MANAGING SUSPECTED, ATYPICAL LYME DISEASE IN NONREFERRAL PRACTICES

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SUMMARY

Lyme disease is the most common vector borne disease in Europe and North America. In the US alone, over 50,000 cases have been reported to the U.S. Centers for Disease Control since 1988 from the Northeast, upper Mideast and far West with some reported incidence rates as high as 1192 cases/100,000 (Nantucket Island, Massachusetts).

Based on actual cost data from the Maryland Eastern Shore from 1997 to 2000, the mean per patient direct medical costs of early-stage LD decreased from $1,609 to $464, and the mean per patient direct medical cost of late-stage LD decreased from $4,240 to $1,380.[1] The estimated median of all costs (direct medical cost, indirect medical cost, nonmedical cost, and productivity loss) aggregated across all patients, was ~$281 per patient; as with many cost of illness studies, a small number of LD patients accounted for the majority of the costs.

To approximate the annual economic impact of LD nationwide, these results extrapolated to the total number of LD cases reported nationwide, 23,763 LD cases in 2002, corresponds to ~$203 million (in 2002 dollars). LD cases reported using the CDC surveillance case definition underreport the true incidence; therefore, the estimate is likely to be low. The decline in average cost per LD case is observed in all cost categories, drug costs, hospital days, diagnostic testing, and may be related to successful adoption of personal protection measures and/or prompt consultation and treatment after exposure or tick bite. It may also be reporting bias.

The description of Lyme disease in the US in 1976 and subsequent characterization of its mode of transmission, causative organism and treatment is an important saga in the history of medicine. In theory, Lyme disease could be prevented and eradicated but in practice it continues to grow as a public health problem and many biological and clinical questions remain unanswered. Typical acute Lyme Disease, by definition, is fairly straightforward to diagnose and treat. However, acute Lyme may not present typically and acute Lyme with persistent symptoms respond to recommended antibiotic regimens. Both forms in practice are major challenges in non-referral practices.

My frame of reference

I live and work in Massachusetts where Lyme Disease can be endemic. Nevertheless, I missed diagnosing chronic Lyme in a physician's wife from Vermont. Her husband and I did internship and residency together, and it has haunted me since. This was an object lesson again that Lyme Disease is always in the differential.

I am a salaried general internist and primary care physician and board-eligible rheumatologist seeing patients since 1969. I am a general internist for patients at the Brigham and Women's Hospital, an academic health center, and in the Veterans Administration. As a clinician-scientist, I study health services, the epidemiology of systemic rheumatic disease, health disparities, determinants of health outcomes, and have done more than 25 investigator-initiated clinical trials.

I also bring the view of a patient with chronic illness having had a six-vessel coronary by-pass operation in 2000 and a strept millerei lung abscess and empyema in 2003 from a dental procedure. I am doing very well, thank you. I am inevitably drawn in as a coach for my extended family when they have a health problem, doing telephone consultations for my three 30+ year old children who work harder than I but are underinsured, internet inhabitants, and use alternative and over the counter therapies whenever they can, as does my bride. I am happy coaching.

Atypical acute Lyme Disease

A major challenge of ministering to patients in non-referral practices is not missing treatable illnesses that might present atypically. A study of consecutive patients with possible early Lyme disease either self- or physician-referred to a general internist with infectious disease training in a region with endemic Lyme disease[2] suggests that about 39% of such patients do not meet CDC criteria nor alternative diagnostic criteria.

Of these nearly 40% had negative Lyme serology and an acute, viral-like illness without objective findings. Many of these patients had already been treated with antibiotics. In a quarter, another diagnosis could be made, including parvovirus, Ramsay Hunt syndrome or varicella zoster virus. About a third had a rash which did not meet criteria for EM and were thought to be local hypersensitivity reactions to tick bites or nonspecific or non-diagnosable lesions.

