Late Stage Lyme Disease: Arguments for an Individualized Approach

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The purpose of this review is to provide arguments in favor of a more liberal approach to the treatment of late stage Lyme disease, specifically the use of intravenous antibiotics for extended periods of time.

Lyme disease is a chronic, persisting, multi-systemic infection, which is caused by Borrelia burgdorferi spirochetes that are transmitted by common deer ticks (Ixodes). Like syphilis, which is another spirochetal infection, Lyme disease may affect several organ systems and proceed through several stages. It may also persist if it is not properly diagnosed and treated in the earliest stage. During the first stage, a pathognomonic bull's eye rash may develop that establishes the diagnosis. It is often accompanied by a flu-like illness. Unfortunately, in 20-50% of those infected with Borrelia, no rash develops, develops in an uncharacteristic form, or is not noticed1,2. Without appropriate antibiotic treatment, the disease becomes disseminated resulting in episodic or persistent neurologic, musculoskeletal, or cardiac symptoms. Several lines of evidence suggest the Lyme disease is very much underreported3 and that perhaps as many as 90% of those affected are not diagnosed.

Ticks that carry the Lyme bacteria also carry co-infections such as Ehrlichia, Babesia, and Bartonella. Approximately 2/3 of patients with Lyme disease have at least one of these co-infections4 but patients are not routinely tested for them. Patients who have Lyme disease together with a co-infection may remain mysteriously ill and unresponsive to standard treatment. Thus, Lyme is a complex illness potentially consisting of multiple tick-derived co-infections. Most physicians agree that when treated very early in the course of the disease that most Lyme patients will get well. Also generally agreed is that Lyme disease patients who have gone undiagnosed and now suffer late stage disease may continue to experience debilitating symptoms following a month-long course of antibiotics. All agree that these symptoms-arthritic, neurologic, and mulisystemic-can last for months or years. The most controversial aspect of the treatment of late stage Lyme disease is the optimal antibiotic regimen.

For the vast majority of bacterial infections, a defined course of antibiotics either eliminates the bacteria or decreases the number of bacteria so that the immune system can eradicate the survivors. Lyme disease is not a typical bacteria in that it shares some of the characteristics of more challenging bacterial infections such as mycobacteria and syphilis: it is difficult to routinely culture, has a slow growth rate, can remain dormant for lengthy periods5, can invade intracellular sites6,7,8,9, and may sequester in areas where antibiotic penetration is problematic such as the CNS, joint cartilage, and anterior chamber of the eye10. To make matters worse, there are no tests that reliably determine when Borrelia has been effectively eradicated. As clinicians, we are left to use our best medical judgment in individualizing care for our patients.

Oral antibiotics are preferred because of the ease of administration and low cost. Intravenous antibiotics are used for infections that are resistant to orally administered antibiotics, when inadequate blood levels are achieved by the oral route, or when penetration into privileged sites (i.e., the CNS) or poorly vascularized tissue (i.e., cartilage) is needed.

Review of the medical literature to determine an evidenced based approach for the treatment of late Lyme disease reveals a paucity of data. The studies that are often quoted as supporting a particular evidenced-based approach to late Lyme disease are summarized in Appendix A.

There are several themes that run through these diverse studies:

