REVIEW

Common Misconceptions About Lyme Disease

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ABSTRACT

Lyme disease, infection with *Borrelia burgdorferi,* is a focally endemic tick-transmitted zoonosis. During the 3 decades since the responsible spirochete was identified, a series of misconceptions and misunderstandings have become widely prevalent, leading to frequent misdiagnosis and inappropriate treatment. Persistent misconceptions concern the reliability of available diagnostic tools, the signs and symptoms of nervous system involvement, the appropriate choice and duration of antimicrobial therapy, the curability of the infection, and the cause of symptoms that may persist in some patients after treatment. Concern about disparate perspectives led the Institute of Medicine to review the subject. In this article we review the principal misconceptions, discussing their origins and the best currently available scientific evidence related to each one.

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Human infection with *Borrelia burgdorferi*, a spirochete transmitted by *Ixodes* ticks, results in the disorder known as Lyme disease or Lyme borreliosis, the most commonly reported vector-borne infection in the US. Incidence has increased with the geographic spread of infected ticks. A great deal is now understood about this infection's clinical phenomenology and treatment; yet a number of misconceptions (**Table**) continue to cause confusion among practitioners and patients—misconceptions that build on each other and are self reinforcing. As pointed out in a recent Institute of Medicine report,[1] ". . . . strong emotions, mistrust, and a game of blaming others who are not aligned with one's views" have resulted in a heated and politicized debate. A number of factors have contributed to this "debate"—perhaps not the least of which is a tension between the concept of evidence-based medicine and medicine's historical inductive approach from anecdotal observation. This tension is reflected in 2 frequently repeated, interrelated assertions—that laboratory testing for Lyme disease is unreliable and that the disease should be defined "clinically"—meaning syndromically.

Both derive from decades-old observations. What we now consider to be Lyme disease was indeed initially defined clinically in Europe as Garin-Bujadoux-Bannwarth syndrome[2] and in the US as Lyme arthritis.[3] The subsequent identification of the causative organism and development of reliable serologic testing allowed these "clinical diagnoses" to be supplanted by biologically based criteria. However, some have continued to argue that the diagnosis should rest principally on the recognition of particular clinical phenomena. The difficulty with syndromic definitions is that they typically lack biologic precision. Failure to respond to recommended antimicrobial therapy in a patient "clinically diagnosed" as having Lyme disease could be due to either misdiagnosis or treatment failure. If laboratory testing is not

considered a valid indicator of infection, and if lack of a response to recommended treatment is interpreted as evidence that the infection presumed to be present is resistant to that treatment rather than of an incorrect diagnosis, the list of clinical disorders attributable to the infection, and therefore the syndromic definition, can be expanded unconstrained by objective evidence.

DIAGNOSIS: ARE SEROLOGIC TESTS FOR LYME DISEASE RELIABLE?

Underlying the assertion of the purported unreliability of serologic testing are observations that some patients with Lyme disease do indeed have negative serologic tests. However, in large part these observations merely reflect the normal evolution of the antibody response. In all infections in which there is a humoral antibody response, there is a lag between the onset of infection and the time at which detectable levels of serum antibodies are first demonstrable. Consequently, many patients with early Lyme disease are seronegative.[4] However, the vast majority of such patients have a characteristic skin lesion called erythema migrans, the consequence of early cutaneous *B. burgdorferi* infection at the site of the tick bite. Because the appearance of erythema migrans is considered sufficiently diagnostic, no laboratory diagnostic testing of any sort is recommended or needed.[5]

Although patients with very early Lyme disease may be seronegative, seronegativity occurs rarely—if ever—in individuals with later manifestations or chronic symptoms of *B. burgdorferi* infection. The diagnosis of, and antibiotic treatment for, Lyme disease can rarely be justified in seronegative patients with symptoms of a month's or more duration. Often cited in support of the concept of late seronegativity is a 1988 report[6] in which 17 patients—12 of whom had arthritis—were thought to have seronegative late Lyme disease. In this study, the diagnosis was based on clinical presentation, response to antimicrobial therapy, and results of a T-cell proliferative assay to *B. burgdorferi*. All 17 patients had previously been treated for early Lyme disease with tetracycline, penicillin, or erythromycin—drugs not currently recommended as first-line therapy in the US, but expected to be effective. It was hypothesized that these patients had become seronegative as a result of partial treatment. The results of this study have never been replicated and in fact, patients with active late Lyme arthritis are now known to be invariably immunoglobulin G (IgG) seropositive for antibodies to *B. burgdorferi*.[7,8]

