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Issues in the Diagnosis and Treatment of Lyme Disease

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Abstract: Since the identification of the causative organism more than 30 years ago, there remain questions about the diagnosis and treatment of Lyme Disease. In this article, what is known about the disease will be reviewed, and approaches to the successful diagnosis and treatment of Lyme disease described.

In considering the diagnosis of Lyme disease, a major problem is the inability of documenting the existence and location of the bacteria. After the initial transfer of the bacteria from the Ixodes tick into the person, the spirochetes spread locally, but after an initial bacteremic phase, the organisms can no longer be reliably found in body fluids. The bacteria are probably present in subcutaneous sites and intracellular loci. Currently, the use of circulating antibodies directed against specific antigens of the Lyme borrelia are the standard means to diagnose the disease, but specific antibodies are not an adequate means to assess the presence or absence of the organism. What is needed is a more Lyme-specific antigen as a more definitive adjunct to the clinical diagnosis.

As for the treatment of Lyme disease, the earliest phase is generally easily treated. But it is the more chronic form of the disease that is plagued with lack of information, frequently leading to erroneous recommendations about the type and duration of treatments. Hence, often cited recommendations about the duration of treatment, eg four weeks is adequate treatment, have no factual basis to support that recommendation, often leading to the conclusion that there is another, perhaps psychosomatic reason, for the continuing symptoms. *B. burgdorferi* is sensitive to various antibiotics, including penicillins, tetracyclines, and macrolides, but there are a number of mitigating factors that affect the clinical efficacy of these antibiotics, and these factors are addressed. The successful treatment of Lyme disease appears to be dependent on the use of specific antibiotics over a sufficient period of time. Further treatment trials would be helpful in finding the best regimens and duration periods.

At present, the diagnosis of Lyme disease is based primarily on the clinical picture. The pathophysiology of the disease remains to be determined, and the basis for the chronic illness in need of additional research. Whether there is continuing infection, auto-immunity to residual or persisting antigens, and whether a toxin or other bacterial-associated product(s) are responsible for the symptoms and signs remains to be delineated.

Keywords: Lyme disease, chronic, brain SPECT.

INTRODUCTION

The causative agent of Lyme disease is the spirochete, Borrelia burgdorferi, the species named after the discoverer of the organism, Willy Burgdorfer [1]. After the initial transfer of the bacteria from the Ixodes tick to the affected individual, the spirochetes spread locally at the site of the bite, but after an initial bacteremic phase that may last for up to 90 days, but usually for a few weeks [2], the organisms can no longer be reliably cultured or otherwise detected in blood, urine, spinal fluid or other body fluids.

The course of Lyme disease was initially described as being in stages, ie I, II, III, but this was later revised as occurring in three phases, ie Early Lyme disease, Early Disseminated Lyme disease, and Late Lyme disease [3]. This latter description is somewhat more accurate, but there is often no separation between early and late or persistent/chronic Lyme disease, ie patients may progress from early to persisting symptoms without having obvious disseminated erythema migrans lesions that are characteristic of Early Disseminated Lyme disease. There are many patients as well who have early disease, but then no further symptoms for a number of weeks or months.

WHAT TO DO ABOUT TICK BITES

One of the issues is what to do if a patient has only a tick bite without a rash or other symptoms. In this case, presuming the tick is imbedded, some advice has been that nothing need be done unless the tick has been imbedded for more than 48 hours [4]. This recommendation relies on the results of animal experiments, but it remains uncertain whether this applies to the natural setting in humans. In the absence of a more definitive way to determine whether the individual has been infected, a practical approach would be to have the tick analyzed to be sure it is an Ixodes tick and it is positive by

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PCR-DNA or IFA for the borrelial spirochete. These tests are available, and results obtained in a few days. If the test is negative, there is no need for any treatment; if positive, the recommendation would be to treat with amoxicillin, cefuroxime, or doxycycline, the duration of treatment unknown, but 1-2 weeks a reasonable period of time in the absence of any symptoms.

In the absence of testing the tick, the choice is either to wait until any rash or other symptoms appear, or empirically treat with a "double-dose" of doxycycline, ie 200mg [5]. Although this treatment might prevent the establishment of infection in most people who have been bit, there are failures to this approach, and patients who are given this treatment should be cautioned to observe for any symptoms over the subsequent few months.

