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Early Lyme Disease

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 26-year-old woman with a summer home on Long Island, New York, had a low-grade fever, malaise, arthralgias, headache, and neck pain one week after removing a tick from her thigh. Examination reveals a nontender oval (8 by 12 cm), homogeneously erythematous lesion at the site of the tick bite, consistent with erythema migrans. How should this case be managed? What if she had presented earlier, just after removing the tick?

The Clinical Problem

Lyme disease is the most common tick-borne disease in the United States and Europe.^{1,2} In the United States, Lyme disease is most often acquired from the bite of the *Ixodes scapularis* tick, with the

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spirochete *Borrelia burgdorferi* the sole cause.³ In Europe, Lyme disease is more commonly caused by *B. afzelii* than by *B. burgdorferi*.³ Erythema migrans is the most common clinical manifestation of Lyme disease.^{1,4} It typically develops 7 to 14 days (range, 3 to 30) after tick detachment and is characterized by a rapidly expanding, erythematous skin lesion that may be round or oval and flat or slightly raised.^{5,6,7} About 75 to 80 percent of patients in the United States who present with erythema migrans have only a single (primary) lesion.^{6,8} The remainder have additional (secondary) skin lesions that are believed to arise through hematogenous dissemination from the site of primary infection.⁸ The majority of patients with erythema migrans in the United States have symptoms resembling those of viral infection, including arthralgias, fatigue, headache, or neck pain; fever may or may not accompany these symptoms.^{5,6} Similar symptoms have been attributed to infection with *B. burgdorferi* in the absence of erythema migrans, but in this circumstance, the diagnosis is less certain.⁹ Prominent respiratory symptoms (such as cough or rhinorrhea) or gastrointestinal symptoms (such as vomiting or diarrhea) would be highly atypical.⁵

Even though the *I. scapularis* tick is approximately twice as likely to be infected with *B. burgdorferi* in the adult stage as in the nymphal stage,¹⁰ most cases of early Lyme disease occur during the late spring and summer, when the nymph is seeking a blood meal.¹¹ This is due at least in part to the fact that adult ticks, which are larger than nymphs, are more readily noticed and thus removed, resulting in insufficient time for the spirochete to be transmitted.^{11,12,13} In experiments in animals, there is almost invariably a delay of at least 36 hours between the time of tick attachment and transmission of *B. burgdorferi*.^{14,15} During this interval, spirochetes present in the midgut of the tick increase in number and migrate to the salivary glands.¹⁵

Without treatment, erythema migrans resolves spontaneously within a median of approximately four weeks.¹⁶ The more serious clinical sequelae of Lyme disease develop as a consequence of the hematogenous spread of the spirochete to extracutaneous sites. Spirochetemia can be found in about 45 percent of patients with erythema migrans at the time of presentation, irrespective of the size or duration of the skin lesion.⁸ Approximately 60 percent of patients with erythema migrans who are not treated will go on to have a monoarticular or oligoarticular arthritis, typically involving the knee; approximately 10 percent will have a neurologic manifestation, the most common of which is facial-nerve palsy; and approximately 5 percent will have a cardiac complication, usually varying degrees of atrioventricular block.¹⁷

Strategies and Evidence

Diagnosis

The diagnosis of erythema migrans is based on recognition of the characteristic appearance of the skin lesion in persons who live in or have recently traveled to regions in which Lyme disease is endemic.^{5,6,7,18} The skin lesion is sufficiently distinctive that serologic testing for antibodies against *B. burgdorferi* is generally considered unnecessary; such testing is also insensitive, with false

negative results in as many as 60 percent of cases.¹⁹ However, the skin lesion cannot be considered pathognomonic of Lyme disease. A similar skin lesion – from southern tick–associated rash illness, or STARI – occurs after the bite of the *Amblyomma americanum* tick (also known as the lone star tick), which cannot transmit *B. burgdorferi*.^{20,21} *A. americanum* ticks are present throughout the southeast and south central regions of the United States and are also found in smaller numbers along the eastern seaboard, as far north as Maine.²² Although more common in the South, cases of STARI have occurred in Maryland²³ and New Jersey,²⁴ and cases may have been mistaken for erythema migrans in other mid–Atlantic or northeastern states.

