9.

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,[255] 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, 273, 685] 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.[674]

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[cf]		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).[320, 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, 763, 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

still attenuate the severity of congenital Lyme borreliosis, even if it does not prevent it completely. MacDonald[33] has described one infant and I have described four additional infants born after antibiotic-treated gestational Lyme borreliosis, who had evidence of symptomatic congenital Lyme borreliosis and who responded to intravenous antibiotic therapy either in the neonatal period or during the first year of life (patients 23, 24, 25, and 26 in Table 11–8).

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

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

A third mother had intermittent disseminated EM with flulike symptoms and polyarthralgias; was treated with almost continuous antibiotic therapy for the first 10 weeks of gestation, initially erythromycin (333 mg three times daily) for about 7 weeks, followed by cefaclor (250 mg three times daily) for 3 days, intravenous cefuroxime (750 mg three times daily) for 4 days, oral cephalexin (500 mg four times daily) for 2 weeks, and then oral cefixime (100 mg daily) for 10 days at 12 to 13 weeks; she delivered an infant with moderate early congenital Lyme borreliosis (patient 25 in Table 11–8) who responded to intravenous antibiotic therapy for 6 days (including ampicillin for 5 days and ceftriaxone/cefotaxime for 3 days). This infant later presented with late chronic congenital Lyme borreliosis that required retreatment with a total of 7 weeks of intravenous ceftriaxone (100 mg/kg daily) between 2.5 and 7 months, and prolonged oral antibiotic therapy with amoxicillin (40 mk/kg daily) for 1 year from 7 to 19 months of age. Each time either a less aggressive course of oral cefaclor or a shorter course of intravenous ceftriaxone was given, a relapse consisting of loss of developmental milestones occurred. Finally, after a total of 7 weeks of intravenous ceftriaxone followed by a 1-year course of oral amoxicillin, the infant remained clinically well and continued to progress to essentially normal neurologic status by 8 years of age; at 9 years of age, he had an episode of arthritis associated with neurologic symptoms, which responded to retreatment with ceftriaxone. Patient 56[44] also had musculoskeletal and neurologic abnormalities considered to be late Lyme borreliosis of many years' duration since birth, after prolonged untreated maternal gestational Lyme borreliosis (EM, arthritis, and neuroborreliosis), and was noted to have a good response to treatment with oral roxithromycin and co-trimoxazole.

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

MacDonald[33] reported on an infant whose placenta grew spirochetes following second-trimester gestational EM treated with oral penicillin (500 mg four times daily) for 15 days and untreated gestational EM 2 weeks before delivery, who was well at birth and was treated promptly with oral penicillin and probenecid and who remained well.

Review of Recommendations for Antibiotic Therapy of Gestational Lyme Borreliosis

Because there has been previous uncertainty about the true incidence of fetal risk associated with gestational Lyme borreliosis, there has been great diversity among recommendations for the management of gestational tick bites and gestational Lyme borreliosis; there are four basic approaches recommended in the medical literature. Prenatal screening for Lyme seropositivity to detect and treat seropositive patients with evidence of active Lyme borreliosis is recommended by some investigators.[27, 189, 799] Some recommend antibiotic prophylaxis of all *Ixodes* tick bites in pregnancy because of evidence that this is successful in the prevention of development of Lyme borreliosis following the bite of an infected tick, and because of concern that early dissemination to the placenta and fetus may occur before initiation of antibiotic therapy if Lyme borreliosis does develop.[211, 799–801] Some recommend antibiotic therapy of gestational Lyme borreliosis determined by the clinical stage and severity of the infection (which usually consists of oral antibiotic therapy for early localized infection and intravenous antibiotic therapy for early disseminated or late infection) because of their impression that the actual risk of development of congenital Lyme borreliosis is exceedingly low, and that there is no need for more aggressive treatment of gestational Lyme borreliosis,* although some of the lengths of therapy recommended are at the longer range of current recommendations. Others recommend longer duration of antibiotic therapy in gestational Lyme borreliosis because of concern about transplacental spread.[731] Yet other investigators recommend more aggressive therapy, such as intravenous antibiotic therapy for all cases of gestational Lyme borreliosis because of concern that there is a significant potential risk to the fetus, which is not yet fully appreciated, following any gestational Lyme borrel-

*See references 27, 36, 189, 723, 729, 730, 783, 793, and 799–806.