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.