

## Review articles

# Lyme borreliosis

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**ABSTRACT.** Lyme borreliosis is an infectious disease caused by spirochaetal bacteria, *Borrelia burgdorferi sensu lato*, which is transmitted by *Ixodes* spp. ticks. Several of *Borrelia burgdorferi* genospecies are pathogenic to humans. Endemic areas of the disease in Europe include: Scandinavia, Eastern Europe, Austria, Germany, Slovenia. In Poland the number of reported cases has increased since 1996 and large majority of all cases are diagnosed in Podlasie and Warmia-Mazuria provinces. The earliest symptom of Lyme borreliosis is characteristic skin rash, erythema migrans. If untreated, it can affect the nervous system, joints and the heart. Initial diagnosis of Lyme borreliosis is based on symptoms, physical findings, and the history of a tick-bite. Centers for Disease Control recommended two-step laboratory testing. The first step is immunoserological testing with enzyme immunoassay (EIA) for the presence of specific antibodies. Only in case of positive or equivocal EIA, the second step with western blot technique should be carried out. Other diagnostic methods are not recommended. In early stages of the disease patients should receive oral antibiotics, e.g. amoxicillin, doxycycline or cefuroxime axetil, with treatment lasting 14–21 days. In some cases (neuroborreliosis, carditis and chronic arthritis) patients require intravenous treatment usually with ceftriaxone or penicillin for 14–28 days. Superiority of longer therapy with higher doses of antibiotics, combination treatment with two or more antibiotics, or sequence therapy is not supported by any results of clinical trials, therefore it should not be applied and recommended according to the principles of evidence based medicine.

**Key words:** Lyme borreliosis, *Borrelia burgdorferi*, erythema migrans, arthritis, neuroborreliosis, Lyme disease

## Introduction

Lyme borreliosis is a bacterial disease with multisystematic inflammation caused by spirochaete: *Borrelia burgdorferi sensu lato*, which are transmitted by *Ixodes* spp. ticks [1].

The first descriptions of tick bite associated erythema migrans or neurologic symptoms came from early 20th century. However, Lyme borreliosis was named many decades later after the name of a town in Connecticut US State in which 12 cases of children arthritis and skin lesions after tick bites were described. In 1982 Willi Burgdorfer isolated spirochaetal bacteria from the saliva of the tick and one year later it was isolated also from patient's blood [2]. In Europe several of *B. burgdorferi* genospecies are pathogenic to humans: *B. burgdorferi sensu stricto*, *B. garini*, *B. afzelii*, *B. valaisiana*, *B. spielmani*, *B. lusitanae* [3]. Spirochetes are

transmitted by ticks (in Poland: *Ixodes ricinus*, *Ixodes persulcatus*). Bacterial reservoir comprises several hundred species of mammals including small and medium-size rodents and some birds. At different points of development cycle ticks feed on different animals and, consequently, transfer bacteria to new hosts including humans, which causes persistence of the bacteria in the environment [4].

## Epidemiology in Europe and Poland

The endemic areas of the disease in Europe coincide with the area inhabited by ticks *I. ricinus* and *I. persulcatus*. The areas where large majority European cases of infection are recorded include: Eastern Europe, Austria, Germany, Scandinavia and Slovenia [2,5]. Annual case reporting of Lyme borreliosis in Poland has been established since

