2008

A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy

B. A. Fallon

J. G. Keilp

K. M. Corbera

E. Petkova

C. B. Britton

See next page for additional authors

Citation/Publisher Attribution

Falon, B. A., Keilp, J. G., Corbera, K. M., Petkova, E., Britton, C. B., Dwyer, E., Slavov, I.,...Sackeim, H. A. (2008). A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology, 70*(13), 992-1003. doi: 10.1212/01.WNL.0000284604.61160.2d

Available at: https://doi.org/10.1212/01.WNL.0000284604.61160.2d

A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy

B.A. Fallon, MD
J.G. Keilp, PhD
K.M. Corbera, MD
E. Petkova, PhD
C.B. Britton, MD
E. Dwyer, MD
I. Slavov, PhD
J. Cheng, MD, PhD
J. Dobkin, MD
D.R. Nelson, PhD
H.A. Sackeim, PhD

Address correspondence and reprint requests to Dr. B.A. Fallon, Columbia University, 1051 Riverside Drive, Unit 69, New York, NY 10032
baf1@columbia.edu

ABSTRACT

Background: Optimal treatment remains uncertain for patients with cognitive impairment that persists or returns after standard IV antibiotic therapy for Lyme disease.

Methods: Patients had well-documented Lyme disease, with at least 3 weeks of prior IV antibiotics, current positive IgG Western blot, and objective memory impairment. Healthy individuals served as controls for practice effects. Patients were randomly assigned to 10 weeks of double-masked treatment with IV ceftriaxone or IV placebo and then no antibiotic therapy. The primary outcome was neurocognitive performance at week 12—specifically, memory. Durability of benefit was evaluated at week 24. Group differences were estimated according to longitudinal mixed-effects models.

Results: After screening 3368 patients and 305 volunteers, 37 patients and 20 healthy individuals enrolled. Enrolled patients had mild to moderate cognitive impairment and marked levels of fatigue, pain, and impaired physical functioning. Across six cognitive domains, a significant treatment-by-time interaction favored the antibiotic-treated group at week 12. The improvement was generalized (not specific to domain) and moderate in magnitude, but it was not sustained to week 24. On secondary outcome, patients with more severe fatigue, pain, and impaired physical functioning who received antibiotics were improved at week 12, and this was sustained to week 24 for pain and physical functioning. Adverse events from either the study medication or the PICC line were noted among 6 of 23 (26.1%) patients given IV ceftriaxone and among 1 of 14 (7.1%) patients given IV placebo; these resolved without permanent injury.

Conclusion: IV ceftriaxone therapy results in short-term cognitive improvement for patients with posttreatment Lyme encephalopathy, but relapse in cognition occurs after the antibiotic is discontinued. Treatment strategies that result in sustained cognitive improvement are needed. *Neurology*® 2008;70:992–1003

GLOSSARY

CDC = Centers for Disease Control and Prevention; **LMM** = longitudinal mixed-effects models; **NAART-R** = North American Adult Reading Test-Revised; **PCS** = Physical Component Scale; **ITT** = intent-to-treat; **VAS** = visual analog scale; **WMS-III** = Wechsler Memory Scale.

Lyme disease, a tick-borne bacterial illness caused by *Borrelia burgdorferi*, can induce cognitive deficits when it affects the CNS.[1] These deficits, often mild to moderate in severity, extend across multiple domains of cognitive function, including memory, working memory, verbal fluency, and psychomotor performance.[2,3] Although treatment with 4 weeks of IV ceftriaxone usually results in marked improvement, in a subgroup this treatment results in only partial or nonsustained benefit.[4,5] Posttreatment cognitive deficits may reflect residual effects of past infection, continuing effects of current low-grade *B burgdorferi* infection, the presence of an unrecognized coinfection, or incorrect diagno-

Supplemental data at www.neurology.org

Editorial, page 986

e-Pub ahead of print on October 10, 2007, at www.neurology.org.

From the Department of Psychiatry (B.A.F., J.G.K., K.M.C., E.P., I.S., J.C., H.A.S.), Department of Biostatistics (E.P.), Department of Neurology (C.B.B.), Department of Medicine (E.D., J.D.), and New York State Psychiatric Institute (B.A.F., J.G.K., K.M.C., E.P., I.S., J.C., H.A.S.), Columbia University, New York; and Department of Cell and Molecular Biology, University of Rhode Island, Kingston (D.R.N.).

Primary location of research: Columbia University Medical Center, New York.

This study was funded by a grant from NINDS to Dr. Fallon (R01- NS38636).

Disclosure: Roche Pharmaceuticals supplied ceftriaxone free of charge for this study but were not involved in any other aspect of the study. Dr. Fallon has given expert testimony at hearings related to Lyme disease and its treatment. The other authors report no conflicts of interest.

sis. Consequently, clinicians are uncertain about optimal treatment strategies. For patients in whom no other cause of symptoms can be found, community practice varies widely, ranging from no treatment to palliative treatment to use of repeated or long-term antibiotic courses.

To evaluate the benefit of additional IV antibiotic therapy, we conducted a trial comparing clinical improvement from 10 weeks of IV ceftriaxone vs IV placebo in patients with previously treated Lyme disease who had objective memory impairment and a currently positive IgG Western blot.

METHODS

Study participants. Between January 2000 and April 2004, healthy volunteers (*controls*) and individuals with a history of Lyme disease (*patients*) between the ages of 18 and 65 years were recruited; follow-up evaluations were completed by April 2005. The institutional review boards at Columbia University and the New York State Psychiatric Institute approved the study, and all participants provided written informed consent. Evaluations were conducted at the New York State Psychiatric Institute and Columbia University Medical Center. Treatments were conducted at each patient's home. Patients met the following criteria: (1) history of physician-documented erythema migrans or U.S. Centers for Disease Control and Prevention (CDC)-defined manifestation of Lyme disease, and a positive or equivocal ELISA confirmed by positive Western blot serology[6,7]; (2) current positive IgG Western blot using CDC surveillance criteria, assessed using a single reference laboratory (University Hospital of Stony Brook); (3) treatment for Lyme disease with at least 3 weeks of IV ceftriaxone, completed at least 4 months before study entry; (4) subjective memory impairment that, by participant report, started after the onset of Lyme disease; and (5) objective evidence of memory impairment as documented by the Wechsler Memory Scale–III[8] compared with age-, sex-, and education-adjusted population norms. These study criteria were conservative and narrow to enhance diagnostic confidence. Prior IV antibiotic therapy was required to ensure that all patients had received treatment considered adequate for neurologic Lyme disease by published guidelines.[9,10]

The control sample of healthy volunteers had (1) negative history of Lyme disease, fibromyalgia, or chronic fatigue; (2) negative IgM and IgG Western blot for Lyme disease; and (3) no evidence of memory impairment on neuropsychological testing.

