REVIEW ARTICLE

CURRENT CONCEPTS

A Critical Appraisal of "Chronic Lyme Disease"

Henry M. Feder, Jr., M.D., Barbara J.B. Johnson, Ph.D., Susan O'Connell, M.D., Eugene D. Shapiro, M.D., Allen C. Steere, M.D., Gary P. Wormser, M.D., and the Ad Hoc International Lyme Disease Group*

From the Departments of Family Medicine and Pediatrics, Connecticut Children's Medical Center, Hartford, and University of Connecticut Health Center, Farmington (H.M.F.); Microbiology Laboratory, Division of Vector-Borne Infectious Diseases, Centers for Diseases Control and Prevention, Fort Collins, CO (B.J.B.J.); Lyme Borreliosis Unit, Health Protection Agency Microbiology Laboratory, Southampton General Hospital, Southampton, United Kingdom (S.O.); Departments of Pediatrics and Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT (E.D.S.); Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston (A.C.S.); and the Division of Infectious Diseases, Department of Medicine, New York Medical College, Valhalla (G.P.W.) Address reprint requests to Dr. Feder at the Departments of Family Medicine and Pediatrics, University of Connecticut Health Center, Farmington, CT 06030, or at hfeder@nso2.uchc.edu.

*Other members of the Ad Hoc International Lyme Disease Group who were authors are listed in the Appendix.

N Engl J Med 2007;357:1422-30.

Lyme disease, the most common tick-borne infection in the northern hemisphere, is a serious public health problem. In North America, it is caused exclusively by *Borrelia burgdorferi* sensu stricto (hereafter referred to as *B. burgdorferi*), whereas in Europe it is caused by *B. afzelii*, *B. garinii*, *B. burgdorferi*, and occasionally by other species of borrelia.[1]

This complex infection has a number of objective manifestations, including a characteristic skin lesion called erythema migrans (the most common presentation of early Lyme disease), certain neurologic and cardiac manifestations, and pauciarticular arthritis (the most common presentation of late Lyme disease), all of which usually respond well to conventional antibiotic therapy.[2] Despite resolution of the objective manifestations of infection after antibiotic treatment, a minority of patients have fatigue, musculoskeletal pain, difficulties with concentration or short-term memory, or all of these symptoms. In this article, we refer to these usually mild and self-limiting subjective symptoms as "post–Lyme disease symptoms," and if they last longer than 6 months, we call them "post–Lyme disease syndrome."

The word "chronic" has been applied to Lyme disease in a wide variety of contexts and is sometimes used interchangeably with the preferred term "late Lyme disease." For example, in Europe, certain late neurologic manifestations of previously untreated or inadequately treated infection, such as borrelial encephalomyelitis or long-standing meningitis, have been referred to as "chronic neuroborreliosis" (Table 1).[1-3] In the United States, reports have described untreated patients with recurrent or persistent arthritis that lasts for up to several years, presumably because of active infection.[4] The focus of this review, however, is not the objective manifestations of late Lyme disease but rather the imprecisely defined condition referred to as "chronic Lyme disease." This term is used by a small number of practitioners (often self-designated as "Lyme-literate physicians") to describe patients whom they believe have persistent *B. burgdorferi* infection, a condition they suggest requires long-term antibiotic treatment and may even be incurable.[5] Although chronic Lyme disease clearly encompasses post–Lyme disease syndrome, it also includes a broad array of illnesses or symptom complexes for which there is no reproducible or convincing scientific evidence of any relationship to *B. burgdorferi* infection. Chronic Lyme disease is used in North America and increasingly in Europe as a diagnosis for patients with persistent pain, neurocognitive symptoms, fatigue, or all of these symptoms, with or without clinical or serologic evidence of previous early or late Lyme disease.

Table 1. Selected Late or Long-Term Manifestations of *Borrelia burgdorferi* Infection.*

Condition	Prevalence	Evidence of Active Infection	Comments
Lyme arthritis (recurrent or persistent swelling, usually of a large joint, especially the knee)	Reported in 60% of untreated U.S. patients with erythema migrans; recent prospective studies suggest that it occurs in ≤10% of patients with Lyme disease	Response to treatment in placebo-controlled trial; seropositivity for antibodies against *B. burgdorferi*; in untreated patients, a synovial-fluid specimen is frequently positive for *B. burgdorferi* DNA on PCR	Persistent joint swelling for months to a few years in about 10% of adults with Lyme arthritis, despite antibiotic therapy and negative PCR results in synovial-fluid and tissue specimens; may be autoimmune
Neurologic Lyme disease			
Lyme encephalopathy	Rare	Mild but objective cognitive abnormalities; response to antibiotics in open-label studies; sometimes accompanied by Lyme arthritis or peripheral neuropathy; seropositivity for antibodies against *B. burgdorferi*; CSF may be normal or have abnormalities such as an elevated protein level and intrathecal antibody production; cranial imaging nondiagnostic; PCR to detect *B. burgdorferi* DNA in CSF typically negative	Pathogenesis thought to be due to toxic or metabolic CNS dysfunction or to low-grade encephalitis; no firmly established diagnostic criteria
Peripheral neuropathy	Rare	Mild axonal peripheral neuropathy; response to antibiotics in open-label studies; seropositivity for antibodies against *B. burgdorferi*; CSF may be normal or have mild, nonspecific abnormalities	Often presents as mononeuritis multiplex
Encephalomyelitis	Extremely rare, with more cases in Europe than in the United States	Objective abnormalities on neurologic examination; CSF shows lymphocytic pleocytosis; response to antibiotics in open-label studies; abnormalities (e.g., CNS lesions) on MRI neuroimaging; seropositivity for antibodies against *B. burgdorferi*	Presents clinically with a progressive rather than a relapsing–remitting course; often referred to as "chronic neuroborreliosis" in European literature
Acrodermatitis chronica atrophicans	Extremely rare in the United States, but often reported in Europe; usually associated with long-standing *B. afzelii* infection	Objective and characteristic abnormalities on cutaneous and histologic examination of involved skin; skin may be culture- and PCR-positive; response to antibiotics in open-label studies; seropositivity for antibodies against *B. burgdorferi*	May be associated with a peripheral neuropathy localized to the involved arm or leg

* PCR denotes polymerase chain reaction, CSF cerebrospinal fluid, CNS central nervous system, and MRI magnetic resonance imaging.