> ## CLINICAL SIGNIFICANCE
>
> - A measurable antibody response requires several weeks to develop, commonly persists after successful treatment, and is not prevented by noncurative therapy.
> - Immunoglobulin (Ig)G rather than IgM Western blots should be used after 1-2 months of illness.
> - No clinical manifestation except erythema migrans allows diagnosis without laboratory confirmation.
> - Two to 4 weeks of oral antibiotics usually suffices, with parenteral antimicrobials reserved for severe involvement.
> - Lyme encephalopathy is not evidence of brain infection.

In retrospect, this early report was flawed for multiple reasons. The T-cell proliferative assay used was later shown to be nonspecific; in one study the false positivity rate was over 60%.[9] Although the patients may have had early Lyme disease previously, there was no laboratory evidence to confirm the presence of infection at the time of enrollment. Although the patients appeared to respond to parenteral antibiotics, treatment was given and responses assessed largely in an unblinded fashion, without a control group, making the results difficult to interpret. Finally, it is not even clear that all of the patients in the study would have been seronegative using currently used serological assays. It is theoretically possible that with current 2-tier testing, which uses higher-sensitivity enzyme-linked immunosorbent assays (ELISA) followed by standardized Western blots to confer specificity, some might have been seropositive.

Studies of partial, noncurative treatment of rabbits experimentally infected with *Treponema pallidum* (syphilis being another spirochetal infection often likened to Lyme disease) provide supporting evidence against the conclusion that partial treatment might abrogate the antibody response. Rabbits that received penicillin during the incubation phase of infection[10] were "either cured or subsequently developed clinically recognizable lesions." Single subcurative doses of penicillin prolonged the "incubation period of experimental syphilis, up to a limit of 30-40 days"; however, when lesions developed, all of the animals became seropositive.

In sum, although there is ample evidence that seronegative *early* Lyme disease is not uncommon, the evidence of seronegative *late* Lyme disease is unconvincing and the concept lacks biologic plausibility.

DOES ANTIBIOTIC THERAPY AFFECT SEROPOSITIVITY FOR LYME DISEASE DURING TREATMENT?

An often-voiced concern is that positive serologic tests for *B. burgdorferi* may become transiently negative during—and because of—antibiotic therapy. There is no precedent in the scientific literature—with respect to Lyme disease or any other identified infection—of noncurative antibiotic treatment transiently suppressing an already-existing antibody response, nor is there a plausible biologic explanation of why this might occur. In patients receiving early, effective treatment for culture-confirmed erythema migrans, the majority still seroconverted.[11] Those who remained serone-

