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Duration of Antibiotic Therapy for Early Lyme Disease

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: **Treatment of patients with early Lyme disease has trended toward longer duration despite the absence of supporting clinical trials.**

Objective: **To evaluate different durations of oral doxycycline treatment and the combination of oral doxycycline and a single intravenous dose of ceftriaxone for treatment of patients with early Lyme disease.**

Design: **Randomized, double-blind, placebo-controlled trial.**

Setting: **Single-center university hospital.**

Patients: **180 patients with erythema migrans.**

Intervention: **Ten days of oral doxycycline, with or without a single intravenous dose of ceftriaxone, or 20 days of oral doxycycline.**

Measurements: **Outcome was based on clinical observations and neurocognitive testing. Efficacy was assessed at 20 days, 3 months, 12 months, and 30 months.**

Results: **At all time points, the complete response rate was similar for the three treatment groups in both on-study and intention-to-treat analyses. In the on-study analysis, the complete response rate at 30 months was 83.9% in the 20-day doxycycline group, 90.3% in the 10-day doxycycline group, and 86.5% in the doxycycline–ceftriaxone group ($P > 0.2$). The only patient with treatment failure (10-day doxycycline group) developed meningitis on day 18. There were no significant differences in the results of neurocognitive testing among the three treatment groups and a separate control group without Lyme disease. Diarrhea occurred significantly more often in the doxycycline–ceftriaxone group (35%) than in either of the other two groups ($P < 0.001$).**

Conclusions: **Extending treatment with doxycycline from 10 to 20 days or adding one dose of ceftriaxone to the beginning of a 10-day course of doxycycline did not enhance therapeutic efficacy in patients with erythema migrans. Regardless of regimen, objective evidence of treatment failure was extremely rare.**

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See editorial comment on pp 761-762.

Although Lyme disease is the most common vector-borne disease in the United States (1), the appropriate duration of treatment for its most common manifestation, erythema migrans, remains unclear. A small open-label prospective study reported in 1983 found that outcome did not improve when tetracycline therapy was extended from 10 days to 20 days (2). However, most recent treatment trials have used antibiotic regimens of approximately 3 weeks (3–5), and some authorities recommend 20 to 30 days of therapy (6). This change in practice has occurred in the absence of additional prospective studies on the duration of treatment and is a source of ongoing controversy.

Another uncertain issue in the management of patients with erythema migrans is whether *Borrelia burgdorferi*, the etiologic agent, has disseminated to the central nervous system at the time of presentation (7). If so, the outcome of therapy might be enhanced by treatment with a parenteral agent such as ceftriaxone, which readily crosses the blood–brain barrier. To address these concerns, we conducted a placebo-controlled study comparing 10 days of doxycycline with both 10 days of doxycycline plus one dose of ceftriaxone and 20 days of doxycycline.

METHODS

Patients at least 16 years of age who had erythema migrans and satisfied the U.S. Centers for Disease Control and Prevention's surveillance definition of Lyme disease (an annular erythematous skin lesion ≥5 cm in diameter) (8) entered the study between 1992 and 1994. Volunteers were recruited primarily through the walk-in Lyme Disease Diagnostic Center at the Westchester Medical Center, Valhalla, New York. Exclusion criteria included pregnancy or lactation, allergy to a tetracycline or a β-lactam antibiotic, receipt of antibiotic treatment for Lyme disease for more than 48 hours before enrollment, meningitis or advanced heart block, or any underlying conditions that might interfere with evaluability or follow-up. All patients gave written informed consent, and the institutional review board at New York Medical College approved the study protocol.

Patients were randomly assigned to one of three treatment groups: 1) a single 2-g dose of intravenous ceftriaxone followed by 10 days of oral doxycycline capsules twice daily, then by 10 days of oral placebo capsules (cornstarch), identical in appearance to the doxycycline capsules, twice daily; 2) a placebo injection (5% dextrose) followed by 10 days of oral doxycycline, 100 mg twice daily, and then by 10 days of oral placebo twice daily; or 3) a placebo injection followed by 20 days of oral doxycycline twice daily. Since ceftriaxone is yellow, infusion bags were kept covered to maintain masking.

