% ac 45% cv 17–53% late cv	68% 5% ACA	+++	no
	Osp C[o]	25% ac 50% cv	40–64% ac 67–85% cv	61% ac 72–80% cv	20–45% Ar, NB	++++	no

ELISA Polyvalent (IgG+ IgM)	Whole *Bb*	12–27% ac 52–60% cv	13–56% ac 19–98% cv	29–100% 77–96% cv	89–100% Ar, NB, ACA	+++	yes
	Flagellin	13–44% ac 53–54% cv	44% ac 53–65% cv	21–100% ac 83–100% cv	89–100% Ar, NB, ACA	+++	no
ELISA-AC[q] IgG	Whole *Bb*	0% ac 13% cv	13% ac 30% cv	0–50% ac 21–63% cv		+++	no
ELISA-AC IgM	Whole *Bb*	25–36% ac 75% cv	46–67% ac 90% cv	50–100% ac 60–100% cv	47%	++++	no
	Flagellin		50% ac 44% cv 54% late cv	65% ac 60% cv 47% late cv	12%	+++	no
ELISA-AC Polyvalent (IgG + IgM)	Whole *Bb*	25% ac	67% ac 93% cv	71% ac 93–100% cv		+++	no
ELISA-IC[r] IgG	Whole *Bb* Osp A		33–100% 36% ac		95–100%	+++	no
ELISA-IC IgM	Osp A		73% ac				
ELISA-AC/IC (EMIBA) IgM	Whole *Bb*	55% ac	70% ac	89% ac		++++	no
	Whole *Bb* + Flagellin	73% ac	85% ac	100% ac		++++	no
Western blot[s] IgG	Whole *Bb*	0–6% ac 13–16% cv	0–48% ac 16–80% cv 49–50% late cv	17–72% ac 25–71% cv	70–100% Ar, NB, ACA	++++	yes
	83–100 kd		23% ac 13–35% cv	28–29% ac 83% cv	76–100% Ar, NB, ACA		
	66 kd HSP		7% cv	56–83% cv	72–92% Ar, NB		
	58–60 kd HSP		0–54% ac 19–70% cv	84%	92–100% Ar, NB		
	41 kd Flagellin	0% ac 25% cv	57–85% ac 87–100% cv	92–100%	83–100% Ar, NB, ACA		
	31–33 kd Osp A	0% late cv	0–20% ac 5–7% cv	0–4%	40–100% Ar, NB 0–15% ACA		
	34–35 kd Osp B		0–5% ac 0–8% cv	0%	36–100% Ar, NB		
	20–25 kd Osp C		47–77% ac 19–83% cv	10–28%	48–95% Ar, NB 0–19% ACA		
	28–30 kd ?Osp D[t] 17–19 kd ?Osp E[u] 25–27 kd ?Osp F[v]		0% 0–5%	28–44% 84% 50% cv	72–100% Ar, NB 80–100% Ar, NB 49% Ar		
	45–46 kd		100% ac 70% cv	80%	46% Ar 72–84% Ar, NB		
	39 kd		85% ac 14–91% cv	20%	88–97% Ar, NB		
	37 kd 35 kd		46% ac 57% cv	4%	44% Ar, NB		
Western blot IgM	Whole *Bb*	24–36% ac 44–60% cv	23–87% ac 27–86% cv	31–76% ac 36–96% cv		++++	yes
	83–100 kd	33% cv	8–42% ac 5–49% cv	7–25% ac 7–10% cv	14% ACA		
	66 kd HSP		4–68% ac 8–80% cv	24%			
	58–60 kd HSP		28–58% ac 22–87% cv	36%			

Table continued on following page

TABLE 11–17
Laboratory Diagnosis of Lyme Borreliosis (LB) *Continued*

ASSAY FOR *B. BURGDORFERI* (*Bb*)	*B. BURGDORFERI* COMPONENT DETECTED BY OR USED IN ASSAY	TIME COURSE OF POSITIVE RESULT (% PATIENTS WITH POSITIVE ASSAY RESULT DURING DIFFERENT STAGES OF LB)				ASSAY SPECIFICITY FOR *B. BURGDORFERI*[b]	ASSAY COMMERCIALLY AVAILABLE
		Early Localized LB		Early Disseminated LB	Late LB		
	41 kd Flagellin	33–65% ac 73–90% cv	14–68% ac 36–77% cv	39–100% ac	33–40% Ar, NB 19% ACA		
	31–33 kd Osp A		0% ac 5–11% cv	0–12% ac	0–4% ACA		
	34–35 kd Osp B	0% cv 0% cv	0–5% ac 0–4% cv	0–12% ac 0%	20–100% Ar		
	20–25 kd Osp C		44–84% ac 52–91% cv	37–68% ac	19% ACA		
	45–46 kd		32–74% ac 20–83% cv	28%			
	39 kd		4–84% ac 8–94% cv	0% ac			
	37 kd		24–53% ac 32–80% cv	28% ac			
	35 kd		47% ac 13–63% cv				
Western blot Polyvalent (IgG + IgM)	Whole *Bb*		25–55% ac 14–86% cv	83–100% ac	100% Ar 100% NB	++++	yes
	Flagellin		75% ac 100% cv		83–100% Ar		
	Osp A		0% ac 0% cv		50% Ar		
	Osp B		0% av 0% cv		50% Ar		
LPA[a]	Whole *Bb*, killed or sonicated		0–36%		45–100%	+++	no
	Whole *Bb*, live		50–91%		82–100%	+++	no
	66 kd HSP				36%		no
	58 kd HSP				14%		no
	Flagellin		82%		21–68%	+++	no
	Osp A		82%		29–76%	++++	no
	Osp B				14%	++++	no
	Osp C				29%		no
PCR	*Bb* DNA sequence			25–100% CSF		++++	no
IFA	Whole *Bb*			92% CSF		+++	yes
Antigen-capture ELISA	Whole *Bb*			49% CSF		++++	no
	Osp A			24–100% CSF			
	Osp B			27% CSF			
	Flagellin			30% CSF			

ELISA IgG	Whole *Bb* or Flagellin	10–100% CSF		yes
ELISA IgM	Whole *Bb* or Flagellin	19–100% CSF		yes
	Osp A	20–100% CSF		
	Osp B	20–100% CSF		
	Osp C	50–100% CSF		
ELISA Polyvalent	Whole *Bb*	48–100% CSF		yes
ELISA-AC	Whole *Bb*			no
Polyvalent		42–100% CSF		
IgM		40–100% CSF		
ELISA-IC	Whole *Bb*			no
Polyvalent		38–43% CSF		
IgG		47% CSF		
IgM		64% CSF		
Western blot	Whole *Bb*	92% CSF	+++	yes
LPA	Whole *Bb*, sonicated	100% CSF	+++	no
	Whole *Bb*	100% CSF	+++	no

Culture data obtained from references 18–20, 22, 79, 80, 95, 183, 184, 260, 267, 280, 301, 302, 374, 434, 436, 439, 591, 595, 621, and 751.
Stain data obtained from references 82, 177, 596, 618, 621, and 695.
PCR data obtained from references 143, 280, 282, 287, 312, 313, 315–317, 436, 439, 595, 753, 754, and 755.
IFA data obtained from references 1, 18, 20, 39, 209, 235, 250–252, 466, 600, 621, 638, 644, 756, and 869.
ELISA data obtained from references 107, 124, 223, 224, 226, 232–236, 239–242, 246, 247, 251, 252, 267, 278, 621, 746, 756, and 757.
Western blot data obtained from references 108, 124, 222, 223, 225, 226, 229, 232–237, 239–241, 247, 249, 621, and 756.
LPA data obtained from references 208–210, 212, 213, 218, 219, 221, 267, 621, and 765.
CSF data obtained from references 214, 259, 260, 267, 282, 283, 285–287, 293, 309, 621, 654, 661, and 755.
[a]Estimation of specificity is given for RPR-negative sera (see Table 11–16).
[b]EM = erythema migrans skin lesion.
[c]ACA = acrodermatitis chronicam atrophicans skin lesion.
[d]BL = borrelial lymphocytoma skin lesion.
[e]Snv = synovial.
[f]CSF = cerebrospinal fluid.
[g]Warthin-Starry, Bosma-Steiner, or Dieterle silver stains, or *B. burgdorferi*–specific polyclonal or monoclonal FA (fluorescent antibody) stains.
[h]PCR = polymerase chain reaction.
[i]Excluding patients with antibiotic-resistant chronic arthritis, in whom a 96% polymerase chain reaction–positivity rate is found.
[j]IFA = immunofluorescence assay.
[k]ELISA = enzyme-linked immunosorbent assay.
[l]Ar = arthritis.
[m]NB = neuroborreliosis.
[n]Osp A = outer surface protein A.
[o]Osp B = outer surface protein B.
[p]Osp C = outer surface protein C.
[q]ELISA-AC = ELISA–antibody capture.
[r]ELISA-IC = ELISA–immune complex.
[s]Western blot: kd-kilodalton size of individual *B. burgdorferi* antigens.
[t]Osp D = outer surface protein D.
[u]Osp E = outer surface protein E.
[v]Osp F = outer surface protein F.
[w]LPA = lymphocyte proliferative assay.

of both immune-complex dissociation techniques and biotin-avidin Western blots has increased the sensitivity of detection of IgM and IgG Osp A antibody early in infection, when it may be located in immune complexes.[246]

Cross-reactivity with other spirochetes and the presence of low levels of positivity in control sera from endemic areas make it difficult to estimate the true incidence of false-positive Western blot assays, but it is considered to be low.

