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ORIGINAL RESEARCH

Benefit of intravenous antibiotic therapy in patients referred for treatment of neurologic Lyme disease

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Background: We have shown previously that extended intravenous antibiotic therapy is associated with low morbidity and no mortality in patients referred for treatment of neurologic Lyme disease. In this study, we evaluated the benefit of extended intravenous antibiotic therapy in patients with symptoms of neurologic Lyme disease.

Methods: Patients with significant neurologic symptoms and positive testing for *Borrelia burgdorferi* were treated with intravenous antibiotics, and biweekly evaluation of symptom severity was performed using a six-level ordinal scale. Four symptoms were selected a priori as primary outcome measures in the study, ie, fatigue, cognition, myalgias, and arthralgias. Patients were placed into five groups according to time on treatment (1–4, 5–8, 9–12, 13–24, and 25–52 weeks), and changes in the primary symptoms as a function of time on treatment were analyzed using a mixed-effects proportional odds model.

Results: Among 158 patients with more than one follow-up visit who were monitored for up to 1 year, there were on average 6.7 visits per person (median 5, range 2–24). The last follow-up day was on average 96 days after enrollment (median 69, range 7–354 days), corresponding to the length of antibiotic therapy. Each primary symptom was significantly improved at one or more time points during the study. For cognition, fatigue, and myalgias, the greatest improvement occurred in patients on the longest courses of treatment (25–52 weeks) with odds ratios (OR) for improvement of 1.97 ($P = 0.02$), 2.22 ($P < 0.01$), and 2.08 ($P = 0.01$), respectively. In contrast, arthralgias were only significantly improved during the initial 1–4 weeks of therapy (OR: 1.57, $P = 0.04$), and the beneficial effect of longer treatment did not reach statistical significance for this symptom.

Conclusion: Prolonged intravenous antibiotic therapy is associated with improved cognition, fatigue, and myalgias in patients referred for treatment of neurologic Lyme disease. Treatment for 25–52 weeks may be necessary to obtain symptomatic improvement in these patients.

Keywords: Lyme disease, *Borrelia burgdorferi,* intravenous antibiotics, neurologic symptoms

Video abstract

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Introduction

Lyme disease caused by the spirochete *Borrelia burgdorferi* is the most common tick-borne illness in the world today.[1–4] Although prompt diagnosis and treatment results in a favorable outcome in patients with acute *B. burgdorferi* infection, tick exposure and acute infection with the Lyme spirochete often go unrecognized, and patients with untreated infection may go on to develop a chronic debilitating multisystem illness that is difficult to manage.[1–4]

The approach to the treatment of patients with persistent symptoms of Lyme disease has been controversial. The International Lyme and Associated Diseases Society

(ILADS) advocates open-ended treatment linked to symptom resolution for what is considered to be a persistent spirochetal infection, claiming that the benefit of such treatment outweighs the risk.[5] In contrast, the Infectious Diseases Society of America (IDSA) believes that persistent symptoms in these patients are due to "post-Lyme syndrome", a noninfectious complication of acute spirochetal disease.[6] According to the IDSA, treatment with prolonged antibiotics is considered inappropriate and even dangerous.[6–10]

In a previous prospective study, we showed that prolonged intravenous antibiotic therapy was associated with low morbidity and no mortality in closely monitored patients referred for treatment of neurologic Lyme disease.[11] We have now examined the benefit of this therapy in a similar cohort of patients with neurologic Lyme disease symptoms.

Materials and methods

Patients

From April 2008 through August 2009, 225 consecutive patients were enrolled in this study. Patients from 18 states across the US were referred by their treating physicians to a single homecare company that administers intravenous antibiotic therapy in the outpatient setting. All patients had significant neuropsychiatric symptoms for at least 3 months and positive testing for *B. burgdorferi*, considered to be consistent with a diagnosis of neurologic Lyme disease by their treating physicians.[11–14] Neuropsychiatric symptoms included Bell's palsy, meningoradiculitis, migraine, encephalopathy, mood disorders, and/or psychosis associated with tick exposure in a Lyme endemic area. Neurologic involvement was confirmed with brain magnetic resonance imaging, single-photon emission computed tomographic brain scans, and/or formal neuropsychiatric evaluation.[11–14] Serologic testing for *B. burgdorferi* was ordered and interpreted by the treating physicians.

