

## Challenge to the Recommendation Regarding Post-treatment Lyme Disease Symptoms

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This challenge is to Recommendation #2 on page 1120, regarding post-treatment symptoms of Lyme disease; the recommendation states: *“To date, there is no convincing biologic evidence for the existence of symptomatic chronic B. burgdorferi infection among patients after receipt of recommended treatment regimens for Lyme disease. Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (>6 months) subjective symptoms after administration of recommended treatment regimens for Lyme disease (E-I).”*<sup>1</sup>

The persistence of symptoms following antibiotic treatment for Lyme disease has vexed researchers, clinicians and patients ever since such therapy was found to be curative for some. In their 1983 paper, Steere et al. noted that 50% of their patients experienced symptoms post-treatment. *“These complications consisted primarily of recurrent episodes of headache, migratory musculoskeletal pain, or lethargy that were often reminiscent of their initial symptoms but generally milder.”*<sup>2</sup> Subsequent researchers have also reported the existence of post-treatment symptoms.<sup>3-14</sup>

Persistent symptoms may be observed after treatment for any stage of the illness.<sup>2-14</sup> In patients with post-treatment symptoms, the initial response to antibiotics is variable. Symptoms may persist with or without some improvement, completely resolve then recur, new Lyme disease symptoms may develop after, and despite, treatment or a combination of these outcomes may be noted. There appears to be a positive correlation between the occurrence of post-treatment symptoms and the initial severity of the illness, the duration of symptoms prior to treatment initiation and treatment of the infection in its later stages.<sup>2,9,10</sup>

Post-treatment symptoms have been known to slowly resolve over time in some patients.<sup>8</sup> The guidelines suggest that this improvement occurs as the inflammatory process associated with the illness recedes once the infection has been cleared. While this hypothesis is attractive in its simplicity, it fails to explain the chronic nature of the symptoms that many patients experience. Several studies have documented that patients may remain symptomatic many years post-treatment, a time course incompatible with a resolving post-infectious inflammatory process.<sup>3,4,11,12</sup>

What is unknown is the true extent of this phenomenon. While the 2006 IDSA guidelines state on page 1114 that *“a minority of patients continue to report signs or symptoms”* after conventional treatment for Lyme disease, there is no attempt to quantify the size of this patient subgroup. There is data from retrospective and prospective studies suggesting that this minority group may be fairly large. In 1994, Asch et al. reported a retrospective review of 215 patients with definite Lyme disease (patients had to meet the 1990 CDC surveillance case definition and test positively for Lyme disease during their illness).<sup>3</sup> *“Only 82 (38%) were asymptomatic at followup.”* A 1999 retrospective study by Shadick et al. also demonstrated significant post-

treatment symptomatology.<sup>4</sup> “Sixty-seven case-patients (36%) reported symptoms of Lyme disease at study evaluation despite receiving previous treatment.” A more recent prospective study of early Lyme disease by Wormser et al demonstrated that at their 12 month re-evaluation, 17% of the patients in the 20 day doxycycline arm had incomplete resolution of their symptoms or had developed symptoms compatible with late Lyme disease.<sup>8</sup> Another 32% of patients were unevaluable; thus, the potential for an even higher rate of post-treatment symptoms exists. Table 1 lists treatment outcomes from other prospective treatment trials.

Table 1  
Treatment outcomes in Selected Treatment trials

Study	Disease stage	Patients	Treatment	Follow-up Period	Asymptomatic N, (%)	Persistent or new symptoms of Lyme disease	Unevaluable
Nadelman	EM	45	Doxycycline 100mg TID for 20 days	12 months	29 (64%) <sup>a</sup>	9 (20%)	7 (16%)
Lugar	EM	89	Doxycycline 100mg TID for 20 days	12 months	48 (54%) <sup>a</sup>	5 (6%)	36 (40%)
Logigian 1990	Late neurologic	27	Ceftriaxone 2gm qd for 14 days	6 months	None <sup>b</sup>	All (100%)	NA
Logigian 1999	Late neurologic	18	Ceftriaxone 2gm qd for 30 days	12-24 months	7 (39%) <sup>c</sup>	11, (61%)	NA

<sup>a</sup> No signs or symptoms of late disease throughout follow-up period

<sup>b</sup> Per authors' description of outcomes: improvement vs. relapse vs. no change

<sup>c</sup> Patients self-rating that they were “back to normal”; 1 patient retreated at 8 months, asymptomatic at final follow-up

