Curr Infect Dis Rep (2017) 19: 27
DOI 10.1007/s11908-017-0582-9

PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Management of Lyme Disease in European Children: a Review for Practical Purpose

Matteo D'Alessandro[1] · **Anna Loy**[1] · **Elio Castagnola**[1]

Published online: 5 July 2017

Abstract
Purpose of Review Lyme disease is a tick-borne zoonosis transmitted through a bite of a tick carrying a spirochete belonging to *Borrelia* species. In the last 20 years, the reported incidence of Lyme disease is increased by three times in Europe. Clinically, the illness develops through a primary stage with a typical skin rash (erythema marginatum), then a secondary stage with possible neurologic or cardiac involvement. The last stage (chronic Lyme disease) is mainly represented by arthritis or late neurological complications but nowadays is rarely seen due to precocious antibiotic use.
Recent Findings The diagnosis of Lyme disease is essentially based on history in agreement with tick exposure (living/recent traveling in endemic area or tick bite) and clinical findings compatible with the disease. At present, no laboratory diagnostic tool available can neither establish nor exclude the diagnosis of Lyme disease. The management of Lyme disease should comprise a prophylactic administration of antibiotic in selected population (patients exposed to a tick bite in endemic regions) in which the typical signs of Lyme disease are not yet appeared; conversely, patients with current signs of Lyme disease should undergo a standard therapeutic course. First-line therapy should be oral tetracycline or oral penicillin/cephalosporin (in pediatric populations, beta-lactamic drugs are preferred). In severe courses, intravenous route should be preferred.
Summary The aim of this review is to provide an updated guide to the management of pediatric Lyme patients, from prophylaxis to first- and second-line therapy in European setting.

Keywords Tick-borne zoonosis · *Borrelia burgdorferi* · Erythema marginatum · Facial nerve palsy

Introduction

Lyme disease (LD) is a tick-borne zoonosis primarily caused by several spirochetes belonging to *Borrelia* species. Humans acquire the infection through a bite of a tick whose gastrointestinal tract is colonized by the spirochete. Many ticks can be the vectors of this disease but they are mainly comprised in the genus *Ixodes*. The reservoirs of the spirochete in nature are several species of small mammals and birds [1].

The aim of this paper is to provide an up-to-date presentation of Lyme disease, its diagnostic approach, and therapeutic possibility, oriented in particular to the pediatric population in the European setting.

Epidemiology and Microbiology

LD is the most prevalent arthropod-transmitted human infection in northern Europe, North America, and temperate Asia [2]. Spirochetes primarily involved in this illness are *Borrelia burgdorferi* sensu stricto and *B. burgdorferi* sensu lato (*Borrelia afzelii* and *Borrelia garinii*). Spirochetes have two cellular membranes like Gram-negative bacteria, are 8 to

This article is part of the Topical Collection on *Pediatric Infectious Diseases*

✉ Elio Castagnola
eliocastagnola@gaslini.org

[1] Istituto Giannina Gaslini – Ospedale Pediatrico IRCCS, Largo G. Gaslini 5, 16147 Genoa, Italy

30 μm in length, and about 0.2 μm in width. Their narrowness accounts for the inability to see unstained or Gram-stained cells by standard light microscopy. Culture is not available in most clinical laboratories and the test is often negative due to the small copy number of spirochetes directly present in tested tissues.

Europe

In the last 20 years, the reported incidence of LD is increased by three times in Europe. In 2010, there were been around 35,000 reported cases of LD in Europe, and Central Europe is the region with the highest incident (Czech Republic, Estonia, Lithuania, Slovenia) [3••]. The ticks able to spread the disease in Europe are *Ixodes ricinus*, *Ixodes persulcatus*, *Dermacentor reticulatus*, and *Hyalomma marginatum.* The European Center for Disease Prevention and Control (ECDC) drew a map of tick diffusion divided by regions (http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET-maps-tick-species.aspx). The spirochetes involved in LD are *B. afzelii* and to a lesser extent *B. garinii* and *B. burgdorferi*.

No consensus diagnostic criteria are available at the moment so these data should be revised critically, and discrimination from probable to confirmed case is often tricky. Moreover, these data refer to general population because no specific pediatric data are available.

The USA

Several regions in the USA are high prevalence areas, notably Northern and Eastern states (CT, ME, MA, PA, NJ, NY). All these states have reported each one more than 1000 cases of LD in 2014. Globally, LD incidence in the USA in 2014 is 7.9 per 100,000 inhabitants [4••]. The Centers for Diseases Control and Prevention (CDC) drew a map of tick diffusion divided by regions (https://www.cdc.gov/lyme/stats/maps.html). In the USA, the spirochete related to borreliosis is virtually only the *B. burgdorferi* sensu stricto. The bites of *Ixodes scapularis* and *Ixodes pacificus* are responsible for human infection.

Clinical Features

As aforementioned, three genospecies of spirochetes cause LD and all have been detected in Europe. There is evidence of varying clinical presentations of LD caused by these different genospecies [5]. Historically, the illness has been divided in localized and disseminated disease. Dissemination and complications occur when the primary phase has not been treated appropriately.

Early Localized Lyme Disease

This is the initial stage of LD mainly revealed by the typical skin rash named *erythema migrans* (EM). The rash is round or ovalar shaped, with slow enlargement, starting from few centimeters but may reach 25–30 cm in diameter. During migration, EM tends to resolve from the center causing the typically "bull's eye" appearance and should not be itchy or painful. EM typically appears 7 to 14 days after (median 11, usually before 30) in the site of a tick bite. That is usually around axilla, inguinal region, popliteal fossa, and belt line. Sometimes, an aspecific skin rash may appear around the bite in a few hours, due to reaction to the salivary tick antigens injected through the bite. This rash, and eventually cellulitis, should not be confused with EM. During the first days of LD, there could be systemic symptoms such as diffuse arthromyalgia, fatigue, headache, mild neck stiffness, and regional lymphadenitis [1].

