Erythema Migrans

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KEYWORDS

• Lyme disease • Erythema migrans • *Borrelia burgdorferi*

KEY POINTS

- Erythema migrans (EM) is the most common objective manifestation of *Borrelia burgdorferi* infection. It is associated with systemic symptoms in most but not all cases. Despite a characteristic appearance, EM should not be considered pathognomonic for Lyme disease because it must be distinguished from other similar-appearing skin lesions, including local reactions to uninfected arthropod bites in endemic areas, and southern tick-associated rash illness in nonendemic areas.
- An evaluation for early Lyme disease by health care practitioners should include a complete skin examination with all patient clothes removed, in order to uncover EM skin lesions that may otherwise go unrecognized.
- EM should be considered a clinical diagnosis, and serologic and polymerase chain reaction assays are not necessary.
- Leukopenia and thrombocytopenia are not characteristic of Lyme disease and should be considered to indicate either an alternative diagnosis or a coinfection with the agents of human granulocytic anaplasmosis or babesiosis.
- EM has an excellent prognosis when appropriate antimicrobial treatment is initiated promptly.

INTRODUCTION

Erythema migrans (EM; previously known as erythema chronicum migrans), the distinctive skin lesion of early Lyme disease, has a unique appearance, so early investigators were able to describe the clinical manifestations of Lyme disease years before the discovery of the causative pathogen, *Borrelia burgdorferi*, or the development of the first diagnostic laboratory assays. Transmission by an *Ixodes* tick vector was recognized after noting that EM develops at the exact site of a tick bite that occurred days to weeks earlier.[1–5] EM is the most common objective manifestation of Lyme disease, accounting for about 90% of cases.[1,6–8]

Historical Perspective

Two Connecticut mothers, Polly Smith and Judith Mensch, can be credited with spurring the investigations that eventually led to the recognition of the clinical manifestations and,

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ultimately, the pathogenesis and treatment of Lyme disease. They were skeptical of the diagnosis of juvenile rheumatoid arthritis given to their children and many others by physicians in October 1975, and requested a formal investigation from Connecticut health authorities and the US Centers for Disease Control and Prevention (CDC).[3] As a result, it was found that, in Old Lyme, Connecticut, an inflammatory joint syndrome occurred at a frequency more than 100 times that of juvenile rheumatoid arthritis. It was preceded in many cases by a characteristic skin rash that was noted by some patients to follow an arthropod bite after a median of 12 days. A team of researchers led by Dr Allen Steere realized that this skin lesion was reminiscent of the European erythema chronicum migrans (ECM) lesion, initially described in 1909,[3,4] which had been associated with the bite of the *Ixodes ricinus* tick. A quarter of a century before Dr Steere's investigation, some European physicians had observed a favorable response of ECM to penicillin treatment, as might be expected with a bacterial illness.[9] By 1982, a previously unrecognized spirochete, subsequently named *B burgdorferi*, was isolated from *Ixodes dammini* (now known as *Ixodes scapularis*) ticks from Shelter Island, New York, and also from the blood, skin, and cerebrospinal fluid of human patients with Lyme disease, finally establishing the cause and vector.[3] Treatment studies soon confirmed the efficacy of certain antimicrobial medications in improving patient outcomes.[10]

CLINICAL DIAGNOSIS

Primary EM is an expanding erythematous skin lesion, usually round or oval, that develops at a site where ticks belonging to certain *Ixodes* species have inoculated the spirochete *B burgdorferi*, 7 to 14 days (range, 1–36 days) earlier.[2,5,11–13] Secondary EM lesions may develop after *B burgdorferi* spreads from the site of the tick bite through the blood and back to other areas of skin (discussed later). In order to increase the specificity of the diagnosis, the CDC and others have designated 5 cm in largest diameter as a minimum size for primary EM lesions.[14] Use of this cutoff is helpful in differentiating EM from other lesions; in particular, a localized and transient inflammatory reaction to the bite of an arthropod that is not associated with infection and, in contrast with EM, resolves spontaneously within a day or two.[2,15–17] The 5-cm size limitation is useful for increasing accuracy in the clinical diagnosis of Lyme disease and, in particular, in clinical and epidemiologic studies, but should not be used alone to exclude the diagnosis of EM in individual patients with otherwise suggestive clinical and epidemiologic features.[2,6,14,16]