CHRONIC LYME DISEASE

The diagnosis of chronic Lyme disease and its treatment differ substantively from the diagnosis and treatment of recognized infectious diseases. The diagnosis is often based solely on clinical judgment rather than on well-defined clinical criteria and validated laboratory studies, and it is often made regardless of whether patients have been in areas where Lyme disease is endemic.[6,7] Although proponents of the chronic Lyme disease diagnosis believe that patients are persistently infected with *B. burgdorferi*, they do not require objective clinical or laboratory evidence of infection as a diagnostic criterion.[5,8-10]

Several lines of reasoning are used to provide support for this diagnostic rationale. One is the unproven and very improbable assumption that chronic *B. burgdorferi* infection can occur in the absence of antibodies against *B. burgdorferi* in serum (Table 2). Negative results of serologic tests are often attributed to previous antibiotic therapy or to the theory that chronic infection with *B. burgdorferi* suppresses humoral immune responses;

Table 2. Laboratory Diagnosis of Lyme Disease and Chronic Lyme Disease in North America.*

Test	Technique	Use	Limitations	Putative Role in the Diagnosis of Chronic Lyme Disease†
Detection of antibodies against *Borrelia burgdorferi* in serum	Two-tier testing in which a positive result requires both a positive or equivocal ELISA or IFA and a positive immunoblot; positive results on an IgM immunoblot are generally useful only during the first few weeks after infection and should not be relied on thereafter because false positive results occur, and the IgG immunoblot is usually positive by about 1 mo after infection	Serum samples during acute or convalescent phase (2–6 weeks after sample from acute phase is obtained) should be positive by means of two-tier testing in untreated patients with Lyme disease; patients with erythema migrans, who are often seronegative at time of presentation, may not seroconvert if promptly and successfully treated with antibiotics; patients may remain seropositive after resolution of infection; seroprevalence may be high among residents of areas of highly endemic disease as a result of asymptomatic infection, which is believed to occur in approximately 10% of *B. burgdorferi* infections	Single-tier testing (either an ELISA or immunoblot alone) is less specific than two-tier testing; positive test results provide support for a clinical diagnosis, but in the absence of objective clinical features they have no proven diagnostic value; immunoblots should be interpreted with the use of the recommended evidence-based criteria‡; the use of other criteria may be associated with poor validity; testing should be performed when the pretest likelihood of infection is at least 20% — otherwise, the positive predictive value is too low to be helpful diagnostically	Seropositivity for antibodies against *B. burgdorferi* not considered essential; many patients with this diagnosis are seronegative or are seropositive only on testing in a "Lyme specialty laboratory" or when unvalidated criteria with poor specificity are used to interpret the immunoblot; diagnosis may be made on the basis of IgM seropositivity alone despite long duration of symptoms
Detection of antibodies against *B. burgdorferi* in CSF	Intrathecally produced antibodies are determined by testing simultaneously drawn samples of CSF and serum with the use of ELISA	Testing for intrathecal production of antibodies against *B. burgdorferi* may be helpful in the diagnosis of early neurologic Lyme disease	May be negative in neurologic Lyme disease in the United States; CSF antibodies to *B. burgdorferi* may persist for prolonged periods after antibiotic treatment; the specificity of positive results in seronegative patients is not well established in the United States	No convincing evidence that these patients have intrathecal production of antibodies against *B. burgdorferi*
Detection of *B. burgdorferi* DNA	PCR	Often positive in synovial-fluid samples from patients with Lyme arthritis and in skin-biopsy specimens from patients with erythema migrans and other cutaneous manifestations; may be positive in CSF in a minority of patients with neurologic Lyme disease	PCR testing of blood and urine specimens not well standardized and thus not recommended; false positive results may occur as a result of contamination by the laboratory performing the test; PCR cannot distinguish live from dead microorganisms	One study reported positive urine specimens on PCR testing, but amplicons not sequenced to confirm identity
Detection of *B. burgdorferi* by means of culture	Cultures established in Barbour–Stoenner–Kelly medium	Highest sensitivity in cutaneous infection; not routinely used clinically	Growth may not be detected for several weeks; most laboratories do not offer this test; false positive results are rare	Positive cultures of blood reported in one study, but results could not be confirmed by subsequent investigators
Urinary antigen test	Antigen-capture–inhibition ELISA	None	Assays thus far have been inaccurate	Often used diagnostically

* ELISA denotes enzyme-linked immunosorbent assay, IFA immunofluorescence assay, CSF cerebrospinal fluid, and PCR polymerase chain reaction.
† Other tests sometimes used to confirm chronic Lyme disease include dot blots and "reverse Western blots" for urinary antigens, immunofluorescence staining or fluorescence-activated cell sorting for cell wall–deficient or cystic forms of *B. burgdorferi*, lymphocyte transformation tests, and quantitative CD57 lymphocyte assays; none of these tests have been validated.
‡ Information is from the Centers for Disease Control and Prevention.[11]

neither theory is well supported by scientific data.[12-14] When physicians who diagnose chronic Lyme disease obtain laboratory tests to provide support for their diagnoses, they often rely heavily on "Lyme specialty laboratories." Such laboratories may perform unvalidated in-house tests that are not regulated by the Food and Drug Administration, or they may perform standard serologic tests interpreted with the use of criteria that are not evidence-based.[11,12,15-17]

