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MAJOR ARTICLE

Antibiotic Treatment Duration and Long-Term Outcomes of Patients with Early Lyme Disease from a Lyme Disease–Hyperendemic Area

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(See the editorial commentary by Dattwyler, on pages 521–2.)

Background. The length of antibiotic therapy and long-term outcomes in patients with early Lyme disease are incompletely described. We report the long-term clinical outcomes of patients with early localized and early disseminated Lyme disease based on the duration of antibiotic therapy prescribed.

Methods. A retrospective cohort study and follow-up survey of patients diagnosed as having early localized and early disseminated Lyme disease from 1 January 2000 through 31 December 2004 was conducted in a Lyme disease–hyperendemic area.

Results. Six hundred seven patients met the study inclusion criteria. Most patients (93%) were treated with doxycycline for treatment durations of ≤10 days, 11–15 days, or ≥16 days in 17%, 33%, and 47% of doxycycline-treated patients, respectively. Treatment failure criteria, defined before performing the study, were met in only 6 patients (1%). Although these 6 patients met a priori treatment failure criteria, 4 of these patients' clinical details suggested reinfection, 1 was treated with an inappropriate antibiotic, and 1 developed facial palsy early in therapy. Reinfection developed in 4% of patients. The 2-year treatment failure–free survival rates of patients treated with antibiotics for ≤10 days, 11–15 days, or ≥16 days were 99.0%, 98.9%, and 99.2%, respectively. Patients treated with antibiotics for ≥16 days had lower 36-item Short-Form Health Survey social functioning scores on the follow-up survey. No other differences were found in follow-up clinical status or 36-item Short-Form Health Survey scores by duration of antibiotic treatment.

Conclusions. Patients treated for ≤10 days with antibiotic therapy for early Lyme disease have long-term outcomes similar to those of patients treated with longer courses. Treatment failure after appropriately targeted short-course therapy, if it occurs, is exceedingly rare.

Lyme disease is the most common tickborne illness in the United States. In North America it is caused by the spirochete *Borrelia burgdorferi sensu stricto*. Lyme disease usually presents with the characteristic erythema migrans lesion (~80% of cases) or a systemic febrile illness [1, 2]. Untreated patients may develop late manifestations, including arthritis and various neurologic complications [3]. However, if diagnosed early and treated appropriately with antibiotics, late objective complications of infection are rare [4]. Persistent subjective complaints are relatively common, occurring in 35% of patients 20 days after antibiotic therapy in 1 prospective study [5]. Some suggest, without convincing scientific evidence, that these persistent symptoms are due to persistent *B. burgdorferi* infection despite targeted antibiotic therapy [6, 7]. Thus, physicians may prescribe prolonged or repeated courses of antibiotics for early Lyme disease despite evidence of the effectiveness of short-course doxycycline. Not only do published studies report no proven clinical benefit of prolonged treatment of early Lyme disease [5, 8], but also antibiotic overuse contributes to higher rates of antibiotic-related complications and antibiotic resistance. We sought to determine clinically documented or patient-perceived long-term differences in outcomes of patients with early Lyme disease treated with short, me-

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Table 1. Demographic and Infection Characteristics in 607 Patients with Early Lyme Disease

Characteristic	Patients with early Lyme disease (n = 458)	Patients with early disseminated Lyme disease (n = 149)	All patients (n = 607)
Age at diagnosis, years			
Mean ± SD	47.5 ± 15.7	48.2 ± 17.2	47.7 ± 16.1
Range	18–96	18–91	18–96
Male sex	260 (57)	79 (53)	339 (56)
Tick exposure	322 (70)	95 (64)	417 (69)
Known tick bite	159 (35)	23 (15)	182 (30)
Systemic symptoms at diagnosis	240 (52)	83 (56)	323 (53)
Erythema migrans			
Single	275 (60)	0 (0)	275 (45)
Multiple	0 (0)	129 (87)	129 (21)
Carditis	0 (0)	3 (2)	3 (0.5)
Facial paralysis	0 (0)	21 (14)	21 (3)
Acute aseptic meningitis	0 (0)	2 (1.3)	2 (0.3)
Month of diagnosis			
January	1 (0.2)	1 (0.7)	2 (0.3)
February	2 (0.4)	0 (0)	2 (0.3)
March	1 (0.2)	0 (0)	1 (0.2)
April	7 (1.5)	1 (0.7)	8 (1.3)
May	45 (9.8)	3 (2.0)	48 (7.9)
June	141 (30.8)	41 (27.5)	182 (30.0)
July	129 (28.2)	57 (38.3)	186 (30.6)
August	63 (13.8)	21 (14.1)	84 (13.8)
September	14 (3.1)	17 (11.4)	31 (5.1)
October	23 (5.0)	5 (3.4)	28 (4.6)
November	24 (5.2)	3 (2.0)	27 (4.5)
December	8 (1.8)	0 (0)	8 (1.3)