Patients and controls were excluded if their history revealed a prior learning disability or medical condition that could confound neuropsychological assessment. Patients with cephalosporin allergy or a history of major psychiatric disorder before the onset of Lyme disease were also excluded. The control and patient samples were matched on the mean, variance, and shapes of the distributions of age and education, and the distribution of gender.

Study design. ***Treatment.*** The controlled phase of this study consisted of 10 weeks of randomized treatment with either IV ceftriaxone (2 g/d) or IV placebo (0.9% normal saline), and then 14 weeks off all antibiotics. Ceftriaxone was chosen because it is the recommended treatment for neurologic Lyme disease and has excellent penetration of the blood–brain barrier.[9] A 10-week duration was chosen because of reports of persistent or relapsing symptoms after 3 weeks of IV ceftriaxone, and because of case series suggesting that longer courses of antibiotic therapy may be more effective.[4,11] After week 24, treatment assignment was revealed by a research staff member not involved in data collection, and no further constraints were placed on subsequent care. Participants underwent one follow-up assessment at week 48. This report concerns only the controlled phases of the study, from baseline to week 24.

Randomization. Patients were assigned in a 2:1 ratio to IV ceftriaxone or IV placebo, using permuted blocks of size 20 based on a computer-based randomization list. A 2:1 randomization schedule was used to encourage enrollment.

Masking. An unmasked off-site pharmacist, who had no contact with patients, ensured that patients were sent the assigned treatment; this pharmacist was the only unmasked individual during the 24 weeks of each patient's masked treatment. The neuropsychological technicians were not privy to information about adverse events. To assess success of masking, patients were asked to guess treatment assignment at both the week 12 and 24 evaluations.

Compliance with treatment. Compliance and safety were monitored by home infusion nurses who visited twice weekly. Patients had weekly telephone contact with a research physician and monthly in-person evaluations with the patient's private physician. Study medication was packaged in pressured infusion devices, numbered from 1 to 70. Both the visiting nurse and the research physician recorded the number of completed infusions. Patients who missed a day's dose were instructed to continue in consecutive sequence until all 70 doses were infused.

Sample size. The target sample size of 45 Lyme patients (30 randomized to active treatment and 15 randomized to placebo) provided at least 80% power to detect an effect size of 1.1 with a two-sided test with $\alpha = 0.05$. Power calculations were based on the results of an uncontrolled pilot study,[4] with the outcome measure of *memory* assessed with the Buschke Selective Reminding Test total verbal memory score. Although cognitive improvement was expected in both visual and verbal memory, as well as in multiple other cognitive domains, verbal memory was selected for the power analysis, given the lack of pilot data for other aspects of cognition.

Assessments. ***Screening.*** Subjects were screened for memory impairment with the Wechsler Memory Scale (WMS-III),[8] which measures immediate, delayed, and working memory in auditory and visual domains. Demographically adjusted *t* scores were computed for all indices, correcting for the influence of sex, ethnicity, and education level. Memory impairment was defined as a *t* score of one or more SD below population norms on at least one of the six primary WMS-III indices. Premorbid IQ was estimated using the Barona demographic formula[12] and the North American Adult Reading Test–Revised (NAART-R).[13]

Outcome measures. The primary clinical outcome measure assessed neurocognitive performance, and the primary biologic outcomes assessed brain structure and function. Relative to the placebo and control groups, IV antibiotic therapy was hypothesized to lead to superior outcome in the memory domain scores, as well as across

cognitive domains. The cognitive assessments sampled six domains: motor function (finger tapping, simple reaction time, choice reaction time), psychomotor function (Trail Making A&B; Digit Symbol), attention (Continuous Performance Test, Stroop task), memory (Buschke Selective Reminding Test [verbal memory]; Benton Visual Retention Test [visual memory]), working memory (A, Not B Logical Reasoning Test; N-Back Test), and verbal fluency (Controlled Oral Word Association Test and Category Fluency Test). Descriptions of these measures may be found elsewhere.[14,15] Scores on these tests were z transformed relative to either published norms or a reference sample of healthy controls and were adjusted for the effects of age, gender, and education. Domain scores represent the average of the z scores for the primary tests within each cognitive domain. To characterize overall performance, the six domain scores were averaged to produce a cognitive "index" score; this index was not used in the primary mixed-model analyses. Brain imaging measures included MRI and PET scans; these imaging results will be reported elsewhere.

Assessments of physical outcome included the rheumatologist's exam (trigger points, total number of joints in pain at rest or on movement) and self-report measures of fatigue (Fatigue Severity Scale–11[16]), pain (McGill Pain Questionnaire–Short Form[17]), and physical functioning (Short Form–36 Physical Component Scale [PCS][18,19]). Psychopathology was assessed with respect to depression (Beck Depression Inventory[20]), anxiety (Zung Anxiety Scale[21]), mental functioning (SF-36 MCS[18,19]), and global symptoms (SCL-90 Global Symptom Index[22]).

Time of assessment. Major assessments occurred at baseline, week 12, and week 24. The primary end point for efficacy analyses was week 12. The week 24 assessments evaluated durability of benefit. Controls were assessed at the same time points to allow correction for the impact of practice effects on the repeated neurocognitive measures. The secondary outcome self-report scales were collected at 4-week intervals (baseline and weeks 4, 8, 12, 16, 20, and 24). The rheumatologist exam was conducted at baseline, week 12, and week 24. The lumbar puncture (for patients) and neurology exam (for all participants) were done only at baseline. The neurologic exam assessed five areas: cranial nerves, reflexes, sensory, motor, and associated motor (cerebellar and basal ganglia) functions. For the standardized neurology exam, a summary score (0–5) indicated the number of areas with at least one minor or major abnormal finding. An objective neurologic abnormality was considered major if it was associated with either a significant deficit or impairment in the person's functioning.

Laboratory assessments. Screening serum was sent for Lyme IgM and IgG Western blot testing. Enrolled patients had serum examined by IFA for signs of coinfection with *Anaplasma phagocytophila* (human granulocytic erhlichiosis) and *Babesia microti* (Babesiosis). Samples of whole blood and CSF were tested by PCR assay for *B burgdorferi* DNA, using the plasmid *ospA* primer. CSF was sent for cell count, protein, glucose, total gammaglobulin, Lyme ELISA, and oligoclonal bands. Serum and CSF were sent for determination of Bb-specific intrathecal Ab production to University Hospital of Stony Brook using the whole-cell sonicate ELISA (positive cutoff ≥ 1.1). To determine whether viable *B burgdorferi* cells were present, spinal fluid was cultured in BSKII containing kanamycin (5 μg/mL) at 33°C and was checked weekly for up to 12 weeks.

Statistical analysis. Efficacy analyses were performed using all randomized participants, the intent-to-treat (ITT) sample. Lyme patient and healthy controls were compared with respect to demographic and baseline clinical characteristics, using t tests for continuous measures and χ^2 tests for categorical measures.