Table Common Misconceptions Related to Lyme Disease		
	Misconception	Evidence
Serologic tests		
False negatives	"Blood tests are unreliable with many negatives in patients who really have Lyme disease"	Just as with all antibody-based testing, these are often negative very early before the antibody response develops (<4-6 weeks). They are rarely if ever negative in later disease
Isolated IgM seropositivity	"Patients with many months of symptoms may have only a positive IgM Western blot"	Because the IgG response develops in 4-6 weeks, patients with symptoms of longer duration than this should be IgG positive; isolated IgM bands in such patients are almost always a false +
Seropositivity after treatment	"Positive blood tests after treatment mean more treatment is needed"	After any infection resolves, the immune system continues to produce specific antibodies for an extended period. This is not an indication of persistent infection
Antibiotics effect on serologic tests	"Antibiotics make blood tests negative during treatment"	There is no evidence that this happens and no biologic reason it would
The clinical diagnosis of Lyme disease	"Lyme disease is a clinical diagnosis that should be made based on a list of symptoms"	No clinical features, except erythema migrans or possibly bilateral facial nerve palsy—in the appropriate context—provide sufficient specificity or positive predictive value. Laboratory confirmation is essential except with erythema migrans
Persisting fatigue & cognitive symptoms in isolation as evidence of brain infection	"Patients with fatigue and memory difficulties have *Borrelia burgdorferi* infection of the brain"	These symptoms are not specific for *B. burgdorferi* infection and only rarely are evidence of a brain disorder.
Severity of Lyme disease	"*B. burgdorferi* infection is potentially lethal"	Although Lyme disease can cause heart or brain abnormalities, there have been remarkably few—if any—deaths attributable to this infection
Prolonged treatment	"If, following treatment, symptoms persist, or serologic testing remains positive, additional treatment is required"	Multiple well-performed studies demonstrate that recommended treatment courses cure this infection. Retreatment is necessary occasionally, but not frequently
Symptomatic improvement on antibiotics as validation of the diagnosis	"Rapid symptomatic improvement on treatment proves the diagnosis despite negative blood tests"	Non-microbicidal effects of antibiotics may result in symptomatic improvement. In controlled trials, 1 patient in 3 improved in response to placebo.

Ig = immunoglobulin.

gative clearly had been treated and cured of Lyme disease before a measurable antibody response had developed.

IS PERSISTENT SEROPOSITIVITY FOLLOWING TREATMENT SIGNIFICANT?

Strongly IgG or immunoglobulin M (IgM) seropositive patients may remain seropositive—and even cerebrospinal fluid-positive—for decades[12,13] despite resolution of the clinical manifestation of Lyme disease for which they were treated. When serially collected serum samples are tested in parallel, a gradual decline in antibody levels is usually observed in treated seropositive patients.[7] Conversely, patients with ongoing infection can develop increasing antibody levels with increasing numbers of bands on Western blots.[8,14] However, this requires that samples be saved over

time to permit such parallel testing, something that is not practical in usual clinical practice.

This normal persistence of the humoral immune response is sometimes misconstrued as evidence of persistent infection. Such a conclusion is biologically illogical, unsupported by scientific evidence, and without precedent in other infections. Unfortunately, this conclusion can lead to unnecessary retreatment, even to the point of advocating treating until the antibody response disappears. This misconception may have evolved from the concept of treating syphilis until the titer of nonspecific reaginic antibodies decreases—a humoral response entirely different from the specific antibody response measured by Lyme disease serologies. Specific serologic tests such as these cannot be used as a test of cure. Interest in the development of tests for active *B.*

burgdorferi infection has intensified in part because rates of persistent background seropositivity can be considerable in high-risk older populations, especially in Europe.[15] Because of this, an important clinical question that always needs to be addressed is whether the patient's clinical symptoms and signs are coincidentally or causally related to seropositivity.

IS ISOLATED IgM SEROPOSITIVITY SIGNIFICANT IN LONGSTANDING INFECTION?

Currently recommended 2-tier serologic testing for Lyme disease includes testing all first-tier (usually ELISA) reactive patients by separate IgM and IgG immunoblots.[16] The IgM immunoblot should be used only for the diagnosis of early infection. In infections, the host immune system initially produces IgM antibodies; IgG antibodies are usually demonstrable by about 4 weeks after onset of *B. burgdorferi* infection. False-positive IgM immunoblots are common in clinical practice[17] and appear to reflect both over-reading of weak bands (of which only 2 are required by IgM interpretation criteria) and the greater cross-reactivity and binding strength of IgM antibodies. Consequently, only the IgG immunoblot is recommended in patients with possible later Lyme disease or in patients ill for >4 weeks. A positive IgM immunoblot without a positive IgG immunoblot well beyond 4 weeks after exposure is more likely to be a false-positive result than an indication of *B. burgdorferi* infection.

SHOULD LYME DISEASE BE PRIMARILY A "CLINICAL DIAGNOSIS"?