The pharmacy dispensed study medications in accordance with a randomization schedule that was based on a computer-generated random-number code with a permuted block size of 9. Clinical staff involved in recruitment of participants or in assessing clinical outcomes were

Context

Optimal antibiotic treatment for patients with early Lyme disease is unclear.

Contribution

This single-center randomized, double-blind, placebo-controlled trial found that patients with erythema migrans given any of the following regimens had high response rates, defined as resolution of erythema migrans and symptoms at 30 months: 20 days of doxycycline, 83.9%; 10 days of doxycycline, 90.3%; and 10 days of doxycycline plus a single intravenous dose of ceftriaxone, 86.5%. Patients given doxycycline plus ceftriaxone more often had diarrhea than patients given doxycycline alone.

Implications

Oral doxycycline alone for 10 days is sufficient treatment for patients with early Lyme disease that manifests as erythema migrans.

–The Editors

isolated from the allocation process and blinded to treatment assignment. Randomization was stratified by whether patients were symptomatic (defined as having any systemic symptoms or having multiple erythema migrans lesions) or asymptomatic (defined as having a single erythema migrans lesion and no systemic symptoms). This was done to ensure that patients who may have had dissemination of *B. burgdorferi* were equally represented in the three treatment groups.

Evaluation

Trained study personnel interviewed participants and performed physical examination at baseline and 10 days, 20 days, 3 months, 6 months, 12 months, 24 months, and 30 months after initiation of therapy. If appointments were missed, patients were interviewed by telephone; however, this occurred in fewer than 5% of patient interactions. A neurologist performed complete neurologic examination at baseline, 20 days, 3 months, 12 months, 24 months, and 30 months. At 18 months, an evaluation was conducted by telephone. Structured questionnaires using both closed- and open-ended questions were used. Symptom scores were recorded on a visual analogue scale (9). A blood sample was obtained for serologic testing (enzyme-linked immunosorbent assay) at all visits. Complete blood count was determined and serum chemistries were performed at baseline, day 10, and day 20. Electrocardiography was done at baseline and was repeated if results were abnormal.

Patients were considered unevaluable if they did not adhere to study medication. Nonadherence was defined as taking fewer than 90% of prescribed capsules or not returning pill containers at the 10- or 20-day visit, receiving an intercurrent antibiotic within the first 20 days, not meeting study inclusion criteria, or not attending follow-up visits after the baseline visit. Patients who had an intercurrent episode of erythema migrans due to reinfection were considered unevaluable from that point onward.

Outcome was characterized as complete response, partial response, or failure. Early treatment response was assessed at 20 days. At this time, complete response was defined as resolution of erythema migrans and associated symptoms and return to pre–Lyme disease health status. Partial response was defined as resolution of erythema migrans but incomplete resolution or development of subjective symptoms. Failure was defined as the occurrence of any one of the following during the first 20 days: no clinical improvement by day 10; recurrence of erythema migrans; recurrence of fever attributed by the study physician to Lyme disease; development of new objective rheumatologic, cardiac, or neurologic manifestations of Lyme disease that were not present within the first 10 days; or the occurrence of meningitis, advanced heart block, or other objective manifestation of Lyme disease requiring intravenous therapy.

Late response was evaluated at 3 months, 12 months, and 30 months. Complete response was defined as no recurrence of erythema migrans or associated symptoms and the continued absence of objective rheumatologic, cardiac, or neurologic manifestations of Lyme disease, with return to pre–Lyme disease health status. Partial response was defined as no recurrence of erythema migrans and the continued absence of objective manifestations of Lyme disease, but incomplete resolution or development of subjective symptoms of uncertain cause. Failure was defined as the occurrence of objective manifestations of Lyme disease.

Safety Assessment

Drug safety was monitored by recording adverse events (solicited by open-ended semi-structured interview) and results of laboratory tests during treatment.