NOTE. Data are no (%) of patients, unless otherwise indicated.

dium, and prolonged courses of antibiotics in a Lyme disease hyperendemic area.

METHODS

Study design. After institutional review board approval, we conducted this retrospective cohort study of patients with early localized and early disseminated Lyme disease diagnosed during the study years 2000–2004. Through *International Classification of Diseases, Ninth Revision* (ICD-9), codes associated with Lyme disease and review of inpatient and outpatient medical records, we identified patients who met our criteria for early Lyme disease, according to our case definitions. We sent a clinical status questionnaire along with the 36-item Short-Form Health Survey (SF-36) to these patients to assess their current health status. Patients were grouped into 3 categories for analysis: those treated with targeted antibiotics for ≤10 days, 11–15 days, and ≥16 days. Long-term outcomes as determined through medical record review and patient survey results were then collected for all patients.

Patient population and definitions. The study was conducted at a regional health system based in La Crosse, Wisconsin. An electronic inpatient and outpatient medical record aided in the capture of long-term clinical follow-up data. La Crosse is an area of Lyme hyperendemicity [9, 10]. The medical records of all adult patients (age, ≥18 years) in our health system with Lyme disease–related ICD-9 codes from 1 January 2000 through 31 December 2004 were reviewed. Patients were included in the study for further data collection if the following criteria were met: (1) physician- or physician associate–confirmed erythema migrans or (2) systemic symptoms compatible with Lyme disease (eg, fever, myalgias, arthralgias, and headache) plus laboratory confirmation (results of an immunofluorescence assay or enzyme-linked immunosorbent assay and/or Western blot test positive for Lyme disease). Patients with documented erythema migrans lesions were considered to have definite cases of Lyme disease, and patients without documented erythema migrans were considered to have probable cases of Lyme disease. Only patients with early localized or early disseminated Lyme disease were included in this study. Early localized Lyme disease was defined as either a single erythema migrans skin lesion or systemic symptoms compatible with early Lyme disease plus laboratory confirmation. Early

Table 2. Antibiotic Treatment Information in 607 Patients with Early Lyme Disease

Antibiotic used and duration, days	Patients with early Lyme disease	Patients with early disseminated Lyme disease	All patients	Duration, mean days ± SD
Doxycycline				
≤10[a]	77 (18)	19 (14)	...	...
11–15	148 (35)	39 (28)	...	...
≥16	187 (44)	78 (56)	...	...
Unknown	12 (3)	3 (2)	...	...
Total	424 (93)	139 (93)	563 (92.8)	17.4 ± 6.2
Amoxicillin				
≤10[b]	4 (22)	0 (0)	...	...
11–15	5 (28)	0 (0)	...	...
≥16	8 (44)	3 (100)	...	...
Unknown	1 (6)	0 (0)	...	...
Total	18 (4)	3 (2)	21 (3.5)	17.5 ± 5.2
Other				
≤10	0 (0)	0 (0)	...	...
11–15	4 (25)	2 (29)	...	...
≥16	5 (31)	4 (57)	...	...
Unknown	7 (44)	1 (14)	...	...
Total[c]	16 (3)	7 (5)	23 (3.8)	19.0 ± 5.1

NOTE. Data are no (%) of patients, unless otherwise indicated.

[a] Antibiotic duration was 10 days for 91 patients, 7 days for 4 patients, and 3 days for 1 patient.

[b] Antibiotic duration was 10 days for all 4 patients.

[c] Five patients received amoxicillin-clavulanate, 5 patients received cefuroxime, 4 patients received ceftriaxone, 3 patients received tetracycline, 3 patients received cefadroxil, and 3 patients had insufficient information available on the antibiotic they received.

disseminated Lyme disease was defined as multiple erythema migrans lesions, Lyme carditis, Lyme acute aseptic meningitis, or Lyme-associated seventh nerve paralysis. Patients were excluded from the study for the following reasons: (1) age <18 years, (2) history of Lyme disease before the study years, (3) history of receiving the Lyme disease vaccine, and (4) presentation with late Lyme disease (eg, arthritis and late neurologic disease).

