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PSEUDO-LYME DISEASE

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Retrospective reviews at two Lyme disease (LD) referral centers showed that most patients evaluated did not have LD (1,2). Among those seen at our center for possible LD have been patients with ankylosing spondylitis, rheumatoid arthritis, osteoarthritis, lupus, anti-cardiolipin antibody syndrome, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, brain tumors, and various other non-LD diseases. On the other hand, by careful clinical and laboratory analysis we have identified LD in patients previously thought to have multiple sclerosis, senile dementia, gout, rheumatoid arthritis, and "viral syndromes."

OVERDIAGNOSIS OF LYME DISEASE

Although one cannot extrapolate to general practice, it is likely that overdiagnosis of LD is quite common. Given the ease with which people travel, it is common to see a patient who might have LD in nonendemic areas. The print and broadcast media disseminate incomplete or erroneous stories about LD. Lyme disease support groups and newsletters spread stories and speculation as if fact. In this climate, people who don't feel well search for answers and often consider and occasionally embrace the diagnosis of LD. It has become a diagnosis of exclusion even in areas where there has never been a documented case of LD, resulting in therapy-related morbidity (3,4) and expense (5). Why is LD overdiagnosed?

The great imitator. One reason for LD's overdiagnosis is the misapplication of the concept of LD as the great imitator: Early in the delineation of the syndrome(s) caused by *Borrelia burgdorferi*, LD's spectrum was thought to be so broad as to mimic many medical and neurologic syndromes. Thus the definition of LD was open ended. The spectrum of LD is now well described (6). The diagnosis of LD is made all too frequently in patients with "symptoms compatible with LD" but whose examinations lack objective findings. In such patients, a seemingly common missed diagnosis is fibromyalgia (7–9). They may have cognitive dysfunction, thought to be central nervous system (CNS) Lyme disease, and achiness, ascribed to Lyme arthritis. There are no objective findings, no spinal fluid analysis or neuropsychologic testing to establish CNS LD, and no true inflammatory joint disease to suggest Lyme arthritis. Nonetheless, the diagnosis is late Lyme disease and antibiotic treatment follows. The lack of response heightens anxiety about the purported incurability of LD.

Poor reputation of serologic testing. A second reason for LD's overdiagnosis is the poor reputation of serologic testing in LD. Recent studies have instilled realistic confidence in serologic confirmation of LD (10). However, tests should not be used to make the diagnosis of LD (see the sidebar), only to confirm a clinical diagnosis. False-positive enzyme-linked immunosorbent assay (ELISA) results are common, seen in 7% or more of the general population (2, 11). Because the incidence of LD is well below 1% even in hyperendemic areas, most positive ELISAs are false positives. All positive or equivocal ELISAs should be corroborated by immunoblot.

False negativity in real LD is relatively rare. "Seronegative LD" is a common explanation for poorly described complaints without objective evidence of disease – ie, diagnosis by exclusion. Seronegativity in patients diagnosed by a process of exclusion, or by viewing clinical practice through the peculiar prism of "everything is LD," is incorrectly viewed as proof that the tests are inaccurate. In reality, the tests are good; it is the compulsion to diagnose LD that is in error.

No diagnostic criteria. A third reason for LD's overdiagnosis is the absence of verified criteria for diagnosing LD: The

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DIAGNOSING LYME DISEASE

- Lyme disease (LD) cannot be diagnosed by serologic testing – one can only use testing to confirm the diagnosis. Of relevance to the use of diagnostic testing is Bayes' theorem, which describes the predictive value of results based on the pretest (clinical) likelihood of diagnosis. This is especially important in LD, in which there is a high frequency of false-positive test results.
- If the pretest likelihood of LD is high, the predictive value of a positive test is very high – ie, a positive test confirms the clinical (pretest) impression of LD.
- If the pretest likelihood of LD is low, the predictive value of a positive test is quite low – ie, a positive test is much more likely to be a false positive than to indicate that the patient has LD. Thus, screening serologic testing in a population with a low incidence of LD is not only useless, it can create serologically based diagnoses of pseudo-LD.
- The term "LD test" is incorrect. We measure antibodies binding to *Borrelia burgdorferi*, which may not be specific and do not necessarily have intrinsic diagnostic value. Seroreactivity is neither proof of the diagnosis of LD, nor of active LD.

epidemiologic Centers for Disease Control and Prevention (CDC) LD criteria cannot be used to diagnose LD. The absence of set standards and the persisting, incorrect concept of LD as the great imitator causes the diagnosis of LD to fill the void of non-disease (12). Additionally, anger focused at the "needlessly rigid" CDC criteria fans the flames of LD anxiety.

Slow resolution of symptoms. A fourth explanation of LD's overdiagnosis is the slow resolution of symptoms related to LD: In true LD, resolution may be delayed for months (13). Further antibiotic therapy will not hasten the steady response. If the initial diagnosis of LD was incorrect, lack of response to antibiotics is predictable. A lack of response is often misinterpreted as indicating that the organism is refractory or dormant. There is no evidence that *B. burgdorferi* is resistant to any of the standard antibiotics used for LD. Lack of response to appropriate therapy should suggest the original diagnosis was erroneous (13).