Tick Bite

Only about 25% (range, 14%–32%) of US patients with EM recalled the preceding tick bite that transmitted the infection.[12,16,18] One explanation for this is that the nymphal stage of *I scapularis*, the principal vector for Lyme disease in the United States, is only about the size of a poppy seed, and most tick bites are unassociated with pruritus or pain.[2,16,19] In addition, tick bites that result in infection occur at body sites such as the back or posterior thigh in adults or the hairline of children, where the tick can feed for days without being noticed.[2,12,20] The reason for this is that the transmission of *B burgdorferi* takes at least 36 hours, during which time the spirochete must move from the tick midgut to the salivary glands before it can be transmitted to the skin of the human host.[21] The locations of primary EM lesions in one study of 79 adult patients whose EM was culture confirmed are listed in **Table 1**.[12]

Evolution of Erythema Migrans and Central Clearing

EM begins as a small macule or papule at the tick bite site and progresses into a slowly enlarging erythematous patch over days.[5,11,13,22] A depressed or raised area (punctum)

Table 1
Body location of EM in 79 patients with culture-confirmed infection

Location	No. (%)
Thigh	14 (18)
Back	12 (15)
Shoulder	11 (14)
Calf	8 (10)
Groin	6 (8)
Popliteal	5 (6)
Flank	5 (6)
Axilla	4 (5)
Buttock	4 (5)
Upper arm	4 (5)
Other[a]	6 (8)

[a] Chest, 2 (2.5%); abdomen, 2 (2.5%); neck, 1 (1%); ankle, 1 (1%).

From Nadelman RB, Nowakowski J, Forseter G, et al. The clinical spectrum of early Lyme borreliosis in patients with culture-confirmed erythema migrans. Am J Med 1996;100(5):502–8; with permission.

may remain at the center of the lesion at the site where the tick had previously detached (**Fig. 1**).[11,13,23,24] As the lesion expands over days to weeks, it may take on an annular or targetlike appearance as clearing develops in or around the center. The EM lesion remains flat, blanches with pressure, and usually does not desquamate or vesiculate at the periphery, although these changes may occur centrally.[2,5,12,13,18,22] The median diameter in each of 5 studies involving more than 500 US patients was between 10 and 16 cm but lesions may exceed 70 cm.[5,12,13,18,25,26] EM size is a function of its duration,[4,11,12,26] varying in a linear fashion with a correlation coefficient of 0.7.[12] Spirochetes migrate in an outward direction from the inoculation site, resulting in a growth rate of 20 cm^2/d for early EM lesions.[11] European patients with infection caused by *Borrelia garinii* may have even more rapid expansion of EM.[27]

Using special culture media, *B burgdorferi* can regularly be isolated from the leading margin of the lesions and even from adjacent normal-appearing skin external to the lesion.[2,12,18,27–29] The organism may also be isolated from the center of the lesion.[26,27] As with EM size, central clearing is a function of duration of EM.[4,11,26] Thus, an annular

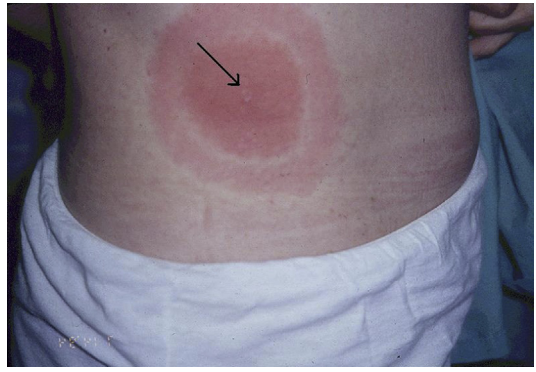

Fig. 1. EM lesion with punctum (*arrow*).

appearance was emphasized in the early descriptions of the long-standing rashes (ie, then known as ECM) that were most commonly observed before the recognition of effective antimicrobial treatment. In addition, the first descriptions of EM were in Europe, where most cases have been shown to be associated with *Borrelia afzelii*, and EM has a different clinical course and appearance than that associated with *B burgdorferi* sensu stricto in the United States.[4,26,29–31] Although 80% of cases had central clearing in one early Swedish study in which lesions had been present for 5 to 6 weeks,[4] central clearing occurred in only 37% and 9% of cases respectively in 2 large studies conducted in the northeastern United States, involving nearly 200 patients with culture-confirmed EM.[12,18] Central clearing was also much more likely to occur in Slovenian patients with infection caused by *B garinii* than in American patients in Westchester County, New York, caused by *B burgdorferi* sensu stricto (61.2% compared with 35.3%; $P<.0001$), despite similar duration of EM.[27] Aside from the variations in rash morphology attributed to the distinctly separate genospecies causing illness in the two continents, the lack of central or paracentral clearing at the time of presentation in US patients is also likely partly related to the more rapid diagnosis and treatment (within 1–2 weeks of onset) of EM in the United States during the last 25 years.[2,6,12,18]