Informed consent for intravenous antibiotic therapy and monitoring was obtained from all subjects, and the potential risks of extended parenteral therapy as well as the responsibility of patients to comply with the homecare treatment protocols were clearly defined, as previously described.[11] Patients also agreed that information obtained from their treatment could be used for research purposes provided that strict confidentiality was maintained, as outlined in the guidelines of the US Department of Health and Human Services for observational studies (http://www.hhs.gov/ohrp/irb/irb_guidebook.htm). Consent forms acknowledging compliance with the Patient Bill of Rights and the Health Insurance Portability and Accountability Act guidelines were signed by all patients or their legal guardians. The study was granted exemption from review under 45 CFR 46.101(b)(4) by the Western Institutional Review Board, Olympia, WA, because it involved collection of data "in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects".

Treatment protocol

Intravenous antibiotics were administered to all patients via an intravascular device using the SASH (saline/admixed drug/saline/heparin) protocol.[11] This protocol involves initial infusion of a 10 mL normal saline flush to clear the line, then administration of the antibiotic in normal saline followed by a second 10 mL normal saline flush, and then 5 mL of heparin (100 units/mL) to maintain intravascular device patency. Dressing change and intravascular device assessment were performed on a weekly basis by homecare nurses, with monitoring for medication reactions and intravascular device infection, clotting, or infiltration according to the standard homecare protocol. Medication-related and catheter-related complications were immediately reported to the treating physician and the homecare service, and appropriate measures were taken to deal with the complication.

For the purpose of this study, only patients receiving intravenous ceftriaxone were included in the analysis. Patients with allergy to ceftriaxone were excluded from the study, and the ceftriaxone dose was determined by the treating physician. Patients on ceftriaxone therapy had liver function testing performed every 2 weeks, and ursodiol therapy was offered in conjunction with this antibiotic to prevent gallbladder toxicity. Probiotic therapy with daily oral acidophilus and/or saccharomyces was routinely recommended to all patients to prevent *Clostridium difficile* enterocolitis, as previously described.[11] Ursodiol and probiotic therapy were dosed according to the manufacturer's recommendations.[15,16]

Outcome measures

All patients completed a biweekly monitoring tool that assessed three broad symptom complexes, ie, pain, neurologic function, and general symptoms. The monitoring tool was developed during the previous safety study[11] and contained questions about 28 separate symptoms. Participants were asked to rate each symptom's severity and impact on their daily life as one of six ordinal classes, ie, 0 = not affected, 1 = slight, barely noticeable problem, 2 = minor yet noticeable problem, 3 = moderate problem, interferes with some daily activities, 4 = major problem, interferes with most daily activities, and 5 = disabling problem. Aside from measuring

symptomatic changes, the use of the monitoring tool had two additional purposes, ie, to determine which symptoms caused the most functional disability and to mask the most significant symptoms in order to avoid response bias on the part of study participants who might focus on these symptoms.

Four symptoms were selected a priori as primary outcome measures in the study, and changes during treatment in these outcome measures were evaluated, ie, fatigue, cognition ("brain fog"), myalgias (muscle aches), and arthralgias (joint pain). These four symptoms comprised the most disabling factors for patients based on levels 4 and 5 ratings in the previous study. Questioning about these symptoms was randomly mixed with other questions in the monitoring tool.

Statistical analysis

Changes in the primary outcome measures as a function of time on treatment were analyzed using a mixed-effects proportional odds model (also referred to as a mixed-effects cumulative logit model), with measurement times nested within each participant.[17] For each outcome, the validity of the proportional odds assumption was evaluated by fitting five mixed-effects binomial logistic models, categorizing the outcomes as 0 or 1, with each level used as a threshold, ie, 0 vs $\geq$1, $\leq$1 vs $\geq$2, $\leq$2 vs $\geq$3, $\leq$3 vs $\geq$4, and $\leq$4 vs 5. The log odds of the effects from each of the five models were examined using the point estimate and 95% confidence interval (CI). If the log odds for all of the five models appeared similar, then the proportional odds assumption was determined to represent the data well. If one or two models for a specific outcome had very different log odds, the ordinal classes were combined such that this assumption was met. If the assumption was not met, the model was not fit.