Table 3. Treatment Failure Stratified by Antibiotic Treatment Duration in 607 Patients with Early Lyme Disease after a Mean Clinical Follow-Up Duration of 2.9 Years

	Duration of antibiotic treatment, days			
Outcome	≤10 (n = 100)	11–15 (n = 198)	≥16 (n = 285)	Unknown (n = 24)
Patients with definite Lyme disease				
No. of patients	77	130	179	18
Treatment failure	0 (0)	3 (2.3)	1 (0.6)	0 (0)
Subsequent infection	5 (6.5)	4 (3.1)	11 (6.1)	0 (0)
Possible treatment failure	1 (1.3)	6 (4.6)	10 (5.6)	1 (5.6)
Total	6 (7.8)	13 (10.0)	22 (12.3)	1 (5.6)
Patients with probable Lyme disease				
No. of patients	23	68	106	6
Treatment failure	1 (4.3)	0 (0.0)	1 (0.9)	0 (0)
Subsequent infection	0 (0.0)	2 (2.9)	2 (1.9)	0 (0)
Possible treatment failure	2 (8.7)	5 (7.4)	12 (11.3)	0 (0)
Total	3 (13.0)	7 (10.3)	15 (14.2)	0 (0)
All patients				
No. of patients	100	198	285	24
Treatment failure	1 (1.0)	3 (1.5)	2 (0.7)	0 (0)
Subsequent infection	5 (5.0)	6 (3.0)	13 (4.6)	0 (0)
Possible treatment failure	3 (3.0)	11 (5.6)	22 (7.7)	1 (4.2)
Total	9 (9.0)	20 (10.1)	37 (13.0)	1 (4.2)

NOTE. Data are no. (%) of patients, unless otherwise indicated. See Methods for definitions of treatment failure, subsequent infection, and possible treatment failure.

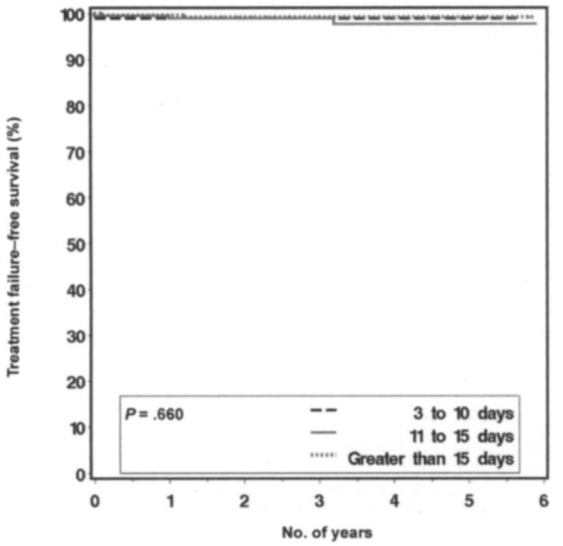

Figure 1. Kaplan-Meier treatment failure–free survival curves in 607 patients with early Lyme disease, by duration of antibiotics received.

Outcomes measured. The primary outcome was treatment failure. Treatment failure was considered to have occurred if a patient developed (1) persistent erythema migrans, defined as persistence of the erythema migrans lesion(s) despite antibiotic therapy resulting in additional medical evaluation; or (2) objective clinical and laboratory findings of progressive Lyme disease not present on initial diagnosis and not explained by an alternative diagnosis after antibiotic therapy for early Lyme disease. Progressive Lyme disease syndromes included pauciarticular arthritis, aseptic meningitis, and confirmed neurologic deficits (eg, facial paralysis and radiculopathy) Patients who developed a second episode characterized by erythema migrans skin lesion(s) during a subsequent tick season were considered to have a reinfection not treatment failure.

The secondary outcome measured was possible treatment failure. Physician- or physician associate–diagnosed treatment failure in the absence of objective examination findings was considered possible treatment failure. During patient follow-up, patients additionally treated with antibiotics based on a laboratory test result positive for Lyme disease were considered to have possible treatment failure because serologic assays for Lyme disease do not reliably distinguish between active and previous infection [11].