Erythema migrans skin lesions are typically 5 cm or more in their largest diameter.²⁵ Smaller lesions may occur merely as a result of hypersensitivity reactions to tick saliva. Early erythema migrans lesions may be homogeneously erythematous and often do not have central clearing or the characteristic bull's–eye or target–like appearance (Figure 1).^{6,7,20} Erythema migrans lesions usually occur in locations that would be unusual for community–acquired cellulitis, such as the axilla, popliteal fossa, back, abdomen, and groin; this distribution can be helpful for diagnosis.⁵ Typically, these lesions are minimally tender or pruritic.²⁰ Consequently, a complete skin examination should be performed to look for erythema migrans lesions in patients who have been exposed to ticks and who also have symptoms like those of a viral infection or other potential manifestations of early Lyme disease, including facial–nerve palsy, aseptic meningitis, radiculopathy, or heart block.

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Figure 1. Erythema Migrans Lesions in Patients from New York State with Culture–Confirmed Lyme Disease.

Panel A shows a single erythema migrans lesion (8.5 by 5.0 cm) on the abdomen that was homogeneous in color except for a prominent central punctum (the presumed site of the tick bite). Panel B shows a single erythema migrans lesion (11.5 by 7.5 cm) in the popliteal fossa of the left leg, with more intense erythema to the right of the center of the lesion. Panel C shows erythema migrans lesions, with prominent central clearing, on the abdomen. This patient had more than 40 lesions altogether.

Serologic testing is warranted only in atypical cases and then in conjunction with serologic testing during the convalescent phase.¹⁹ For most patients, a serum sample obtained two weeks after the initial sample will be positive, but prompt antibiotic treatment of a seronegative patient may prevent seroconversion.²⁶ Although helpful in research studies, polymerase–chain–reaction (PCR) assay of a skin–biopsy sample and borrelial cultures of skin or blood are too

cumbersome and expensive to be carried out in routine clinical practice.¹⁹

Analogous to antibody testing in patients infected with the human immunodeficiency virus, a two-tier serologic-testing protocol was introduced in 1995 for the diagnosis of Lyme disease.²⁷ In this protocol, a serum sample that is positive or equivocal according to a first-stage assay, such as a polyvalent enzyme immunoassay, is retested with the use of separate IgM and IgG immunoblots. To improve test accuracy further, evidence-based guidelines for immunoblot interpretation were also recommended.²⁷ The change to two-tier testing was prompted by the lack of specificity of the commercially available enzyme immunoassays. As compared with the use of immunoblot testing alone, the two-tier protocol is slightly more specific and considerably less expensive.^{28,29}

Coinfection

The same ixodes tick species that transmit *B. burgdorferi* may be infected with and transmit *Anaplasma phagocytophilum* (previously referred to as *Ehrlichia phagocytophila*), which causes human granulocytic anaplasmosis (HGA) (previously called human granulocytic ehrlichiosis). *I. scapularis* ticks may also be infected with *Babesia microti*, the primary cause of babesiosis, but infection with the parasite in humans has been recognized only in limited parts of the regions in which Lyme disease is endemic. As many as 2 to 12 percent of patients with early Lyme disease may also have HGA,^{30,31,32} and 2 to 40 percent of patients with early Lyme disease may also have babesiosis, depending on the region.^{30,32,33} Diagnostic testing (e.g., blood smears, antibody assays, PCR assays) for these infections should thus be considered in patients with erythema migrans with symptoms that are more severe than those typical of Lyme disease alone (e.g., high-grade fever for more than 48 hours despite antibiotic therapy), with symptoms resembling those of a viral infection that fail to improve or that worsen despite resolution of the skin lesion, or who present with leukopenia, thrombocytopenia, or anemia.

