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Myths and facts about Lyme disease

KEY POINTS:

Lyme disease is uncommon, and serologic tests for it are sensitive but relatively nonspecific. Therefore, the tests should be used only to confirm a clinical diagnosis, not to screen for Lyme disease in the general population.

Lyme disease almost always responds to a conventional course of antibiotic therapy, although symptoms may take time to resolve.

Physicians need to apply more intellectual rigor in diagnosing Lyme disease to combat the epidemic of pseudo-Lyme disease now underway.

ABSTRACT: Lyme disease has taken hold in the imagination of the general public and physicians alike. Although the disease is real, the diagnosis is often false. Patients demanding an explanation for feeling out of sorts, and physicians too willing to oblige them with improper use of serologic tests and useless therapies both foster a mythology that conscientious physicians should try to combat. This article debunks the myths and presents the facts.

Misconceptions about Lyme disease cause some physicians to diagnose it in many patients who do not actually have it. In fact, patients improperly labeled with Lyme disease may outnumber those who truly have it, at least among patients sent to referral centers such as ours.[1,2]

This misdiagnosis is costly[3] and anxiety-provoking,[4] as patients often undergo lengthy, useless, and potentially harmful treatment for a disease they do not have,[5,6] while foregoing treatment for the conditions they really have. And paradoxically, the failure of such misdirected treatment often reinforces some of the misconceptions about Lyme disease.

DEBUNKING THE MYTHS OF LYME DISEASE

Myth and reality agree that Lyme disease is caused by infection with *Borrelia burgdorferi*, acquired by the bite of infected *Ixodes* ticks.[7,8] However, the myth of Lyme disease holds that it is common, protean in its manifestations, and incurable. In reality, Lyme disease is none of these things.

MYTH: Lyme disease is common

In the early days of the Lyme disease epidemic, we worried that clinicians would fail to diagnose it. Now, Lyme disease has become a diagnosis of exclusion even in areas where there has never been a documented case of it.

FACT: Most patients with "Lyme disease" do not have it

The incidence of Lyme disease is well below 1%, even in endemic areas. Retrospective studies found that most patients referred to two

TABLE 1

CLINICAL MANIFESTATIONS OF LYME DISEASE

Early localized disease (occurs a few days to 1 month after the tick bite)
- **Erythema migrans** (in 50% to 70% of patients; multiple in 50% of patients with erythema migrans)
- **Fatigue, malaise, lethargy**
- **Headache**
- **Myalgia, arthralgia**
- **Regional, generalized lymphadenopathy**

Early disseminated disease* (occurs days to 10 months after the tick bite)
- **Carditis**
  - Approximately 8% to 10% of untreated patients
  - Conduction defects
  - Mild cardiomyopathy, myopericarditis
- **Neurologic**
  - Approximately 10% to 12% of untreated patients
  - Lymphocytic meningitis
  - Encephalitis
  - Cranial neuropathy (most often facial, can be bilateral)
  - Peripheral neuropathy, radiculoneuropathy
  - Myelitis
- **Musculoskeletal**
  - Approximately 50% of untreated patients
  - Migratory polyarthritis or polyarthralgias
  - Fibromyalgia
- **Other**
  - Skin: Lymphadenosis benigna cutis (lymphocytoma), erythema nodosum
  - Lymphadenopathy: Regional, generalized, or both
  - Eye: Conjunctivitis, iritis, choroiditis, vitritis, retinitis
  - Liver: Liver function test abnormalities, hepatitis
  - Kidney: Microhematuria, proteinuria

Late disease (occurs months to years after the tick bite)*
- **Musculoskeletal**
  - Approximately 50% of untreated patients develop migratory polyarthritis
  - Approximately 10% of untreated patients develop chronic monarthritis, usually in the knee
  - Fibromyalgia†
- **Neurologic**
  - Chronic, often subtle encephalopathy, encephalomyelitis, peripheral neuropathy
  - Ataxia, dementia, sleep disorder
- **Cutaneous**
  - Acrodermatitis chronica atrophicans
  - Morphea (possibly), localized scleroderma-like lesions

*May occur in the absence of any previous features of Lyme disease
†Not a feature of active infection; a "post-Lyme disease" syndrome
From Sigal LH, reference 12

Lyme disease centers did not have Lyme disease.[1,2] Most patients referred to our center actually had musculoskeletal or neurologic syndromes such as lupus erythematosus, anticardiolipin antibody syndrome, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, patellofemoral joint dysfunction, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, brain tumors, and other remediable syndromes. Another common missed diagnosis is fibromyalgia,[9-11] where the cognitive dysfunction is often mistaken for Lyme disease of the central nervous system, and achiness is mistaken for Lyme arthritis.

