Lyme Disease

Davut Özdemir, Nevin İnce

Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Düzce University, Düzce, Turkey

ABSTRACT

Lyme disease (LD) is caused by the spirochete, *Borrelia burgdorferi* sensu lato complex. Humans are infected by a tick bite to the skin. This disease is a non-contagious infectious disease. It has been known since the 19th century. LD has a worldwide distribution. It is endemic in Europe, North and South America. There are case reports since 1990 in Turkey. The clinical presentation varies depending on the stage of the disease. Lyme disease is classified into three stages: early localized disease, early disseminated disease, and late disease. The main manifestation of the early stage of the disease is erythema migrans (EM). The disease affects many systems. In all of the clinical presentations, most patients with Lyme disease have resolution of their clinical symptoms when treated with appropriate antimicrobials but recurrence, chronic Lyme borreliosis or post-Lyme syndrome can also be seen. The diagnosis of LD is based on epidemiological, clinical and laboratory findings. Treatment depends on the stage of the disease. Doxycycline, amoxicillin, azithromycin, cefuroxime axetil, erythromycin, ceftriaxone, cefotaxime and crystalline penicillin are used for treatment. LD can be prevented by reducing contact with ticks. There is no vaccine for the disease.

Key words: Lyme disease, tick, zoonosis

INTRODUCTION

Lyme disease (LD) or Lyme borreliosis (LB) is caused by the spirochete, *Borrelia burgdorferi* sensu lato complex. Humans are infected by a tick bite to the skin. This disease is a non-contagious infectious disease. Cases that were reported in Europe as Bannwarth syndrome (painful radiculitis, cranial neuritis and lymphocytic meningitis), acrodermatitis chronica atrophicans, erythema chronicum migrans (ECM) in the 19th century can retrospectively be designated as manifestations of LB.4 In 1977, in Lyme city of USA, the association of ECM and arthritis was observed in young patients. This association was called Lyme disease. In 1982, Burgdorfer et al. noticed the presence of spirochetes in the gut of ticks of the Ixodes dammini species, which were called *Borrelia burgdorferi* sensu lato. Later, through polymerase chain reaction (PCR), DNA sequences of *Borrelia burgdorferi* (*B. burgdorferi*) were detected from patients with LD. Considering the not always chronic evolution of the disease,
Detmar et al. proposed in 1989 that the best designation for this disease was erythema migrans (EM) and not ECM.\textsuperscript{1,5}

**MICROBIOLOGY**

*B. burgdorferi* sensu lato complex are fastidious, gram-negative, microaerophilic, vigorously motile, corkscrew-shaped bacteria that replicate slowly. The bacteria require special media to grow. The organism has been subclassified into more than 20 species: Of these species, five genospecies predominate as human pathogens: a) *B. burgdorferi* sensu stricto b) *B. garinii* c) *B. afzelii* d) *B. spielmanii* and e) *B. bavariensis*. *Borrelia valaisiana*, *B. lusitaniae* have also been isolated or detected by PCR in specimens from small numbers of patients. In the US, *B. burgdorferi* sensu stricto is the only species found. All of the species are present in Europe.\textsuperscript{1,6-8} *B. burgdorferi* sensu stricto, *B. garinii* ve *B. afzelii* were isolated in ticks collected from Istanbul and Thrace regions in Turkey.\textsuperscript{9} Different genomospecies are associated with increased certain specific manifestations of LD. *B. burgdorferi* sensu stricto causes arthritis, while *B. garinii* is associated with an increased risk of neurologic manifestations of LD.\textsuperscript{6,10} *B. burgdorferi* may be isolated from skin, blood, synovial fluid or cerebrospinal fluid of patients. The biodiversity of strains that are isolated from skin is greater than others.\textsuperscript{11}

**EPIDEMIOLOGY**

LB has a worldwide distribution. The disease is endemic in Europe, North and South America. Currently more than 20,000 cases have been noted yearly, making Lyme disease the most common vector borne infection in the United States.\textsuperscript{1,6,12} In Europe, the highest estimates of the prevalence and incidence of Lyme disease are reported from central Europe and Scandinavia, particularly from Austria, Germany, Sweden and Slovenia.\textsuperscript{13-17} Although, the exact prevalence of the disease is unknown in Turkey, there are case reports since 1990.\textsuperscript{18-20} *B. burgdorferi* seropositivity is 6-44% in high risk groups, while it is 2-6% in the general population.\textsuperscript{21-24} In Lyme disease-endemic states of the US where the epidemiologic purpose might primarily be to monitor geographic, clinical, and demographic trends, intensive statewide surveillance is not essential. Most cases are reported among people aged 5-14 years and 50-59 years.\textsuperscript{1,6,25-28}

