

Therapy of Lyme borreliosis

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S U M M A R Y

Despite many studies that have been carried out recently, there is still no standard treatment for Lyme borreliosis. The factors that must be taken into consideration in treating the disease are the intrinsic sensitivity of the pathogen *Borrelia burgdorferi*, tissue penetration of the antibiotic, the characteristics of the pathogen, such as long generation time (7-20 h), intracellular localization, persistence in tissues with a poor blood supply (e.g. synovia), penetration of the blood-brain barrier, and varying antibiotic resistance of different pathogen strains. A generally accepted antibiotic treatment regimen has yet to be established, and all treatment recommendations are essentially provisional.

Introduction

Decades before *Borrelia burgdorferi* was identified as the causative agent of Lyme borreliosis, antibiotic treatment of adults with penicillin was shown to be associated with a faster resolution of erythema migrans and its associated symptoms. However, clinical studies have since demonstrated the possibility of treatment failures with penicillin, and other antibiotics appear to be superior to penicillin. Despite many studies that have been carried out recently, there is still no standard treatment for Lyme borreliosis and further improvements are necessary. The most effective antibiotic, the optimal dosage and the appropriate duration of treatment have not been exactly determined for any of the many clinical manifestations of the disease.

Present therapeutic recommendations are based on

in-vitro studies, observations from animal models, and the clinical experience (1-16).

Early localized stage

This stage comprises erythema migrans and the less frequent lesions of borrelial lymphocytoma. Oral therapy is generally sufficient if the patient takes the drug as instructed.

Classical regimens are:

Amoxicillin 3 x 500-1000 mg p.o. x 14-21 days or Doxycycline 2 x 100 mg p.o. x 14-21 days (tetracyclines are contraindicated for pregnant or lactating women and

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children younger than 8 years) or cefuroxime 2 x 500 mg p.o. x 14 days.

Macrolides have a very good *in-vitro* activity, but the clinical experience is limited, therefore they should not be used as first line agents and are recommended only for patients with documented hypersensitivity to standard antibiotics (1).

Patients treated with macrolides should be followed closely.

Despite therapy sequelae can occur in around 1-3% of cases. In such cases, *Borrelia* may have already colonized the subarachnoid space or the joints, where oral antibiotics achieve only low concentrations. In these cases, intravenous treatment with a third-generation cephalosporin should be performed (ceftriaxone 2 g i.v. daily x 14-21 days) and the patients should be monitored frequently. Patients in whom symptoms, such as headache, fever or arthralgias indicate a disseminated infection prior to treatment are particularly predisposed for later complications. Good response of the erythema is achieved within days after initiation of treatment. In untreated patients the disease course is longer and the risk of complications higher. Clearing of the skin lesions without treatment is no proof that *Borrelia burgdorferi* has been eliminated. Monitoring of the clinical course and counselling of the patient is always recommended.

Early disseminated stage

This stage comprises neurological, rheumatological, cardiac and ophthalmological manifestations. Considering pathophysiological aspects and the poor penetration into cerebrospinal fluid, intravenous antibiotic therapy is generally preferable. In smaller prospective reports, no significant differences were noted between different antibiotics (15). Treatment failures have been reported. For some of the *Borrelia* strains isolated, penicillin therapy seems to be ineffective and the use of third-generation cephalosporins is suggested.

Some authors have recommended oral antibiotics for uncomplicated cases of Lyme arthritis or ophthalmoborreliosis reserving intravenous antibiotic treatment for refractory cases only (15).

Steroid administration prior to antibiotic therapy, according to some authors, can promote the development of chronic arthritis while non-steroidal anti-inflammatory agents cause no problems as concomitant medication.

Chronic stage

In the late stage of Lyme borreliosis, the clinical signs and symptoms can still respond to antibiotics. As secondary immunological mechanisms are very likely to

play a role in the pathogenesis of late Lyme borreliosis, immunosuppressants have been used in late neuroborreliosis, both alone and in combination with antibiotics. For example, progressive encephalomyelitis, chronic Lyme arthritis, and acrodermatitis chronica atrophicans respond, at least partially, well to antibiotics. The cure is often inadequate, however, in case of delayed start of therapy.

Intravenous treatment with a third generation cephalosporin over 3 weeks (ceftriaxone 2 g i.v. daily; penicillin G 20 x 10⁶ IU i.v. daily is the treatment of choice for this stage of the disease. The penicillin dosage should be reduced for patients with impaired renal function) (1).

In chronic arthritis intrarticular steroid injections or synovectomy may be necessary when antibiotic treatment has been inefficient (1).

Therapy during pregnancy

It is known that transplacental passage of *Borrelia burgdorferi* is possible and a causal relationship between maternal infection and malformation or death of the child has been suspected; however it is not possible to define a typical malformation syndrome. For a successful treatment it is necessary to achieve an adequate concentration of the antibiotic in maternal as well as fetal tissues, which is a difficult task during pregnancy, where physiologic changes may influence the pharmacokinetics of the drug applied. In the study of Maraspin et al. (3), the authors conclude that prompt intravenous administration of antibiotics, such as ceftriaxone (2 g i.v. daily x 14 days) is a successful and safe approach to Lyme borreliosis in pregnancy.

Monitoring the treatment of the several features of Lyme borreliosis is very important. Whereas erythema migrans disappears within days after initiation of therapy, articular pain and swelling improve only slowly. Radicular pain responds quickly, while pareses show a slow tendency to improve. Follow up examinations should be performed at 3, 6, and 12 month after treatment. In neuroborreliosis, repeated analysis of cerebrospinal fluid is crucial; the cell count must return to normal within 6 month.

A second 3-week treatment cycle with ceftriaxone should be performed if symptoms persist over 6 months.

Antibiotic treatment can trigger Jarisch-Herxheimer reaction in rare case. Supplementary steroids given before may then be beneficial (15).

Elevated antibody titers are often still present after adequate antibiotic treatment and the concentration may decline slowly over years varying from one individual to the next, and depending on the clinical manifestation of Lyme borreliosis.

In conclusion, in patients with unequivocal Lyme borreliosis, response to treatment is generally excellent in case of early and appropriate therapy. No laboratory test can provide definite proof of cure. Thus clinical signs and symptoms remain the principal parameters for the assessment of the efficacy of treatment. The most

effective antibiotic and the most appropriate duration of treatment have not been exactly determined (16). The choice of antibiotic depends upon many aspects, including pharmacokinetic profile, efficacy, side effects, and price. Recommendations for treatment are continuing to evolve.

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