Patients with a strong clinical history of objective symptoms of Lyme disease and seropositivity by both ELISA and Western blot[279, 742, 763, 764] usually improve clinically with antibiotic therapy[742]; however, patients with only subjective symptoms, with either negative ELISA and negative Western blot or positive ELISA but negative Western blot, usually have some other inflammatory or rheumatologic disease instead of Lyme disease[279, 742, 763, 764] and do not improve with antibiotic treatment. Most patients with late Lyme borreliosis, such as arthritis, chronic neuroborreliosis, and ACA, who are seropositive by ELISA are also seropositive by Western blot.[223, 234–236]

LYMPHOCYTE PROLIFERATIVE ASSAY

Lymphocyte proliferative assay (LPA) determines specific reactivity of viable peripheral blood, CSF, or synovial fluid lymphocytes to whole *B. burgdorferi*, whole disrupted (sonicated) *B. burgdorferi*, or individual *B. burgdorferi* antigens incubated with these lymphocytes in vitro.[208, 209, 213, 218–221, 765] Some assays use peripheral blood mononuclear cells.

The development of the T cell response to Lyme disease precedes the antibody response, and the LPA may be positive in IFA- and ELISA-seronegative patients with early Lyme disease.[208, 219] After successful antibiotic therapy of Lyme disease, there may be some decrease in the level of LPA positivity.[213, 221]

The LPA may be positive in other patients who are IFA- and ELISA-seronegative as a result of prompt antibiotic therapy of early Lyme disease. The LPA was positive in all of 40 chronic Lyme disease patients in six studies, who were IFA- and ELISA-seronegative because of early antibiotic therapy.[208–210, 218]

In some patients, CSF[214, 220] and synovial fluid[221] lymphocytes are more reactive in the LPA than are peripheral blood lymphocytes; therefore, sensitivity may be increased by using these fluids.

The sensitivity of LPA is 50 to 91% in early Lyme disease, and 82 to 100% in late Lyme disease. Cross-reactions occur with other spirochetes, and the LPA positivity rate in healthy controls is 0 to 5%; in patients with non-Lyme inflammatory diseases, it is 5 to 11%.[210, 214, 218]

Although the LPA is more sensitive than antibody assays in certain patients, it requires use of live lymphocytes and whole *B. burgdorferi* or *B. burgdorferi* antigens, and is available only in research laboratories. The LPA therefore should be reserved for the diagnosis of Lyme disease in seronegative patients with good clinical objective evidence of Lyme disease, or for babies with potential congenital Lyme disease; it is not considered useful in following patient immune responses sequentially.

ANTIGEN CAPTURE ELISA ASSAY

The antigen capture ELISA, using either antibody against whole, sonicated *B. burgdorferi* or monoclonal antibodies against individual antigens such as recombinant outer surface proteins and flagellin, has been used to detect specific *B. burgdorferi* antigens in CSF.[283] In very early Lyme disease with neurologic involvement, this method detected specific antigen in CSF even before the development of specific CSF antibody. The Western blot method has also been used to determine the presence of specific antigens in CSF.[283] However, neither of these methods is commercially available.

Laboratory Variability and Efforts at Serodiagnostic Standardization

One of the major problems with laboratory diagnosis of Lyme disease is the wide intra- and interlaboratory variability of results both in the United States[739, 740, 750] and in Europe.[529, 738] Several comparisons in which standard Lyme disease case or control sera were sent simultaneously to different commercial, hospital, state, and national reference or research laboratories for *B. burgdorferi* antibody testing, usually ELISA or IFA, with or without Western blot testing, demonstrated that the percentage of laboratories that reported concordant results ranged from 10 to 93%, and the reproducibility of results within the same laboratory ranged from 27 to 96%. Agreement among laboratories was greatest for sera with high positive titers to *B. burgdorferi*, and least for sera with low positive titers.

There has been concern that *B. burgdorferi* strain heterogeneity in Europe may be responsible for variability in serologic results, but this may be more significant in Western blot assays than in ELISA assays.[257, 529]

Because of the problem of interlaboratory variability, proficiency testing programs have been recommended[478] for laboratories that perform *B. burgdorferi* testing, and these have been implemented in several areas.[739, 740] A study of a proficiency testing program in New York State, implemented in 1989 for clinical laboratories applying for *B. burgdorferi* antibody testing permits, found that performance improved during the study, partially because laboratories that initially used poorly performing test kits tended to change to better-performing kits, and overall sensitivity of ELISA, IFA, or solid-phase IFA assays was 95.4%; overall specificity 98.9%.[740]

Variability in results may therefore be due to differences in strains of *B. burgdorferi* used for preparation of the diagnostic kits, differences in the methods of kit preparation, use of different assays by different laboratories, differences in definitions of negative and positive results, geographic differences in the incidence of background Lyme seropositivity, and differences in quality control within individual laboratories. Better standardization of commercially available assays for Lyme disease is needed because the more specific, sensitive, and repro-

ducible research laboratory tests generally are not available.

Avoidance of Over- or Underdiagnosis

Establishment of a correct diagnosis of Lyme disease, with avoidance of over- or underdiagnosis,[24, 279, 763, 767, 768] allows selection of antibiotic therapy that is adequate and appropriate for the specific clinical presentation, as well as avoidance of over- or undertreatment, which is important for achieving maximal therapeutic efficacy with minimal adverse effects, both in the individual patient and in the population as a whole.

Between 38 and 79% of patients referred to Lyme disease or rheumatology specialty clinics for Lyme disease in endemic areas had been overdiagnosed and did not have active Lyme disease, and between 38 and 57% had alternate diagnoses made. Patients with only vague persisting symptoms, such as fatigue, headache, myalgia, and arthralgia, rarely had active Lyme disease and usually had fibromyalgia or fatigue syndrome (with or without previous Lyme disease); improvement in these patients did not correlate with antibiotic therapy.[279, 715, 763, 764, 767, 768, 770]

Although long-term persistence of active *B. burgdorferi* infection has been confirmed by culture,[200, 304, 306–308] and suggested by PCR,[312, 314] it is rare, particularly after adequate antibiotic therapy. Demonstration of objective evidence of persistent infection, preferably by culture positivity, but at least by PCR or diagnostic changes in specific *B. burgdorferi* antibody, is important because retreatment of true persistent infection is usually successful.[312, 314] Failure of a patient with a diagnosis of Lyme disease to respond to appropriate antibiotic therapy should raise the possibility that the initial diagnosis of Lyme disease may be incorrect, or that symptoms are not due to active *B. burgdorferi* infection.[24, 279, 767]

Alternately, underdiagnosis is also a potential problem, particularly after acquisition of the infection during travel to an endemic area and presentation with the clinical illness after return to a nonendemic area where the diagnosis may not be initially, or ever, considered. (See section Lyme Borreliosis in Travelers to Endemic Areas.)

Recommendations for Diagnostic Testing for Evaluation of Nongestational, Gestational, and Congenital Lyme Borreliosis

Because of wide variability in clinical case definitions used in the diagnosis of Lyme borreliosis, as well as in performance and interpretation of supportive *B. burgdorferi* diagnostic tests, there have been ongoing efforts in North America[238, 254, 478, 633, 741, 748] and Europe[8, 502, 738] to standardize clinical case definitions, as well as laboratory testing guidelines. The European Union Concerted Action on Lyme Borreliosis (EUCALB) has developed standardized European clinical case definitions[8, 502] (see Table 11–11), but serodiagnostic guidelines are not yet available.[738] Current CDC clinical case definitions of Lyme disease[633] (see Table 11–10) are intended for use in combination with CDC and FDA laboratory diagnostic test guidelines in the United States[238, 254, 633]; although they were initially designed for epidemiologic surveillance purposes, they have found widespread acceptance as a way to standardize the diagnosis of Lyme disease.