EM was the most common presentation of early Lyme disease in this case-series. However, prior misdiagnosis were common, similar to experiences reported from other endemic areas. While 80% of EM in the United States are uniformly red, only 19% have the stereotypical bull's eye appearance. Typically circular or oval, it can also be triangular, rectangular or distorted in other ways when occurring in areas such as the neck. Atypical EM may appear erythematous with central induration, urticarial-like, confluent red-blue lesions, vesicles, and with central necrosis.

If erythema migrans goes unnoticed, the disease may present months after the initial tick bite when the spirochete has disseminated. Disseminated Lyme disease often has symptoms of malaise, fatigue, or generalized or regional lymphadenopathy. Patients may have multiple, slow-growing erythema migrans lesions. Joint inflammation occurs in up to 70% of untreated patients with dessiminated disease and is typically mono- or oligo-articular, migratory, and involves the large joints and often recurring over several years.

Neurological Lyme involvement manifests as meningitis, cranial neuritis or radiculoneuritis. The most pronounced symptom is painful radiculoneuritis involving the chest or abdomen and like most neuropathies, prominent at night. The facial nerve is the cranial nerve most commonly involved and can be bilateral.

Diagnosis[3]

Early Lyme disease is best diagnosed by recognizing an erythema migrans lesion, which is present in 70-90% of cases. Laboratory testing should be used to confirm a clinician's suspicion of Lyme disease rather than to be the sole basis of diagnosis. Serology is often negative early in the disease and may take three to four weeks for IgM antibodies to borrelia to appear and four to six weeks for IgG to be present. The American College of Physicians guidelines indicates that a patient with a high index of suspicion for Lyme disease in an endemic area for the disease may require no testing and that a diagnosis can be made solely on the clinical picture.

Serological testing is used to confirm Lyme disease in patients with disseminated disease with arthritis, carditis, or neurological involvement. Unfortunately the options for testing are not ideal and the results can be unreliable. One study demonstrated that 14-21% of laboratories failed to correctly identify positive samples.[4]

A two-test algorithm for active disease and for previous infection using a sensitive enzyme immunoassay (EIA) or immunofluorescent assay (IFA) followed by a Western immunoblot is recommended by the CDC[5]. Specimens positive or equivocal by the EIA or IFA should be tested by a standardized Western immunoblot. Specimens negative by a sensitive EIA or IFA need not be tested further. When Western immunoblot is used during the first 4 weeks of disease (early LD), both IgM and IgG procedures should be used. A positive IgM test result alone is not recommended for determining active disease in persons with illness greater than 1 month's duration because the likelihood of a false-positive test result for a current infection is high for these persons. If a patient with suspected early LD has a negative serology, serologic evidence of infection is best sought by obtaining acute and convalescent serum samples. Serum samples from persons with disseminated or late-stage LD almost always have a strong IgG response to Borrelia burgdorferi antigens.

It was recommended that IgM immunoblots be considered positive if two of the following three bands are present: 24 kDa (OspC)*, 39 kDa (BmpA), and 41 kDa (Fla) (1). It was further recommended that an that IgG immunoblot be considered positive if five of the following 10 bands are present: 18 kDa, 21 kDa (OspC)*, 28 kDa, 30 kDa, 39 kDa (BmpA), 41 kDa (Fla), 45 kDa, 58 kDa (not GroEL), 66 kDa, and 93 kDa." This serial testing has a specificity of 99-100%, but low sensitivity due to variable interpretation of results across laboratories.

Culture is labor-intensive, expensive, and time-consuming. Polymerase chain reaction (PCR) detects the genetic material of the spirochete; positive results do not neccesarily indicate active infections. PCR may be helpful in suspected cases of co-infection or to confirm a clinical suspicion of Lyme disease. While PCR is useful for identifying the spirochete in skin, the technique is of marginal usefulness, as these cases can be diagnosed clinically.

