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.

iosis infection; also, they believe that high-dose intravenous antibiotic therapy is more successful at achieving antibiotic levels above the MIC of the spirochete on both the maternal and fetal sides of the placenta,[38, 48, 211, 225, 530, 725, 804] and that parenteral antibiotic therapy[435] should be considered for some patients with gestational Lyme borreliosis, particularly in those with first- or early second-trimester or disseminated gestational Lyme borreliosis.[23, 731, 791, 807] Others say it is unclear how best to treat gestational Lyme borreliosis.[808]

Some reports favor prenatal screening. Carlomagno and colleagues[27] and Cryan and Wright[189] recommended prenatal screening for *B. burgdorferi* seropositivity, and treatment of all seropositive patients, even those with asymptomatic gestational *B. burgdorferi* seropositivity, with oral or intramuscular penicillin or with intravenous ceftriaxone. Williams and Strobino[799] also recommended prenatal screening but advised use of antibiotic treatment only for those with evidence of active infection. Bracero and associates[47] recommend antibiotic therapy according to the stage of the disease for all seropositive and symptomatic pregnant women. Some recommend against prenatal screening,[530] and others recommend no antibiotic therapy for asymptomatic seropositive patients during pregnancy.[804]

Some reports favor antibiotic prophylaxis of gestational *B. burgdorferi* vector tick bites. Edly[801] recommended prophylaxis for bites only in the first half of pregnancy during the period of maximum susceptibility to teratogens; Williams and Strobino,[799] Ostrov and Athreya,[211] and the American College of Obstetricians and Gynecologists[800] recommended prophylaxis of all gestational bites in endemic areas. Segura-Porta and coworkers recommend amoxicillin orally for 10 days in certain situations wherein Lyme borreliosis risk is high and follow-up is difficult, or patient anxiety is high.[804] When specified, the most commonly recommended prophylactic regimens consisted of oral amoxicillin 500 mg three times daily, or oral penicillin 500 mg four times daily, for 3 weeks.

Other reports favor antibiotic therapy of gestational Lyme disease based on guidelines for nonpregnant patients, with no special modifications for pregnancy other than not using doxycycline or probenecid. Markowitz and colleagues favor oral penicillin (500 mg four times daily for 10 to 20 days) for early infection and consideration of intravenous penicillin for late infection.[36] Stiernstedt,[723] Williams and Strobino,[799] and Segura-Porta[804] suggested oral penicillin or amoxicillin for 2 to 3 weeks for localized EM, and intravenous penicillin or cephalosporin therapy for 2 to 3 weeks for disseminated EM or neuroborreliosis. Carlomagno and colleagues,[27] Cartter and colleagues,[802] Smith and colleagues,[793] Nocton and Steere,[730] and the American Academy of Pediatrics[803] recommended treatment for gestational Lyme borreliosis but made no special modifications in the recommendations for more aggressive therapy of gestational infection. Nocton and Steere,[730] however, recommend that normal infants born to mothers with untreated gestational Lyme borreliosis should be evaluated with a higher level of suspicion, and that treatment may be considered; they also advise that in treatment of ill newborns, consideration should be given to use of antibiotics known to treat *B. burgdorferi*, and that in any of these infants, cord blood or serum *B. burgdorferi* IgM antibodies may be helpful.

There are investigators who favor more aggressive therapy for gestational Lyme disease. The National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute of Allergy and Infectious Diseases[791] recommended consideration of intravenous antibiotic therapy for first-trimester gestational Lyme borreliosis, and routine therapy according to guidelines for the clinical stage of disease for other trimesters. Podolsky[23] suggests that intravenous ceftriaxone may provide greater protection for the fetus than oral penicillin. MacDonald and colleagues,[35] Weber and associates,[38] and Ostrov and Athreya[211] favor intravenous penicillin therapy (20 million units daily for 10 to 14 days) and possibly intravenous ceftriaxone (2 to 4 g daily for 10 to 14 days)[211] for all gestational Lyme borreliosis cases. Dattwyler and co-workers[225] recommend antibiotic therapy of gestational Lyme borreliosis to achieve eradication of spirochetes on both the maternal and fetal sides of the placenta, and imply that this is best accomplished by high-dose intravenous therapy. Rahn and Malawista[807] recommend intravenous penicillin (20 million units daily) for 14 to 21 days for all cases of gestational Lyme borreliosis except single localized EM with no associated systemic symptoms, for which they recommend oral amoxicillin (500 mg three times daily) for 21 days. Christen and colleagues recommend intravenous penicillin G (500,000 IU/kg/day with a maximum of 20 megaunits daily) for 10 to 14 days for all pregnant women with Lyme borreliosis, but note that amoxicillin or azithromycin might be effective.[435, 530] Maiwald[809] recommends a slightly longer duration of antibiotic therapy for gestational Lyme borreliosis: 21 days of amoxicillin (500 mg three times daily) for early localized Lyme borreliosis, and 14 to 21 days of intravenous ceftriaxone (4 g daily) or cefotaxime (3 g twice daily) for early disseminated or late Lyme borreliosis. Sicuranza and Baker[731] recommend treatment of uncomplicated EM with amoxicillin (or erythromycin 250 mg four times daily), and treatment of disseminated or late Lyme disease or first-trimester gestational Lyme disease with intravenous penicillin G (20 million IU daily) or ceftriaxone (2 g daily). In 1996, Maraspin and colleagues[48] recommended intravenous antibiotic therapy, preferably with ceftriaxone 2 g daily for 14 days, for all gestational Lyme borreliosis, based on their large prospective study of 58 consecutively enrolled patients treated for gestational EM; this advice is offered out of concern that neither the occurrence of transplacental dissemination nor the timing of such occurrence during the acute infection can be accurately assessed.

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

Tables 11–20 and 11–21 show antibiotic regimens recommended for different stages of Lyme borreliosis,

which have been developed based on the literature* and my own experience; these include specific recommendations for gestational and congenital Lyme borreliosis.

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

For treatment of nongestational, nonlactating, and noncongenital early localized or mild disseminated Lyme borreliosis without CNS involvement (see Table 11–20), 14- to 30-day courses of oral doxycycline (100 mg twice daily, or 2–4 mg/kg per day twice daily for children older than 8 years) or oral amoxicillin (500 mg three to four times daily, or 50 mg/kg per day two or three times daily for children) are the regimens of choice. Many recent sources prefer 21- to 30-day courses, and the durations of therapy are not well defined. Doxycycline should not be used either in pregnant or lactating women, or in children younger than 8 years of age. Oral probenecid (500 mg three to four times daily, or 50 mg/kg per day for children) may be given optionally with amoxicillin to increase serum antibiotic concentrations. Oral cefuroxime axetil (500 mg twice daily, or 40 mg/kg per day for children) is an effective alternative. Oral erythromycin (250–500 mg three to four times daily, or 30–50 mg/kg per day for children) has been associated with frequent treatment failures; its use should be reserved for patients in whom no other acceptable therapy is possible. Clarithromycin has been found to be as efficacious as amoxicillin and is a good alternative for penicillin- or cephalosporin-allergic patients, but it should not be used in pregnancy. Azithromycin is slightly less efficacious and has a slightly higher relapse rate than amoxicillin for treatment of EM. There are no data on the efficacy of clarithromycin or azithromycin for treatment of pediatric Lyme borreliosis. There are differing opinions regarding whether oral antibiotic therapy of isolated cranial neuritis, including facial palsy, requires confirmation of a negative CSF evaluation for neuroborreliosis; however, because of the frequency of abnormal CSF in such patients, many recent recommendations favor CSF evaluation in this situation,[291, 657, 661] along with the use of intravenous ceftriaxone (2 g daily) or cefotaxime (6 g daily), as for CNS neuroborreliosis if CSF abnormalities such as pleocytosis, elevated protein, intrathecal specific antibody, or PCR positivity are found.