Before the development of reliable laboratory testing, diagnosis of what is now known to be *B. burgdorferi* infection was based on clinical phenomenology. The development of reliable laboratory testing now provides a far more accurate means of diagnosis in all but a small number of well-defined circumstances—accuracy that can be described quantitatively in terms of those tests' positive predictive value[18] (defined as the probability that a patient who has a positive test result truly has Lyme borreliosis). Any assertion that a particular clinical syndrome provides more accurate diagnostic support for the diagnosis of Lyme disease can be similarly tested by determining its positive predictive value. For example, in the appropriate context (an endemic area in warmer months), erythema migrans is essentially pathognomonic—that is, there are no false positives, so the positive predictive value (true positives/[true positives + false positives]) would be nearly 1.0.

Extracutaneous manifestations of Lyme disease, however, are far less specific. Facial nerve palsy, for example, is considered one of the more common clinical manifestations. The annual incidence of Bell's palsy (idiopathic facial nerve palsy)[19] is estimated at 23/100,000; about 1% of cases are bilateral (0.23/100,000). There are approximately 30,000 cases of Lyme disease annually in the US (10/100,000); about 8% have facial nerve palsy,[20] of which about 25% are bilateral (0.2/100,000).[21] Hence the positive predictive

value of bilateral facial nerve palsy would be about 46% (0.2/[0.23 + 0.2]). In highly endemic areas, where Lyme disease incidence can reach 300/100,000, the number of patients with Lyme disease-related unilateral facial nerve palsies might be expected to reach 24/100,000, equal to the background rate of Bell's palsy—that is, the positive predictive value of a unilateral facial nerve palsy would still be only 50%, mandating the use of a confirmatory laboratory test before treatment. Only in the case of bilateral palsies, of which 6 cases/100,000 might be due to Lyme disease but only 0.23 to Bell's palsy—with similarly low numbers attributable to other disorders such as sarcoidosis (neurosarcoidosis incidence approximately 0.2/100,000[22]) or Guillain-Barré syndrome (overall incidence approximately 1/100,000[23]) limited to the facial musculature—might this finding be considered diagnostic (96% of cases being Lyme disease related), although confirmatory laboratory testing would still be reasonable, depending on the potential risks of treatment.

Other signs or symptoms seen in Lyme disease—such as radicular pain without a mechanical cause, lymphocytic meningitis, relapsing large joint oligoarthritis, and heart block in an otherwise healthy young individual—could be due to Lyme disease if there has been potential tick exposure in an endemic area. However, given the lower relative frequencies of these disorders in Lyme disease, and their substantial background prevalence due to other causes, laboratory confirmation is essential.

At the other end of the spectrum are many common and highly nonspecific symptoms, such as fatigue, malaise, headaches, diffuse aches and pains, and cognitive slowing, that are common to virtually all inflammatory—and many other—disorders. Perceived cognitive difficulty is a symptom frequently cited as a reason to be concerned about Lyme disease.[24] However, severe cognitive difficulties are reported by about 2% of the US population,[25] with less severe difficulties in many more. The positive predictive value of this symptom as a diagnostic feature of Lyme disease can be calculated just as in facial nerve palsies. To provide the benefit of the doubt to the proponents of using this symptom to diagnose Lyme disease, the calculation can be biased to maximize its potential impact by adopting several of their assumptions. First, assume that the incidence of Lyme disease is actually 10 times that reported by the Centers for Disease Control and Prevention (CDC) (despite the absence of any compelling evidence to that effect). Second, assume that half of all patients with Lyme disease develop severe cognitive difficulty, also probably a substantial overestimate. This would lead to an estimated incidence of Lyme disease-associated severe cognitive difficulty of 150 cases/100,000 population. Compared with a background prevalence of 2%, or 2000 cases/100,000, the positive predictive value of this finding would be <8%. This number clearly could never justify treatment in the absence of more specific evidence, such as laboratory confirmation. Applying the CDC-reported incidence of Lyme disease to the calculation for this symptom would lower the positive predictive value to <1%.

Clearly, diagnosing Lyme disease based on even less specific clinical findings is unsupportable.

IS PERSISTENT FATIGUE AND PERCEIVED MEMORY AND COGNITIVE DIFFICULTY EVIDENCE OF BRAIN INFECTION DUE TO *B. BURGDORFERI*?