*B. burgdorferi* is transmitted by various Ixodid ticks. The risk of infection is highly variable depending on the density of infected ticks and on their feeding habits and life cycle; these have evolved differently in different geographic locations, a fact which is believed to explain the geographic and seasonal distribution of Lyme disease.\textsuperscript{1,6,27,29} Although ticks of the genus Ixodid may be seen throughout Turkey, they are generally seen in northern Anatolia.\textsuperscript{18}

Ticks have three life stages: larva, nymph and adult, each lasting one to two years. Larvae emerge from eggs laid in spring, attach to small vertebrates and are usually not infected with *B. burgdorferi*. The tick may become infected at any stage of its life cycle by feeding on a host that is a natural reservoir for *B. burgdorferi*. Larvae transform into nymphs, and during the subsequent spring and summer, the nymphs feed for the second time. In most cases it is the bite of a nymph that transmits *B. burgdorferi* to people. In late summer the nymphs transform into adult forms. Adult females, which stay attached to large animals like deer or sheep throughout the winter, lay eggs and they die. The next spring a new life-cycle that lasts 2 years begins.\textsuperscript{3,6,12,30}

Transmission of *B. burgdorferi* occurs through injection of tick saliva during feeding. An infected tick generally must feed for 48-72 hours or longer to transmission. The bacteria live in the mid-gut of the tick, which needs to become engorged with blood before the bacteria migrate to the salivary glands and the saliva. Tick bites are painless and many patients do not recall having had contact with ticks.\textsuperscript{1,6,10}

**CLINICAL PRESENTATION**

The clinical presentation is variable and changes according to the stage of the disease. Lyme disease is classified into three stages: early localized disease, early disseminated disease, and late disease (Table 1). Despite this clinical division, it is possible to observe clinical manifestations of the different clinical stages of the disease concomitantly. Lyme disease most frequently appears in spring, summer and early autumn. The main manifestation of the early stage of the disease is EM, reported in 60-83% of patients. It is pathognomonic.\textsuperscript{1,6,30,31} EM can occur at the site of the tick bite and in any part of the skin. In adult patients erythema migrans is most often located on the legs and feet; in children, the upper part of the body is more frequently affected than in adults. EM appears 3 to 30 days after the bite. This manifestation is initially characterized by erythematous macules or papules, which increase in size, forming isolated or multiple plaques with discontinuous edges and central clearing, cyanotic...
Erythema migrans lesions from infection by *B. burgdorferi* sensu stricto last longer and are more exuberant with systemic manifestations, when caused by *B. afzelii* and *B. garinii*, manifestations are often shorter with fewer frequent local symptoms and are rarely accompanied by systemic involvement.¹,²,⁶,¹²,¹⁶,¹³

In early disseminated Lyme disease stage; within several days to weeks of the onset of the ini-
tial EM lesion, new EM lesions may develop, resulting from dissemination of bacteria. These lesions may appear with the primary lesion or after its disappearance, and usually smaller than, the primary lesion. Another important cutaneous manifestation of the initial phase of LD is lymphocytoma cutis. It is also called lymphadenosis benigna cutis. It is clinically characterized by a single erythematous nodule or plaque, 1 to 5 centimeters in diameter, usually located on the face, pinna, scrotal bag or mammary areola. Lymphocytoma is often associated with infection by B. afzelii and garinii and more frequent in European patients.1,6