On the other hand, we have found Lyme disease in patients thought to have multiple sclerosis, senile dementia, gout, and rheumatoid arthritis.

MYTH: Lyme disease can account for almost any symptom

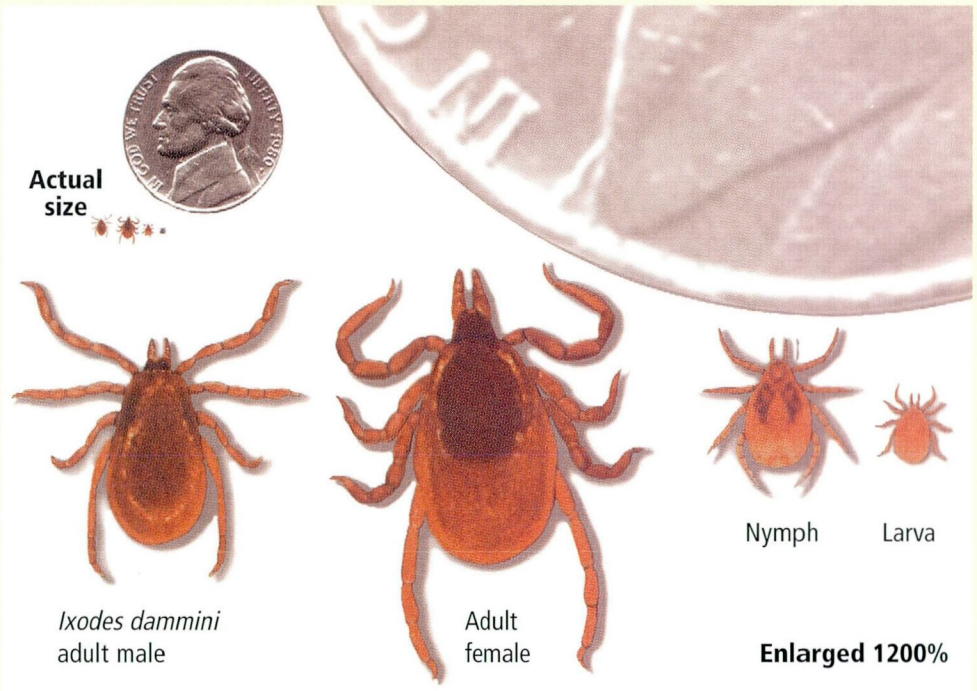
In the past, Lyme disease was thought to mimic many syndromes. The term "the great imitator" was often used. Even now, it is diagnosed all too frequently solely on the basis of "symptoms compatible with Lyme disease" without objective findings.

FACT: Lyme disease has well-defined manifestations

Early localized disease. An average of 1 week (range, 1 day to 1 month) after the tick bite (which only about one third of patients recall), a distinctive rash appears at the site of the bite in 50% to 70% of patients. Called erythema migrans, the rash starts as an erythematous macule or papule and expands, often clearing from the middle. It fades spontaneously, even without antibiotic treatment. The most common sites are the groin, axillae, waistline, and popliteal fossae. The rash is usually painless, although some patients note burning or stinging at the site.

Do not confuse erythema migrans with local reactions to tick bites. Many persons mount an allergic reaction to components of tick saliva and may develop an erythematous lesion approximately 1 cm in diameter that does not expand and fades within a day or two. Spider bites are almost always very painful and

Of mice and ticks and spirochetes



Three closely related species of spirochete can cause Lyme disease: *Borrelia burgdorferi*, *B afzelii*, and *B garinii*. Only the first is found in the United States; it is found in Europe and Asia as well. Differences between the organisms may account for differences in the manifestations in Europe and the United States (more arthritis and more multiple erythema migrans lesions are seen in the United States).

Infected *Ixodes* ticks spread the infection—*I scapularis* (formerly known as *I dammini*) in the Eastern and North-central United States; *I pacificus* in the Western United States; *I ricinus* in Europe; and *I persulcatus* in Asia. Lyme disease is endemic in some areas but not in others, depending on whether large *Ixodes* populations are present. About 90% of US cases occur in Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania, Minnesota, Wisconsin, and California. The incidence is not uniform across each state; there are hot spots of disease. A travel history is crucial in evaluating a patient with possible Lyme disease; even if a patient does not reside in an endemic area, he or she may have acquired the infection while traveling.