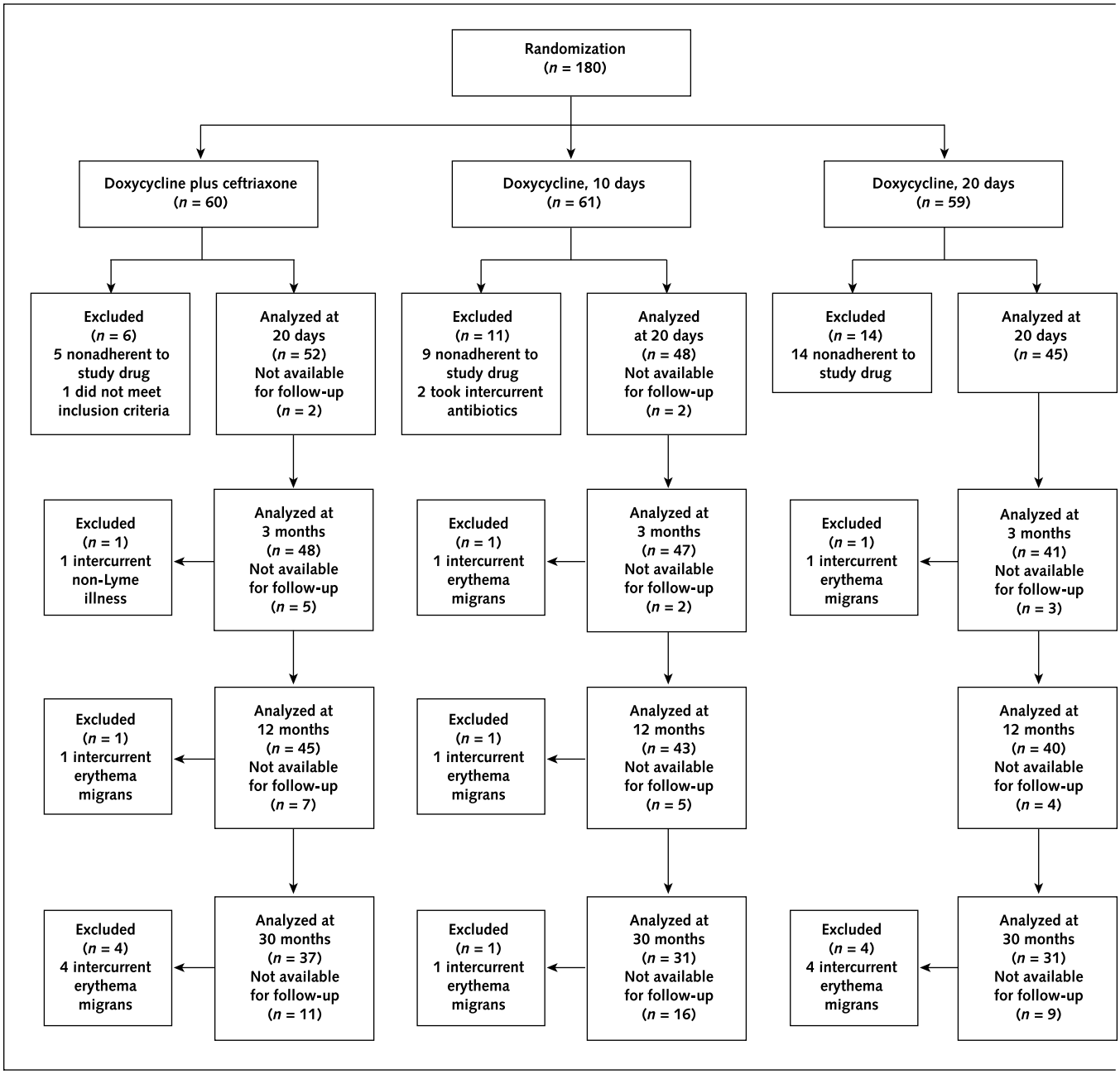
Neurocognitive Evaluation

At baseline, 12 months, and 30 months, a psychologist performed neurocognitive testing consisting of the Booklet Categories Test, the California Verbal Learning Test, the Wechsler Memory Scale—Revised, the Block Design Test, the Trail Making Test (Parts A and B), the Boston Naming Test, the Symbol Digit Modalities Test (written and oral), the Beck Depression Inventory, and the Symptom Checklist-90—Revised. Healthy volunteers without a history of Lyme disease were recruited to serve as controls for the psychiatric interview and the neuropsychological testing. Spouses were preferred as controls since they were usually similar to the patients in age, socioeconomic level, and place of residence. Controls were 27 persons with a mean age ($\pm$SD) of 42.6 $\pm$ 15.2 years; 22% were men.