Each participant was placed into one of the five strata, based on duration of intravenous antibiotic treatment, and separate treatment effects were estimated for each patient stratum. Patient strata were 1–4 weeks (n = 32), 5–8 weeks (n = 33), 9–12 weeks (n = 28), 13–24 weeks (n = 37), and 25–52 weeks (n = 28) on intravenous therapy, resulting in patient groups with similar numbers of participants. To relax assumptions about the functional form of the relationship between treatment duration and symptom severity, time on intravenous treatment was categorized as 0–1 week, 1–4 weeks, 5–8 weeks, 9–12 weeks, 13–24 weeks, and 25–52 weeks. Treatment effectiveness by patient stratum expressed as the conditional odds and 95% CI of being in a lower (less severe) class are presented comparing responses during the final period of intravenous treatment with responses from first week on treatment.

The Akaike information criterion was used to measure the relative goodness of fit of the statistical model.[18] Three models were fitted to each outcome, and the result of the model with the lowest Akaike information criterion is presented. The three models include a factor variable for time on treatment, factors for time on treatment and patient stratum, and factors for time on treatment, patient stratum, and their interaction. The best model was confirmed using likelihood ratio tests.

Statistical analysis was performed using R 2.12.2 software (R Foundation for Statistical Computing, Vienna, Austria), and two-sided *P* values less than 0.05 were considered to be statistically significant.

Results

A total of 225 participants were initially enrolled in the study. In order to ensure treatment uniformity, only ceftriaxone-treated subjects with more than one visit over at least 1 week and up to 1 year of follow-up were included in the analysis. There were 158 patients who met these criteria (32 men and 126 women) accounting for 1051 study visits. The mean patient age was 41.1 (range 15–67) years. There were on average 6.7 visits (median 5, range 2–24) per person. The last follow-up day was on average 96 days after enrollment (median 69, range 7–354 days), corresponding to the length of antibiotic therapy. The number of participants in each stratum, based on duration of treatment, was similar: 32 patients were on treatment 1–4 weeks, 33 for 5–8 weeks, 28 for 9–12 weeks, 37 for 13–24 weeks, and 28 for 25–52 weeks.

Baseline scores for all outcomes are shown in Table 1. The scores for the 28 symptoms varied significantly, with patients showing a predominance of neurologic symptoms (74% with scores $>$ 0) over non-neurologic symptoms (65% with pain scores $>$ 0, 52% with systemic symptom scores $>$ 0). This symptom distribution was consistent with the clinical diagnosis of neurologic Lyme disease made by the treating physician. However, the four target symptoms made up the majority of significant (levels 4 and 5) severity scores at baseline, ie, myalgias (41%), arthralgias (48%), fatigue (66%), and cognition (42%). Of the other 24 symptoms, only neck pain (37%), headache (35%), back pain (33%), and insomnia (32%) had similar severity scores.

The baseline symptom severity scores stratified by duration of time on treatment are presented in Table 2. A likelihood ratio test showed significant differences in baseline scores according to patient stratum for the fatigue measure, with those on treatment for 9–12 and 13–24 weeks presenting with worse fatigue than the other groups. Baseline scores for the other three primary outcomes were not significantly different