For treatment of gestational early localized or mild early disseminated Lyme borreliosis, as well as more serious disseminated Lyme borreliosis (see Table 11–20), intravenous antibiotic therapy is preferred because of reported failures of oral antibiotic therapy to reliably prevent the development of congenital Lyme borreliosis, including miscarriage, stillbirth, and early or late congenital infection. The drugs of choice are ceftriaxone (2 g daily), cefotaxime (6 g daily), and penicillin (24 million units daily) for 2 weeks for mild localized Lyme borreliosis without neurologic manifestations, and for longer durations for early disseminated and late Lyme borreliosis. Ampicillin (8 g daily) is considered an acceptable alternative to penicillin. If antibiotic-induced gastroenteritis develops because of an intravenous cephalosporin, either a change to penicillin or treatment of the diarrhea with oral vancomycin is indicated; if other serious complications of intravenous antibiotic therapy develop, a change of antibiotic or route is indicated. Intravenous antibiotic therapy is preferable. However, because oral antibiotic therapy has also been associated with a decreased incidence of adverse outcomes of gestational Lyme borreliosis, if intravenous antibiotic therapy is not feasible, reasonable oral alternatives would be amoxicillin (500 mg four times daily) or possibly cefuroxime axetil (500 mg twice daily) for 3 to 4 weeks; a prolonged course during gestation could be considered. The use of erythromycin for treatment of gestational Lyme borreliosis is to be discouraged unless no other options are possible, as it has been associated with failure to prevent congenital infection. If it is used, a prolonged course should probably be considered, and it should be discontinued at least 1 week before delivery to avoid neonatal hyperbilirubinemia.

For treatment of more severe nongestational early disseminated or late Lyme borreliosis (see Table 11–20), 14- to 30-day courses of intravenous antibiotic therapy with either ceftriaxone 2 g (or 50–100 mg/kg per day for children) daily, cefotaxime 6 g (or 150 mg/kg per day for children) daily, or penicillin 24 million units (or 300,000 units/kg per day for children) daily given every 4 hours are the regimens of choice. For arthritis without neurologic manifestations, oral amoxicillin (500 mg PO tid–qid, or 50 mg/kg per day for children) or doxycycline (100 mg PO bid, or 2–4 mg/kg daily for children over 8 years) for 30 to 60 days is an acceptable alternative. However, if even subtle neurologic manifestations are present, oral therapy increases the risk of later neuroborreliosis; in such instances, CSF evaluation is advisable, and intravenous antibiotic therapy should be used if CSF is abnormal. Higher daily pediatric doses, 100 mg/kg of ceftriaxone, 180 mg/kg of cefotaxime, and 400,000 units/kg of penicillin, may be needed for the most serious manifestations of Lyme disease. Current evidence supports ceftriaxone, or cefotaxime, as the first-choice drug;

*See references 24, 98, 190, 202, 203, 275, 324, and 795, in addition to those in Table 11–20.

clinical efficacy has been greater than with penicillin, although there is less difference in efficacy when longer durations of antibiotic therapy are used. Although the durations of therapy are not well defined, many sources recommend a longer treatment duration—30 days for severe, chronic, late, recurrent, or persistent infection, including neuroborreliosis, severe arthritis, significant neuro-ophthalmic or neuro-otologic involvement, severe carditis, myositis, and late chronic Lyme disease, including ACA. Some sources also recommend durations of 42 days for severe, progressive meningoencephalomyelitis. Although intravenous therapy is preferable, if this is impossible, alternatives include amoxicillin and optional probenecid (500 mg of each three to four times daily, or 50 mg/kg daily for children) or cefuroxime axetil (500 mg three times daily, or 40 mg/kg daily for children) for 30 days or, for nonpregnant and nonlactating patients older than 8 years of age, oral doxycycline 100 mg twice daily for 30 days. Although chloramphenicol was found to be effective in some cases, it has failed in others, and its use for the treatment of Lyme disease cannot be advocated unless no other antibiotic alternatives are possible; it should not be used in pregnant or lactating women.

Treatment of congenital Lyme borreliosis is summarized in Table 11–21; antibiotic dosages and intervals vary according to the age of the infant to be treated. For treatment of asymptomatic infants born to mothers who had adequate treatment of their pregestational or gestational Lyme borreliosis, no antibiotic therapy is necessary. However, if there is any question of adequacy of maternal treatment, the infant could be treated with oral amoxicillin for 10 to 30 days while evaluation is pending. If maternal Lyme borreliosis was inadequately treated, even an infant who is asymptomatic at birth may be at risk for congenital Lyme infection, and prompt antibiotic therapy should be started at birth with either intravenous cefotaxime or ceftriaxone for 2 to 4 weeks. If the infant is already symptomatic at birth, this indicates more severe infection, and prompt antibiotic therapy is essential and may be lifesaving; the longer duration of 4 weeks may be preferable because of concern regarding the risk of late chronic Lyme borreliosis with its associated developmental and neurologic deterioration. For the infant who either presents with or later develops signs of late congenital infection, intravenous therapy with ceftriaxone or cefotaxime for 4 to 6 weeks is recommended.

Intravenous ceftriaxone or cefotaxime is preferred to penicillin for treatment of congenital Lyme borreliosis because of lower *B. burgdorferi* MICs, higher cure rates of late chronic Lyme borreliosis,[775] and some reports of possible clinical resistance of neuroborreliosis to penicillin therapy.[794, 795] However, if intravenous penicillin or ampicillin has been used rather than ceftriaxone or cefotaxime for initial therapy of congenital Lyme borreliosis because of treatment of an initially different diagnosis, and if there is no clinical improvement, the patient should be changed to intravenous ceftriaxone or cefotaxime. This was done in one infant with severe early congenital infection (patient 24 in Table 11–8), and it resulted in dramatic clinical improvement.

If clinical relapse occurs after initial treatment of either gestational or congenital Lyme borreliosis, retreatment with a more aggressive antibiotic regimen such as a longer course of intravenous ceftriaxone or cefotaxime is indicated. Prolonged oral antibiotic therapy following this retreatment should be considered either for the duration of the pregnancy in gestational infection or, in the case of congenitally infected infants, until growth and developmental and neurologic assessment indicate that no further improvement is expected.

Clinical studies of antibiotic prophylaxis for tick bites are discussed in the section on prophylaxis, and recommendations are given in Table 11–22. The author prefers to recommend gestational antibiotic prophylaxis of *B. burgdorferi* vector tick bites in endemic areas because of the established success of antibiotic therapy in the prevention of Lyme borreliosis, and because some cases of congenital Lyme borreliosis have occurred in the absence of clinical symptoms of gestational Lyme borreliosis. Oral amoxicillin 500 mg three times daily for 10 days would be the first choice; a possible alternative includes cefuroxime axetil 500 mg twice daily or erythromycin 500 mg four times daily for 10 days. Antibiotic prophylaxis for tick bites of infants and children with histories of previous congenital Lyme borreliosis is also recommended because of concern that reinfection with *B. burgdorferi* may lead to unusual, possibly immunologically mediated, manifestations of infection. Antibiotic prophylaxis of tick bites of nonpregnant and non–congenitally infected individuals is not routinely recommended but may be considered if the estimated risk of acquisition of Lyme borreliosis from the bite exceeds 1%, or if unusual circumstances exist.