Statistical Analysis

Groups were compared by using one-way analysis of variance for continuous variables and the chi-square test for categorical variables (two-tailed). Data were analyzed both for participants who adhered to the study protocol and on

Figure. **Flow diagram.**



an intention-to-treat basis. Patient blinding was evaluated at the 30-month visit by using the chi-square test and the κ statistic (10).

For the neuropsychological tests, analysis of variance techniques were used to examine differences among treatment and control groups. For analysis of raw test scores, analysis of covariance was used, controlling for the effects of age, sex, and education. Test scores that were normalized to population standards (11–19) were analyzed by using one-way analysis of variance.

For all analysis of variance models, residual plots were generated to verify adequate model fit. In the few situations in which test scores were not normally distributed or model fit was questionable, nonparametric procedures (the Kruskal–Wallis test) or conventional transformations were applied. For categorical results, the chi-square test or the Fisher exact test was used. If the treatment variable in the global tests achieved the liberal cut-point of a P value less than 0.10, pairwise comparisons were conducted. In these instances, the Bonferroni adjustment was applied to the P value to control for multiple comparisons.

Sample size was based on the estimated frequency of "post–Lyme disease syndrome," defined as an array of subjective symptoms, such as fatigue, arthralgias, or myalgias,

Table 1. **Selected Baseline Demographic, Clinical, and Laboratory Characteristics of the Study Sample**

Characteristic	Doxycycline–Ceftriaxone Group ($n = 60$)	10-Day Doxycycline Group ($n = 61$)	20-Day Doxycycline Group ($n = 59$)	*P* Value
Age, *y*				0.113
Mean ± SD	46.7 ± 14.1	41.5 ± 12.6	43.9 ± 13.9	
Median	45.5	39	42	
Range	16–82	16–73	20–74	
Men, *n* (%)	39 (65.0)	42 (68.9)	35 (59.3)	>0.2
Ethnicity, *n* (%)				>0.2
White	57 (95.0)	57 (93.4)	57 (96.6)	
African American	2 (3.3)	1 (1.6)	1 (1.7)	
Hispanic	1 (1.7)	2 (3.3)	1 (1.7)	
Asian	0	1 (1.6)	0	
History of Lyme disease, *n* (%)	8 (13.3)	5 (8.2)	7 (11.9)	>0.2
Presence of multiple erythema migrans lesions, *n* (%)	8 (13.3)	14 (23.0)	14 (23.7)	>0.2
Median diameter of primary erythema migrans lesion, *cm*	14.8	15.0	16.0	>0.2
Median duration of erythema migrans, *d*	4	3	5	0.038
Systemic manifestations, *n* (%)*	43 (71.7)	43 (70.5)	45 (76.3)	>0.2
Leukocyte count				
Mean ± SD, $\times 10^9$ *cells/L*	8.03 ± 2.1	7.48 ± 2.0	7.91 ± 2.3	>0.2
$<3.5 \times 10^9$ cells/L, *n/n* (%)	0/59	0/59	1/57 (1.8)	>0.2
Platelet count				
Mean ± SD, $\times 10^9$ *cells/L*	248 ± 62.0	251 ± 73.7	263 ± 87.1	>0.2
$<150 \times 10^9$ cells/L, *n/n* (%)	4/58 (6.9)	0/59	1/56 (1.8)	0.087
Positive skin biopsy culture, *n/n* (%)	20/43 (46.5)	17/39 (43.6)	23/44 (52.3)	>0.2
Positive results on serologic examination at baseline, *n/n* (%)	15/55 (27.3)	15/58 (25.9)	25/57 (43.9)	0.103

* Clinical symptoms, multiple erythema migrans lesions, or both were present.

that may occur after infection. It was assumed that 30% of patients receiving the least effective treatment would develop post–Lyme disease syndrome. A more effective treatment was assumed to reduce the rate to 5%. Using an α level of 0.05, two-tailed testing, and a Bonferroni multiple comparison procedure to control each of the three comparisons against risk for false-positive findings, we calculated that a required sample size at 1 year of 42 patients per group would yield 80% power. To account for attrition and for unassessable participants, the required sample size was estimated to be 60 patients per group.