Therefore, clinicians have to work with the limitations of the technology available. In most situations, as with most diagnostic testing, if the test result will not change how one treats or follows a patient or what they tell them, it should not be done. Serodiagnostics indicate exposures and whether the exposure has been recent or remote. Re-exposure and/or treatment can alter the results. The diagnostic test performance characteristics (i.e., its sensitivity, specificity, predictive value positive, and predictive value negative) of any test or testing

algorithm is determined by the prior probability of the disease given a particular combination of symptoms and signs.

Treatment of Early Lyme Disease

The aims in treating Lyme disease are to relieve symptoms and prevent the late stage complications. Delay in treatment increases a patient's risk for treatment failure. In patients who present with or shortly after a tick bite, the question of antibiotic prophylaxis arises. A randomized, double-blind, placebo-controlled trial in a hyper-endemic area showed that Doxycycline as a single 200 mg dose was associated with fewer cases of subsequent erythema migrans; the primary endpoint of the study.[6] While these results are significant, it is important to note that only a small number of subjects in the control group developed Lyme disease, resulting in a wide confidence interval. Also important is that 30% of patients treated with doxycyline experienced a drug adverse event such as nausea, vomiting, and diarrhea.

The 2006 IDSA guidelines suggest antibiotic prophylaxis only if all of the following four conditions are met; the attached tick is positively identified as an adult or nymphal Ixodes scapularis tick which has been attached for more than 36 hours, prophylaxis can be started within 72 hours of tick removal, local ecologic information demonstrates that local ticks have a borrelia burgdorferi infection rate of greater than 20%, and there are no contraindications to doxycycline use.[7] For pregnant or lactating women and children less than 8, in whom doxycycline should not be used, the guidelines do not recommend the use of substitute prophylaxis. Whether or not patients meet the criteria for antibiotic prophylaxis, the guidelines recommend that all patients who remove a tick should be observed for thirty days and treated promptly Lyme disease, human granulocytic anaplasmosis, or babesia.

When a patient presents with signs and symptoms suggestive of early Lyme disease, whether localized or disseminated, doxycycline, amoxicillin, and cefuroxime axetil are effective. The IDSA recommends 10-21 days of oral doxycycline (100mg twice daily), 14-21 days of amoxicillin (500mg three times daily), or 14-21 days of cefuroxime (500mg twice per day) for the treatment of early, localized or disseminated disease. While 10 days may be a sufficient course of doxycycline, at least two weeks is needed for beta-lactam antibiotics because of their shorter half-lives. [7]

Doxycycline is the drug of choice as it is also effective against human granulocytic anaplasmosis, which may occur as a co-infection with Lyme disease. Amoxicillin is used when there is a contra-indication to using doxycycline. When a patient is unable to take both doxycycline and amoxicillin, cefuroxime or erythromycin may be used. Cefuroxime is as efficacious as doxycycline but is more expensive.

A randomized, double-blind, placebo-controlled study of one hundred and eighty patients with erythema migrans compared the efficacy of 10 days of oral doxycycline versus 20 days of oral treatment and combination oral doxycycline and intravenous ceftriaxone. The study concluded that treating patients for 10 days with oral doxycycline was as efficacious as the two other regimens studied.[8] More than 83% of patients in each treatment group described complete resolution of symptoms at the 30 month evaluation.

While antibiotics for the treatment of early Lyme disease are effective, 10-17% of patients continue to have problems[8] and it is not clear as to why some patients with early Lyme disease improve and others do not.

Some patients with early Lyme disease have central nervous system involvement, such as radiculopathy, neuropathy, meningitis, or facial nerve palsy. Such patients require treatment with intravenous ceftriaxone (2g once daily) for 10-28 days. Alternatives to ceftriaxone include intravenous penicillin G or intravenous cefotaxime. Ceftriaxone has the advantage of once-daily dosing, making it the preferred agent. Intravenous administration is preferred to ensure adequate penetration of the blood-brain barrier. Data from Europe show that oral regimens, particularly doxycycline are also efficacious in neuroborreliosis. There is no definitive data to establish the superiority of either oral or parenteral therapy in the treatment patients with CNS involvement. Patients with evidence of increased intracranial pressure (papilledema, sixth cranial nerve palsy), may benefit from the addition of steroids, serial lumbar punctures, or CSF shunting. Although antibiotic treatment may not hasten the resolution of facial nerve palsy, treatment is recommended to prevent further sequelae such as Lyme arthritis.