In general, with antibiotic therapy of either early localized or early disseminated Lyme borreliosis, EM skin lesions begin to improve within 2 to 3 days and resolve within a few weeks; the mild, associated flulike symptoms improve within a few days and resolve within a few weeks. Arthralgias should improve within a few days but may take a few months to fully resolve. Improvement is generally gradual in patients with chronic borreliosis who respond to antibiotic therapy. Subjective improvement usually becomes noticeable several weeks after the start of antibiotic therapy, and objective improvement is seen months later.[208, 775] Symptoms of arthritis improve within a few weeks and resolve by 3 months; symptoms of neuroborreliosis, including neuropathies, show initial improvement within a few weeks but may take as long as 24 months to resolve.

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

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

Predictors of Antibiotic Therapy Cure

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

TABLE 11–22
Recommendations for Use of Recombinant Osp A Lyme Vaccine[a]

Should consider for:	Persons (15 to 70 years of age) who reside, work, or engage in recreation in high[b] or moderate[c] Lyme disease risk areas, and have frequent or prolonged tick exposure
	Travelers (15 to 70 years of age) to high or moderate Lyme disease risk areas, with expected frequent or prolonged tick exposure
	Persons (15 to 70 years of age) with prior uncomplicated Lyme disease, with continued high Lyme disease risk
May consider for:	Persons (15 to 70 years of age) who reside, work, or engage in recreation in high or moderate Lyme disease risk areas, but have only infrequent and brief tick exposure
Not recommended for:	Persons who reside, work, or engage in recreation in low or no Lyme disease risk areas
	Persons younger than 15 years or older than 70 years of age
	Persons with treatment-resistant Lyme arthritis
	Pregnant women[d]
No recommendations available for[e]:	Persons with immunodeficiency, musculoskeletal disease[f], Lyme-related chronic arthritis or neurologic disease, second- or third-degree AV block
Vaccine schedules:	Initial dose, IM
	Second dose, IM, 1 month after first, several weeks before Lyme disease transmission season
	Third dose, IM, 12 months after first, several weeks before Lyme disease transmission season
	Boosters may be needed, but no recommendations available yet
	If administration simultaneously with other vaccines is necessary, requires separate syringe and injection site

[a]Adapted from Centers for Disease Control and Prevention Recommendations for the Use of Lyme Disease Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 48(RR7):1–25, 1999.[818]
[b]High predicted Lyme disease risk occurs in some or all areas in northeastern United States (Maine, New Hampshire, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Pennsylvania, Delaware, and Maryland) and upper midwestern United States (Minnesota and Wisconsin).
[c]Moderate predicted Lyme disease risk occurs in some or all areas in the above states, plus Vermont, Michigan, Indiana, Illinois, Iowa, and California.
[d]Registration of inadvertent vaccination of pregnant women is encouraged (SmithKline Beecham, 1-800-366-8900, ext. 5231).
[e]Limited or no data available to allow recommendations to be made.
[f]Arthritis, including rheumatoid arthritis, or diffuse musculoskeletal pain.

Most patients treated promptly with antibiotic therapy appropriate for the clinical stage and severity of the infection have good outcomes.[206, 274, 324, 594, 643, 648, 716, 790, 810] Delay in therapy, or therapy inadequate for the initial presentation of the infection, may be associated with a higher incidence of dissemination and the development of long-term sequelae.[206, 308, 312, 314, 325, 683, 714, 756, 757] Dissemination is a risk factor for late relapse. After adequate antibiotic therapy, most symptoms resolve within weeks to months: erythema migrans within 3 to 5 weeks,[202, 203, 643, 784] borrelial lymphocytoma within 3 to 8 weeks,[644, 646, 865] meningitis within 4 weeks,[643] facial palsy within 4 to 8 weeks,[643, 654] carditis including AV block within 1 to 4 weeks,[643, 687] acute arthritis within 1 to 3 months,[256, 274, 324, 643] retreated antibiotic-responsive, persistent arthritis within 4 to 12 months,[314, 324] early neuroborreliosis (meningoencephalitis/radiculitis, polyneuritis) by 1 to 9 months,[520] peripheral neuropathy and radiculitis within 3 to 6 (possibly up to 24) months,[275, 291] and late chronic neuroborreliosis within 1 to 3 years.[520] The edema of ACA resolved within 2 weeks, the erythema within 2 to 10 weeks,[316] the arthritis of ACA within 1 to 3 months,[697] and other symptoms of ACA within several months, but atrophic changes tended to persist. Most of the nonspecific symptoms of early disseminated European Lyme borreliosis usually resolve within 2 weeks to 3 months—fever, nausea, vomiting, weight loss, headache, neurocognitive deficits, and arthralgia within 2 weeks, and malaise and fatigue within 3 months.[275]

Persistence or relapse of symptoms of Lyme borreliosis after antibiotic therapy,[269, 312, 318] beyond expected times of resolution, is due either to persistent *B. burgdorferi* infection because of use of an inadequate antibiotic regimen or survival of the spirochete in privileged sites inaccessible to antibiotics or the immune response; autoimmune phenomena related to *B. burgdorferi* molecular mimicry and HLA-DR specificity; *B. burgdorferi*–induced cytokine-mediated inflammatory reactions; post-Lyme fibromyalgia syndrome or other intercurrent non-Lyme illnesses; an incorrect initial diagnosis of Lyme disease; or residual *B. burgdorferi*–induced damage. Increased duration and severity of Lyme borreliosis increase the risk of irreversible damage; antibiotic therapy is able to halt further damage but does not alter irreversible damage.[206, 308, 311, 324, 786]

Inadequate antibiotic therapy of Lyme borreliosis is a risk factor for development of persistent, relapsing, or new symptoms, and *B. burgdorferi* persistence, and may be due to lack of antibiotic treatment; treatment with an ineffective antibiotic; or treatment with an inadequate dose, duration, or route of delivery of an adequate antibiotic, as occurred in some early clinical trials before the development of currently recommended antibiotic regimens.[325, 522, 648, 681, 683, 684] Some antibiotic regimens may not achieve or maintain adequate CSF levels[269, 778, 779] to eliminate early CNS dissemination, which may progress to neuroborreliosis with persistence of *B. burgdorferi*.[206, 253, 284, 311, 319, 324] Predictors of failure of antibiotic treatment, which correlate with the development of late manifestations, include persistence or recurrence of the skin lesions, survival of *B. burgdorferi* organisms in biopsies,[811] persistence of *B. burgdorferi* antigen positivity after antibiotic therapy,[253, 269, 283, 287, 311, 312, 314] progression of arthritis after the first week of antibiotic therapy or beyond one month after the end of antibiotic therapy,[274, 324] and development of new CNS vasculitic lesions detectable by MRI.[311] Persistence of facial nerve palsy longer than 3 months after antibiotic therapy suggests that there may be permanent damage.[786]

Persistent infection should be confirmed. If previous antibiotic therapy was inadequate, retreatment with an adequate course is indicated; if previous treatment was

considered adequate, retreatment should be done with a different antibiotic, or with a higher dose and a longer duration of the same antibiotic. Retreatment is usually but not always effective when adequate antibiotic therapy regimens are used.[206, 269, 274, 287, 310-312, 314, 324, 790] Although demonstration of culture positivity is the definitive proof of persistence of active infection, the sensitivity of antigen-detection methods such as PCR and antigen capture ELISA is greater. Demonstration of *B. burgdorferi*–specific antigens in tissues or fluids is usually predictive of antibiotic responsiveness.[186, 187, 283, 287, 310, 312, 314]

Reduction of *B. burgdorferi* antibody titers has been reported following successful antibiotic therapy of Lyme disease,[274-277, 776] but Lyme seropositivity or seronegativity is not always a reliable indicator of antibiotic cure.[225, 244, 318] Patients may be seronegative even though inadequate antibiotic therapy may have failed to eradicate the infection because early antibiotic therapy aborts the development of the mature IgG antibody response to *B. burgdorferi* infection.[18, 208, 209, 273] Patients may be IgG-seropositive even though antibiotic therapy has successfully eradicated the infection if the antibiotic therapy was given later in infection, after the mature IgG antibody has already developed.[244] Persistence of *B. burgdorferi*–specific IgM antibody beyond the first few weeks after early treatment of infection, and particularly years after infection,[325] significant and sustained antibody titer increases (in IgG as well as IgM antibody),[325, 811] and expansion of the antibody repertoire by Western blot evaluation accompanied by persisting or relapsing symptoms of Lyme disease[206, 318, 324] are also predictors of possible persistent infection and appear to correlate with increased severity and dissemination of the initial Lyme borreliosis and with the development of late complications.

