THERAPY OF LYME BORRELIOSIS - A REVIEW

K. Weber

ABSTRACT

There is some confusion regarding the recommended therapy of Lyme Borreliosis. In the present paper current treatment standards are outlined based on a review of the literature.

Most patients with Lyme Borreliosis benefit from a single course with an effective antibiotic. However, in many but not all patients with recalcitrant Lyme Borreliosis, repeated courses with the same or other effective antibiotics may be necessary and prove to be beneficial.

KEY WORDS

Lyme Borreliosis, therapy

THERAPY OF ERYTHEMA MIGRANS

The aim for treating patients with erythema migrans (EM) is to clear the erythema, relieve associated signs and symptoms and to prevent later manifestations. Recent therapeutical studies have shown a beneficial effect of several antibiotics (Table I). There was no significant difference between these antibiotics, although azithromycin and penicillin V each performed worse in one subgroup analysis (1-5, quot. 3-10 in ref. 1). However, there were quite different study designs in the investigations cited. A couple of patients developed major or minor sequelae despite antibiotic treatment. Major sequelae consisted of meningitis (meningo-radiculoneuritis, meningoencephalitis) in 1.1.% and of arthritis in 1.0% of 1137 patients treated in randomized trials. The percentage of major sequelae was somewhat different regarding the antibiotics used (Table II).

There are a couple of problems involved with the interpretation of arthritis and meningitis. Regarding arthritis, swelling is not always pronounced enough to distinguish arthritis from arthralgia. Distinction from other types of arthritis is not always possible as in two patients of Luger et al. (3) and arbitrary exclusion of short-term arthritis has influenced the interpretation of a study result (6). The development of meningitis in an EM patient treated with oral antibiotics often raises the question whether *Borrelia burgdorferi* (*Bb*) had already invaded the central

Table I. Recommended therapy for Lyme Borreliosis (according to ref. 1)

STAGE	ANTIBIOTIC	DOSAGE	DURATION (days)	ROUTE OF APPLICATION
1	Doxycycline	1x200 mg	14	oral
	Amoxicillin	3x750 mg[a]	14	oral
	Cefuroxime axetil	2x500 mg	14	oral
	Ceftriaxone	1x1 g 5	IM	
	Minocycline	2x100 mg[b]	14	oral
	Azithromycin	1x500 mg	6[a]	oral
	Penicillin V	3x1 g	14	oral
2	Ceftriaxone	1x2 g	14	IV
	Cefotaxime	3x2 g	14	IV
	Penicillin G	4x3 g	14	IV
	Doxycycline or amoxicillin as above *		14	oral
3	Doxycycline or amoxicillin as above *		21	oral
	Ceftriaxone	1x2 g	21	IV **
	Cefotaxime	3x2 g	21	IV **
	Penicillin G	4x3 g	21	IV **

a = modified; b = 75 mg in case of dizziness; IM = intramuscular; IV = intravenous; * = for less severe disease; ** = for more severe disease

nervous system before the therapy was started (7). Post-treatment meningitis was established by lumbar puncture in some studies (2,4, quot. 3-6,8 in ref. 1), but not in others (3, quot. 9 in ref. 1).

EM fades more or less slowly after appropriate antibiotic therapy and remnants might easily be overlooked by the patient.

Minor sequelae such as fatigue, headache, arthralgia, fever, myalgia, stiff neck, dysesthesia, sore throat, dizziness, chills and palpitations develop in 11 - 25% of the patients despite antibiotic therapy (Table II). In many instances, minor sequelae disappear spontaneously within about 3 months. There is a significant correlation between the severity of pre-treatment disease and the development of minor sequelae (6, quot. 5,11 in ref. 1). Early retreatment might be beneficial to alleviate or prevent minor sequelae, but it precludes the appropriate evaluation of the primary antibiotic. A treatment failure can be assumed when EM recurs or persists for more than 3 months, major sequelae appear, *Bb* persists and/ or a significant and persistent increase of antibody titres is noted (8).

THERAPY OF STAGE 2 MANIFESTATIONS

More severe stage 2 manifestations such as meningitis, carditis and severe ocular involvement require parenteral antibiotic and possibly additional supportive therapy (1).

EARLY NEUROLOGICAL INVOLVEMENT

The evaluation of antibiotic therapy in patients with early neurological involvement is difficult because of spontaneous remission of signs and symptoms and because placebo-controlled studies are not possible for ethical reasons. No significant difference was noted among patients treated with ceftriaxone, cefotaxime, high-dosed penicillin G and doxycycline in randomized trials (11, quot. 18-21 in ref. 1). Not very severe cases of meningo-radiculoneuritis can probably most appropriately be treated with 2g ceftriaxone intravenously on an outpatient basis (1).

Table II. Major and minor sequelae in 1137 patients randomly treated for erythema migrans.