Other common manifestations of early disseminated Lyme disease are neurologic manifestations. These occur in 15-25% of the cases. The most common disorders are encephalitis, cranial nerve palsies, meningitis and myelitis. In Europe, the most common neurologic manifestation is Banwarth’s syndrome. Bell’s palsy, caused by VII cranial nerve involvement, is the most frequent manifestation of neuroborreliosis in children and adolescents and may occur in up to 50% of the cases. Facial palsy may occur alone, and in rare instances, it may be the presenting manifestation of the disease. Other pairs of cranial nerves may also be affected. Pseudotumor cerebri and cerebellar ataxia can also occur. Eye problems in Lyme borreliosis seem to be very rare and are usually associated with other signs of the disease more frequently in European patients. Ocular involvement in Lyme borreliosis is symptomatic and a routine ophthalmologic evaluation is not necessary for adult patients. There are case reports of iritis followed by panophthalmitis, choroiditis with exudative retinal detachments, or interstitial keratitis, conjunctivitis, optic nerve neuropathy and diplopia. In children, blindness can develop. Argyll-Robertson pupil, Claude Bernard-Horner syndrome, chronic intraocular inflammation and intraorbital myosit is can also be observed.1,7,34,35

In meningitis, symptoms may fluctuate. Patients usually have neck stiffness only on extreme flexion. Kerning’s and Brudzinski signs are not present. Sometimes meningitis is accompanied by papilledema and increased intracranial pressure. Fever, myalgia, arthralgia, headache, and fatigue are also common in this stage.1,7,12

Cardiac involvement is found in 6-10% of the cases, mainly in patients infected with B. garinii and B. afzelii within one to two months after infection. Lyme carditis is characterised by changing atrioventricular blocks (first degree, Wenckebach or complete) as a result of conduction disturbances. Also pancarditis and left ventricular dysfunction can be seen. The patients don’t have heart murmurs. Cardiac involvement can cause death.1,7,36,37

Articular involvement which is more frequent in infection by B. burgdorferi sensu strict and is usually monoarticular or oligoarticular and affects the large joints, particularly the knee. The arthritis occurs weeks to months after the initial infection. There is edema and pain. Although Lyme arthritis can be difficult to be distinguished from septic arthritis, the intense pain associated with a septic arthritis is usually not present. Joint fluid analyses frequently reveal strikingly elevated joint leukocyte counts with both diseases. In most patients who develop arthritis, erythema migrans never develops. Panniculitis, osteomyelitis and myositis, periostitis or joint subluxations below acrodermatitis can also occur. The course of Lyme arthritis is very variable, usually recurrent, and can last several years. In the beginning the attacks of arthritis are frequent and short, later they may be longer. Chronic and erosive arthritis can be observed in untreated patients and they can lead to the progressive destruction of cartilage and bone. However, even in untreated patients, intermittent or persistent arthritis usually resolves completely within several years. In European patients, articular manifestations are less frequent and the symptoms are more subtle. 1,6,12,25,38,39

Other clinical manifestations are mild or recurrent hepatitis, nonexudative sore throat, nonproductive cough, orchitis, microscopic hematuria or proteinuria in second stage LD.1,2 In late-stage borreliosis, characteristic skin changes called acrodermatitis chronica atrophicans (ACA) or Pick-Hexheimer disease may occur. Acrodermatitis chronica atrophicans is generally associated with infection by B. afzelii. It is a relatively frequent chronic skin manifestation of Lyme borreliosis that does not resolve spontaneously. Clinically, it begins with an erythematous plaque, progressing to cutaneous atrophy and prominent blood vessels, located mainly in the extensor sites of the hands and feet. Face and trunk may also be affected. In addition to these lesions, scleroderma plaque, lichen sclerosus (LS), anetodermia, atrophoderma of Pasini-Pierini (APP), and granuloma annulare may occur.1,2,16

Multifocal encephalitis, encephalopathy, demyelinating disease, Banwarth’s syndrome, ataxic gait, subtle mental disorder, spastic paraparesis and polyneuropathy are also manifestations of late Lyme disease.6,12 Although there are case reports that the congenital disease is caused by Lyme disease during pregnancy, this is not certain. Trans-
mission of Lyme disease by breastfeeding has also not been documented.  

CHRONIC LYME BORRELIOSIS or POST-LYME SYNDROME

Although objective manifestations of Lyme disease resolve with antibiotic treatment, some patients have chronic fatigue, chronic musculoskeletal pain, headache, drowsiness, irritability and cognitive impairment (memory loss, difficulty concentrating and thinking, reduced judgment ability, among others) for more than 6 months. These symptoms called Chronic Lyme Disease or Post-Lyme Disease Syndrome may be due to persistent infection, inflammatory and autoimmune phenomena. Clinicians should be careful to differentiate these symptoms. They may result from a post-infectious phenomena or another illness. This syndrome does not require additional treatment with antimicrobials and usually respond to non-steroidal anti-inflammatory agents.  