Table 1 Baseline values of symptom severity

	0 (not affected)	1 (slight, barely noticed)	2 (minor yet noticeable problem)	3 (moderate problem, interferes some daily activities)	4 (major problem interferes most daily activities)	5 (disabling problem)
Overall	8 (5%)	4 (2%)	15 (9%)	59 (36%)	60 (36%)	20 (12%)
Pain						
Tender glands	106 (62%)	23 (13%)	13 (8%)	14 (8%)	13 (8%)	3 (2%)
Sore throat	107 (62%)	22 (13%)	20 (12%)	13 (8%)	6 (3%)	4 (2%)
Abdominal, testicular, pelvic	76 (44%)	25 (15%)	28 (16%)	18 (10%)	17 (10%)	8 (5%)
Chest	100 (58%)	21 (12%)	20 (12%)	15 (9%)	9 (5%)	7 (4%)
Back	43 (25%)	11 (6%)	23 (13%)	38 (22%)	38 (22%)	19 (11%)
Muscles	32 (19%)	10 (6%)	22 (13%)	37 (22%)	50 (29%)	21 (12%)
Headache	26 (15%)	19 (11%)	33 (19%)	35 (20%)	32 (19%)	27 (16%)
Neck	33 (19%)	14 (8%)	18 (10%)	43 (25%)	36 (21%)	28 (16%)
Joints	18 (10%)	13 (8%)	20 (12%)	39 (23%)	50 (29%)	32 (19%)
Neurologic						
Fatigue	4 (2%)	3 (2%)	12 (7%)	38 (22%)	61 (35%)	54 (31%)
Numbness, tingling	45 (26%)	32 (19%)	32 (19%)	32 (19%)	21 (12%)	10 (6%)
Lightheadedness	27 (16%)	30 (18%)	42 (25%)	40 (23%)	19 (11%)	13 (8%)
Poor balance	29 (17%)	32 (19%)	37 (22%)	35 (20%)	21 (12%)	18 (10%)
Tremor	74 (43%)	26 (15%)	28 (16%)	17 (10%)	18 (10%)	9 (5%)
Skin sensitivity	70 (41%)	20 (12%)	25 (15%)	33 (19%)	14 (8%)	10 (6%)
Vision	65 (38%)	26 (15%)	30 (17%)	28 (16%)	12 (7%)	11 (6%)
Sound or light sensitivity	54 (32%)	18 (11%)	23 (13%)	37 (22%)	25 (15%)	14 (8%)
Tinnitus	66 (39%)	27 (16%)	30 (18%)	28 (16%)	11 (6%)	9 (5%)
Cognition ("brain fog")	28 (16%)	19 (11%)	20 (12%)	33 (19%)	44 (26%)	28 (16%)
Mood swings	33 (19%)	27 (16%)	36 (21%)	31 (18%)	29 (17%)	16 (9%)
Systemic						
Bladder	102 (59%)	21 (12%)	19 (11%)	12 (7%)	11 (6%)	7 (4%)
Libido	82 (49%)	12 (7%)	13 (8%)	18 (11%)	14 (8%)	29 (17%)
Gastrointestinal	61 (36%)	29 (17%)	24 (14%)	29 (17%)	16 (9%)	12 (7%)
Shortness of breath	72 (42%)	20 (12%)	31 (18%)	28 (16%)	14 (8%)	5 (3%)
Cough	108 (63%)	28 (16%)	13 (8%)	16 (9%)	5 (3%)	1 (1%)
Heart palpitations	88 (51%)	24 (14%)	28 (16%)	19 (11%)	9 (5%)	4 (2%)
Sleeping a lot	111 (65%)	12 (7%)	10 (6%)	11 (6%)	16 (9%)	11 (6%)
Sleep difficulty	37 (22%)	16 (9%)	27 (16%)	38 (22%)	26 (15%)	27 (16%)

by treatment duration. The proportional odds assumption appears to have been met for all models after combining the highest two ordinal classes for cognition and joint pain and/or the lowest two ordinal classes for cognition.

Table 3 shows the estimated changes in symptom severity at the end of treatment compared with the first week on treatment for each patient stratum. The severity of the four primary symptoms was significantly improved in at least one patient stratum ($P < 0.05$), and most P values were <0.10 in all groups for arthralgias, myalgias, and fatigue. For myalgias, arthralgias, and cognition, the model with the lowest Akaike information criterion included only the factor representing time on treatment; for fatigue it included both treatment duration and patient stratum. Those in treatment weeks 1–4 had significantly better arthralgia scores at the end of treatment compared with baseline, with the odds of being in a less severe ordinal group 1.57 times greater at the end of treatment compared with baseline (95% CI: 1.02–2.4). This corresponds to a 19% decrease in the proportion of patients reporting severe or disabling arthralgias after 1–4 weeks and a 17% drop after 25–52 weeks of treatment compared with baseline. Although the odds ratios were similar for the other participant groups, the effects were only marginally significant (<0.10).