Data collection. Data collection was performed retrospectively by medical record review using the predetermined definitions described herein and a standardized data collection sheet. A standardized clinical status questionnaire and an SF-36 health assessment survey were sent to each living patient included in the study. The SF-36 is a validated health assessment tool widely used to assess current health status [12]. Any potential case of treatment failure was independently reviewed by 3 of the study authors (W.B., T.J.K., and S.T.) and classified as reinfection, treatment failure, possible treatment failure, or no treatment failure. In cases where the reviewers' classifications were discordant, consensus was reached before data entry and analysis. This determination was performed blinded to the survey results.

Statistical analysis. Descriptive statistics were used to summarize the demographic and treatment information for patients included in the study. Analysis of variance was used to detect whether statistical differences were present by antibiotic treatment duration. Kaplan-Meier graphs were used to visualize treatment failure–free survival, with log-rank statistics used to test for survival differences among groups. Comparison of survey responders and nonresponders was completed using the t test for continuous variables and the χ^2 test for categorical variables. Data from the definite and probable Lyme disease cohorts were first analyzed separately, and then the cohorts were combined and the data analyzed together. Patients whose duration of antibiotic therapy could not be definitively ascertained from review of the medical record were included in the study's descriptive statistics for completeness but were excluded from the comparative analysis of the survey results.

RESULTS

Patient characteristics and treatment. A total of 607 patients met the study inclusion criteria, of whom 458 had early localized Lyme disease and 149 had early disseminated Lyme disease. Baseline patient characteristics are given in Table 1. Sixty-nine percent of patients reported tick exposure, but only

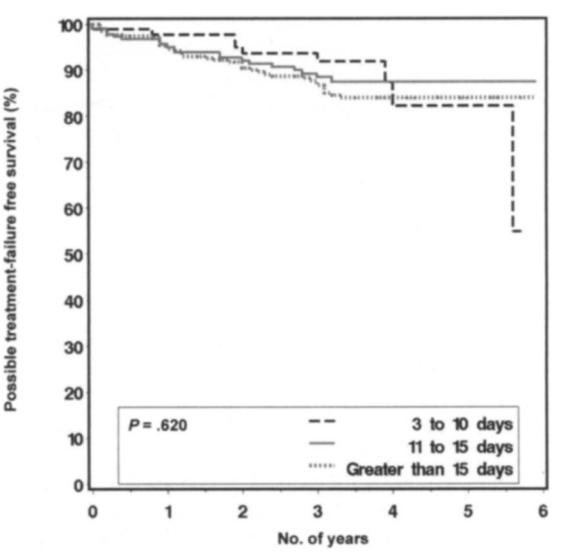

Figure 2. Kaplan-Meier possible treatment failure–free survival curves in 607 patients with early Lyme disease, by duration of antibiotics received. See Methods for the definition of possible treatment failure.

Table 4. Survey Results Comparing Follow-Up Clinical Complaints by Antibiotic Treatment Duration in 299 Patients with Early Lyme Disease after a Mean Follow-Up Duration of 4.5 Years from Diagnosis to Survey