Individual post-treatment symptoms may be nonspecific and relatively common. The guidelines note this and suggest that the symptoms in question are not related to the infection preceding their onset but simply reflect “background” symptoms routinely encountered in the general population. The logic here is problematic. First, following successful treatment, one would expect patients to return to their pre-morbid health status; that many do not suggests a causal relationship between the infection and the subsequent symptoms. Second, the timing of symptom onset, either with the initial infection or shortly thereafter, does not lend itself to being a chance event. Third, the background rates cited in the guidelines may not be directly applicable to the cohort with post-treatment symptoms. For example, in the cited 2003 National Health Interview Survey, physician diagnosed arthritis was present in only 7.8% of respondents in the 18-44 year old age group.<sup>15</sup> The mean age of patients in the study by Asch was 38.9 years yet 41% of the patients had arthritis;<sup>3</sup> a frequency 5 times higher than that seen in the national survey. Fourth, post-treatment symptoms usually occur in clusters; few would seriously suggest that an isolated, nonspecific, post-treatment symptom is definitive of post-treatment Lyme disease. Rather, it is a clustering of such symptoms which raises the possibility. Thus, the frequency of individual symptoms is less important than the frequency of symptom clusters in the general population. For example, in the 18-44 year old age group, arthritis and fatigue would be expected in 1.6 – 2.3% (7.8 x 20-30%) of the general population while in the Asch et al. study, 31% of the patients with post-treatment symptoms reported having both conditions.<sup>3</sup>

The lack of post-treatment physical findings is mentioned. This is not surprising; multiple researchers have commented on the fact that findings on physical exam are often limited prior to treatment.<sup>16,17</sup>

Having established the existence of post-treatment Lyme disease symptoms and their likely relationship to the original infection, the clinical significance of these symptoms warrants consideration. The impact of post-treatment symptoms on patients' lives has been documented by multiple investigators. Various quality of life indicators have been used as tools to measure this impact. In the study by Klemmner et al., baseline data on the SF-36 suggested that patients had physical functioning consistent with that seen in congested heart failure.<sup>11</sup> Patients in the study by Krupp et al. had profound fatigue as measured by the FSS-11.<sup>12</sup> Fallon et al. found that patients reported pain consistent with post-operative pain.<sup>13</sup> In each of these studies, the patient groups had physical functioning/fatigue/pain well in excess of that seen in age-matched control groups. Therefore, it is incorrect to assert that the symptoms seen in post-treatment Lyme disease are "merely the aches and pains of daily living".

Determining the pathophysiologic mechanisms responsible for the occurrence of post-treatment symptoms has not been accomplished; several theories exist. These include the presence of other, untreated infections, Lyme disease-triggered conditions, permanent tissue damage, auto-immune phenomenon, persistent infection and post-infectious inflammatory states (previously discussed).

The guidelines hypothesize that post-treatment symptoms are potentially indicative of other illnesses or infections. It is wise to evaluate patients with post-treatment symptoms for other tick-borne diseases as patients with Lyme disease can be co-infected and there is significant symptom overlap between these various infections and Lyme disease. It is less likely that post-treatment symptoms represent newly developed cases of fibromyalgia. While there may be similarity between the two entities, the patterns of physical symptoms and the results of neuropsychiatric testing differ between patients with fibromyalgia and those with post-treatment Lyme disease symptoms.<sup>4,14,18</sup>

Another hypothesis is that post-treatment symptoms represent permanent damage. Studies to demonstrate the permanent nature of these symptoms have not been done. For example, in the paper by Clark et al. (cited as supporting evidence for this theory) the duration of the various antibiotic therapies used in the patients with facial nerve palsy was not stated nor was it disclosed if those with persisting deficits were given an alternative course of therapy.<sup>19</sup> Thus, it is unknown if the post-treatment weakness was truly permanent or merely unresponsive to the treatment administered.

Persistent symptomatology and/or findings due to permanent damage from an eradicated infection would be expected to remain fairly stable. However, the treatment trials for late neurologic Lyme disease noted that several patients, appropriately treated for early disease, had objective evidence of disease progression. *"In addition, more than half had previously received antibiotic therapy thought to be appropriate for their stage of disease and still had progression*

*of the illness.*”<sup>9</sup> Treatment, and even subsequent retreatment, for late disease produced improvement in some patients; under these circumstances, the positive response to antibiotic therapy makes the permanent damage hypothesis untenable.<sup>9,10,21</sup>

The auto-immune hypothesis dates back to at least 1980, prior to the discovery of *B. burgdorferi*. In a paper from that year, Steere et al stated: “We believe that the later manifestations of the disease – neurologic, cardiac, and joint – are immune mediated.”<sup>21</sup> This theory remains unproven; studies to date have failed to identify auto-immune markers that would explain post-treatment symptoms.<sup>22</sup>

Persistent infection is another potential explanation for ongoing post-treatment symptoms. Please see paper by Phillips for a detailed discussion of the microbiologic facts, animal studies and human case reports which support this hypothesis. As mentioned earlier, additional antibiotic treatment produced demonstrable improvements in some patients. Symptom relapse followed by antibiotic therapy and symptom improvement offers indirect evidence of a potential infectious cause.<sup>10</sup> While it is true that antibiotics have anti-inflammatory properties, it is difficult to envision them working solely through this mechanism, particularly if the use of other, more traditional anti-inflammatory agents, is ineffective in ameliorating non-painful post-treatment symptoms.