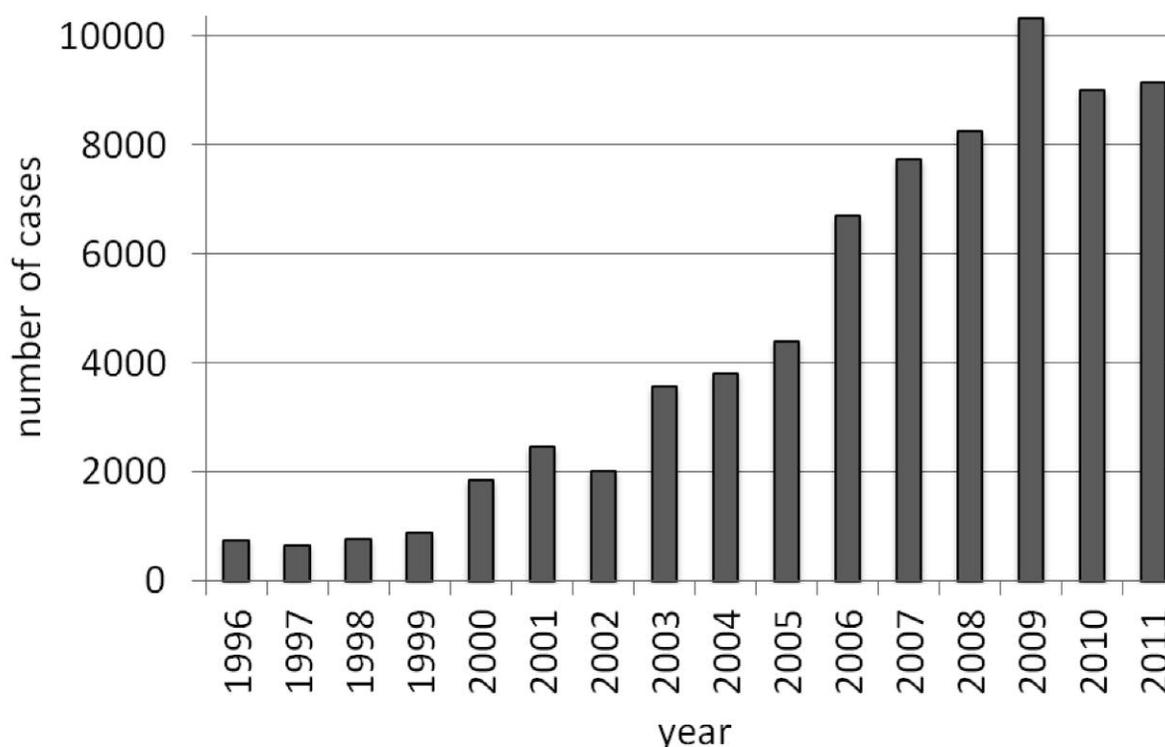


Fig. 1. Annual number of reported cases of Lyme disease in Poland between 1996 and 2011 according to National Institute of Health data

1996. The number of cases increased from 751 in 1996 up to 9.159 in 2011 (Fig. 1). The prevalence is not the same across the country, because most cases are diagnosed in Podlasie and Warmia-Mazuria provinces (Fig. 2) [6]. We should also remember that not all „real” cases are reported and, on the other hand, some not confirmed cases are reported.

### Symptoms

Lyme disease is a multi-organ disease and can affect the skin, the nervous system, joints and the heart [7].

### Skin involvement

Erythema migrans (Fig. 3) is the most frequent cutaneous form of Lyme borreliosis and constitutes 60–80% of cases [1]. It is the only manifestation of Lyme borreliosis which can be diagnosed based on the clinical picture without laboratory confirmation. The lesion appears several days to weeks after a tick bite increasing the diameter over the next few days and finally exceeding 5 cm. Skin lesion may have a characteristic central clearing, but it is not

obligatory for diagnosis. Sometimes it can demonstrate unusual irregular shape, resembling hemorrhagic lesions. The size of the skin lesion is required to distinguish between non-specific inflammatory skin reaction to the tick bite, occurring immediately after the incident and usually not exceeding 2 cm. Some patients may report pruritus, lymphadenopathy and general symptoms like fever, headache, muscular and articular pains [8].

*Borrelia lymphocytoma* is detected in less than 1% of patients, mostly in children [9]. It nearly always affect the earlobes, nipples, scrotum. Lesions occur in the form of hard bluish nodule and the diagnosis requires serological and histological confirmation [10].

