

TREATMENT OF LYME BORRELIOSIS

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SUMMARY

Lyme borreliosis is a multi system disease, which is caused by the spirochete *Borrelia burgdorferi* and transmitted by *Ixodes* ticks. In this article treatment with antibiotics in patients with Lyme borreliosis at the University Department of Infectious Diseases in Ljubljana is presented.

In the early localized disease, which is characterized by erythema migrans and often associated with flu-like symptoms, patients are treated orally with doxycycline, tetracycline, amoxicillin, azithromycin, phenoxymethylpenicillin or erythromycin. The treatment lasts two weeks, with the exception of azithromycin, which is prescribed for five days.

For the manifestations of Lyme borreliosis in the second stage (cardiac, neurologic and joint involvement) and third stage (acrodermatitis chronica atrophicans, neuroborreliosis, arthritis) intravenous treatment with antibiotics, currently with ceftriaxone or benzylpenicillin, is used. The exception are patients with mild cardiac involvement (first degree A-V block) who are treated with oral antibiotics.

Patients with Bell's palsy and pregnant women with erythema migrans are treated with intravenous antibiotics. Prophylactic treatment after tick bites is not recommended.

KEY WORDS

Lyme borreliosis, antibiotics, treatment.

INTRODUCTION

Lyme borreliosis is the most common tick-borne illness in Europe and the United States (1, 2, 3). The infection is caused by the spirochete *Borrelia burgdorferi* (4,5), which is transmitted by *Ixodes*

species ticks. The disease may affect many organic systems. Because of different clinical manifestations and long-standing evolution it has been divided into three stages (6). Recently, similar to syphilis, early

localized, early disseminated and late manifestations are recognized (7,8). Treatment with antibiotics has been shown to be effective during early and also late stages of the disease (9), but it has not yet been established, which antibiotic is the most efficacious (10-14).

Penicillin was the first antibiotic used in Europe and it remained the only one for many years. After discovery of *Borrelia burgdorferi*, in vitro studies to determine antibiotic sensitivities of the causative agent were performed as well as studies on experimental animals (15-18). In 1983, Steere et al. reported that phenoxymethylpenicillin, tetracycline and erythromycin are effective drugs for resolving erythema migrans and preventing the development of the later manifestations of the disease (10). It was found out that tetracycline appeared to be the most effective drug, followed by penicillin and finally erythromycin (8, 19). Amoxicillin and amoxicillin plus probenecid (20) as well as cefuroxime axetil (21) and ceftriaxone (22) are also effective in the treatment of early stage of Lyme borreliosis. Recently studies to determine the in vitro effectiveness of some other cephalosporins (ceftizoxime, FK 037), and of several new macrolides (clarithromycin, 14-OH clarithromycin, dirithromycin) were published (23,24). Clinical efficacy of these agents has not been evaluated. Studies on azithromycin demonstrate that it represents a suitable agent for treatment of erythema migrans (25-27).

For the majority of the manifestations of Lyme borreliosis in the second and third stage, intravenous treatment with antibiotics is indicated. Third generation cephalosporins (cefotaxime, ceftriaxone) and benzylpenicillin, which are currently used, have been shown to be effective (8,19,28-31).

Since failures or relapses have been reported with all regimens, the optimal antibiotic, the optimal dosage and optimal duration of antibiotic therapy have to be determined (14,27,29,32,33).

The treatment of patients with Lyme borreliosis at the Department of Infectious Diseases of the University Medical Centre in Ljubljana is reported.

TREATMENT OF THE FIRST STAGE OF LYME BORRELIOSIS

(EARLY LOCALIZED INFECTION)

The pathognomonic skin lesion at this stage is erythema migrans which usually appears within one

month after a tick bite. It may be accompanied by nonspecific symptoms such as fatigue, malaise, lethargy, headache, myalgias, arthralgias, regional or generalized lymphadenopathy. Some patients are totally asymptomatic (6,8,11,13). Although erythema migrans can disappear spontaneously, treatment with antibiotics in this stage is important because it reduces the duration of the cutaneous lesion and associated symptoms and prevents later manifestations of the illness (8,10,13,21,25-27).

At the Department of Infectious Diseases in Ljubljana adult patients are treated with doxycycline (100 mg orally twice daily), tetracycline (250 mg orally four times daily), amoxicillin (500 mg orally three times daily) or phenoxymethylpenicillin (1 million units orally three times daily) for two weeks. Treatment with azithromycin for five days (500 mg twice daily for the first day, followed by 500 mg once daily for four days) is also used.