Clinical status question	Duration of antibiotic treatment, days			P
	≤10	11–15	≥16	
Patients with definite Lyme disease				
No. of patients	41	65	103	
Do your joints frequently ache?	22 (53.7)	29 (44.6)	47 (45.6)	.620
Do your muscles frequently ache?	19 (46.3)	23 (35.4)	44 (42.7)	.484
Do you have numbness, tingling, or burning in your arms or legs?	15 (36.6)	22 (33.8)	39 (38.6)	.824
Do you have difficulties with coordination?	3 (7.3)	4 (6.2)	13 (12.6)	.317
Do you suffer from seizures?	0 (0)	0 (0)	0 (0)	
Do you suffer from unusual amounts of fatigue?	11 (26.8)	15 (23.1)	29 (28.2)	.724
Do you have persistent depression or sad thoughts?	3 (7.3)	8 (12.3)	18 (17.5)	.256
Do you have difficulties concentrating?	3 (7.3)	12 (18.5)	24 (23.3)	.081
Do you have wide swings in your emotions?	4 (9.8)	12 (18.5)	14 (13.6)	.444
Do you have difficulty sleeping?	13 (31.7)	28 (43.1)	37 (35.9)	.443
What is your marital status?				.616
Married	30 (73.2)	49 (75.4)	80 (76.9)	
Widowed	2 (4.9)	5 (7.7)	5 (4.8)	
Divorced	3 (7.3)	7 (10.8)	7 (6.7)	
Separated	1 (2.4)	1 (1.5)	0 (0)	
Never married	5 (12.2)	3 (4.6)	11 (10.6)	
What is the highest degree or level of school you have completed?				.381
Some high school (or less)	0 (0)	3 (4.6)	3 (2.9)	
High school graduate or GED	11 (26.8)	13 (20.0)	32 (31.1)	
Some college	11 (26.8)	14 (21.5)	18 (17.5)	
Associate degree	3 (7.3)	15 (23.1)	13 (12.6)	
Bachelor's degree	8 (19.5)	10 (15.4)	17(16.5)	
Professional or advanced degree	8 (19.5)	10 (15.4)	20 (19.4)	
Patients with probable Lyme disease				
No. of patients	9	30	51	
Do your joints frequently ache?	3 (33.3)	14 (46.7)	31 (60.8)	.210
Do your muscles frequently ache?	4 (44.4)	13 (43.3)	24 (47.1)	.946
Do you have numbness, tingling, or burning in your arms or legs?	3 (33.3)	11 (36.7)	20 (39.2)	.934
Do you have difficulties with coordination?	0 (0)	5 (16.7)	5 (9.8)	.341
Do you suffer from seizures?	0 (0)	0 (0)	0 (0)	
Do you suffer from unusual amounts of fatigue?	1 (11.1)	8 (26.7)	20 (39.2)	.182
Do you have persistent depression or sad thoughts?	1 (11.1)	2 (6.7)	9 (17.7)	.375
Do you have difficulties concentrating?	2 (22.2)	10 (33.3)	13 (25.5)	.693
Do you have wide swings in your emotions?	1 (11.1)	8 (26.7)	13 (25.5)	.614
Do you have difficulty sleeping?	2 (22.2)	11 (36.7)	21 (41.2)	.633
What is your marital status?				.789
Married	8 (88.9)	23 (76.7)	34 (66.7)	
Widowed	0 (0)	2 (6.7)	3 (5.9)	
Divorced	0 (0)	2 (6.7)	7 (13.7)	
Separated	0 (0)	0 (0)	2 (3.9)	
Never married	1 (11.1)	3 (10.0)	5 (19.8)	
What is the highest degree or level of school you have completed?				.339
Some high school (or less)	0 (0)	0 (0)	1 (2.0)	
High school graduate or GED	5 (55.9)	10 (33.3)	10 (19.6)	
Some college	1 (11.1)	10 (33.3)	12 (23.5)	
Associate degree	0 (0)	2 (6.7)	10 (19.6)	
Bachelor's degree	2 (22.2)	3 (10.0)	9 (17.7)	
Professional or advanced degree	1 (11.1)	5 (16.7)	9 (17.7)	
All patients				
No. of patients	50	95	154	
Do your joints frequently ache?	25 (50.0)	43 (45.3)	78 (50.6)	.699
Do your muscles frequently ache?	23 (46.0)	36 (37.9)	68 (44.2)	.536
Do you have numbness, tingling, or burning in your arms or legs?	18 (36.0)	33 (34.7)	59 (38.3)	.801

Table 4. ***(Continued.)***

Clinical status question	Duration of antibiotic treatment, days ≤10	11–15	≥16	*P*
Do you have difficulties with coordination?	3 (6.0)	9 (9.5)	18 (11.7)	.487
Do you suffer from seizures?	0 (0.0)	0 (0.0)	0 (0.0)	NA
Do you suffer from unusual amounts of fatigue?	12 (24.0)	23 (24.2)	49 (31.8)	.301
Do you have persistent depression or sad thoughts?	4 (8.0)	10 (10.5)	27 (17.5)	.137
Do you have difficulties concentrating?	5 (10.0)	22 (23.2)	37 (24.0)	.092
Do you have wide swings in your emotions?	5 (10.0)	20 (21.1)	27 (17.5)	.248
Do you have difficulty sleeping?	15 (30.0)	39 (41.1)	58 (37.7)	.441
What is your marital status?				.935
Married	38 (76.0)	72 (75.8)	114 (74.0)	
Widowed	2 (4.0)	7 (7.4)	8 (5.2)	
Divorced	3 (6.0)	9 (9.5)	14 (9.1)	
Separated	1 (2.0)	1 (1.1)	2 (1.3)	
Never married	6 (12.0)	6 (6.3)	16 (10.4)	
What is the highest degree or level of school you have completed?				.662
Some high school (or less)	0 (0)	3 (3.2)	4 (2.6)	
High school graduate or GED test	16 (32.0)	23 (24.2)	42 (27.3)	
Some college	12 (24.0)	24 (25.3)	30 (19.5)	
Associate degree	3 (6.0)	17 (17.9)	23 (14.9)	
Bachelor's degree	10 (20.0)	13 (13.7)	26 (16.9)	
Professional or advanced degree	9 (18.0)	15 (15.8)	29 (18.8)	