*Acrodermatitis chronica atrophicans* (ACA, chronic atrophic dermatitis) occurs in the skin of extremities in the form of increased pigmentation accompanied by telangiectasia. Flattening of the epidermis can be observed in the atrophic stage and patients report pain of extremities. ACA can be associated with peripheral neuropathy and/or degenerative arthritis. The disease is more common in females and older people. This manifestation of

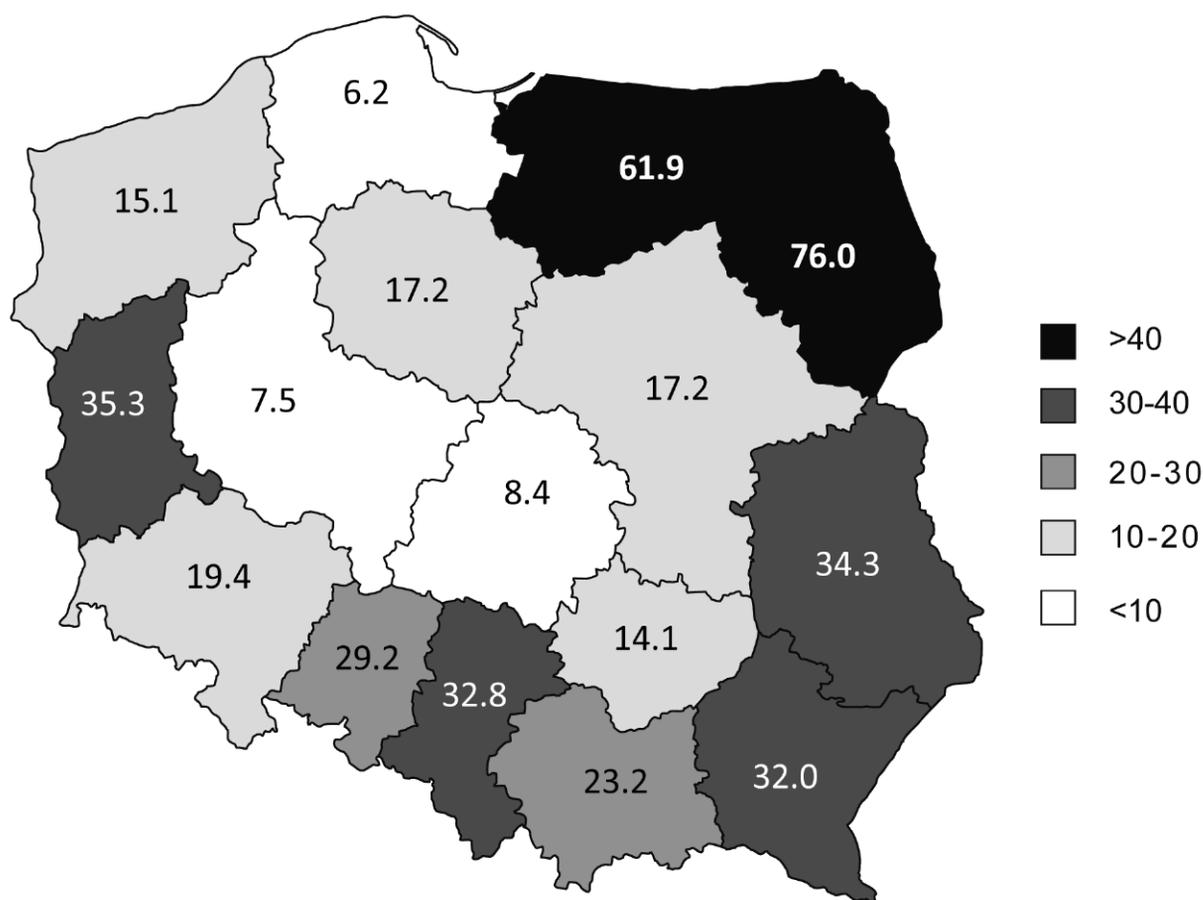


Fig. 2. Incidence of Lyme disease in particular provinces in 2010 according to National Institute of Health data (number of cases per 100.000 inhabitants/year)

Lyme borreliosis requires both serological and histological confirmation of the diagnosis [9,10].

