

**A Rheumatologist's Viewpoint:
Lyme Disease -- Suboptimal Standard of Care
In the Infectious Diseases Society of America (IDSA) Guidelines**

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This Challenge is to the following IDSA Recommendations (page 1113):

1. Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally (tables 2 and 3). Doxycycline (B-I), amoxicillin (B-I), or cefuroxime axetil (B-III) for 28 days is recommended for adult patients without clinical evidence of neurologic disease. For children, amoxicillin (B-I), cefuroxime axetil (B-III), or doxycycline (if ≥8 years of age) (B-I) is recommended (tables 2 and 3). Oral therapy is easier to administer than intravenous antibiotics, is associated with fewer serious complications, and is considerably less expensive. However, it is important to recognize that a small number of patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require intravenous therapy with a b-lactam antibiotic for successful resolution. Further controlled trials are needed to compare the safety and efficacy of oral therapy with intravenous therapy for Lyme arthritis. Neurologic evaluation that may include lumbar puncture should be performed for patients in whom there is a clinical suspicion of neurologic involvement. Adult patients with arthritis plus objective evidence of neurologic disease should receive parenteral therapy with ceftriaxone (tables 2 and 3) (AII). Cefotaxime or penicillin G administered parenterally is an acceptable alternative (B-II). For children, intravenous ceftriaxone or intravenous cefotaxime is recommended (B-III); penicillin G administered intravenously is an alternative (B-III) (tables 2 and 3).

2. Patients who have persistent or recurrent joint swelling after a recommended course of oral antibiotic therapy should be re-treated with another 4-week course of oral antibiotics or with a 2–4-week course of intravenous ceftriaxone (B-III) (tables 2 and 3). A second 4-week course of oral antibiotic therapy is favored by panel members for the patient whose arthritis has substantively improved but has not yet completely resolved, reserving intravenous antibiotic therapy for those patients whose arthritis failed to improve at all or worsened. Clinicians should consider waiting several months before initiating re-treatment with antimicrobial agents because of the anticipated slow resolution of inflammation after treatment. During this period, NSAIDs may be used, but intra-articular injections of corticosteroids are not recommended (D-III). If patients have no resolution of arthritis despite intravenous therapy, and if PCR results for a sample of synovial fluid (and synovial tissue, if available) are negative, symptomatic treatment is recommended (B-III). Symptomatic therapy might consist of NSAIDs, intra-articular injections of corticosteroids, or DMARDs, such as hydroxychloroquine; expert consultation with a rheumatologist is recommended. If persistent synovitis is associated with significant pain or limitation of function, arthroscopic synovectomy may reduce the duration of joint inflammation (B-II). should be performed for patients in whom there is a clinical suspicion of neurologic involvement. Adult patients with arthritis plus objective evidence of neurologic disease should receive parenteral therapy with ceftriaxone (tables 2 and 3) (AII). Cefotaxime or penicillin G administered parenterally is an acceptable alternative (B-II). For children, intravenous ceftriaxone or intravenous cefotaxime is recommended (B-III); penicillin G administered intravenously is an alternative (B-III) (tables 2 and 3).

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Introduction

As a rheumatologist and internist, I provide care to a large number of individuals of all ages, both sexes and various races infected with Lyme disease and other tick-borne diseases (TBD). I am deeply concerned over the limited clinical presentations addressed and the restrictive nature of the Practice Guidelines for treating rheumatic manifestations of Lyme disease, published by the Infectious Disease Society of America (IDSA), prepared and outlined by Wormser, G. et al.¹

Lyme complex, my preferred term for this devastating chronic disease, is an emerging disease: the IDSA guidelines authors do not recognize the full spectrum of manifestations. It is far too early to designate a finite definition of Lyme Complex, and doing so now will leave many cases without treatment. Moreover, many of those fortunate enough to be diagnosed according to the Guidelines would receive insufficient treatment under the Guideline's protocols. None of the treatment recommendations addresses atypical presentations, thus treating patients with atypical presentations inadequately, inappropriately, subjecting them to a lingering lifetime of pain. Sub-optimal treatment of individuals with Lyme disease increases the rate of disability leading to financial hardship, negatively affecting one's family livelihood, imposing significant personal and interpersonal difficulties. Disability also leads to an inestimable loss in productivity and an absolute dependency on Social Security and Medicare systems.

Specific concerns

There are several areas of concern regarding the IDSA Guidelines' handling of Lyme disease as addressed below. In my professional opinion, the Guidelines are deficient in the following ways:

1. The over-reliance on the presence of the Erythema Migrans (EM) rash in the diagnostic criteria;
2. Over-reliance on poor and inaccurate serologic testing in establishing the diagnosis of Lyme disease;
3. The assumption that the infection is indolent, therefore harmless and treatable with a short course of antibiotics;
4. The assumption that after a short course of antibiotic therapy, all persistent symptoms are due to an immunologic disturbance and not the persistence of the spirochete;
5. The recommendation that a very short course of antibiotics early in the disease will take care of everything;

6. The recommendation that if the symptoms persist, another short course of antibiotics will suffice;
7. Lack of recognition and acknowledgment of the special needs of immuno-compromised individuals with Lyme disease;
8. Lack of recognition that the *Borrelia burgdorferi* spirochete is in itself immuno-compromising, and therefore every individual with a spirochetal infection is to some degree immuno-compromised and should be treated from the onset with an adequate course of antibiotic therapy to manage and treat the infections effectively without allowing this systemic infection to enter into later phases of disease;
9. Lack of recognition that there are physical sites or niches, both intracellular and extracellular, that allow the Lyme spirochete to persist, survive and resurge at a later date;
10. Lack of recognition that previously damaged joints from trauma, surgery, pre-existing inflammatory arthritis, crystal arthritides, allow the Lyme spirochete to flourish in a protected environment. Individuals with the aforementioned difficulties should be treated from the onset with a course of antibiotic therapy usually reserved for individuals for chronic persistent septic arthritis;
11. Lack of recognition that the Lyme spirochete mimics a large number of disease manifestation and diseases and therefore can go unrecognized as the underlying basis of many medical disorders. When eventually recognized, these individual will require a prolonged course of anti-microbial therapy;
12. Lack of recognition that treatment requirements in individuals with a combination of tick borne diseases should be more aggressive than those individuals with Lyme spirochete infection alone.