1. Antibiotics are accepted as mandatory in active Lyme disease treatment. However, the ideal antibiotics, their dosage, route of administration and duration of therapy have not been established.
2. Many patients remain well after a single course of oral, IM or IV antibiotics. However, many other patients with Lyme disease, initially improve while on antibiotics but relapse when antibiotic treatment is discontinued. There is often relief of symptoms when antibiotics are reinitiated, implying persistence of the bacterial infection.
3. Many of the antibiotics used in the studies do not penetrate the CNS, such as doxycycline11. Thus, persistence of neuroborreliosis would be expected.
4. The most effective treatments for late Lyme disease include at least 2 weeks of intravenous ceftriaxone or cefataxime. Retreatment protocols, for relapses and treatment failures, include significantly longer treatment courses, i.e., greater than 4 weeks.
5. None of the studies included evaluation and treatment for the co-infections such as Rocky Mountain spotted fever, bartonella, babesiosis, or ehrlichia that are present in as many as 2/3 of patients. Thi may explain the poor response to treatment in some of the studies using 30 days of IV antibiotics.
6. Persistence12 of symptomss or relapse is quite common13,14 implicating that duration of treatment and/or the type of antibiotic used is inadequate. Relapse and failure to respond to intensive antibiotic treatment has been attributed solely to an autoimmune reaction related to the presence of Borrelia15. However, there are studies documenting the persistence of Borrelia burgdorferi in antibiotic-treated patients16 and following up to 12 months of intravenous antibiotic therapy17,18,19. Appendix B summarizes the studies that demonstrate persistence of Borrelia burgdorferi after antibiotic treatment.
7. Most of the studies involved highly selected patient populations. Lyme patients present with a broad spectrum of symptoms and response to antibiotics. Thus, the relevance of the conclusions of these studies to most patients with late Lyme disease is problematic.
8. Many antibiotic regimens do not take into account that many antibiotics only kill actively dividing organisms. The fact that some cultures of Borrelia burgdorferi have taken up to 10 months to grow suggests that most treatment guidelines recommend a too short period of antibiotic treatment20
9. Given the range of symptoms related to Lyme disease and the widely divergent response to antibiotic therapy, treatment needs to be individualized. This means that some

patients may require much longer treatment with oral and/or intravenous antibiotics.
10. There is not sufficient evidence from the studies published to date to develop treatment guidelines.

In spite of the paucity of data, two groups of physicians that treat Lyme disease independently developed peer-reviewed 'evidence-based' treatment guidelines using the same literature (Appendix A) to formulate their treatment guidelines. The Infectious Disease Society of America (IDSA) advocate a maximum of 30 days of oral or intravenous antibiotics and assume that the remaining symptoms reflect a self-perpetuating autoimmune response21. The International Lyme and Associated Diseases Society (ILADS), which is composed of physicians from a variety of specialties who primarily treat Lyme disease, assume that the persistent symptoms reflect on-going infection and gauge the duration of treatment by the patient's individual clinical response. These physicians believe that there is insufficient evidence at this point to adopt standardized treatment protocols22.

While each viewpoint has a strong underlying hypothesis, the scientific evidence supporting either viewpoint is equivocal. Outcomes research is limited and conflicting. The NIAID has only funded three double-blind, placebo-controlled treatment outcome studies for long-term treatment of persistent Lyme disease. The findings of two studies (Klempner and Krupp-Appendix A) are contradictory, with one indicating that continued treatment is beneficial for treating fatigue and the other indicating that it is not. The third NIAID-funded study (Fallon-Appendix A) has recently been completed and preliminary results support continued antibiotic treatment for patients with persistent Lyme disease. The findings of nine non-controlled studies (Appendix A) support continued treatment. The existence of limited or conflicting controlled studies is not uncommon in the practice of medicine.

When a variety of viable treatment options exist, therapy is decided by weighing the individual's risks and benefits. Use of antibiotics can be associated with side effects, allergic reactions, development of drug resistance and cost. The benefits of antibiotics are the relief from a severe multisystemic bacterial infection that is difficult to eradicate with short-term antibiotic treatment. Witholding adequate antibiotic treatment for late-stage Lyme disease (when it is known that Borrelia persist in many treated patients-see Appendix B) is analogous to the Tuskegee experiment performed by the Public Health Service23, which has been widely criticized for the failure to adequately treat African American men with late-stage syphilis, another spirochete disease.

Insurance companies have adopted guidelines reflecting short-term treatment approaches, which are governed by cost-containment considerations. However, the legal standard of care for treating a condition is determined by the consensus of physicians who actually treat patients, not by treatment guidelines24. One survey found that 57% of responding physicians treat persistent Lyme disease for three months or more25. Fallon notes that for over 3400 patients screened for the Columbia University study of persistent Lyme disease, the mean duration of IV treatment was 2.3 months and the mean duration of oral antibiotic therapy was 7.5 months26. In another survey, "50% of the responders

considered using antibiotics for a time greater than one year in a symptomatic seropositive Lyme disease patient. Almost that same number would extend therapy to 18 months if needed."27

When more than one standard of care exists, the critical question becomes who decides the appropriate course of treatment for the patient. Under the medical ethical principle of autonomy, the treatment decision belongs to the patient. Hence, the American Medical Association requires that the physician disclose and discuss with the patient not only the risks and benefits of the proposed treatment, but also the risks and benefits of available alternatives28. Treatment choices involve trade-offs between the risks and benefits of treatment options that only patients, who know the kinds of risks they are willing to run and the types of quality of life outcomes that matter to them, are uniquely suited to make.