### Carditis

Lyme carditis is usually diagnosed incidentally along with other forms of Lyme borreliosis. In large majority of cases patient do not report any cardiac symptoms and the only evidence of cardiac involvement is presence of ECG changes. Usually, there are blocks of the atrioventricular node and other conduction or rhythm abnormalities. In some rare cases myocarditis, pericarditis, cardiomyopathy related to Lyme borreliosis have been described, but they are not recognized as a part of typical clinical picture of the disease [11].

### Arthritis

Lyme arthritis may occur in several clinical forms. The most frequent are muscle ache, pain in bones and joints which appears few weeks

following infection. Recurrent joint pain with or without swelling separated by periods of remission are characteristic for Lyme arthritis. Usually asymmetrically involved joints of lower limbs are affected. Recurrent pain is frequently accompanied by swelling, increased warmth, pain during movement. Involvement of small joints is not typical. Very often there is no abnormalities in laboratory tests, including signs of inflammation. Untreated acute arthritis in early phase of the disease may turn into chronic arthritis and then changes can become irreversible. This form of Lyme borreliosis requires serological confirmation of specific antibodies and exclusion of other causes of arthritis and muscular inflammatory diseases [8].

### Neuroborreliosis

In the early phase of Lyme borreliosis the manifestation of the nervous system involvement is usually in the form of meningitis, encephalitis or/and myelitis, lymphocytic choriomeningitis,

a)



b)



Fig. 3. Typical erythema migrans (a) and acrodermatitis chronica atrophicans (b) lesions

cranial nerve palsies (usually facial), nerve root or peripheral nerves palsy. In the late phase chronic encephalopathy may occur manifested by sleepiness, irritability, concentration difficulties, memory impairment. Peripheral neuropathy with paraesthesia, impaired sensation and paresis are also common signs of late nervous system involvement. Lyme neuroborreliosis should be confirmed by presence of IgM or IgG specific antibodies in serum or in cerebrospinal fluid. Patients with meningitis usually demonstrate mononuclear pleocytosis accompanied by elevated protein concentration in cerebrospinal fluid. In such a cases of acute

meningitis the presence of antibodies in serum is usually sufficient for diagnosis. Imaging techniques with magnetic resonance in the first place are necessary to exclude other central nervous system diseases [12].

### Post-treatment Lyme borreliosis syndrome

Occurrence of this condition seems to be very controversial and is based on persistence of some symptoms for many months or years following antibiotic therapy in 10–20% of patients [13]. The most frequent symptoms related to post Lyme disease syndrome are joint pains, fatigue, sleep disturbance, cognitive deficits. Some physicians recognize these symptoms as related to still ongoing infection, and therefore recommend continuing „adequate” antibiotic treatment. However, this syndrome can be related to autoimmune response developed during active infection and successful treatment which persists even after clearance of the infection. Up to now there is no sufficient evidence based data confirming effect of long-term or combined antibiotic medication on the course of infection and disease [14–19].

### Diagnosis

Erythema migrans is the most characteristic clinical manifestation of Lyme borreliosis and its diagnosis should be based merely on the clinical picture only. In other clinical manifestations laboratory confirmation through demonstration of anti-*Borrelia burgdorferi* antibodies is necessary. There is no need to perform any laboratory tests in the absence of characteristic signs of the disease because, even if antibodies are demonstrated, the diagnosis of Lyme borreliosis should not be established in such a cases. Immunoserological testing with enzyme immunoassay (EIA) for presence of specific antibodies is the most frequently used approach. Since it demonstrates high sensitivity but lower specificity, the second step with western blot technique demonstrating higher specificity but lower sensitivity compared to EIA should be carried out in any EIA positive or equivocal sample to avoid false positive results (Fig. 4). False negative results may occur in the initial weeks of the disease. Western blot test should not be performed as the only because of possibility of false positive results. The use of other methods is not recommended due to their small utility. This