MANAGING THE PATIENT WITH ERYTHEMA MIGRANS RASH

If a typical erythema migrans rash appears, the diagnosis is confirmed, and a course of treatment with doxycycline, amoxicillin, or cefuroxime has been shown to be efficacious [6]. The duration of treatment is usually 2-4 weeks, but it would seem logical and prudent to continue treatment if there are associated symptoms, albeit non-specific in nature, until those symptoms resolve, usually another few weeks, especially as there is no diagnostic tool to determine whether the infection is still present or has been eradicated. If there are subsequent or relapsing symptoms, treatment should be promptly reinstituted, usually with doxycycline, but may require other treatments to resolve the symptoms.

MANAGING PATIENTS WITHOUT TYPICAL ERYTHEMA MIGRANS RASH

Patients with early Lyme disease may not have a typical erythema migrans rash, making the diagnosis more difficult. Indeed, half or more patients who have a rash do not have a typical "bulls-eye" rash [7]. In this case, the clinician needs to include the diagnosis of Lyme disease if there are other symptoms, albeit non-specific, if the patient has an otherwise unexplained persisting illness. Serologic testing for Lyme disease is often helpful, but if the screening ELISA type tests are negative, a Western Blot should be performed, looking especially for IgM reactivity [8]. Treatment of such patients would be empirical, consisting of similar regimens as with patients with typical early Lyme disease.

MANAGING PATIENTS WITH NO TICK BITE OR RASH WHO PRESENT WITH LATE LYME DISEASE

Patients with early Lyme disease, and some who were not aware of any tick bite or rash, may present several weeks or even a few months later with one of several clinical pictures that can be classified as late Lyme disease. These include aseptic meningitis, Bell's palsy, heart block, and arthritis. In this case, ELISA tests are usually positive, but if negative, a Western Blot should be performed [8]. Treatment of such patients may require more prolonged treatment, or antimicrobial agents other than doxycyline, amoxicillin, cefuroxime, or intravenous ceftriaxone.

DIAGNOSIS OF LYME DISEASE IN PATIENTS WITH PERSISTING OR RELAPSING SYMPTOMS

There are patients who are not aware of any tick bite or any rash, who present with an illness consisting of a combination of symptoms, but without objective signs, that include persisting fatigue, arthralgias or myalgias, paresthesias, and neurocognitive dysfunction that could be due to Lyme disease (Table **1**). Such patients frequently undergo various numerous evaluations, including rheumatology, neurology, and infectious disease consultations, without any definitive diagnosis, and are often classified as having chronic fatigue syndrome, fibromyalgia, or depression. They are also often told they do not have Lyme disease. The facts, however, are that there are no currently available tests to determine whether the spirochetes are actually present or not present in an individual, and whether the bacteria are active or inactive. Hence, often cited recommendations about the duration of treatment, eg four weeks is curative or adequate treatment, have no factual basis to support that recommendation, disregarding the clinical picture, and leading to the conclusion that there is another, perhaps psychosomatic reason, for the continuing symptoms. As there is overlap in symptomatology between patients who are diagnosed as having chronic fatigue syndrome, fibromyalgia, and those who have persisting symptoms with Lyme disease [8, 9], there is great difficulty clinically in knowing who amongst those with chronic fatigue and fibromyalgia might have persisting Lyme disease.

In patients with relapsing or persisting symptoms, screening tests such as ELISA are usually negative, but Western Blots often show antibody reactions to highly specific proteins, eg 23kd, 31kd, 34kd, 39kd, 93k, especially by IgM, that support the clinical diagnosis [8,10,11] (Table **2**). The Western Blot criteria that were initially adopted for sur-

Table 1. Symptoms of Chronic Lyme Disease

MUSCULOSKELETAL	90%*
FATIGUE	84%
HEADACHE	78%
COGNITIVE	74%
MOOD CHANGES	57%
STOMACH PAIN or NAUSEA	48%
PARESTHESIAS	46%
NECK PAIN	43%
EYE SYMPTOMS	40%
FEVERS OR SWEATS	39%
OTHER	79%#

*Percentage of symptoms in 101 pediatric patients with chronic Lyme disease

#Other symptoms include dizziness (51%), sleep dysfunction (25%), palpitations or tachycardia (19%), sore throats (19%), dyspnea (18%), tremors, "seizures" (18%), jaw or tooth pain (13%), rashes or bruises (13%), dysuria (11%)

Table 2. Western Blot vs ELISA in Chronic Lyme Disease

ELISA	Western Blot	
	Positive	**Negative**
Positive	72 (29%)*	2 (1%)
Negative	133 (52%)	47(18.5%)