Insurance companies have placed the full weight of their economic clout behind the less expensive short-term treatment protocols. More expensive longer-term treatment options are discredited as "experimental" or "not evidence-based." The point, of course, is that the science underlying both the short-term and the longer-term treatment options is equally uncertain. It is estimated that only 20% of medicine practiced today is rooted in double-blind studies29 The bulk of medicine today is practiced in the grey zone. Evidence-based medicine requires only that medicine be practiced in accordance with the evidence that currently exists, not that treatment be withheld pending research. As for the cost considerations, healthcare costs generally are lower when the patient's preference is supported30.

In an ideal world, decisions would be based on strong scientific evidence, consensus opinion, and the views of the treating physician. However, seldom are all three available. A recent symposium by the National Institute of Health Care Management Research and Educational Foundation found a general consensus that care should not be denied because evidence is limited, conflicting, or even non-existent. Rather, decisions should be based on the best information available. It has been noted that:

Much, if not most, medical care, even that which is generally accepted in the medical community, would be denied under an evidence-based standard because so few health care services have been subject to rigorous research. At particular risk for denial of needed services are disabled persons because of the lack of treatments proven effective through clinical trials." (Independent Review of Managed Care Decisions by Honorable Mary C. Morgan. (Retired.)

Most patients who require prolonged intravenous antibiotics are denied coverage and subsequently undergo an independent medical review as part of the appeal process. First, it is imperative that those responsible for performing independent medical reviews be made aware of the fact that there are two recognized treatment approaches and that both sets of treatment guidelines be used as part of the review process. Second, the reviewers need to consider all of the data that illustrate the variability of treatment approaches physicians treating persistent Lyme Disease use (see Appendix A for the references). Third, the view of the treating physician needs to be given more weight, given that

treatment outcomes research to date illustrate that the population being studied is enormously heterogeneous. In these situations, the clinical course of the individual patient is more a predictor of response to treatment than heterogeneous group studies. Fourth, the variation in treatment practices that currently exists should be resolved by promoting more outcomes research to help resolve the scientific uncertainty and patient's preference should be supported.

There are a number of ways that medical necessity may be determined: on facts and evidence, on a consensus of medical opinion, or on the judgment of individual physicians. Where outcomes research is limited or equivocal, decisions should be based on the best information available - which in the case of heterogeneous populations may well be the unique clinical course of the individual patient.

Appendix A

Summary of Clinical Studies for Treatment of Late Stage Lyme Disease Randomized placebo-controlled Studies

Steere, 198531 - 40 patients with established Lyme arthritis were randomized to receive weekly IM injections of benzathine penicillin or placebo. 35% of the treated patients had complete resolution of their symptoms and remained symptom-free during a mean follow-up period of 33 months. None of the placebo treated patients improved. As compared with nonresponders, penicillin responsive patients were more likely to have received antibiotics for early Lyme disease and less likely to have received intra-articular steroids.

Klempner, 200132; Kaplan 200333 - 78 seropositive (by Western Blot) and 51 seronegative patients with post-treatment Lyme disease were randomized to receive 30 days IV ceftriaxone followed by oral doxycycline 100mg bid or placebo for 60 days. Patients underwent standardized testing at baseline, 90 and 180 days. There were normal baseline neuropsychological scores in all patients. There were no significant differences between seropositive and seronegative patients in outcomes, nor were there significant differences between treated and untreated patients. Of note is the fact that 64% of patients had persistent symptoms after standard treatment for the disease. Thus, the validity of this study has been questioned.