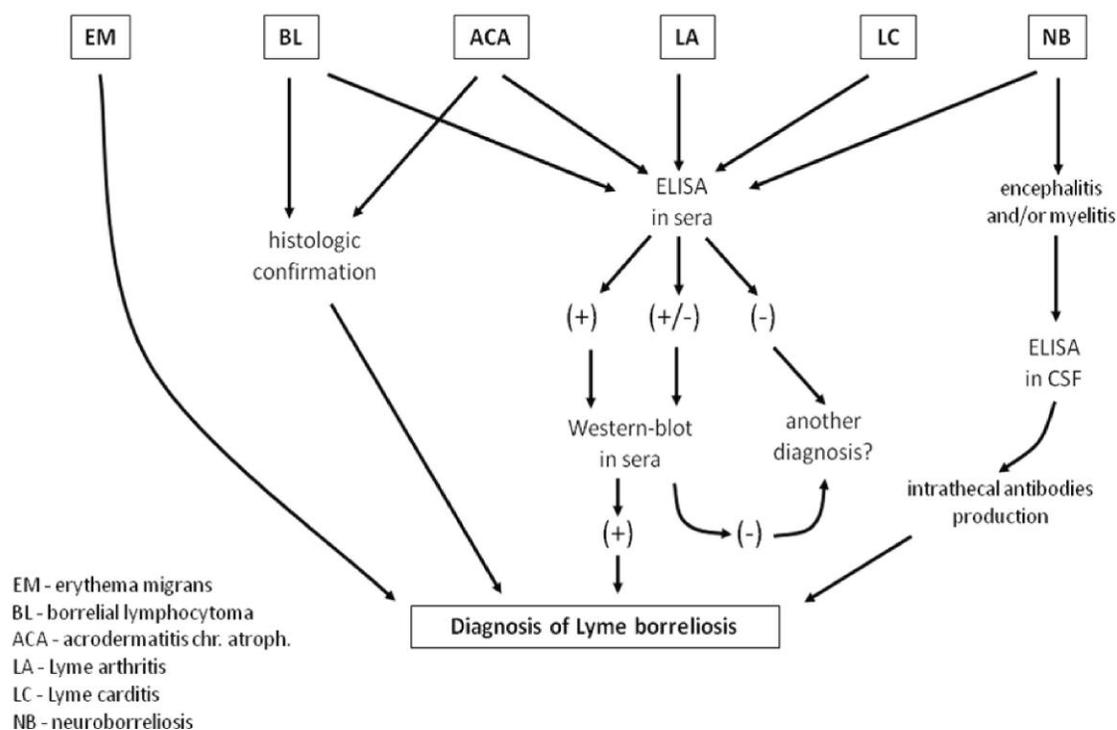


Fig. 4. Two-step laboratory testing

includes isolation, bacterial cultures, immunofluorescence staining, PCR, tests in synovial fluid, capture assays for antigens in urine, quantitative CD57 lymphocyte assays. Some health departments offer tick identification and testing, but it is not recommended by US Centers for Diseases Control and Prevention because majority of tick bites do not result in infection and the disease development [20–22].

## Treatment

The therapy is antibiotics based and usually oral treatment is applied in the early stage, and intravenous in the late stage of Lyme disease. Oral optimal medication includes: amoxicillin, doxycycline, or cefuroxime axetil. In neuroborreliosis or carditis and chronic arthritis patients require intravenous treatment usually with ceftriaxone or penicillin. Measurement of antibodies level for evaluation of treatment efficacy is not recommended because the only manifestation of therapeutic success is clinical improvement. Detailed recommendation of the treatment according to guidelines of Polish Society of Epidemiologists and Infectiologists is presented in Table 1.

