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A Randomized Trial of Ceftriaxone versus Oral Penicillin for the Treatment of Early European Lyme Borreliosis

Summary: In a prospective randomized multicenter trial for the therapy of erythema migrans, 40 patients received ceftriaxone 1 g daily for 5 days and 33 patients obtained phenoxymethylpenicillin, 1 million units 3 times daily, for 12 days. Follow-up was for a mean of 10 ± 5 months. Eight oral penicillin recipients (24%) and six ceftriaxone recipients (15%) developed minor consecutive manifestations. Two ceftriaxone and one penicillin recipient(s) still had elevated IgG antibody titers 10 to 20 months after therapy. *Borrelia burgdorferi* could be isolated from the erythema migrans in 29 out of 56 patients (52%) before therapy and in one oral penicillin recipient but none of 24 other patients after therapy. Ceftriaxone was superior to oral penicillin in a subgroup of patients with more than one symptom prior to therapy ($p < 0.01$), but not in the overall evaluation of clinical, serological and bacteriological outcome data. Ceftriaxone ought to be preferred to oral penicillin in patients with more severe early Lyme borreliosis.

Zusammenfassung. *Ein randomisierter Vergleich zwischen Ceftriaxon und oralem Penicillin zur Therapie der frühen europäischen Lyme-Borreliose.* In einer prospektiven, randomisierten Multizenter-Studie zur Therapie des Erythema migrans wurden 40 Patienten mit täglich 1 g Ceftriaxon intramuskulär über fünf Tage und 33 Patienten mit täglich 3 x 1 Mill. I. E. Phenoxymethylpenicillin über 12 Tage behandelt. Die Nachbeobachtung betrug durchschnittlich 10 ± 5 Monate. Acht mit Penicillin (24%) und sechs mit Ceftriaxon behandelte Patienten (15%) entwickelten leichtere spätere Manifestationen. Zwei mit Ceftriaxon und ein mit Penicillin Behandelter wiesen erhöhte IgG Antikörper-Titer 10 bis 20 Monate nach Therapie auf. *Borrelia burgdorferi* konnte bei 29 von 56 Patienten (52%) vor und bei einem Patienten der Penicillingruppe, aber bei keinem Patienten der Ceftriaxongruppe nach Behandlung aus dem Erythema migrans isoliert werden. Ceftriaxon war dem Oral-Penicillin bei einer Untergruppe von Patienten mit mehr als einem Symptom vor Therapie überlegen ($p < 0{,}01$), aber nicht bei der Gesamtauswertung klinischer, serologischer und bakteriologischer Erfolgsdaten. Ceftriaxon sollte dem oralen Penicillin bei Patienten mit schwererer früher Lyme-Borreliose vorgezogen werden.

Introduction

During the past few years, oral penicillin, tetracycline, erythromycin and amoxicillin have been used in one randomized investigation [1] and in other non-randomized studies [2–5] to treat patients with early Lyme borreliosis. Oral penicillin has not been able to prevent consecutive manifestations of the disease in all patients [1–7] or an infection in an offspring [8]. However, the other aforementioned antibiotics have not definitely been proven to perform better than oral penicillin [1–4]. Tetracyclines tend to prevent "major late manifestations" better [1] and tend to lead to a faster reduction of IgM antibody titers against *Borrelia burgdorferi* within a year [4]. Provisionally, tetracyclines have therefore been recommended as treatment of first choice [1–4]. However, there are also examples of treatment failure among patients treated with tetracyclines [9]. Recent investigations *in vitro* and in animals have demonstrated that ceftriaxone belongs to the most promising antibiotics against *B. burgdorferi* [10–12]. A study in patients with late Lyme borreliosis demonstrated a beneficial effect of ceftriaxone [13]. We wanted to check whether or not ceftriaxone is superior to oral penicillin in early Lyme borreliosis.

Patients and Methods

Patients: From July 1987 until December 1988, patients with erythema migrans seen at the study centers were randomly assigned to one of the treatment regimens. Final evaluation of patients was carried out in early 1989. Erythema migrans was defined as an expanding homogeneous or ringlike erythema of the skin, with or without a history of a tick bite in the center of the lesion [14]. 81 patients were selected. Three patients refused to sign the informed consent, one patient did not comply and four patients had to be excluded because of other, although related diagnoses such as non-specific tick-bite reaction (in one), borrelial lymphocytoma (in two) and initial acrodermatitis chronica atrophicans (in one).