Definitions

To minimize confusion when referring to and comparing various publications referenced through this viewpoint article, I will begin with the categorization of Lyme disease (LD) in its various stages of presentation. The IDSA's definition of these stages of Lyme disease includes the following:

- a. Early Lyme disease, which is categorized into two subgroups:
 - i. Early localized infection presenting as a solitary erythema migrans (EM) rash, referred to in the older literature as Stage 1 Lyme disease, and
 - ii. Early disseminated infection, presenting with multiple erythema migrans lesions, carditis, cranial-nerve palsy, meningitis, or acute radiculopathy (previously referred to as Stage 2 Lyme disease).
- b. Late Lyme disease - includes oligoarthritis, encephalopathy manifested as memory deficit, irritability and somnolence, and neuropathy, manifested primarily by distal paresthesias i.e. numbness, tingling, burning or pins and needles, or radicular pain (sciatica-like pain). These are known in the older literature as Stage 3 Lyme disease.

The IDSA definition and categorization of various Lyme presentations should be further updated to include acute Lyme arthritis and various ophthalmologic manifestations in the early disseminated category and three new categories be added representing all the atypical presentation of Lyme disease. The first new category can be labeled Latent Lyme or any representative and accurate term of the IDSA choosing. Latent Lyme represents those patients with Lyme that present with multiple sclerosis, Lou Gehrig's disease, rheumatoid arthritis, systemic lupus erythematosus, Wegener's granulomatosis, Sarcoidosis, seizure disorder, dementia including Alzheimer's as examples. The current treatment recommendation of the Guidelines does not apply to this category and further investigation and research should be conducted on this large and underrepresented group of patients with Lyme disease. The second new category can be labeled Tick-Borne Disease complex or any representative and accurate term of the IDSA choosing. The Tick-Borne Disease Complex represents manifestation in patients with a combination of tick borne diseases such as Lyme and Bartonellosis, Lyme and Babesiosis, Lyme and Ehrlichiosis, or any other combination thereof. The treatment requirements for individuals with Tick-Borne Disease Complex are not addressed by the current Guidelines and if the treatments as outlines in the Guidelines are applied to this category of patients the clinical outcome would be devastating. The final new category can be labeled Latent Tick-Borne Disease Complex representing a patient manifesting features of latent Lyme and combination of tick borne diseases.

In general, most studies reviewed by the IDSA Board while preparing the Guidelines categorized persistent signs and symptoms after treatment as "minor," including headache, fatigue, supra-ventricular tachycardia (rapid heartbeat), arthralgia, brief episodes of arthritis of less than two weeks duration, or isolated facial palsy or "major" which included meningitis, meningo-encephalitis, carditis, or recurrent attacks of arthritis. I believe this is too simplistic and should be eliminated all together.

Historical Background

To understand Lyme disease, it is important to know or study the causative bacterium, a spirochete known as *Borrelia burgdorferi* (Bb) and its characteristics. The following are excerpts from an eloquent description of the Lyme disease by Dr. Allen Steere, published by the *New England Journal of Medicine (NEJM)* first in 1989² and updated in 2001³:

Borrelia species, along with the leptospira and treponema, belong to the eubacterial phylum of spirochetes. Like all spirochetes, the *Borrelia* species have a protoplasmic cylinder that is surrounded first by a cell membrane, then by flagella, and finally by an outer membrane, that is only loosely associated with the underlying structures. The *Borrelia* are longer and more loosely coiled than the other spirochetes, and their outer membrane is unique in that the genes encoding it are located on plasmids, an arrangement that may be advantageous to the organism in making antigenic changes in these proteins. The entire outer membrane can move to one end of the cylinder, a phenomenon called capping or patching that may be important in cell adherence.

“It is relatively easy to obtain a primary isolate of this spirochete from ticks, but it is difficult to do from patients. As compared with most bacteria, *Borrelia* grow quite slowly; each spirochete elongates for 12 to 24 hours and then divides into two cells.

Asbrink has proposed a modified plan, analogous to that used in classifying syphilis, in which Lyme borelliosis is essentially divided into early and late infection. Early infection consists of stage I (localized erythema migrans), followed within days or weeks by stage 2 (disseminated infection) and within weeks or months by intermittent symptoms. Late infection, or stage 3 (persistent infection), usually begins a year or more after the onset of the disease. A patient may have one or all of the stages, and the infection may not become symptomatic until stage 2 or 3.

Within days or weeks after inoculation, the Lyme disease spirochete may spread in the patient's blood or lymph to many sites. The spirochete has been recovered several times from blood during this stage, and it has also been seen in small numbers in specimens of myocardium, retina, muscle, bone, synovium, spleen, liver, meninges, and brain.

In the rat model of the disease, *B. burgdorferi* can be cultured from all organs five days after inoculation, but positivity gradually disappears from most sites. It seems likely that this also occurs in patients.

The musculoskeletal pain of Lyme disease is generally migratory in joints, bursae, tendons, muscle, and bone, lasting only hours or days in a given location. At this stage,

patients often appear quite ill, and they frequently have debilitating malaise and fatigue, which may be the predominant symptoms. Except for fatigue, the symptoms are typically intermittent and changing. Widely disseminated hematogenous infection seems to be more common in the United States than in Europe.

By this time, patients' mononuclear cells begin to have heightened responsiveness to *B. burgdorferi* antigens and mitogens, less suppressor-cell suppressor-cell activity than normal, and decreased natural-killer-cell activity. The specific IgM response, which is often directed first against the 41-kd flagellar antigen of the spirochete, peaks between the third and the sixth weeks but may persist. The specific IgM response is frequently associated with evidence of the polyclonal activation of B Cells, including elevated total serum IgM levels, and the presence of cryoprecipitates, including immune complexes, and occasionally, rheumatoid factor, antinuclear antibodies, or anticardiolipin antibodies. Gradually, specific IgG antibody develops, primarily of the IgG1 and IgG3 subclasses, to an increasing array of spirochetal polypeptides, particularly the 31-, 34-, and 66-kd outer-surface proteins, the 41-kd flagellar antigen, and the 55/58-kd antigen. Immune antibodies are required for the serum-mediated killing of the spirochete by the classical complement pathway. Both polymorphonuclear leukocytes and monocytes readily phagocytose and kill the spirochete.