Some physicians, mostly involved in the International Lyme and Associated Diseases Society (ILADS) recommend an alternative methods of treatment. They suggest longer therapy with higher doses of antibiotics, combination treatment with two or more antibiotics, intramuscular administration (benzathine penicillin) or sequential intravenous therapy followed by oral. Other alternative methods include: traditional Chinese medicines, homeopathy, anti-oxidants, hyperthermia, hyperbaric oxygen therapy, cholestyramine, antifungal therapy and antiviral agents. None of these methods can be accepted according to the principles of evidence based medicine because they have never been shown superior to the standard of care and some of them can harm patients owing to side effects. The ILADS recommends continuation of the therapy until spirochete is eradicated [23]. Unfortunately, up to now there has not been reliable laboratory method available to confirm clearance of borrelia infection, so clinical improvement is the only method.

## Prophylaxis

Active prophylaxis (vaccination) against Lyme borreliosis is not available. Post-exposure

Table 1. Treatment of Lyme disease according to guidelines of Polish Society of Epidemiologists and Infectiologists

Clinical manifestation	Antibiotic	Dose	Route of administration	Treatment duration (days)
Erythema migrans	Amoxicillin	3x500 mg (children: 50 mg/kg/day)	oral	14-21
	Doxycycline	2x100 mg or 1x200 mg	oral	14-21
Borrelial lymphocytoma	Cefuroxime axetil	2x500 mg (children: 30 mg/kg/day)	oral	14-21
	Azithromycin *	1x500 mg (children: 10 mg/kg/day)	oral	7-10
Paralysis of cranial nerves	Clarithromycin *	2x500 mg (children: 15 mg/kg/day)	oral	14-21
	Penicillin V	3x1000 mg	oral	14-21
Arthritis (the first line)	Amoxicillin	3x500-1000 mg (children: 50mg/kg/day)	oral	14-28
	Doxycycline	2x100 mg or 1x200 mg	oral	14-28
	Cefuroxime axetil	2x500 mg (children: 30 mg/kg/day)	oral	14-28
Neuroborreliosis (encephalitis, meningitis)	Ceftriaxone	1x2000 mg (children: 50-75mg/ kg/day)	intravenous	14-28
Arthritis (the second line)	Cefotaxime	3x2000 mg (children: 150-200mg/kg/day in 3-4 doses)	intravenous	14-28
Myocarditis	Penicillin G	3-4 MU every 4 hours (children: 0.2-0.4 MU/kg/dz. in 4-6 doses)	intravenous	14-28
Acrodermatitis chronica atrophicans	Amoxicillin	3x500-1000 mg	oral	14-28
	Doxycycline	2x100 mg or 1x200 mg	oral	14-28
	Ceftriaxone	1x2000 mg	intravenous	14-28
	Cefotaxime	3x2000 mg	intravenous	14-28
	Penicillin G	3-4 MU every 4 hours	intravenous	14-28

\* Azithromycin and Clarithromycin recommended only in cases of hypersensitivity to beta-lactam antibiotics

prevention of the disease after tick bite with antibiotics can be considered in some cases related to multiple tick bites in the endemic area of persons living permanently outside of this area. In such an event single oral dose of 200 mg doxycycline can be administered in adults and 4mg/kg (up to 200 mg) can be given to children of age above 8. Such a prophylaxis must be commenced within 72 hours after tick bite, otherwise is not effective. However, the most important for prevention is protection

against ticks bites in places of their living by means of protective clothing, repellents, and prompt removal of attached tick [7,9,24].

## Conclusion

The number of registered cases of Lyme borreliosis is increasing in Poland and in some areas of Europe. Practice guidelines for the diagnosis and treatment have not changed for many years because

of no additional significant data supporting their modification. In addition, there is no evidence based confirmation of benefits from alternative methods for diagnosis and treatment. Therefore, Lyme borreliosis still remains a challenging condition that needs development of laboratory methods testing the disease activity and efficacy of the treatment.

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