Krupp, 200334 - Double blind placebo controlled trial on 55 patients with continued fatigue 6 or more months after antibiotic treatment (3 weeks oral Abs or IV ceftriaxone) for Lyme disease. Patients were randomized to receive placebo or 4 weeks of IV ceftriaxone. Outcome measures were fatigue, cognitive speed, and clearance of OspA antigen from the CSF. 64% of patients given antibiotics were improved compared with 18.5% given placebo. Further, for patients with positive western blots at baseline, the responder rate was 80% vs 13%. For seronegative patients, the responder rate was 46% vs 27%. Patients receiving antibiotics also had significantly lower pain scores than those receiving placebo. There were no differences between groups in results of neurocognitive tests. The authors concluded that repeated antibiotic therapy had a substantial positive

effect on late Lyme disease outcome.

Fallon, 200435 - completed a trial of 10 weeks of IV antibiotic therapy in patients with late Lyme disease symptoms who had previously been treated with at least 3 weeks of IV antibiotics and then relapsed. There was significant improvement in cognition and other symptoms. This study was part of a $4.7 million NIH funded study. The manuscript is in preparation. Randomized Trials

Dattwyler, 198836 - 23 patients with clinically active late Lyme disease were randomly assigned to IV treatment with either penicillin or ceftriaxone. Of the 10 treated with penicillin, 5 were judged treatment failures; of the 13 who received ceftriaxone, only 1 patient did not respond. An additional 31 patients were subsequently treated with ceftriaxone with similar results. Patients that were unresponsive to ceftriaxone were more likely to have received corticosteroid treatment.

Pfister, 198937 -21 patients with radiculitis or neuroborreliosis associated with Lyme disease were randomized to receive a 10 day treatment with either IV penicillin G or cefataxime. There were no differences in the outcomes of the two groups. See Pfister, 1991 below.

Hassler, 199038 -135 patients with late-stage Lyme disease were randomized to receive IV penicillin G or IV cefotaxmine for 10 days. Cefotaxamine was significantly more effective than penicillin G with 87.9% vs 61.3% reporting full or partial remission of symptoms 24 months later.

Pfister, 199139 -33 patients with Lyme neuroborreliosis were randomized to receive a 10 day course of either IV ceftriaxone or Cefotaxime. Neurologic symptoms improved or subsided in 26/30 patients-there was no difference in treatment groups. At a mean follow-up of 8 months, 17/27 patients were clinically asymptomatic. Bb was isolated from the CSF of one patient 7 months after ceftriaxone therapy. Since 10 patients remained symptomatic, the authors concluded that a prolongation of therapy might be necessary.

Steere, 199440 -38 patients with Lyme arthritis were randomly assigned to 30 days of treatment with either doxycycline or amoxicillin plus probenecid. Patients who had persistent arthritis 3 months following treatment were given IV ceftriaxone for 2 weeks. 16/18 of the patients treated with amoxicillin and 18/20 treated with doxycycline had resolution of arthritis symptoms within 3 months of treatment. However, neuroborreliosis later developed in 5 patients. Of 16 patients with persistent arthritis who were treated with IV ceftriaxone, none had resolution of arthritis within 3 months. The authors concluded that even with resolution of specific manifestations of Lyme disease with oral antibiotics, there is still a risk of developing additional symptoms of Lyme at a later time. Persistent arthritis may be related to an autoimmune phenomenon (although they did not rule out persistent infection with PCR or culture). Others concluded that 2 weeks of IV ceftriaxone may be insufficient to address Lyme arthritis.

Wahlberg, 199441 -100 consecutive late-Lyme disease patients were treated with

different antibiotic regimens and followed up for 12 months after treatment. Treatment outcome was successful in 4/13 patients treated with IV ceftriaxone for 14 days, 50/56 patients treated with ceftriaxone followed by 100 days of amoxicillin with probenecid, and 19/23 of those treated with IV ceftriaxone for 14 days followed by 100 days of cephadroxil.

Okski, 199842 -randomized 60 patients with disseminated Lyme borreliosis based on CDC diagnostic criteria to receive either cefexime and probenecid orally for 100 days or ceftriaxone IV for 14 days followed by oral amoxicillin and probenecid for 100 days. The immediate outcome after antibiotics was not different between the two treatment groups. However, after a year of follow-up, there were significantly greater relapses, treatment failures, and positive PCR tests. The results of this study support the use of intravenous antibiotics along with prolonged antibiotic therapy in patients with late-stage Lyme disease.