Ixodid tick larvae hatch in the summer and search for a blood meal, usually from mice. Fewer than 1% of ticks emerge infected, even in hyperendemic areas; rather, they acquire the organism from field mice. After feeding, the tick molts and re-emerges the following spring as a nymph, which then searches for a blood meal. Infected nymphs account for most cases of Lyme disease; the incidence is greatest in the late spring, summer, and early fall, when nymphs are looking for a blood meal.

The nymph drops off the host after feeding and molts to an adult in the fall. Adults seek a blood meal in the late fall, winter, and even the spring. Adult ticks cause only a few cases of Lyme disease, as they are more easily seen and felt than are nymphs, fewer people are outside during the winter, and people wear more clothing than in the summer.

Ticks take approximately 24 hours to find a suitable place for their blood meal and an additional 24 to 36 hours to transmit the organism. The tick is not very efficient in transmitting infection; in a prospective study of tick bites in an endemic area, only about 1% of all bites resulted in infection.[19]

may become necrotic.

Other early symptoms are flu-like: fever, myalgia, arthralgia, and headache (TABLE 1).[12] Notable by their absence are coryza and upper respiratory and gastrointestinal findings.

Early, disseminated disease may appear slightly later, as the infection spreads throughout the body. Manifestations can include:

- Multiple erythema migrans rashes.
- Cardiac disease. Conduction block is the major cardiac manifestation, although it is usually asymptomatic. Mild cardiomyopathy can also occur. In almost all cases, both resolve entirely.
- Neurologic disease, including cranial nerve palsies (especially facial palsy), lymphocytic meningitis, and radiculoneuropathy. These features usually resolve even without treatment, and nearly all patients, untreated or treated, make a full recovery.

TABLE 2

CRITERIA FOR REPORTING CASES OF LYME DISEASE, ACCORDING TO THE CDC

Erythema migrans,
or
At least one of the following late manifestations (if no alternate explanation can be found), plus laboratory confirmation of infection

Musculoskeletal system
Recurrent brief attacks of objective joint swelling in one or several joints, sometimes followed by chronic arthritis in one or several joints*

Nervous system
Lymphocytic meningitis
Cranial neuritis, particularly facial palsy (may be bilateral)
Radiculoneuropathy
Encephalomyelitis alone or in combination (rare)†

Cardiovascular
Acute-onset, high-grade (2nd or 3rd degree) atrioventricular conduction defects that resolve in days to weeks and are sometime associated with myocarditis‡

*Manifestations not considered as criteria:
Chronic progressive arthritis not preceded by brief attacks
Chronic symmetrical polyarthritis
Arthralgia, myalgias, or fibromyalgia syndromes alone

†Encephalomyelitis must be confirmed by antibodies against *B burgdorferi* in the cerebrospinal fluid (CSF), demonstrated by a higher titer of antibody in CSF in serum. Headache, fatigue, paresthesias, or a mild stiff neck alone are not accepted as criteria for neurologic involvement.

‡Palpitations, bradycardia, bundle branch block, or myocarditis alone are not accepted as criteria for cardiovascular involvement.

From Wharton et al, reference 17

Late Lyme disease may develop weeks to months after infection, often insidiously. Patients may experience:

- Arthritis—polyarthralgia, migratory polyarthritis, and, in a small proportion, monarthritis (usually affecting the knee).
- Neurologic problems (tertiary neuroborreliosis)—mild to moderate encephalopathy (cognitive dysfunction or irritability or both) and peripheral neuropathy.

Patients do not necessarily progress smoothly through each phase. Some have erythema migrans but no further disease; others either never had or do not recall an erythema migrans lesion, but present initially with later symptoms.

MYTH: Serologic tests are useless in diagnosing Lyme disease

Those practitioners who believe that "everything is Lyme disease" view negative test results as proof that the tests are inaccurate and often explain vague complaints without objective evidence of disease as "seronegative Lyme disease."

FACT: The tests are accurate if used properly

Recent studies[13] have instilled realistic confidence in serologic tests to confirm Lyme disease—with some caveats.

The serologic tests such as the enzyme-linked immunosorbent assay (ELISA) and the Western blot detect antibodies capable of binding to *B burgdorferi*. However, seroreactivity does not prove the diagnosis of Lyme disease, for several reasons. The very term "Lyme disease test" is misleading and suggestive; a more accurate alternative is "anti-*B burgdorferi* antibody assay."

The tests are not specific. False-positive ELISA results are common, seen in 7% or more of the general population.[2,14] Even in hyperendemic areas, false-positive ELISA results outnumber true-positive ones.