Several studies, including predictive statistical models[734–736] as well as prospective[767] and retrospective[279, 763, 768] clinical laboratory studies, have evaluated various approaches to the problem of how, when, and in whom to do diagnostic testing for Lyme disease. The American College of Physicians recently developed guidelines describing indications for diagnostic evaluation for Lyme disease.[478, 748]

The diagnosis of Lyme borreliosis in the nonpregnant patient should be a clinical diagnosis, made according to accepted case definitions, and supported by appropriate laboratory confirmation when needed, interpreted according to accepted criteria. According to the CDC case definition of Lyme disease (see Table 11–10), classic physician-diagnosed erythema migrans with endemic area exposure does not require laboratory confirmation, but other acute, early disseminated manifestations, including acute neuroborreliosis and carditis, or late manifestations require either positive culture or serologic confirmation by diagnostic CSF or serum levels of *B. burgdorferi* IgM or IgG antibody, according to the two-step method (by ELISA or IFA), followed by retesting of all positive or equivocal results by Western blot.[238, 254, 633] The EUCALB case definitions of Lyme borreliosis (see Table 11–11), similarly, do not require laboratory confirmation for classic erythema migrans, but do for other acute early manifestations, including borrelial lymphocytoma, acute neuroborreliosis, and carditis, and for late manifestations.[8, 502] There has been no standardization of diagnostic CSF *B. burgdorferi* antibody levels required for confirmation of neuroborreliosis,[478] but CSF IgM or IgG *B. burgdorferi* antibody levels exceeding serum levels are usually considered to indicate intrathecal antibody production.

The ELISA test, either polyvalent or IgM and IgG, is the most widely available assay for serodiagnosis of Lyme borreliosis; it is often preferred over the IFA for use as the initial test because of its suitability for large-volume testing. Antibody capture ELISA may have increased sensitivity and specificity but is not as widely available. Using Western blot retesting of sera that are positive or equivocal by initial ELISA or IFA tests increases specificity. Both IgM and IgG testing is recommended for evaluation during the first 4 weeks of early Lyme disease. Because negative serologic results during the first 2 weeks of illness are not sufficient to exclude Lyme disease, if early Lyme disease is strongly suspected and the first sample is negative, testing a 2- to 4-week convalescent sample is recommended. Although current CDC guidelines recommend only Western blot testing of ELISA-positive or equivocal sera, the Western blot may be useful in initial evaluation of early Lyme disease because its increased sensitivity may allow detection of more cases than ELISA during the first and second weeks of illness.[232, 233, 236] The Western blot may also

provide additional information regarding the time course of the infection.[233] Criteria for Western blot positivity are stringently defined in the CDC recommendations.[233, 234, 238] Use of IgM testing alone after the first 4 weeks of illness is not recommended, as a diagnosis of active Lyme disease should not be made on this basis alone. Use of IgM testing alone even for evaluation of early infection is not recommended, because some patients who have been reinfected with *B. burgdorferi* may have only an IgG response, which would be missed if IgG testing were not done.[233]

The lymphocyte proliferative assay is useful for diagnosis of seronegative patients with suspected Lyme borreliosis but is not generally available commercially. Biopsies of involved tissues for histopathology, culture, PCR, or silver or IFA staining are usually best reserved for special clinical circumstances, when serologic diagnosis is insufficient; culture of more readily accessible sites such as the CSF, blood, synovial fluid, or skin may be useful, but yields are low, except from erythema migrans lesions, and culture is not widely available. PCR is usually reserved for research purposes, but culture or PCR is useful when identification of the *B. burgdorferi* strain is needed. Although PCR provides evidence for the presence of *B. burgdorferi* DNA, it does not indicate the presence of viable spirochetes; culture of *B. burgdorferi* remains the only definitive proof of active ongoing infection.

The diagnosis of Lyme borreliosis in a pregnant woman should also be made according to the currently accepted CDC or EUCALB case definitions (see Tables 11–10 and 11–11 and section on Clinical Manifestations), with the additional recommendation that laboratory confirmation of the diagnosis is advisable, even for the clinical presentation as classic erythema migrans, to avoid later uncertainty, which might arise if only a clinical diagnosis were made. Because specific IgM seropositivity may be transient and development of specific IgG seropositivity may be prevented by early antibiotic therapy, immediate acute serum and several convalescent sera should be collected at approximately 2-week intervals over a period of approximately 8 weeks and at delivery. The initial acute sera should be sent for polyvalent or IgM and IgG Lyme ELISA, and also IgM and IgG Western blot; the remaining convalescent sera may be sent if no confirmation is obtained with the first sera. It is advisable to save aliquots of sera for possible future testing with more sensitive assays if they become available. The Western blot is advisable in evaluation of pregnant women with early Lyme disease, in whom early serologic confirmation is preferable, because of its increased sensitivity during the first 2 weeks of illness,[232, 233, 236] and because it may provide useful information regarding the time course of the infection.[232, 233] Although it is not recommended that biopsies of involved tissues be performed routinely in pregnancy, this could be done for diagnostic confirmation if clinically indicated. It is important to determine whether dissemination has occurred as this influences selection of antibiotic therapy and may affect pregnancy outcome; blood evaluation for evidence of spirochetemia, by culture, or possibly PCR, and CSF examination for evidence of early neuroborreliosis may be indicated for this purpose in some pregnant women.

There is no basis for routine *B. burgdorferi* antibody screening of asymptomatic healthy persons, because the incidence of false positivity exceeds the incidence of active Lyme disease in this group.[748] For the same reason, in the absence of studies indicating otherwise, there is no indication for routine prenatal *B. burgdorferi* antibody screening of asymptomatic healthy women. *B. burgdorferi* antibody serosurveys have demonstrated that seroprevalence in pregnant women[27, 37, 40, 45–47] reflects community seroprevalence; the rate of asymptomatic seroconversion was only 0.8% in one study during pregnancy.[45]

Any infant with possible congenital Lyme borreliosis should undergo evaluation by *B. burgdorferi* IgM and IgG ELISA and IgM and IgG Western blot on paired maternal and cord blood at delivery, and on the infant's blood and preferably CSF after birth, and if possible, *B. burgdorferi* culture and PCR as well on these samples. If the index of suspicion is high for congenital Lyme borreliosis and these assays are negative, the LPA should be performed (at a research center), as it appears to be more sensitive than serologic testing for confirmation of Lyme borreliosis in congenitally infected patients. Histopathology, Bosma-Steiner or Warthin-Starry silver stains, *B. burgdorferi*–specific antibody stains, culture, and PCR of the placenta are recommended. If biopsy specimens of involved tissues, such as skin, are obtained, they should be sent for the same studies, as these may be useful in diagnosis. Cardiac and neurologic evaluation should be obtained if there is a clinical suspicion of congenital heart disease or neurologic involvement. It is also advisable to store samples of sera, CSF, or tissues for possible additional future testing.

A full histopathologic evaluation is recommended of any placenta, miscarriage, stillbirth, or perinatal death from a pregnancy complicated by Lyme borreliosis. In addition, Bosma-Steiner or Warthin-Starry silver stains, *B. burgdorferi*–specific antibody stains, culture and PCR of the brain, heart, lungs, kidneys, liver, spleen, lymph nodes, bone marrow, synovium, and any other histologically abnormal tissues, and antibody assays, PCR, and culture of any blood or CSF available are recommended. Serum, CSF, and other samples should also be stored for future diagnostic tests.

Because the incidence of congenital Lyme disease is quite low, and needs more complete characterization, it is important to evaluate any suspected cases as fully as possible. The physician may wish to contact a center engaged in Lyme research for help in processing of these samples. The author has agreed to be available, by prearrangement, for discussion of infants suspected of having congenital Lyme borreliosis: Tessa Gardner, M.D., 314–727–9101.

Differential Diagnosis of Lyme Borreliosis

The differential diagnosis of Lyme borreliosis (Table 11–18), including gestational Lyme borreliosis, is extensive and depends on the particular stage and manifesta-

TABLE 11–18
Differential Diagnosis of Lyme Borreliosis[a] (LB)

DISEASE	RASH	FLULIKE ILLNESS	MUSCULOSKELETAL SYMPTOMS	CARDIAC SYMPTOMS	NEUROLOGIC SYMPTOMS	REFERENCES
Granuloma annulare	+					596, 639
Ringworm	+					599, 639, 763, 768, 870
Cellulitis	+					595, 599, 639, 767, 768, 870
Impetigo	+					595
Pityriasis rosea	+					763
Contact/atopic dermatitis	+					595, 639, 763, 768, 870
Erythema annulare centrifugum	+					639
Tick/insect bite reaction	+					595, 599, 639, 768, 870
Cutaneous malignancy	+					599, 644
Circulatory insufficiency[b]	+					599
Brown recluse spider bite	+	+				871
Serum sickness	+	+	+			243, 768, 870
Erythema nodosum	+					596, 598, 599
Erythema multiforme/urticaria	+	+	+			243, 274, 277, 279, 639, 763, 767, 768
Henoch-Schönlein purpura	+					596
JRA/RA[c]	+	+	+	+		274, 279, 651, 763, 767, 768
Lupus	+	+	+		+	243, 599
Dermatomyositis	+	+	+			599, 617
Scleroderma	+				+	596
Reiter's syndrome			+			651
Fibromyalgia		+	+		+	279, 715, 763, 767, 769, 770
Chronic fatigue syndrome		+	+			279, 763, 767, 768
Inflammatory bowel disease		+	+			279
Rheumatic fever	+	+	+	+	+	243, 687, 872
Bacterial endocarditis		+	+	+		693, 745
Acute myocarditis		+		+		279, 687, 785
Chronic cardiomyopathy				+		368, 607, 692
Syphilis	+		+	+	+	286
Relapsing fever		+				873
Sarcoidosis		+			+	211, 599
Mycoplasma pneumoniae infection	+	+	+	+	+	
Urinary retention, bladder neuropathy					+	669, 678
Diaphragmatic paralysis					+	679
Epstein-Barr virus mono	+	+	+	+	+	243, 763
Cytomegalovirus mono	+	+	+	+	+	763
Echo/coxsackievirus infection	+	+	+	+	+	687