Once the diagnosis of chronic Lyme disease is made, patients are commonly treated for months to years with multiple antimicrobial agents, some of which are inactive in vitro against *B. burgdorferi*.[2,5,18-20] Antibiotics may be prescribed either simultaneously or sequentially, and they are often administered parenterally. Occasionally, these patients are treated with unconventional and highly dangerous methods such as bismuth injections or deliberate inoculation of plasmodia to cause malaria.[2,21,22] No other spirochetal infection, including the neurologic complications of tertiary syphilis, is managed in an analogous fashion.[2,23] The duration of treatment commonly prescribed for chronic Lyme disease often far surpasses even the conventional 6-month course of therapy successfully used for most cases of tuberculosis.

CATEGORIES OF CHRONIC LYME DISEASE

Diagnoses of chronic Lyme disease appear to fall predominantly into one of four categories (Fig. 1).[8-10] Patients with category 1 disease do not have objective clinical manifestations or laboratory evidence of *B. burgdorferi* infection, and they receive a diagnosis on the basis of the presence of nonspecific symptoms such as fatigue, night sweats, sore throat, swollen glands, stiff neck, arthralgia, myalgia, palpitations, abdominal pain, nausea, diarrhea, sleep disturbance, poor concentration, irritability, depression, back pain, headache, and dizziness.[5] Nonspecific symptoms such as these are common, and some occur in more than 10% of the general population, regardless of whether Lyme disease is endemic in the area.[24,25]

Patients with category 2 disease have identifiable illnesses or syndromes other than Lyme disease. Such patients may or may not have a history of Lyme disease. They have received either a misdiagnosis or a diagnosis (e.g., multiple sclerosis) that they are reluctant to accept and have sought an alternative diagnosis from a physician willing to treat them for chronic Lyme disease.

Data from studies of patients who underwent reevaluation at academic medical centers suggest that the majority of patients presumed to have chronic Lyme disease have category 1 or 2 disease.[8-10] Since patients in these two categories do not have evidence of active infection with *B. burgdorferi*, the potential benefit of treating them with antibiotics, beyond a placebo effect, would be attributable to the antiinflammatory or other nonantimicrobial effects of antibiotics.[26] Antibiotic therapy in these patients is not warranted.

Patients with category 3 disease do not have a history of objective clinical findings that are consistent with Lyme disease, but their serum samples contain antibodies against *B. burgdorferi*, as determined by means of standardized assays that were ordered to investigate chronic, subjective symptoms of unknown cause.[27] Patients with disease in this category have at most only equivocal evidence of *B. burgdorferi* infection, since the predictive value of positive serologic results in this setting is low.[27,28] Although some clinicians would offer patients with category 3 disease an empirical trial of 2 to 4 weeks of an oral antibiotic, such patients should be told that the diagnosis is uncertain and that a benefit from treatment is unlikely.

Patients with category 4 disease have symptoms associated with post–Lyme disease syndrome.[29-31] In prospective studies of patients with erythema migrans, subjective symptoms of unknown cause were present 1 year or more after treatment in 0.5 to 13.1% of patients.[31] Whether this prevalence exceeds that of such symptoms in the general population is unknown, since none of these studies included a control group. A meta-analysis suggested that the prevalence of such symptoms exceeded that in control groups without Lyme disease, but this analysis relied on several retrospective studies in which the diagnosis and treatment of Lyme disease often did not meet current standards.[30,31]

TREATMENT OF POST–LYME DISEASE SYMPTOMS

Controlled treatment trials have been conducted only for patients with category 4 disease. Data from three double-blind, randomized, placebo-controlled trials have shown that there is substantial risk, with little or no benefit, associated with

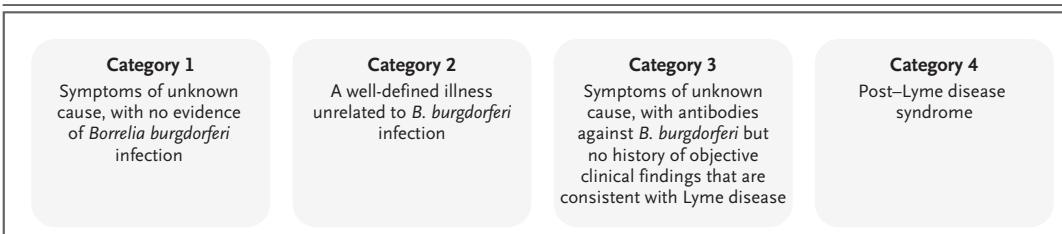

Figure 1. The Four Predominant Categories of Disease Associated with Chronic Lyme Disease.
Only patients with category 4 disease have post–Lyme disease symptoms.

additional antibiotic treatment for patients who have long-standing subjective symptoms after appropriate initial treatment for an episode of Lyme disease.[32-34]

One of these trials enrolled 78 patients who were seropositive for antibodies against *B. burgdorferi* at trial entry; a second trial enrolled 51 patients who were seronegative.[32] All patients had antecedent objective signs of Lyme disease, most often physician-diagnosed erythema migrans. Patients were treated either with a 1-month course of ceftriaxone administered intravenously, followed by 2 months of doxycycline given orally, or with identical-appearing intravenous and then oral placebos. Patients were assessed at enrollment and 3 months after completion of treatment with the use of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36). There were no significant differences in the scores between the patients in the antibiotic and placebo groups.

