REVIEW

Antibiotic treatment of Lyme borreliosis: what is the evidence?

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Antibiotic treatment of all disease manifestations after infection with *Borrelia* sensu lato spp aims at resolving the presenting disease manifestation and preventing late stage disease. The goals are resolution of the preventing manifestation and prevention of the spread of bacteria to prevent late disease like arthritis. Different borrelial species prevail in Europe. The natural disease course of European borreliosis is not well defined and the effect of antibiotic treatment is unclear.

In analogy with *Treponema pallidum* infections, all disease manifestations after infection with *Borrelia* spp are treated with antibiotics (table 1). The goals are resolution of the presenting disease manifestation and prevention of the spread of bacteria which might cause later stage disease, arthritis being one of the most severe late manifestations. Most studies in favour of this concept have been performed in the United States of America, where only one borrelial genospecies pathogenic for humans (*Borrelia burgdorferi* sensu stricto) is endemic. Are there sufficient data to support this therapeutic concept in a European context, where different strains prevail?

ERYTHEMA MIGRANS

Studies from America suggest that early disease manifestations like erythema migrans respond to antibiotic treatment. To our knowledge, only one placebo controlled non-randomised trial has been performed, which proved that penicillin shortens the duration of erythema migrans from a median of 10 to 3 days. However, even in the control group, all skin lesions disappeared within 6 weeks.[1] Further trials compared different antibiotic regimens and did not observe relevant differences in outcome between short and long courses of doxycycline, amoxicillin/probenecid, cefuroxime or ceftriaxone,[2–4] except that a short course of azithromycin appeared to be less effective than a long course of amoxicillin.[5] The median time to response was comparable to the first trial.

No placebo controlled or systematic longitudinal studies of untreated patients have been carried out in Europe. An early observational study suggests that the clinical evolution of untreated erythema migrans in Europe is probably similar to the one described in America.[6] European studies only support the conclusion that different antibiotic regimens are equally effective,[7–11] even though the time to resolution of erythema appears to be longer than in America.[7 9 12] Unfortunately, no study so far has assessed the natural course of the disease dependent on the borrelial species involved. Although we know that different borrelial species are associated with different clinical presentations,[12 13] we do not know how this correlates with outcome.

ARTHRITIS

Arthritis is the most thoroughly investigated late stage manifestation. An American placebo controlled study in 40 patients showed that penicillin led to the resolution of arthritis in 55% of patients, whereas no placebo treated patient improved.[14] The other placebo controlled study included 60 patients with a positive enzyme linked immunosorbent assay (ELISA) response to *Borrelia burgdorferi* and chronic arthritis like rheumatoid arthritis, psoriatic arthritis, or vasculitis.[15] Treatment with ceftriaxone led to improvement in 48% compared with 10% of untreated patients, irrespective of the form of arthritis. However, the arthritis worsened in 60% of the initial responders after a follow up of 6–18 months.[15] The inclusion of differentiated forms of arthritis impedes the interpretation of this study; the efficacy of ceftriaxone on all forms of chronic arthritis could be viewed as a non-specific anti-inflammatory effect.

> ''The outcome of Lyme borreliosis may depend on the borrelial species causing the infection''

Two small American studies compared different antibiotic regimens—the first, penicillin with ceftriaxone,[16] the second, doxycycline with amoxicillin/probenecid.[17] Of the 16 patients with arthritis in the first study,[16] half had been treated with oral tetracycline or penicillin previously. A subsequent study reported in the same publication[16] compared two doses of ceftriaxone in 23 patients, of whom two thirds had been treated previously. Three of nine penicillin treated patients improved, whereas arthritis resolved in 27/30 patients in both ceftriaxone arms within 6 months. Both regimens of the second study[17] led to a resolution of attacks of intermittent arthritis in 90% of 40 patients within 3 months.