Tests and estimates of differences between groups (IV antibiotic, IV placebo, and healthy controls) with respect to the multivariate measure of cognition (six domains: motor, psychomotor, working memory, attention, verbal fluency, and memory) over time (baseline, week 12, and week 24) were based on longitudinal mixed-effects models (LMM),[23] which account for the correlation between the domains and between the repeated observations over time.[24] The LMM included main effects and all interaction terms. Time was modeled as a nominal factor rather than a continuous variable.

Including all two- and three-way interactions, the model for the covariance structure was selected based on maximizing Bayesian information criteria.[25,26] Keeping the model for the covariance as selected, stepwise backward elimination was used to select the "best" model for the mean structure. Inference regarding the comparison between the groups was based on the best model. Significant omnibus tests for ITT differences among the three groups over time (two-sided $\alpha = 0.05$) were followed by pairwise comparisons; the p values for these post hoc tests are reported unadjusted.

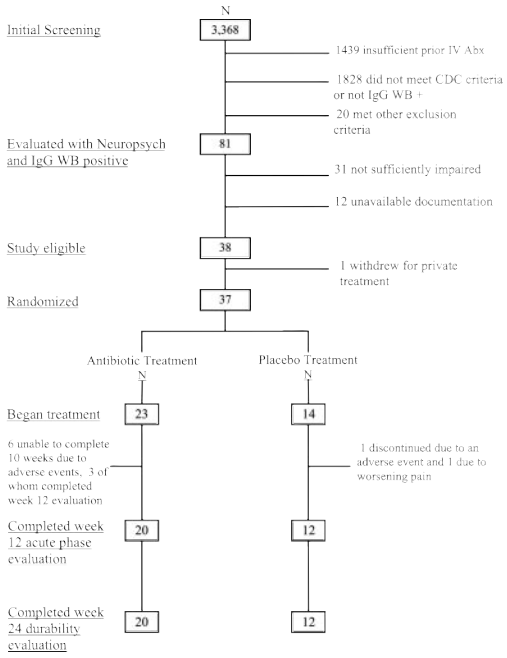
Secondary outcome measures were analyzed with LMMs, using a similar strategy. Healthy controls were not included because practice effects were not of concern. For the outcome *number of joints with pain*, a Poisson variable, an appropriate generalized LMM[23] was employed, using log link. As initially planned, the LMMs included the baseline value of the outcome as a continuous covariate to account for heterogeneity in clinical characteristics and to remedy potential floor effects. The significance of the interaction terms was judged at a two-sided $\alpha = 0.15$, to avoid the erroneous omission of potentially important effects for which the study was not powered; the significance of a main effect for drug vs placebo was still judged at $\alpha = 0.05$. To illustrate the impact on outcome of different baseline severity scores, an estimate of the mean response based on the best model for each outcome was computed at weeks 4, 12, and 24 for drug and placebo for *hypothetical* subjects with baseline symptom severity equal to the lowest (first) or highest (third) quartile of the observed baseline severities. The reporting of outcomes for "low" and "high" baseline severity is for illustration purposes only: the actual analysis based on LMMs included all patients and used baseline severity as a continuous covariate without dichotomizing it into low and high values. All analyses were performed using SAS software version 9[25]; the LMMs were fit using PROC MIXED and PROC GLIMMIX.

To explore whether particular patient subgroups had preferential benefit from active treatment, ANCOVAs tested for associations between selected demographic, clinical, and laboratory variables and the primary and secondary outcomes at week 12 and week 24 that had shown a treatment effect in the LMM analyses. Treatment group, baseline severity of the outcome measure, and (dichotomous or continuous) potential predictor were examined as fully factorial, between-subject factors.

RESULTS

Study population. ***Healthy controls.*** Of 305 individuals contacted by telephone, 58 were invited for on-site screening, and 20 were enrolled. Reasons for exclusion included laboratory abnormalities, memory deficits on testing, or

Figure Flow diagram of patient enrollment



other exclusions. Of the 20 enrolled, two participants had impaired scores on baseline neuropsychological testing and were excluded.

Patients. Of 3368 initial clinic contacts, 1439 were excluded because of insufficient prior IV treatment, and 1316 were excluded because the patient had not met the CDC criteria for Lyme disease (figure). Among the remaining 613 patients, 512 were excluded because their serum was not IgG Western blot positive, and 20 were excluded for other reasons. Of the 81 patients invited to Columbia for neuropsychological screening, 31 did not have sufficient memory impairment, 12 were not able to provide adequate documentation of their clinical history, and one patient who had been deemed eligible for the study withdrew for private treatment before randomization. Thirty-seven patients were randomized to interventions, representing 1% of all patients screened for the study. Of these 37 patients, five withdrew from the study during the first 12 weeks: three within the first 3 weeks of therapy (two because of thrombus and one because of hemolytic anemia; all three on antibiotic), one after 8 weeks because of a systemic infection (on placebo), and one after 10 weeks (on placebo) because of intolerable joint pain that required narcotic medications for relief. Three additional patients had adverse events that required early termination of study medication (one at week 6 and two at week 8), but each of these patients continued in a masked fashion through to the week 12 and 24 evaluations. No patients withdrew from the study between weeks 12 and 24.

Laboratory results for enrolled patients. ***Blood.*** All samples were IgG WB positive, and 18 of 37 were IgM WB positive. No patient samples were PCR positive using the *OspA* primer assay. None of the serum samples were IgM positive on either of the two coinfection tests, whereas low positive IgG results were noted on 4 of 37 (10.8%) samples for *Anaplasma phagocytophila* and on 10 of 37 (27.0%) samples for *Babesia microti*.

Cerebrospinal fluid. Baseline lumbar puncture, conducted in 33 of the 37 patients, revealed few abnormalities: mildly elevated WBC (two samples), mildly elevated protein (four samples), and elevated gammaglobulin (one sample). Positive results were noted for 22 on Lyme ELISA, 28 on IgG WB, and none on IgM WB. For intrathecal Ab production, samples tested positive for 4 of 31 (12.9%) patients; each positive intrathecal sample was also seropositive. No patient had a positive CSF PCR. When cultured, one sample was positive for growth and revealed spirochetes by both phase contrast and dark-field microscopy. To exclude contamination as an explanation, the cells's DNA was extracted and was used as a template for PCR amplification of the *spoT* gene. Examination of the PCR amplicon by agarose gel electrophoresis revealed an approximately 3-kbp band, whereas a PCR amplicon from wild-type strains was approximately 2 kbp. Additionally, the *B burgdorferi* isolated from the CSF culture was able to grow when transferred into BSKII containing kanamycin (5 μg/mL) plus streptomycin (100 μg/mL). These results strongly suggest that the *B burgdorferi* strain found in the CSF culture was the result of contamination by a *spoT* mutant strain (WC07) of *B burgdorferi* containing a deletion of part of the *spoT* gene plus the insertion of a streptomycin resistance gene; *spoT* mutant strains were under investigation in the lab at the time of the culture.