Table continued on following page

TABLE 11–18
Differential Diagnosis of Lyme Borreliosis[a] (LB) *Continued*

DISEASE	RASH	FLULIKE ILLNESS	MUSCULOSKELETAL SYMPTOMS	CARDIAC SYMPTOMS	NEUROLOGIC SYMPTOMS	REFERENCES
Rubella	+	+	+		+	
Rubeola	+	+	+		+	
Hepatitis	+	+	+			698
Mumps		+	+	+	+	687
Rocky Mountain spotted fever	+	+	+		+	639
Babesiosis		+	+		+	639
Ehrlichiosis	+	+	+		+	639
Influenza		+	+	+		687
Adenoviral infection	+	+	+	+	+	687
Fifth disease (parvovirus)	+	+	+	+		744, 763
Arboviral infection		+			+	874
Herpes simplex	+	+			+	595
Zoster	+	+	+		+	338
Osteomyelitis			+			699, 763
Gonococcal arthritis			+			
Yersinia arthritis			+	+		687
Septic arthritis			+			653
Traumatic arthritis			+			768
Gout			+			279, 637
Temporomandibular joint disorder			+			875
Vertebral disk herniation			+		+	876
Vestibular neuronitis					+	518, 708
Meniere's disease					+	518
Orbital myositis					+	703
Retinal detachment					+	705
Papilledema, pseudotumor cerebri					+	289, 435, 530
Temporal arteritis					+	706
Aseptic meningitis	+	+			+	243, 530, 663, 763, 767
Idiopathic cranial/peripheral neuropathy[d]					+	279,659, 662, 763, 767, 768
European tick-borne encephalitis					+	639
Myasthenia gravis					+	767
Behçet's disease	+	+	+		+	211
Mollaret's meningitis		+			+	211
Multiple sclerosis		+			+	279, 608, 663
Amyotrophic lateral sclerosis					+	211, 279, 663, 677
Guillain-Barré syndrome, transverse myelitis		+			+	289, 530, 663, 669
Migraine					+	763, 768
Seizure disorder					+	279, 311, 325, 655, 663
Stroke, paresis, cerebral vasculitis, focal encephalitis					+	286, 292, 311, 663, 668, 672–676

TABLE 11–18
Differential Diagnosis of Lyme Borreliosis[a] (LB) *Continued*

DISEASE	RASH	FLULIKE ILLNESS	MUSCULOSKELETAL SYMPTOMS	CARDIAC SYMPTOMS	NEUROLOGIC SYMPTOMS	REFERENCES
Dementia					+	613, 663, 767
Catatonia, psychosis					+	663, 664
Brain tumor					+	279, 311, 610, 671
Meningeal lymphoma					+	768
Narcolepsy					+	289
Depression					+	767
Anorexia nervosa					+	663
Cryptococcal meningitis					+	
Severe pain syndrome[e]					+	279, 680

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

tion of infection, as described in the section Clinical Manifestations. Because Lyme borreliosis may manifest with symptoms relating to almost any organ system, a pregnant woman with Lyme disease may seek medical care from physicians in diverse medical or surgical specialties. Familiarity with the various clinical manifestations of Lyme borreliosis and a careful clinical and epidemiologic history, including history of tick bite or exposure to endemic areas, are necessary to allow correct diagnosis, especially when the clinical presentation is unusual. If the initial diagnosis of gestational Lyme borreliosis is not made, the neonatologist, pediatrician, or family practitioner may be presented with either a miscarriage, stillbirth, or congenitally infected infant and may need to make a retrospective diagnosis of maternal gestational Lyme borreliosis.

The characteristic rash of EM is usually easily recognized but may be misdiagnosed if it is vesicular, necrotic, or otherwise unusual in appearance. Usually, a careful clinical history of the rash will lead to the correct diagnosis, which may be confirmed by serologic testing, by biopsy, or by response to antibiotic therapy. Borrelial lymphocytoma is less widely recognized in the United States than in Europe and may therefore be mistaken for cellulitis or cutaneous malignancy, but a careful clinical history and serologic or biopsy confirmation usually lead to the correct diagnosis. A common error is to misdiagnose the initial presentation of ACA, a swollen painful bluish red leg, as circulatory insufficiency, even in Europe where ACA is prevalent; the diagnosis of ACA may be missed because it may present in a patient living in a nonendemic area, years after the initial infection was acquired in an endemic area. Nearly all patients with ACA are *B. burgdorferi* IgG–seropositive.[529]

The flulike illness associated with early Lyme borreliosis may be indistinguishable from that caused by other generalized infections or inflammatory illnesses, such as viral infections, connective tissue disorders, and drug hypersensitivity reactions. The correct diagnosis usually can be made by clinical and epidemiologic history, confirmation of Lyme seropositivity, and, when necessary, serologic exclusion of the other causes. It is important to consider Lyme borreliosis in patients with even fleeting objective signs, such as arthritis, meningitis, or neurologic symptoms, in Lyme-endemic areas.[636, 768]

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

When the presenting symptoms are acute and neurologic, without antecedent EM, the diagnosis of Lyme borreliosis may be difficult to make. In acute neuroborreliosis, cranial nerve palsies, such as Bell's palsy, Horner's syndrome, or Argyll Robinson pupil, may be misdiagnosed as idiopathic rather than Lyme-related; radiculitis may produce localized pain severe enough to be mistaken initially for an acute abdominal emergency, cholecystitis or cholelithiasis, ulcer, nephrolithiasis, vertebral disk herniation, myocardial infarction, or zoster, but these usually may be excluded by the absence of the expected abnormalities by appropriate radiographic, sonographic, or other diagnostic tests, and by Lyme seropositivity, as most patients with acute neuroborreliosis[234, 236, 529] are *B. burgdorferi*–seropositive by sensitive and specific assays. The central nervous system manifestations of neuroborreliosis initially may be mistaken for viral meningoencephalitis, stroke, multiple sclerosis, brain tumors, or even dementia or psychiatric disorders, but the correct diagnosis can usually be established by serologic testing for Lyme borreliosis, as most patients

with chronic neuroborreliosis[234, 236] are *B. burgdorferi*–seropositive and have diagnostic levels of CSF antibody, and by appropriate testing to exclude the other diagnoses. When the presentation mimics brain tumor, a biopsy is indicated, and if Lyme borreliosis is in the differential diagnosis, the specimen should be sent for *B. burgdorferi* culture, staining, and possibly PCR, as well as for histopathologic examination.

The musculoskeletal manifestations of Lyme borreliosis, particularly Lyme arthritis, initially may be confused with rheumatoid arthritis and occasionally with septic arthritis, but the diagnosis of Lyme disease usually may be made by clinical history, negative rheumatoid factor, negative joint fluid cultures for standard bacteria, and Lyme seropositivity, as most Lyme arthritis patients are IgG *B. burgdorferi*–seropositive at presentation.[234–236] There may be slight increases in rheumatoid factor during Lyme arthritis, but these should be transient. Presentation with a ruptured Baker's cyst or with quadriceps femoris muscle atrophy, with resultant patellofemoral joint dysfunction, is characteristic for late complications of Lyme arthritis.[318]

Other spirochetal infections, such as leptospirosis and syphilis, and other tickborne infections, such as ehrlichiosis and babesiosis, may result in false seropositivity for *B. burgdorferi* by some screening tests, but usually can be distinguished from Lyme disease by Western blot testing and by careful clinical and epidemiologic evaluation. False seropositivity is also a problem with non-Lyme borrelial relapsing fever, and distinguishing the two diseases can be difficult serologically even with Western blot testing[233, 236]; however, the clinical presentations and epidemiologic niches of the diseases are quite different and are usually helpful in diagnosis.