In a single-center trial conducted by Krupp et al., 55 patients with severe fatigue (as measured by an 11-item questionnaire) after treatment of well-documented Lyme disease underwent randomization to receive ceftriaxone or an identical-appearing placebo for 28 days.[33] The investigators reported a reduction in scores for fatigue severity in the ceftriaxone group that exceeded the reduction in the placebo group by 13 percentage points (i.e., a reduction of 22% vs. 9%; $P=0.01$) but no significant improvement in cognitive function. There was no significant difference between the groups with regard to the degree of improvement in reported health status on the basis of the SF-36 score. Patients in the ceftriaxone group were significantly more likely than those in the placebo group to identify their treatment assignment correctly at the end of therapy, raising a concern that masking was compromised and that a placebo effect may explain the greater improvement in scores for fatigue severity in the treated group.[33]

Antibiotic therapy can cause considerable harm to patients treated for chronic Lyme disease or post–Lyme disease symptoms.[2] Life-threatening anaphylaxis[33] and biliary complications requiring cholecystectomy[35] have occurred after ceftriaxone administration. Candidemia from infection of an intravenous catheter has resulted in death.[36] In an unpublished study in which 37 patients underwent randomization to receive 10 weeks of treatment with either ceftriaxone or placebo, about one fifth of the patients had serious adverse events, the majority of which were related to intravenous catheters.[37] In light of the risk of serious adverse events in their study, Krupp et al. concluded that "repeated courses of antibiotic treatment are not indicated for persistent symptoms following Lyme disease, including those related to fatigue and cognitive dysfunction."[33]

Eligibility criteria for two controlled trials stipulated that symptoms must be severe enough to interfere with the patient's ability to function.[32] Thus, the physical health status of the patients enrolled in these two studies was equivalent to that of patients with congestive heart failure or osteoarthritis.[32] This finding was preordained by the study design, but it has been incorrectly interpreted by some to indicate that patients with post–Lyme disease symptoms typically are severely disabled.

The investigators who conducted the controlled treatment trials had great difficulty finding patients who met the criteria for entry, despite intensive efforts that included both the notification and involvement of Lyme disease support groups and associations.[32,33] For two of the three studies, additional sites had to be engaged,[32] and the enrollment period had to be extended for all three studies.[32,33] To enroll 55 patients in one of the studies, investigators had to screen more than 500 people, most of whom were excluded because of the absence of a substantiated history of Lyme disease.[33]

This difficulty with enrollment appears to reflect the scarcity of persons with well-documented Lyme disease in whom clinically significant problems develop after conventional treatment.

Although anecdotal evidence and findings from uncontrolled studies have been used to provide support for long-term treatment of chronic Lyme disease,[18-20] a response to treatment alone is neither a reliable indicator that the diagnosis is accurate nor proof of an antimicrobial effect of treatment. Many patients with intermittent or self-limited symptoms may feel better over time as a result of the natural course of their condition, and controlled trials indicate that nearly 40% of patients with post–Lyme disease symptoms have a positive response to placebo.[32] In addition, the assessment of a change in symptoms may be confounded by antiinflammatory and other nonantimicrobial effects of antibiotics.[26] Furthermore, the published reports of uncontrolled trials of antibiotic treatment for chronic Lyme disease used poorly standardized case definitions and either undefined criteria for interpreting immunoblots or criteria that have subsequently been found to have very low specificity (approximately 60%).[38]

PERSISTENT *B. BURGDORFERI* INFECTION AND POST–LYME DISEASE SYMPTOMS

A report by Phillips and colleagues[39] is often cited to provide support for the hypothesis of persistent *B. burgdorferi* infection. They indicated that they detected *B. burgdorferi* in blood specimens from 43 of 47 patients who had received or were receiving prolonged antibiotic therapy for chronic Lyme disease (91%). Other investigators have been unable to reproduce these findings in patients with well-documented post–Lyme disease syndrome.[32,40-42] Moreover, Phillips and colleagues used a new culture medium that specifically included Detroit tap water; this medium was subsequently shown to be bactericidal for *B. burgdorferi*.[41] In contrast to the findings from their report,[39] *B. burgdorferi* could not be detected in any of 843 specimens of blood or cerebrospinal fluid, tested by means of either culture or polymerase chain reaction (PCR), from the 129 patients enrolled in two of the controlled treatment trials.[32,40] Moreover, there was no serologic evidence of tick-borne coinfections in the vast majority of patients.[32]

In another report, DNA of *B. burgdorferi* was detected by means of PCR in urine specimens from nearly three quarters of 97 patients who had received the diagnosis of chronic Lyme disease.[43] However, the authors did not sequence the amplicons to confirm that the DNA was from *B. burgdorferi*. Such a high rate of positive results among patients who had been treated extensively with antibiotics is unlikely when one considers that only 1 of 12 urine samples (8%) from untreated patients with erythema migrans was found to be positive in a careful evaluation of this technique's value as a diagnostic test.[44] Moreover, detection of bacterial DNA is not necessarily an indicator of either active infection or clinical disease.[45] The central question is not whether a few spirochetes might persist after antibiotic treatment, but whether clinical disease can be attributed to their presence.