Role of the Funding Source

The funding source had no role in the collection, analysis, and interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Study Sample

One hundred eighty patients were randomly assigned to one of three treatment groups (**Figure**). Sixty patients were assigned to receive 10 days of oral doxycycline preceded by one 2-g dose of intravenous ceftriaxone, 61 patients were assigned to receive 10 days of oral doxycycline, and 59 patients were assigned to receive 20 days of oral doxycycline. Aside from duration of erythema migrans, the three treatment groups were similar in baseline demographic characteristics, clinical characteristics, and laboratory test results (**Table 1**). Approximately three fourths of patients (70.5% to 76.3%) had systemic illness, including 13.3% to 23.7% who had multiple erythema migrans lesions.

Table 2. **Clinical Response for Evaluable Patients***

Evaluation	Complete Response			Partial Response			Failure		
	Doxycycline–Ceftriaxone Group	10-Day Doxycycline Group	20-Day Doxycycline Group	Doxycycline–Ceftriaxone Group	10-Day Doxycycline Group	20-Day Doxycycline Group	Doxycycline–Ceftriaxone Group	10-Day Doxycycline Group	20-Day Doxycycline Group
	← *n (%)* →								
20 days	34 (65.4)	34 (70.8)	29 (64.4)	18 (34.6)	13 (27.1)	16 (35.6)	0	1 (2.1)	0
3 months	36 (75.0)	36 (76.6)	30 (73.2)	12 (25.0)	10 (21.3)	11 (26.8)	0	1 (2.1)†	0
12 months	37 (82.2)	36 (83.7)	30 (75.0)	8 (17.8)	6 (14.0)	10 (25.0)	0	1 (2.3)†	0
30 months	32 (86.5)	28 (90.3)	26 (83.9)	5 (13.5)	2 (6.5)	5 (16.1)	0	1 (3.2)†	0
Last‡	47 (87.0)	44 (88.0)	39 (86.7)	7 (13.0)	5 (10.0)	6 (13.3)	0	1 (2.0)†	0

* There were 54 evaluable patients in the doxycycline–ceftriaxone group, 50 evaluable patients in the 10-day doxycycline group, and 45 evaluable patients in the 20-day doxycycline group. Percentages given are percentages of evaluable patients at each time point. See the **Figure** for the flow of patients through the study. For all comparisons of proportions of complete responders, $P > 0.2$.
† Refers to the patient deemed to have treatment failure at 20 days.
‡ Refers to last contact with patient regardless of time point.

Two patients, both in the 20-day doxycycline group, had unilateral facial palsy. One developed facial palsy 4 days into treatment; it improved by day 10 and resolved completely by 6 months. This patient was categorized as having a complete response at 12 months and was lost to follow-up thereafter. The second patient had facial nerve palsy at the baseline visit but was enrolled because examination of cerebrospinal fluid did not show evidence of meningitis. The patient's only symptom after day 20 was a mild residual facial palsy that resolved by the 30-month visit.

Evaluability

The number of evaluable patients did not differ significantly among the three groups ($P = 0.137$). Of the 60 patients in the doxycycline–ceftriaxone group, 6 (10%) were not evaluable; 5 did not adhere to the study medication, and 1 had been inadvertently enrolled despite meeting exclusion criteria (because of taking >6 doses of doxycycline before baseline). Eleven patients (18.0%) were not evaluable in the 10-day doxycycline group; 2 took intercurrent antibiotics, and 9 were nonadherent. Fourteen patients (23.7%) were deemed not evaluable in the 20-day doxycycline group because of nonadherence.

Response to Therapy

Among evaluable patients, no significant differences in clinical outcome were found at 20 days ($P > 0.2$) (**Table 2**). Approximately two thirds of patients in each group had a complete response at this time point. There was also no significant difference in treatment outcome at 30 months ($P > 0.2$), when 83.9% to 90.3% of patients had a complete response. A partial response at the 30-month time point was observed in 6.5% to 16.1% of patients. Also, no significant differences in treatment outcome were found among patients at either the 3- or 12-month time points. On the basis of the 95% CIs surrounding the difference in complete response rates at 12 and 30 months, 20-day doxycycline treatment might have been slightly more effective than 10 days of therapy (at most, a difference of 8.7 to 10.2 percentage points).