Study centers: (name of the responsible physicians and/or the number of patients seen at each center in parenthesis). Departments of Dermatology, University of Munich (Dr. med. *U. Neubert;* 11), University of Tübingen (Dr. med. *C. Scherwitz;* 7), University of Göttingen (Dr. med. *S. Quadripur;* 4), University of Düsseldorf (Dr. med. *S. Bottenbruch,* Dr. med. *J. Kloos;* 2),

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Randomization: The study centers received blocks with the randomly distributed two antibiotics and were requested to strictly follow the rank of order of the randomization schedule. The number of assigned treatment regimens were stratified for each study center.

Antibiotic therapy: After informed consent was obtained, patients received either ceftriaxone (Rocephin®, Hoffmann La Roche) 1 g intramuscularly daily on five days (Saturday or Sunday were allowed to be skipped) or phenoxymethylpenicillin 1 million units 3 times daily per os for 12 consecutive days. Patients on penicillin were asked to fill out compliance sheets.

Evaluation of clinical data and follow-up: Patients were seen prior to therapy and 3 weeks and 3 months after initiation of therapy. Skin lesion and regional lymph nodes were examined and patients were requested to complete questionnaires at these visits. The questionnaire included a detailed list of associated symptoms; only symptoms which could be attributed to Lyme borreliosis were included. Twelve patients were evaluated neurologically (n = 5, including lumbar puncture in 3), cardiologically (EKG, 24-h-EKG, echocardiogramm, n = 5) or rheumatologically (n = 2) before or after therapy. The study design required the exclusion of patients with complications such as established meningoradiculitis or carditis. Some patients had more visits than scheduled, but a few skipped one of the follow-up visits. All but one patient were treated on an outpatient basis. A final telephone interview – the final follow-up – was made by the principal investigator in all patients at the end of the study period. The data of the questionnaires were checked at this interview and missing data were amended; conflicting data were clarified with the physicians of the study centers. None of the patients was lost to follow-up. The severity of initial disease was evaluated by counting the number of associated symptoms prior to therapy as described previously [3].

Serology: Prior to therapy, 3 weeks and 3 months after therapy and if indicated more often, an indirect immunofluorescence test to determine IgM and IgG antibody titers against *B. burgdorferi* was performed in the laboratory of *B. Wilske* as previously described [15–17]. This procedure included thorough absorption with *Treponema phagedenis.* Antibody titers of ≥ 1 : 64 were considered as positive and those of 1 : 32 as borderline according to a cut-off value above the 98% – and the 95% – percentile, respectively [16]. In this paper, titers of 1 : 32 were counted as significantly elevated.

Bacteriology: (non-mandatory procedure). In 56 patients, a biopsy from the border of the erythema migrans, 3 to 4 mm in size, was taken before and (adjacent to the scar of the first biopsy) 3 months after therapy. This procedure was performed in local anaesthesia after disinfection of the skin with 70% isopropanol. The removed skin was immediately placed in modified Kelly medium. Isolation of *B. burgdorferi* was attempted in the laboratory of *V. Preac-Mursic* as previously described [11, 18]. The modified Kelly medium used contained a somewhat lower content of neopeptone (3 g), glucose (3 g), rabbit serum (5%) and 35% bovine serum albumin (5%) and omitted yeastolate and agar.

Approval: The protocol for this study was approved by the Ethical Committee of the Medical Faculty of the University of Munich. Each study center signed the protocol.

Definitions: Consecutive manifestations were defined as signs and symptoms still present or newly occurring 3 weeks after initiation of therapy and later; they were not called late manifestations because the term late is commonly associated with signs and symptoms of late Lyme borreliosis such as acrodermatitis chronica atrophicans. Definite treatment failure was defined as clear-cut clinical or laboratory evidence that the scheduled antibiotic therapy was not effective, meaning persistence or new development of major consecutive manifestations or minor ones (see references 1, 3, 4) in so far as the latter were promptly cured by retreatment, persistence of *B. burgdorferi* or an at least fourfold rise and subsequent persistence of the IgG antibody titer at ≥ 1 : 256 for ≥ 6 months; possible treatment failure was assumed when clinical symptoms persisted as minor consecutive manifestations (not cured by retreatment if any) or if antibody titers persisted at ≥ 1 : 256 for ≥ 6 months or at 1 : 32 to 1 : 128 for ≥ 12 months.