Local Characteristics of Erythema Migrans

EM lesions are warmer than surrounding normal-appearing skin and usually have regular margins. The periphery is not raised compared with the interior. Lesions are usually oval or circular, with the shape partly determined by lines of skin tension.[2,11,13,23] For instance, groin lesions tend to be oval along the horizontal axis (**Fig. 2**).[2,13,23] Unusual configurations such as triangles may appear when spirochetes migrate over skin folds (**Fig. 3**).[11] Central vesicles were observed in 8% of lesions in one study and may be clear, cloudy, or hemorrhagic (**Fig. 4**).[32] Vesicular EM lesions may be difficult to differentiate from bacterial cellulitis, arthropod bite, contact dermatitis, or even herpes simplex and varicella zoster virus infection.

Scaling is uncommon in EM lesions, occurring primarily at the tick bite site (punctum), in fading rashes of long duration, or after antimicrobial treatment.[2] Use of topical steroids may also lead to scaling, in addition to giving EM an uncharacteristic pallor.[2] Although EM lesions characteristically display a shade of erythema from faint pink to dark red, lesions on the lower extremities may develop a bluish color.[11,13] Lesions in dark-skinned persons may be difficult to recognize (**Fig. 5**). Pruritus or pain may be noted at the site of EM but is almost always mild in severity.[4,12,13,31,33] A minority of patients, most often in Europe, complain of transient numbness or tingling at the site of EM.[4,5,12,13,18,29,31] Spirochetemia may result in secondary skin lesions (discussed later). The characteristics of EM from 79 patients from Westchester County, New York, with culture-proven EM are summarized in **Table 2**.[12]

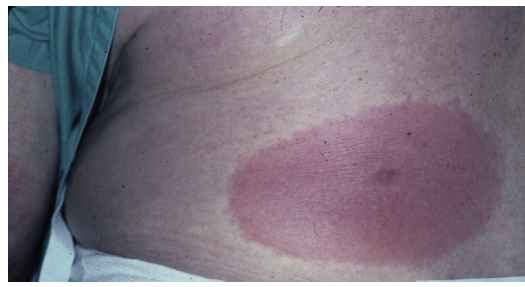

Fig. 2. Oval EM lesion.

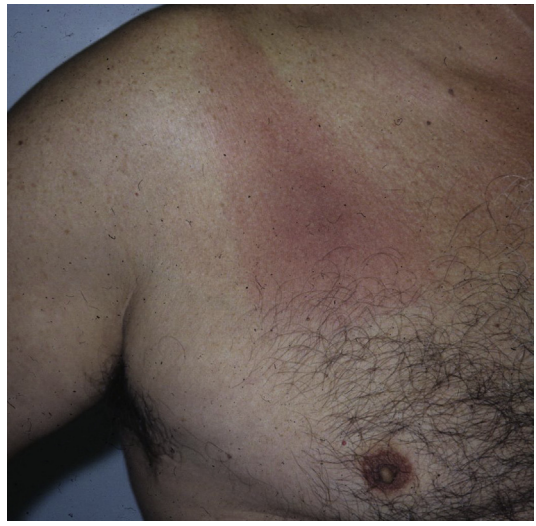

Fig. 3. Triangular EM lesion.

Associated Systemic Symptoms

As many as 80% of patients in the United States with EM have simultaneous systemic symptoms.[5] These symptoms are often experienced together with the EM but may precede the onset or develop after resolution of skin lesions.[2,11] The most common systemic symptoms in more than 600 US patients enrolled in 4 large prospective

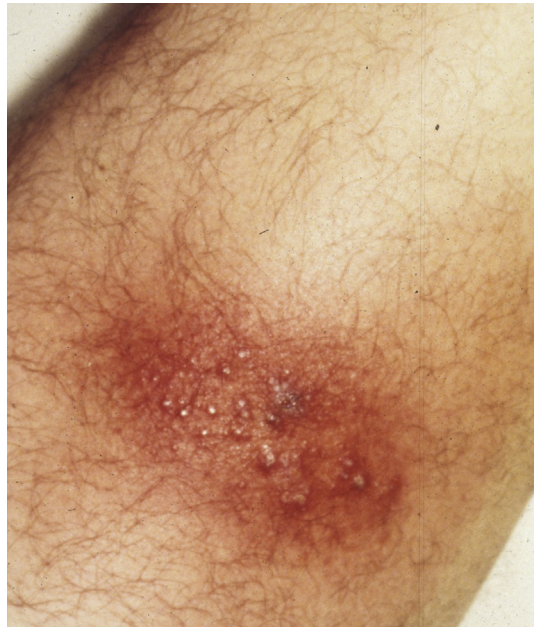

Fig. 4. Vesicular EM lesion.