*Numbers of patients (%) with chronic Lyme disease with positive or negative ELISA and Western Blot reactions.

veillance purposes, then subsequently used clinically, were based on patients with Late Lyme Disease, who have objective signs, such as swelling in usually a single joint such as the knee, that appeared subsequent to a documented tick bite and/or typical erythema migrans rash and whose screening ELISA test is strongly positive [12,13]; however, these criteria did not include patients with chronic persisting symptoms, and subsequent studies have demonstrated that two-thirds or more of these patients have negative screening tests, but positive Western Blot reactions, especially by IgM. Even in those patients with more obvious late Lyme disease, the criteria of needing 5 of ten reactions on IgG Western Blot to make a diagnosis is not supported by the published data, wherein a reaction to even one specific protein of B. burgdorferi has a 90% positive correlation with the clinical diagnosis.

There are additional issues relating to the criteria for a positive IgM test on Lyme Western blot. The recommended criteria for diagnosis of early Lyme disease are that there be 2 of 3 positive reactions to one of three borrelial proteins, ie 23kd, 39kd, or 41kd proteins. But if there are similar reactions in patients with later manifestations or persisting symptoms, the recommended interpretation is that these are false positive results. This interpretation lacks any logical or scientific foundation, and has added to confusion about the value of serologic data. Observations in numerous patients over the past 25 years suggest that these positive IgM reactions in patients with chronic symptoms are meaningful as a surrogate for disease activity [8,10,11].

Brain SPECT scans can often be helpful in supporting the clinical diagnosis of chronic active Lyme disease. Perfusion deficits occur in 75% of patients with neurocognitive dysfunction [14]. The deficits occur primarily in the temporal, parietal, and frontal lobes (Table **3**), and these deficits resolve with successful treatment. In contrast, MRI of the brain may in 15% of patients show T2 signal hyperintense lesions indistinguishable from those seen with multiple sclerosis. Hence, SPECT scans and MRI studies of the brain in patients with relapsing, persisting symptoms can be useful adjuncts to the clinical diagnosis.

What has not been particularly helpful is analysis of CSF fluid in patients with persisting symptoms. There is a continuing recommendation that patients who have neurologic symptoms such as short-term memory loss or mood changes will have positive antibody or PCR-DNA results in spinal fluid, but only rarely have spinal fluid examinations yielded positive results.

There are other adjunctive tests that may be helpful in the diagnosis and management of patients with persisting symptoms. CD57 levels have been proposed as a means of monitoring the severity of the illness, but its specificity for Lyme disease has not been demonstrated [15], and there are patients who are symptomatic with normal CD57 levels and those who are not with subnormal CD57 levels. Similarly, the role of other immunologic responses, specifically cell-mediated associated responses, in the diagnosis and management of patients with Lyme disease remains to be proven. It seems reasonable to assume that the cell-mediated arm of the immune system is involved in chronic and intracellular based infections, and there are some observations that cell-mediated responses to specific Lyme antigens are increased in patients with Lyme disease, but more studies are needed, especially longitudinal studies, to evaluate the utility of these tests in such patients.

PATHOGENESIS AND PATHOPHYSIOLOGY OF LYME DISEASE

Once the spirochetes enter the subcutaneous tissue, they likely localize in neuronal tissues [16,17], probably sensory ganglia, commensurate with the various clinical manifestations, but perhaps as well in other sites and cells such as endothelial or glial cells [8]. They may persist in subcutaneous sites, but their long-term survival is likely in intracellular loci. The location in subcutaneous tissues, especially near the surface, is consistent with the ability of larvae of the Ixodes ticks to become infected when they take a blood meal from a deer or white-footed mouse, as well as in experiments of xenodiagnosis [18]. Whether the spirochetes are randomly located in subcutaneous space or whether they are present in endothelial cells of capillaries or in the ends of dendritic cell processes has yet to be determined. As for an intracellular locus, an acidic endosome such as the lysosome or a late

Table 3. Localization of Brain SPECT Scan Perfusion Deficits in Patients with Chronic Lyme Disease*

1. Temporal lobe (46%)
2. Frontal lobe (40%)
3. Parietal lobe (33%)
4. Temporal + Frontal lobes (27%)
5. Temporal + Frontal + Parietal lobes (15%)
6. Temporal + Parietal lobes (7%)
7. Frontal + Parietal lobes (6%)
8. No deficits (25%)

*Results of studies of 183 patients with chronic Lyme disease

endosome is the likely location, support for which hypothesis are the observations that macrolide antibiotics, which are highly effective *in vitro* and which can be transported to all endosomes, are ineffective clinically, but are effective if the acidic endosome can be alkalinized, as with agents such as hydroxychloroquine and amantadine [11,19]. Further supporting this hypothesis is that acidifying agents such as ascorbic acid (vitamin C), appear to counteract the effect of the lysosomotropic agents.