It is highly unlikely that post–Lyme disease syndrome is a consequence of occult infection of the central nervous system. This conclusion is based on evidence such as the absence of inflammation in the cerebrospinal fluid,[32,33] negative results of both cultures and PCR assays for *B. burgdorferi* in the cerebrospinal fluid,[32,40] the absence of structural abnormalities of the brain parenchyma,[46] and normal neurologic function, with no effect of antibiotic therapy (as compared with placebo) on cognitive function.[33,34]

Additional evidence against the hypothesis that chronic symptoms are due to persistent infection is the fact that antibodies against *B. burgdorferi* in many of these patients are undetectable, which is inconsistent with the well-established immunogenicity of the spirochete's lipoproteins.[13,14,20,29,32,47] Patients in whom treatment for most infectious diseases, including syphilis, has failed typically have persistent or rising titers of antibodies because of ongoing B-cell stimulation by microbial antigens.[23]

The lack of convincing evidence for the persistence of *B. burgdorferi* in treated patients (Table 3) is not surprising.[2,20,23,24,29-33,40,47-49] The failure of treatment for bacterial infections typically occurs as a result of pathogens that either have or acquire resistance to antibiotics, difficulties in achieving sufficient concentrations of antibiotic at sites of infection, or impaired host-defense mechanisms.[2] None of these factors are generally applicable to infection with *B. burgdorferi.* Although *B. burgdorferi* can develop into cystlike forms in vitro under certain conditions that can be created in the laboratory,[50] there is no evidence that this phenomenon has any clinical relevance. *B. burgdorferi* may pen-

Table 3. Evidence against Active Infection in Patients with Subjective Symptoms Persisting for More Than 6 Months after Antibiotic Treatment for Lyme Disease.

Signs and symptoms
Absence of concomitant objective clinical signs of either disease or inflammation and no progression to objective signs or development of inflammation[29,32]
Similar symptoms common in persons who have never had Lyme disease[24,25,30,31,48]
Laboratory tests
Persistence of symptoms independently of persistent seropositivity[20,29,32,47]
Absence of either positive cultures or positive polymerase-chain-reaction results from clinical specimens[32,40]
Treatment
No substantive response to antibiotic therapy in controlled treatment trials[32-34]
No documented resistance of *Borrelia burgdorferi* to recommended antibiotics[2]
Absence of recognized risks for failure of antibiotic therapy; these include host immunodeficiency or an infection in which there is local ischemia, a foreign body (biofilm), a sequestrum, or an abscess[2]
Other evidence
Certain studies in animals[2]
Lack of precedent for the use of long-term antibiotic treatment in other spirochetal infections[23,49]

etrate cells in vitro, but there is no evidence that the organism may be sheltered from antibiotics during an intracellular phase and then disseminate and cause clinical relapse.[51,52] Indeed, the strategies used by *B. burgdorferi* to adapt to the vertebrate host and evade host defenses indicate an extracellular existence.[53]

ADVICE TO CLINICIANS

How should clinicians handle the referral of symptomatic patients who are purported to have chronic Lyme disease? The scientific evidence against the concept of chronic Lyme disease should be discussed and the patient should be advised about the risks of unnecessary antibiotic therapy. The patient should be thoroughly evaluated for medical conditions that could explain the symptoms. If a diagnosis for which there is a specific treatment cannot be made, the goal should be to provide emotional support and management of pain, fatigue, or other symptoms as required.[54-56] Explaining that there is no medication, such as an antibiotic, to cure the condition is one of the most difficult aspects of caring for such patients. Nevertheless, failure to do so in clear and empathetic language leaves the patient susceptible to those who would offer unproven and potentially dangerous therapies. Additional advice to clinicians is included in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

CHRONIC LYME DISEASE IN THE PUBLIC DOMAIN

Physicians and laypeople who believe in the existence of chronic Lyme disease have formed societies, created charitable foundations, started numerous support groups (even in locations in which *B. burgdorferi* infection is not endemic), and developed their own management guidelines.[5] Scientists who challenge the notion of chronic Lyme disease have been criticized severely.

The attorney general of Connecticut has begun an unprecedented antitrust investigation of the Infectious Diseases Society of America, which issued treatment guidelines for Lyme disease that do not support open-ended antibiotic treatment regimens.[2] In some states, legislation has been proposed to require insurance companies to pay for prolonged intravenous therapy to treat chronic Lyme disease. The media frequently disregard complex scientific data in favor of testimonials about patients suffering from purported chronic Lyme disease and may even question the competence of clinicians who are reluctant to diagnose chronic Lyme disease. All these factors have contributed to a great deal of public confusion with little appreciation of the serious harm caused to many patients who have received a misdiagnosis and have been inappropriately treated.

CONCLUSIONS

Chronic Lyme disease is the latest in a series of syndromes that have been postulated in an attempt to attribute medically unexplained symptoms to particular infections. Other examples that have now lost credibility are "chronic candida syndrome" and "chronic Epstein–Barr virus infection."[57,58] The assumption that chronic, subjective symptoms are caused by persistent infection with *B. burgdorferi* is not supported by carefully conducted laboratory studies or by controlled treatment trials. Chronic Lyme disease, which is equated with chronic *B. burgdorferi* infection, is a misnomer, and the use of prolonged, dangerous, and expensive antibiotic treatments for it is not warranted.[2]

Dr. Feder reports receiving lecture fees from Merck and serving as an expert witness in medical-malpractice cases related to Lyme disease. Dr. Johnson reports holding patents on diagnostic antigens for Lyme disease. Dr. O'Connell reports serving as an expert witness related to Lyme disease issues in civil and criminal cases in England. Dr. Shapiro reports serving as an expert witness in medical-malpractice cases related to Lyme disease, reviewing claims of disability related to Lyme disease for Metropolitan Life Insurance Company, and receiving speaker's fees from Merck and Sanofi-Aventis. Dr. Steere reports receiving a research grant from Viramed and fees from Novartis. Dr. Wormser reports receiving research grants related to Lyme disease from Immunetics, Bio-Rad, and Biopeptides and education grants from Merck and AstraZeneca to New York Medical College for visiting lecturers for infectious-disease grand rounds, being part owner of Diaspex (a company that is now inactive with no products or services), owning equity in Abbott, serving as an expert witness in a medical-malpractice case, and being retained in other medical-malpractice cases involving Lyme disease. He may become a consultant to Biopeptides. No other potential conflict of interest relevant to this article was reported.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

We thank Alex P. Butensky, Julie Chacko, Rachel Hart, and Lisa Giarratano for assistance.