NOTE. Data are no. (%) of respondents who answered affirmatively, unless otherwise indicated. GED, general education development.

30% of patients recalled a tick bite. Mean duration of clinical retrospective medical record review follow-up from diagnosis was 2.9 years.

Antibiotic treatment information is given in Table 2. Most patients (93%) were treated with oral doxycycline. Mean antibiotic duration was 17.1 days in patients with early Lyme disease and 18.4 days in patients with early disseminated Lyme disease. Eight percent of patients were treated for longer than 21 days. Twenty-four patients did not have sufficient information in the medical record to determine the duration of antibiotic treatment. Of the 100 patients who received ≤10 days of antibiotic therapy, 95 received 10 days of therapy and only 1 patient received fewer than 7 days of treatment.

Treatment failure. Treatment failure criteria, as defined in Methods, were met by 6 patients (1%). Of these 6 patients, 4 patients' clinical courses were compatible with reinfection, 1 patient was treated with an inappropriate antibiotic (cefadroxil), and 1 patient developed facial paralysis early in the treatment course. Brief descriptions of each treatment failure follow to fully characterize their course. Patient 1 was initially diagnosed as having early localized Lyme disease based on an erythema migrans lesion. Three years later and with continuous tick exposure and bites, she developed a seventh nerve palsy during a subsequent tick season. Her Lyme disease titer was positive at initial diagnosis, reverted to negative on follow-up testing, and then turned strongly positive again with the facial paralysis, suggestive of reinfection. Patient 2 was initially diagnosed as having Lyme disease on the basis of an erythema migrans lesion. One year later, with continuous tick exposure, he presented with seventh nerve paralysis and laboratory evidence of Lyme disease. Patient 3 initially had a systemic febrile illness and headache with laboratory evidence of Lyme disease. After treatment with doxycycline for 10 days, systemic symptoms improved. Another deer tick was identified and removed from the patient ~2 weeks after her initial diagnosis. She subsequently had a recurrence of headache and a mild, transient facial palsy that lasted <5 days on objective examination. Patient 4 was initially diagnosed as having Lyme carditis with heart block and clinically responded to antibiotics. The next summer, with continuous tick exposure, he developed another systemic febrile illness and again developed heart block. Laboratory evidence of Lyme disease was persistently present. Patient 5 was initially diagnosed as having early Lyme disease based on an erythema migrans lesion. He was treated with cefadroxil for 20 days, after refusing to take doxycycline. Three weeks later he developed facial palsy with aseptic meningitis that promptly responded to doxycycline therapy. Patient 6 was initially diagnosed as having early Lyme disease based on an erythema migrans lesion with a systemic febrile illness. After 12 days of doxycycline therapy and while still receiving therapy, he developed a seventh nerve paralysis.

Table 3 summarizes cases of treatment failure, possible treat-

Table 5. Survey Scores on the 36-item Short-Form Health Survey (SF-36), by Antibiotic Treatment Duration in 299 Patients with Early Lyme Disease