Statistical analysis: Differences of quantitative data depicted in Table 1 were analysed by the Mann-Whitney test and qualitative data shown in Tables 2 to 4 by Fisher's exact test. All p values were two-tailed.

Results

Out of our 73 patients with erythema migrans, 31 (42%) had a positive serological test, in 29 patients (40%) *B. burgdorferi* was isolated from the skin and 44 patients (60%) were serologically and/or bacteriologically positive. Thus, in 29 patients the diagnosis was based on clinical grounds only. Thirteen of the latter group had a history of a tick bite. Associated symptoms prior to therapy included fatigue, headache, arthralgia, myalgia, palpitations, fever, dizziness and a few others in 34 patients (47%). There was a trend that more ceftriaxone recipients compared to oral penicillin recipients had more associated symptoms ($p = 0.07$; Table 1). None of the patients was severely ill or had established meningoradiculitis or carditis. The number of patients was unequal among the two therapeutic groups because three patients, later excluded, received oral penicillin and because some study centers treated an uneven number of patients.

Clinical Outcome

Jarisch-Herxheimer reaction, clearance of erythema migrans and associated symptoms and the number and duration of consecutive manifestations were not statistically significantly different in the two groups (Table 1). The subgroup of patients with 2 to 6, but not with 0 to 1 associated symptoms prior to therapy had significantly less consecutive manifestations when treated with ceftriaxone compared to oral penicillin ($p<0.01$; Table 2).

The Jarisch-Herxheimer reaction consisted of fatigue or intensification of fatigue in 8 patients, intensification of redness and sometimes of subjective symptoms within the erythema migrans in 8 patients, fever and/or chills in 3 patients and headache in one patient.

Complete disappearance of the erythema migrans occurred usually within a few weeks. A 50-year-old male ceftriaxone recipient with a six month history of erythema migrans had

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spontaneous clearing of his skin lesion prior to therapy; *B. burgdorferi* was isolated from normal appearing skin at the site of the previous erythema migrans before but not three months after therapy. Clearance of associated symptoms and signs took place in the majority of patients within the first three weeks after initiation of therapy, usually within the first week. None of our patients became seriously ill or developed definite evidence of meningitis, carditis or other more severe organ involvement.

Consecutive manifestations occurred in several patients. Among eight oral penicillin recipients, five patients developed arthralgia for a median of 12 (range eight to 15) weeks, two patients developed sensory disturbances for a median of 38 [12–64] weeks. A few patients complained of fatigue, sleeplessness, headache and palpitations, respectively, for a median of 12 [8–12] weeks. Four out of six ceftriaxone recipients experienced arthralgia for a median of 20 [12–32] weeks and four ceftriaxone recipients (two of them had also arthralgia) developed dizziness, myalgia, tachycardia, palpitations, sensory disturbances and facial palsy (one to three symptoms in individual patients) for a median of 15 [6–28] weeks. There was a statistically significant correlation between initial severity of disease as measured by the number of associated symptoms (subgroups of 0–1 versus 2–6) prior to therapy and clinical outcome ($p < 0.01$; Table 2). This was due to the influence of the group of oral penicillin recipients ($p = 0.001$), not of the ceftriaxone recipients (no difference). The duration of the erythema migrans prior to therapy had no significant effect on clinical outcome.

Two ceftriaxone recipients experienced remarkable side effects; a 39-year-old man developed a feeling of heat in the mouth, confusion, tachycardia and lowering of blood pressure within minutes after the first injection, so that he was then treated with oral penicillin (with no adverse reactions) and a 46-year-old man suffered from febrile enterocolitis for several days, starting on the day following the last injection.

Serological Outcome (see Tables 1 and 4 and Figures 1 and 2)

The median of the elevated IgM antibody titers was 1 : 64 and of the elevated IgG antibody titers 1 : 128 (range 1 : 32

Table 1: Pretreatment and outcome characteristics (n = 73).