Demographics and pretreatment clinical characterization of patients and controls. The patients and healthy controls did not differ in the matching variables of age, gender, or education (table 1). The patients' clinical histories indicated that all had rheumatologic symptoms, and most had neurologic symptoms associated with cognitive complaints. Nearly half (49%) had had a prior lumbar puncture; only three of these patients had had elevated *B burgdorferi*–specific intrathecal Ab production. The total amount of prior antibiotic therapy for Lyme disease was extensive, with 57% of the patients in each treatment group having had more than 1 month of prior IV antibiotic

Table 1 Demographic and clinical characteristics of all participants by study group

Characteristic	Patients			Controls
	Ceftriaxone group (n = 23)	Placebo group (n = 14)	Total (n = 37)	(n = 18)
Age in years, mean (SD)	45.3 (13.7)	44.8 (12.7)	45.1 (13.2)	45.6 (11.3)
Female, n (%)	14.0 (61.0)	8.0 (57.1)	22.0 (59.0)	13.0 (72.2)
Years of education, mean (SD)	14.7 (2.4)	14.8 (2.7)	14.7 (2.5)	15.6 (2.4)
White, n (%)	23.0 (100)	14.0 (100)	37.0 (100)	17.0 (94.4)
Employment, n (%)				
Working full- or part-time	14 (60.9)	7 (50.0)	21 (57.0)	7 (33.9)
School full- or part-time	0 (0.0)	2 (14.3)	2 (5.4)	1 (5.5)
On leave from work or disabled	3 (13.0)	4 (28.6)	7 (18.9)	0 (0.0)
Other	6 (26.1)	1 (7.1)	7 (18.9)	10 (55.6)
Lyme disease symptom history, n (%)				
Erythema migrans	13 (56.5)	7 (50.0)	20 (54.1)	
Arthralgias or myalgias	23 (100.0)	14 (100.0)	37 (100.0)	
Arthritis	20 (87.0)	11 (78.6)	31 (83.8)	
Facial nerve palsy	3 (13.0)	6 (42.9)	9 (24.3)	
Meningitis or encephalitis	3 (13.0)	2 (14.3)	5 (13.5)	
Polyneuropathy	18 (78.3)	11 (78.6)	29 (78.4)	
Cognitive problems	23 (100.0)	14 (100.0)	37 (100.0)	
Months of prior IV antibiotics, mean (SD)	2.5 (2.0)	1.9 (1.3)	2.3 (1.6)	
Months of prior oral antibiotics, mean (SD)	7.9 (10.2)	5.9 (7.6)	7.2 (9.2)	
Rheumatology exam, mean (SD)				
No. of joints with pain at rest or motion	5.9 (4.5)	6.4 (7.2)	6.1 (5.6)†	0.6 (0.7)†
No. of fibromyalgia trigger points	1.4 (2.7)	2.3 (3.4)	1.8 (3.0)†	0.0 (0.0)†
No. of tender joints	1.1 (2.4)	1.1 (2.1)	1.1 (2.3)†	0.1 (0.2)†
No. of swollen joints	0.9 (1.6)	0.3 (.83)	0.7 (1.4)†	0.0 (0.0)†
Neurology exam, n (%)				
Sensory exam abnormality	16 (69.6)	11 (78.6)	27 (73)‡	4 (22.2)‡
Motor exam abnormality	8 (34.8)	6 (42.9)	14 (37.8)*	2 (11.1)*
Associated motor exam	7 (30.4)	5 (35.7)	12 (32.4)	3 (16.7)
Cranial nerves	3 (13.0)	4 (28.6)	7 (18.9)	2 (11.1)
Reflex exam	3 (13.0)	4 (28.6)	7 (18.9)	2 (11.1)

* $p < 0.1$.
† $p < 0.01$.
‡ $p < 0.001$.

therapy. Patients reported having been symptomatic with Lyme disease for a mean of 1.7 (SD 3.5) years before diagnosis, and they reported having been ill for a total of 9.0 (SD 6.8) years.

Patients and controls on the screening measures. The groups did not differ in estimated premorbid IQ according to the Barona method (111.5 [SD 6.2] for patients vs 113.7 [SD 5.5] for controls), although healthy controls had superior IQ as estimated by the NAART (108.9 [SD 8.1] for patients vs 115.9 [SD 6.0] for controls, $p < 0.01$). There were pronounced differences between the groups in WMS-III scores for immediate memory (93.1 [SD 12.4] for patients and 119.7 [SD 11.4] for controls, $p < 0.01$) and delayed (general) memory (94.7 [SD 10.2] for patients and 122.1 [11.5] for controls, $p < 0.01$). The magnitude of these differences in memory substantially exceeded the difference between the groups in estimated IQ.

Patients and controls on postscreening measures. Participants were entered into the study based on a predetermined level of impairment (patients) or lack of impairment (controls), using the WMS-III. Because Lyme disease typically affects multiple aspects of cognition,[2,27] patients and controls were expected to differ at baseline on other cogni-

tive domains as well. It was also expected, based on prior studies of posttreatment Lyme disease,[5,28,29] that the two groups might differ on several of the secondary clinical outcome measures.

Patients and controls differed significantly on all clinical outcome measures, both primary and secondary. Mean difference of at least one SD (moderate impairment) occurred in the psychomotor, memory, working memory, and verbal fluency domains. In the secondary measures, the impairment was severe in the physical measures (fatigue, current pain, physical functioning, joint pain on exam) and was mild in the psychopathology measures (depression, anxiety, general symptom index, mental component scale). Compared with published samples, reports of pain were similar to those of postsurgery patients,[17] fatigue was similar to that of patients with multiple sclerosis[16], and limitations in physical functioning were comparable with those of patients with congestive heart failure.[19] Individual subject scores on secondary measures ranged from mild to severe, reflecting our enrollment criteria, which did not preselect patients based on a level of impairment in these areas.

Patients, compared with controls, had significantly more trigger points, joints with pain, and joint swelling on rheumatologic exam (table 1). Patients averaged 1.8 (SD = 3.00) trigger points, with only one subject meeting the criteria for fibromyalgia with more than 10 trigger points. Joint pain was common, elicited on exam in 35 patients, with pain on motion (34/37) being more common than tenderness (13/37, McNemar $\chi^2 = 17.39$, $df = 1$, $p < 0.01$) or swelling (10/37, McNemar $\chi^2 = 22.04$, $df = 1$, $p < 0.01$). The number of abnormal areas on neurologic exam was greater in patients (mean 1.8 ± 1.2, median 2) than in controls (0.67 ± 1.1, median 0; $t = 3.3$, $df = 53$, $p < 0.01$). Major neurologic abnormalities were infrequent in the patients and absent in the controls (3/37 vs 0/18, $p =$ NS). However, minor abnormalities on neurologic exam were found in 73% of the patients vs 27.8% of the controls (Fisher $p < 0.01$); most frequent was a mild sensory abnormality among the patients.