How the spirochetes cause symptoms remains to be determined. It would seem unlikely that their physical presence alone would cause any symptoms. It's more likely that they either produce a noxious substance or substances, ie toxin, that perturbs the nerve cell or other cells that may be involved, causing symptoms such as pain, paresthesias, cognitive impairment, or that there is some host response to the spirochete or a product thereof. The possibility that there may auto-immune reactions has been raised, but there is not compelling evidence that this is the major pathophysiologic mechanism involved in the disease. Nor is there any evidence that persisting symptoms might be due to post-infectious sequelae such as damage to certain cells. That has been discovered a toxin that affects neuronal and other neural-related cells in tissue culture, and it remains to be determined whether this is a responsible mechanism for the symptomatology [20].

ANTIBIOTIC TREATMENT OF PATIENTS WITH LATE OR CHRONIC LYME DISEASE

Patients who have previously been diagnosed as having Lyme disease who have relapsing symptoms are often given the diagnosis of post-treatment Lyme disease, the implication being that they no longer have the infection, but this assumption is not based on any specific diagnostic criteria. The assumption is primarily based on the lack of improvement in a treatment trial that used a regimen consisting of one month of intravenous ceftriaxone followed by two months of oral doxycyline [21]. That regimen did indeed seem to be ineffective, but the reasons for the lack of efficacy were not adequately addressed, especially the lack of consideration that there may be other regimens that might be effective. *B. burgdorferi* is sensitive *in vitro* to various antibiotics, including the penicillins, tetracyclines, and macrolides, but there are a number of mitigating factors that affect the clinical efficacy of these antibiotics. Not all antibiotics are equally effective in treating various infections, so it should not be surprising that there might be other successful regimens. Indeed, based on pharmacologic considerations, there appear to be highly effective regimens consisting of either tetracycline itself, or the combination of a macrolide anitibiotic (eg erythromycin, clarithromycin, azithromycin) with a lysosomotropic agent such as hydroxychloroquine [10,11].

There continue to be various recommendations regarding antibiotic treatment of patients with relapsing or persisting symptoms. While there have not been agreed upon uniform regimens, there has been agreement amongst practitioners involved in treating such patients that more prolonged treatment is needed for more successful outcomes. With the exception of the study that involved a month of intravenous ceftriaxone followed by two months of oral doxycycline, and subsequent studies of either one month or ten weeks of intravenous ceftriaxone [22], there have been no randomized, placebo-controlled trials of longer duration, using other antibiotic regimens. It should not be surprising that longer regimens would be required to treat a chronic infection, especially if the causative organism is not rapidly replicating and is in a protective niche such as an intracellular locus. Such is the case with a number of other infections, including tuberculosis, Q fever, various parasitic and fungal infections, and viral infections such as hepatitis B, hepatitis C, and HIV. In the case of hepatitis B and C, initial recommendations were for 6 weeks of treatment, but with further studies, the recommendation for the duration of treatment was then extended to 12 weeks, then to 24 weeks, and perhaps longer to resolve the infection.

In assessing whether treatment of patients with Lyme disease who have chronic symptoms are responding to the treatment, the lack of objective manifestations and more definitive means to determine whether the infection is being resolved, makes it more difficult to prove that the infection is being successfully treated. Nonetheless, it is the patient's assessment of whether there is any improvement, just as in treatment of any other medical condition, that is the determinant of progress and success. There are also potential confounding factors, such as whether a given antibiotic is exerting a specific or non-specific effect. In the case of beta-lactam antibiotics such as penicillin and cephalosporins, especially ceftriaxone, recent evidence shows that these antibiotics can affect glutamate transport in the nervous system [23], and that their clinical effects on patients' symptoms might not be anti-bacterial in nature, but symptomatic. Patients and physicians have often concluded, perhaps erroneously, that additional treatments with these antibiotics are needed, and in our experience, treatment with this class of antibiotics, including several months of intravenous ceftriaxone, is not curative in patients with chronic symptoms.