	Oral penicillin (n = 33)	Ceftriaxone (n = 40)
Pretreatment characteristics		
Sex: M/F (ratio)	15/18 (0.8)	18/22 (0.8)
Age (y)	46 ± 14	45 ± 15
Size of erythema migrans (cm)	15 ± 10	17 ± 13
Duration of erythema migrans (weeks)	5 ± 8	5 ± 6
Number of associated symptoms	32	50
Patients with associated symptoms (n [%])	11 (33)	23 (58)
Elevated IgM antibody titers (n)[a]	10	11
Elevated IgG antibody titers (n)[b]	4	10
Outcome characteristics		
Follow-up (days)	302 ± 150	324 ± 154
Jarisch-Herxheimer reaction (n)	7	9
Resolution of erythema migrans (days)	10(3–150)[c]	10(3–36)[c]
Resolution of associated symptoms within first 3 weeks (days)	7	9
Consecutive manifestations		
Number of patients	8	6
Number of symptoms	11	10
Duration (weeks)	17 ± 9	16 ± 8
Elevated IgM antibody titers after 4 months (n)	2	2
Elevated IgG antibody titers after 7 months (n)	2	3

There was no statistically significant difference between both therapeutic groups. Numbers indicate mean ± SD unless stated otherwise; a: values of 5 patients developing within 3 weeks after initiation of therapy included; b: value of 2 patients 3 and 9 weeks, respectively, after initiation of therapy included; c: median (range); n = number of patients.

Table 2: Correlation between severity of initial disease and consecutive manifestations; comparison of two subgroups.[a]

Therapeutic groups	Symptoms prior to therapy	Consecutive manifestations (n) No	Yes	p value
Oral penicillin	0–1	24	2	< 0.001[b]
	2–6	1	6	
Ceftriaxone	0–1	24	4	< 0.01[c]
	2–6	10	2	
Both groups	0–1	48	6	< 0.01[c]
	2–6	11	8	

n = number of patients; b: $p < 0.01$ and c: $p < 0.05$ if alpha-adjusted according to *Bonferroni*.

Table 3: Number of patients with isolation of *Borrelia burgdorferi* from the erythema migrans.

	Oral penicillin (n positive/n total)	Ceftriaxone (n positive/n total)
Pretreatment	12/26 (46%)	17/30 (57%)
Posttreatment	1/10 (10%)	0/15 (0%)

The difference between both therapeutic groups was statistically not significant. n positive = number of patients with positive culture; n total = number of patients in whom a culture was performed; percentage in parenthesis.

Table 4: Number of patients with remarkable outcome events.

	Oral penicillin (n = 33) n (%)	Ceftriaxone (n = 40) n (%)
Consecutive manifestations	8 (24)	6 (15)
Persistent IgG antibody titer	1 (3)	2 (5)
Isolation of *Borrelia burgdorferi*	1 (3)	0 (0)
Total outcome (without side effects)	10 (30)	7 (18)[a]
Major side effects	0 (0)	2 (5)
Total	10 (30)	9 (23)

n = number of patients; percentage in parenthesis; a = one patient had persistent IgG antibody titer and developed consecutive manifestations.

to 1 : 512 for IgM and IgG antibody titers, highest value per patient). A transient fourfold rise in IgM antibody titers up to 1 : 64 after initiation of therapy occurred in five patients. IgM and IgG antibody titers persisted for more than four and more than seven months, respectively, in several patients (Figures 1 and 2). Three patients had no serological controls.

Bacteriological Outcome (Tables 3 and 4)

Out of 25 posttreatment controls, *B. burgdorferi* could be isolated from a 43-year-old male penicillin recipient three months after therapy although the erythema migrans had disappeared and the IgG antibody titers had decreased from 1 : 128 to 1 : 32 within three months; three months after retreatment with ceftriaxone, a second control culture from a skin biopsy was negative (there were no clinical signs and symptoms before and after therapy).

Repeated Treatment

Ceftriaxone Recipients: A 30-year-old woman had recurrence of erythema migrans and arthralgia eight weeks after the first course of ceftriaxone; she then received 1 g ceftriaxone intramuscularly daily for ten days, but experienced facial palsy, dysesthesia and again arthralgia two weeks after the second ceftriaxone treatment; six weeks later, she received doxycycline 100 mg twice daily for eight days and her symptoms cleared completely within a few days (follow-up 17 months).

Oral Penicillin Recipients: Three patients treated with oral penicillin obtained retreatment (two patients, see bacteriological outcome and Figure 2). A ten-day course of doxycycline 200 mg per day led to improvement of the arthralgia in a 58-year-old woman five months after therapy.