Early Disseminated Lyme Disease

This is the secondary stage of LD that develops if early localized Lyme disease (ELLD) is not treated properly. This stage starts from 3 to 5 weeks after tick bite and patients could present multiple EM on skin, sign of blood dissemination of the spirochete. During early disseminated Lyme disease (EDLD), clinicians should be aware of cranial nerve palsy, especially of the facial nerve (bilateral facial nerve palsy is virtually pathognomonic of LD) [6], pseudotumor cerebri, meningitis, and carditis, which are the most common complications of spirochete dissemination. In this stage, fatigue, headache, mild fever, and arthralgia are usually present in more than half of the patients [1].

Lymphocytic meningitis, cranial neuropathy (particularly facial palsy), and radiculoneuritis (motor or sensory or both) constitute the classic triad of acute, early neurologic LD, which affect nearly 15% of LD patients [6]. These manifestations may occur alone or in combination, but radiculoneuritis is diagnosed less commonly than meningitis or facial palsy. Lymphocytic meningitis of LD is largely indistinguishable from viral meningitis and many patients with peripheral or cranial nerve involvement have mild inflammatory cerebrospinal fluid [7]. In childhood, the most frequent symptoms and signs are headache due to meningitis and facial palsy [8].

Accurate data about prevalence of cardiac complications (Lyme carditis) among children are lacking although in adults, LD has some degree of cardiac involvement in about 5% of patients [9]. Anyway, its global incidence seems to be decreasing probably due to a better recognition of the disease and early treatment [10]. An old prospective study performed in the USA described a 30% prevalence of conduction abnormalities among children with confirmed LD [11]. Cardiac

involvement can appear as atrioventricular block (AVB) of any severity, from first degree to complete AVB, and can have clinical features (such as syncope) or not. Moreover, Lyme carditis may rarely have clinical evidence with heart failure or pericarditis. Frequently, AVB is a complete block but it can fluctuate rapidly from third to first and backwards. Complete AVB typically improves to lesser degrees of AV block within 1 week of therapy, and more minor conduction disturbances usually resolve within 6 weeks [12]. Borrelial lymphocitoma (lymphadenosis benigna cutis) is a rare skin complication of LD. It is described as a painless dark red or blue nodule, usually found on the ear lobe, markedly in infancy. Histological examination is mandatory when the diagnosis is not reliable; intense polyclonal B lymphocytic infiltrate is usually found [13•].

Late Lyme Disease

Late complications of Lyme disease (late Lyme disease [LLD]) occur weeks to months after the initial infection if this was not treated effectively. Arthritis is the most common manifestation of LLD. The arthritis is usually monoarticular or oligoarticular and affects the large joints, particularly the knee, which is involved in more than 90% of cases. Clinical features of Lyme arthritis may overlap bacterial arthritis due to severe swelling, loss of function, and laboratory findings in synovial fluid. Nevertheless, patients with Lyme arthritis are usually able to take a short walk even with the involved joint. Furthermore, natural history of the Lyme arthritis is far different from bacterial one and compatible with chronic relapses for several weeks or months, with almost invariably full resolution of the symptoms, even without antibiotic therapy. Anyway, the prognosis for children with treated Lyme arthritis is excellent [14, 15]. Neurological findings, such as low-grade encephalitis, have become extremely rare in the antibiotic era.

Diagnosis

Case Definition

The large variety of symptoms (most aspecific) that can be attributed to LD led to the formulation of as much as possible specific diagnostic criteria (e.g., for arthritis, https://www.medicalalgorithms.com/clinical-score-for-diagnosis-of-pediatric-lyme-disease-arthritis). Although the majority of LD patients fulfill these criteria, at time, they are not validated and should not be intended for clinical use but only for surveillance and epidemiological studies. These criteria are similar for North American [16•] and European [13•] cases of Lyme disease (Table 1).

Antibodies Detection

Serology is usually the first diagnostic tool used by clinicians. It should be kept in mind that the diagnosis of LD is essentially based on history in agreement with tick exposure (living/recent traveling in endemic area or tick bite) and clinical findings compatible with the disease. Patients should not be tested unless both the aforementioned conditions are fulfilled [13•, 17].

At present, no diagnostic tool available can neither establish nor exclude the diagnosis of LD. A positive or negative serologic test for LD simply changes the probability that a patient has been infected with *Borrelia*.

Positive predictive value (PPV) of a test depends on test sensibility, but also on the prevalence of the disease among local population; the lower the prevalence is, the lower the PPV is. Therefore, data obtained from serological studies, especially in low-prevalence population, should be considered with caution [13•]. A two-tier approach is recommended to support the diagnosis of LD, both in the USA and Europe [13•]. The first test should be based on enzyme-linked immunosorbent assay (ELISA) followed by a more specific Western blot (WB) on the same blood sample [17]. If the ELISA test is negative, no more examinations should be performed on that blood sample and the serology should be reported as negative. In case of positive or equivocal ELISA test, a second test (WB) should be performed. If WB is negative, the serology should be reported as negative; if positive (according to country-specific interpretation criteria), it should be reported as positive. Criteria for the interpretation of WB results have been proposed by the European Concerted Action on Lyme Borreliosis (EUCALB) [18] and Center for Disease Control and Prevention (CDC) [19]. These criteria should be carefully followed, and on the web, there are several tools that can help in interpreting serological results (e.g., https://www.medicalalgorithms.com/diagnosis-of-lyme-disease-western-blot or https://www.medicalalgorithms.com/criteria-of-hauser-et-al-for-the-serodiagnosis-of-lyme-borreliosis-in-europe-using-western-blot-testing). False-positive ELISA testing can be observed in patients affected by not only other borrelial diseases (e.g., relapsing fever) but also other spirochetal diseases (e.g., syphilis) because antigens used in ELISA test, especially first-generation test, are derived from *Borrelia* whole cell; therefore, cross-reaction is common. Also, autoimmune diseases (e.g., systemic lupus erythematosus or rheumatoid arthritis) may cause false-positive results. False-positive IgM testing is more common than false-positive IgG testing, although both can occur [20]. IgM seropositivity alone should be considered with extreme caution, especially if the patient does not develop IgG in the following weeks. Consequently, a two-tier approach with only IgM positivity (ELISA and Western blot), without IgG