SF-36 dimension	SF-36 scores, by duration of antibiotic treatment, days			
	≤10	11–15	≥16	*P*
Patients with definite Lyme disease				
No. of patients	41	65	103	
Pain	74.7	78.8	74.9	.482
Role limitations due to physical health	78.0	80.3	75.3	.646
General health	66.7	69.9	65.9	.385
Social functioning	90.5	88.7	84.1	.162
Vitality (energy/fatigue)	58.4	60.5	55.4	.392
Role limitations due to emotional problems	87.8	87.7	85.0	.785
Emotional well-being	80.0	78.3	76.1	.478
Physical functioning	78.8	81.6	80.7	.831
Patients with probable Lyme disease				
No. of patients	9	30	51	
Pain	72.2	72.9	71.1	.947
Role limitations due to physical health	72.2	80.3	64.7	.182
General health	68.3	69.5	62.5	.275
Social functioning	93.1	85.8	77.9	.068
Vitality (energy/fatigue)	50.2	56.0	54.3	.782
Role limitations due to emotional problems	77.8	87.8	73.9	.148
Emotional well-being	71.6	71.7	73.3	.922
Physical functioning	84.4	86.6	77.8	.191
All patients				
No. of patients	50	95	154	
Pain	74.3	77.0	73.6	.524
Role limitations due to physical health	77.0	80.3	71.8	.162
General health	67.0	69.8	64.7	.125
Social functioning	91.0	87.8	82.1	.012
Vitality (energy/fatigue)	56.9	59.1	55.1	.411
Role limitations due to emotional problems	86.0	87.7	81.3	.221
Emotional well-being	78.5	76.2	75.2	.537
Physical functioning	79.8	83.2	79.7	.476

ment failure, and reinfection stratified by duration of antibiotic therapy in patients with definite and probable Lyme disease. Twenty-four patients (4%) developed reinfection with Lyme disease. As would be expected for reinfection, as opposed to infection relapse, all of these patients developed their symptoms and were diagnosed as having reinfection between April and November of a subsequent tick season. Possible treatment failure, as defined in Methods, occurred in 36 patients (6%). Figures 1 and 2 demonstrate Kaplan-Meier treatment failure–free survival curves by duration of antibiotics received in the entire cohort of patients. In this combined cohort the 2-year treatment failure–free survival rates of patients treated with antibiotics for ≤10 days, 11–15 days, or ≥16 days were 99.0%, 98.9%, and 99.2% using the primary end point of treatment failure and 93.8%, 92.0%, and 90.4% using the secondary end point of possible treatment failure, respectively.

Survey results. Of the 607 patients included in the study, 12 were deceased at the time the clinical status questionnaire and SF-36 survey were sent. Of the 595 questionnaires and surveys sent, 299 (50%) were completed and included in the analysis. Mean duration from diagnosis to survey results was 4.5 years in the combined cohort. Questionnaire and survey results of patients with definite and probable early Lyme disease, stratified by duration of antibiotic treatment, are given in Tables 4 and 5. Presence of persistent symptoms was not significantly different based on duration of antibiotic treatment in the definite, probable, or combined cohorts (Table 4). Furthermore, SF-36 scores were similar among treatment duration groups

for all dimensions in the independent analysis of the definite and probable cohorts. When data from the definite and probable cohorts were combined and analyzed, scores of social functioning were lower for patients who received longer durations of antibiotic treatment ($P = .012$) (Table 5).

To assess selection bias in survey returners versus nonreturners, we compared clinical characteristics, treatment regimens, and treatment outcomes between the 2 groups. The only significant difference was that patients with treatment failure had a higher rate of survey return than those without ($P = .028$).

DISCUSSION

The optimal antibiotic treatment for early Lyme disease continues to be controversial for some physicians and the public at large [6, 7]. We sought to assess the long-term outcomes of patients with well-defined early localized and early disseminated Lyme disease by duration of antibiotic treatment in an area of Lyme hyperendemnicity. This clinical outcome study, which is to our knowledge the largest reported series of patients with early localized and early disseminated Lyme disease, suggests no difference in treatment failure rates or long-term health function among patients treated with targeted antibiotics for ≤10 days, 11–15 days, and ≥16 days.

Treatment failure as defined for this study was rare. Furthermore, although 6 patients met our predetermined criteria for treatment failure, 4 of these had ongoing tick exposure and periods of feeling well before redeveloping symptoms accompanied by objective evidence of disease; thus, these cases were more compatible with reinfection than with treatment failure. One patient who developed treatment failure was treated with an ineffective antibiotic, which readily explains the "treatment failure." Finally, 1 patient who met our definition of treatment failure developed seventh nerve palsy 12 days into a course of doxycycline therapy but no other clinical evidence of progressive disease. Progression of facial paralysis in the absence of any other clinical evidence of treatment failure is well described even in patients still receiving potent intravenous antibiotics and may well be related more to inflammation than to progressive infection [13]. Taking these factors into account, our study provides strong evidence that persistent active infection with Lyme disease after appropriately targeted antibiotic against borreliosis is exceedingly rare, if it occurs at all.