Overall Evaluation

Table 4 summarizes all important outcome events representing definite or possible treatment failures.

Discussion

This open randomized multicenter trial for the treatment of early European Lyme borreliosis has failed to reveal a statistically significant difference between oral penicillin and ceftriaxone regarding an overall evaluation of outcome criteria. However, among a subgroup of patients with more severe initial disease, ceftriaxone reduced the number of

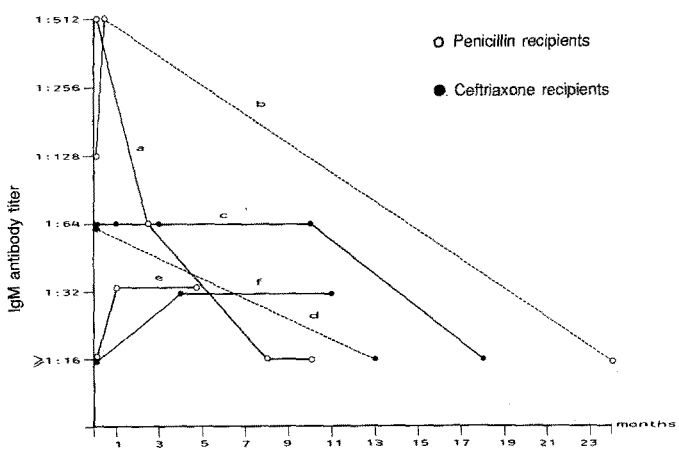

Figure 1: Patients with elevated IgM antibody titer > 4 months after therapy. Patients a–d = no sequelae; e = man, age 28, with arthralgia; f = man, age 64, with muscle tenderness in affected calf starting 6 months after therapy; dotted lines: only a single late serological control available.

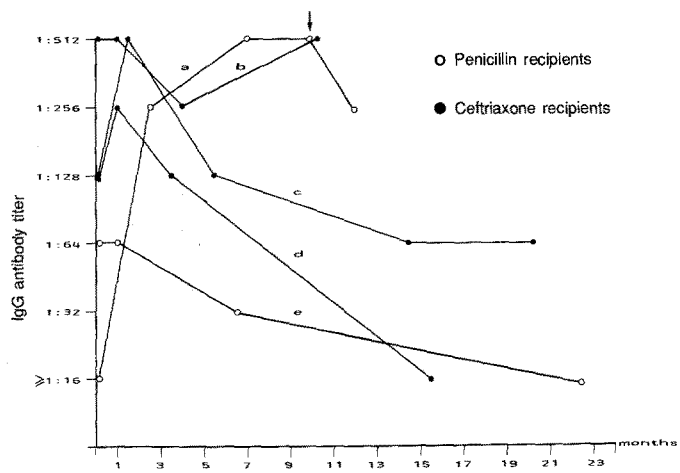

Figure 2: Patients with elevated IgG antibody titer > 7 months after therapy. Patients: a = woman, age 54, no sequelae (same as patient a, Figure 1), arrow: retreatment with tetracycline; b = man, age 71, 3-month history of large erythema migrans, no sequelae; c = woman, age 40, 4-month history of erythema migrans, started to develop arthralgia 16 months after therapy; d = man, age 45, with reinfection, no sequelae; e = man, age 83, no sequelae.

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consecutive manifestations significantly compared to oral penicillin. Consecutive manifestations are probably the most important clinical criterion of response. All consecutive manifestations observed by us were minor ones according to a previous classification [1] and own experiences [3, 4]. To a certain degree, the findings of this study support the assumption that these minor consecutive manifestations may represent definite or possible treatment failures. So far, none of the antibiotics tested has been able to prevent consecutive manifestations [1–5]. Ceftriaxone as used in the present study has performed similarly in this respect. Accordingly, one of our ceftriaxone recipients experienced, even after prolonged retreatment with the same antibiotic, what appears to be a definite treatment failure since retreatment with doxycycline led to rapid alleviation of all consecutive signs and symptoms.