		MAJOR SEQUELAE		MINOR SEQUELAE
ANTIBIOTIC	NUMBER OF PATIENTS	Meningitis[a]	Arthritis	
		n/%	n/%	n/%
Minocycline	18[b]	0/0	0/0	2/11
Ceftriaxone IM	40	0/0	0/0	6/15
Amoxicillin	162	1/0.6[c]	0/0	18/11
Azithromycin	292	3/1.0[d]	0/0	60/21
Doxycycline	328	5/1.5[e]	5/1.5[e]	60/21
Cefuroxime axetil	163	1/0.6	5/3.1	32/20
Penicillin V	134	2/1.5	3/2.2	23/25[f]
All antibiotics	1137	12/1.1	13/1.0	201/18[f]

a = 4 cases were not proven, but 2 additional cases with facial palsy were not included
b = in addition, 21% of 28 patients (9) and 28% of 36 patients (10) treated non-randomly had minor sequelae and one of the patients developed meningoradiculoneuritis (8)
c = or 2 cases and d = or 2 cases because of the unclear statement in the abstract of Luft et al. (quot. 10 in ref. 1)
e = one patient had meningitis and arthritis
f = of 94 patients because of lacking details in (6)
IM = intramuscular

OTHER STAGE 2 MANIFESTATIONS

Most other manifestations of stage 2 such as less severe carditis and ocular involvement, erythemata migrantia and borrelial lymphocytoma can be treated with oral antibiotics similar to the treatment of EM (Table I).

THERAPY OF STAGE 3 MANIFESTATIONS

ARTHRITIS AND ACRODERMATITIS CHRONICA ATROPHICANS

The most common stage 3 manifestations, arthritis and acrodermatitis chronica atrophicans (ACA), should be treated primarily with oral antibiotics such as doxycycline or amoxicillin (Table I).

A randomized trial has revealed no difference between both antibiotics mentioned regarding the treatment of patients with arthritis, but a couple of the patients did not have a favorable response even when retreated with ceftriaxone; unresponsive patients were found to be HLA-DR4 positive and OspA reactive (12).

No randomized therapeutical trial has been reported concerning ACA. Patients with ACA may be treated with the oral antibiotics used for EM (Table I). The patients should be observed for 6 months or longer after therapy because the response is often delayed. The discoloration should fade, but the atrophy remains; fibroid nodules usually respond rather quickly. If there is no satisfactory clinical response after about 6 months, retreatment with another oral antibiotic is indicated (1).

LATE NEUROLOGICAL INVOLVEMENT

Severe manifestations such as encephalomyelitis and cerebral vasculitis should be treated with intravenous antibiotics (Table I). Peripheral neuropathy associated with ACA can primarily be treated with oral antibiotics (1).

OTHER RANDOMIZED STUDIES

Several randomized therapeutical trials (quot. 24-26 in ref. 1) for late LB are only of limited value. In the trial of Steere et al. (quot. 24 in ref. 1), benzathin penicillin was superior to placebo in 40 well-defined patients with arthritis but it is probably inferior to high-dosed penicillin. The two other trials mentioned selected patients with a variety of late signs and symptoms, some of which were not easy to follow or to compare; in the trial of Dattwyler et al. (quot. 25 in ref. 1) a total of only 23 patients was included in the randomized part. Despite these doubts, ceftriaxone and cefotaxime are now widely used antibiotics for complicated LB. It is, however, questionable whether high-dosed penicillin G performs significantly worse than the two mentioned cephalosporins.

TREATMENT FOR CHILDREN

In children under the age of 9, tetracyclines are contraindicated. For other antibiotics, equivalent doses should be used as in adults (1).

TREATMENT DURING PREGNANCY

There are only very few reports showing a deleterious outcome in fetuses or newborns, whose mothers suffer from LB. Pregnant women with LB may be treated with amoxicillin 500 mg four times daily or 750 mg three times daily. Cefuroxime 500 mg twice daily may be an alternative. Tetracyclines are contraindicated. Penicillin V is not recommended. Ceftriaxone or cefotaxime should be restricted to the second and third trimester. Azithromycin may be an alternative in penicillin-sensitive women (1).

REFERENCES

1. Weber K, Pfister HW. Clinical management of Lyme Borreliosis. Lancet 1994; 343: 1017-20.

2. Strle F, Preac-Mursic V, Cimperman J et al. Azithromycin versus doxycycline for treatment of erythema migrans: clinical and microbiological findings. Infection 1993; 21: 83-88.

3. Luger SW, Paparone P, Wormser GP 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: 661-67.

4. Strle F, Maraspin V, Lotric-Furlan S et al. Azithromycin and doxycycline for treatment of Borrelia culture-positive erythema migrans. Infection 1996; 24: 64-68.

5. Breier F, Kunz G, Klade H et al. Erythema migrans: three weeks treatment for prevention of late Lyme Borreliosis. Infection 1996; 24: 69-72.

6. Steere AC, Hutchinson GJ, Rahn DW et al. Treatment of early manifestations of Lyme disease. Ann Intern Med 1983; 88: 22-26.

7. Weber K. Erythema-chronicum-migrans-Meningitis - eine bakterielle Infektionskrankheit? Münch Med Wochenschr 1974; 116: 1993-98.

8. Weber K. Treatment failure in erythema migrans - a review. Infection 1996; 24: 73-75.

9. Weber K, Thurmayr R. Oral penicillin versus minocycline for the treatment of early Lyme Borreliosis. Zbl Bakt Hyg A 1989; 18 (Suppl.): 263-68.

10. Muellegger RR, Zoechling N, Schluepen EM et al. Polymerase chain reaction control of antibiotic treatment in dermatoborreliosis. Infection 1996; 24: 76-79.

11. Karlsson M, Hammers-Berggren S, Lindquist L et al. Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. Neurology 1994; 44: 1203-7.

12. Steere AC, Levin RE, Molloy PJ et al. Treatment of Lyme arthritis. Arthritis Rheum 1994; 37: 878-88.

AUTHOR'S ADDRESS

Klaus Weber, MD, Dermatological Private Practice, Rosenstrasse 6, D-80331 Munich, Germany