Reinfection was much more common than treatment failure. Subsequent infection with *B. burgdorferi* is a well-described phenomenon. In our cohort, 4% of patients developed subsequent infection with early Lyme disease, consistent with previous reports [14]. This finding highlights the importance of counseling patients on the risk of subsequent infection with Lyme or other tickborne disease and instituting appropriate preventive measures, particularly in an area of Lyme hyperendemicity. Such natural reoccurrences also highlight the difficulty of developing an effective Lyme vaccine, similar to syphilis infections in humans.

We defined possible treatment failure as being physician-directed additional treatment for Lyme disease for subjective complaints in the absence of objective findings of persistent disease. This group of patients, as we have defined it, falls under the broad category of post–Lyme disease syndrome [4]. No convincing evidence has been reported that antibiotic therapy beyond the initial course provides benefit in this patient population [4, 6]. Despite that, in our cohort, 6% of patients received additional antibiotics for these complaints. These patients had no objective evidence of persistent infection; it is likely that the subsequent treatment of these patients was unnecessary.

Antibiotic treatment guidelines for early Lyme disease were developed by our infectious disease physicians and used in our health system for many years, including the years encompassed by this study. The guidelines have consistently recommended a 10-day course of doxycycline for uncomplicated early Lyme disease. Thus, we anticipated that a relatively high percentage of patients with early Lyme disease would have treatment durations of ≤10 days; however, only 16% of patients were given ≤10 days of doxycycline treatment, whereas 44% of patients received ≥16 days of doxycycline treatment. This study supports short-course therapy with doxycycline.

We have observed, then, 2 interesting treatment patterns in our cohort. First, despite treatment guidelines both locally in our health system and nationally that recommend short-course doxycycline for early Lyme disease, longer courses of therapy were routinely prescribed. Second, despite a paucity of evidence for benefit and the certain attendant adverse effect risks [5, 6, 8], many physicians chose to treat patients again for Lyme disease based on persistent or recurrent subjective complaints. In our opinion, the use and misuse of antibiotics in this circumstance are not justified.

Reasons for physician nonadherence to the treatment guidelines were not studied; however, at our institution guideline nonadherence may be unique to treating Lyme disease. Group A streptococcal pharyngitis is another common infectious disease problem for which both our local health system and national guidelines are equally available to physicians. However, although 93% of pharyngitis patients are treated in accordance with local guidelines (internal data), only 19% of patients with early uncomplicated Lyme disease are so treated. On the basis of years of clinical conversations with patients and physicians, we speculate that both patients and physicians perceive a need for more prolonged courses of antibiotics to effectively treat both early and late Lyme disease. This study and others suggest otherwise [4, 5, 15, 16].

Our study has a number of strengths. First, to our knowledge, ours is the largest cohort of patients with early Lyme disease to have long-term follow-up data on health status after therapy. Second, our health system is from an area of Lyme hyperendemicity [9, 12]. Thus, both patients and physicians are relatively aware of Lyme disease, which helps expedite patient presentation, diagnosis, and treatment. Furthermore, we used strict case criteria for study inclusion. This, combined with a relatively high pretest probability of Lyme disease in an area of hyperendemicity, strongly predicted a cohort that had early infection with *B. burgdorferi.*

Our study limitations are primarily those inherent to a retrospective study design. To minimize data ascertainment bias, however, definitions were developed before data collection. In addition, cases were classified as treatment failures or subsequent infection only after being independently reviewed by at least 3 of the authors, and in areas of differing classification, consensus was reached with the authors masked to the survey results. The survey return rate was 50%. We analyzed for baseline differences in survey returners and nonreturners and found no evidence of a selection bias in returners. Because all patients in the study were diagnosed as having early Lyme disease, the likelihood of differential recall bias based on duration of antibiotic treatment is likely low compared with a case-control study. Finally, our study was focused on cases of early Lyme disease. Results cannot necessarily be extrapolated to cases of late Lyme disease.

In conclusion, we have studied the long-term outcomes of a large cohort of patients with early Lyme disease and found no differences in outcome according to duration of antibiotic treatment. Future studies should try to identify reasons physicians prescribe prolonged antibiotics for patients with Lyme disease in the absence of peer-reviewed data and against the recommendations of local and national treatment guidelines.

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