An estimated 10%-15% of patients with *B. burgdorferi* infection develop central nervous system involvement.[26] This most often consists of meningitis; rarely, there are clinically evident focal findings. As with all central nervous system infections, there is almost always supporting laboratory evidence (ie, imaging or cerebrospinal fluid abnormalities) of both the infection and nervous system involvement.[27]

Some patients with Lyme disease—who have other signs and symptoms of active infection—develop fatigue, memory and cognitive difficulty, often termed Lyme encephalopathy. No clear data are available to estimate its incidence; anecdotally it appears to occur rarely in isolation and in only a minority of individuals with other manifestations of Lyme disease.[28,29] Importantly, Lyme encephalopathy is not synonymous with central nervous system infection—in fact, such patients rarely if ever have any evidence of this.[27] Rather, patients with symptomatic *B. burgdorferi* infection *outside the central nervous system* may experience the same cognitive and memory problems seen in patients with urinary tract infections, bacterial pneumonia, active rheumatoid arthritis, or other active inflammatory states. This represents a metabolic encephalopathy—clinically indistinguishable from the cognitive difficulty described in over 2% of the general population—most likely due to the neuroactive effects of soluble immunomodulators.[28,30] Misattribution of these symptoms to central nervous system infection is terrifying to patients and intimidating to physicians; it has contributed greatly to the overall anxiety and confusion about this disease.

Finally, although there are case reports of patients with Lyme disease developing a broad range of psychiatric disorders, no epidemiologic study has ever demonstrated a statistically meaningful association between Lyme disease and psychiatric disease beyond that noted with other systemic diseases, or of a unique psychiatric presentation of Lyme disease. No biologically plausible mechanism for such an association has ever been proposed.

LYME DISEASE—CAN IT BE LETHAL?

A few case reports suggest that Lyme carditis might have contributed to a patient's death.[31-33] This question was formally examined as part of a review of 1999-2003 US death certificate data.[34] Lyme disease was a listed diagnosis on 119 of the reviewed death certificates. Among these, only one patient had symptoms consistent with Lyme disease. If this one patient actually died because of Lyme disease, a comparison to the reported Lyme disease incidence data during the same period would suggest a mortality rate of approximately 1/100,000 cases. Certainly, in any disease

with such extraordinarily low suspected mortality, a causal relationship must be highly suspect.

IS THERE A RATIONALE FOR LONGER TREATMENT COURSES?

Numerous studies have now shown that Lyme disease can be effectively treated with fairly short courses of recommended antibiotics.[5] Controlled treatment trials have repeatedly demonstrated that more prolonged antibiotic treatment results in no lasting benefit,[5,35-37] but significantly increases risk. The treatment durations recommended for Lyme disease are consistent with those for syphilis and most other bacterial infections.[38]

The argument for extended antibiotic therapy arises from 3 sets of observations. As with many infections, some of a patient's objective clinical symptoms may continue long after the infection has been cured microbiologically. If a patient has facial nerve palsy, time is required for the nerve to recover from the damage that has occurred. An inflamed knee may continue to be painful and swollen for months to years post treatment, even after *B. burgdorferi* can no longer be detected in synovial tissue or fluid by polymerase chain reaction.[39]

Second, analogous to some other infections such as bacterial pneumonia or viral meningitis, purely subjective complaints such as fatigue may sometimes continue for weeks to months after successful treatment. As has been suggested over the years with a number of other infections,[40] in some patients these difficulties have been apparent for years after treatment. No prospective study has addressed whether the frequency of such symptoms at 6 months is any greater in US patients treated for Lyme disease than in controls, although the difficulty identifying patients to enroll in studies of post Lyme disease syndrome[41] suggests a frequency approximating the previously quoted 2%. It should be noted that carefully performed microbiologic evaluations have failed to provide evidence of *B. burgdorferi* infection in treated patients with subjective symptoms lasting >6 months, including studies that have focused on occult central nervous system infection.[37,41-43] Randomized, placebo-controlled retreatment trials in persistently symptomatic patients have clearly shown that additional antibiotic therapy fails to provide meaningful benefit to previously treated individuals.[36,37,41]