Table 1 Case definition criteria as stated by EUCALB and CDC

Clinical condition	EUCALB criteria	CDC criteria
Erythema migrans	Expanding red or bluish-red patch (≥5 cm in diameter)[a] with or without central clearing. Advancing edge typically distinct, often intensely colored, not markedly elevated	Red macule or papule which expands over a period of days to weeks to form a large round lesion, often with partial central clearing. A single primary lesion must reach greater than or equal to 5 cm in size across its largest diameter. Secondary lesions also may occur
Borrelial lymphocitoma	Painless bluish-red nodule or plaque, usually on the ear lobe, ear helix, nipple, or scrotum; more frequent in children (especially on the ear) than in adults	
Acrodermatitis chronica atrophicans	Long-standing red or bluish-red lesions, usually on the extensor surface extremities. Initial doughy swelling. Lesions eventually become atrophic. Possible skin induration and fibroid nodules over bony prominences	
Lyme neuroborreliosis	In adults mainly meningoradiculitis, meningitis; rarely encephalitis, myelitis; very rarely cerebral vasculitis. In children mainly meningitis and facial palsy	Any of the following, alone or in combination: lymphocytic meningitis; cranial neuritis, particularly facial palsy (may be bilateral); radiculoneuropathy; or rarely encephalomyelitis. Encephalomyelitis must be confirmed by demonstration of antibody production against *Borrelia burgdorferi* in the cerebrospinal fluid, evidenced by a higher titer of antibody in CSF than in serum. Headache, fatigue, paresthesia, or mildly stiff neck alone are not criteria for neurologic involvement
Lyme arthritis	Recurrent attacks or persisting objective joint swelling in one or a few large joints. Alternative explanations must be excluded	Recurrent, brief attacks (weeks or months) of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints. Manifestations not considered as criteria for diagnosis include chronic progressive arthritis not preceded by brief attacks and chronic symmetrical polyarthritis. Additionally, arthralgia, myalgia, or fibromyalgia syndromes alone are not criteria for musculoskeletal involvement
Lyme carditis	Acute onset of atrioventricular (I–III) conduction disturbances, sometimes myocarditis or pancarditis	Acute onset of high-grade (II or III degree) atrioventricular conduction defects than resolve in days to weeks and are sometimes associated with myocarditis. Palpitations, bradycardia, bundle branch block, or myocarditis alone are not criteria for cardiovascular involvement

[a] If <5 cm in diameter, a history of tick bite, a delay in appearance (after the tick bite) of at least 2 days, and an expanding rash at the site of the tick bite are required

seroconversion within 2 months from the first test, should be regarded as false-positive result [21••]. The research for newer and more reliable tests led to the isolation of specific antigens of the spirochete usable in an ELISA test (VlsE C6 ELISA). Use of this method alone has been compared with a classic two-tier approach with old generation-based ELISA test, showing comparable specificity in ELLD, but slightly lower in EDLD and LLD [22•]. However, this assay does not completely eliminate the problem of cross-reactivity, and its usefulness seems less relevant in European setting: in fact, the selected antigens may not be as highly conserved among strains of the three major pathogenic *Borrelia* genospecies [23, 24]. WB allows detection of antibodies direct against specific components of the spirochete hence providing more information regarding which antigens of *B. burgdorferi* have resulted in an immune response in the host. WB can be performed to detect either IgM or IgG antibodies. Both IgM and IgG should be tested in case of EDLD, only IgG in case of LDD. Serological studies should not be performed in case of ELLD and therapy should be directly started based on the diagnosis of erythema migrans. If WB is positive, according to the aforementioned

diagnostic criteria, serology should be reported as positive; if WB is negative, serology should be reported as negative.

In case of neuroborreliosis, detection of intrathecal antibody production through estimation of specific antibody index (AI) may be helpful and evaluated according to the following formula:

$$\mathrm{CSF}\Big/ serum\ index\ [\mathrm{AI}] = \frac{ELISA\ units\ in\ the\ \mathrm{CSF} \times total\ \mathrm{IgG}\ in\ the\ serum}{ELISA\ units\ in\ the\ serum \times total\ \mathrm{IgG}\ in\ the\ \mathrm{CSF}}$$

IgM and IgG may persist for years after the disease, even if properly treated; therefore, a serological-based follow-up is not indicated.

Other Methods

Polymerase chain reaction (PCR)-based investigations have been evaluated over the years. Synovial fluid (SF) and cerebrospinal fluid (CSF) may be tested for the presence of borrelial genome. The sensibility of PCR-based test is low due to the small number of copies of spirochete in the specimens; thus, a negative PCR result does not exclude either neurologic LD or Lyme arthritis. False positives may results from persistent DNA in synovial and CSF; PCR test alone is not so useful in the diagnostic work-up for LD [25, 26].

B. burgdorferi has been cultured from skin biopsy specimens, blood, CSF, and synovial liquid but cultures are extremely difficult and slow growing. The specificity of this test is virtually 100% but the extreme low sensibility strongly limits its role in clinical practice [27].

Other methods such as urinary antigen detection or T cell proliferative responses of human mononuclear cells to borrelial antigens are not validated; hence, they should be used only for research purposes [28, 29].

Management

Figure 1 depicts a flow chart for patient's management based on clinical and laboratory data.

Management of a Patient Presenting with a Tick Bite and Prophylaxis for LD

Ticks have three stages in their life cycle: larva, nymph, and adult. The transmission of LD is mainly linked to nymphal ticks, which are typically most active during the late spring and early summer. Adult ticks can also transmit LD, but this occurs less commonly because adult ticks are less likely to bite humans and because they are larger and thus more likely to be detected and removed promptly. Individuals who live in high prevalence regions and have occupational (e.g., forestry) or recreational (e.g., hunting, camping) exposure to ticks are more prone to develop LD. It should be kept in mind that LD less often results from a recognized tick bite, since removal of the tick within 2 to 3 days of attachment usually prevents transmission of spirochete. Hence, LD is usually transmitted by the unrecognized tick that feeds for about 4 to 5 days and then falls off while the patient is completely unaware [17].