Patients with cardiac involvement, namely first or second-degree atrioventricular block, should be treated with either oral or parenteral antibiotics for 14 days. Patients presenting with syncope, chest pain, or other cardiac symptoms, require hospitalization to allow for continuous monitoring. The degree of heart block associated with Lyme disease is known to fluctuate and therefore careful monitoring is required. Intravenous ceftriaxone is felt to be useful in the management of hospitalized patients with cardiac involvement, but there are no studies addressing this. The placement of a cardiac pacemaker may be indicated in cases of severe heart block. Patients may switched to the standard oral antibiotic treatment for early Lyme disease once they are stable enough to be followed as outpatients.

Lyme arthritis can be treated with either oral or intravenous antibiotics. The majority of patients improve with one month of oral antibiotics, either doxycycline or amoxicillin. If arthritis persists after the initial course of treatment, then a second course should be tried. The improvement may be slow. A minority of patients continue to have arthritic symptoms, and non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injections, and hydroxychloroquine, methotrexate, or infliximab have been used successfully.

The optimal length of intravenous antibiotics in late Lyme disease has not been determined. A prospective, open-label, randomized, multi-center study with one hundred and forty three participants compared a 14- to 28-day regimen. All participants had a history of erythema migrans at least 3 months, dermatological, rheumatological, and neurological manifestations of disease, and no prior treatment for Lyme disease. The 14 days of ceftriaxone relieved the symptoms of late Lyme disease in 70% of patients; the same improvement rate was observed in the 28 day treatment group. Patients in both groups had higher cure rates at 12 months than when evaluated at 3 months; demonstrating that patients continue to improve even after completion of treatment.[8] Of note, 30% of patients remained symptomatic at the end of this study.

Approximately 15% of patients experience a Jarisch Herxheimer-like reaction in the first 24 hours of starting treatment. This involves worsening of systemic symptoms and an increase in the size and intensity of skin lesions. The majority of patients notice improvement by the end of the course of treatment. Erythema migrans lesions usually respond first and typically resolve within one to two weeks. Systemic symptoms, however, take longer to resolve. Three months after treatment, one in four patients may still have systemic complaints. Patients should be forewarned that they may still experience symptoms at the end of treatment and be reassured that in most cases they will improve steadily with time.

Treatment of Persons with Persistent Symptoms after Treatment for Lyme Disease

Some patients experience symptoms following treatment with appropriate antibiotic therapy for Lyme disease, a phenomenon known as post-Lyme syndrome (PLS). While the IDSA guidelines used the term PLS[7], the International Lyme and Associated Diseases Society (ILADS) uses the term "chronic Lyme disease"[10]. The IDSA proposes a definition of the post-Lyme syndrome as persons who develop subjective symptoms within 6 months of their Lyme disease diagnosis, which last at least a further 6 months. Symptoms include cognitive dysfunction, fatigue, or persistent musculoskeletal complaints. The ILADS lists similar symptoms under their discussion of chronic Lyme disease.

The IDSA definition points out the importance of excluding pre-existing or concomitant disease that may account for the symptoms. Some of these may occur in "healthy" persons. For example, chronic fatigue occurs in up to 20-30% of the population. When a patient fails to respond to accepted antibiotic therapy it is important to consider the possibility of co-infection with another tick borne illness. Controversy exists as to whether PLS reflects persistent infection or not, and this has implications in the debate over how to manage such patients.