Histologically all affected tissue show an infiltration of lymphocytes with plentiful plasma cells. Plasma-cell precursors are large and can resemble immunoblasts or Reed-Sternberg cells. Some degree of vascular damage, including mild vasculitis or hypercellular vascular occlusion, may be seen in multiple sites, suggesting that the spirochete or immune complexes may have been present in and around blood vessels. After hematogenous spread, *B. burgdorferi* seems to be able to sequester itself in certain niches. How the organism does this remains a mystery. Perhaps it can coat itself with a "slime" layer that includes host proteins, or perhaps it is able to survive in certain intracellular sites...

After several weeks or months, as the infection begins to localize, about 15 to 20 percent of the patients in the United States develop frank neurologic involvement. A mean of six months after the onset of the disease (range, two weeks to two years), commonly after intermittent episodes of arthralgia or migratory musculoskeletal pain, about 60 percent of the patients in the United States begin to have brief attacks of asymmetric, oligoarticular arthritis, primarily in the large joints, especially the knee. Some attacks may affect the periarticular structures, including the peripheral entheses. The reasons for the activity or latency of *B. burgdorferi* are not clear, but this pattern is characteristic of the involvement of the joints in this infection. White-cell counts in the joint fluid range from 500 to 110,000 per cubic millimeter and consist of predominantly polymorphonuclear

leukocytes. Immune complexes, which correlate with the total granulocyte count, are uniformly present.

Late infection: Stage 3 (persistent infection) – Although the pattern varies, episodes of arthritis often become longer during the second and third years of the illness, lasting months rather than weeks, and chronic arthritis – defined as a year or more of continual joint inflammation- characteristically begins during this period. Typically, only one or a few large joints are affected, most commonly the knee. Synovial lesions show villous hypertrophy, the deposition of fibrin, a heavy infiltrate of mononuclear cells, the intense expression of HLA-DR on many cell types, and sometimes a few spirochetes in and around blood vessels along with a form of endarteritis obliterans [a full vasculitis with destruction of blood vessel and occlusion of the vessel caused by the spirochete and immune response to the presence of the spirochete]. In severe cases, chronic Lyme arthritis may lead to the erosion of cartilage and bone and, rarely, to permanent joint disability.

The production of interleukin-1, which can be stimulated directly by *B. burgdorferi*, is found in joint fluid, as are elevated levels of collagenase and prostaglandins E₂; this lymphokine is likely to be one of the mediators that cause synovial proliferation and activate collagenase. The number of patients who have recurrences increased by 10 to 20 percent each year, and even patients with chronic arthritis rarely have continual joint inflammation for more than several years.

The best example of prolonged latency followed by persistent infection in Lyme borreliosis is acrodermatitis chronic atrophicans, the late skin manifestation of the disorder, which has been observed primarily in Europe..... *B. burgdorferi* has been cultured from these lesions as long as 10 years after their onset.... In longstanding cases, chronic joint and bone involvement, including periostitis and subluxation of the small joints, may be seen underlying the cutaneous lesions, suggesting the spread of the spirochete by direct extension.

The treatment of stage 3 joint or neurologic abnormalities has generally been problematic than that of Lyme disease of other manifestations, and the response, particularly in patients with arthritis, may be slow.

Musculoskeletal Manifestations

Musculoskeletal symptoms in Lyme disease are commonly present in all stages of the disease. Lyme arthritis (LA), whether intermittent, chronic and/or constant, is a hallmark of late Lyme disease. Arthritis is a dominant feature in most patients with Lyme disease, but the pattern of arthritis varies during the different stages. In the United States, arthritis is the most common manifestation of late disseminated Lyme disease (LD). Arthritis is observed in about 60% of untreated or incompletely treated patients, developing a few months after the onset of disease.⁴ Initially, this is an intermittent asymmetric mono- or oligo-arthritis of large joints, with a predilection for the knee joints. Recurrent inflammation may continue for weeks or months. If left untreated, many of these patients eventually develop an acute or subacute arthritis of one or both knee joints, which progresses in adults as a septic arthritis, crystalline-induced arthritis, or reactive arthritis. The affected joint may have a large effusion with a non-purulent synovial fluid, which is inflammatory. Eighty five (85%) of patients with LA may have serum immunoglobulin G (IgG) antibodies to *Borrelia burgdorferi* (Bb) by Western blotting.⁷ A culture test of the synovial fluid does not reveal Bb, but Bb DNA can be demonstrated by polymerase chain reaction (PCR) in a majority of untreated patients.^{5,6}

The pathogenesis of Lyme arthritis is directly related to the spirochete infection and invasion. IDSA postulates that later manifestations of LD are only due to immunologic abnormalities. In other words, they believe it to be an infectious disease that behaves like a rheumatic or autoimmune disease without the presence of a persistent spirochete infection. What is often forgotten in cases of late disseminated Lyme disease presenting with chronic arthritis is the direct invasion of the spirochete in the joint includes its capsule, surrounding tendons, ligaments and most importantly the enthesis. Because of the poor blood supply to these soft tissue structures, delivery of antibiotics is limited and therefore, these soft tissue structures become safe havens or niches for spirochete.