Several conditions may increase or decrease the ability of a tick bite to transmit LD; the risk is higher when (1) tick belongs to *Ixodes* genus; (2) tick is estimated to have been attached for ≥36 h (the tick is blood filled at time of removal); and (3) local rate of infection of ticks with *B. burgdorferi* is ≥20%. In case of high risk of transmission, antibiotic prophylaxis has been demonstrated safe and effective against the progression toward clinically manifest LD. The only drug that has been demonstrated effective in adults is doxycycline (200 mg only once; 4 mg/kg max. 200 mg in pediatric population older than 12 years) [30]. If doxycycline is contraindicated in the patient, other drugs should not be used [17]. In the presence of specific contraindications for the use of tetracycline (e.g., in children), a reasonable approach could be observation of tick bite site for the development of EM, for about 30 days after the bite. Indeed, the pathognomonic EM occurs in approximately 80% of patients [31] and treatment at this early stage of illness results in complete resolution of symptoms in at least 90% of patients [32].

Therapy

The goal of therapy is to shorten the duration of the signs and symptoms of localized disease and to reduce the risk of dissemination, hence limiting cardiac, neurological, and articular complications. Several randomized and prospective trials have been performed about efficacy of antibiotic treatment in LD patients but a variety of biases limit the utility of these studies. Biases are mainly related to the small number of patients enrolled and the difference between North American and European LD: *B. afzelii*, first cause of LD in Europe, has demonstrated a lower trend to hematogenous dissemination in respect of *B. burgdorferi*, so the ability to cause neuroborreliosis and carditis is probably lower; in this case, the choice of a shorter course of antibiotics could be legitimated [17].

Treatment of Localized Disease (Early Localized Lyme Disease)

Doxycycline, amoxicillin, and cefuroxime axetil have equivalent efficacy for the treatment of ELLD. Without specific contraindications, doxycycline is superior to amoxicillin and cefuroxime axetil because it is active also against *Anaplasma*, a potential co-infecting agent brought by the same tick, causing

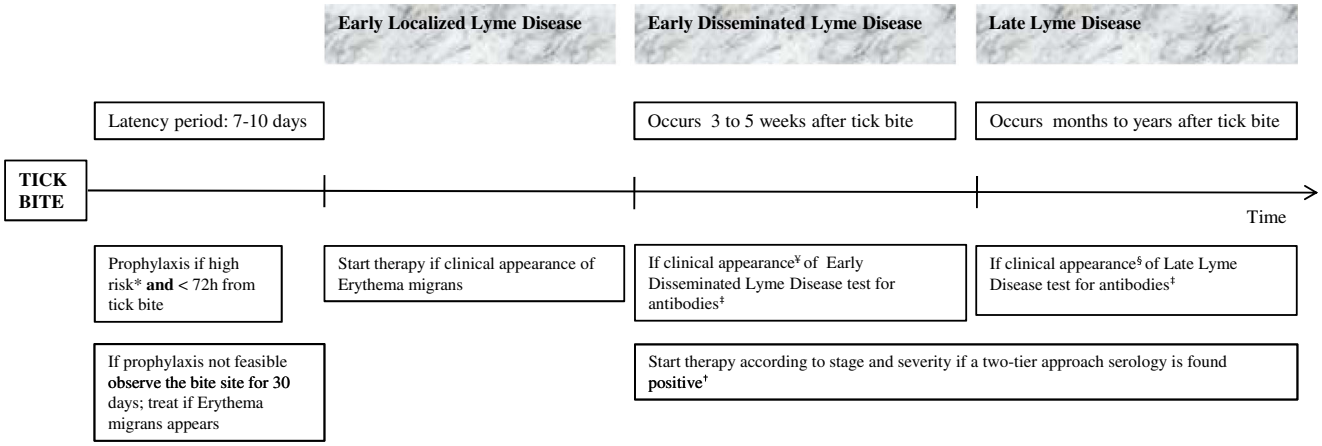

Fig. 1 Time course for clinical features, diagnostic approach, and general management strategies. *Asterisk*: High-risk patients as defined by tick attached for more than 36 h and tick full of blood at the time of removal and endemic region for Lyme borreliosis. *Yen sign*: Consider early disseminated Lyme disease if multiple erythema migrans or neurological involvement (lymphocytic meningitis, cranial neuritis, radiculoneuropathy, or encephalomyelitis) or cardiac involvement (acute onset of second- or third-degree atrioventricular conduction defects sometimes associated with myocarditis). Headache, fatigue, and paresthesia or mildly stiff neck alone are not criteria for neurological involvement as much as palpitations, bradycardia bundle branch block, or myocarditis alone are not criteria for cardiovascular involvement. *Section sign*: Consider late Lyme disease if recurrent brief attacks of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or few joints. Arthralgia and myalgia alone are not criteria for musculoskeletal involvement. *Double dagger*: Test for antibodies only if history and clinical signs are presents. At time, no diagnostic tool available can by itself neither establish nor exclude the diagnosis of Lyme disease. A positive or negative serologic test simply changes the probability that a patient had been infected by *Borrelia*. Start with ELISA test than perform Western blot confirmation only in case of positive or doubtful ELISA results. *Dagger*: A Western blot test should be interpreted according to regional (European vs. North American) specific criteria; false-positive IgM is more common than IgG. IgM seropositivity alone should be considered with extreme caution especially if the patient does not develop IgG in the following weeks. Isolated IgM positivity (ELISA and Western blot) without IgG seroconversion within 2 months from the first test should be regarded as a false-positive result. IgM and IgG may persist for years after infection, even if properly treated; hence, a serological-based follow-up is not indicated

human granulocytic anaplasmosis. An European trial compared a 10-day course of doxycycline with a 15-day course for patients with ELLD, showing that a 10-day regimen of oral doxycycline is non-inferior to a 15-day regimen [33]. Therefore, a shorter course of oral doxycycline for ELLD seems to be safe and effective in Europe. Another European randomized trial showed that azithromycin (500 mg on day 1 followed by 250 mg for other 4 days) and doxycycline (100 mg two times a day for 14 days) have similar results in the treatment of ELLD [34]. Hence, in Europe, in the presence of specific contraindications against all the first-line drugs, macrolides could be used for the treatment of ELLD. The use of macrolides cannot be recommended in the USA where strains of *B. burgdorferi* showing resistance to macrolides have been reported [35]. In pediatric population, the deposition of tetracyclines in growing bone and teeth (by binding to calcium) causes staining and occasionally dental hypoplasia. Therefore, in the USA, in patients younger than 12 years, a beta-lactam should be used as a first-line drug. Since initial skin rash of ELLD may sometimes be confused with cellulitis, amoxicillin-clavulanate should be preferred over amoxicillin at least in the first phases of observation. For specific dose and duration of therapy, see Table 2. The majority of patients with ELLD who receive appropriate antibiotic therapy have complete resolution of the signs and symptoms of infection within 20 days [36]. Up to 15% of patients with ELD experience a transient worsening of symptoms during the first 24 h of therapy which is due to the host immune response to antigens released by dying organisms (Jarisch-Herxheimer reaction) [37].