Differential Diagnosis of Congenital Lyme Borreliosis

The differential diagnosis of congenital Lyme borreliosis (Table 11–19) includes bacterial and viral sepsis and meningoencephalitis, toxoplasmosis, syphilis, leptospirosis, relapsing fever, ehrlichiosis, babesiosis, idiopathic congenital heart disease, immunodeficiency and recurrent infections, infantile multisystem inflammatory disease, and even sudden infant death syndrome. Early severe congenital Lyme borreliosis may be misdiagnosed as acute fulminant sepsis and meningoencephalitis or severe congenital heart disease, because of its similar presentation. Early mild congenital Lyme borreliosis may be mistaken for viral meningitis or sepsis because standard bacterial cultures are negative; as a result, the clinical improvement resulting from intravenous antibiotic therapy (commonly with antibiotics that also treat *B. burgdorferi*) given for the possibility of bacterial sepsis is attributed to spontaneous resolution of the presumed viral infection rather than to treatment of the *B. burgdorferi* infection. Late congenital Lyme borreliosis may manifest with symptoms of a more chronic congenital infection, such as failure to thrive, developmental delay, hypotonia, or recurrent infection. It is possible that neurocognitive abnormalities may be currently underrecognized sequelae of late congenital Lyme borreliosis, similar to recent reports of neurocognitive abnormalities related to chronic Lyme encephalopathy in older patients (discussed in the section Clinical Manifestations: Neuroborreliosis).

The diagnosis of congenital Lyme borreliosis may be made in infants with these presentations by obtaining a history of maternal gestational illness compatible with Lyme disease (see earlier section Differential Diagnosis); by serologic, culture, or PCR confirmation of maternal gestational Lyme disease; by exclusion of the other causes by serologic and/or culture evaluation of the infant; and, if possible, by serologic, culture, PCR, or lymphocyte proliferative assay confirmation of *B. burgdorferi* infection of the infant. If placental tissue is available, histopathology, culture, PCR, and special stains for *B. burgdorferi* spirochetes may confirm the diagnosis.

Because of histopathologic similarities between con-

TABLE 11–19
Differential Diagnosis of Congenital Lyme Borreliosis (CLB)[a]

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

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

genital and placental Lyme borreliosis and syphilis, it is advisable to rule out syphilis serologically in infants with suspected congenital Lyme borreliosis. Because Lyme borreliosis, ehrlichiosis, and babesiosis often share tick vectors and geographically endemic areas, it is also advisable to evaluate infants with suspected congenital Lyme borreliosis for ehrlichiosis and babesiosis, and to consider the possibility that these co-infections may require additional antibiotic coverage or may increase the severity of illness. Congenital Lyme disease should also be considered as a possible cause of some cases of infantile multisystem inflammatory disease, a chronic progressive inflammatory disease of so far undetermined etiology, with cutaneous, neurologic, ophthalmologic, lymphoreticular, and joint involvement, particularly as one of these patients was considered to have congenital Lyme disease.[624, 625] Lyme borreliosis also appears to be involved in some instances of sudden infant death syndrome and should therefore be considered in infants with missed sudden infant death syndrome.[33]

THERAPY

Antibiotic therapy has been used for treatment of Lyme borreliosis since 1958 when Hollstrom found that penicillin cured the skin lesions of European EM.[331] Between 1977 and 1979, following the initial description of North American Lyme disease and EM by Steere and associates,[15] it was unclear whether antibiotic therapy was beneficial in Lyme disease. However, because of the similarities between Lyme disease and European EM, the improvement of European EM with penicillin therapy, and the suspicion that the etiology of both was spirochetal, trials of antibiotic therapy for Lyme disease were conducted between 1977 and 1983 by Steere and colleagues, and a definite response to antibiotic therapy of the cutaneous, arthritic, and neurologic manifestations was found.[201, 339, 619, 771] It is currently accepted that delayed or inadequate antibiotic therapy of early Lyme borreliosis may increase the risk of dissemination and long-term sequelae.[206, 308, 312, 314, 325, 683, 714]

Clinical antibiotic therapy trials are discussed in the remainder of the subsections of the section Therapy; recommendations for antibiotic therapy are discussed and provided in the subsection Recommendations for Antibiotic Therapy of Gestational, Nongestational, and Congenital Lyme Borreliosis, and in Tables 11–20 and 11–21.

Antibiotic Therapy Efficacy Trials

Early antibiotic therapy trials by Steere and coworkers[201, 339] between 1976 and 1981 demonstrated that low-dose, short (7- to 10-day) courses of oral penicillin or tetracycline for treatment of EM led to more rapid resolution of EM than did erythromycin. Tetracycline prevented development of major late manifestations, penicillin decreased this incidence to 8%, and erythromycin to 14%.[201] Penicillin decreased the incidence of later development of Lyme arthritis from 74% to 35% and shortened the duration of Lyme arthritis from 17 weeks to 4 weeks when it occurred, but it did not affect the incidence of later cardiac (4%) or neurologic (14%) involvement.[201, 339] The severity of the minor late systemic symptoms of headache and musculoskeletal pain correlated with the severity of the initial presentation. Patients who were seen more than 2 weeks after the onset of symptoms of early Lyme disease had evidence of clinical dissemination.[757]

Further trials by the same group in 1983[619, 771] showed that high-dose intravenous penicillin (20 million units daily for 10 days) was effective for treatment of chronic Lyme arthritis and acute Lyme meningitis. The possibility was raised that penicillin treatment failures,[79, 619, 771] with progression of early EM to later complications, could be due to failure to eradicate spirochetes in the central nervous system or synovia or other immunologically protected sites, either because of the short penicillin half-life, the relatively high and variable penicillin MIC of *B. burgdorferi* (see Table 11–1), or the failure to achieve and maintain spinal fluid or synovial fluid levels above the MIC of the spirochete. Inadequate antibiotic therapy may be due to inappropriate choice of antibiotic, route, dose, or duration of therapy.

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

Intravenous ceftriaxone was found to be more effective than intravenous penicillin by Dattwyler and associates,[775] and it cured approximately 90% of refractory patients with late chronic Lyme disease, including arthritis and peripheral neuropathy of over 1 year's duration. Hassler and colleagues[776] found intravenous cefotaxime to be more effective than intravenous penicillin for treatment of late European Lyme borreliosis, including patients with oligoarthritis, peripheral neuropathies, radicular pain, ACA, and borrelial lymphocytoma. They proposed that success with cefotaxime was related to high tissue antibiotic concentrations above the MIC of *B. burgdorferi* during the entire dose interval and to excellent CSF penetration, and that high sustained levels above the MIC are needed because of reduced tissue permeability that may occur in late Lyme borreliosis as a result of microangiopathic changes in the synovia and nervous system.

If antibiotic therapy of the initial early Lyme disease has been inadequate for eradication of the spirochete but has been given promptly enough to attenuate or eliminate the *B. burgdorferi* antibody response,[18, 208, 209, 218, 272] seronegative late chronic Lyme borreliosis may develop.

Because rates of cure for late chronic Lyme borreliosis were less than 100%, even with high-dose intravenous cefotaxime or ceftriaxone therapy,[200, 269, 281, 283, 287, 304, 311–315] several studies were done to determine whether longer courses of therapy or use of different antibiotics was indicated to eliminate the spirochete in potentially se-

TABLE 11–20
Treatment of Lyme Borreliosis

CLINICAL CLASSIFICATION	ADULT, NONPREGNANT	CHILD, NON–CONGENITALLY INFECTED[a]	ADULT, PREGNANT[b]
Early localized[c] (Erythema migrans; borrelial lymphocytoma) *or* Early disseminated, mild[c] (Multiple erythema migrans; isolated cranial neuropathy; mild arthritis; mild cardiac, or other organ involvement; no evidence of central nervous system (CNS) involvement)	Doxycycline[d] 100 mg PO bid × 14–30 d *or* Amoxicillin[e] 500 mg PO tid–qid × 14–30 d *or* Cefuroxime axetil 500 mg PO bid × 14–30 d	Doxycycline[d] (for >8 yrs old) 2–4 mg/kg/day PO bid × 14–30 d *or* Amoxicillin[e] 50 mg/kg/day PO bid-tid × 14–30 d *or* Cefuroxime axetil 40 mg/kg/day PO bid × 14–30 d	Ceftriaxone 2 g IV QD × 14 d *or* Cefotaxime 6 g/day IV tid × 14 d *or* Penicillin G[f] 20–24×10[6] units/day IV q4h × 14 d
Early disseminated, serious (Severe arthritis[g], CNS or severe neurologic[h] involvement; severe cardiac, or other organ involvement) *or* Late disseminated (Chronic arthritis[g]; chronic meningitis, encephalitis, peripheral neuropathy[h], chronic cardiac, or other organ involvement; >6–12 months)	Ceftriaxone 2 g IV QD × 14–30 d *or* Cefotaxime 6 g/day IV tid × 14–30 d *or* Penicillin G[f] 20–24×10[6] units/day IV q4h × 14–30 d Doxycycline, amoxicillin, or cefuroxime axetil PO × 30–60 d alternative for arthritis[g]	Ceftriaxone 50–100 mg/kg/day IV qd × 14–30 d *or* Cefotaxime 150 mg/kg/day IV tid × 14–30 d *or* Penicillin G[f] 300,000 units/kg/day IV q4h × 14–30 d Doxycycline, amoxicillin, or cefuroxime axetil PO × 30–60 d alternative for arthritis[g]	Ceftriaxone 2 g IV QD × 14–30 d *or* Cefotaxime 6 g/day IV tid × 14–30 d *or* Penicillin G[f] 20–24×10[6] units/day IV q4h × 14–30 d

Recommendations for children and nonpregnant adults are adapted from references 265, 291, 635, 639, 642, 652, 657, 784, 786, 877, 887, and 888, and recommendations for pregnant women are based on limited data from Tables 11–8 and 11–13 of adverse outcomes of gestational Lyme borreliosis following oral antibiotic therapy. Lengths of therapy are not well established. The author prefers consideration of the higher and longer dosages and lengths of therapy, and recommends cerebrospinal fluid evidence of absence of CNS involvement if isolated cranial neuritis is to be treated orally.