Two randomized controlled trials examined whether antibiotics are efficacious in PLS. One study examined fatigue and cognitive impairment as endpoints; the other improvement in quality of life. The first compared 28 days of placebo or intravenous ceftriaxone in 55 patients with PLS. While ceftriaxone improved fatigue, there was no improvement in either group in cognitive function. The authors concluded that antibiotics had no role in the treatment of PLS and pointed out that 7% of patients receiving ceftriaxone experienced serious side effects requiring hospitalization.[11]

The second study, of one hundred and twenty nine patients, received either one month intravenous ceftriaxone followed by 60 days of oral doxycycline or placebo. Of note, none of the participants had evidence of persistent infection with borrelia burgdorferi by culture and PCR. The study was stopped after a planned interim analysis revealed no difference between the two groups in terms of quality of life.[12] While the authors conclude that antibiotics do not improve health related quality of life in patients with PLS, the findings could be interpreted more specifically that the antibiotic regimen of intravenous ceftriaxone and oral doxycycline does not benefit PLS patients.

The IDSA guidelines present the case against persistent infection in PLS while the ILADS guidelines support the idea. One expert guideline states that patients with chronic symptoms of Lyme disease do not benefit from antibiotics, while the other expert group advocates their use. That two expert panels differ underscores the need to elucidate the pathogenesis of PLS and to develop improved treatment. Crucial to this effort will to develop a universally accepted definition of PLS to provide a framework in which to work.

Chronic previously unexplained symptoms attributed to Lyme Disease

As problematic as post-Lyme syndrome is the association of chronic previously unexplained symptoms (often cognitive difficulties and fatigue) with Lyme Disease. These persons have usually had exhaustive unproductive evaluations eventually having serologic testing for Lyme Disease which may be "positive." One school of thought maintains that this is a subset of Lyme; the other believe that chronic Lyme disease is only the latest syndrome postulated to attribute previously unexplained symptoms to particular infections - other examples

that have lost credibility being "chronic candida syndrome" and "chronic Epstein–Barr virus infection." A review stated in no uncertain terms:

> "The assumption that chronic, subjective symptoms are caused by persistent infection with B. burgdorferi is not supported by carefully conducted laboratory studies or by controlled treatment trials. Chronic Lyme disease, which is equated with chronic B. burgdorferi infection, is a misnomer, and the use of prolonged, dangerous, and expensive antibiotic treatments for it is not warranted."[13]

When there is no answer

For some individuals, this declaration, although technically correct and the dominant opinion, provides no comfort nor acknowledgment of their suffering. Furthermore it may be heard or felt as being dismissive or disbelief in their symptoms.

I schedule an open-ended appointment, try to review all previous records before the visit or shortly after the encounter, and write my summary of what has been done. I take a careful review of systems and "park" anything that needs more detail to complete or check later., Some patients have found me by word of mouth or Googling and these patients don't walk into my practice but I have screened them…so they come prepared. I ask them to keep a 24 diary of their routine and symptoms noting what has been tried, helped a little or not at all, and any side effects in case some treatments might be recycled or gradually increased to tolerance. It's important as one marches through trials of therapy that options are not abandoned if they have not had a chance to work.

I use my network of senior doctors for help. Nowadays I might even ask the question of Google. If there is any inkling, I have no reticence to refer the patient. When I don't know or I don't have any ideas, I think I am secure enough to tell the patient. I follow the adage, primum non nocere, and deconstruct what I am looking for and why and ask them to help me help them. Reassurance is not about saying something is ruled out but saying

Unexplained fatigue, cognitive dysfunction, lancinating pain without focal abnormalities occur but when they persist are a source of consternation for both the person and the physician asked to sort it out and treat. The exhaustive differential diagnosis is in theory long but after a year or 2 in diagnostic pursuit of a label, and the symptoms unchanged is unlikely to be related to life threatening disease but it is a major source of suffering.

The longer the symptoms and the higher the number of previous unsuccessful therapy, the less probable is it that I will come up with a new possibility (although I have) or that all symptoms will vanish with treatment. It's important to be honest in establishing expectations that they be attainable.

