

Antibiotic treatment of Lyme borreliosis: our experiences

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S U M M A R Y

Treatment with antibiotics is indicated in all stages of Lyme borreliosis and for all clinical manifestations. It has been, however, most effective in the early course of illness. The choice of antibiotic depends on many factors, including the efficacy, pharmacokinetics, side effects, expected compliance, and price. For the majority of manifestations, the most effective antibiotic, the optimal dosage, and the most appropriate duration of treatment have not been exactly determined.

Basic principles of antibiotic therapy of Lyme borreliosis and recommendations for treatment of this disease as used in Slovenia are presented.

The objective of this report is to summarize the principles of antibiotic therapy of Lyme borreliosis and to outline the treatment approach as used in Slovenia.

Basic principles of treatment

Clinical signs and symptoms are essential for the correct diagnosis of Lyme borreliosis (LB). Only a reliable diagnosis enables rational treatment. The fact is that in Lyme borreliosis with its insufficient clinical specificity and the lack of standardized serological tests, a reliable diagnosis is usually not an easy goal to achieve. Solid knowledge of clinical manifestations is a prerequisite for rational treatment (1).

Treatment with antibiotics is indicated in all stages

of LB and for all clinical manifestations, it is however most effective in the early course of the illness (2). The efficacy of treatment depends on clinical manifestations (severity, duration, and involvement of a particular organ/organ system) and the choice of an effective antibiotic that should be given in an optimal dosage and for an appropriate time, and on the compliance of the patient. Selection of an antibiotic implicates many factors including the efficacy, pharmacokinetics, side effects, expected compliance, and price.

The aim of antibiotic therapy is to eradicate bacteria causing infection. Eradication of pathogenic bacteria is a precondition, but unfortunately not a guarantee for cure, nor for exclusion of eventual sequelae. Healing of the injured tissue (caused by bacteria or associated inflammation) may take much longer than the effective eradication. In such cases some clinical features may

K E Y W O R D S

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Table 1. Recommendations for treatment of early Lyme borreliosis with antibiotics in Slovenia.

Manifestation	Antibiotic	Route	Dosage (per day)		Duration (days)	Contraindications
			Adults	Children		
Erythema migrans, Lymphocytoma	amoxicillin	oral	3x500-1000 mg	20-50 mg/kg	14 (10-30)	allergy
	or					
	azithromycin	oral	2x500 mg	20 mg/kg	1st day	allergy
	or		1x500 mg	10 mg/kg	4 days	
	cefuroxime	oral	2x500 mg	30-40 mg/kg	14 (10-30)	allergy
	or					
	doxycycline	oral	2x100 mg		14 (10-30)	children, pregnancy lactation, allergy
	or					
phenoxy- methylpenicillin	oral	3x0.5-1.0 MIU	0.1-0.15 MIU/kg	14 (10-30)	allergy	
erythromycin ^a	oral	4x250 mg	30 mg/kg	14 (10-30)	allergy	
ceftriaxone ^b	i.v.	2 g	50-100 mg/kg (up to 2 g/day)	14	allergy	
or						
penicillin G ^b	i.v.	20 MIU	0.25-0.5 MIU/kg	14	allergy	

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MIU = million international units

^a erythromycin only for patients allergic to penicillin and/or tetracyclines^b ceftriaxone and penicillin G are used for treatment of erythema migrans only in specific situations

persist in spite of successful antibiotic therapy. Thus, in certain infectious diseases including LB, persistence of signs or symptoms should not necessarily lead to of antibiotic treatment until the complete disappearance of all signs and symptoms.

The most effective antibiotic, the optimal dosage and the appropriate duration of treatment have not been exactly established for any of the many clinical manifestations of LB. Some physicians would treat only patients who fulfil all the rigorous criteria for LB, while others treat patients with poorly defined symptoms of chronic LB with repeated or prolonged courses of antibiotics. Sometimes even antibiotics are used to which *Borreliae* are in vitro resistant. Current shortcomings of therapy should be a stimulus for well designed investigations to study the unresolved problems (1).

In the last few years a trend of prolongation of treatment of Lyme borreliosis has been observed. Reasons for this prolongation have been predominantly based on disappointments with the results of treatment performed according to current recommendations. These are often based on reports or personal experiences of individual treatment failures, and not on the results of controlled studies. It is however possible that such studies would show that a prolonged treatment is superior to a shorter one. Anyway, it is reasonable to expect that the recommendations for treatment (1-10) will be chang-

ing in future.

Because of different pathogenesis of LB in North America and Europe, differences in clinical presentation of the disease (11-13), and paucity of data comparing the outcome of the illness on either side of the Atlantic, it may be prudent to consider the existing information with caution.

Antibiotic treatment of Lyme borreliosis as used in Slovenia

Recommendations for treatment of Lyme borreliosis as used in Slovenia are shown in Tables 1, 2 and 3.

Early localized Lyme borreliosis

Recommendations for treatment of the early localized disease (Table 1) were introduced in our country in 1992, and have not changed substantially. Patients with solitary erythema migrans and borrelial lymphocytoma are treated with amoxicillin, azithromycin, doxycycline, cefuroxime-axetil, or phenoxymethylpenicillin (the last one predominantly in children). With the exception of azithromycin the usual duration of treatment

Table 2. Approaches in a case of treatment failure in erythema migrans as used in Slovenia.