Lack of response to appropriate antibiotics is a rare event in true LD. Worsening of true inflammation, extension to a new area (developing arthritis in a previously unaffected joint), or progression to later features of LD (development of peripheral neuropathy in someone previously treated for erythema migrans) might suggest that prior therapy had not been effective. Ticks that spread LD can also transmit other pathogens, including *Babesia microti* and a newly described *Ehrlichia*. Patients acquiring symptoms after tick bites not responding to standard therapy for LD might have another infection.

Effects of the media. A fifth explanation of LD's overdiagnosis lies in the effects of the media, lay and medical: Exciting stories tend to sell advertising in the broadcast and print media. Spectacular but unsubstantiated accounts of the pain and suffering of LD are printed without verification, and the public accepts them as fact. The medical literature has compounded our problem by publishing peculiar cases of LD 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, reinforcing the impression of LD as the great imitator.

PSEUDO-LYME DISEASE

Although these are all explanations for overdiagnosis and treatment of LD, the real reason for this phenomenon is a lack of rigor in making the diagnosis and following the patient. An LD alternative reality has been accepted in some communities: LD can cause any picture in clinical practice, the serologic tests are worthless, and therapy does not eradicate the bug – ie, LD cannot be cured. A new diagnosis has emerged, "pseudo-LD," to coin a term. It describes the certainty that LD is present when there is no verifiable evidence of disease. Antibiotic therapy is given for this "LD," followed by more treatment when symptoms do not resolve promptly.

In practicing medicine we must demand objective findings to diagnose patients; we must develop and use diagnostic criteria; and we must include the possibility of intercurrent disease or evolution of the process in our ongoing analysis of patients. With certain points in mind, pseudo-LD can be identified (see sidebar).

IDENTIFYING PSEUDO-LYME DISEASE

- In the absence of documented objective evidence of Lyme disease (LD) (eg, rash, arthritis, neurologic findings, cardiac arrhythmias), the diagnosis of LD should be questioned.
- Be skeptical if the diagnosis hinges on the presence of "symptoms compatible with or suggestive of LD." The symptoms of LD are nonspecific and can be found in many other diseases.
- Immunoblotting is necessary to confirm positive or equivocal enzyme-linked immunosorbent assays (ELISAs). In 1995, a positive ELISA without corroboration does not denote seropositivity. Equivocal ELISAs are often incorrectly imbued with diagnostic weight.
- Be wary of the diagnosis in a patient who has had multiple tests, all (or all but one) negative. "Seronegative LD" (which does occur, albeit rarely) in the absence of historical or physical findings suggesting LD should be questioned.
- There is no role for "urinary antigen tests" in evaluating LD. Polymerase chain reaction (PCR) is a technique that allows one to identify the DNA of the organism. The results are highly dependent on the quality of the laboratory doing the testing. PCR is experimental and should not be used to diagnose LD.
- Repeated courses of oral or intravenous antibiotic therapy, especially if given for nonspecific complaints not corroborated by objective findings, should raise suspicion about the original diagnosis.

Pseudo-LD is more common and more insidious than LD and more difficult to treat. It is often quite difficult to dissuade the patient from belief in pseudo-LD as the explanation of all problems. Pseudo-LD is the most recent in a long line of explanations that are acceptable to patients who feel "out of sorts." We must not overdiagnose or underdiagnose real LD. We must identify and debunk pseudo-LD whenever we find it.

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VACCINATION IN THE IMMUNOCOMPROMISED PERSON

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Large numbers of people with inflammatory or autoimmune diseases are immunocompromised by immunosuppressive medications. When treating these patients, the clinician is faced with the question of whether vaccines are safe and effective. In this review we will discuss the use of live vaccines, killed vaccines, and toxoids in immunocompromised persons. These discussions are summarized in Tables 1–3. For further information about the use of vaccines in the immunocompromised, refer to the recently published guidelines in *Morbidity and Mortality Weekly Report* from the Centers for Disease Control and Prevention (1).

LIVE-VIRUS VACCINES

The use of live vaccines is contraindicated in immunocompromised people. In general, the immunocompromised should not be given live vaccines. In addition, oral polio vaccine (OPV) should not be given to any household contact of a severely immunocompromised person. Measles-mumps-rubella (MMR) vaccine is not contraindicated in the close contacts (including health-care providers) of immunocompromised patients. Those whose immunosuppressive therapy has been stopped for at least 3 months are not considered severely immunosuppressed for the purpose of receiving live-virus vaccines (2). If immunosuppressive therapy is being considered, vaccination should ideally precede therapy initiation by 2 weeks or more. Patients vaccinated while on immunosuppressive therapy, or in the 2 weeks before starting therapy, should be considered unimmunized and should be revaccinated at least 3 months after therapy discontinuation. Passive immunoprophylaxis with immunoglobulins may be indicated in immunocompromised persons instead of, or in addition to, vaccination.

Steroid therapy and immunosuppression. Steroid therapy usually does not contraindicate live-virus vaccine administration as long as the therapy meets one of these criteria: short term (less than 2 weeks); low to moderate dose; long-term, alternate-day treatment with short-acting preparations; maintenance physiologic doses (replacement therapy); or administered topically (skin, respiratory system or eyes) or by intra-articular, bursal, or tendon injection. The exact amount of systemic corticosteroids and the duration of administration needed to suppress the immune system in an otherwise healthy person are not well defined. The immunosuppressive effects of steroid treatment will vary, but many clinicians consider an immunosuppressive dose to be equivalent to either 2 mg/kg of body weight or a total of 20 mg per day of prednisone. Patients who have received high-dose, systemic