Treatment

Randomized, prospective studies demonstrate that doxycycline, amoxicillin, and cefuroxime axetil are effective treatments for erythema migrans.^{18,34,35} No available data indicate the superiority of one of these antibiotics over the others, and serious adverse events are infrequent with all of them (Table 1). Doxycycline has the advantage of effectively treating HGA, which may occur simultaneously with Lyme disease.^{18,30,31,32}

Table 1. Treatment and Prevention of Early Lyme Disease.

A Jarisch–Herxheimer–like reaction – characterized by an increase in systemic symptoms and in the size or intensity of the erythema of the skin lesion – occurs in about 15 percent of patients within 24 hours after the initiation of antimicrobial therapy.³⁵ Erythema migrans lesions typically resolve within one to two weeks after the start of

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antibiotic therapy, but systemic symptoms often take longer to disappear; three months later, approximately 25 percent of patients may still have mild symptoms.³⁷ The development of objective complications is extremely rare in treated patients.^{18,38} Erythema migrans may recur, however, if the patient is bitten by another infected tick in a subsequent summer or, rarely, later during the same summer.^{7,37,38} The duration of antibiotic therapy was addressed in a double-blind, controlled treatment trial of 180 patients with erythema migrans.³⁷ Patients were randomly assigned to receive a 10-day course of doxycycline, a single intravenous dose of ceftriaxone followed by a 10-day course of doxycycline, or a 20-day course of doxycycline. The outcomes were similar in all three treatment groups over a follow-up period of 30 months. In view of the much shorter serum half-lives of amoxicillin and cefuroxime axetil, it is unclear whether a 10-day course of these drugs would be as effective as a 10-day course of doxycycline. For uniformity, a 14-day course of therapy has been recommended for all first-line oral agents.¹⁸

The results of a head-to-head trial that enrolled only patients with erythema migrans who also had objective evidence of the widespread dissemination of spirochetes indicate that parenteral antibiotic therapy with ceftriaxone is not more effective than oral treatment with doxycycline.³⁹ Parenteral therapy is much more expensive and has greater potential for serious adverse effects.⁴⁰ Therefore, such therapy is not recommended for patients with erythema migrans, except in unusual circumstances (i.e., in patients with advanced heart block from Lyme carditis or with neurologic manifestations of Lyme disease, aside from uncomplicated facial-nerve palsy) (Table 1).¹⁸

Evidence from controlled trials indicates that macrolides (specifically, erythromycin, azithromycin, and roxithromycin) are significantly less effective than other antibiotic therapies in the resolution of erythema migrans or associated symptoms.^{34,41,42} Thus, macrolides are not recommended as a first-line therapy.¹⁸

Cephalexin and other first-generation cephalosporins are not effective for the treatment of Lyme disease.^{43,44} In cases in which there is uncertainty whether a skin lesion is erythema migrans or bacterial cellulitis, either cefuroxime axetil or amoxicillin-clavulanic acid is a reasonable choice, since each will effectively treat both types of infection.^{18,43}

Prevention

People can prevent Lyme disease by avoiding tick-infested environments and, when in such environments, by covering up the skin as much as possible and using insect repellents containing N,N-diethyl-3-methylbenzamide (DEET) on exposed skin.^{18,36} The acaricide permethrin kills ticks on contact but should be applied to clothing rather than to skin. Daily inspections of the entire surface of the skin (including the scalp) and removal of any attached ticks are recommended. Clinical studies have demonstrated that without any other intervention, more than 96 percent of patients who find and remove an attached *I. scapularis* tick will remain free of Lyme disease, even in regions in which the disease is the most highly endemic.^{12,18} If a tick is not found and removed within 72 hours after attachment, the

probability of infection approaches the rate of infection in the regional tick population (typically, 20 to 40 percent of *I. scapularis* nymphs are infected in areas of the Northeast and Midwest in which the disease is highly endemic).^{12,45}