[a]Pediatric antibiotic doses should not exceed adult doses. Doxycycline (or tetracycline) should not be used in children <8 years of age.

[b]Doxycycline (or tetracycline) should not be used in pregnant or lactating women. The author prefers to recommend intravenous therapy, but if this is not feasible, amoxicillin 500 mg tid–qid, or cefuroxime axetil 500 mg bid, may be used for a prolonged period, not shorter than for nonpregnant patients, ranging from 21–30 days to the duration of pregnancy.

[c]Erythromycin 250–500 mg (30–50 mg/kg/day, pediatric) PO tid–qid is less effective but may be used in penicillin-, cephalosporin-, or tetracycline-allergic patients with early localized or early mild disseminated infection. It is not a first-line choice, and if used in pregnancy, it should be discontinued 1 week prior to delivery. Clarithromycin (500 mg PO bid × 10–30 d) is an alternative, but not in pregnancy,[235] and no data are available on its use for treatment of pediatric Lyme borreliosis.

[d]Tetracycline 500 mg PO qid (25–50 mg/kg/day qid for >9 years of age) is considered a doxycycline alternative by some.

[e]Addition of probenecid 500 mg (50 mg/kg/day, pediatric) PO tid–qid to enhance serum antibiotic levels is optional. Phenoxymethylpenicillin 500 mg (50 mg/kg/day pediatric) PO qid is considered an amoxicillin alternative by some.

[f]Ampicillin 8 g/day (200 mg/kg/day, pediatric) IV qid is considered a penicillin alternative.

[g]Oral alternative for arthritis in nonpregnant patients, in the absence of CNS involvement: doxycycline 100 mg (2–4 mg/kg/day, pediatric, for >8 yrs of age) PO bid, or amoxicillin 500 mg (50 mg/kg/day, pediatric) (+ optional probenecid) PO tid–qid or (for doxycycline- or penicillin-allergic patients) cefuroxime axetil 500 mg (40 mg/kg/day, pediatric) PO bid × 30–60 d. Doxycycline (or tetracycline) should not be given to pregnant or lactating women. In some antibiotic-refractory chronic Lyme arthritis patients, arthroscopic synovectomy may be considered.

[h]Some recommend longer, up to 42-d treatment for encephalomyelitis. Ceftriaxone 2 g IV qd × 30 d is recommended for treatment of late Lyme encephalopathy. Possible alternative for neuroborreliosis in penicillin- or cephalosporin-allergic nonpregnant patients: doxycycline 100 mg IV or 100–200 mg PO q12h × 30 d,[190, 275, 885] or chloramphenicol 1 g IV q6h × 14–30 d,[795] although insufficient data are available on long-term outcomes with doxycycline, and failures have been reported with chloramphenicol.[676]

questered sites that were less accessible to the immune response or antibiotic therapy.[199, 208, 265, 269, 273, 276, 310, 667]

Between the mid-1980s and the present, many antibiotic efficacy trials, ranging from small, open-label pilot studies to large, comparative, randomized, double-blind multicenter studies, were done to determine the optimal antibiotic, route of administration, and duration of therapy for the various clinical manifestations of Lyme borreliosis, predominantly in North America and Europe. Optimal therapeutic regimens should not only treat the existing Lyme borreliosis, but should ideally prevent development of later manifestations of Lyme disease, such as meningoencephalitis, myocarditis, and arthritis. The question has arisen regarding management of asymptomatic persons with histories of previous untreated Lyme borreliosis; one group has recommended oral doxycycline (100 mg twice daily for 1 month), if not contraindicated, for such individuals to reduce the likelihood of development of late Lyme disease.[777]

ERYTHEMA MIGRANS, BORRELIAL LYMPHOCYTOMA, AND ACRODERMATITIS CHRONICA ATROPHICANS

Data from several antibiotic therapy trials indicate that prompt antibiotic therapy of early EM results in cure

TABLE 11–21
Treatment of Congenital Lyme Borreliosis (CLB)[a]

CLINICAL CLASSIFICATION OF CLB	AGE AT TIME OF ANTIBIOTIC THERAPY		
	Neonate, <1 Week	Neonate, 1–4 Weeks	Infant >4 Weeks
Gestational LB exposure: Asymptomatic infant, born to adequately treated mother[b]	No antibiotic *or* Amoxicillin 40 mg/kg/day PO tid × 10–30 d	No antibiotic *or* Amoxicillin 50 mg/kg/day PO tid × 10–30 d	No antibiotic *or* Amoxicillin 50 mg/kg/day PO tid × 10–30 d
Gestational LB exposure: Asymptomatic infant, born to inadequately treated mother[c] *or* Early CLB: Infant symptomatic in first 2 weeks of life[cf]	Ceftriaxone 50 mg/kg/day IV/IM q24h × 14–30 d *or* Cefotaxime 100 mg/kg/day IV/IM q12h × 14–30 d	Ceftriaxone[d] 75 mg/kg/day IV/IM q24h × 14–30 d *or* Cefotaxime[e] 150 mg/kg/day IV/IM q8h × 14–30 d	Ceftriaxone 100 mg/kg/day IV/IM q12h × 14–30 d *or* Cefotaxime[e] 150 mg/kg/day IV/IM q8h × 14–30 d
Late CLB: Infant symptomatic after first 2 weeks of life[ef]		Ceftriaxone[d] 75 mg/kg/day IV/IM q24h × 14–42 d[f] *or* Cefotaxime[e] 150 mg/kg/day IV/IM q8h × 14–42 d[f]	Ceftriaxone[d] 100 mg/kg/day IV/IM q12h × 14–42 d[f] *or* Cefotaxime[e] 150 mg/kg/day IV/IM q8h × 14–42 d[f]

Recommendations are based on limited data, and lengths of therapy are not well established.
[a]Different age-appropriate doses are shown, but treatment is recommended as soon as possible after birth.
[b]Because there is a wide range in what is considered adequate therapy, the alternative of oral amoxicillin therapy to be given pending further evaluation of the neonate for CLB is offered.
[c]Because ceftriaxone should not be used if hyperbilirubinemia is present, cefotaxime is offered as an alternative, although clinical experience in therapy of Lyme borreliosis is not as extensive as with ceftriaxone.
[d]Ceftriaxone dose 50 mg/kg/day IV/IM q24h if weight <2000 g.
[e]Cefotaxime dose 100 mg/kg/day IV/IM q12h if weight <1200 g.
[f]Prolonged oral amoxicillin (40 mg/kg/day) after the course of IV antibiotic therapy may be considered, depending on the clinical course of the infant.

rates of 76 to 92% with oral penicillin 10 to 12 days,[201, 785] 87 to 95% with oral amoxicillin plus probenecid for 10 to 21 days,[193, 782] 88 to 98% with oral doxycycline for 10 to 21 days,[193, 782, 784] 93 to 95% with oral cefuroxime axetil for 20 days,[783, 784] and 76 to 98% with oral azithromycin for 5 to 7 days,[193, 203] but that more severe early disseminated infection with multiple EM, arthralgia, or subtle neurologic symptoms is associated with increased risk of treatment failure, including late symptoms, and requires more aggressive antibiotic therapy.[643, 719, 720, 784, 786, 789]

Several European studies have demonstrated efficacy of antibiotic therapy for European borrelial lymphocytoma and ACA.[315, 316, 645, 646, 697]

B. burgdorferi PCR of skin biopsies of EM and ACA lesions has been reported to be useful in determining cure after antibiotic therapy.[143, 316]

LYME ARTHRITIS

Several studies have found that antibiotic therapy of chronic Lyme arthritis results in cure rates of 28 to 55% with intravenous penicillin,[619, 775, 776] and 81 to 100% with intravenous ceftriaxone,[775] intravenous cefotaxime,[776] oral doxycycline,[324] or oral amoxicillin and probenecid for periods of 10 to 30 days.[274, 424, 652, 775, 776] The major disadvantage of oral therapy for Lyme arthritis is that, in one large study, 12% developed later neuroborreliosis[324]; these patients all had subtle neurologic symptoms initially. It is now recognized that oral therapy should not be used in patients with even subtle neurologic involvement; they should be treated with IV ceftriaxone for at least 30 days.[652]