Fallon, 199943 -studied 23 Lyme patients who complained of persistent memory difficulties after IV antibiotic therapy of 4-16 weeks. Four months after their initial treatment, 18 of the patients received additional IV antibiotics and compared with the others who did not receive additional antibiotics. Those receiving additional IV antibiotics scored better on cognition tests, greatest functional improvement in energy, pain, and physical functioning than untreated patients. Based on the results from this pilot study, the authors concluded that there was enough evidence to plan a larger study investigating the utility of repeated courses of IV antibiotics (see Fallon, 2004).

Logigian, 199944 -a series of 18 consecutive patients with Lyme encephalopathy and symptoms of memory difficulty, minor depression, somnolence, or headache were treated with 30 days of IV ceftriaxone. At the beginning of treatment, 89% had abnormal memory scores, 89% had CSF abnormalities and all tested had perfusion defects on SPECT scan. Six months after treatment, memory scores were significantly improved, CSF protein levels were significantly less, and post-treatment perfusion was significantly improved. 12-24 months after treatment, all patients rated themselves as improved or back to normal.

Observational studies

Hassler, 199145 -reported on two patients with antibiotic resistant Lyme disease that were treated with pulsed high-dose cefataxime with 2 days of treatment followed by 6 days without antibiotics over a ten-week period of time. One patient was symptom-free 6 months after antibiotic treatment, the other was improved and skin biopsies showed no evidence of Borrelia.

Cimmino, 199246 -reported 2 cases of chronic Lyme arthritis, refractory to standard antibiotic treatment, who were treated with Valesov, 199647 -reported on the outcome of a 36-month follow-up of patients with late stage Lyme arthritis after 2 weeks of ceftriaxone therapy. At 36 months 19/26 continued to be symptom-free, 6 had relapsed and 1 presented with new late-Lyme symptoms.

Donta, 199748 -277 patients with chronic Lyme disease and symptoms of fatigue, musculoskeletal pain, neuropsychiatric dysfunction, and paresthesias were treated with tetracycline for 1-11 months (mean 4 months). Overall 20% of the patients were cured, 70% significantly improved (degree of improvement 75-100%), and 10% did not improve. Improvement frequently did not take place for several weeks: after 2 months of treatment, 33% were significantly improved, after 3 months 61% were significantly improved. Improvement showed as early as one to two weeks after the start of treatment; however, in patients who were symptomatic for more than a year, it frequently took 4-6 weeks on the antibiotic for evidence of improvement. This slow rate of improvement was postulated to be due to the slow rates of multiplication and metabolism in Borrelia. This study underscores the necessity of an individualized approach to the treatment of late-stage Lyme disease.

Okski, 199949 -13 patients who had clinical relapses and were PCR positive after at least 3 months of oral antibiotics were treated with IV ceftriaxone for 4-6 weeks. None of the patients were PCR positive after treatment and 9 showed good therapeutic responses. The authors concluded that treating late Lyme disease with appropriate antibiotics for more than 3 months may not always eliminate Borrelia and that longer courses may be necessary.

Donta, 200350 -235 patients with chronic Lyme disease symptoms of fatigue, musculoskeletal pain, and neurocognitive dysfunction with positive serology for Borrelia were treated with macrolide antibiotics and hydroxychloroquine for one or more months based on their level of improvement during the course of treatment. 120 patients who were improved at the discontinuation of therapy had relapsing symptoms and were retreated with antibiotics. Of those retreated with macrolide/hydroxychloroquine, 32/33 had improvement, tetracycline 54/74 had improvement, IV ceftriaxone 9/23 had improvement. Thus, tetracycline and IV ceftriaxone had a much lower success rate than macrolide/hydroxychloroquine therapy.

Reviews

Cimmino, 199651 -reviewed the results of antibiotic treatment of Lyme arthritis in peer-reviewed journals between 1985 and 1991. The studies were small or medium-sized and not blinded. The antibiotics included Benzathine penicillin, IV penicillin G, IV ceftriaxone, IV Cefotaxime, oral doxycycline or oral amoxicillin plus Probenecid. The authors concluded that "There is no consensus on the therapeutic protocol to be adopted in Lyme arthritis. Many questions are still open about the antibiotic agents to adopt as well as the best duration of treatment."

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