Doxycycline chemoprophylaxis can further reduce the chance of Lyme disease after a bite from an *I. scapularis* tick. In a randomized trial, a single 200-mg dose of doxycycline administered within three days after tick removal reduced the risk of erythema migrans at the bite site from 3.2 to 0.4 percent – that is, a risk reduction of 87 percent.¹² In regions in which the disease is highly endemic, the use of a single dose of doxycycline should be considered for persons who are known to have been bitten by a nymphal or adult *I. scapularis* tick that was estimated to have been attached for at least 36 hours.³⁶ (Larval *I. scapularis* ticks are not infected, owing to the absence of transovarian transmission, and pose no risk of Lyme disease.) Since the patient's own estimate of the duration of tick attachment is often unreliable (usually an underestimate), it is useful for physicians to learn to differentiate engorged from unengorged *I. scapularis* ticks on the basis of appearance (Figure 2).^{12,45,47} The use of culture or PCR to determine whether the tick is infected with *B. burgdorferi* is not recommended, because the clinical utility of such testing is unknown.⁴⁵ A previously licensed vaccine was effective in preventing Lyme disease in approximately 80 percent of patients, but it was withdrawn from the market by the manufacturer in 2002.⁴⁸

Figure 2. *Ixodes scapularis* Ticks.

Panel A (left to right) shows an *I. scapularis* larva, nymph, and adult female. Panel B shows nymphal *I. scapularis* ticks in various stages of engorgement with blood according to the hours of attachment to humans. The ticks at 0 hour correspond in size to the middle (nymphal) tick in Panel A. Photographs courtesy of Dr. Richard Falco and James Vellozzi. Reprinted from Wormser and Fish⁴⁶ with the permission of the publisher.

Areas of Uncertainty

The majority of patients with erythema migrans who are treated with an appropriate antibiotic regimen have an excellent outcome.^{7,18,34,35,37,49} Nevertheless, when evaluated 6 to 12 months after treatment, approximately 5 to 15 percent of patients report subjective symptoms such as fatigue or musculoskeletal pains,^{37,38} and about 10 percent of patients have similar types of symptoms 5 or more years after treatment.³⁸ These subjective symptoms are typically mild and may wax and wane in intensity.³⁸ If the symptoms interfere with function, some refer to them as post-Lyme disease syndrome, post-treatment chronic Lyme disease, or chronic Lyme disease.⁵⁰ Research on post-Lyme disease syndrome has been hampered by the lack of a standardized case definition, although one is under development by the Infectious Diseases Society of America. A prospective investigation is needed to clarify whether the rates of such symptoms after early

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Lyme disease are greater than the rates in appropriate control populations. Studies indicate that the retreatment of patients with prolonged subjective symptoms after treatment for Lyme disease, with additional oral and parenteral courses of antibiotics, is no more effective than treatment with placebo.^{50,51} Therefore, symptomatic treatment is recommended.¹⁸

Guidelines

Guidelines for the treatment of Lyme disease have been published by the Infectious Diseases Society of America (www.idsociety.org)¹⁸ and are currently being updated. The recommendations in this article are consistent with these guidelines.

Conclusions and Recommendations

The patient described in the vignette apparently has erythema migrans at the site of a tick bite. Had she presented with an engorged tick in hand within three days after removing it, I would have prescribed a single 200-mg dose of doxycycline (in the absence of contraindications). I would not prescribe the drug, however, if she did not have the tick or had presented later than three days after being bitten, since reported tick bites are frequently not from the relevant tick species (or not from a tick at all) and the efficacy of single-dose chemoprophylaxis beyond the three-day time limit is unknown. With or without chemoprophylaxis, the patient should be educated about the signs and symptoms of tick-borne diseases (such as rash or illness similar to that from viral infection). Besides Lyme disease, HGA and babesiosis should be considered in patients who have fever after being bitten by an ixodes tick in a region in which these infections are endemic.

In a patient who presents with erythema migrans, doxycycline for 10 to 14 days would be my first treatment choice, because it is also effective against HGA. However, if exposure to the sun is likely or if the patient may be pregnant or is breast-feeding, I would prescribe amoxicillin. Cefuroxime axetil is also effective but is more expensive than these agents. Because reinfection may occur, the patient should be told how to prevent tick bites (including wearing protective clothing and using insect repellents that contain DEET on exposed skin when in tick-infested areas). Useful information about Lyme disease is available at www.acponline.org and www.cdc.gov.

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