Treatment of Disseminated Disease and Complications (Early Disseminated Lyme Disease, Late Lyme Disease, Post-Lyme Disease Syndrome)

Treatment recommendations for this stage of LD are derived from small clinical studies conducted in the USA and Europe. This stage is characterized by neurologic and cardiac manifestations that should drive the therapeutic approach. For treatment purposes, neurologic manifestations could be divided in mild (isolated cranial nerve palsy) or severe (meningitis, pseudotumor cerebri, multiple neuritis). In Europe, oral doxycycline is routinely used as it has been demonstrated to be safe and effective for neurologic manifestation of EDLD, including meningitis [38–40]. Whether there are evidence or not, according to international guidelines, it seems cautious to administer parenteral drugs in severe form of neurological involvement, allowing oral route in milder cases [17]. Parenteral antibiotics such as ceftriaxone and cefotaxime are as effective as penicillin G in treating EDLD [41, 42]. In

Table 2 Treatment recommendations

Clinical stage		Drug	Adult dosage	Pediatric dosage
Erythema migrans (early localized Lyme disease)		Doxycycline	100 mg q12h for 10–21 days PO	2 mg/kg (maximum 100 mg) q12h for 10 to 21 days PO[a]
		Amoxicillin	500 mg q8h for 14–21 days PO	20 mg/kg (maximum 500 mg) q8h for 14–21 days PO
		Cefuroxime axetil	500 mg q12h for 14–21 days PO	15 mg/kg (maximum 500 mg) q12h for 14–21 days PO
Neurologic disease (early disseminated Lyme disease and late Lyme disease)	Isolated facial nerve palsy (mild disease)	Doxycycline	100 mg q12h for 14–28 days PO	2 mg/kg (maximum 100 mg) for 14–28 days PO[a]
	More serious disease (meningitis, radiculopathy, encephalitis)	Ceftriaxone	2000 mg q24h for 28 days IV (range 10–28 days)	50–75 mg/kg (max 2000 mg) q24h for 28 days (range 10–28 days) IV
Carditis (early disseminated Lyme disease)	Mild (first-degree atrioventricular block with PR interval <300 ms)	Doxycycline	100 mg q12h for 21 days (range 14–21 days) PO	2 mg/kg (maximum 100 mg) q12h for 21 days (range 14–21 days) PO*
		Amoxicillin	500 mg q8h for 21 days (range 14–21 days) PO	20 mg/kg (maximum 500 mg) q8h for 21 days (range 14–21 days) PO
		Cefuroxime axetil	500 mg q12h for 21 days (range 14–21 days) PO	15 mg/kg (maximum 500 mg) q12h for 21 days (range 14–21 days) PO
	More serious disease (symptomatic, second- or third-degree atrioventricular block with PR interval ≥300 ms)	Ceftriaxone	2000 mg q24h for 28 days IV (range 21–28 days)	50–75 mg/kg (max 2000 mg) q24h for 28 days (range 21–28 days) IV
Arthritis (late Lyme disease)	Arthritis without neurological disease	Doxycycline	100 mg q12h for 28 days PO	2 mg/kg (maximum 100 mg) q12h for 28 days PO[a]
		Amoxicillin	500 mg q8h for 28 days PO	20 mg/kg (maximum 500 mg) q8h for 28 days PO
	Arthritis with neurological disease	Ceftriaxone	2000 mg q24h for 28 days IV	50–75 mg/kg (max. 2000 mg) q24h for 28 days IV
	Recurrent arthritis	Ceftriaxone	2000 mg q24h for 14–28 days IV	50–75 mg/kg (max. 2000 mg) q24h for 14–28 days IV

[a] Careful use in children, age limitation depends on specific national guidance

milder cases, oral doxycycline is the first drug of choice, followed by amoxicillin and cefuroxime axetil. In Europe, a 10- to 14-day treatment course with beta-lactam drug was associated with excellent outcomes in two randomized, controlled trials [38–42]. In the USA, the Infectious Disease Society of America (IDSA) guideline recommends a therapeutic course of 14 days, even if a 10 to 28 course is acceptable. Resolution of neurological symptoms is often delayed, and persistence of symptoms is not inevitably related to treatment failure. For this reason, longer courses of antibiotics (21 to 28 days), particularly for those with evidence of severe symptoms, are advocated.

Late neurological complications, most often represented by encephalitis, encephalomyelitis, or cerebral vasculitis, are rare nowadays due to improvement in antibiotic treatment. This late neurological complications are far more rare in children and a thorough diagnostic work-up should be performed to exclude other diagnostic possibilities. The specific treatment for this condition is comparable to that suggested for severe form of early neurological involvement. For specific dose and duration of therapy, see Table 2.

Lyme carditis is another feature of EDLD. AVB of any degree could be the heralding symptom; because of potential life-threatening complications, patients who are symptomatic or having second- to third-degree AVB should be hospitalized and monitored. In this case, treatment with intravenous antibiotic is recommended. Ceftriaxone is the drug of choice, but cefotaxime and penicillin G are also effective. The duration of therapy should be 21 to 28 days and intravenous route is mandatory until ECG abnormalities are resolved or consistent only of first-degree AVB. For milder cardiac involvement, oral therapy with doxycycline (or amoxicillin and cefuroxime axetil) for 14 to 21 days is allowed [17].