Early Lyme borreliosis without a history of either tick bite or EM is a risk factor for progression to late manifestations because the initial infection is often undiagnosed and therefore remains inadequately treated.[274, 648]

The routine use of intra-articular or systemic steroid therapy of Lyme disease has been associated with an increased risk of dissemination; development of chronic complications such as persistent arthritis, meningitis, and multifocal encephalitis; neuro-ophthalmic or neuro-otologic disorders; cardiac sequelae; and lack of responsiveness to antibiotic therapy, including high-dose penicillin or ceftriaxone.*

HLA-DR4 specificity and Osp A or Osp B IgG seropositivity are strong risk factors for the development of chronic Lyme arthritis[256, 324, 325] and are predictive of poor antibiotic response[256, 324, 325] if antibiotic therapy is delayed in patients with chronic Lyme arthritis.

Presentation with neurocognitive or neurologic symptoms during or shortly after an initial episode of Lyme disease was found to be associated with an increased risk of development of late neuroborreliosis in patients treated with delayed or inadequate antibiotic therapy.[324, 681, 683, 684]

Overdiagnosis of Lyme disease[24, 279] in patients who do not meet diagnostic criteria, which occurs in 38 to 79% of patients referred to Lyme disease clinics for evaluation,[763, 767, 768] is a major reason for apparent failure of response to antibiotic therapy, although some of these patients may show either a placebo effect or a response to antibiotic therapy of an unrecognized non-Lyme infectious disease. Many studies indicate that prompt treatment of correctly diagnosed Lyme borreliosis with antibiotic therapy considered adequate, in choice of drug, duration of therapy, and route of administration, for the stage and severity of the presentation, is a predictor of complete recovery without sequelae.[274, 643, 716, 764, 790]

PREVENTION

Methods to reduce the risk of development of Lyme borreliosis include attempts at reducing the population density, geographic distribution, and incidence of *B. burgdorferi* infection of the tick vectors and their animal hosts; development of animal and human *B. burgdorferi* vaccines; use of personal protective clothing and other methods to reduce the risk of tick bite and *B. burgdorferi* transmission; use of prophylactic antibiotic therapy for tick bites in endemic areas; and development of educational programs to increase awareness of Lyme disease risk and to promote early diagnosis and treatment of cases in the early stage to reduce the incidence of late manifestations.

Tick Vector and Animal Reservoir/ Host Control Measures

The large mammalian hosts of the adult *Ixodes ricinus* complex ticks determine the geographic distribution and population density of the larval and adult stages of the tick vectors; the small mammalian or other small reservoir hosts of *B. burgdorferi* determine the infection rate in the tick population.[347, 407, 408, 812] In hyperendemic areas, almost all of the nymphs and reservoir mice may be infected. In areas where the tick infection rate is very high, even small changes in tick density may significantly change the risk of Lyme disease exposure and the incidence of Lyme disease.[559]

When deer are the only large mammalian host, as in hyperendemic coastal islands of the northeastern United States, elimination or reduction of the deer population results in reduction of the *I. scapularis* tick population and of the incidence of Lyme disease.[407] Use of deer fencing, either electrified or 8 feet tall, for at least 2 years, decreases the nymphal tick density by up to 80% and reduces the incidence of Lyme disease; however, it is difficult to maintain and expensive,[6, 347, 812] and it must completely exclude deer from an area to be effective, as even small deer populations can support an infected tick population.[492, 812] When domestic animals such as cattle or sheep are the only large mammalian host, as in some endemic areas in Europe, pasture rotation results in

*See references 284, 309, 311, 314, 324, 619, 620, 674, 676, 709, 771, and 775.

reduction in the *I. ricinus* tick population and is more effective than acaricides.[407]

Rodent reservoir control is difficult and not necessarily effective,[6, 812] but elimination of bird feeders on residential property eliminates the attraction of rodents and other small mammalian reservoirs capable of transporting ticks onto the property.[347]

Because ticks inhabit humid areas of dense vegetation, tick populations may be reduced by habitat control measures[407, 812] or by changes in climatic conditions. Dry springtime weather conditions and light snowfall may temporarily decrease tick densities. Methods such as springtime burning and mowing of brushy areas in the northeastern United States reduce the questing nymph population and therefore the subsequent adult tick population by 70 to 88% for approximately 1 year, but the effects of such drastic measures on the risk of human Lyme disease are not known. Mowing of lawns reduces the adult tick population by 70% but does not eliminate nymphal ticks in hyperendemic areas. Removal of leaf litter, underbrush, and shrubs from the edges between lawns and forests, use of fences or dry border material between lawns and forests, and use of deer-proof fencing have had some success in reducing tick populations when these measures are sustained.

Chemical control of the tick population has been attempted using acaricides applied to small mammalian reservoirs, large mammalian hosts, or the environment.[407, 812, 813] Early studies found acaricide treatment of deer unsuccessful in reducing the number of ticks feeding on deer, but future efforts to apply acaricides to deer at feeding stations are planned. Acaricide applied to mice by distribution of permethrin-treated rodent nest materials in early spring and mid-summer, to kill nymphs and larvae, showed early promise in reducing the tick population and the incidence of Lyme disease, but it was not found to be successful in other tests.[347, 407]

Various acaricides, such as carbaryl, chlorpyrifos, diazinon, and cyfluthrin, have been applied to the environment in high-risk residential areas for immediate 97 to 100% reduction of the *Ixodes* tick populations within 3 days, but these measures only temporarily reduce the tick population for up to 1 year and are most useful for treatment of well-maintained lawns—not for wooded areas.[6, 407] Granular preparations of these acaricides target ticks in the soil before host seeking, and are easier to apply than liquids.[347] Single applications of granular carbaryl even to forested residential areas have achieved 70 to 90% reductions in nymphal ticks on host mice and are expected to decrease subsequent adult tick density.[813] Biologic tick attractants, such as *Ixodes* species pheromones, may be useful in the future to attract ticks to acaricide-containing traps.[407]

Efforts are being made to limit the spread of Lyme disease at the margins of endemic areas; mouse immunization via distribution of vaccine-containing food, to reduce acquisition of spirochetemia by uninfected young mice during infected tick feeding, and therefore remove these mice from the enzootic cycle, has been proposed.[812]

Biologic control of ticks has been attempted by introduction of a wasp species that lays eggs in *I. scapularis* larvae into two northeastern coastal islands, but this was unsuccessful in one island and reduced the *I. dammini* population by only 50% in the other.[407]

The combination of annual environmental acaricide application in the spring for nymph tick control, and in the fall if adult tick control is desired, and deer management methods for overall reduction of tick population density appears to achieve the best reduction in human risk of acquisition of Lyme disease in endemic areas of North America.