APPENDIX

The following members of the Ad Hoc International Lyme Disease Group were also authors: *Gundersen Lutheran Medical Foundation, La Crosse, WI* — W.A. Agger; *National Microbiology Laboratory, Health Canada, Winnipeg, MB, Canada* — H. Artsob; *Johns Hopkins Medical Institutions, Baltimore* — P. Auwaerter, J.S. Dumler; *St. Luke's Hospital, Duluth, MN* — J.S. Bakken; *Yale University School of Medicine, New Haven, CT* — L.K. Bockenstedt, J. Green; *New York Medical College, Valhalla* — R.J. Dattwyler, J. Munoz, R.B. Nadelman, I. Schwartz; *Danbury Hospital, Danbury, CT* — T. Draper; *Johns Hopkins Medical Institutions, Crofton, MD* — E. McSweegan; *Atlantic Neuroscience Institute, Summit, NJ, and the New York University School of Medicine, New York* — J.J. Halperin; *Boston University School of Medicine and Boston Medical Center, Boston* — M.S. Klempner; *University of Connecticut School of Medicine and Connecticut Children's Medical Center, Farmington* — P.J. Krause; *Centers for Disease Control and Prevention, Fort Collins, CO* — P. Mead; *University of British Columbia, Vancouver, Canada* — M. Morshed; *University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, Piscataway* — R. Porwancher; *University of Connecticut Health Center, Farmington* — J.D. Radolf; *Maine Medical Center, Portland, ME* — R.P. Smith, Jr.; *Schneider Children's Hospital at North Shore, Manhasset, NY* — S. Sood; *Washington Hospital Center and Georgetown University Medical Center, Washington, DC* — A. Weinstein; *Wadsworth Center, New York State Department of Health, Albany* — S.J. Wong; and *Connecticut Children's Medical Center, University of Connecticut, Hartford* — L. Zemel.

REFERENCES

1. Steere AC. Lyme disease. N Engl J Med 2001;345:115-24.
2. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43:1089-134.
3. Stanek G, O'Connell S, Cimmino M, et al. European Union concerted action on risk assessment in Lyme borreliosis: clinical case definitions for Lyme borreliosis. Wien Klin Wochenschr 1996;108:741-7.
4. Steere AC, Schoen RT, Taylor E. The clinical evolution of Lyme arthritis. Ann Intern Med 1987;107:725-31.
5. Cameron D, Gaito A, Harris N, et al. Evidence-based guidelines for the management of Lyme disease. Expert Rev Anti Infect Ther 2004;2:Suppl 1:S1-S13.
6. Harvey WT, Salvato P. 'Lyme disease': ancient engine of an unrecognized borreliosis pandemic? Med Hypotheses 2003; 60:742-59.
7. Burdge DR, O'Hanlon DP. Experience of a referral center for patients with suspected Lyme disease in an area of nonendemicity: first 65 patients. Clin Infect Dis 1993;16:558-60.
8. Reid MC, Schoen RT, Evans J, Rosenberg JC, Horwitz RI. The consequences of overdiagnosis and overtreatment of Lyme disease: an observational study. Ann Intern Med 1998;128:354-62.
9. Steere AC, Taylor E, McHugh GL, Logigian EL. The overdiagnosis of Lyme disease. JAMA 1993;269:1812-26.
10. Sigal LH. Summary of the first 100 patients seen at a Lyme disease referral center. Am J Med 1990;88:577-81.
11. Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep 1995;44:590-1.
12. Wormser GP, Dattwyler RJ, Shapiro ED, et al. Single-dose prophylaxis against Lyme disease. Lancet Infect Dis 2007;7: 371-3.
13. Akin E, McHugh GL, Flavell RA, Fikrig E, Steere AC. The immunoglobulin (IgG) antibody response to OspA and OspB correlates with severe and prolonged arthritis and the IgG response to P35 correlates with mild and brief arthritis. Infect Immun 1999;67:173-81.
14. Dressler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. J Infect Dis 1993; 167:392-400.
15. Klempner MS, Schmid CH, Hu L, et al. Intralaboratory reliability of serologic and urine testing for Lyme disease. Am J Med 2001;110:217-9.
16. Notice to readers: caution regarding testing for Lyme disease. MMWR Morb Mortal Wkly Rep 2005;54:125-6.
17. The laboratory diagnosis of Lyme borreliosis: guidelines from the Canadian Public Health Laboratory Network. Can J Infect Dis Med Microbiol 2007;18:145-8.
18. Donta ST. Macrolide therapy of chronic Lyme disease. Med Sci Monit 2003;9: I-136–I-142.
19. *Idem.* Tetracycline therapy of chronic Lyme disease. Clin Infect Dis 1997;25: Suppl 1:S52-S56.
20. Fallon BA, Tager F, Fein L, et al. Repeated antibiotic treatment in chronic Lyme disease. J Spirochetal Tickborne Dis 1999; 5:94-102.
21. Food and Drug Administration. Warning on bismacine. FDA Consumer 2006; 40:5.
22. Imported malaria associated with malariotherapy of Lyme disease — New Jersey. MMWR Morb Mortal Wkly Rep 1990;39:873-5.
23. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep 2006;55(RR-11):1-94.
24. Wessely S. Chronic fatigue: symptoms and syndrome. Ann Intern Med 2001;134: 838-43.
25. Luo N, Johnson JA, Shaw JW, Feeny D, Coons SJ. Self-reported health status of the general adult U.S. population as assessed by the EQ-5D and Health Utilities Index. Med Care 2005;43:1078-86.
26. Nieman GF, Zerler BR. A role for the anti-inflammatory properties of tetracyclines in the prevention of acute lung injury. Curr Med Chem 2001;8:317-25.
27. Lightfoot RW Jr, Luft BJ, Rahn DW, et al. Empiric parenteral antibiotic treatment of patients with fibromyalgia and fatigue and a positive serologic test for Lyme disease: a cost-effectiveness analysis. Ann Intern Med 1993;119:503-9.
28. Tugwell P, Dennis DT, Weinstein A, et al. Laboratory evaluation in the diagnosis of Lyme disease. Ann Intern Med 1997; 127:1109-23.
29. Nowakowski J, Nadelman RB, Sell R, et al. Long-term follow-up of patients with