Completeness of follow-up. Eighty-seven percent (32/37) of patients and 100% (18/18) of controls completed the week 12 acute-phase efficacy evaluation and week 24 follow-up durability evaluation, representing 20 patients in the ceftriaxone group, 12 in the placebo group, and all healthy controls.

Primary outcome: Treatment effects on neuropsychological tests. Arithmetic means and standard deviations are given in table 2. The inference regarding ITT comparisons between the groups over time is based on the best-fitting LMM that contained the main effects for group, time, and domain, and the two-way interactions of group by time and group by domain (table 3).

The primary omnibus LMM analysis revealed a group-by-time interaction effect ($p = 0.04$), indicating that with respect to cognition, the groups (drug, placebo, and healthy controls) differed in change over time (week 0 to week 12; week 12 to week 24) across all domains. The lack of a three-way interaction among group, domain, and time indicates that differential improvement over time between the domains was not demonstrated as had been hypothesized for memory and that the joint effect of time and group can be described without reference to a cognitive domain. Because the primary omnibus p value was significant, we then conducted model-based estimation of the effect of time within groups and pairwise comparisons of the effect of time between the groups. These comparisons demonstrated within-group cognitive improvement (as measured by the six cognitive domains) during the acute course of treatment (from week 0 to week 12) for the patients given ceftriaxone ($p < 0.01$) but not for the patients given placebo ($p = 0.15$) or the healthy controls ($p = 0.51$). The cognitive improvement between baseline and week 12 in the drug-treated patients was better than in the healthy controls ($p < 0.01$) and better than in the placebo-treated patients ($p = 0.053$).

During the antibiotic-free interval to week 24, the patients initially on ceftriaxone lost the preferential cognitive gains seen at week 12, whereas the two control groups (placebo and healthy volunteers) continued to show the same mild cognitive improvement as they had demonstrated in the acute phase. At week 24, the within-group improvement from baseline continued to be significant for the drug-treated group, but it was also now seen in the placebo-treated group. At week 24, the between-group treatment effects were no longer seen. In summary, the inability of the drug-treated group to sustain the distinguishing acute-phase improvement in cognition during the subsequent antibiotic-free interval resulted in a loss of the differential treatment effect among the three groups at week 24.

Secondary outcomes. Arithmetic means are presented in table e-1 on the *Neurology*® Web site (www.neurology.org), and the best-fitting models for each secondary outcome measure are presented in table e-2. Table e-2 also provides model-based estimates of the means over time for

Table 2 Neuropsychological test results (raw scores) by domain, treatment group, and time

	Baseline	Week 12		Week 24	
	Mean (SD)	Mean (SD)	Effect size*	Mean (SD)	Effect size*
Drug group	(n = 23)	(n = 20)	12/base	(n = 20)	24/base
Motor	−0.23 (1.34)	0.58 (0.88)	0.67	0.33 (1.05)	0.70
Psychomotor	−0.21 (0.75)	0.19 (0.89)	0.54	0.12 (0.88)	0.56
Attention	−0.12 (0.76)	0.15 (0.80)	0.27	0.18 (0.83)	0.36
Memory total	−0.75 (1.07)	−0.44 (1.29)	0.50	−0.62 (1.30)	0.37
Buschke	−1.13 (1.33)	−0.79 (1.71)	0.42	−0.98 (1.44)	0.31
Benton	−0.36 (1.21)	−0.08 (1.20)	0.25	−0.26 (1.43)	0.16
Working memory	−0.92 (1.09)	−0.42 (0.94)	0.52	−0.54 (0.89)	0.33
Fluency	−0.73 (0.94)	−0.38 (1.04)	0.55	−0.30 (0.98)	1.1
Index	−0.49 (0.63)	−0.05 (0.74)	0.81	−0.14 (0.68)	1.1
Placebo group	(n = 14)	(n = 12)		(n = 12)	
Motor	−0.06 (1.19)	0.06 (1.31)	0.13	0.36 (0.64)	0.49
Psychomotor	−0.16 (0.61)	0.14 (0.57)	0.58	0.29 (0.71)	0.88
Attention	0.04 (1.20)	0.34 (0.70)	0.40	0.37 (0.92)	0.35
Memory total	−0.36 (0.95)	−0.20 (0.74)	0.06	−0.22 (0.61)	0.03
Buschke	−0.78 (1.37)	−0.72 (1.44)	−0.13	−0.86 (1.26)	−0.18
Benton	0.06 (1.09)	0.33 (0.73)	0.22	0.42 (0.62)	0.29
Working memory	−0.32 (0.73)	−0.37 (0.75)	−0.34	0.04 (0.70)	0.37
Fluency	−0.80 (0.38)	−0.49 (0.39)	0.53	−0.46 (0.44)	0.60
Index	−0.28 (0.54)	−0.09 (0.50)	0.30	0.06 (0.46)	0.72
Control group	(n = 18)	(n = 18)		(n = 18)	
Motor	0.58 (0.63)	0.56 (0.68)	−0.08	0.66 (0.68)	0.15
Psychomotor	0.98 (0.75)	0.93 (0.74)	−0.11	1.18 (0.89)	0.38
Attention	0.35 (0.85)	0.60 (0.71)	0.43	0.65 (0.66)	0.59
Memory total	0.56 (0.43)	0.62 (0.49)	0.16	0.67 (0.55)	0.23
Buschke	0.38 (0.76)	0.72 (0.74)	0.51	0.72 (0.86)	0.46
Benton	0.73 (0.46)	0.52 (0.65)	−0.32	0.62 (0.73)	0.17
Working memory	0.34 (0.69)	0.38 (0.64)	0.01	0.43 (0.70)	0.19
Fluency	0.48 (0.66)	0.57 (0.68)	0.18	0.59 (0.86)	0.21
Index	0.55 (0.40)	0.61 (0.36)	0.26	0.70 (0.37)	0.58

Benton negative scoring has been adjusted.
An effect size of 0.2 reflects small improvement, 0.5 reflects moderate improvement, and 0.8 reflects large improvement.[40]

subjects' baseline severity scores corresponding to the lowest or highest quartile of the distribution of baseline scores of all 37 patients. These means are obtained from the respective LMMs (given in the right-hand side of table e-2) by substituting the selected baselines in the models. When the LMM contained an interaction involving group, post hoc comparisons between groups were performed within baseline severity level.