In addition, probable late Lyme disease has been described recently. Aucott et al. suggest that patients with probable late Lyme disease share features with both confirmed late Lyme disease and post-treatment Lyme disease syndrome.  

PATHOGENESIS

*B. burgdorferi* is carried in the midgut of unfed Ixodes ticks. When an infected tick takes a blood meal, the ingested spirochetes increase in number and undergo phenotypic changes, including the expression of outer surface protein C (OspC), down-regulation of OspA, which allows them to invade the host tick’s salivary glands. The spirochete can spread through skin and other tissues and this spread may be facilitated by the binding of OspC to human plasminogen. Borrelia spp. have ability to evade host immune response. VlsE (Variable major protein-like sequence expressed) and OspC have an important role in this situation. Also, Borrelia spp. can express complement regulator-acquiring surface proteins (CRASPs), preventing complement mediated killing. Recently, another protein, Lmp1, was suggested to be important for evasion of the host adaptive immune responses. As a result, escaping the host defense system, inflammatory response and tissue damage are caused by bacteria spread throughout the body.

DIAGNOSIS

The diagnosis of Lyme disease, especially in the absence of the characteristic rash, may be difficult, because the other clinical manifestations of Lyme disease are not specific. Sometimes the rash of erythema migrans initially may be confused with nummular eczema, granuloma annulare, an insect bite, ringworm, or cellulitis. The diagnosis of LD is based on epidemiological, clinical and laboratory findings but diagnosis of early Lyme borreliosis associated with EM needs no serological testing. Before this decision of The Centers for Disease Control and Prevention (CDC), serologic testing have been made for all possible Lyme cases in that endemic area in USA. There is no Lyme Disease in Turkey as in USA and there can be a doubt in diagnosis; as such, we think that serology will valuable in Turkey.

Laboratory diagnosis is based on serology (detection of specific antibodies) and/or presence of the etiologic agent. Histology, immunohistochemistry, PCR and culture are also important.

The detection of anti-*B. burgdorferi* IgM or IgG antibodies is commonly used for serologic diagnosis and epidemiological investigation. The Centers for Disease Control and Prevention recommends a 2-tiered approach for serodiagnostic testing. ELISA (Enzyme linked immunosorbent assay) or indirect immunofluorescence (IIF) are first tests. These tests may show false positive results, given the crossreaction with other diseases such as collagenoses, leishmaniasis, and syphilis. If that result is positive or equivocal, it should be confirmed by a separate IgM and IgG Western immunoblot. On the other hand, humoral response starts with IgM antibodies, which usually appear 2 to 4 weeks after infection, and therefore, antibody testing for patients with early localized Lyme disease is insensitive. It is clear that serological tests cannot be used to confirm or rule out the diagnosis of Lyme disease, and should only be ordered in case of well-founded clinical suspicion for Lyme borreliosis.

Branca et al. have combined ELISA and IgG Western blot with a recombinant VlsE bands in their study. They have found that their test has equivalent sensitivity in stage 1 and 3 LD, significantly better sensitivity in stage 2 disease, and equivalent specificity in all control groups compared with standard test. Once serum antibodies to *B. burgdorferi* develop, both IgG and IgM may persist for many years, even if adequate treatment is applied and clinical cure of the illness is achieved. It is not nec-
essary to repeat serology after therapy to determine the effectiveness of treatment.\textsuperscript{1,6}

Hematoxylin-eosin (HE) staining and silver staining (Warthin-Starry technique) are considered suggestive. But the sensitivity of these techniques are variable. Immunohistochemistry for the detection of Borrelia spp. associated with focus floating microscopy (FFM) has good sensitivity and specificity.\textsuperscript{1}