Certain parameters may have influenced the clinical outcome in our patients. Comparably mild initial disease as commonly found in Europe compared to the United States [14, 19] and benefical effect of early antibiotic therapy may have prevented consecutive manifestations in some of our patients. A long-term follow-up would possibly uncover more cases with consecutive manifestations as exemplified by one of our ceftriaxone recipients who started to develop arthralgia 16 months after therapy. In agreement with two previous reports [1, 3], there was a significant correlation between the severity of initial disease and clinical outcome in our present study. This in turn has increased the chance to find a relatively great number of patients with consecutive manifestations in the subgroup of more severe initial disease.

Persistence of elevated IgG and IgM antibody titers as reported in one of our previous studies [4] was also noted in some of our present patients. Clinical setup before treatment, duration of antibody titer persistence and degree of antibody titer elevation probably play a role in evaluating such cases of presumed treatment failure. One of our oral penicillin recipients (patient a, Figure 2) has had a more than fourfold rise and subsequent persistence of the IgG antibody titer so that one must regard this case as definite treatment failure. Possible treatment failures have been suspected in the other two patients with persistently elevated IgG antibody titers (patients b and c, Figure 2), both of whom received ceftriaxone for long-lasting erythema migrans; one of these patients still had no decline and the other one started to suffer from arthralgia ten and 16 months, respectively, after therapy. These cases show some resemblance to one of our previously observed patients with a persisting IgG antibody titer of 1 : 64 [4] who later turned out to have had meningoradiculitis *(H.-W. Pfister* and *K. Weber*, unpublished observation). Two of our three patients with persistently elevated IgM antibody titers (patients e and f, Figure 1) had a possible treatment failure because of minor consecutive manifestations, but a treatment failure could not be assumed in the third patient because of normalization of the IgM antibody titer after 18 months.

In this investigation, we have also tried to control the success of antibiotic treatment by isolating *B. burgdorferi* after therapy. One of our oral penicillin recipients still had a positive isolate three months after therapy and must therefore be regarded as definite treatment failure although his erythema migrans cleared. In animal studies in which isolation of *B. burgdorferi* was attempted [10, 11], ceftriaxone performed much better than penicillin. We were therefore not surprised about the positive posttreatment culture in one of our penicillin recipients. It was, however, somewhat unexpected that only one single patient remained positive. Had oral penicillin been of no effect, the posttreatment isolation rate should have been about 50% instead of 10% which we have found now, provided other factors such as spontaneous healing could be neglected. The situation among our ceftriaxone recipients was even more clear-cut since none out of 15 patients had a positive culture after therapy.

We found it difficult to evaluate the necessity of retreatment in some of our patients. The decision sometimes depends on rather subjective factors.

If clinical, serological and bacteriological criteria of response are taken together as shown in Table 4, there was no statistically significant difference between the groups. The same statement can be made regarding the occurrence of definite treatment failures; two among oral penicillin recipients (6%) can be compared with one among ceftriaxone recipients (3%). The definite treatment failures uncovered in two of our oral penicillin recipients demonstrated the necessity to follow up patients with early Lyme borreliosis not only with regard to clinical outcome but also by means of appropriate laboratory controls.

We used a relatively short course of five ceftriaxone injections for several reasons. First, animal studies have shown that a five day regimen of daily i. m. injections is sufficient to exert a convincing therapeutic effect [10, 11]. Second, a single daily injection for five days is, although still more inconvenient than oral therapy, relatively easy to tolerate. Third, the cost of this regimen does not appear to be disproportionately high. Fourth, so far there has been no proof of the need to carry out long-term treatment in early Lyme borreliosis. The regimen used turned out to be effective in the majority of our patients. We doubt that higher dosage and longer regimen would have made a significant difference.

Our study has shown that even a short-term course of ceftriaxone is superior to oral penicillin in patients with more severe early Lyme borreliosis and that evaluation of the severity of initial disease can be based simply on the number of associated symptoms. This means that patients with erythema migrans should be carefully checked for associated symptoms prior to therapy in order to decide whether or not an appropriate antibiotic such as ceftriaxone ought to be recommended. Furthermore, we believe that patients with erythema migrans and complications like meningitis should primarily be treated for their complications and therefore be excluded from studies like our present one.

Although oral penicillin is not definitely inferior to the other oral antibiotics mentioned above, it has not been proved so far that ceftriaxone performs better than these antibiotics in patients with more severe early Lyme borreliosis.

Conclusion

Ceftriaxone should be preferred to oral penicillin in patients with erythema migrans who have two or more associated symptoms prior to therapy.

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