Animal Models

Animal models of Lyme borreliosis have been of value in evaluating vaccine efficacy[814, 822–828] and in investigating the pathogenesis of Lyme disease.[815–821]

Transplacental transmission in mice has been investigated in several models.[732, 830] Two pregnant mice collected in the wild, *P. leucopus* and *Mus musculus*, were found to have *B. burgdorferi* in fetal tissues by culture.[831] Mice experimentally infected intradermally with *B. burgdorferi* developed arthritis 2 weeks later. Mice infected 5 days before or 4 days after mating, with gestation coinciding with acute infection, had a fetal death rate of 12 to 14% at 2 weeks of gestation; *B. burgdorferi* PCR showed that all uteri were positive, one placenta was faintly positive, all fetuses were negative, and 46% of the mice had litters with at least one fetal death. In contrast, mice infected 3 weeks before mating, with gestation coinciding with chronic rather than acute infection, had no fetal deaths and no PCR-positive uteri, placentas, or fetuses despite development of severe chronic arthritis. Fetal death was not associated with an inflammatory infiltrate, transplacental transmission occurred rarely and was not required for fetal death, and the increased rate of fetal death was thought to be due to a maternal response to infection rather than to fetal infection. Uterine persistence of *B. burgdorferi* was necessary for fetal loss to occur, consistent with production of intrauterine inflammatory mediators such as IL-1 and TNF in response to *B. burgdorferi* outer response to infection and the mechanism of *B. burgdorferi*–induced surface proteins. This model should prove useful in evaluation of intrauterine fetal death. Transplacental transmission has not been found in rats.[832]

B. burgdorferi causes arthritis and spontaneous abortion in horses[833] and cows, and transplacental infection has been demonstrated in one aborted calf and one newborn calf.[833] A closely related species, *Borrelia coriaceus*, transmitted by the soft tick *Ornithodoros coriaceus*, has been suspected to be the cause of epizootic bovine abortion in California.

Transplacental *B. burgdorferi* infection has been documented in beagle dogs.[834] Dogs were experimentally infected intradermally with *B. burgdorferi* on the first day of estrus and at two weekly intervals during pregnancy. All infected dogs delivered litters with at least some infected pups (either positive PCR or culture), and four pups had documented infection at younger than 2 days of age, supporting the transplacental route of infection. Infected pups had no increased mortality rate and showed no evidence of inflammation when sacrificed at

6 weeks for autopsy. Pups had evidence of passive maternal IgG antibody, which declined by 6 weeks; three had evidence of positive IgM response at 6 weeks, which persisted in two pups, and the possibility of tolerance was raised.

Vaccine Development

Lyme disease is a major worldwide public health problem, and fear of acquisition of Lyme borreliosis has interfered with outdoor activities and led to loss of real estate value in hyperendemic regions.[120] In addition, pets and domestic animals in endemic areas have also been affected by *B. burgdorferi* infection. Because elimination of wildlife reservoirs has been impractical, and reduction of vector ticks has not been completely successful, there has been and continues to be intense interest in the development of vaccines for wildlife, domestic animals, and humans.[120] Extensive animal model immunization studies,[120, 139, 140, 814, 822–827] and human clinical trials[835–841] have led to the development of two lipidated Osp A human Lyme disease vaccines, LYMErix, licensed by the U.S. Food and Drug Administration in January 1999,[418, 842–845] and ImuLyme,[418, 844] for which licensing is still pending as of the time of this writing. These vaccines are unique among all human vaccines because they are arthropod-specific transmission-blocking vaccines, which act primarily in the tick to inactivate the spirochete before it is transmitted during the tick bite.[139, 140]

Currently, selective rather than widespread vaccination with LYMErix, the recently licensed vaccine, based on a combination of individual risk and geographic risk in specific groups, is recommended (see Table 11–22).[120, 418, 842, 845] Maes and colleagues[846] also recommend targeting of selected groups for vaccination, based on cost-of-illness estimations.

Pregnant women were excluded from the vaccine trials, and Lyme disease vaccine is not currently recommended for use in pregnancy. However, because inadvertent vaccination may occasionally occur, the manufacturer has created a registry for such patients (1–800–366–8900, ext. 5231), and registration is encouraged.[843] Women contemplating pregnancy should be given the Lyme vaccine according to CDC guidelines based on geographic and individual Lyme disease risk, ideally with all three vaccine doses given before pregnancy to provide adequate protection throughout pregnancy.

A significant concern regarding the Lyme vaccine is that it may provide a false sense of security and result in the reduced use of other very important protective methods against tick bites, including personal protective methods, which would place vaccine recipients with inadequate immunity at risk for acquisition of Lyme disease.[842] In addition, Lyme vaccine recipients remain susceptible to other tickborne pathogens, including ehrlichiosis and babesiosis, which require continued tick bite precautions, and both of which have been associated with rare cases of transplacental transmission.[396, 630–632]

Borrelia burgdorferi subunit antigens have been considered better human vaccine candidates[120, 145, 814] than whole inactivated spirochetes because of concerns that some *B. burgdorferi* antigens such as flagellin and the heat shock proteins may induce cross-reactive antibodies to human tissues such as synovia, axons, liver, heart, and skeletal muscle. Osp A, which is highly immunogenic in animal models and has minimal strain variation among U.S. strains, has been the major human vaccine candidate; Osp B and Osp C are also highly immunogenic but have been less promising human vaccine candidates because they have greater strain heterogeneity. The lipid moiety of Osp A enhances its immunogenicity even without potent and potentially toxic adjuvants. Patients with Lyme disease have minimal or no early Osp A antibody response because Osp A expressed by *B. burgdorferi* inside of ticks is suppressed during tick feeding[828] and further suppressed after spirochete entry into the host.[844] Osp A vaccine has a unique dual mode of action—direct neutralization of the spirochete immediately after transmission when small amounts of Osp A are still expressed, but, more importantly, inactivation of the spirochete in the tick before transmission when it actively expresses Osp A.[139, 140, 826–828, 843, 844] Mouse immunization studies indicating protection by Osp A and Osp B vaccines against heterologous as well as homologous tick-transmitted strains[827] raise the possibility that monoclonal human Osp A vaccine may be effective against more diverse strains than was initially expected, in the actual clinical setting of human tick-transmitted infection.

The current Lyme disease vaccine is a recombinant lipidated Osp A subunit vaccine derived from the German ZS7 *B. burgdorferi sensu stricto* isolate adsorbed onto aluminum hydroxide adjuvant.[843] In 1994, Keller and colleagues published the first human clinical trial,[835] which demonstrated safety and immunogenicity of two 10-microgram doses of either aluminum-adsorbed or -unadsorbed recombinant Osp A vaccine in normal human volunteers. In 1995, Schoen and associates, in a clinical trial of an aluminum hydroxide–adsorbed vaccine in persons with previous histories of Lyme disease,[836] also demonstrated safety, and found that immunogenicity was greatest when three 30-microgram vaccine doses were used. Because of reports of the association of high Osp A antibody levels and treatment-resistant chronic Lyme arthritis,[255, 256, 587] the vaccine was not studied in persons with treatment-resistant chronic arthritis. Van Hoecke and co-workers[838, 839] compared several vaccine formulations and found that lipidated Osp A given on a 0-, 1-, 2-, and 12-month vaccination schedule produced the best Osp A antibody and Osp A protective epitope antibody responses in human volunteers.