Table 2—**Continued**

Group Differences in Complete Response Rates (95% CI)		
Doxycycline–Ceftriaxone vs. 10-Day Doxycycline	**20-Day Doxycycline vs. 10-Day Doxycycline**	**Doxycycline–Ceftriaxone vs. 20-Day Doxycycline**
← *percentage points* →		
−5.4 (−23.7 to 12.8)	−6.4 (−25.4 to 12.6)	0.9 (−18.1 to 20.0)
−1.6 (−18.8 to 15.6)	−3.4 (−21.6 to 14.8)	1.8 (−16.4 to 20.1)
−1.5 (−17.2 to 14.2)	−8.7 (−26.1 to 8.7)	7.2 (−10.2 to 24.7)
−3.8 (−19.0 to 11.3)	−6.4 (−23.1 to 10.2)	2.6 (−14.4 to 19.6)
−1.0 (−13.7 to 11.7)	−1.3 (−14.7 to 12.1)	0.3 (−13.0 to 13.7)

Because some patients were lost to follow-up at or before 30 months (**Figure**), we also analyzed clinical response at time of last contact with the patient. Duration of follow-up at time of last contact was not significantly different among treatment groups. Mean duration of follow-up (±SD) was 24.42 ± 9.94 months for the doxycycline–ceftriaxone group, 22.30 ± 10.67 months for the 10-day doxycycline group, and 24.90 ± 8.69 months for the 20-day doxycycline group ($P > 0.2$). Treatment outcomes were also similar ($P > 0.2$) (**Table 2**).

Only one patient in the entire study was considered to have treatment failure at any time point. This patient, who was in the 10-day doxycycline group, developed a low-grade fever, headache, and nuchal rigidity 18 days after baseline. Examination of cerebrospinal fluid showed pleocytosis. The patient's condition improved with a 2-week course of ceftriaxone. Neurocognitive testing did not show evidence of deterioration.

An intention-to-treat analysis was performed for all patients, regardless of adherence, receipt of intercurrent antibiotics, or development of a second episode of erythema migrans during the study period. Complete response rates were similar at the 20-day, 3-month, 12-month, and 30-month time points (**Table 3**). In the intention-to-treat analysis, the mean duration (±SD) of follow-up at time of last contact was 26.24 ± 8.03 months for the doxycycline–ceftriaxone group, 23.77 ± 10.66 months for the 10-day doxycycline group, and 24.46 ± 9.26 months for the 20-day doxycycline group ($P > 0.2$). Treatment outcomes were also similar ($P > 0.2$) (**Table 3**).

Among patients in the three treatment groups who had neurocognitive testing, there were no significant differences in age, sex, or education. The control group, however, included significantly more women ($P < 0.02$). The groups did not differ significantly in the results of neurocognitive testing, the Beck Depression Inventory, or the Symptom Checklist-90—Revised at the three time points; scores in all groups tended to improve with retesting. We also compared the number of tests and subtests in which a patient scored more than 1 SD below the age-, sex-, or education-adjusted mean. No significant differences were noted.

Adverse Events

One patient in the 10-day doxycycline group withdrew from the study because of nausea, vomiting, and diarrhea, all of which developed on the 6th day of therapy. Treatment was changed to amoxicillin. Immediately after completion of the ceftriaxone infusion, one patient in the doxycycline–ceftriaxone group experienced urticaria, which responded to symptomatic treatment with diphenhydramine hydrochloride. Diarrhea occurred most often in the doxycycline–ceftriaxone group (35%) ($P < 0.001$) (**Table 4**).

Table 3. **Clinical Response Based on an Intention-To-Treat Analysis of Patients for Whom Information Was Available***

Evaluation	Complete Response			Partial Response			Failure		
	Doxycycline–Ceftriaxone Group	10-Day Doxycycline Group	20-Day Doxycycline Group	Doxycycline–Ceftriaxone Group	10-Day Doxycycline Group	20-Day Doxycycline Group	Doxycycline–Ceftriaxone Group	10-Day Doxycycline Group	20-Day Doxycycline Group
	← *n (%)* →								
20 days	36 (65.4)	37 (71.2)	34 (59.6)	19 (34.5)	14 (26.9)	23 (40.4)	0	1 (1.9)	0
3 months	40 (76.9)	41 (74.5)	39 (75.0)	12 (23.1)	13 (23.6)	13 (25.0)	0	1 (1.8)‡	0
12 months	42 (82.4)	44 (86.3)	39 (78.0)	9 (17.6)	6 (11.8)	11 (22.0)	0	1 (2.0)‡	0
30 months	39 (83.0)	35 (85.4)	35 (85.4)	8 (17.0)	5 (12.2)	6 (14.6)	0	1 (2.4)‡	0
Last§	51 (85.0)	50 (83.3)	50 (86.2)	9 (15.0)	9 (15.0)	8 (13.8)	0	1 (1.7)‡	0