It has been suggested that post-treatment symptoms might be due to small numbers of residual spirochetes. While small numbers of organisms might remain following usually recommended treatment,[44] there is no evidence these cause symptoms or elicit a host response. Some suggest that spirochetes might remain concealed in immunologically protected sites—possibly in altered forms such as cysts or in biofilms. Even if there were evidence to indicate clinical relevance of this conjecture, it would remain challenging to provide a pathophysiologic explanation of how this might cause symptoms. On the one hand, the argument presumes there is no inflammatory response to these hidden—and yet to be demonstrated—in vivo—organisms.

Thus, the symptoms could not be due to the soluble neuro-immunomodulators presumed responsible for encephalopathies in other inflammatory disorders. On the other hand, there is no evidence that *B. burgdorferi* can elaborate an exotoxin[45] that might elicit such symptoms. In contrast, there is ample precedent for asymptomatic latent infections, as illustrated by the persistence of *Mycobacterium tuberculosis* in one third of the world's population.

Finally, given the misconceptions about how to diagnose Lyme disease, it is likely that in at least some patients, symptoms fail to respond because they are not due to *B. burgdorferi* infection. Proponents of prolonged treatment have created a self-reinforcing logical construct. If patients improve after prolonged treatment, this is taken as validation of the diagnosis, disregarding any potential for a placebo response that occurs in about one third of patients given placebo in Lyme disease treatment trials.[36] If the patient's condition does not improve, this is interpreted as evidence that the infection is treatment resistant. If the patient worsens, this is interpreted as a Herxheimer reaction—regardless of when in the course of treatment this occurs. This explanation seems particularly difficult to understand given that a Herxheimer reaction is generally thought to occur with initiation of treatment when a large number of spirochetes die simultaneously. If these patients are believed to harbor only a small number of organisms, it is difficult to understand how this might occur. However, if the diagnosis is made syndromically with no reliable laboratory confirmation, and any of the 3 possible treatment responses is viewed as validating the diagnosis, it is readily apparent how some patients may find themselves treated for an extended period of time for no logical reason.

DOES SYMPTOMATIC IMPROVEMENT WHILE ON ANTIBIOTIC THERAPY CONFIRM THE DIAGNOSIS OF LYME DISEASE?

When patients rapidly feel better while taking antibiotics, they often assume that this proves that they did indeed have *B. burgdorferi* infection, regardless of whether or not the initial evidence of Lyme disease was compelling. However, at least 3 other factors may contribute to such symptomatic improvement. First, other infections, if present, can respond to the same antimicrobials. Second, in blinded, placebo-controlled trials of patients with persisting symptoms, improvement occurred in up to one third of placebo-receiving individuals.[36] Third, many of the antimicrobials used have other important pharmacologic actions. Tetracyclines, for example, have a broad range of anti-inflammatory actions including inhibiting matrix metalloproteinases.[46,47] They can also directly alter neurophysiologic activity, modulate neuronal function[48-50] including pain perception. Ceftriaxone upregulates the glutamate transporter in the central nervous system, decreasing concentrations of glutamate, an important neurotransmitter,[51,52] with resultant decreases in pain and other neurobehavioral symptoms. Consequently, just as persistent symptoms following appropriate therapy

do not disprove the diagnosis, rapid relief of nonspecific or neurobehavioral symptoms does not prove it.

CONCLUSION

Lyme disease has been the source of considerable controversy, with the debate spilling over into political and other arenas. It is regrettable that this has detracted from a reasoned approach to the scientific evidence. The latter has advanced sufficiently over the past 2 decades that diagnosis and treatment of this infection are now generally quite straightforward. Legitimate biologic questions remain to be studied, with answers that may well be relevant in the study of other disorders. However, the existence of these remaining biologic questions does not negate the fact that the approach to diagnosis and treatment is now well defined, and that there is no reasonable basis for the broad range of unconventional and potentially dangerous therapeutic approaches that continue to be recommended by some.

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