A substudy[17] analysed the effect of ceftriaxone in 16 patients with continuous arthritis refractory to previous antibiotic regimens, including intravenous penicillin. No patient responded within the first 3 months, but arthritis resolved

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in all patients within 2 years, even though recurrence was noted in three patients. Six patients were synovectomised arthroscopically, with resolution of arthritis within 1 month, suggesting that non-antimicrobial treatments may also be efficacious. The only published report on the natural history of Lyme arthritis in America shows that the disease waxes and wanes over the course of 2–4 years before spontaneous resolution.[18] Thus, while treatment with doxycycline or amoxicillin for 30 days or ceftriaxone for 2 weeks appears to reduce the frequency of attacks of intermittent arthritis in America, the effect of treatment on continuous arthritis remains equivocal. No study assessed the benefit of sequential or prolonged treatment—that is, doxycycline for 60 days followed by ceftriaxone for 2 weeks.[19]

In Europe, no placebo controlled trials have been published. A trial on 35 Czech patients with arthritis associated with a positive western blot for *Borrelia* associated antigens who had been treated with 2 g ceftriaxone once daily for 2 weeks showed complete resolution of arthritis in 80% of patients at 12 months.[20] However, at 36 months, 14/26 evaluable patients again showed signs of arthritis. Another trial comparing penicillin with cefotaxime[21] in 83 patients with arthritis and positive borrelial ELISA showed response rates of 50–80%, but only 40% of cefotaxime treated patients were free of symptoms 2 years after treatment. Twenty per cent continued to have arthritis, 40% had ''partial remission'', presumably meaning persisting arthralgias.[21] Unfortunately, no interim data were presented.

An observational study in 55 children disclosed an effect of first line treatment with ceftriaxone in 60% of patients, but arthritis was persistent in 20% of patients despite treatment with up to six different antibiotics.[22] The authors argue that part of this disappointing result may be due to inappropriate use of intra-articular steroids in a subgroup analysis of nine patients. None of these studies analysed borrelial subspecies. Owing to the absence of placebo control, none took into

Table 1 Antibiotic regimens used in the studies cited in this manuscript

Reference (first author)	Manifestation	Treatment	Dose	Duration (days)
1 (Steere)	Erythema migrans	Penicillin G IV	0.25 Mio U qod	7–10
		Erythromycin po	250 mg qod	7–10
		Tetracycline	250 mg qod	7–10
2 (Dattwyler)	Erythema migrans	Amoxicillin/probenecid po	500 mg tid	21
		Doxycycline po	100 mg bid	21
3 (Nadelman)	Erythema migrans	Cefuroxime po	500 mg tid	14
		Doxycycline po	100 mg bid	14
4 (Wormser)	Erythema migrans	Doxycycline po	100 mg bid	10
		+/− Ceftriaxone IV	2 g od	1
		Doxycycline po	100 mg bid	20
5 (Luft)	Erythema migrans	Azithromycin po	500 mg od	7
		Amoxicillin/probenecid po	500 mg tid	21
7 (Weber)	Erythema migrans	Ceftriaxone IM	1 g od	5
		Phenoxymethylpenicillin po	1 Mio U tid	12
8 (Weber)	Erythema migrans	Azithromycin po	500 mg od	10
		Penicillin V po	1 Mio U tid	10
9 (Strle)	Erythema migrans	Azithromycin po	500 mg bid	2
		Followed by azithromycin po	500 mg od	4
		Doxycycline	100 mg bid	14
10 (Barsic)	Erythema migrans	Azithromycin po	500 mg bid	2
		Followed by azithromycin po	500 mg od	4
		Doxycycline	100 mg bid	14
11 (Breier)	Erythema migrans	Minocycline	100 mg bid	21
		Phenoxymethylpenicillin po	1,5 Mio U tid	21
14 (Steere)	Arthritis	Benzathine penicillin i.m	1.2 Mio U/week	21
		Penicillin G IV	3.3 Mio U 6/d	10
15 (Caperton)	Arthritis	Ceftriaxone IV	2 g od	14
16 (Dattwyler)	Arthritis	Penicillin G IV	4 Mio U 6/d	10
	Neuropathy	Ceftriaxone IV	2 g bid	14
	Encephalopathy	Ceftriaxone IV	2 g od	14
17 (Steere)	Arthritis	Amoxicillin/probenecid po	500 mg q.od	30
		Doxycycline po	100 mg bid	30
		Ceftriaxone IV	2 g od	14
20 (Valesova)	Arthritis	Ceftriaxone IV	2 g od	14
21 (Hassler)	Arthritis	Penicillin G IV	10 Mega bid	10
	Neuropathy	Cefotaxime IV	3 g tid	10
22 (Bentas)	Arthritis	Ceftriaxone IV	50 mg/kg od	14
34 (Hansen)	Meningoradiculitis	Penicillin G IV	3–5 Mio U q.od	10
35 (Pfister)	Meningoradiculitis	Penicillin G IV	5 Mio U q.od	10
		Cefotaxime IV	2 g tid	10
36 (Karlsson)	Neuropathy	Penicillin G IV	3 g qod	14
	Meningoradiculitis	Doxycline po	200 mg od	14
37 (Logigian)	Neuropathy Encephalitis	Ceftriaxone IV	2 g od	14
38 (Kindstrand)	Neuropathy	Benzylpenicillin IV		14
	Acrodermatitis	Followed by doxycycline od	200 mg od	14
		Cefuroxime IV followed by		14
		doxycycline po	200 mg od	14
		Doxycyclinee po	200 mg od	21
39 (Klempner)	Encephalopathy	Ceftriaxone IV followed by	2 g od	30
	chronic	doxycyline po	100 mg bid	60

Treatment modalities are indicated with the respective borrelial disease manifestations.

