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Lyme disease: a turning point

'...the medical community should keep an open mind regarding treatment options for Lyme disease and not jump to conclusions based on a solitary study with poor generalizability.'

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Lyme disease is one of the most controversial illnesses in the history of medicine [1,2]. Over the past decade, two opposing camps have emerged in the controversy over this tick-borne illness. One camp is represented by the Infectious Diseases Society of America (IDSA), which maintains that Lyme disease is a rare illness localized to well-defined areas of the world. According to the IDSA, the disease is 'hard to catch and easy to cure' because the infection is rarely encountered, easily diagnosed in its early stage by means of accurate commercial laboratory tests and effectively treated with a short course of antibiotics over 2–4 weeks. Chronic infection with the Lyme spirochete, *Borrelia burgdorferi*, is rare or nonexistent [3].

The opposing camp is represented by the International Lyme and Associated Diseases Society (ILADS), which argues that Lyme disease is not rare and, because its spread is facilitated by rodents, deer and birds, it can be found in an unpredictable distribution around the world accompanied by other tick-borne coinfections that may complicate the clinical picture. According to the ILADS, tick bites often go unnoticed and commercial laboratory testing for Lyme disease is inaccurate [1,4]. Consequently, the disease is often not recognized and may persist in a large number of patients, requiring prolonged antibiotic therapy to eradicate persistent infection with the evasive Lyme spirochete [1,4].

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The battle over chronic Lyme disease has taken some unprecedented turns. As of 2007, more than 19,000 scientific articles about tick-borne diseases have been published, and the dichotomy between basic science studies and clinical research articles is striking: while basic science studies continue to highlight the invasiveness and elusiveness of *B. burgdorferi* in culture systems and animal models, clinical research articles adhere to the dogma that *B. burgdorferi* produces a limited infection that is eradicated easily [5,6]. Patients with persistent symptoms are labeled as having 'post-Lyme syndrome', hypothesized to be an autoimmune response to the previously eradicated infection. To date, attempts to elucidate the autoimmune mechanism of post-Lyme syndrome have been unsuccessful [7,8].

While IDSA followers have embraced the post-Lyme syndrome concept and foresworn long-term antibiotic treatment, followers of the ILADS have continued to use antibiotics to treat persistently symptomatic Lyme patients for chronic infection with *B. burgdorferi* and coinfecting tick-borne agents. They cite animal studies that demonstrate persistent infection by a complex organism, as well as numerous clinical reports that document failure of the standard 2–4 weeks of antibiotic therapy recommended by the IDSA [1,9–12]. The controversy came to a head in November 2006 when the IDSA released new guidelines severely limiting treatment options for patients with persistent Lyme symptoms [3]. The guidelines were so restrictive that the Attorney General of Connecticut (USA) initiated an unprecedented investigation into possible antitrust violations by the IDSA, the dominant infectious disease society in the USA, in its formulation of the guidelines [13,101].

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To support its restrictive stance on Lyme disease, the IDSA cites a study by Klempner and colleagues published in the *New England Journal of Medicine* in 2001 [14]. Sponsored by the US NIH, the trial examined a well-defined cohort of patients with persistent symptoms of Lyme disease despite treatment with standard antibiotic therapy. The patients were randomized to receive either placebo or 1 month of intravenous ceftriaxone followed by 2 months of oral doxycycline. Treatment was administered in a blinded fashion and response to treatment was evaluated with a validated quality-of-life outcome tool in an intent-to-treat analysis. The conclusion of this randomized, controlled trial was that patients who received 90 days of antibiotic therapy were no more likely to improve than patients who received placebo. In fact, 60% of patients in the study either stayed the same or became worse, regardless of treatment.

The results of this investigation were interpreted as showing that long-term antibiotic therapy is ineffective for patients with persistent symptoms of Lyme disease [15,16]. Owing to the prestigious nature of the study sponsor and publisher, this interpretation was circulated widely in the medical literature and the lay press, and was immediately adopted by insurance companies, who used the study results to deny antibiotic therapy beyond the 2–4-week IDSA limit to patients with chronic Lyme disease. As a result of the IDSA's promotion of the study conclusions, chronic Lyme disease ceased to be a treatable infection in the eyes of the medical community. Physicians who continued to treat beyond the IDSA limit risked medical board sanctions or medical license revocation based on this solitary study [11].

More than 5 years after publication of the Klempner article, the 'over-reaching impact' of the study has finally been challenged. Cameron examined the generalizability of the Klempner study findings in terms of the patient cohort, the treatment regimen and subsequent studies of prolonged antibiotic therapy in chronic Lyme disease [17]. Patients in the study cohort had been sick for an average of 4.7 years and had been treated with an average of three courses of antibiotics, making this a 'retreatment' study of patients who had already failed similar therapy. Furthermore, based on the health-related quality-of-life scale that was used, the treatment regimen was inadequate for the degree of functional compromise in these patients in terms of intravenous antibiotic duration and oral antibiotic dose. Cameron concluded that the study represents a 'too-little too-late' approach to a highly selected, extensively treated patient group that differs significantly from more typical chronic Lyme patients who are either untreated or undertreated. Based on the lack of generalizability of the study results, the blanket interpretation that long-term antibiotics are ineffective for chronic Lyme disease is invalid [17].