PCR has high specificity, but variable sensitivity (20-81\%). Differentiation of reinfection from relapse in recurrent Lyme disease can be made by PCR.\textsuperscript{1,46} Diagnosis of Lyme arthritis should not be based on \textit{B. burgdorferi} immunoblot testing from synovial fluid. A positive \textit{B. burgdorferi} DNA PCR test of synovial fluid provides adjunctive evidence implicating the pathogen. PCR testing is greatly superior to culture in the detection of \textit{B. burgdorferi} in joint fluid.\textsuperscript{47,48}

Culture, using BSK medium (Barbour, Stroeven, Kelly) shows 100\% specificity. However, its sensitivity is relatively low.\textsuperscript{1}

The cerebro spinal fluid (CSF) analysis is helpful in the diagnosis of Lyme meningitis. In Lyme patients, the CSF cell count is increased up to several hundred cells per milliliter (lymphocytic pleocytosis), usually together with an elevated protein but a normal glucose level. To confirm neuroborreliosis, antibodies against \textit{Borrelia burgdorferi} are assessed in serum and cerebrospinal fluid. By comparing antibody concentrations in serum and cerebrospinal fluid, it is possible to detect intrathecal antibody production. In the early stages, CSF abnormalities may be absent or minimal, and there may be little increase in protein levels. PCR in cerebrospinal fluid is often positive only in very early cases when there are not yet antibodies against \textit{B. burgdorferi} present. Although a positive PCR supports the diagnosis of neuroborreliosis, a negative PCR does not exclude it.\textsuperscript{1,12,31} Recently, the chemokine CXCL-13 in CSF has been shown to be a promising future diagnostic/treatment marker for Lyme neuroborreliosis (LNB), and the gelsolin concentration in the blood of patients with LNB has been found significantly lower compared to the control group. Plasma gelsolin is a multifunctional protein present in the extracellular environment.\textsuperscript{7,49} In addition, distinct cerebrospinal fluid proteomes can be used to differentiate post-treatment Lyme disease from chronic fatigue syndrome recently.\textsuperscript{50}

In Lyme disease, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may increase. Leukocytosis or leukopenia, anemia, and hypergammaglobulinemia may be observed.\textsuperscript{51}

In addition, in a study using healthy volunteers as a control group, elevated complement factors, such as C3a and C4a, have been associated with acute and chronic Lyme disease.\textsuperscript{4}

**Differential Diagnosis**

Differential diagnosis is influenced by the stage of the disease. Erythema migrans, which is the rash of early Lyme disease, must be differentiated from inflammation associated with insect bites, erythema multiforme, drug eruptions, nummular eczema, granuloma annulare, ringworm, and cellulitis. Other causes of carditis include viral agents, specifically Coxsackie enteroviruses. Lyme arthritis can be confused with bacterial septic arthritis, rheumatologic, and oncologic processes. Differential diagnosis includes in addition aseptic meningitis, Bell’s palsy due to herpes simplex virus 1, Ramsey-Hunt syndrome due to varicella zoster virus and chronic fatigue syndrome. Ixodes ticks may transmit Babesia, Anaplasmula, other Borrelia species, and viruses. These agents may be transmitted with or without \textit{B. burgdorferi}.\textsuperscript{6,12,38}

**TREATMENT**

In all clinical presentations, most patients with Lyme disease have resolution of their clinical symptoms when treated with appropriate antimicrobials.\textsuperscript{6,12}

Treatment depends on the stage of the disease. Erythema migrans is best treated orally with doxycycline (100 mg, every 12 hours) or amoxicillin (500 mg, every 8 hours) or azithromycin (20 mg/kg, once daily) for 14 days. 10 days of therapy also may be adequate. A 5-day azithromycin treatment can also be used but it may be inferior when compared with amoxicillin.\textsuperscript{1,6,52} In pregnant women, erythromycin is recommended at a dose of 500 mg, per oral (PO), every 6 hours, for 14 days. Individuals younger than 8 years of age should not be treated with doxycycline. Cefuroxime is also used for the treatment of Lyme disease. Early disseminated and late disease can also be treated with oral doxycycline or oral amoxicillin. Additional treatment with non-steroidal anti-inflammatory agents may provide symptomatic benefit. A 21- or 28-day intravenous therapy with ceftriaxone (2 g/day), cefotaxime (2 g/day) or crystalline penicillin (18 to 24 million units / day, divided into six daily doses) is often used for Lyme meningitis. Oral doxycycline is as effective as ceftriaxone in Lyme meningitis. Another indica-
tion for ceftriaxone is myocarditis and heart block in symptomatic patients requiring hospitalization. When the symptoms improve, these patients can complete the therapy with an oral agent.\textsuperscript{1,6,53} Some authors recommend a 14-day intravenous therapy for meningitis and carditis.\textsuperscript{52}