Table 2 Inclusion criteria and results of treatment trials for Lyme arthritis

Reference (first author)	Inclusion criteria	Disease duration	Response criteria	Treatment	Response rate		Remarks
14 (Steere)	History of erythema, Bell's palsy followed by arthritis within 1 year	Average of 29 and 39 months	Absence of arthritis and no recurrence within 3–12 months	Penicillin *v* placebo	7/20 0/20		10 Patients were previously treated with antibiotics
				Penicillin open label	11/20		12 Patients were previously treated with antibiotics
15 (Caperton)	Chronic arthritis of different origins positive ELISA	?	Absence of arthritis follow up 1–2 years	Ceftriaxone *v* placebo	19/40 2/20		Placebo patients were treated later, 27/58 responded in total, 16/27 relapsed later half of patients had other differentiated forms of arthritis
16 (Dattwyler)	Erythema or ELISA and two organ manifestations	Average of 28–35 months	Absence of arthritis after 3 months	Penicillin *v* ceftriaxone Ceftriaxone 4 g *v* 2 g	2/7 9/9 11/13 9/10		Half of the patients were previously treated with antibiotics Other antibiotic agents failed in 63% of all ceftriaxone treated patients
17 (Steere)	Arthritis and positive ELISA	Average of 11 months	Resolution of arthritis and no recurrence within 12 months	Doxycycline *v* amoxicillin	18/20 18/20	Intermittent arthritis	Effect within 3 months' follow up for up to 48 months
				Ceftriaxone open label	13/16	Chronic arthritis	Long duration until response, six patients synovectomised
20 (Valesova)	Arthritis and positive ELISA and western blot	?	Intensity of arthritis none/mild/ moderate severe follow up for 3 years	Ceftriaxone	27/33 without arthritis at 12 months	At 36 months: 14/26 free of arthritis	Detection of borrelia by electron microscopy in 11 patients (2/3 in synovia, 7/11 in blood, 1/3 in skin)
21 (Hassler)	Arthritis and positive ELISA/IF no other rheumatic disease	?	Full remission, partial remission follow up for 2 years	Penicillin, cefotaxime	4/34 FR 17/39 FR	No effect 15/34 No effect 7/39	Incomplete definition of response criteria

account possible spontaneous remissions in those apparently responding to treatment. A possible difference in outcome of intermittent or continuous arthritis was not discussed.

Case series suggest that the least common European species *Borrelia burgdorferi* sensu stricto is associated with most cases of arthritis in Europe. However, DNA from all species has been found in synovial fluid.[23 24] It is not clear to what extent which borrelial species is responsible for arthritis and whether the prognosis depends on the subspecies. While some studies imply the clearance of borrelial DNA from synovial fluid with antibiotic treatment,[25] others have not been able to reproduce this finding.[26] One study described the lack of borrelial DNA in inflamed joints in patients resistant to antibiotic treatment,[27] raising the question of an autoimmune disease that is only triggered by infection and perhaps is independent of bacterial clearance.[28 29] To confound matters further, borrelial DNA can be found in the synovial fluid of patients with arthritis, but no other clinical feature of borreliosis and no serological response to borrelial proteins.[30] It is difficult to define unambiguous diagnostic criteria for European borrelial arthritis and the spontaneous evolution of the disease has never been characterised.