The majority of the physical self-report measures (fatigue, current pain, physical functioning) indicate interaction effects at week 12 favoring drug over placebo as a function of baseline severity, with the drug effect increasing with higher baseline impairment. Improvement continued to week 24, but only for current pain and physical functioning. For example, for physical functioning as measured by PCS, table e-2 indicates a two-way interaction ($p = 0.06$) for baseline severity and treatment, such that the beneficial effect of drug over placebo increased as baseline severity increased; model-based comparisons reveal the main effects of drug vs placebo ($p < 0.05$) at high levels of baseline severity. As an illustration of the LMM results, figure e-1 shows that among hypothetical subjects starting with a higher current

Table 3 Summary of the model for the six domains of neurocognitive performance

	Model information						
Type 3 tests for fixed effects	G	T	D	G × T	G × D	T × D	G × T × D
Numerator *df*	2	2	5	4	10		
Denominator *df*	53.1	96.6	259	96.6	259		
F test	16.25	13.10	9.46	2.59	2.09		
p Value	<0.01	<0.01	<0.01	0.04	0.03		

	Model-based contrasts related to group × time interaction					
Week 12/week 0	Est.	SE	*df*	*t* Value	*p* Value	95% CI
Within group						
Drug	0.43	0.09	98.0	5.05	<0.01	(0.27,0.61)
Placebo	0.16	0.11	98.3	1.43	0.15	(−0.06,0.38)
Control	0.06	0.09	95.3	0.66	0.51	(−0.12,0.24)
Between groups						
Drug vs placebo	0.28	0.14	98.2	1.96	0.05	(−0.01,0.56)
Drug vs control	0.38	0.13	96.6	2.98	<0.01	(0.12,0.63)
Placebo vs control	0.10	0.15	97.1	0.69	0.49	(−0.10,0.30)
Week 24/week 0						
Within groups						
Drug	0.35	0.09	98.0	4.08	<0.01	(0.18,0.53)
Placebo	0.31	0.11	98.3	2.78	<0.01	(0.09,0.53)
Control	0.15	0.09	95.3	1.61	0.11	(−0.03,0.33)
Between groups						
Drug vs placebo	0.04	0.14	98.2	0.30	0.76	(−0.24,0.33)
Drug vs control	0.21	0.13	96.6	1.62	0.11	(−0.05,0.46)
Placebo vs control	0.16	0.15	97.1	1.12	0.27	(−0.13,0.45)

G = group (drug, placebo, control); T = time (baseline/week 0, week 12, week 24); D = domain (motor, psychomotor, attention, memory, working memory, fluency); SE = standard error; *df* = degrees of freedom.
* Indicates exploration of interaction between variables.

pain severity (visual analog scale [VAS] = 8.1), there is a greater improvement in pain for the drug group compared with placebo ($p < 0.05$) that is sustained to week 24, whereas among those starting with a lower pain severity (VAS = 2.1), there is little difference between treatment groups.

In a post hoc analysis with time as a continuous variable, we examined whether there would be a treatment effect for the secondary outcome measures of current pain, fatigue, and physical functioning during the 24 weeks if baseline severity were not included as a covariate in the LMM analysis. No significant interactions (group and week) or main group effects were noted, except on one outcome measure (physical functioning, measured by PCS), for which there was a weak interaction between group and week ($p < 0.15$), such that improvement in physical functioning was greater across time for the ceftriaxone group compared with the placebo group, with the magnitude of improvement increasing to week 24.

On the rheumatologist assessment of joint pain (at rest and with movement), the treatment effect was not dependent on baseline severity, but there was a group-by-time interaction. There was no difference between drug and placebo at week 12 or at week 24 in improvement compared with baseline, whereas between weeks 12 and 24 the placebo-treated patients improved more than the drug group ($p = 0.052$). On measures of psychopathology and its effects (depression, anxiety, global symptoms, mental functioning), there were no differences between drug and placebo at weeks 12 or 24, although there was a transient treatment difference on the global psychopathology index at week 4 when patients with low baseline symptoms who had received the drug had less improvement than did patients with low baseline symptoms who had received the placebo.

Variables associated with outcome measures. Selected baseline variables were examined for interaction effects with treatment group on the cognitive and self-report physical outcomes. Likelihood of improvement with ceftriaxone vs placebo was not related to demographic variables, CSF values, or clinical history (amount of prior oral or IV antibiotic therapy; the interval since last antibiotic course). Interaction effects between baseline physical exam and treatment on outcome were noted. On joint exam, patients with more joints in pain at baseline had a preferential improvement with ceftriaxone on the measures of cognitive index at week 12 ($p = 0.06$) and at week 24 ($p = 0.04$), and on the self-report measures of fatigue ($p = 0.11$) and pain ($p = 0.07$) at week 24. On neurologic exam, patients with more areas of abnormality at baseline had a preferential improvement with ceftriaxone on the measure of memory at week 24 ($p = 0.11$) and on the self-report measures of fatigue at week 12 ($p = 0.06$) and week 24 ($p < 0.01$) and physical functioning as measured by PCS ($p = 0.09$) at week 24.

Adverse events. Five patients withdrew from the study because of adverse events: two because of thrombus (both on drug), one because of staphylococcal infection (on placebo), one because of an allergic reaction (on drug), and one because of worsening joint pain (on placebo) that required narcotic pain medication. Four patients remained in the study despite adverse events that required either early termination of study medication (three on drug; two with allergic reactions, and one with abdominal pain) or hospitalization (one on drug; cholecystectomy at week 16); for these patients, ratings at weeks 12 and 24 continued to be conducted without revealing treatment randomization. The adverse reactions of seven of these nine patients were thought likely to have been directly related to the study treatment (presence of a PICC line or medication), for a rate of treatment-related adverse events of 6 of 23 (26.1%) among patients given IV ceftriaxone and 1 of 14 (7.1%) among patients given IV placebo; all patients recovered fully.

Masking. Patients assigned to ceftriaxone did not differ from those assigned to placebo in their rate of guessing whether they had received active medication either at week 12 (68.4% vs 53.8%; $p = 0.40$) or at week 24 (75.0% vs 58.3%, $p = 0.32$). Analyses of covariance found no relationship to outcome of a patient's guess of medication vs placebo and the actual treatment assignment at week 12. At week 24, there were trends for patients who believed that they had received active medication to report less fatigue ($p = 0.08$) and less impairment in physical function ($p = 0.05$), but this main effect was independent of actual treatment assignment. Finally, patients who had severe side effects were not more likely to report a beneficial effect from ceftriaxone; indeed, there was a trend for patients with severe side effects to report worsened physical functioning at week 12.

Compliance. Compliance was excellent. Weekly notes indicate that patients completed all 70 doses, except for those who terminated early. Of 37 patients who began treatment, 30 completed the full 10-week course (17 on ceftriaxone; 13 on placebo). Among the seven who did not complete the full course, one person on placebo completed 58 doses, and among the six antibiotic noncompleters, the total numbers of completed doses were 5, 11, 19, 35, 54, and 58; patients with the latter three totals returned for week 12 assessments.