The prodromal symptom of early Lyme during the Erythema migrans [EM] rash resembles a typical viral syndrome with polyarticular arthralgia in both large and small joints. Frank arthritis develops within months or a few years (depending on the patient) following a tick bite in untreated or inadequately treated patients and is a manifestation of late disseminated Lyme disease. It also affects one or more joints in two distinct patterns, intermittent arthritis and chronic arthritis.⁵

Intermittent arthritis develops in at least 60% of patients with Lyme disease who are not treated during the early stage of the infection.^{4,6} The pattern of joint involvement is either an asymmetric oligo-arthritis (involving a few joints) or a mono-arthritis (involving one joint), primarily affecting large joints. The knee is the most commonly involved joint, and the ankle and the wrist are the next most common site of arthritis⁸. During episodes of arthritis, the affected joint may become very swollen, warm, and mildly painful. Effusions in one or both knee joints are typical of the intermittent arthritis of Lyme disease. Also described are very large knee effusions, Baker cyst formation and spontaneous rupture.⁹ This type of arthritis lasts weeks to months. Generally, the frequency and duration of the arthritis attacks are

greater in the early years of the disease. Between episodes of joint inflammation, the patient has no joint symptoms.

About 10% of untreated patients with recurrent attacks of arthritis lose the typical periodicity of flares and develop chronic arthritis in up to three of the large joints.^{4,6} One or both knees are most often involved.^{4,6} Chronic Lyme arthritis clinically causes unremitting joint swelling and pain for at least one year. The portion of patients with Lyme arthritis who do not have a history of EM is increasing and the lack of EM should not exclude patients with characteristic arthritis from being tested for Lyme disease.

The aforementioned observations lead Dr. Steere to state that "Lyme arthritis is an indolent bacterial infection and damage is delayed for months or years. The *Borrelia* spirochete lacks the enzymatic activity of other bacterial pathogens that may affect the joints. The joint damage occurs largely due to an exuberant inflammatory response. The synovial pathology in Lyme arthritis is similar to non-bacterial inflammatory arthritis. This includes synovial hypertrophy, vascular proliferation and infiltration of the synovial membrane with mononuclear cells but lack the typical rheumatoid arthritis findings of germinal centers and follicular hyperplasia. As in indolent infections cultures are often negative."⁴

Synovial fluid analysis shows a mild elevation of white blood cells, usually less than 50,000 cells/cubic millimeters, hence the description as "non-pyogenic". White cells are seen, but the concentration is not what is normally seen in a virulent bacterial infection like that seen in a full bacterial infection. Radiologic findings include soft tissue changes, including knee effusions, synovial hypertrophy, edema of the infra-patellar fat pad and enthesitis.⁴ Additional findings include symmetric articular cartilage loss, juxta-articular osteopenia and erosions at the bare areas at the margins of the cartilage all signs of permanent damage. Radiologic films of the involved joints in the early stages of Lyme arthritis are typically normal.^{9,10,12}

Approximately 10% of patients with Lyme arthritis do not respond to either oral or intravenous antibiotic therapy, the treatment normally prescribed according to the standard prescribed recommendation.^{10,11} IDSA panel members believe that such patients have antibiotic refractory arthritis, which is defined by persistent joint swelling for three or more months after the start or at least 4 weeks of IV antibiotics therapy of at least eight weeks of oral antibiotic therapy, or occasionally both. The possibility of persistent infection is unlikely, they claim, but the persistent arthritis results from immunologic abnormalities. This assumption is made because of the rare finding spirochetes either by culture or spirochetal DNA found in the synovial fluid.¹⁴ Both these techniques are documented to be of very low yield in the literature in any patient with a chronic presentation.¹³ Patients with this condition have a higher incidence of HLA-DRB1 alleles which are similar to rheumatoid arthritis alleles and are thought to have greater immune reactivity to *Borrelia burgdorferi* outer surface protein A (OspA).³

The general recommendation provided by IDSA is to treat these patients with oral non-steroidal anti-inflammatory drugs, hydroxychloroquine (interestingly this is an anti-malarial antibiotic), sulfasalazine (a weak antibiotic with anti-rheumatic properties) or intra-articular steroids (anti-inflammatory with immunosuppressive properties).¹ However, this recommendation is qualified by noting that intra-articular steroids should not be used for Lyme arthritis if the patient has not previously been treated with adequate antibiotic therapy. An additional treatment strategy in patients with persistent arthritis is arthroscopic synovectomy,¹ despite the fact that it is surgically difficult to achieve a complete synovectomy through arthroscopy. There is a published report in the orthopedic literature of persistent *Borrelia burgdorferi* infection an individual after repeated synovectomies and multiple courses of oral and intravenous antibiotics.¹⁶ Synovectomy may surgically eliminate the spirochete-infested synovium but does not address the local invasion in the surrounding tendons, ligaments, muscle, joint capsule or entheses.

However, chronic Lyme arthritis is a septic arthritis, septic peri-arthritis and a septic enthesitis, and should be treated as such. According to Mandell,¹³ "infectious arthritis of single or multiple joints may be caused by any of a number of diverse microorganisms. Bacterial arthritis, also known as suppurative, pyogenic, or septic arthritis, is the most common, and arguably most important joint infection, and is considered a rheumatologic emergency".¹³ Predisposing factors in bacterial arthritis include rheumatoid arthritis, crystal-induced arthritis, osteoarthritis, Charcot's arthropathy, diabetes mellitus, chronic renal failure, chronic liver disease, collagen vascular disease, malignancy, HIV infection, immunosuppressant therapy including systemic steroid, hypogammaglobulinemia, intra-articular glucocorticoid injections, penetrating injury, skin disease, prosthetic joint, intravenous drug use and endocarditis.¹³ The morbidity of septic arthritis is considerable, with up to 50% of patients reporting decreased joint function or mobility after infection.¹⁵ This morbidity and mortality has not changed appreciably in the past two to three decades despite improved antimicrobial agents, adjunct treatment measures and hospital care.¹⁷ The extremely vascular synovial membrane of the joint lacks a limiting basement membrane increasing the susceptibility to invasion of bacteria during bacteremia.¹⁸ The clinical manifestations, severity, treatment and prognosis of septic arthritis are dependent on the identity and virulence of the infecting bacterium, source of joint infection and underlying host factors such as immune status, co-morbid illness and abnormal joint architecture resulting from disease of surgery.¹³

Chronic infectious arthritis is a constellation of monoarticular or less commonly oligoarticular joint infection characterized by an insidious onset, indolent course, paucity of symptoms and progressive joint destruction resulting in considerable loss of articular function.¹³ Chronic infectious arthritis is an emerging problem in immuno-compromized or chronically ill hosts. A noteworthy aspect is its ability to mimic other inflammatory joint disorders such as rheumatoid arthritis, causing little clinical suspicion, and resulting in considerable delays in diagnosis. Moreover, establishing a pathogen-specific diagnosis is difficult and the response to treatment is slow and incomplete.¹³ The infectious causes of chronic monoarticular or oligoarticular arthritis include *Borrelia burgdorferi*, *Treponema pallidum*, *Nocardia*, fungi, mycobacteria and parasites.¹³

Selective Review of Literature

1986

Craft JE, et al. [Steere, AC] *Journal of Clinical Investigation*. Oct;78(4):934-9.