Other infectious diseases can produce false-positive results on the anti-*B burgdorferi* ELISA (eg, syphilis, other spirochetoses, endocarditis, Epstein-Barr virus), as can some rheumatologic diseases (eg, rheumatoid arthritis, lupus erythematosus).

The patient may not have active disease, having previously been treated successfully or resisted an infection. Some groups in endemic areas at especially high risk of exposure, such as forestry workers, may have a rate of seropositivity of up to 20% but not have Lyme disease.[15] Because antibody levels may stay elevated in patients who have been cured, follow-up testing of asymptomatic patients has no role.

False negativity is relatively rare. However, seroconversion may never occur if the patient receives early antibiotic therapy, even if inadequate. In addition, serologic

results may be "falsely" negative if inadequate time has elapsed since infection: seroconversion occurs in most patients by 4 weeks, but in some the ELISA may remain negative up to 8 weeks.

Using serologic tests properly. One should diagnose Lyme disease on the basis of the history, signs, and symptoms, and use laboratory tests only to confirm the clinical diagnosis. Western blot analysis is recommended to confirm positive or equivocal ELISA results.

Evidence of expansion of the immunologic response, such as a rising ELISA result or increasing numbers of bands on the Western blot in the presence of persisting complaints, is evidence of ongoing infection, but such comparisons are best made by testing paired samples, ie, a frozen baseline sample and a current sample, run concurrently. In patients with inflammatory disease in the central nervous system or articular spaces, higher levels of antibody in the spinal or synovial fluids than in the serum suggest that the neurologic or joint disease is due to *B burgdorferi*.

The polymerase chain reaction (PCR) test, which detects the nucleic acids of the organism, is not yet established as clinically useful for Lyme disease. False-positive results due to poor sample handling and poor technique are common in some laboratories, and false negativity occurs as well.

Although PCR detects nucleic acids, a positive result does not necessarily indicate that live organisms are present. We do not yet know how long *B burgdorferi* persists after it has been killed in vivo; therefore, the utility of PCR testing is unclear in decision-making about patients who continue to have symptoms.[16]

Neuropsychologic and electrophysiologic testing (cardiac and neurologic) and magnetic resonance imaging of the brain can document abnormalities, but the findings are not specific for the damage of *B burgdorferi* infection.

MYTH: The CDC criteria for Lyme disease are too rigid

Cases of Lyme disease must be reported to public health authorities, using criteria from the Centers for Disease Control and Prevention (CDC) (TABLE 2).[17] Critics find the CDC criteria needlessly rigid.

FACT: The CDC criteria are not used for diagnosis

The CDC intended its criteria to be used for epidemiologic purposes, not for diagnosis. The diagnosis of Lyme disease should be based on firm knowledge of the clinical features of *B burgdorferi* infection and the patient's history of potential exposure, clinical complaints, and physical findings. The absence of set standards for diagnosing Lyme disease and the persisting and incorrect concept of Lyme disease as "the great imitator" causes the diagnosis of Lyme disease to fill the void of nondisease.[18]

MYTH: Lyme disease is incurable

If a patient does not have Lyme disease in the first place, antibiotics predictably do not help. At this point, instead of considering whether the diagnosis was correct, some clinicians prescribe more antibiotic treatment. And when patients still do not get better, the treatment regimens diverge more and more from those generally accepted.

TABLE 3

ANTIBIOTIC REGIMENS FOR TREATING LYME DISEASE

Antibiotic	Dosage	Duration
Oral therapy for early localized Lyme disease		
Adults		
Doxycycline	100 mg twice a day	3 to 4 weeks
Amoxicillin	250 to 500 mg three or four times a day	3 to 4 weeks
Children		
Amoxicillin	40 mg/kg/day, divided dose	3 to 4 weeks
Doxycycline	100 mg twice a day	3 to 4 weeks
Erythromycin	30 mg/kg/day, divided dose	3 to 4 weeks
Penicillin G	25 to 50 mg/kg/day, divided dose	3 to 4 weeks
Intravenous therapy for early disseminated and late or chronic Lyme disease		
Adults		
Ceftriaxone	2 g daily or 1 g twice a day	2 to 4 weeks
Cefotaxime	3 g twice a day	2 to 4 weeks
Penicillin G	20 million units in 6 divided doses	2 to 4 weeks
Chloramphenicol	50 mg/kg/day in 4 divided doses	2 to 4 weeks
Children		
Ceftriaxone	75 to 100 mg/kg/day	2 to 4 weeks
Cefotaxime	90 to 180 mg/kg/day in 2 or 3 divided doses	2 to 4 weeks
Penicillin G	300 000 U/kg/day in 6 divided doses	2 to 4 weeks

From Sigal LH, reference 18

Some "experts" recommend months or years of treatment with drugs that have never been tested in Lyme disease. Years ago there was a fad in which patients went to Mexico or Panama to receive infusions of malarial blood; now some practitioners are using vitamin and mineral supplementation, and at least one is treating Lyme disease with silver salts!