Treatment of Lyme arthritis is based upon antibiotic and anti-inflammatory drugs, sometimes in addition to surgical intervention (e.g., synovectomy). The choice of antimicrobial drug and duration depends on coexisting neurological symptoms associated with arthritis. If the patient presents only articular involvement, oral route (doxycycline or amoxicillin) should be used. The recommended duration is 1 month. If there are neurological symptoms associated with arthritis, intravenous antibiotic is

mandatory (ceftriaxone, cefotaxime, or penicillin G) and the duration should be the same as for oral route [17]. More than 80% of patients with arthritis completely respond to a single course of oral therapy. For those in which articular involvement has not come to complete resolution after 1 month of therapy, a second course of the same antibiotic is suggested. On the contrary, patients who have had little or no improvement after the initial 28-day course of oral therapy should be treated with intravenous therapy (ceftriaxone) [17]. It is noteworthy that not all patients respond to antibiotic therapy immediately and sometimes clinical response may require several months [43]. These patients have been successfully treated with anti-inflammatory drugs and synovectomy [44].

Acrodermatitis chronica atrophicans is a late complication of *B. afzelii* infection. This condition is essentially treated as ELLD but with a longer duration (21 days). Clinical signs fade usually within 6 months [17].

As stated before, the treatment of LD is based upon antibiotic course administration of variable duration, mostly depending on severity of symptoms. Also the choice of the administration route is depending on clinical presentation, saving the intravenous route for complicated disease (neurological symptoms except isolated facial nerve palsy; cardiac symptoms except low-grade atrioventricular block, articular symptoms associated with other extracutaneous localizations, and recurrent arthritis). LD is characterized by a high grade of symptom resolution following antibiotic treatment based on international guidelines; hence, long-term sequelae are very rare. Despite this, there is a little amount of patients complaining of persistent symptoms after correct therapy; in the vast majority of cases, these symptoms are subjective and nonspecific.

Differences Between North American and European Approach to Lyme Disease

Several minor differences were found in European and North American Lyme disease. The so-called diagnostic criteria are quite similar between these two areas (Table 1), but the interpretation of Western blot results differs from Europe and the USA, as they are specific to the *Borrelia* species mainly involved in a specific region. Hence, a positive or negative result depends on criteria proposed by the European Concerted Action on Lyme Borreliosis (EUCALB) [18] and Center for Disease Control and Prevention (CDC) [19].

The therapeutic approach in Europe is less aggressive than North American with shorter course of antibiotics (10 vs. 14 days) and also oral route suggested as first-line therapy in localized and disseminated LD without severe symptoms. This is probably because in Europe, LD is primarily due to the group *B. burgdorferi* sensu lato: in respect of *B. burgdorferi* sensu stricto, it is the first cause of LD in North America, and with a lesser tendency to disseminate, and therefore a probably milder disease. Moreover, in Europe, macrolides are a safe and effective alternative to tetracycline, especially in pediatric population, whereas in North America, strains of *B. burgdorferi* resistant to macrolides have been reported, possibly precluding the use of this class of antibiotics.

Post-Lyme Disease Syndrome and Chronic Lyme Disease

The term post-Lyme disease syndrome (PLDS) is often used to describe the nonspecific symptoms (such as headache, fatigue, and arthralgia) that may persist for months after treatment of LD. For the majority of patients, these symptoms improve gradually over 6 months to 1 year [45, 46]. There is substantial evidence that long-term treatment with antimicrobials for PLDS is not associated with benefit, but is associated with a variety of potential deleterious effects [47]. Currently available evidence does not support the hypothesis that persistent infection with *B. burgdorferi* is the cause of chronic subjective symptoms that may occur after recommended courses of antibiotic therapy for LD. This is mainly due because at time, we lack reports of *Borrelia* strains resistant to recommended first-line antibiotics even if there are some reports in mice of surviving spirochetes after LD treatment. The cause of persistent nonspecific symptoms after treatment for LD remains an area of uncertainty; however, in a recent study comparing patients previously affected by LD and diagnosed with PLDS after correct treatment and controls, a high grade of psychiatric disorders was found in a case group. Moreover, the proportion of patients who develop PLDS is relatively small [47].

Special Conditions: Pregnancy and Breastfeeding

Historically, there has been a concern about the possibility of congenital Lyme disease because both *Borrelia* and *Treponema* belong to a spirochetal genogroup and the latter is known to be related to congenital abnormalities. Current evidence suggests that there is no definable congenital LD syndrome, and recent studies have not supported an association between LD in pregnancy and adverse fetal outcomes [48–50]. In pregnant women, first-line therapy should be the same as for non-pregnant women but doxycycline should be avoided because of concern about side effects of tetracycline administered during pregnancy, and a beta-lactam agent should be preferred. In pregnant and penicillin-allergic women, azithromycin could be used as an alternative [20]. The same recommendations may be applied for breastfeeding women affected by LD: the risk of transmission of LD to the newborn through breast milk has not been well established; however, to date, no case of mother-to-breastfeeded infant transmission has been reported. There are concerns also about the use of doxycycline in breastfeeding women for the risk of permanent staining of newborn's teeth and bone deposition, although drug level in milk is low and its

absorption by the newborn is inhibited by bivalent ions (Ca^{2+}) in breast milk. Hence, a short-term use of doxycycline is acceptable in nursing mothers, monitoring the infant for rash and for possible effects on the gastrointestinal flora, such as diarrhea or candidiasis [51, 52].

Special Populations: Immunocompromised Patients

Data on LD in immunocompromised patients are scarce. First reports were about HIV-positive patients and the natural history of *B. burgdorferi* infection during different phases of their disease [53, 54]. Concerns about a more severe course of LD in these patients raised mainly from the experience of another spirochetal-HIV co-infection (*Treponema pallidum*) in which there is a higher rate of asymptomatic infection, a faster progression to secondary phase which is often more aggressive with a significant predisposition for the development of neurological *sequelae* [55]. Despite this experience, no significant effects on clinical course, sequelae, and response to treatment were observed in the few immunocompromised (mainly receiving antineoplastic chemotherapy or chronic immunosuppression after organ transplantation) patients found infected with *Borrelia* [56].

Conclusions

LD is an infrequent disease in pediatrics with regional distribution. Diagnosis can be easy in the early localized stages, and in this case, the infection is easy to treat. In early and late disseminated stages, diagnosis (because of a large variety of symptoms, most aspecific, that can be attributed to LD) and treatment are more difficult, with the risk of developing late severe complications in untreated patients.