For children with erythema migrans we use phenoxymethylpenicillin (30000-50000 units/kg/day) or amoxicillin (40 mg/kg/day). In case of allergy to penicillin erythromycin (30 mg/kg/day) is used. A study of the use of azithromycin in children is currently in course at our department.

The same antibiotics are in use also for the treatment of borrelial lymphocytoma, a rare manifestation of Lyme borreliosis described in Europe (3,7,34,35).

TREATMENT OF THE SECOND STAGE OF LYME BORRELIOSIS

(EARLY DISSEMINATED INFECTION)

Symptoms in this stage begin usually 2 to 3 months after the onset of erythema migrans, sometimes as late as 9-10 months after the beginning of infection (8).

A minority of patients with erythema migrans in Europe develop multiple skin lesions as a result of hematogenous dissemination of *Borrelia burgdorferi* (11,13).

In patients with neurologic involvement may develop a classical Bannwarth's syndrome, often associated with certain neurological manifestations such as meningitis, encephalomyelitis, neuritis of the cranial nerves (especially of the facial nerve), radiculoneuritis, and peripheral neuritis (6,8,36-38). Heart involvement (myocarditis, endocarditis and/or pericarditis) is usually asymptomatic. Carditis typically manifests with various degrees of atrioventricular conduction defects,

sometimes with tachyarrhythmias, ECG signs of myo(pericarditis and rarely with mild congestive heart failure (6,8,39).

Other manifestations in this stage of Lyme borreliosis are also migratory pains in joints, muscles, tendons and bones and recurrent attacks of large joints' arthritis (6,8).

In all these patients we use intravenous therapy with ceftriaxone (for adults 2 g once daily and for children 50-80 mg/kg/day) or benzylpenicillin (for adults 20 million units daily, for children 0.25-0.40 million units/kg/day) for two weeks.

Since patients with clinically isolated Bell's palsy frequently have asymptomatic meningitis, we treat them with an intravenous antibiotic.

Only patients with mild cardiac involvement, such as first degree atrioventricular block with P-R interval less than 0.30 second, are treated orally with above mentioned antibiotics for treatment of early localized infection.

TREATMENT OF THE THIRD STAGE OF LYME BORRELIOSIS

(LATE INFECTION)

The chronic stage occurs a year or more after the onset of infection with *Borrelia burgdorferi*, usually following a latent period (6,8).

The typical cutaneous lesion is acrodermatitis chronica atrophicans, occurring predominantly on the lower arms and legs (6,7,13,40,41). Neurological involvement of this stage, the so-called late neuroborreliosis, is manifested as progressive encephalomyelopathy, peripheral neuritis, and as mental and/or psychiatric disorders (6,8). Patients can display symptoms of chronic arthritis, which typically affects knees (6,8).

In the patients with late Lyme borreliosis we use intravenous ceftriaxone or benzylpenicillin in the same doses as in the second stage, but for a longer period (usually three weeks).

TREATMENT OF LYME BORRELIOSIS IN PREGNANCY

Because of the possibility of fetal anomalies or death (42-44), pregnant women with erythema migrans are treated with ceftriaxone (2 g daily i.v.) or benzylpenicillin (20 million units daily i.v.) for two weeks.

PREVENTION OF LYME BORRELIOSIS

Although Lyme borreliosis in Slovenia is endemic, we don't recommend prophylactic therapy with antibiotics in persons which experienced tick bites, because the risk to develop the disease is probably very low (45). We recommend wearing proper clothing and eventual use of repellents, and stress the importance of early tick removal (preferable within the first 24 hours).

CONCLUSIONS

Treatment with antibiotics is reasonable in any stage of Lyme borreliosis. However it is much more effective in the early localized and early disseminated infection than in chronic disease. The response may be delayed especially in patients with long-lasting illness. There is also a correlation between the severity of the early stage of disease and/or the presence of multiple erythema migrans lesions and progression to later stages (8). However, even the mildest or unapparent cases of Lyme borreliosis in early stage may progress (8,46). To prevent further manifestations of the disease it is important to start treatment promptly with an adequate antibiotic regimen. In view of the described failures of antibiotic treatment in Lyme borreliosis, further studies are needed to determine the optimal drug for various clinical manifestation, its dosage as well as duration of therapy.

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