Because several studies have found that intra-articular or systemic steroid therapy of patients with Lyme disease is associated with lack of response to antibiotic therapy, including intravenous penicillin and ceftriaxone treatment of late Lyme arthritis, steroid therapy is not currently recommended in the initial routine treatment of Lyme arthritis.[620, 775] Steere and co-workers recommend intra-articular steroids only once or twice for antibiotic-unresponsive patients with negative synovial fluid PCR and persistent arthritis despite anti-inflammatory agents.[652]

Arthroscopic synovectomy has been successful in treating patients with chronic Lyme arthritis who had failed to respond to appropriate antibiotic therapy or intra-articular steroids.[652, 792] It has been suggested that PCR positivity of synovial fluid could be used to indicate the need for intravenous antibiotic therapy, and PCR negativity the need for anti-inflammatory agents (including hydroxychloroquine or intra-articular steroids) and possibly synovectomy.[312, 324, 652]

LYME CARDITIS

A 94% recovery rate was reported for 105 North American and European patients with Lyme carditis who were treated with various therapies, including penicillin, tetracycline, third-generation cephalosporins, steroids, and nonsteroidal anti-inflammatory agents.[689] A temporary pacemaker was required in 28% of these patients.[689] Improvement in patients with *B. burgdorferi*–associated chronic dilated cardiomyopathy has also been reported with intravenous ceftriaxone.[692]

Intravenous ceftriaxone or high-dose penicillin is preferable for treatment of serious carditis, although oral antibiotic therapy may be acceptable for mild carditis such as first-degree heart block (see Table 11–20). Systemic steroid therapy (1 to 2 mg/kg per day prednisone) may also be indicated for severe carditis if it is unresponsive to initial antibiotic therapy,[98, 687, 689, 793] and temporary pacemaker placement may be needed for complete heart block.[98, 689]

NEUROBORRELIOSIS

Clinical trials of antibiotic therapy of neuroborreliosis have reported cure rates of 66 to 100% with intravenous penicillin for 10 days,[275, 775, 776] 63 to 100% with intravenous ceftriaxone for 10 to 14 days,[291, 655, 662] and 60 to 90% with intravenous cefotaxime for 10 to 14 days.[776, 794]

Some recent studies of oral antibiotic therapy for the treatment of mild European neuroborreliosis have found over 90% efficacy with oral doxycycline for 10 to 20 days,[190, 191, 275, 883] and 80 to 93% efficacy with intravenous ceftriaxone for 14 days followed by oral amoxicillin or cefadroxil plus probenecid for 100 days, or with oral cefixime alone for 100 days.[276, 310]

Most studies have found ceftriaxone and cefotaxime superior to penicillin,[776] and longer courses of antibiotic therapy more efficacious for treatment of neuroborreliosis.[287, 291, 310, 324, 684]

B. burgdorferi has been demonstrated by PCR to invade the central nervous system (CNS) early in Lyme disease, even in the absence of CNS symptoms.[282] This has significant therapeutic implications and lends support to the concept that maintenance of high spinal fluid antibiotic levels during treatment of disseminated Lyme borreliosis is essential in order to eradicate the spirochete in the CNS, where it is in a relatively protected environment. Antibiotic therapy for disseminated Lyme disease, with or without cranial neuritis, should be selected to achieve high spinal fluid levels.

It has been suggested that PCR might be useful in therapeutic decisions: A positive CSF PCR in an untreated or an inadequately treated patient probably indicates that treatment or retreatment is indicated, and conversion of a CSF PCR from positive to negative probably indicates that therapy has been successful.[186, 287, 309]

The optimal duration and choice of antibiotic therapy for neuroborreliosis are still not well defined, although most sources currently recommend 2 to 4 weeks of intravenous ceftriaxone or cefotaxime for both early disseminated and late chronic neuroborreliosis with CNS involvement[657, 797]; longer courses are being evaluated.[265] Several sources note that treatment of isolated cranial neuropathy without CSF abnormalities with oral doxycycline or oral amoxicillin for 2 to 4 weeks is acceptable.[291, 654, 657, 661, 797] Four- to 6-week courses of intravenous antibiotic therapy may be needed for parenchymal brain neuroborreliosis,[292, 657] and it may be advisable to reevaluate CSF after the first 2 weeks to assess the need for further antibiotic therapy.[657] Steroid therapy is not recommended for neuroborreliosis,[657] and has been reported to be adversely associated with the course of neuroborreliosis.[674, 676]

Although optimal antibiotic therapy for ophthalmic Lyme borreliosis has not been determined, several sources currently recommend more aggressive antibiotic therapy than for other manifestations of early localized Lyme borreliosis, such as 30 days of oral antibiotic therapy for early disease (conjunctivitis, Bell's palsy, keratitis, and episcleritis), and 14 to 30 days of intravenous antibiotic therapy for more serious or late disease (optic nerve, posterior segment, or neuro-ophthalmic disease).[520, 702] Systemic steroid therapy in the absence of antibiotic therapy is not recommended[702] because of reports of adverse effects on the course of ophthalmic Lyme borreliosis.

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

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

Early comparisons of the clinical efficacy of various antibiotics in the treatment of Lyme disease demonstrated that tetracycline was best, penicillin next best, and erythromycin worst[201]; these results correlated with efficacy studies in animal models. The cephalosporins ceftriaxone, cefotaxime, cefuroxime, and cefixime all had good activity against *B. burgdorferi* by both in vitro MIC and in vivo animal model efficacy studies.[188, 195]

B. burgdorferi is killed slowly by antibiotics and requires prolonged levels above the MIC of the organism for cure,[192] suggesting the possible need for longer than 10 days of high-dose antibiotic therapy to kill *B. burgdorferi* in the spinal fluid.

Several studies correlating CSF antibiotic levels with clinical outcome of neuroborreliosis treated with oral or intravenous doxycycline,[190, 191, 194, 779] intravenous ceftriax-

one,[194, 319, 778] intravenous cefotaxime,[190, 319] and intravenous penicillin[194, 778, 779] have been done.

Ceftriaxone, cefotaxime, or doxycycline may be preferable to penicillin for therapy of Lyme borreliosis because their longer half-lives allow maintainance of tissue antibiotic concentrations above the MIC for *B. burgdorferi* during the entire course of therapy.

Jarisch-Herxheimer Reaction and Other Antibiotic Therapy Side Effects

Symptoms of the Jarisch-Herxheimer reaction, which may occur in 7 to 50% of patients treated with antibiotics for Lyme borreliosis, are most likely due to antibiotic-induced spirochetal lysis, which releases lipoproteins capable of inducing tumor necrosis factor and other cytokines, and produces cytokine-mediated responses.[781] Typical symptoms initially consist of vasoconstriction with hypertension, pallor, and chills in the first 6 to 18 hours, followed by vasodilation with hypotension, headache, flushing, and exacerbation of arthralgias, myalgias, rash, and fever for 24 to 48 hours.[776] Development of the Jarisch-Herxheimer reaction is more common if the Lyme borreliosis is severe,[201] disseminated,[719] or chronic,[269, 704, 776] presumably because the spirochetal burden is high, but this may also occur with treatment of uncomplicated solitary erythema migrans.[781] In unusual instances, Jarisch-Herxheimer reactions in patients with chronic neuroborreliosis have been reported to be associated with transient visual deterioration, confusion, stupor, dysarthria, myoclonic jerks, or dense hemiparesis[269, 704]; similar observations have been made in occasional patients with ophthalmic syphilis.[704]

The incidence of occurrence of a Jarisch-Herxheimer reaction within 24 hours after initiation of antibiotic therapy of Lyme borreliosis is 10 to 50% with penicillin or amoxicillin,[201, 435, 719, 771, 776, 782] 0 to 16% with tetracycline,[201, 719] 8 to 12% with doxycycline,[782–784] 7% with erythromycin,[201] 12 to 29% with cefuroxime axetil,[783, 784] and 22 to 40% with cefuroxime, cefotaxime, or ceftriaxone.[775, 776, 783] Development of a Jarisch-Herxheimer reaction may be considered evidence of a response to antibiotic therapy. It is important to recognize this reaction, including the increased rash that may occur, as a Jarisch-Herxheimer reaction rather than an allergic reaction to the antibiotic, in order to prevent unnecessary discontinuation of the antibiotic therapy. Treatment of Jarisch-Herxheimer reactions consists of supportive management until the self-limited symptoms resolve. Symptoms may be prevented if desired by prophylactic treatment with 80 mg of triamcinolone acetonide intravenously 30 minutes before the start of antibiotic therapy.[776]

Frequently overlooked adverse side effects of the incorrect overdiagnosis of Lyme disease[24, 787] include the monetary costs[734–736, 767] of overdiagnosis and overtreatment, including the cost of intravenous antibiotic therapy and management of any adverse effects of antibiotic therapy[734–736, 767, 787]; the effects of failure to diagnose and treat the real illness, with its likely continuation and progression[279, 765, 767]; and the emotional burden of a disabled self-image resulting from the perception by misdiagnosed patients that they have a chronic, debilitating, incurable disease.[767]

Because complications of antibiotic therapy, particularly of intravenous therapy, have been reported in patients being treated for Lyme disease who did not meet diagnostic case definitions,[767, 788] it continues to be important to avoid overdiagnosis and overtreatment of Lyme disease, and to follow accepted guidelines for antibiotic therapy.