The safety, efficacy, and immunogenicity of LYMErix, an aluminum hydroxide–adsorbed recombinant lipidated Osp A Lyme disease vaccine, were evaluated in a large multicenter, double-blind, randomized, placebo-controlled study at 31 U.S. sites in ten highly Lyme-endemic areas by Steere and colleagues,[841] which led to licensing of this vaccine in January 1999. In the winter of 1995, before the start of the spring tick feeding season, 5469 vaccinees and 5467 controls, aged 15 to 70 years, were enrolled and followed clinically and serologically for 20 months. High levels of protection were found against clinical Lyme disease and asymptomatic

seroconversion after three 30-microgram doses of recombinant lipidated Osp A vaccine with aluminum hydroxide adjuvant, at 0, 1, and 12 months. After two doses, during the first year of Lyme disease exposure, the vaccine was 49% effective in prevention of clinical disease and 83% effective in prevention of asymptomatic seroconversion; after three doses, during the second year of Lyme disease exposure, it was 76% and 100% effective, respectively. Lower levels of antibody against the protective epitope of Osp A correlated with breakthrough Lyme disease. Mild to moderate local injection-site reactions occurred in 24.1% of vaccinees and 7.6% of controls, and brief mild flulike systemic reactions occurred in 19.4% of vaccinees and 15.1% of controls. Pregnant or lactating women, and persons with recent Lyme disease, long-term antibiotic therapy, arthritis, musculoskeletal pain, or AV block were excluded from the study.

The safety and efficacy of ImuLyme™, a recombinant lipidated Osp A vaccine without aluminum hydroxide adjuvant, were evaluated in a multicenter, double-blind, randomized, placebo-controlled study at 14 U.S. sites in highly Lyme-endemic areas by Sigal and colleagues,[840] but it has not yet been licensed. In the spring of 1994, 5149 vaccinees and 5156 controls, older than 18 years of age, were enrolled and followed clinically for two Lyme disease transmission seasons. Three doses of 30 micrograms of vaccine were given at 0, 1, and 12 months. After two doses, the vaccine was 68% effective in the prevention of clinical Lyme disease during the first year after vaccination; it was 92% effective in the second year among recipients of all three vaccine doses. Although volunteers were not followed serologically for asymptomatic seroconversion, none who were asymptomatic during the trial have so far developed late Lyme disease, supporting the absence of asymptomatic infection. Mild brief local reaction at the injection site was the most common adverse reaction, and adverse reactions were reported in 32 to 36% of vaccinees and 28 to 32% of controls. Persons with recent Lyme disease, previous Lyme vaccination within 18 months, or long-term antibiotic therapy were excluded from the study. The vaccine was found to have a lower efficacy of uncertain etiology, 40% in the first year and 37% in the second, in a subset of 1634 of these volunteers enrolled at a single site in Westchester County, New York.[857]

There are several areas of concern regarding LYMErix immunization that still require further study.[418, 842, 844, 845] The duration of protection and the need for booster immunization need to be determined. Optimal dosing schedules to achieve adequate protection in a single tick feeding season are needed, as the present schedule provides only 49% protection during the first season, and Osp A antibody must be present before *B. burgdorferi* exposure to be effective.[841, 843, 844] Vaccine evaluation in adults older than age 70 years and in children is needed, particularly because children have a higher incidence of tick exposure. Because of exclusions from the clinical vaccine trials, little or no information is available on safety and efficacy in pregnant, lactating, or immunocompromised persons, or persons with chronic arthritis, musculoskeletal conditions, treatment-resistant Lyme arthritis, Lyme-related chronic arthritic or neurologic illness, or second- or third-degree AV block. Long-term surveillance for assessment of infrequent or late adverse vaccine events is needed, as is further evaluation of the theoretical possibility of vaccine-induced immunopathogenicity related to molecular mimicry of Osp A and the role of Osp A antibody in treatment-resistant Lyme arthritis. Because Osp A antibody in vaccinees results in positive standard ELISA assays, serologic evaluation for Lyme disease in vaccinees currently requires the more expensive Western blot; additional serologic screening tests such as ELISA assays using Osp A–negative *B. burgdorferi* strains are needed to distinguish natural infection from vaccine immunity.[847] The efficacy of the current vaccine for prevention of Eurasian Lyme borreliosis is unknown, and clinical trials of vaccines designed for Eurasian use are needed. Ongoing post-licensing studies of vaccine safety, efficacy, and cost effectiveness are needed.

A canine *B. burgdorferi* bactericin vaccine, licensed by the U.S. Department of Agriculture in 1992,[584, 814] requires two initial doses, separated by 2 to 3 weeks, and yearly boosters; induces antibodies to Osp A and Osp B; and is protective against homologous or closely related heterologous *B. burgdorferi* strains. Additional vaccines for household and domestic animals are being developed. Many veterinarians in Lyme-endemic areas recommend vaccination of dogs.

Recreational and Occupational Lyme Borreliosis Risk, and Methods for Individual Protection Against Tick Bites

One of the most important methods of protection against the development of Lyme borreliosis is avoidance of exposure to tick-infested endemic areas during the seasons of maximal tick feeding activity, and this is strongly recommended during pregnancy[26]; however, if such exposure is unavoidable, as is the case with individuals who live or work in endemic areas, there are additional effective precautions that are recommended.[7, 305, 347, 407, 418, 459, 848]

Particularly high-risk recreational and residential activities include residential property maintenance such as landscaping and clearing leaf litter, underbrush, or wood piles; and outdoor activities such as hunting (Dutch hunters[514]), fishing, camping, hiking, orienteering (Swiss orienteers and sportsmen[521, 522, 572]), and other outdoor activities in endemic areas (see Table 11–7).

Particularly high occupational risk includes work in forestry*; wildlife management and game keeping[541, 542]; zookeeping[470]; park management[543]; nature conservancy[538, 539]; farming and cattle raising[541, 542, 409, 504, 512, 549]; veterinary medicine[409]; the military[305, 517, 576]; and other outdoor occupations.[495, 504] Relatives of military personnel stationed in Lyme-endemic areas are at risk to ac-

*See references 344, 346, 409, 433, 450, 504, 512, 523, 524, 527, 529, 533, 541, 542, 549, 554, and 573.

quire Lyme borreliosis during recreational activities in these areas[576] (see Table 11–7).

It is best to remain on trails and avoid leaf litter, tall grass, and low-lying vegetation in wooded and brushy areas frequented by deer and rodents. Use of hats and light-colored, long-sleeved, long-legged, smooth-fabric clothing, with pants tucked into socks and shirts tucked into pants, reduces the risk of tick attachment. One study[305] of Dutch military personnel, training in a hyperendemic forest, found that use of protective clothing reduced the incidence of tick bites to 6.4% compared with previously reported rates of 55 to 78% in Swiss orienteers and Dutch forestry workers.

Clothing, shoes, and socks may be treated with chemical tick repellents[7, 347, 459, 848] such as *N*-diethyltoluamide (DEET), or acaricides such as permethrin, which discourage ticks from adhering to clothing; DEET may be applied to exposed skin according to the manufacturer's directions and U.S. Environmental Protection Agency guidelines.[848] Permethrin tick repellent kills ticks on contact but is not indicated for skin application, although other permethrin preparations are approved for treatment of scabies mites and head lice.[848] Tick repellents containing 0.5% permethrin are 100% protective, and mosquito repellents containing 30% DEET are 92% protective against all stages of Lyme disease vector ticks.[848, 849] However, these may be toxic or teratogenic, and there is concern regarding their use in pregnant women; one report urges use of DEET in pregnancy only if clearly indicated.[799]

Prompt and proper tick removal reduces the risk of transmission of the spirochete because *B. burgdorferi* is transmitted most often after 48 to 72 hours of feeding.[341, 342, 347, 430] In a study in a highly endemic area of New York, transmission was between 18 and 25% after nymphal and female tick attachment for over 72 hours, compared with 1% for less than 72 hours.[430] Because of some recent reports of transmission of Lyme borreliosis after tick attachment of less than 24 hours,[9, 430–432] and even less than 2 hours,[9] frequent inspection every few hours for tick attachment and immediate tick removal are recommended during exposure to tick-infested areas.[407] Shower, shampoo, and total body tick checks are recommended on return from tick-infested areas, and also 1 to 2 days later, as small nymphal or larval ticks may be detected more easily after they engorge. Clothing worn into tick-infested endemic areas should be placed into sealed plastic bags until washed in hot water, and cars and camping equipment should be inspected for ticks that may be seeking hosts.