Serological diagnosis must be based both on ELISA and WB, with specific diagnostic in case of positive result criteria, that must be followed carefully, but a positive or negative serologic test for LD simply changes the probability that a patient has been infected with *Borrelia*. Therefore, the diagnosis of LD is essentially based on history in agreement with tick exposure (living/recent traveling in endemic area or tick bite) and clinical findings compatible with the disease, and patients should not be tested for antibody research unless both the aforementioned conditions are fulfilled.

PCR-based diagnostic tests are highly specific, but their extreme low sensibility strongly limits their role in clinical practice.

Doxycycline is the only drug that has been demonstrated effective and can be used in patients older than 12 years. If it is contraindicated in the patient, other drugs should not be used. Prophylaxis should be offered in patients from high endemicity regions (local rate of *B. burgdorferi* infected ticks ≥20%) and tick is estimated to have been attached for ≥36 h (the tick is blood filled at time of removal). Oral doxycycline is also indicated for treatment of LD, but when this drug cannot be used, other drugs as azithromycin (in Europo but not in the USA), cefuroxime axetil, or amoxicillin can be used. Intravenous therapy with ceftriaxone must be reserved for severe complications with administration of ceftriaxone, cefotaxime, or penicillin G.

Compliance with Ethical Standards

Conflict of Interest Drs. D'Alessandro, Loy, and Castagnola have no conflicts of interests to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2012;379:461–73.
2. Smith R, Takkinen J. Lyme borreliosis: Europe-wide coordinated surveillance and action needed? Euro Surveill. 2006;11:E060622.1.
3. •• European Centre for Disease Prevention and Control (ECDC). Fact sheet Lyme borreliosis (Eng) - ECDC–Europa. 2014. http://ecdc.europa.eu/en/healthtopics/vectors/world-health-day-2014/documents/factsheet-lyme-borreliosis.pdf. Accessed 25 Sept 2016. **Gives important information on the diffusion of Lyme disease in Europe, underlying regions at higher risk, with higher probability of infection, and where prophylaxis could be recommended**.
4. •• Centers for Disease Control and Prevention (CDC). Lyme disease data tables. Reported cases of Lyme disease by state or locality, 2005–2014. 2015. http://www.cdc.gov/lyme/stats/tables.html. Accessed 25 Sept 2016. **Gives important information on the diffusion of Lyme disease in the USA, underlying regions at higher risk, with higher probability of infection, and where prophylaxis could be recommended**.
5. Derdáková M, Lencáková D. Association of genetic variability within the Borrelia burgdorferi sensu lato with the ecology, epidemiology of Lyme borreliosis in Europe. Ann Agric Environ Med. 2005;12:165–72.
6. Pachner AR, Steere AC. The triad of neurologic manifestations of Lyme disease: meningitis, cranial neuritis, and radiculoneuritis. Neurology. 1985;35:47–53.
7. Wormser GP, Halperin JJ. Toward a better understanding of European Lyme neuroborreliosis. Clin Infect Dis. 2013;57:510–2.
8. Christen HJ, Hanefeld F, Eiffert H, Thomssen R. Epidemiology and clinical manifestations of Lyme borreliosis in childhood. A prospective multicentre study with special regard to neuroborreliosis. Acta Paediatr. 1993;386:1–75.
9. Steere AC, Batsford WP, Weinberg M, Alexander J, Berger HJ, Wolfson S, et al. Lyme carditis: cardiac abnormalities of Lyme disease. Ann Intern Med. 1980;93:8–16.
10. Fish AE, Pride YB, Pinto DS. Lyme carditis. Infect Dis Clin N Am. 2008;22:275–88. **vi**