Problem	Solution
Persistence of skin lesion (> 4 weeks)	Check diagnosis Re-treatment with an alternative ^a (oral) antibiotic
Reappearance of skin lesion	Check diagnosis Re-treatment with an alternative ^a (oral) antibiotic
Persistence of <i>Borreliae</i> in skin	Re-treatment with an alternative ^a (oral) antibiotic
Appearance of minor manifestations of Lyme borreliosis	Wait and watch; check diagnosis Eventual antibiotic treatment (ceftriaxone i.v.?)
Appearance of major manifestations of Lyme borreliosis	Treatment with ceftriaxone i.v.

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^a beta-lactam antibiotics (amoxicillin or cefuroxime axetyl) are replaced by tetracyclines (doxycycline) or macrolides (azithromycin) and vice versa.

is 14 days. The efficacy is similar but there are differences in dosage (from one time to 3 times daily), side effects (relatively frequent with doxycycline) as well as the price (the most expensive is cefuroxime axetil while the cheapest is doxycycline).

Parenteral therapy with ceftriaxone or penicillin G is used only exceptionally in patients with erythema migrans. It is limited to:

- i) patients with multiple skin lesions; an article from the USA demonstrating that therapy of multiple erythema migrans with doxycycline was as effective as treatment with ceftriaxone was published recently (14);
- ii) patients with erythema migrans and concomitant other manifestations of LB (e.g. neurological involvement);
- iii) erythema migrans in pregnancy (15); and
- iv) parenteral antibiotic treatment might be indicated also for immunodeficient patients with erythema migrans; however, there are not enough data to support this decision (16).

In case of a treatment failure in erythema migrans we use approaches as shown in Table 2.

Early disseminated and late Lyme borreliosis

Recommendations for treatment of early disseminated and late LB in Slovenia are shown in Table 3. Nervous system involvement and severe Lyme carditis are as a rule treated with ceftriaxone or penicillin G for 2 to 3 weeks and only exceptionally orally with doxy-

cycline or amoxicillin (Table 3).

For therapy of acrodermatitis chronica atrophicans and arthritis, ceftriaxone, penicillin G, doxycycline or amoxicillin are recommended. Parenteral therapy is used because of the possible involvement of the central nervous system. Duration of intravenous treatment is as a rule 3 weeks for acrodermatitis chronica atrophicans and 2 weeks for arthritis, while the duration of oral therapy is 4 weeks (Table 3).

Asymptomatic persons with a positive borrelial antibody titre, persons with a recent tick bite

No reliable data support the use of antibiotics in asymptomatic persons with a positive borrelial serologic test. Decision to treat a patient with an antibiotic should always be based on the presence of at least suggestive clinical signs and symptoms. Thus, our general approach in the case of an asymptomatic person with positive borrelial antibody serum titres is to wait and watch (1). As a rule we use a similar approach in an asymptomatic person reporting a recent tick bite (1,17).

Reasons for antibiotic treatment failure

There are several reasons for antibiotic treatment failure in LB. One possibility is the persistence of *Borreliae* in tissues. There are convincing clinical and

Table 3. Recommendations for treatment of late Lyme borreliosis with antibiotics in Slovenia.

Manifestation	Antibiotic	Route	Dosage (per day)		Duration (days)	Contraindications
			Adults	Children		
CNS involvement (early or late)	ceftriaxone	i.v.	2 g	50-100 mg/kg	14 (10-30)	allergy
	or penicillin G	i.v.	20 MIU	0.25-0.5 MIU/kg	14 (10-30)	allergy
Heart involvement						
Possible exceptions ^a	doxycycline	oral	2x200 mg		28 (14-30)	children, pregnancy lactation, allergy
	or amoxicillin	oral	3x0.5-1 g	20-50 mg/kg	28 (14-30)	allergy
Arthritis (intermittent or chronic)	doxycycline	oral	2x100-200 mg	-	14 (10-30) ^b	children, pregnancy lactation, allergy
	or amoxicillin	oral	3x0.5-1 g	20-50 mg/kg	14 (10-30) ^b	allergy
Acrodermatitis chronica atrophicans ^b	ceftriaxone	i.v.	2 g	50-100 mg/kg	14 (10-30) ^b	allergy
	or penicillin G	i.v.	20 MIU	0.25-0.5 MIU/kg	14 (10-30) ^b	allergy

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CNS = central nervous system

^a Possible exceptions: - peripheral facial palsy alone (normal cerebrospinal fluid examination results)
- atrio-ventricular block of first degree (P - Q < 0.30 s)

^b Treatment of acrodermatitis chronica atrophicans is as a rule longer than 14 days (ceftriaxone 21 days, doxycycline 28 days)

experimental data, predominantly in the European literature, showing that after so called adequate (recommended) treatment *Borreliae* can persist in tissue (18-20), it is however difficult to assess the significance of this problem.

In some cases a possible explanation for treatment failure could be an irreversible tissue damage caused during active borrelial infection or inflammation or the induction of auto-immune mechanisms; in such cases treatment with an antibiotic can be ineffective (1,3).

An important and probably a common cause for treatment failure is wrong diagnosis. It is quite possible that treating a patient with, for example, arthralgias and myalgias and a positive borrelial antibody titre in se-

rum, is not a treatment of LB but "therapy" of serological tests (1,3,8,9).

Conclusion

A well-established principle in medicine says that a reliable diagnosis is the basis for rational treatment. However, in LB with its lack of clinical specificity and lack of standardized serological tests, a reliable diagnosis is usually not an easy goal to achieve. Antibiotic therapy is indicated in all stages of LB and for all clinical manifestations, however, it is more effective in the early stage of the illness.

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