DISCUSSION

This placebo-controlled, double-masked trial tested the efficacy and safety of repeated IV antibiotic treatment in a sample of patients with posttreatment Lyme encephalopathy. Conservative inclusion criteria were used to attain high diagnostic confidence. More than half of the patients had prior courses of IV antibiotic therapy that exceeded the standard recommendations for neurologic Lyme disease. Although enrollment required objective memory deficits, the patients had generalized, mild to moderate cognitive deficits. They also had more sensory and joint abnormalities on physical exam and self-reports of marked pain, fatigue, and impaired physical functioning, replicating earlier findings.[4,28]

The primary result was that the three groups (ceftriaxone, placebo, health control) differed in cognitive improvement over time ($p = 0.04$), favoring ceftriaxone at week 12 but not at week 24. At week 12, the end point for efficacy selected a priori, patients given 10 weeks of IV ceftriaxone had better within-group and between-group improvement in cognition compared with the placebo group or healthy controls. This improvement was manifested broadly across several cognitive domains—not specific to the domain of memory. Benefits from ceftriaxone exceeded the benefits expected from retesting, both in the healthy controls and the placebo group. For the drug vs placebo comparison, the borderline p value of 0.053 reflects both the modest magnitude of cognitive improvement and the small sample size, and it indicates that this finding has a slightly

elevated risk of having occurred by chance: 5.3% vs 5%. On self-report measures, a benefit of ceftriaxone relative to placebo was observed at week 12 for physical functioning, current pain, and fatigue for those patients with greater severity of symptoms at baseline.

Durability of benefit was assessed at week 24 after patients had been off of all treatment for 14 weeks. At this time point, there was no difference among the three groups in cognitive improvement from baseline. Sustained improvement, however, was noted in physical functioning and current pain among patients with greater baseline impairment, suggesting that ceftriaxone may have both short- and long-term benefits for these symptoms. A post hoc analysis suggested that the ceftriaxone group's sustained improvement in physical functioning to week 24 could also be seen when baseline severity of impairment was not included as a covariate.

Ceftriaxone has both infection-independent neuroprotective and infection-dependent antimicrobial effects that could account for improvement in both primary and secondary measures. Ceftriaxone upregulates the expression of glutamate transporters on the astroglia of rat brains with neuroprotective effects[30]—presumably because of reduced extracellular glutamate, a potentially neurotoxic neurotransmitter. This could explain short-duration improvement in that continued exposure to ceftriaxone would be required for sustained upregulation of the glutamate transporter. Another explanation for the observed relapse is that the course of ceftriaxone may have killed some borrelia, but it exerted little effect on other organisms in sequestered sites.[31,32] There is one North American report of persistent *B burgdorferi* by culture after antibiotic therapy,[33] and there are several such European cases.[34-38] However, in our study, the baseline CSF specimens were PCR- and culture negative for *B burgdorferi*.

Few variables at baseline showed consistent associations with the primary or secondary outcome measures, perhaps because of inadequate sample size, which limits the power to detect interaction effects. However, the analysis suggests that the physical exam may be an important predictor variable of short- and long-term response, because patients with more painful joints or more areas of neurologic abnormality at baseline were more likely to benefit from ceftriaxone than placebo on various outcome measures.

We did not find evidence that unmasking contributed significantly to the positive results in this study, because patients in each treatment group did not differ in the rate of guessing assignment to ceftriaxone. Further, patients' guesses had no relation with treatment response at the primary outcome time point of week 12. At week 24, although patients' guesses of ceftriaxone were associated with greater improvement in physical functioning, this was true for both the drug and placebo groups; when only those who guessed ceftriaxone were included in the analysis, a nonsignificant pattern continued to be evident of greater improvement in the drug group compared with the placebo group, supporting a drug effect independent of guess. Third, the presence of severe side effects was not associated with a more favorable outcome on the primary or secondary measures at either week 12 or 24.

How do these findings compare with those of other placebo-controlled studies of posttreatment Lyme disease? In two trials,[28] 3 months of antibiotics conferred no greater benefit than did placebo on the primary SF-36 functional measure or the secondary outcome measure of cognition. Inability to detect a treatment effect may reflect a true failure of repeated antibiotic therapy or limitations of the study design (e.g., lack of severity standard for study enrollment).[28,39] In contrast, in a study of posttreatment Lyme disease for patients with at least moderate fatigue, improvement at 6 months on the Fatigue Severity Scale was noted among 64% of patients who received 1 month of IV ceftriaxone vs 18.5% who received IV placebo ($p < 0.001$).[29] Improvements in cognition or spinal fluid levels of *OspA* protein were not detected, but patients were not required to manifest impairment on either of these measures at study entry.[29] For post hoc comparison, we reanalyzed our data using the post-Lyme fatigue's study enrollment criteria, and we applied the same definition for response (change ≥ 0.7 on FSS). Our results were compatible: at 6 months, 66.7% of ceftriaxone-treated patients vs 25% of placebo-treated patients were responders (Fisher exact test, $p = 0.05$).

The strengths of this study were recruitment of a rigorously diagnosed patient sample, use of quantitative measures of cognition with multiple alternative forms, use of self-report instruments employed in other trials to facilitate comparison, inclusion of a healthy control group to account for practice effects, and the randomized, placebo-controlled design that included a discontinuation phase to test durability. Noteworthy is that the pattern of change and degree of cognitive improvement during the 24 weeks were nearly identical for the healthy volunteers and placebo-

treated patients; the healthy control group, therefore, served to increase the precision of the estimates of the treatment effect and to provide enhanced power for the overall analysis to detect treatment effects in the active drug group, thus reducing the risk of a type II error. The primary limitations of this study were its restrictive inclusion criteria (only 1% of screened patients were enrolled), the relatively small sample size, and the lack of posttreatment lumbar puncture or neurologic exam. Therefore, generalizability is uncertain to posttreatment Lyme patients without cognitive impairment or to seronegative patients with persistent symptoms.

Conclusions from this study are mixed. At the primary efficacy end point of week 12, IV ceftriaxone treatment resulted in greater improvement in cognition and, among the more impaired, in physical functioning, pain, and fatigue. Clinical significance, however, depends on long-term effects. Notable were the long-term benefits for the ceftriaxone group on physical functioning and pain among the more severely affected patients at baseline, because these are among the most troubling aspects of posttreatment Lyme disease.[28] However, our primary interest in this study was on cognition, for which the improvement was not sustained to week 24. Further, adverse effects attributed to IV ceftriaxone occurred in 26% of patients. Therefore, considering both the limited duration of cognitive improvement and the risks, 10 weeks of IV ceftriaxone and then 14 weeks of no antibiotic is not an effective strategy for sustained cognitive improvement. Although certain subgroups (patients with more joint or neurologic abnormalities) may experience long-term benefit from ceftriaxone, the predictor analyses were exploratory rather than hypothesis driven, and they require independent confirmation. Pending such confirmation, treatment strategies that are safer and more durable are needed.