- The appearance of a new IgM response and the expansion of the IgG response late in the illness, and the lack of such responses in patients with early disease alone, suggest that *B. burgdorferi* remains alive throughout the illness.

1991

Ruberti, G. [Steere AC] et al. *Human Immunology*. May; 31(1):20-7.

- Increase in DRB1*1301 allele resulting in rheumatoid arthritis like presentation.

1994

☞ Nocton J. J., et al. [Steere AC] *New England Journal of Medicine*. Jan 27; 330(4):229-34

- *B. burgdorferi* DNA by PCR was detected in 85% of patients with Lyme arthritis and in none of the control patients.

2001

Pachner, A.R., et al. *Annals of Neurology*. Sep; 50(3):330-8.

- Antibody measured in serum may not predict the severity of neurologic infection. Spirochetal density in the nervous system and other tissues by PCR were compared to anti-*Borrelia burgdorferi* antibody in the serum and cerebrospinal fluid and to inflammation in tissue in a primate model of Lyme neuroborreliosis. Despite substantial presence of *B. burgdorferi* in the central nervous system, only minor inflammation was present compared to skeletal and cardiac muscle, which contained similar levels of spirochete, were highly inflamed. Lyme neuroborreliosis is a persistent infection, spirochetal presence is a necessary but not sufficient condition for inflammation and that antibody measured in serum may not predict the severity of neurologic infection.

Immunosuppressive Nature of *Borrelia Burgdorferi*

It is imperative to understand that *Borrelia burgdorferi* as an infectious organism causes immunosuppression of the host independent of the host's premorbid immune status. *Borrelia burgdorferi* causes immunosuppression by the following mechanisms: 1. Complement inhibition,¹⁹ 2. Inhibitory cytokine induction of IL10 leading to suppression of immune response.¹⁹ 3. Antibody sequestration in immune complexes¹⁹ 4. Phase and antigenic variation of Bb,^{19,20} 5. Gene switching, including mutation and recombination, variable antigen expression, fibronectin binding,²⁰ 6. Physical seclusion in intracellular sites including synovial cells, endothelial cells, fibrocytes, macrophages and kupffer cells,^{20,21,22} 7. Physical seclusion in extracellular sites including joints, eyes, central nervous system, and binding to proteoglycan, collagen, plasminogen, integrin and fibronectin,^{23,24} 8. Secretory factors, including hemolysin, porin, adhesion, pheromones, aggrecanase.^{25,26,27} Biofilm formations are probably an additional mechanism of sequestration.

Immunosuppression leads to a number of difficulties in the host defense system. These include inadequate antibody response and hence false negative diagnostic testing for the spirochete by ELISA and or Western blots testing, diminished bacterial killing via the complement and the T and NK cellular pathways, and unmasking of latent infections like Streptococci, parasites and especially intracellular organism such as chlamydia pneumonia, mycoplasma species, EBV, HSV, and HHV6. Additionally switch from cellular to humeral immune response accentuated symptoms of allergies, asthma and an inflammatory cascade leading to marked systemic inflammation. Collectively, the Bb, the latent infections and the accentuated inflammatory response further wreck havoc on the infected individual accentuating all manner of symptoms that lead to additional significant morbidity. Sequestration and physical seclusion sites allow Bb to evade the immune system and antibiotic effectiveness leading to need for combination antibiotic therapies with beta-lactams and macrolides the latter inhibit protein synthesis via an intracellular mechanism.

Treatment Relapses, Failures and Persistent *Borrelia burgdorferi* Infection

There are numerous references in the published literature reporting treatment relapses and treatment failures. Additionally, several publications document a persistent infection by culture or PCR testing despite treatment. Some of these references follow (*references marked [B] are included in ILADS binder*):

1. Bradley, J. F., et al. (1994). The persistence of spirochete nucleic Acids in Active Lyme Arthritis. *Annals of Internal Medicine*. 487-9.
2. [B]Fraser, D. D., et al. (1992). Molecular detection of persistent *Borrelia burgdorferi* in a man with dermatomyositis. *Clinical and Experimental Rheumatology* 10:387-390.
3. [B]Battafarano, DF, et al. (1993). Chronic septic arthritis caused by *Borrelia burgdorferi*. *Clinical Orthopedics and Related Research*. (297):238-41.
4. [B]Georgilis, K., et al. (1992). Fibroblasts protect the Lyme disease spirochete, *Borrelia burgdorferi*, from ceftriaxone in vitro. *The Journal of Infectious Diseases*. 166:440-444.
5. Girshick, H. J., et al. (1996). Intracellular persistence of *Borrelia burgdorferi* in human synovial cells. *Rheumatology International*. 16(3): 125-132.
6. [B]Haupt, T., et al. (1993). Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. *Arthritis and Rheumatism*. 36:1621-1626.
7. [B]Ma, Y., et al. (1991). Intracellular localization of *Borrelia burgdorferi* within endothelial cells. *Infection and Immunity*. 59:671-678.
8. [B]Montgomery, R. R., et al. (1991). The fate of *Borrelia burgdorferi* within endothelial cells. *Infection and Immunity*. 59:671-678

9. Nanagara, R., et al. (1996). Ultrastructural demonstration of spirochetal antigens in synovial fluid and synovial membrane in chronic Lyme disease: possible factors contributing to persistence of organism. *Human Pathology*. 27:1025-1034.
10. Nocton, J. J., et al. (1994). Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis. *New England Journal of Medicine*. 330(4):229-234.
11. Schmidli, J., et al. (1988). Cultivation of *Borrelia burgdorferi* from joint fluid three months after treatment of facial palsy due to Lyme borreliosis. *Journal of Infectious Diseases*. 158:905-906.
12. Wolbart, K., et al. (1998). Detection of *Borrelia burgdorferi* by PCR in synovial membrane, but not synovial fluid from patients with persistent Lyme arthritis after antibiotic therapy. *Annals of Rheumatic Diseases*. 57(2):118-21.