FACT: Antibiotics almost always cure Lyme disease

Early and appropriate antibiotic treatment (TABLE 3) prevents Lyme disease from progressing to later stages, although it may not decrease the duration or severity of many of its features.[12] No evidence supports giving oral therapy after intravenous therapy, prolonging the therapy, or increasing the dosage.

A Jarisch-Herxheimer reaction (fever, chills, headache, myalgia, exacerbation of rashes) occurs in the first days of therapy in 5% to 10% of patients with early Lyme disease, and lasts for about 1 day.

Lack of response should suggest that the original diagnosis was erroneous

Therapy during pregnancy should be the same as in nonpregnant patients, except that doxycycline is contraindicated. Amoxicillin and the cephalosporins are safe for the fetus. Recent studies suggest that the risk to the fetus from maternal infection is small.

Prophylactic therapy after a tick bite is not currently recommended, as studies suggest that the risk of contracting Lyme disease from a known tick bite is very small.[19]

Symptoms resolve slowly, and may not disappear entirely for months.[20] Further antibiotic therapy will not hasten the steady response.

Lack of response. There is no evidence that *B burgdorferi* is resistant to any of the standard antibiotics used for Lyme disease. Lack of response to appropriate therapy should suggest that the original diagnosis was erroneous,[20] although there are *rare* examples of lack of response to appropriate antibiotics. Worsening of true inflammation, extension to a new area (eg, arthritis developing in a previously unaffected joint), or progression to later features of Lyme disease (eg, development of peripheral neuropathy in someone previously treated for erythema migrans), might suggest that therapy has not been effective.

In many areas in which Lyme disease is endemic, ticks that spread Lyme disease can transmit other pathogens, including *Babesia microti* and the newly described human granulocytic *Ehrlichia*. Patients acquiring symptoms after a tick bite who do not respond to standard therapy for Lyme disease might have a different infection.

WHY THE OVERDIAGNOSIS OF LYME DISEASE?

The media inundates the public with exciting but incomplete or erroneous stories about the pain and suffering from Lyme disease, and the public accepts them as fact. Lyme disease support groups and newsletters spread speculation and rumors. Local "experts" set up practices specializing in Lyme disease, and patients who "just don't feel right" and want an explanation go to them.

The medical literature compounds the problem by publishing peculiar cases of Lyme disease without defining the universe from which these rare cases are drawn. Describing "numerator" without "denominator" gives the false sense that these clinical outliers are common.

The misapplication of the concept of Lyme disease as "the great imitator," the poor reputation of serologic tests, the absence of verified criteria for diagnosing Lyme disease, the slow resolution of symptoms, and the effects of the lay and medical media all help explain the overdiagnosis and improper treatment of Lyme disease. However, the real reason for this phenomenon is a lack of intellectual rigor in making the diagnosis and following the patient.

RECOGNIZING PSEUDO-LYME DISEASE

Some communities have accepted an alternative reality about Lyme disease, using it as an explanation for a host of problems. The resulting disease—pseudo-Lyme disease—is more common and more insidious than real Lyme disease, and more difficult to treat. Warning

signs of pseudo-Lyme disease include:

- Absence of documented objective evidence of Lyme disease (eg, erythema migrans, arthritis, neurologic findings, cardiac arrhythmias).
- A diagnosis based on "symptoms compatible with or suggestive of Lyme disease"; equivocal ELISA results unconfirmed by immunoblot assay; urinary antigen tests; or polymerase chain reaction (PCR) testing.
- A history of multiple tests, all (or all but one) negative; and repeated courses of antibiotic therapy, especially if given for nonspecific complaints not corroborated by objective findings.

Pseudo-Lyme disease is the most recent in a long line of explanations for being "out-of-sorts" that patients find acceptable, a lineage that includes chronic candidiasis, chronic Epstein-Barr virus infection, and chronic fatigue syndrome. It is often quite difficult to dissuade a patient that he or she does not have Lyme disease. Nevertheless, we must not overdiagnose or underdiagnose real Lyme disease. We must identify and debunk pseudo-Lyme disease whenever we find it. ■

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