culture-confirmed Lyme disease. Am J Med 2003;115:91-6.
30. Cairns V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. Int J Epidemiol 2005; 34:1340-5.
31. Shapiro ED, Dattwyler R, Nadelman RB, Wormser GP. Response to meta-analysis of Lyme borreliosis symptoms. Int J Epidemiol 2005;34:1437-9.
32. 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.
33. 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: 1923-30.
34. Kaplan RF, Trevino RP, Johnson GP, et al. Cognitive function in post-treatment Lyme disease: do additional antibiotics help? Neurology 2003;60:1916-22.
35. Ettestad PJ, Campbell GL, Welbel SF, et al. Biliary complications in the treatment of unsubstantiated Lyme disease. J Infect Dis 1995;171:356-61.
36. Patel R, Grogg KL, Edwards WD, Wright AJ, Schwenk NM. Death from inappropriate therapy for Lyme disease. Clin Infect Dis 2000;31:1107-9.
37. Fallon BA, Sackheim HA, Keilp J, et al. Double-blind placebo-controlled retreatment with IV ceftriaxone for Lyme encephalopathy: clinical outcome. Presented at the 10th International Conference on Lyme Borreliosis and Other Tick-Borne Diseases, Vienna, Austria, September 11–15, 2005.
38. Wormser GP, Dattwyler RJ, Shapiro E, et al. Reply to Pollack, Donta, Wilson and Arnez. Clin Infect Dis 2007;44:1137-9.
39. Phillips SE, Mattman LH, Hulinská D, Moayad H. A proposal for the reliable culture of *Borrelia burgdorferi* from patients with chronic Lyme disease, even from those previously aggressively treated. Infection 1998;26:364-7.
40. Klempner MS. Controlled trials of antibiotic treatment in patients with post-treatment chronic Lyme disease. Vector Borne Zoonotic Dis 2002;2(4):255-63.
41. Marques AR, Stock F, Gill V. Evaluation of a new culture medium for *Borrelia burgdorferi.* J Clin Microbiol 2000;38:4239-41.
42. Tilton RC, Barden D, Sand M. Culture of *Borrelia burgdorferi.* J Clin Microbiol 2001; 39:2747.
43. Bayer ME, Zhang L, Bayer MH. *Borrelia burgdorferi* DNA in the urine of treated patients with chronic Lyme disease symptoms: a PCR study of 97 cases. Infection 1996;24:347-53.
44. Rauter C, Mueller M, Diterich I, et al. Critical evaluation of urine-based PCR assay for diagnosis of Lyme borreliosis. Clin Diagn Lab Immunol 2005;12:910-7.
45. Hellyer TJ, Fletcher TW, Bates JH, et al. Strand displacement amplification and the polymerase chain reaction for monitoring response to treatment in patients with pulmonary tuberculosis. J Infect Dis 1996;173:934-41.
46. Morgen K, Martin R, Stone RD, et al. FLAIR and magnetization transfer imaging of patients with post-treatment Lyme disease syndrome. Neurology 2001;57:1980-5.
47. Asch ES, Bujak DI, Weiss M, Peterson MG, Weinstein A. Lyme disease: an infectious and postinfectious syndrome. J Rheumatol 1994;21:454-61.
48. Sigal LH, Patella SJ. Lyme arthritis as the incorrect diagnosis in pediatric and adolescent fibromyalgia. Pediatrics 1992; 90:523-8.
49. Wormser GP. Lyme disease: insights into the use of antimicrobials for prevention and treatment in the context of experience with other spirochetal infections. Mt Sinai J Med 1995;62:188-95.
50. Alban PS, Johnson PW, Nelson DR. Serum-starvation-induced changes in protein synthesis and morphology of *Borrelia burgdorferi.* Microbiology 2000;146:119-27.
51. Livengood JA, Gilmore RD Jr. Invasion of human neuronal and glial cells by an infectious strain of *Borrelia burgdorferi.* Microbes Infect 2006;8:2832-40.
52. Pachner AR, Gelderblom H, Cadavid D. The rhesus model of Lyme neuroborreliosis. Immunol Rev 2001;183:186-204. [Erratum, Immunol Rev 2002;187:139.]
53. Pal U, Fikrig E. Adaptation of *Borrelia burgdorferi* in the vector and vertebrate host. Microbes Infect 2003;5:659-66.
54. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388-95.
55. Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. Lancet 2006; 367:346-55.
56. Richardson RD, Engel CC Jr. Evaluation and management of medically unexplained physical symptoms. Neurologist 2004;10:18-30.
57. Sigal LH, Hassett AL. Contributions of societal and geographical environments to "chronic Lyme disease": the psychopathogenesis and aporology of a new "medically unexplained symptoms" syndrome. Environ Health Perspect 2002;110: 607-11.
58. Renfro L, Feder HM Jr, Lane TJ, Manu P, Matthews DA. Yeast connection among 100 patients with chronic fatigue. Am J Med 1989;86:165-8.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Feder HM Jr, Johnson BJB, O'Connell S, et al. A critical appraisal of "chronic Lyme disease." N Engl J Med 2007;357:1422-30.