ACKNOWLEDGMENT

National Institutes of Neurological Disorders and Stroke (Al Kerza-Kwiatecki, PhD, Michael Nunn, PhD), National Institute of Neurological Disorders and Stroke DSMB (Justin McArthur, MBBS, Andrew Pachner, MD, Thomas Marcotte, PhD, Jorge Benach, PhD, Roland Martin, MD, Bruce Barton, PhD), Columbia University research team (Megan Romano, Dexterie Clemente, MA, Tani Viera, Marcia Kimmeldorf, PhD), Irving Center for Clinical Research at Columbia University (Karen Marder, MD, Yakov Stern, PhD, Michael J. Taylor, PhD, Robert Heaton, PhD, Wendy Coy, PhD), Home Care Services, Roche Pharmaceuticals, participating private physicians (especially Emilia Eiras, MD, Andrea Gaito, MD, Kornelia Keszler, MD, and Kenneth Liegner, MD), community leaders who helped arrange screening clinics, Patricia Smith, Lyme Disease Association, Inc, Time for Lyme, Inc, National Research Fund for Tick-Borne Diseases, Phyllis Mervine, MEd, The Lyme Times, Medical Diagnostic Laboratories, University Hospital of Stony Brook, Mel Evans, Richard Tilton, PhD, Steven Schutzer, MD, Allen Steere, MD, and Mark Klempner, MD.

Received February 12, 2006. Accepted in final form June 26, 2007.

REFERENCES

1. Halperin JJ, Krupp LB, Golightly MG, Volkman DJ. Lyme borreliosis-associated encephalopathy. Neurology 1990;40:1340–1343.
2. Keilp JG, Corbera K, Slavov I, Taylor MJ, Sackeim HA, Fallon BA. WAIS-III and WMS-III performance in chronic Lyme disease. J Int Neuropsychol Soc 2006;12:119–129.
3. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. N Engl J Med 1990;323:1438–1444.
4. Fallon BA, Tager F, Fein L, et al. Repeated antibiotic treatment in chronic Lyme disease. J Spirochetal Tick-borne Dis 1999;6:117–122.
5. Berglund J, Stjernber L, Ornstein K, Tykesson-Joelsson K, Walter H. 5-y follow-up study of patients with neuroborreliosis. Scand J Infect Dis 2002;34:421–425.
6. Centers for Disease Control and Prevention (CDC). Case definitions for public health surveillance. MMWR Morb Mortal Wkly Rep 1990;39:19–21.
7. Centers for Disease Control and Prevention (CDC). Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep 1995;44:590–591.
8. Wechsler D. Wechsler Memory Scale Scale, 3rd ed. San Antonio: The Psychological Corporation; 1997.
9. Halperin JJ, Logigian EL, Finkel MF, Pearl RA. Practice parameters for the diagnosis of patients with nervous system Lyme borreliosis (Lyme disease). Neurology 1996;46:619–627.
10. Wormser GP, Nadelman RB, Dattwyler RJ, et al. Practice guidelines for the treatment of Lyme disease. The Infectious Diseases Society of America. Clin Infect Dis 2000;31(suppl 1):1–14.
11. Donta ST. Tetracycline therapy for chronic Lyme disease. Clin Infect Dis 1997:25(suppl 1):52–56.
12. Barona A, Reynolds C, Chastain R. A demographically based index of premorbid intelligence for the WAIS-R. J Consult Clin Psychol 1984;52:885–887.
13. Utti B. North American Adult Reading Test: age norms, reliability, and validity. J Clin Exp Neuropsychol 2002;24:1123–1137.
14. Sackeim HA, Keilp JG, Rush AJ, et al. The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression. Neuropsychiatry Neuropsychol Behav Neurol 2001;14:53–56.
15. Keilp JG, Sackeim H, Mann JJ. Correlates of trait impulsiveness in performance measures and neuropsychological tests. Psychiatry Res 2005;135:191–201.
16. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–1123.
17. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191–197.

18. Ware JE, Kosinski M, Keller SD. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston: The Health Institute; 1994.
19. Ware J, Kosinski M. SF-36, Manual for Users, Version 1. Boston: The Health Institute; 1994.
20. Beck A, Steer RA. Beck Depression Inventory Manual San Antonio: Psychological Corporation; 1987.
21. Zung W. A rating scale for anxiety disorders. Psychosomatics 1971;12:371–379.
22. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report. Br J Psychiatry 1976;1:280–289.
23. Diggle P, Heagerty P, Linag K-Y, Zeger S. Analysis of Longitudinal Data Oxford: Oxford University Press; 2002.
24. Little RJA, Rubin DB. Statistical Analysis with Missing Data, 2nd ed. Hoboken: Wiley & Sons, Inc; 2002.
25. Cary N. SAS/STAT V9. Chicago: SAS Institute, Inc.
26. Schwarz G. Estimating the dimension of a model. Ann Stat 1978;6:461–464.
27. Krupp LB, Masur D, Schwartz J, et al. Cognitive functioning in late Lyme borreliosis. Arch Neurol 1991;48: 1125–1129.
28. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med 2001;345:85–92.
29. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology 2003;60: 1923–1930.
30. Rothstein JD, Regan MR, Haenggeli C, et al. B-Lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature 2005;433:73–77.
31. Singh SK, Girschick J. Molecular survival strategies of the Lyme disease spirochete Borrelia burdorferi. Lancet Infect Dis 2004;4:575–583.
32. Malawista SE. Resolution of Lyme arthritis, acute or prolonged: a new look. Inflammation 2000;24:493–504.
33. Liegner KB, Duray P, Agricola M, et al. Lyme disease and the clinical spectrum of antibiotic responsive chronic meningoencephalomyelitides. J Spirochetal Tick-borne Dis 1997;4:61–73.
34. Schmidli J, Hunziker T, Moesli P, Schaad UB. Cultivation of Borrelia burgdorferi from joint fluid three months after treatment of facial palsy due to Lyme borreliosis. J Infect Dis 1988;158:905–906.
35. Pfister HW, Preac-Mursic V, Wilske B, Schielke E, Sorgel F, Einhaupl KM. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. J Infect Dis 1991;163:311–318.
36. Oksi J, Marjamaki M, Nikoskelainen J, Viljanen MK. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med 1999;31:225–232.
37. Haupl T, Hahn G, Rittig M, et al. Persistence of Borrelia burgdorferi in ligamentous tissue from a patient with chronic Lyme borreliosis. Arthritis Rheum 1993; 36:1621–1626.
38. Preac-Mursic V, Pfister HW, Spiegel H, et al. First isolation of Borrelia burgdorferi from an iris biopsy. J Clin Neuroophthalmol 1993;13:155–161.
39. Kaplan RF, Trevino RP, Johnson GM, et al. Cognitive function in post-treatment Lyme disease: do additional antibiotics help? Neurology 2003;60:1916–1922.
40. Cohen J. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. New York: Academic Press; 1988.

A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy

B. A. Fallon, J. G. Keilp, K. M. Corbera, et al.

Neurology 2008;70;992-1003 Published Online before print October 10, 2007
DOI 10.1212/01.WNL.0000284604.61160.2d