* Percentages given are percentages of patients for whom information was available at each time point. See the **Figure** for the flow of patients through the study. For all comparisons of proportions of complete responders, $P > 0.2$.
† No information at a particular time point.
‡ Refers to the patient deemed to have treatment failure at 20 days.
§ Refers to last contact with patient regardless of time point.
‖ Did not return after baseline visit.

Intercurrent Lyme Disease

A new erythema migrans rash developed in 5 of 54 patients in the doxycycline–ceftriaxone group (9.3%), 3 of 50 patients in the 10-day doxycycline group (6.0%), and 5 of 45 patients in the 20-day doxycycline group (11.1%) ($P > 0.2$).

Table 4. **Adverse Drug Events**

Adverse Event	Doxycycline–Ceftriaxone Group (*n* = 60)	10-Day Doxycycline Group (*n* = 61)	20-Day Doxycycline Group (*n* = 59)
Skin, *n*			
Photosensitivity	3	5	2
Urticaria	0	0	0
Other	0	0	0
Gastrointestinal, *n*			
Anorexia	2	1	6
Diarrhea	21	4	5
Nausea	15	16	12
Vomiting	3	2	4
Abdominal discomfort	3	2	4
Anogenital inflammation	2	0	0
Odynophagia	2	1	0
Dysphagia	1	0	0
Esophageal discomfort	1	3	2
Ear, nose, throat, *n*			
Glossitis	1	0	0
Genitourinary, *n*			
Vaginitis	2	1	0
Central nervous system, *n*			
Headache	0	0	1
Dizziness	1	0	0
Other, *n*			
Immediate hypersensitivity or possible angio-neurotic edema	1	0	0
Palpitations	1	0	0
Bitter taste	1	0	0
Total, *n* (%)*	37 (61.7)†	27 (44.3)	25 (42.4)

* Adverse events are not additive since some patients reported having had more than one adverse event.
† The doxycycline–ceftriaxone group was more likely than the 10-day doxycycline group ($P = 0.055$) and the 20-day doxycycline group ($P = 0.035$) to have an adverse drug reaction. The doxycycline–ceftriaxone group had a significantly higher incidence of diarrhea than the other groups within the first 20 days ($P < 0.001$).

Intercurrent Antibiotics

A large proportion of patients received one or more courses of antibiotics for unrelated conditions, such as sinusitis, during the 30-month study period: 35 of 54 patients in the doxycycline–ceftriaxone group (64.8%), 24 of 50 patients in the 10-day doxycycline group (48.0%), and 22 of 45 patients in the 20-day doxycycline group (48.9%) ($P = 0.154$). At the last evaluation, the complete response rate of patients who did not take intercurrent antibiotics was similar in each of the groups (19 of 19 in the doxycycline–ceftriaxone group [100%], 23 of 26 in the 10-day doxycycline group [88.5%], and 20 of 23 in the 20-day doxycycline group [87.0%] [$P > 0.2$]).

Patient Blinding

Most patients were unable to identify correctly the group to which they had been assigned. There was no significant difference among treatment groups ($P > 0.2$) (**Table 5**).

DISCUSSION

Our study demonstrates that 10 days of doxycycline, 20 days of doxycycline, and 10 days of doxycycline plus one dose of ceftriaxone have similar efficacy for resolution of erythema migrans and associated systemic symptoms and for prevention of objective and subjective sequelae. More than 83% of the evaluable patients in each treatment group had a complete response at 30 months (**Table 2**). The 95% CIs for the difference in complete response rates between the 20-day and the 10-day doxycycline treatment groups at the 12- and 30-month visits demonstrated that 20 days of treatment could have been associated with only a small improvement in outcome (at most, 8.7 to 10.2 percentage points). Such a small potential difference in efficacy is consistent with the results of other antibiotic trials in patients with early Lyme disease in which treatment regimens were considered therapeutically equivalent (3, 20). The generally favorable outcomes among the three

Table 3—**Continued**

Not Assessable†		
Doxycycline–Ceftriaxone Group	**10-Day Doxycycline Group**	**20-Day Doxycycline Group**
← *n* →		
5	9	2
8	6	7
9	10	9
13	20	18
0	1‖	1‖

groups also did not differ significantly in an intention-to-treat analysis that included patients who did not adhere well to treatment and patients who developed a subsequent episode of erythema migrans during the study period (**Table 3**).