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

Table 11–14 shows the frequency of adverse outcomes of 263 pregnancies complicated by Lyme borreliosis reported in the literature, including four of my cases. Although there are relatively small numbers of patients in each trimester who were either treated or not treated with antibiotic therapy, the overall adverse outcome rate for all trimesters was 67% for untreated and 15% for treated gestational Lyme borreliosis. This protective effect of antibiotic therapy was seen in each trimester, so that the incidence of adverse outcomes of pregnancy decreased from 73% to 18% for first-trimester Lyme borreliosis, from 67% to 16% for second-trimester infection, and from 50% to 9% for third-trimester infection.

Antibiotic therapy for gestational Lyme borreliosis may be successful, partially successful, or unsuccessful in preventing congenital Lyme borreliosis; outcome probably depends on the choice, dose, route of administration, and duration of antibiotic therapy, as well as the trimester of the gestational Lyme borreliosis and the duration of infection before initiation of antibiotic therapy.

There are several reports of antibiotic therapy of gestational Lyme borreliosis that was associated with normal outcomes of pregnancies[33, 42, 47, 48, 536, 622, 719–723, 798]; most of these successful antibiotic regimens consisted of either prolonged oral penicillin for 2 to 4 weeks, or intravenous penicillin or third-generation cephalosporins. In 1986 and 1988, Berger[719, 720, 798] reported four patients with 12-, 14-, 22-, and 24-week gestational Lyme borreliosis that was treated promptly (within 4 to 10 days of onset of early localized EM) with oral penicillin (500 mg four times daily) for 3 to 4 weeks who all delivered normal infants. In 1987, Mikkelsen and Palle[622] reported a patient with third-trimester gestational EM who was treated with phenoxymethyl penicillin (3 million units daily) for 10 days and delivered a normal infant. In 1989, MacDonald[33] reported a patient with second-trimester gestational EM and neuroborreliosis who was treated with intravenous penicillin for 10 days and delivered a normal infant with no evidence of spirochetes in the placenta. In 1990, Luger[721] noted five patients with gestational Lyme borreliosis, including five with EM, carditis, facial palsy, and temporomandibular arthritis, who were treated with unspecified regimens of intravenous antibiotics and who all delivered normal infants. Also in 1990, Stiernstedt[723] reported three patients with gestational Lyme borreliosis who all were treated with antibiotic therapy and all delivered normal

infants: One with localized EM was treated with oral penicillin of unspecified duration; one with disseminated EM was treated with intravenous penicillin for 4 days and then with oral penicillin for 10 days; and one with neuroborreliosis was treated with intravenous cefuroxime for 14 days. In 1991, Schutzer[722] and associates noted a patient with 27-week gestational EM treated within 3 days with intravenous ceftriaxone (2 g daily) for 3 weeks who delivered a normal infant. In 1992, Bracero and colleagues[47] reported three patients with symptomatic *B. burgdorferi* seropositivity in the first or early second trimester who all were treated with antibiotic therapy (noted as either amoxicillin or erythromycin 500 mg qid, or IV penicillin 20 million units per day, or ceftriaxone 2 g per day) for 14 days and delivered normal infants. In 1993, Isailovic and co-workers[536] reported a patient with first-trimester gestational EM treated with intramuscular jugocillin 800,000 units per day for 20 days, who delivered a normal infant.

In 1993, Hercogova and associates[42] reported a series of 15 patients treated prospectively for gestational Lyme borreliosis with EM. Ten patients had normal pregnancy outcomes after treatment (four in the first, three in the late second, and three in the third trimester) with either PO penicillin for 10 to 16 days, or IV penicillin or ampicillin for 14 to 21 days (one first- and one second-trimester patient); two of these patients also received benzathine penicillin of unspecified duration. However, in the same series, similar treatment resulted in five adverse outcomes: Treatment of four patients with early second- and third-trimester infection with PO penicillin for 14 days (and one additionally with benzathine penicillin of unspecified duration), and treatment of one with first-trimester infection with PO penicillin for 24 days, resulted in live-born term infants who were found later to have abnormalities, including persistent PDA (patient 51, Table 11–8), cryptorchidism (patient 52, Table 11–8), developmental delay (patient 55, Table 11–8), and hypoplastic dental enamel (patients 53 and 54, Table 11–8).

In 1996, Maraspin and colleagues,[48] reported a large prospective study from 1990 to 1994 of antibiotic therapy (2 with PO penicillin 1 million units tid, 3 with IM benzylpenicillin 10 million units bid, and 53 with IV ceftriaxone 2 g daily) for 14 days of 58 consecutive patients with gestational EM (13, 27, and 18 in the first, second, and third trimesters). Fifty-one of the pregnancies resulted in normal term infants who remained normal at follow-up (including all of those treated with either PO or IM penicillin); three infants were born with slight prematurity at 36 to 37 weeks and remained well at later follow-up; one pregnancy miscarried (patient 62, Table 11–8) at 9 weeks after severe gestational Lyme borreliosis at 6 weeks (of 1 week's duration before ceftriaxone); one 26-week premature infant (patient 59, Table 11–8) born after early second-trimester EM (of 1 week's duration before ceftriaxone) had respiratory distress and survived; another 36-week premature infant (patient 60, Table 11–8) born after severe early second-trimester Lyme borreliosis (of 1 week's duration before ceftriaxone) had major cardiac anomalies and respiratory distress and survived; and one infant (patient 61, Table 11–8) born after prolonged gestational EM throughout the third trimester (treated initially with PO cefadroxil 500 mg tid for 14 days, and then with ceftriaxone for 13 days) was normal at birth but was found at 7 months to have ureteral stenosis and hydronephrosis.

There are also several reports of antibiotic therapy for gestational Lyme borreliosis that did not prevent adverse fetal outcomes[26–29, 36, 38, 39, 42]; most of these "unsuccessful" antibiotic regimens consisted of short (7- to 14-day) courses of oral penicillin or erythromycin or unspecified oral antibiotics. However, in one series, treatment consisted of 14 days of IV ceftriaxone.[48] In 1986 and 1988, Weber and associates[38, 39] reported on a patient with first-trimester gestational EM treated with oral penicillin (3 million units daily) for 1 week who delivered an infant (patient 22 in Table 11–8) with severe fatal early congenital Lyme borreliosis. In 1986, Markowitz and colleagues[36] and the CDC[28] reported on three patients with gestational EM treated with oral antibiotic therapy who had adverse fetal outcomes: One patient with 6-week gestational EM with associated headache, stiff neck, and arthritis was treated with oral penicillin for 10 days and had a fetal death at 20 weeks (patient 14 in Table 11–8); one patient with 20-week gestational EM associated with headache, stiff neck, and arthralgia was treated with oral erythromycin for 10 days and then with oral penicillin of unspecified duration at 27 weeks and delivered an infant with syndactyly (patient 16 in Table 11–8); and one patient with 27-week gestational EM treated with oral penicillin for 10 days delivered an infant who developed cortical blindness and developmental delay (patient 17 in Table 11–8). In 1987, Cieszelski and co-workers[29] reported on two patients with first-trimester gestational Lyme borreliosis treated with unspecified antibiotics: One patient with 4-week gestational infection had a miscarriage at 13 weeks (patient 19 in Table 11–8), and the other with 7-week gestational infection delivered an infant with syndactyly (patient 20 in Table 11–8). In 1988, Carlomagno and associates[27] noted a *B. burgdorferi*–seropositive patient who had a tick bite; she was treated with unspecified antibiotic therapy before pregnancy and had a miscarriage at 9 weeks of gestation (patient 35 in Table 11–8).

If the episode of maternal gestational Lyme borreliosis is untreated and if the fetus survives and is born alive, prompt antibiotic therapy is beneficial. There are reports of three infants born with early congenital Lyme borreliosis after undiagnosed and/or untreated gestational Lyme borreliosis who responded to prompt antibiotic therapy at birth.[28, 33, 36] In 1986, Markowitz and colleagues[36] reported on an infant with mild early illness following untreated gestational Lyme borreliosis 1 week before delivery, who recovered after 10 days of intravenous penicillin (patient 18 in Table 11–8). In 1989, MacDonald[33] reported on an infant with severe early congenital infection after an unremarkable gestation who recovered after treatment with unspecified intravenous antibiotic therapy (patient 12 in Table 11–8), and another infant with severe early congenital infection after a toxemic gestation who recovered after being treated with intravenous penicillin (patient 13 in Table 11–8).

Antibiotic therapy for gestational Lyme disease may