Subsequent randomized, placebo-controlled trials of antibiotic treatment in chronic Lyme disease have failed to support the conclusions of the Klempner trial (TABLE 1). Krupp *et al*. showed that 1 month of intravenous ceftriaxone improved the primary outcome measure of fatigue in a cohort of chronic Lyme patients [18]. For the other two primary outcome measures, cognitive function remained unchanged and borrelial antigen persisted in cerebrospinal fluid in a subset of patients after this relatively short treatment course (1 vs 3 months in the other placebo-controlled trials described here). Of interest, patients who had not received previous intravenous antibiotic therapy did significantly better than controls in terms of improvement in fatigue (69 vs 0% improvement; $p < 0.01$). This observation underscores the significance of prior treatment failure and the poor generalizability of the Klempner trial. Three cases of life-threatening sepsis occurred in the placebo group (11%) versus none in the ceftriaxone group (0%). This finding demonstrates the relative safety of indwelling

Table 1. Placebo-controlled trials of antibiotic treatment in chronic Lyme disease.

Study	Treatment	Results	Comment	Ref.
Klempner *et al*. (2001)	Ceftriaxone iv. for 4 weeks, then oral doxycycline for 2 months vs placebo	No improvement in fatigue or quality of life	Study criticized because subjects had been sick for an average of 4.7 years and had already failed similar treatment. Treatment regimen inadequate for degree of functional impairment	[14]
Krupp *et al*. (2003)	Ceftriaxone iv. for 4 weeks vs placebo	Significant improvement in fatigue noted in 64% of treatment group vs 19% of controls. No improvement in cognition	Exact duration of illness not stated (≤6 months). Relatively short treatment. Previously untreated patients did significantly better than controls in terms of fatigue improvement (69 vs 0%; $p < 0.01$)	[18]
Fallon *et al*. (2005)	Ceftriaxone iv. for 10 weeks vs placebo	Significant improvement in cognitive and physical functioning at 12 weeks in treatment group vs controls	Improvement in physical functioning but not cognitive functioning sustained in treatment group at 24 weeks	[20]
Cameron (2005)	Oral amoxicillin for 3 months vs placebo	Significant improvement in cognitive and physical functioning in treatment group vs controls	Treatment successful in two-thirds of patients with best initial quality of life but failed in a third of patients with worst initial quality of life	[22]

iv.: Intravenous.

catheters when antibiotic therapy is administered through these catheters [19] [STRICKER RB, UNPUBLISHED DATA]. Conversely, the risks of placebo treatment with these catheters may limit future controlled trials of long-term therapy in chronic Lyme disease.

In two additional studies, Fallon *et al*. showed that retreatment with 10 weeks of intravenous ceftriaxone improved cognitive and physical function in chronic Lyme patients [20]. Although improvement in physical functioning was sustained for 14 weeks after treatment cessation, cognitive improvement was not. The investigators employed a highly sensitive testing system to define the cognitive deficits in their patients [21]. Cameron showed that 90 days of oral amoxicillin improved quality of life in a similar group of patients [22]. In this study, patients with the best initial quality of life did significantly better with retreatment than patients with the worst initial quality of life. Cameron noted that patients with the best quality of life were significantly different from patients in the Klempner trial in terms of baseline level of dysfunction and treatment failure rate [22]. In a subsequent analysis, Cameron found that poor quality of life was associated with delay of initial antibiotic treatment, a variable that was not examined in the Klempner trial [23]. Taken as a whole, these studies support the conclusion that longer antibiotic therapy is effective in subsets of patients with chronic Lyme disease, and that adoption of the opposite interpretation based on the Klempner study is premature.

In the absence of consensus regarding the diagnosis and treatment of Lyme disease, the battle will continue over appropriate treatment of patients with persistent symptoms of this tick-borne illness [24]. It is helpful to recall that *B. burgdorferi* shares certain pathophysiological features with mycobacterial and other chronic infections, including secretion of autoinducer enzymes designed to resuscitate dormant organisms [25], signaling via the same cell receptors [26] and induction of immunosuppressive factors [10,27–29]. Furthermore, chronic infection with these organisms may require prolonged antibiotic therapy (6–36 months), and the risks of long-term treatment are considered justifiable in those situations [24]. The lesson here is that the medical community should keep an open mind regarding treatment options for Lyme disease and not jump to conclusions based on a solitary study with poor generalizability.

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