Similar to previous studies (3, 20), 6.5% to 16.1% of our patients were classified as partial responders at the 30-month visit. These patients had subjective symptoms and no other known illness to explain them. A systematic evaluation for other causes of these symptoms was not done; therefore, these figures should be considered an upper limit for the frequency of post–Lyme disease symptoms. Because the rate of seropositivity was not higher in partial responders than in the group of complete responders at the same time point (data not shown), these symptoms were probably unrelated to persistent *B. burgdorferi* infection. Furthermore, in a recent controlled study, a prolonged course of antibiotic therapy was not superior to placebo in ameliorating post–Lyme disease symptoms (21).

In the only small retrospective study that previously attempted to assess the outcome of treatment for patients with erythema migrans using different durations of therapy with doxycycline, extending therapy from 14 to 21 days did not enhance benefit (22). Experience in the treatment of other *Borrelia* infections is consistent with our observations. Treatment courses of 10 days or fewer are usually successful for tick-borne relapsing fever, and single-dose therapy is standard practice for louse-borne relapsing fever (23, 24).

Despite the potential for *B. burgdorferi* to disseminate to the central nervous system in some patients with erythema migrans (7), the addition of a single dose of ceftriaxone to a 10-day course of doxycycline in our study did not improve outcome. It did, however, significantly increase the risk for diarrhea, a recognized adverse effect of ceftriaxone (25). On the basis of serial neurologic examinations and neurocognitive testing, there was no evidence for the development of neurologic deficits in any of the treatment groups.

Demographic features, frequency of multiple erythema migrans lesions, and prevalence of systemic symptoms in our patients were similar to those in patients from other recent U.S. treatment trials of early Lyme disease (4, 5), and our three treatment groups were well matched (**Table 1**). Although frequency of intercurrent antibiotic use was high, a well-recognized phenomenon in the general population (26), this is unlikely to have biased our results. The frequency of intercurrent antibiotic use was similar across the treatment groups ($P = 0.154$), and an analysis of outcome at time of last patient contact for patients who had not received intercurrent antibiotics showed similar clinical response rates ($P > 0.2$).

Some patients were not assessable at various time points because they did not return for follow-up evaluation. Since blinding was well maintained (**Table 5**) and since the proportion of volunteers who could not be assessed was similar in the 10- and 20-day doxycycline groups (**Table 3**), it is unlikely that the distribution of complete and incomplete responders among these patients would have substantively altered the study findings. At the 20-day, 3-month, or 1-year time points, 20 days of doxycycline would not have been significantly more effective than 10 days of therapy, even if all of the unassessable patients in the 10-day groups were hypothetically classified as incomplete responders and all those in the 20-day group were classified as complete responders. Furthermore, duration of follow-up and treatment outcomes were similar at time of last patient contact in all groups (**Tables 2** and **3**). Our study was conducted at a single medical center, but the results are expected to be generalizable in the United States, where Lyme disease is believed to be caused by a single genospecies of *B. burgdorferi* (9). Our findings may or may not pertain to Europe, where the genospecies of *Borrelia* are more diverse (27).

In conclusion, extending treatment with doxycycline from 10 to 20 days or adding one dose of ceftriaxone to a 10-day doxycycline regimen did not enhance therapeutic efficacy in patients with early Lyme disease associated with erythema migrans. Regardless of regimen, objective evidence of treatment failure was extremely rare.

Table 5. **Assessment of Study Blinding at the 30-Month Visit***

Patient Guess	Doxycycline–Ceftriaxone Group (*n* = 44)	10-Day Doxycycline Group (*n* = 37)	20-Day Doxycycline Group (*n* = 39)
	← *n* (%) →		
Correct	16 (36.4)	8 (21.6)	12 (30.8)
Incorrect	28 (63.6)	29 (78.4)	27 (69.2)

* Patients who did not respond to the question about study group assignment are not included in this table. For comparisons among groups, $P > 0.2$.

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