The severity of myalgias improved during the study as well, with more improvement seen in patients with longer duration of intravenous treatment. In those treated for 25–52 weeks, the odds of being in a less severe ordinal group were 2.08 (1.2–3.50) times greater at the end of treatment compared with baseline. This corresponds to about a 31% reduction in the proportion of patients reporting a major or disabling problem with myalgias (ordinal group 4 or 5) after 25–52 weeks of treatment compared with baseline.

Table 2 Baseline symptom severity for each follow-up duration group. Only those on follow-up of more than 1 week and less than 1 year are included

Time on treatment	Not affected (0)	Slight, barely noticed (1)	Minor yet noticeable problem (2)	Moderate problem, interferes some daily activities (3)	Major problem, interferes with most daily activities (4)	Disabling problem (5)	Total
Arthralgias							
1–4	4 (13%)	1 (3%)	3 (9%)	11 (34%)	7 (22%)	6 (19%)	32 (100%)
5–8	3 (9%)	4 (12%)	5 (15%)	6 (18%)	9 (27%)	6 (18%)	33 (100%)
9–12	1 (4%)	0 (0%)	1 (4%)	9 (32%)	12 (43%)	5 (18%)	28 (100%)
13–24	3 (8%)	5 (14%)	4 (11%)	7 (19%)	11 (30%)	7 (19%)	37 (100%)
25–52	5 (18%)	1 (4%)	4 (14%)	6 (21%)	6 (21%)	6 (21%)	28 (100%)
Total	16 (10%)	11 (7%)	17 (11%)	39 (25%)	45 (28%)	30 (19%)	158 (100%)
Fatigue							
1–4	1 (3%)	0 (0%)	2 (6%)	6 (19%)	15 (47%)	8 (25%)	32 (100%)
5–8	2 (6%)	1 (3%)	4 (12%)	10 (30%)	9 (27%)	7 (21%)	33 (100%)
9–12	0 (0%)	1 (4%)	1 (4%)	4 (14%)	8 (29%)	14 (50%)	28 (100%)
13–24	0 (0%)	1 (3%)	2 (5%)	7 (19%)	13 (35%)	14 (38%)	37 (100%)
25–52	1 (4%)	0 (0%)	2 (7%)	8 (29%)	10 (36%)	7 (25%)	28 (100%)
Total	4 (3%)	3 (2%)	11 (7%)	35 (22%)	55 (35%)	50 (32%)	158 (100%)
Myalgias							
1–4	6 (19%)	0 (0%)	4 (13%)	8 (25%)	10 (31%)	4 (13%)	32 (100%)
5–8	6 (18%)	3 (9%)	6 (18%)	7 (21%)	6 (18%)	5 (15%)	33 (100%)
9–12	4 (14%)	1 (4%)	3 (11%)	5 (18%)	13 (46%)	2 (7%)	28 (100%)
13–24	6 (16%)	3 (8%)	7 (19%)	9 (24%)	9 (24%)	3 (8%)	37 (100%)
25–52	8 (29%)	1 (4%)	0 (0%)	7 (25%)	7 (25%)	5 (18%)	28 (100%)
Total	30 (19%)	8 (5%)	20 (13%)	36 (23%)	45 (28%)	19 (12%)	158 (100%)
Cognition							
1–4	8 (25%)	0 (0%)	1 (3%)	9 (28%)	8 (25%)	6 (19%)	32 (100%)
4–8	6 (18%)	8 (24%)	3 (9%)	6 (18%)	7 (21%)	3 (9%)	33 (100%)
8–12	1 (4%)	4 (14%)	5 (18%)	5 (18%)	7 (25%)	6 (21%)	28 (100%)
12–24	9 (24%)	3 (8%)	5 (14%)	5 (14%)	9 (24%)	6 (16%)	37 (100%)
24–52	3 (11%)	2 (7%)	4 (14%)	8 (29%)	6 (21%)	5 (18%)	28 (100%)
Total	27 (17%)	17 (11%)	18 (11%)	33 (21%)	37 (23%)	26 (16%)	158 (100%)

The findings for fatigue were similar to those for myalgias, with improvement shown in all patient strata, and the most improvement occurring in patients on the longest courses of intravenous treatment. There was an estimated 22% reduction in the proportion of patients reporting disabling fatigue after 25–52 weeks of treatment compared with baseline. Significant improvement in cognition was only seen in the group on treatment for 25–52 weeks, with an odds ratio of being in a less severe symptom group of 1.97 (95% CI: 1.11–3.48) at the end of treatment compared with baseline. This corresponds to a 26% decline in the number of patients reporting cognitive problems to be disabling or a major problem at the end of treatment compared with baseline.