I try never start a treatment with potential side effects if I cannot state à priori what the criteria of success will be. It's essential that the criteria for success be discussed with the person affected and that they agree and believe it.[14] I give my rationale as to why the medication might be helpful, its mode of action, and guess how likely it is to work, all conceivable side effects. I might increase the dose to what is a therapeutic dose by increasing the medication to tolerance and/or effect. Cost is almost never a consideration unless the patient is paying for it. Interestingly, some patients elect the most expensive option because they believe it to be better ("you pay for what you get"). The decision should never be made on one visit.

When I can find no objective evidence of Lyme exposure nor make an alternative diagnosis to explain the symptoms, there is no book on what to do next. Being older, acknowledging my inability to make a specific diagnosis doesn't make me feel anxious or less competent. I am also comfortable asking, "Could this be due to depression or stress?" It may help validate and legitimize their feelings and give them permission to discuss difficulties instead of a medical problem.

I explain that we are not always able to find a reason for many symptoms but this does not prevent us from trying things that might help balancing harms and benefits for the most troubling symptoms while providing support.[15] Every person and patient is slightly different but the trials of therapy have a patient chart and rate their symptoms and moves from realistic assessment of what we can do, revising expectations often, to life style modification ("working and living within their ability") before trials of medications directed at sleep disturbance, pain management.

Prevention of Lyme Disease

Not emphasized enough and unfortunately not covered in the reimbursement of health care is the teachable moment or opportunity that is afforded when a person comes in with suspected Lyme Disease in an endemic area. Prevention strategies directed at the environment, ticks and/or the vector, reviewed elsewhere, theoretically could put a stop to Lyme disease[16, 17] Protective behaviors, tick-avoidance or tick checking and removal, can be highly effective, voluntary, economical, and suitable for residents and visitors to endemic areas. Avoidance involves recognition and reduction of time spent in high-risk areas (woods, brush, and tall grass). Protective clothing, such as long-sleeved shirts and long pants, should be light colored so that ticks can be easily detected. Tick repellents can be applied to skin or clothing. The repellant DEET (N,N-diethyl-meta-toluamide, Morflex® Inc. Greensboro, NC) may be used on the skin, however it is harmful to children in large doses, is neurotoxic, and must be reapplied every few hours for maximal effect. Permethrin, a repellant applied to clothing, kills ticks upon exposure, but should not come into contact with skin.

Effective tick check and removal behaviors are truly "green" approaches and take advantageous of the fact that an infected tick has to be attached and feed for anywhere from 24 to 72 hours to transmit infection. The messages must be combined with an appreciation of the barriers to their practice.[18] A daily visual and manual search of exposed skin after visiting tick-infested areas provides an opportunity to identify and remove feeding ticks. A novel effective theory-based public education intervention demonstrating tick avoidance and removal health behaviors directed towards travelers to an epidemic area reduced the incidence of disease and is a model that could be implemented elsewhere.[19]

In 1998 a recombinant vaccine against Lyme disease was approved by the FDA but was withdrawn after 4 years due to poor sales. This probably occurred due to lingering concerns about its long-term safety and because its immunization schedule was inconvenient requiring 3 injections before transmission season started to ensure optimum antibody levels and boosters because protective antibody titers declined rapidly.

Vaccination is cost effective where the incidence of Lyme disease is greater than 1%[20-22] and would only be recommended for persons who reside, work, or do recreational activities in

high-risk areas. A vaccine is unlikely to be 100% effective, and would not protect against other tick-borne illnesses; therefore, efforts to avoid contact with ticks would still be required.

CONCLUSION

Lyme disease continues to be a problem and even grow as hosts, vectors and man live closer together with the reduction of the forest habitat. While effective antibiotics have been identified for the early localized and disseminated stages of Lyme disease considerable uncertainty surrounds the management of patients with post-Lyme syndrome. More research needs to be done to understand the pathophysiology of persistent symptoms.

Educating patients on prevention strategies is essential in decreasing the annual incidence. Health educational programs in endemic areas beginning in the school and others focused on vacationers in these areas should be a priority. Another vaccine may be developed but is likely to face the same problems in gaining acceptance and reinforce complacency with tick avoidance and tick removal behaviors.

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