Articular manifestations and acrodermatitis chronica atrophicans are treated orally with doxycycline, cefuroxime axetil or amoxicillin for 21-28 days. Patients who do not respond to an initial course of antibiotic therapy and who display objective signs of synovitis should repeat a 4-week course of oral antibiotics or a 2- to 4-week course of parenteral antibiotics. Some adult patients with Lyme arthritis, particularly those with HLA-DRB1 alleles, will develop a chronic autoimmune arthritis which is resistant to antibiotic treatment. In these cases, surgery, non-steroidal anti-inflammatory treatment, corticosteroid treatment, hydroxychloroquine treatment are alternative treatment methods. Such cases aren't seen in Europe.\textsuperscript{1,6,25,52}

Some patients may develop a Jarisch-Herxheimer reaction soon after treatment is initiated. This reaction resolve spontaneously within 24-48 h. Non-steroidal anti-inflammatory drugs are often useful. Antimicrobial treatment during a Jarisch-Herxheimer reaction should not be stopped.\textsuperscript{1,6}

Treatment of Lyme disease has been summarized in table 2.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical presentation</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Erythema chronicum migrans</td>
<td>Doxycycline (PO\textsuperscript{a}, 100 mg, q12h) Amoxicillin (PO, 500 mg, q8h) Azithromycin (PO, 20 mg / kg, q24h) Cefuroxime axetil (PO, 500 mg, q12h) Erythromycin (in pregnant women, 500mg, PO, q6h)</td>
</tr>
<tr>
<td>2</td>
<td>Meningitis</td>
<td>Ceftriaxone (IV\textsuperscript{b}, 2g/q24h) Cefotaxime (IV, 2g/q24h) Crystalline penicillin (IV, 18 to 24 million units / q4h)</td>
</tr>
<tr>
<td></td>
<td>Myocarditis and heart block</td>
<td>Ceftriaxone (IV, 2g/ q24h)</td>
</tr>
<tr>
<td>3</td>
<td>Acrodermatitis chronica atrophicans</td>
<td>Doxycycline (PO, 100 mg, q12h) Amoxicillin (PO, 500 mg, q8h) Cefuroxime axetil (PO, 500 mg, q12h)</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Doxycycline (PO, 100 mg, q12h) amoxicillin (PO, 500 mg, q8h) Cefuroxime axetil (PO, 500 m, q12h)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Per oral  
\textsuperscript{b} Intravenous

PROGNOSIS

The long-term prognosis for patients who are treated with appropriate antimicrobials is excellent in any stages of the disease.\textsuperscript{6}

PREVENTION OF LYME DISEASE

The disease can be prevented by reducing contact with ticks. The best prophylactic strategy is avoiding tick bites. Personal protection measures, including protective clothing, repellents (n-diethylmetatoluamide) or acaricides and pesticides, tick checks, and landscape modifications in or near residential areas, may be helpful. N-diethylmetatoluamide can lead to serious neurologic complications in children. Permethrin (a synthetic pyrethroid) can be used as a spray for clothes. It is particularly effective because it kills ticks on contact. Removal of a tick has been suggested within 6 hours (I. ricinus) to 24 hours (I. scapularis). The risk of infection increases with length of exposure to the tick, approaching 100% on the third day. Persons should check themselves bodies and clothing daily after possible exposure to Ixodid ticks. Analysis of ticks to determine whether they are infected is not indicated. The previously used the vaccine has been withdrawn from the market because of safety issues, and other reasons.\textsuperscript{3,52,54,55}

A single, 200 mg dose of doxycycline may be effective in preventing Lyme disease in adults. A 10-day penicillin, amoxicillin and tetracycline prophylaxis is also recommended. But, recommendation of doxycycline is not routine, because the risk of Lyme disease is low (1-3%), even in highly endemic areas.\textsuperscript{6,56,57}
REFERENCES