As discussed in the paper by Phillips, the guidelines ignore or discount evidence from the literature supporting the theory of persistent infection. The principle argument offered in the guidelines against persistent infection appears to be based on the retreatment trials of Klemmner and Krupp. At its most basic level, this argument suggests that failure to achieve an antibiotic treatment response in these groups proves that bacterial persistence is not the etiology underlying post-treatment symptoms in these patients. In recommending against re-treatment, the guidelines generalize these outcomes to all patients with post-treatment symptoms and all potential antibiotic regimens. Detailed rebuttals to this argument can be found in the statistics paper by Tao Liu, PhD, Allison DeLong, MS and Barbara Blossom, BA, the paper by Green and the previously mentioned paper by Phillips; all part of the ILADS submission. It is interesting to note that Klemmner and Krupp both relied on subjective data (measurement of patient reported symptoms via clinical tools, the SF-36 and FSS-11) to reach their conclusions.<sup>11,12</sup> An additional retreatment study by Fallon et al. employed objective and subjective measures to evaluate treatment response.<sup>13</sup> The response to treatment in these trials was mixed,<sup>11-13</sup> possibly reflecting the heterogeneity of the patient population under study.

All of the retreatment trials used ceftriaxone as the primary antibiotic agent even though many patients in the trials had already received, and failed to improve with that particular antibiotic.<sup>11-13</sup> Comparative antibiotic trials, using a different single agent or combinations of agents have not been done; nor have host factors been adequately investigated. Given the biologic complexity of *Borrelia burgdorferi*, specifically its intracellular and pleomorphic properties and its inter-action with human hosts (see paper by Maloney on agents not recommended for use in Lyme disease), it is premature to dismiss the persistent infection theory.

Discovering the correct etiology(s) of post-treatment Lyme disease symptoms is crucial. Lacking that information, appropriate treatment strategies cannot be formulated. Antibiotics and

palliative medications (narcotic and non-narcotic pain medications, muscle relaxants, sleep medications, anti-depressants and cognitive agents for concentration and memory disorders) have associated risks, risks which increase as the number of agents employed in the treatment protocol grows. Treating the wrong etiology exposes patients to risks while offering little chance of long-term gains. Failure to treat an underlying auto-immune process can cause significant morbidity but the scientific evidence to date does not support that theory. Failure to treat an indolent infection allows the bacteria to become more deeply entrenched, favoring increased debilities and a decreased potential for future bacterial eradication.<sup>23</sup>

Patient considerations and preferences must be discussed and weighed during the informed consent process. When there is uncertainty regarding the relative merits of individual treatment strategies, patient utilities become a more critical factor in the decision.<sup>24-26</sup> Such is the case in treating patients with post-treatment symptoms, where patient morbidity is significant and treatment trials have been limited in both number and scope of employed agents.<sup>11-13</sup> While the guidelines stress the risks attendant with intravenous antibiotics, this may be a moot point. Oral doxycycline has been successfully used to treat some later manifestations of the illness;<sup>27</sup> it would not be difficult to construct combination oral regimens using doxycycline as the foundation while adding different classes of oral agents to eliminate other of the bacteria's survival mechanisms. In recommending strongly against antibiotic retreatment, despite the acknowledged limitations of the scientific understanding of this stage of illness, the guidelines inappropriately deny patients and treating physicians a legitimate avenue towards treatment success.<sup>25</sup>

The semantics involved in identifying patients who remain symptomatic is important. Post-Lyme syndrome implies that there is definitive evidence that the initial bacterial infection has been cleared. Available testing modalities cannot provide such evidence. Nor is there a biologic marker for the "post-Lyme syndrome". Rather, the syndrome seems to be defined based on the failure of a single but variable antibiotic to eliminate Lyme disease-related symptoms in any given individual.

Post-treatment Lyme disease symptoms exist as an extension of the initial bacterial infection. While their etiology remains unknown, the negative effects exerted on patients' quality of life are well documented and may be profound.<sup>3,4,11,13</sup> Until future research resolves questions regarding the origin and elimination of such symptoms, patients with post-treatment Lyme disease symptoms and their physicians should be encouraged to actively weigh potential treatment options in their pursuit of improved health.

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