Areas of Concern and Inconsistency in the Literature

The majority of studies quoted in support of the IDSA recommendations have very restrictive inclusion criteria, evaluating otherwise previously healthy Lyme disease patients who presented with a rash, neurologic, arthritic or carditis. By the enrollment criteria and exclusion criteria, any patients with premorbid conditions including diabetes, hypertension, rheumatoid arthritis, Lupus or patients on immune-compromising medications were excluded. Individuals with pre-existing conditions are not addressed in the Guidelines, but the researchers recommend their conclusions apply to all patients equally. While research should be conducted on immune-compromised individuals to determine optimal treatment recommendations, there is no evidence to support the application of this same criteria of limited antibiotic therapy to these immuno-compromised patients. Hence, treatment duration in these instances should be left to the judgment of the treating physician.

The failure rate in all studies quoted or reviewed by the panel across the board, whether addressing neurologic or arthritic manifestations, was approximately 20%. Therapy for this subgroup of individuals is not further addressed. Patients presenting to rheumatologic clinics across the United States fall into this category, yet no research is conducted on the proper treatment of their ailments.

While the EM rash alone is generally considered diagnostic of Lyme disease, only 68% of CDC reported cases observed an EM rash.²⁸ However, EM rash is still used as a major criteria in defining the disease. Diagnosis and treatment protocols do not reflect this fact. Patients that did not initially present with the EM rash and instead presented with disseminated Lyme are infrequently mentioned in the literature. Early antibiotic therapy of LD can prevent the development of late features such as LA. Thus, detection of erythema migrans (EM), the cardinal clinical sign of early LD, is critical to early diagnosis. But EM can be missed in individuals with colored skin. Fix, et al.,²⁹

analyzed the Maryland Lyme Disease Registry from 1993 to 1996, and among all the manifestations of LD, the greatest difference between Caucasians (C) and African Americans (AA) was in the reported incidence rate (IR) of EM, both across the state (5.7 cases per 100,000 population per year vs. 0.3), an incidence rate ratio (IRR) of 17.7; and in endemic areas, IR (C) 28.0 versus IR (AA) 4.9, IRR 5.7. In contrast, the frequency of LA in an endemic area revealed an IR (C) of 17.4 and IR (AA) of 18.5 with an IRR of 0.9. The authors concluded that the relative increase of LA in AA was related to the decreased recognition of EM, resulting in delayed treatment of LD.²⁹ This is clearly devastating, especially in an ethnic minority who may not have ready access to adequate health care.

The Guidelines' authors assume that "the etiology of residual patient complaints after treatment may include an inflammatory response, unrelated to active infection, or alternative disease processes." ¹ This assumption is dangerous to make because the etiology may be both a persistent infection and an inflammatory response. Antibiotic therapy is therefore required to continuously treat the infectious process that is triggering a cascade of damaging inflammatory response by the immune system. Dr. Steere in a 2006 review on Lyme arthritis therapy states: "For patients who have persistent arthritis after receiving oral doxycycline for 1 month and IV ceftriaxone for 1 month and who have negative PCR results for *B burgdorferi* DNA in joint fluid, we recommend NSAIDs and hydroxychloroquine, which may have both anti-spirochetal (43,44) and anti-inflammatory effects (45). In our experience, breakthrough cases of persistent infection were not identified in DMARD-treated patients, except in one case. Although we have used more potent DMARDs, we are reluctant to recommend them, because our limited experience does not prove efficacy and because of the concern that they might be given to patients in whom infection is still active."¹¹

The Guidelines state that "practitioners must be aware of subtle neurologic symptoms that may require treatment with I.V. antibiotic" in patients with Lyme arthritis. However, the Guidelines also assert that same neurologic symptoms are considered minor and inconsequential thus are to be ignored in patients without arthritic manifestations, negatively influencing their diagnosis and treatment and final outcome.

The Guidelines' authors do admit that "not all patients with Lyme arthritis respond to antibiotic therapy." However, no specific therapy recommendations are provided for this group of patients, and indeed, restrictions are placed on treatment protocols.

Clinical observation is denigrated by the IDSA panel, though clinicians see and treat 98% of Lyme patients in all the odd and atypical presentations. Future studies must include multiple sites with

multiple clinics involvements, both in the field and in research centers, to better define the entire spectrum of the disease manifestation. Not addressed in the Guidelines are Lyme associated myositis, capsulitis, enthesitis, osteomyelitis and panniculitis.^{30,31} As a result, patients thus compromised have no treatment options available to them in the Guidelines.

Discussion

I am a board certified rheumatologist and internist with a special interest in the rheumatic presentations of infectious diseases, an interest sparked during research conducted for an M.S. in biochemistry at Loma Linda University in 1982. Since graduating from the Georgetown University Hospital Fellowship in Rheumatology in 1993, I have devoted my career in finding the underlying causes of some of the more common rheumatic diseases, including fibromyalgia, chronic fatigue syndrome, rheumatoid arthritis, reactive arthritis, autoimmune diseases and vasculitis. Over time, it has become progressively clear to me that in treating patients with a variety of rheumatic presentations, in the majority of rheumatic diseases and probably the majority of all degenerative diseases (such as diabetes, high blood pressure, dementia, strokes, heart attacks, kidney failure, cancer, etc.), which are significantly on the rise today, stem from a combination of genetic predisposition and environmental triggers, collectively known as the individual's phenotype. This leads to the development of the theory of complex causality in which the genotype may interact with chronic infective triggers causing in some a phenotypic presentation of rheumatic diseases. Of the various types of infection that I evaluate and treat in my rheumatology practice, Lyme disease is the most progressively disabling to individuals. The disseminated form of Lyme disease is a systemic, multi-organ persistent infection I refer to as Lyme Complex, one very much underestimated by research centers.