At present, tick removal using tweezers without pressure on the tick's body is recommended, but further evaluation of removal methods is needed. Needham[347, 880] evaluated several methods of removal of both hard (ixodid) and soft (argasid) ticks and found that the best method for complete removal of the intact tick was to grasp it near the skin surface with forceps or protected fingers and pull steadily upward without squeezing, puncturing, or crushing the tick, and without twisting or jerking it so that the mouth parts did not break off. The possibility that inexperienced tick removal with tweezers might cause regurgitation of midgut *Borrelia* and lead to increased *Borrelia* transmission was raised by Hassler[850] because the incidence of Lyme disease in a German hyperendemic region decreased over threefold after the method of tick removal changed from self-removal using tweezers to physician office removal using scalpels to avoid pressure on the ticks' bodies. It is also important to remove the latex-like cement secreted by the tick around the attachment site. The bite site should be disinfected afterward, and the tick disposed of in alcohol or saved in an airtight container with a moist cotton-tipped swab, if analysis for presence of *B. burgdorferi* is desired. The tick may continue to salivate for several minutes after removal, so care must be taken to avoid direct contact with this potentially infectious fluid. Ticks should not be squashed because this increases the risk of exposure to infectious tick body fluids; transmission of Lyme borreliosis has been reported after conjunctival contact with squashed tick intestinal contents.[851]

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

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

Antibiotic Prophylaxis of Tick Bites in Pregnant and Nonpregnant Patients

For nonpregnant patients, there is controversy over whether antibiotic prophylaxis is indicated for tick bites in Lyme-endemic areas; the risks and benefits of both prophylaxis and no prophylaxis should be weighed. Several reports discuss the pros and cons of prophylaxis.[430, 431, 752, 806, 852–857] For pregnant patients, many groups,[211, 799, 801, 858] including the American College of Obstetricians and Gynecologists,[800] recommend antibiotic prophylaxis (some consider it specifically for embedded or engorged ticks in endemic areas),[859] and others recommend against it.[189, 802]

The approach to tick bite antibiotic prophylaxis taken by many physicians practicing in Lyme-endemic areas of North America is often in disagreement with that recommended by researchers. Fix and colleagues[737] found that physicians practicing in 1995 in the Eastern Shore of Maryland, a Lyme-hyperendemic area with an annual incidence of 86 cases per 100,000, prescribed prophylactic antibiotic therapy for 55% of tick bites.[737] Twenty to nearly 50% of physicians practicing in endemic areas of the eastern and northeastern United States routinely prescribed prophylactic antibiotics for tick bites, and an additional 33% sometimes did.[772–774] A more conservative approach recommended by many researchers studying the epidemiology of the disease is to reserve antibiotic prophylaxis for bites with high

TABLE 11–23
Antibiotic Prophylaxis of *Borrelia burgdorferi* Vector Tick Bites in Lyme-Endemic Areas

CLINICAL SITUATION	LYME BORRELIOSIS SYMPTOMS	ANTIBIOTIC PROPHYLAXIS RECOMMENDED[a]
Tick bite, pregnant woman	Asymptomatic	Yes, amoxicillin 500 mg PO tid × 10–21 d[b, c]
	Symptomatic	No, full antibiotic therapy for active Lyme borreliosis instead, according to clinical stage of the infection
Tick bite, infant or child with history of congenital Lyme borreliosis	Asymptomatic	Yes, amoxicillin 50 mg/kg/day PO tid × 10 d[d]
	Symptomatic	No, full antibiotic therapy for active Lyme borreliosis instead, according to clinical stage of the infection
Tick bite, nonpregnant and non–congenitally infected person, with <1% risk of development of Lyme borreliosis	Asymptomatic	No, not routinely recommended
	Symptomatic	No, full antibiotic therapy for active Lyme borreliosis instead, according to clinical stage of the infection
Tick bite, nonpregnant and non–congenitally infected person, with >1%[e] risk of development of Lyme borreliosis	Asymptomatic	Possibly, doxycycline 100 mg PO bid or amoxicillin 500 mg PO tid × 3–10 d[f]
	Symptomatic	No, full antibiotic therapy for active Lyme borreliosis instead, according to clinical stage of the infection

Based on data from references 211, 430, 431, 752, 799–801, 852–854, and 856–859.
[a]Antibiotic prophylaxis would not be recommended for persons who have adequate immunity due to Lyme vaccination.
[b]Possible alternatives are cefuroxime axetil 500 mg PO bid × 10 d, or erythromycin 500 mg PO qid × 10 d, but the efficiency of these for prophylaxis has not been tested in large clinical trials. Erythromycin should not be given during the week before delivery, and tetracycline or doxycycline should not be given to pregnant women.
[c]American College of Obstetricians and Gynecologists recommends 21 days.
[d]Possible alternatives are cefuroxime axetil 40 mg/kg/day PO bid × 10 d, or erythromycin 30 mg/kg/day PO tid × 10 d. Tetracycline or doxycycline should not be given to children <9 years of age, and doses of other antibiotics should not exceed adult doses.
[e]Factors increasing this risk include tick-engorged, nymphal, or adult; tick attached >48 to 72 hours; tick confirmed to contain spirochetes or from a tick population with *B. burgdorferi* infection rate >10%; tick removal by a method that increases transmission risk; multiple tick bites.
[f]Alternatives include penicillin or tetracycline at standard PO doses × 3–10 d, or possibly cefuroxime axetil PO or erythromycin PO at above doses × 3–10 d.

Lyme disease transmission risk, and to withhold it from those with low risk and treat the infection if it develops.[860] Although serologic screening of patients with tick bites for *B. burgdorferi* antibody has been found to be frequent in hyperendemic areas,[737] there is general agreement that this is not recommended, but that if done, is appropriate only if antibiotic prophylaxis is to be withheld and if both short-term and later follow-up serologic testing is done.[238, 860]

In some hyperendemic areas such as southwestern Finland where the incidence of tick bites ranges from 26.9% of army recruits in a single summer to 85% of the overall population, with 28% reporting multiple bites, antibiotic prophylaxis of tick bites has been considered impractical. It has been recommended that education of at-risk individuals about tick recognition and removal, and use of protective clothing, is preferable.[516, 517]

Data regarding risk of infection after single tick bites in nonpregnant individuals suggest that it is reasonable to use antibiotic prophylaxis in carefully selected subgroups in whom the chance of development of Lyme disease is predictably high, but that routine antibiotic prophylaxis of all *B. burgdorferi* vector (*I. scapularis, pacificus, ricinus, persulcatus*) tick bites in endemic areas is not indicated (Table 11–23). There are several factors that should be considered in making this decision. The risk of development of Lyme borreliosis increases if the tick is a nymph or an adult rather than a larva, if the *B. burgdorferi* infection rate in the endemic tick vector population is over 10%, if the tick is shown to be infected, if there are multiple tick bites, if the duration of tick attachment before removal is longer than 48 to 72 hours, or if the tick is engorged and the method of tick removal used was likely to have caused injection of tick contents into the bite site. In addition, if the likelihood of good patient follow-up is low, and therefore adequate treatment of Lyme disease, if it were to develop, would be impossible, it is advisable to use antibiotic prophylaxis for the bite at the time the patient seeks medical attention. In occasional cases, if patient anxiety is high, and if there are significant valid concerns about the potential risk of development of late chronic Lyme borreliosis without the initial EM lesion, it would not be unreasonable to use prophylaxis. Close follow-up for clinical signs of Lyme disease and treatment of diagnosed cases is important for all patients in endemic areas with vector tick bites, even after short-duration attachment, because there are some reports of transmission with attachments of less than 24 hours,[9, 430–432] but routine serologic screening is not necessary.