FURTHER DISEASE MANIFESTATIONS

A detailed discussion of antibiotic treatment in cardiologic and neurological borrelial disease is beyond the scope of this review, but some aspects elaborated above remain pertinent. Although antibiotic treatment for acute isolated facial palsy does not influence its clinical course,[31 32] it is considered to prevent disease spreading.[31] We are not aware of any randomised trial in the USA or in Europe assessing the magnitude of this effect. Antibiotic treatment is considered the standard of care for cardiac conduction defects.[31] In the largest case series published so far, conduction defects resolved with antibiotics, aspirin, corticosteroids, or no treatment.[33] Randomised controlled data are lacking.[31]

European trials report an excellent clinical response to several antibiotic regimens in lymphocytic meningoradiculitis and neuropathy.[21 34–36] American and European case series describe a beneficial effect of several antibiotic regimens on chronic untreated peripheral neuropathy or encephalitis.[37 38] The situation appears more complex in a setting of previous treatment for earlier borrelial disease. A large placebo controlled randomised trial in the USA showed that persisting signs of central nervous dysfunction like radicular pain, fatigue, or mnestic difficulties after standard antibiotic treatment of earlier borrelial disease are not influenced by intravenous ceftriaxone followed by a prolonged course of oral doxycycline.[39] This again raises the issue of whether the disease may not proceed independently of the presence of borrelial spirochaetes in late stages.

PREVENTION OF DISEASE SPREADING

Antibiotic treatment might prevent later disease manifestations. Early American data suggest that treatment of erythema migrans with penicillin, erythromycin, or tetracycline prevents the development of arthritis in about one third of patients.[1] The same treatment did not influence the incidence of subsequent meningoencephalitis, facial palsy, or cardiac abnormalities compared with untreated controls.[1] No systematic studies have been published since. An American study analysing compliance with antibiotic treatment in 192 children with early Lyme disease did not find any late stage disease, even though no antimicrobial activity was found in urine samples after 1 and 2 weeks of treatment in one third of children.[40] One European report retrospectively analysing the outcome of patients with erythema migrans in 82 patients did not find convincing evidence for significant late stage disease in 10 untreated and 18 insufficiently treated patients.[41] Similar findings were described in a large US cohort study.[42] In a Swedish study, two of 16 patients with erythema migrans refusing treatment developed lymphocytic meningitis, one arthritis.[43] An Austrian prevention study did not observe an increased incidence of late stage disease in the one third of patients who did not complete treatment.[11] In contrast, a large proportion of borrelial cases in Europe seems to manifest with late stage disease.[44–46] Either European borrelial species causing arthritis do not cause erythema migrans, the erythema remains frequently unnoticed, or, as most patients with any manifestation of borreliosis are treated with antibiotics in Europe,[46] the development of arthritis is independent of a previous treatment for erythema migrans.

In addition to the paucity of data for a preventive effect of antibiotics, epidemiological studies show a discrepancy between the extent of seropositivity and clinical disease manifestations in Europe. The incidence of manifest borreliosis for rural inhabitants in a given area does not appear to be higher than for city dwellers.[45] Even though up to 80% of forest workers report tick bites and up to 50% show immunoreactivity to *Borrelia* spp,[47–50] the incidence of clinical disease in this population is around 8/1000 irrespective of whether only seropositive or all forest workers are analysed.[48 49] Of 16 subjects with seroconversion, only two developed clinical disease.[49] A high frequency of tick bites and a high rate of transmission of the bacterium is contrasted by the comparatively low rate of clinical disease.[45 50–53] This suggests that European borrelial infection may often be self limiting. We do not know which patients might be at risk for the development of late stage disease.

CONCLUSION

The most intriguing aspects of antibiotic treatment for borrelial disease in Europe are the absence of placebo controlled trials and the disappointing response rate of late stage manifestations to antibiotic treatment. We lack a clear idea of the natural course of borrelial infection dependent on the species involved and we lack long term prospective data on treatment response taking into account the diversity of possible clinical disease manifestations. We neither know to what extent antibiotic treatment truly prevents later disease manifestations, nor how we should properly define borrelial arthritis and how we should best evaluate a treatment response. For arthritis, no study has tested the current recommendations of prolonged oral and intravenous antibiotic treatment.[19] This lack of data is more than a scientific nuisance as severe side effects are not a rare exception.[21 54] Even if the concept of antibiotic treatment with the goal to prevent disease spreading in early stages and to cure later stages is theoretically convincing, clinical experience is often more ambiguous. We should remember that the equally convincing concept of antibiotic treatment in reactive arthritis is not supported by the results of randomised controlled trials.[55] There is a need for a large European study, in which a careful diagnostic investigation is combined with a long term follow up to test what effect antibiotics might have on the disease course of borrelial infection in Europe. In view of the paucity of convincing data, it might be necessary to include a placebo control (while defining rescue treatment) in order to learn more about the influence of subspecies on the clinical course and to define proper indications for antibiotic treatment.

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