It should not come as a surprise that, like its related spirochetal infection, syphilis, Lyme disease is a great mimicker of other diseases. Though when adequately investigated, Lyme is the underlying cause of many persistence disturbance to the organ system. For example, if a patient is predisposed genetically to rheumatoid arthritis and is infected with Lyme from a tick bite, perhaps the phenotypic presentation may be a joint inflammation with synovitis leading to the clinical diagnosed of rheumatoid arthritis. However, if a patient has the genetic predisposition for multiple sclerosis, and was unfortunate enough to be bitten by a tick infected with Lyme spirochete, perhaps the phenotypic presentation may be multiple sclerosis, though the underlying trigger for the disease is Lyme disease.

In my rheumatology practice alone, I have seen and diagnosed Lyme infection in patients presenting with fibromyalgia, chronic fatigue syndrome (CFS), chronic immunodeficiency fatigue syndrome, polymyositis, polymyalgia rheumatic, temporal arteritis (TA)*, rheumatoid arthritis, Reiter's syndrome, reactive arthritis or spondyloarthropathy, and Systemic Lupus Erythematosus (SLE). Other diseases include Wegener's vasculitis, chronic asthma, chronic sinusitis, chronic headache and migraine syndromes, chronic neck pain, lumbago, Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD, both Crohn's Disease and Ulcerative Colitis), Hashimoto's thyroiditis, Lou Gehrig's Disease (ALS), dementia, Alzheimer's dementia, and seizures. Many physicians in the field that treat patients with disseminated Lyme disease share these observations. This list is not exhaustive, either. IDSA does not recognize that tick-borne diseases can cause clotting, strokes, or heart attacks. It is therefore unacceptable to allow them to restrict diagnostic criteria and treatment Guidelines before they fully define the actual disease. Doing so would exclude too many factors involved in the disease, and would condemn many patients to disability and a life of pain and suffering by limiting diagnosis and treatment options.

Part of the difficulty stems from the assumption that because Lyme is known as an indolent infection (i.e. a slow-growing infection), it must be benign. However, this does not necessarily follow: both TB and HIV have long latency periods, but neither infection is considered benign, and both are treated with combination antibiotic or antiviral therapies, respectively, for prolonged periods in excess of a year. The assumption of an indolent infection being benign is therefore not an absolute, and assigning Lyme to this condition is inaccurate.

The disease state was initially defined based on research using a rather small sampling of cases clustered in a tightly-knit group of states. By the direct result of exclusion criteria in study design, subsequent studies eliminated all patients that would skew the data. Patients excluded were those that presented with atypical symptoms. As the FDA and most pharmaceutical companies know, it is only after a drug is used for months or sometimes years before enough individuals use the medication, after which less-common side effects or possibly life-threatening reactions will manifest themselves. In the case of drug trials, most use a special subgroup of individuals in same age range with similar symptoms. This is not so with Lyme and other TBD. The initial description and publication by Dr. Steere and others were very accurate and played a key role in defining case presentations for a disease manifestation. However, as the infection spread to different ethnic groups, different sexes and ages, different individuals with premorbid states, individuals from different socioeconomic levels, different levels of nutrition and different immune-suppressed states,

* PCR positive for Bb on temporal artery biopsy [case report to be published]

the disease manifestation changed. The Guideline's authors, however, excluded all those presentation as none-Lyme cases, despite these individuals having positive test results by Western Blots or PCR proof of Lyme on tissue sampling.

Different *Borrelia* spirochete species may manifest differently in various organs (skin, heart, brain, CSF, blood, lymphatic, muscle, tendons, joints, various organs), and express different groups of surface lipoprotein, inducing variable antibody response and disease manifestations. Moreover, these different *Borrelia* spirochete species may result in more unusual presentations of the disease. Clearly, more research along these lines is necessary. The EM rash is a good example of this: better than 90% of the initial cases in Old Lyme, CT, in the mid 1970s had a classic EM rash that is colloquially known as the Bull's Eye rash. However, today only 25% of patients presenting with refractory arthritis have a history of EM rash.¹¹

The existence of tick-borne co-infections leads to variations of clinical presentation. Different individuals respond to treatment in different ways: a patient with Lyme disease and Babesiosis or Lyme disease and Bartonellosis will have significantly more exhaustive fatigue and neurocognitive and neuropsychiatric manifestations respectively than patients with Lyme disease alone. Their treatment requirements including the choice of antibiotics, the route of treatment, the duration of treatment, monitoring requirements will be different from those manifesting Lyme disease alone.

Additional factors that further expand the disease manifestations and the intensity of various organ system involvement include antecedent infection (chronic infectious states such as EBV, HHV6, CMV, mycoplasma, salmonella, Brucella, Legionella, strep, Giardia, presence of any parasite or worms, childhood diseases), premorbid state(s) (presence of diabetes, congestive heart disease, chronic renal failure, immune-suppressed state, prednisone use, immunosuppressing drugs, cancer, cancer survivors), presence of environmental toxins and genetic mutations that limits the body's ability to detoxify. The outcome of the infection depends on the patient's pre-morbid state, immunogenetics, the virulence of the strain of *Borrelia*, the effect on the system of other tick borne co-infections, as well as concomitant viral, bacterial, fungal, parasitic infections and the presence and concentration of environmental toxins, pollutants, and heavy metals. Lyme infection alone is difficult to treat; Lyme in conjunction with other infections in the setting of a toxic state is infinitely more difficult to treat.

Over-reliance on imperfect tests results in the failure to treat Lyme, leading to disastrous consequences to patients. In an immunosuppressant individual who is diagnosed with rheumatoid arthritis or Lupus or a diabetic, the immune response to Lyme is expected to be blunted or

suppressed by the standard treatments for the rheumatic disease, collectively known as DMARDS, that testing for Lyme with standard serology's (including ELISA or a Western Blot) are likely to be negative, leading to the erroneous conclusion that the spirochete is not present.