Doxycycline is effective treatment for early Lyme disease, but does not appear to be curative in relapsing, persisting Lyme disease. This likely is because of two factors, ie dose, and protein-binding. Most of absorbed doxycycline remains highly protein-bound in the circulation, meaning that the amount of free drug to diffuse into cells is limited. This may be the explanation as to why the original parent compound tetracycline appears to be more effective [10]. The dose of tetracycline used in our published observations that was found to be effective was 1500mg/day; in contrast, doxycycline dosage is 200mg/day, and tetracycline is not highly protein-bound, allowing more free tetracycline to diffuse into cells. In treating patients with tetracycline, a minimum of three months is needed to demonstrate progress, and in patients who have been ill for more than one or two years, 18 months of treatment may be needed to resolve the illness. Whether increasing the dose of doxycycline to 300-400mg/day would be more effective remains uncertain.

The use of a macrolide antibiotic such as clarithromycin or erythromycin, when combined with a lysosomotropic agent such as hydroxychloroquine, has been a very tolerable and successful regimen in treating patients with chronic, persisting symptoms [11]. The use of either antibiotic or

hydroxychloroquine alone does not result in any obvious improvement, supporting the hypothesis that the Lyme spirochetes reside in an intracellular acidic endosome. A controlled clinical trial would however be needed to prove this hypothesis. Further to that point, tetracycline, which is active in an acid milieu, is not benefited by the addition of hydroxychloroquine to the regimen. As with tetracycline, treatment with this regimen may also require a number of months to resolve most, if not all symptoms. As a practical approach, courses of treatment are alternated between tetracycline and the macrolide/hydroxychloroquine regimen, consisting of 6 months for each course, until symptoms are resolved (Table **4**). Patients who have been ill for shorter periods of time can resolve their symptoms in shorter periods of time than those who have had illness for a few years or more. In patients with longer standing illness, it also takes longer to begin to see any progress, often needing 4-6 months; nonetheless, sustained improvement can be seen in most of these patients over a prolonged period of time.

NON-ANTIBIOTIC TREATMENTS

Symptom-based medications can be helpful in providing some relief of the various symptoms. These include gabapentin to help with pain and neuropathy, anti-depressants, and agents such as trazodone to help with sleep issues. Narcotic medications should be avoided, as patients can easily become addicted, and treatment of the underlying illness becomes more difficult to treat.

The use of various supplements has been advocated by some, but evidence of their efficacy not established, and it would seem prudent to minimize the numbers of medications and supplements taken that might not only add difficulty to interpretation of any progress during the treatment period, but perhaps aid the survival of the spirochetes and retard resolution of the illness. In particular, the use of multivitamins and anti-oxidants is to be avoided, as supplemental vitamin C, as previously noted, would counteract the effects of hydroxychloroquine. As for B vitamins, these might theoretically be aiding the spirochete's survival, as they are unable to synthesize their own B vitamins; and our observations are that patients on supplemental B vitamins do not respond as favorably to antibiotic treatment as do those not taking these supplements. Patients not taking supplemental B vitamins do not appear to have any deficiencies in these vitamins, so they are not being put at risk by the lack of supplemention. Vitamin D, however, is to be encouraged as it is frequently low in patients with persistent Lyme disease, and may be helpful in providing anti-inflammatory benefit. The use of anti-oxidants such as coenzyme Q10 and vitamin E should also be avoided, as these agents may retard the host's ability to damage the spirochetes. Recent evidence also suggests that anti-oxidants promote antibiotic tolerance and biofilm formation [24, 25].

Table 4. Recommended Reatment Regimens for Chronic Lyme Disease

1.	Tetracycline: 1500mg/day, divided as either 500mg three times per day 20 minutes before or two hours after meals, or 750mg twice daily 20 minutes before or two hours after meals.
2.	Clarithromycin (or Erythromycin) 500mg twice daily, in combination with hydroxychloroquine 200mg twice daily with, or shortly after, meals. Azithromycin may be substituted for clarithromycin, but the dose of azithromycin of 500mg daily may not be as efficacious.

FUTURE DIRECTIONS

Currently, the use of circulating antibodies directed against specific antigens of the Lyme borrelia are the standard means to diagnose the disease, but specific antibodies do not provide an adequate means of assessing the presence or absence of the organism. What is needed, in the absence of being able to directly culture the organism, is the development of a more direct detection test against Lyme-specific antigens to provide a more definitive diagnosis.

Also needed are more controlled clinical trials to document and establish better treatment regimens. There is sufficient preliminary evidence to suggest that there are effective regimens, and support for clinical trials using these regimens is needed to make additional progress for this disease. And the development of specific vaccines is needed to ultimately prevent the infection.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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