Discussion

Neurologic Lyme disease is characterized by neuropsychiatric symptoms that may be persistent and difficult to treat.[11–14] Intravenous antibiotic therapy is recommended for this condition, but the duration of prescribed treatment is controversial. While the IDSA guidelines recommend a maximum

Table 3 Changes in symptom severity by follow-up time group, at the time of the last follow-up visit

Time on IV treatment	Arthralgias	Myalgias	Fatigue	Cognition
1–4 weeks	1.57 (1.02–2.4), $P = 0.04$	1.41 (0.95–2.11), $P = 0.09$	1.44 (0.96–2.17), $P = 0.08$	1.25 (0.78–1.98), $P = 0.35$
5–8 weeks	1.49 (0.97–2.29), $P = 0.07$	1.56 (1.04–2.34), $P = 0.03$	1.88 (1.25–2.82), $P < 0.01$	1.35 (0.86–2.12), $P = 0.19$
9–12 weeks	1.54 (0.94–2.53), $P = 0.08$	1.52 (0.96–2.4), $P = 0.07$	1.51 (0.94–2.42), $P = 0.09$	0.96 (0.57–1.61), $P = 0.87$
13–24 weeks	1.30 (0.84–2.02), $P = 0.24$	2.14 (1.41–3.25), $P \leq 0.01$	2.12 (1.39–3.23), $P < 0.01$	1.10 (0.69–1.75), $P = 0.69$
25–52 weeks	1.57 (0.93–2.66), $P = 0.09$	2.08 (1.24–3.5), $P = 0.01$	2.22 (1.32–3.73), $P < 0.01$	1.97 (1.11–3.48), $P = 0.02$

Note: Conditional odds ratios (95% confidence intervals) and *P* values are presented using the first week in treatment as the reference

of 30 days of antibiotic therapy,[6] the International Lyme and Associated Diseases Society guidelines take a more open-ended approach, tailoring therapy to resolution of patient symptoms.[5] Although some studies have shown benefit of longer antibiotic therapy in neurologic Lyme disease,[13,19] this therapy has been considered ineffective and even dangerous by IDSA.[6–10] However, in a previous safety study, we showed that prolonged intravenous antibiotic therapy was associated with low morbidity and no mortality in closely monitored patients referred for treatment of neurologic Lyme disease.[11] The mean length of treatment in that study was almost 4 months, and while the safety data was reassuring for that length of therapy, the study did not address the benefit of treatment given to those patients.

The present study evaluated the benefit of prolonged intravenous antibiotic therapy in patients diagnosed with neurologic Lyme disease by their treating physicians. The diagnosis of neurologic Lyme disease was supported by the symptom distribution recorded at baseline in these patients, as shown in Table 1. The predominance of women in our study population is consistent with previous observations that persistent Lyme disease is more commonly diagnosed in women.[20] In contrast with our previous study, only patients receiving intravenous ceftriaxone were included in the analysis. As in the previous investigation, patients received an average of more than 3 months of intravenous antibiotic treatment, and they were closely monitored by homecare nurses. The treatment was associated with low morbidity and no mortality, confirming the safety of this therapy, as described previously.[11]

Previous controlled trials have examined relatively short intravenous antibiotic treatments ranging from 1–3 months for patients with neurologic Lyme disease.[13,21–23] A major criticism of these trials is that the length of treatment was insufficient to eradicate a persistent spirochetal infection. Our results indicate that prolonged antibiotic treatment for 25–52 weeks may be required to induce improvement in symptoms of neurologic Lyme disease. Although a control group was not included in the study, each patient had baseline symptom severity scores and multiple longitudinal measurements for up to 1 year, and the improvement in fatigue, myalgias, and cognition was significant with extended antibiotic therapy.