11. Woolf PK, Lorsung EM, Edwards KS, Li KI, Kanengiser SJ, Ruddy RM, et al. Electrocardiographic findings in children with Lyme disease. Pediatr Emerg Care. 1991;7:334–6.
12. McAlister HF, Klementowicz PT, Andrews C, Fisher JD, Feld M, Furman S. Lyme carditis: an important cause of reversible heart block. Ann Intern Med. 1989;110:339–45.
13.• Stanek G, Fingerle V, Hunfeld KP, Jaulhac B, Kaiser R, Krause A, et al. Lyme borreliosis: clinical case definitions for diagnosis and management in Europe. Clin Microbiol Infect. 2011;17:69–79. Clinical case definition of Lyme borelliosis in Europe
14. Gerber MA, Zemel LS, Shapiro ED. Lyme arthritis in children: clinical epidemiology and long-term outcomes. Pediatrics. 1998;102:905–8.
15. Szer IS, Taylor E, Steere AC. The long-term course of Lyme arthritis in children. N Engl J Med. 1991;325:159–63.
16.• Centers for Disease Control and Prevention (CDC). Lyme disease (*Borrelia burgdorferi*). 2011 Case Definition. 2011;https://wwwn.cdc.gov/nndss/conditions/lyme-disease/case-definition/2011/. Accessed 25 Sept 2016. **Case definition of Lyme borelliosis in the USA**.
17. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43:1089–134.
18. Hauser U, Lehnert G, Wilske B. Validity of interpretation criteria for standardized Western blots (immunoblots) for serodiagnosis of Lyme borreliosis based on sera collected throughout Europe. J Clin Microbiol. 1999;37:2241–7.
19. Dressler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. J Infect Dis. 1993;167:392–400.
20. Centers for Disease Control and Prevention (CDC). Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep. 1995;44:590–1.
21.•• Lantos PM, Branda JA, Boggan JC, Chudgar SM, Wilson EA, Ruffin F, et al. Poor positive predictive value of Lyme disease serologic testing in an area of low disease incidence. Clin Infect Dis. 2015;61:1374–80. **A comprehensive review on serological diagnosis of Lyme disease**.
22. Branda JA, Linskey K, Kim YA, Steere AC, Ferraro MJ. Two-tiered antibody testing for Lyme disease with use of 2 enzyme immunoassays, a whole-cell sonicate enzyme immunoassay followed by a VlsE C6 peptide enzyme immunoassay. Clin Infect Dis. 2011;53:541–7.
23.•• Borchers AT, Keen CL, Huntley AC, Gershwin ME. Lyme disease: a rigorous review of diagnostic criteria and treatment. J Autoimmun. 2015;57:82–115. **A complete review on clinical diagnosis of Lyme disease**.
24. Tjernberg I, Krüger G, Eliasson I. C6 peptide ELISA test in the serodiagnosis of Lyme borreliosis in Sweden. Eur J Clin Microbiol Infect Dis. 2007;26:37–42.
25. Aguero-Rosenfeld ME, Wang G, Schwartz I, Wormser GP. Diagnosis of lyme borreliosis. Clin Microbiol Rev. 2005;18:484–509.
26. Sigal LH. The polymerase chain reaction assay for Borrelia burgdorferi in the diagnosis of Lyme disease. Ann Intern Med. 1994;120:520–1.
27. Liveris D, Schwartz I, Bittker S, Cooper D, Iyer R, Cox ME, et al. Improving the yield of blood cultures from patients with early Lyme disease. J Clin Microbiol. 2011;49:2166–8.
28. Klempner MS, Schmid CH, Hu L, Steere AC, Johnson G, McCloud B, et al. Intralaboratory reliability of serologic and urine testing for Lyme disease. Am J Med. 2001;110:217–9.
29. Pachner AR, Steere AC, Sigal LH, Johnson CJ. Antigen-specific proliferation of CSF lymphocytes in Lyme disease. Neurology. 1985;35:1642–4.
30. Nadelman RB, Nowakowski J, Fish D, Falco RC, Freeman K, McKenna D, et al., Tick Bite Study Group. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an Ixodes scapularis tick bite. N Engl J Med. 2001;345:79–84.
31. Steere AC, Sikand VK. The presenting manifestations of Lyme disease and the outcomes of treatment. N Engl J Med. 2003;348:2472–4.
32. Nadelman RB, Luger SW, Frank E, Wisniewski M, Collins JJ, Wormser GP. Comparison of cefuroxime axetil and doxycycline in the treatment of early Lyme disease. Ann Intern Med. 1992;117:273–80.
33. Stupica D, Lusa L, Ruzić-Sabljić E, Cerar T, Strle F. Treatment of erythema migrans with doxycycline for 10 days versus 15 days. Clin Infect Dis. 2012;55:343–50.
34. Barsic B, Maretic T, Majerus L, Strugar J. Comparison of azithromycin and doxycycline in the treatment of erythema migrans. Infection. 2000;28:153–6.
35. Terekhova D, Sartakova ML, Wormser GP, Schwartz I, Cabello FC. Erythromycin resistance in Borrelia burgdorferi. Antimicrob Agents Chemother. 2002;46:3637–40.
36. Luft BJ, Dattwyler RJ, Johnson RC, Luger SW, Bosler EM, Rahn DW, et al. Azithromycin compared with amoxicillin in the treatment of erythema migrans. A double-blind, randomized, controlled trial. Ann Intern Med. 1996;124:785–91.
37. Luger SW, Paparone P, Wormser GP, Nadelman RB, Grunwaldt E, Gomez G, et al. Comparison of cefuroxime axetil and doxycycline in treatment of patients with early Lyme disease associated with erythema migrans. Antimicrob Agents Chemother. 1995;39:661–7.
38. Karlsson M, Hammers-Berggren S, Lindquist L, Stiernstedt G, Svenungsson B. Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. Neurology. 1994;44:1203–7.
39. Kohlhepp W, Oschmann P, Mertens HG. Treatment of Lyme borreliosis. Randomized comparison of doxycycline and penicillin G. J Neurol. 1989;236:464–9.
40. Ljøstad U, Skogvoll E, Eikeland R, Midgard R, Skarpaas T, Berg A, et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. Lancet Neurol. 2008;7:690–5.
41. Dattwyler RJ, Halperin JJ, Volkman DJ, Luft BJ. Treatment of late Lyme borreliosis—randomised comparison of ceftriaxone and penicillin. Lancet. 1988;1:1191–4.
42. Pfister HW, Preac-Mursic V, Wilske B, Einhäupl KM. Cefotaxime vs penicillin G for acute neurologic manifestations in Lyme borreliosis. A prospective randomized study. Arch Neurol. 1989;46:1190–4.
43. Steere AC, Levin RE, Molloy PJ, Kalish RA, Abraham JH 3rd, Liu NY, et al. Treatment of Lyme arthritis. Arthritis Rheum. 1994;37:878–88.
44. Schoen RT, Aversa JM, Rahn DW, Steere AC. Treatment of refractory chronic Lyme arthritis with arthroscopic synovectomy. Arthritis Rheum. 1991;34:1056–60.
45. Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med. 2001;345:85–92.
46. Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. 2003;60:1923–30.
47. Feder HM Jr, Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP, et al., Ad Hoc International Lyme Disease Group. A

critical appraisal of "chronic Lyme disease". N Engl J Med. 2007;357:1422–30.
48. Silver HM. Lyme disease during pregnancy. Infect Dis Clin N Am. 1997;11:93–7.
49. Strobino BA, Williams CL, Abid S, Chalson R, Spierling P. Lyme disease and pregnancy outcome: a prospective study of two thousand prenatal patients. Am J Obstet Gynecol. 1993;169:367–74.
50. Maraspin V, Cimperman J, Lotric-Furlan S, Pleterski-Rigler D, Strle F. Treatment of erythema migrans in pregnancy. Clin Infect Dis. 1996;22:788–93.
51. NIH U.S. National Library of Medicine. Doxycycline. TOXNET® (TOXicology Data NETwork) Databases. 2016;https://toxnet.nlm.nih.gov/. Accessed 25 Sept 2016.
52. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. Clin Pharmacokinet. 1988;15:355–66.
53. Garcia-Monco JC, Frey HM, Villar BF, Golightly MG, Benach JL. Lyme disease concurrent with human immunodeficiency virus infection. Am J Med. 1989;87:325–8.
54. Cerný R, Machala L, Bojar M, Rozsypal H, Pícha D. Neuroborreliosis in an HIV-1 positive patient. Infection. 2006;34:100–2.
55. Karp G, Schlaeffer F, Jotkowitz A, Riesenberg K. Syphilis and HIV co-infection. Eur J Intern Med. 2009;20:9–13.
56. Fürst B, Glatz M, Kerl H, Müllegger RR. The impact of immunosuppression on erythema migrans. A retrospective study of clinical presentation, response to treatment and production of Borrelia antibodies in 33 patients. Clin Exp Dermatol. 2006;31:509–14.