The Lyme spirochete is capable of surviving in a host despite the application of oral and intensive intravenous antibiotics, even for months or years. This fact is well proven in my practice: I see patients with a wide range of rheumatic manifestations and rheumatic disease labels that have failed treatment provided by other rheumatologists using conventional therapies, most of which are immunosuppressant. I also see patients from other Lyme practices that still fail prolonged antibiotic therapies given either oral or intravenously for months and years. Some patients remain quite ill despite receiving heroic courses of antibiotics. In my opinion, one of the causes of treatment failures may be the presence of an abscess containing bio-films of Lyme infection where the spirochete is protected and thrives. My personal observation is that sinuses, tonsils, gallbladders and previously damaged joints (from trauma, osteoarthritis, gout, CPPD crystal arthritis or in the setting of any inflammatory joint condition) are the most common areas that act like abscesses. PCR testing for Lyme spirochete has been positive on surgical sampling of these organs. I have collected data documenting PCR positivity for Bb on tissue sampling of temporal artery, tonsils, sinuses, gallbladders, duodenal and colon biopsies, prostate, bladder, and synovial tissue from hips and knees. This data will be published in the near future. The individuals from whom the tissue sampling was collected had all received "adequate" antibiotic therapy as outlined in the Guidelines. Limiting treatment to a few weeks of antibiotic therapy would clearly be devastating in these individuals, as it did nothing to treat the disease, and left the spirochete intact to continue its devastation of the patient's body.

Lyme infection induces a wide variety of pathologic manifestations, both directly and mediated through the immune response, highly debilitating those individuals. The guideline's authors assume that after a period, the presence of the spirochete is not required and the persistent disease manifestations are autoimmune. In my observation, the sickest patients are those with exuberant immunologic manifestations proven to have persistent positive Lyme Western Blots, usually an IgM responses, or persistent spirochete infections by PCR testing on surgical samples. The persistence of the spirochete infection induces a destructive and exuberant immunologic response further leading to organ failure and sometimes ultimate demise. That is, the presence of a persistent infection induces the immunologic response to that infection. These are not mutually exclusive.

When Lyme disease is correctly diagnosed and intensely treated in its earlier stages before irreversible neurologic and rheumatic injury occurs, recovery with a favorable outcome is generally

the rule. However, when Lyme disease is underestimated or misdiagnosed or if the Guidelines are followed strictly in late disseminated Lyme disease, the outcome for many patients is unfavorable.

Recommendations

The IDSA definition and categorization of various Lyme presentations should be further updated to include acute Lyme arthritis in the early disseminated category and three new categories be added representing all the atypical presentation of Lyme disease. The first new category can be labeled Latent Lyme or any representative and accurate term of the IDSA's choosing. Latent Lyme represents those patients with Lyme that present with multiple sclerosis, Lou Gehrig's disease, rheumatoid arthritis, systemic lupus erythematosus, Wegener's granulomatosis, Sarcoidosis, seizure disorder, dementia including Alzheimer's as examples. The current treatment recommendation of the Guidelines do not apply to this category and further investigation and research should be conducted on this large and underrepresented group of patients with Lyme disease. The second new category can be labeled Tick-Borne Disease complex or any representative and accurate term of the IDSA's choosing. The Tick-Borne Disease Complex represents manifestation in patients with a combination of tick borne diseases such as Lyme and Bartonellosis, Lyme and Babesiosis, Lyme and Ehrlichiosis, or any other combination thereof. The final new category can be labeled Latent Tick-Borne Disease Complex representing a patient manifesting features of latent Lyme and combination of other tick-borne diseases.

Based on the standard recommendation for treatment of a classic chronic bacterial septic joint infection, the Guidelines should further extend the antibiotic course length in all patients presenting with chronic Lyme arthritis and should categorize these individuals as presenting with chronic septic joint and septic soft tissue syndromes. Intravenous antibiotics are preferred for any patient that fails oral antibiotics or on initial presentation is listed with an immuno-compromised condition defined as having an autoimmune disease such as RA, Lupus, Sarcoidosis, vasculitis, on DMARD, steroids or diabetes, or pre-existing joint damage from osteoarthritis, internal joint damage or crystal arthritis.

The early use of antibiotics combined with an adequate course length of treatment can prevent persistent and refractory Lyme disease and its sequelae. The duration of therapy should be guided by clinical response, rather than by an arbitrary treatment course. The Guidelines should encourage the exercise of clinical judgment taking into account the individual history and presentation of the patient. In addition, the Guidelines should very clearly state that the recommendations' outlines are treatment suggestions, and not limiting or restrictive regimes. Given the potentially infectious

etiology of persisting symptoms and the fact that there is currently no test that can rule out infection for the patient, absolutely no gaps in antibiotic treatment, counter to the recommendation in the Guidelines, should be mandated.

Since there is currently no definitive test for Lyme disease, laboratory results should not be used to exclude an individual from treatment. Diagnosis and treatment Guidelines should clearly state that the following conditions are not addressed and therefore the treatment for these conditions are left to discretion of the treating physician:

1. Lyme induced myositis, both polymyositis and dermatomyositis
2. Lyme induced osteomyelitis
3. Lyme induced panniculitis
4. Lyme induced fasciitis
5. Lyme induced reactive arthritis and spondyloarthropathies including enthesitis
6. Lyme in any immunocompromised individual or documented immune deficiency state such as:
 - a. Lyme in a diabetic
 - b. Lyme in patient with metabolic syndrome (syndrome-X, Insulin resistant state)
 - c. Lyme in any chronic debilitating disease such as congestive heart failure, chronic renal insufficiency, fibromyalgia, or CFS
 - d. Lyme in patients who received or are receiving oral/I.V. steroid therapy.
 - e. Lyme in patients who received or is receiving a DMARD – disease modifying anti-rheumatic drug – or chemotherapeutic such as prednisone/steroids, Solumedrol, Plaquenil, Methotrexate, Immuran, Ridaura, Myochrisine, biologics [Enbrel, Humira, Kineret, etc.], Celcept, Cytosan, Arava, 6-MP
 - f. Lyme in a patient intolerant of oral antibiotic therapy.

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