Numerous studies have documented persistent *B. burgdorferi* infection in patients with persistent symptoms of neurologic Lyme disease following short-course antibiotic therapy.[1–4] Furthermore, animal models have demonstrated that short-course antibiotic therapy may fail to eradicate the Lyme spirochete.[24–26] Persistent spirochetal infection appears to be a more likely explanation for chronic symptoms of Lyme disease than the autoimmune hypotheses that have been postulated but never substantiated, and recent evidence has shed more light on the complex strategies that allow *B. burgdorferi* to evade both the immune response and antibiotic agents.[27–29] The use of prolonged antibiotic therapy to eradicate ongoing spirochetal infection is consistent with the evidence for persistent *B. burgdorferi* infection outlined in these studies, and our results support this therapeutic approach.

Despite the negative view of prolonged antibiotic treatment for neurologic Lyme disease promoted by IDSA, antibiotic therapy ranging from 6 months to more than 5 years is recommended by infectious disease experts for a number of conditions, including drug-sensitive and drug-resistant tuberculosis, leprosy, disseminated atypical mycobacterial disease, brucella spondylitis, complicated actinomycosis, Whipple's disease, Q fever endocarditis, and alveolar echinococcosis (Table 4).[30–34] Furthermore, intravenous antibiotic therapy beyond 30 days is routinely prescribed for osteomyelitis,[35] and asplenia or hyposplenia in children is routinely treated prophylactically for 3–5 years with oral antibiotics,[36,37] while daily macrolide therapy for up to 5 years was recently shown to prevent exacerbations of chronic obstructive pulmonary disease and post-transplant bronchiolitis obliterans.[38] Thus,

Table 4 Precedents for prolonged antibiotic therapy[19,30–34]

Disease	Organism	Treatment	Duration
Tuberculosis (drug-sensitive)	*Mycobacterium tuberculosis*	2–4 antibiotics	6–9 months
Tuberculosis (multidrug resistant)	*Mycobacterium tuberculosis*	3–5 antibiotics	18–24 months
Leprosy	*Mycobacterium leprae*	3 antibiotics	24 months
Atypical tuberculosis	*Mycobacterium chelonae*	IV + oral antibiotics	6–12 months
Brucella spondylitis	*Brucella* spp.	IM + oral antibiotics	6–12 months
Complicated actinomycosis	*Actinomyces* spp.	IV + oral antibiotics	6–18 months
Whipple's disease	*Tropheryma whipplei*	IV + oral antibiotics	12–24 months
Q fever endocarditis	*Coxiella burnetii*	2 antibiotics	36 months
Alveolar echinococcosis	*Echinococcus multilocularis*	Oral antibiotics	5.7 years (mean)

Abbreviations: IV, intravenous; IM, intramuscular.

in certain conditions, the benefit of long-term therapeutic or prophylactic antibiotic therapy is thought to outweigh the risk. Our study suggests that prolonged antibiotic therapy may be required to improve the most disabling symptoms of neurologic Lyme disease, and taken together with our previous safety study, the risks of prolonged antibiotic treatment appear to be justifiable in these patients.

Strengths of this study include the evaluation of significant symptoms that are common in neurologic Lyme disease. The study included a large number of participants, long duration of treatment, and multiple longitudinal measurements per participant. This allowed the use of a flexible statistical model structure, with separate effects estimated by treatment duration. Although the improvements in symptom severity observed in this study are encouraging and, in fact, necessary to infer a causal relationship between treatment and improvement, the lack of randomization into a control or placebo group prevents us from confirming a causal relationship. In addition, treatment duration was not defined a priori, and nonmedical factors such as financial considerations and insurance denial may have influenced treatment duration. These issues need to be addressed in a randomized controlled trial with antibiotic therapy administered beyond 3 months according to clinical need.

In summary, prolonged intravenous antibiotic therapy is associated with improved cognition, fatigue and myalgias in patients referred for treatment of neurologic Lyme disease. In contrast, improvement in arthralgias did not persist after 1–4 weeks of therapy. Treatment for 25–52 weeks may be necessary to obtain significant symptomatic improvement in patients with neurologic Lyme disease.

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Disclosure

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