In pregnant women, antibiotic prophylaxis of all *B. burgdorferi* vector tick bites in known endemic areas is indicated (see Table 11–23) because of the potential risk of congenital Lyme borreliosis following maternal gestational Lyme borreliosis. In lactating women, antibiotic prophylaxis could also be considered because only insufficient data are so far available regarding the poten-

tial risk of transmission to the infant by nursing, although there have been no reports of documented transmission by this route. There are no recommendations to support routine treatment of asymptomatic pregnant women with histories of remote pre-gestational tick bite who have no evidence of active Lyme disease and who have serologic responses consistent with previously resolved Lyme borreliosis. The antibiotic regimen of choice for prophylaxis of tick bites in pregnant women is amoxicillin 500 mg by mouth three times daily for at least 10 days; acute and convalescent sera are indicated if there is any suspicion that asymptomatic infection has occurred following the bite. In penicillin-allergic patients, cefuroxime axetil 500 mg orally twice a day (if the patient has no cross-reacting hypersensitivity) or erythromycin 500 mg orally four times daily for at least 10 days may be used. Doxycycline or tetracycline should not be used in pregnant or lactating women.

No data exist regarding whether antibiotic therapy should be given for tick bite prophylaxis of congenitally infected infants or children because so few of these infants have been recognized. Because some of the chronic complications of Lyme borreliosis may be immunologically mediated and the immune response of congenitally infected infants to future *B. burgdorferi* infection is unknown, the author currently favors use of antibiotic prophylaxis for congenitally infected children, although these recommendations may change as further data become available (see Table 11–23).

Educational Programs to Increase Lyme Disease Awareness

Educational campaigns to increase awareness of Lyme disease and methods of reduction of human risk are widespread in many hyperendemic areas of North America. The European Union Concerted Action on Risk Assessment in Lyme Borreliosis (EUCALB) has prepared a pamphlet[861] that reviews Lyme borreliosis and risk reduction methods, is available via the EUCALB web site,[862] is intended for use in every European country to increase knowledge about Lyme borreliosis in low-awareness groups, and may also be used to educate tourists to Lyme-endemic areas.

However, even in areas where knowledge of Lyme disease is high, tick-avoidance behavior has often been found to be inadequate, particularly among visitors.[577, 863] A survey of 100 women in a Lyme-endemic area of Connecticut, at either prenatal or postnatal visits, found that although almost all would be concerned about tick bites or Lyme disease, and half reported they were concerned about effects on pregnancy, one fourth had misconceptions about Lyme disease transmission and were concerned about exposure to a person with Lyme disease but were unconcerned about working or playing on their lawns.[864] In a hyperendemic area of New Jersey, a survey of over 300 tick bite victims[863] found that only 58% used proper tick removal methods, only 16% treated their residential property with acaricides for tick control, only 0.6% cleared brush or vegetation from near their residences, and 84% of dog and cat owners allowed their pets to roam outdoors and indoors. Eighty-six percent took personal precautions against tick bites as a result of the bite, compared with estimates of 43% of visitors to recreational areas in New Jersey. A case-control study[496] in Hunterdon County, New Jersey, a hyperendemic area with an incidence of 193 cases per 100,000, found that only 55% of patients with Lyme disease did routine tick checks, 47% wore protective clothing, and 16% used tick repellents. A survey[577] of 304 ferry passengers leaving Martha's Vineyard in 1992, an endemic area with an incidence of over 30 cases per 100,000 and 180,000 visitors annually, found that despite a very good level of knowledge about Lyme disease in 73%, only 58 to 59% limited tick exposure or wore protective clothing, 66% did tick checks, and 40% used tick repellent. Visitors followed tick-avoidance and tick-checking recommendations less often than residents. In a hyperendemic area in the Czech Republic, another study[519] found that despite high awareness of ticks and Lyme disease, 87% of people, including both residents and visitors, had a history of tick bite, and few people used proper tick removal methods. A survey of visitors to the endemic Thetford Forest in southeastern Great Britain, which has 1.5 million visitors per year, found that less than half knew that Lyme disease was transmitted by tick bites, and only 13% recognized an unfed nymphal *I. ricinus* tick.[544] There are a million visitors annually to the Aland Islands of Finland, another highly endemic area.[516] Many popular tourist resorts worldwide are in Lyme-endemic areas, and Lyme disease educational programs in these areas are needed.

Although educational campaigns to increase knowledge about Lyme disease and risk-reduction methods are important, it is also necessary to increase actual observance of risk-reduction methods among both residents of, and visitors to, endemic areas by provision of information that convinces individuals at risk that risk-reduction methods are effective and worthwhile. A dramatic reduction in the incidence of seroconversion of New Jersey outdoor workers occurred after 3 years of educational tick bite recognition programs, although climatic factors may also have played a role.[495] Specific programs targeting tourists and visitors to these areas are needed.[577, 861]

As discussed in the Vaccine section previously, it is essential to educate all recipients of the Lyme vaccine, including women who plan to become pregnant, that continued use of protective methods against tick bites, including personal protective methods, is extremely important because of possible waning of effective vaccine-induced immunity. Such precautions are also essential to decrease risk of acquisition of other tickborne pathogens, including ehrlichiosis and babesiosis, and in some areas of Europe, tickborne encephalitis.

PROGNOSIS

Data indicate that the prognosis of gestational Lyme borreliosis is good if the infection is recognized promptly and treated aggressively with antibiotic therapy aimed at crossing the placental barrier. The prognosis is unknown in gestational Lyme borreliosis that lacks

the typical history of tick bite followed by EM or other symptoms that lead to its recognition. It is uncertain how many episodes of gestational toxemia, spontaneous miscarriage, spontaneous abortion, stillbirth, culture-negative neonatal sepsis, failure to thrive, developmental delay, congenital heart disease, or sudden infant death syndrome may be due to unrecognized gestational Lyme borreliosis. Most studies addressing the issue of gestational and congenital Lyme borreliosis have evaluated pregnancy outcomes after the first prenatal visit or at delivery; although they provide useful data, they may either miss adverse events in early pregnancy or underestimate the fetal mortality rate. Determination of true risk to the fetus and infant of maternal gestational Lyme disease requires prospective studies of all pregnancy outcomes of gestational Lyme disease, long-term follow-up of live-born products of these pregnancies, and improved diagnosis of Lyme disease in affected fetuses, placentas, and infants.

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

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

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

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

The index of suspicion should be high that any illness consistent with the late manifestations of Lyme borreliosis reported in children or adults may also theoretically occur in the congenitally infected infant. It will continue to be most important to recognize, treat, and evaluate infants with suspected congenital Lyme borreliosis in order for a more complete description of the syndrome to evolve.

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