Advice to Clinicians Web Addendum

Clinicians who care for patients who have been diagnosed with chronic Lyme disease should carefully review the evidence on which the diagnosis was based, especially for patients who do not have post-Lyme disease syndrome but fall into categories 1-3 (as defined in the text). It is helpful to review symptoms, potential exposure to vector ticks and any laboratory evidence that may have been cited in support of the diagnosis. The nonspecific nature of the symptoms listed in reference 5 should be emphasized and their frequent occurrence in the general population discussed [27,28]. Potential exposure in an endemic area or a remote history of either a rash or an insect bite is not sufficient evidence to assume that a skin lesion was erythema migrans or that the "insect" bite was really the bite of an *Ixodes* tick, the vector of *B. burgdorferi*.

A sizeable proportion of patients with purported chronic Lyme disease will have received "positive" results from laboratories that utilized either unvalidated methods or unproven criteria to interpret the results; both lead to a high rate of false-positive results [15,38]. The poor reliability and the low positive predictive value of such findings should be indicated to patients who have been diagnosed in this fashion [15,28].

Many patients treated for chronic Lyme disease and the clinicians who prescribe their treatment regard an improvement in symptoms following antibiotic treatment as confirmation of the diagnosis. In addition to addressing possible placebo effects, it may be useful to explain that commonly used antibiotics, including tetracyclines, macrolides

and certain beta lactams, have numerous non-antimicrobial properties, including anti-inflammatory, immunomodulatory and neuroprotective effects [26; Ianaro A, Ialenti A, Maffia P, et al. Anti-inflammatory activity of macrolide antibiotics. J Pharmacol Exp Ther 2000;292:156-163; Rothstein JD, Patel S, Regan MR et al. B lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature 2005;433:73-77]. These agents may have temporary modifying effects on many disease processes, but all can cause potentially serious adverse effects as well. In addition, prolonged use of antibiotics will select for antibiotic-resistant bacteria in the patients being treated, which may also spread within the community.

Paradoxically, many patients treated for chronic Lyme disease and the clinicians who prescribe their treatment also interpret worsening of symptoms while being treated with antibiotics as confirmation of the diagnosis, since they believe this to be related to spirochetal killing, i.e., a Jarisch-Herxheimer reaction (or as “herxing” in the jargon frequently used). Some practitioners treating chronic Lyme disease assert that these reactions may occur at any time during the treatment course, despite evidence that these reactions are only seen in early disease and then are usually confined to the first 24 hours of treatment [2]. Making matters worse, reluctance to consider that the patient’s deteriorating state may instead be due to the natural history of the underlying condition that was not diagnosed or to a drug-related adverse event places the patient in jeopardy.

Most patients with medically unexplained symptoms who received a diagnosis of chronic Lyme disease will require emotional and psychological support in addition to symptomatic management. For example, many patients with post-Lyme disease syndrome fear that their symptoms are indicative of a chronic infection that may cause neurologic damage. These concerns should be openly addressed and the patients

reassured [32-34]. There is no substitute for sympathetic listening and explanation [Steere AC. A 58-year-old man with a diagnosis of chronic Lyme disease. JAMA 2002;288:1002-10].

Chronic Lyme disease shares many of the clinical features of functional somatic syndromes, especially the presence of diffuse nonspecific symptoms such as fatigue, muscle and joint pains and problems with memory and concentration, in the absence of objective evidence of tissue inflammation or damage. A collaborative approach between physician and patient is crucial to the goals of palliation of symptoms and rehabilitation, and the patient should be encouraged to take an active role in the treatment process [54-56; Barsky AJ, Borus JF. Functional somatic syndromes. Ann Intern Med 1999;130:910-921.].

Physicians in endemic areas have an opportunity and a responsibility to provide anticipatory counseling to every patient with Lyme disease whom they treat. It is to be expected that the patient will soon encounter inaccurate information about the prognosis from some members of their community or from the internet [Cooper JD, Feder HM Jr. Inaccurate information about Lyme disease on the internet. Pediatr Infect Dis J 2004;23:1105-08]. The physician should “arm” them with an explanation of: the antibiotic-responsive nature of this infection and its lack of persistence; the limited number of manifestations that do occur in Lyme disease; reliable sources of information [Sood SK Effective retrieval of Lyme disease information on the Web. Clin Infect Dis 2002;35:451-64]; and the high likelihood that they will hear otherwise when they share their diagnosis with friends. They should be informed that it is not rare for mild symptoms such as fatigue, musculoskeletal pain and/or perceived difficulties with memory to continue beyond the usual treatment duration of 14 days (range 10-28 days)

[2]. Retreatment with antibiotics does not accelerate the rate of resolution of these symptoms, which typically diminish and resolve over several weeks to several months [Oksi J, Nikoskelainen J, Hiekanen H, et al. Duration of antibiotic treatment in disseminated Lyme borreliosis: a double-blind, randomized, placebo-controlled, multicenter clinical study. Eur J Clin Microbiol Infect Dis 2007;June 22; Wormser GP, Ramanathan R, Nowakowski J, et al. Duration of antibiotic therapy for early Lyme disease. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2003;138:697-704; Dattwyler RJ, Wormser GP, Rush TJ, et al. A comparison of two treatment regimens of ceftriaxone in late Lyme disease. Wien Klin Wochenschr 2005;117:393-7; Wormser GP. Clinical practice. Early Lyme disease. N Engl J Med 2006;354:2794-801.] Patients should be instructed to return to the physician promptly if objective signs develop, such as joint swelling, recurrent skin rash, weakness of facial or other muscles, or severe headache. Such an anticipatory approach provides a positive therapeutic boost to the patient who is often anxious about receiving the diagnosis of Lyme disease, and may help to prevent the spurious diagnosis of chronic Lyme disease.