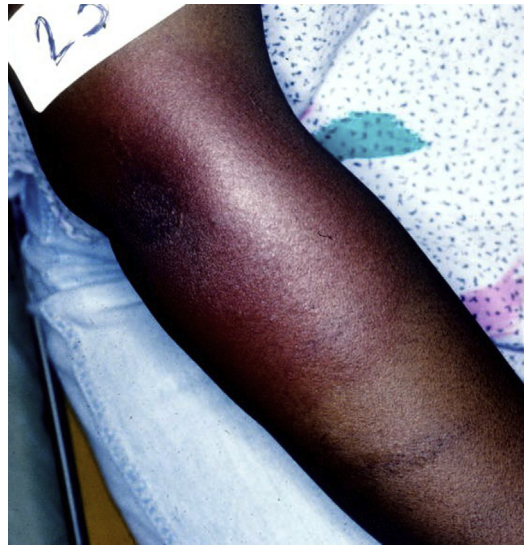

Fig. 5. EM lesion in a patient from the Caribbean who acquired the infection in Westchester County, New York.

studies were malaise (10%–80%), headache (28%–64%), fever and chills (31%–59%), and myalgias and arthralgias (35%–48%), with nausea, anorexia, dizziness, and difficulty concentrating reported less frequently.[5,11,12,18] Respiratory symptoms (ie, cough or rhinorrhea) and diarrhea are not characteristic of Lyme disease and should raise the possibility of an alternative or concurrent process.

European patients are less likely than US patients to experience systemic symptoms (23%–50% of more than 800 patients in representative prospective studies in 6 different European countries).[4,26,27,29–31,33–35] This finding is likely attributable to the lower virulence of *B afzelii* (the major cause of EM in Europe) compared with *B burgdorferi* sensu stricto, the only genospecies that has been implicated as causing human disease in the United States.[1,26,31] *B afzelii* also seems to be less virulent than *B garinii*, another European genospecies.[31] However, European patients with *B garinii* infection also seem to have fewer systemic symptoms and less dissemination to multiple skin sites (secondary EM) than patients from the United States with *B burgdorferi* sensu stricto infection.[27] These differences may be partially caused by the greater ability of *B burgdorferi* sensu stricto to stimulate macrophages to secrete

Table 2
Selected characteristics of EM in 79 patients with culture-confirmed infection

Feature	No. (%)
Central clearing	22 of 59 (37)
Uniform color	16 of 59 (27)
Fading rash at presentation	12 of 59 (20)
Vesicular	4 of 59 (7)
Multiple EM	14 of 79 (18)

From Nadelman RB, Nowakowski J, Forseter G, et al. The clinical spectrum of early Lyme borreliosis in patients with culture-confirmed erythema migrans. Am J Med 1996;100(5):502–8; with permission.

higher levels of chemokines and cytokines and to activate both innate and adaptive immune responses compared with *B afzelii* and *B garinii*.[36]

Associated Physical Findings

Regional lymphadenopathy (23%–41%), fever (14%–31%), and pain on neck flexion (5%–20%) are the most common objective physical findings at the time of diagnosis of EM in patients in the United States.[5,12,18,25] Concurrent cranial nerve palsies (usually facial nerve) are reported in 1% to 6% of patients.[5,12,18,25] Patients with associated heart block may have bradycardia or irregular heart beats.

Patients with EM from New York State with infection caused by *B burgdorferi* sensu stricto were significantly more likely than those from Slovenia with either *B afzelii* or *B garinii* infection to have more physical findings, including regional lymphadenopathy and fever.[26,27] Regional lymphadenopathy was the most common finding in European patients, found in 7.2% of 316 patients from 2 prospective studies from Slovenia.[26,33]

Multiple Erythema Migrans and Spirochetemia

Half of a cohort of 314 patients in an observational study in Connecticut conducted from 1976 to 1982 developed multiple annular secondary lesions,[5] with 40 of the 314 (13%) patients having more than 20 secondary lesions, and 2 patients having more than 100 (**Fig. 6**). Secondary lesions were similar in morphology to the initial solitary (ie, primary) lesion with which most patients presented, but tended to be smaller (usually 2–3 cm) and did not have an indurated center (ie, punctum).[5,13,23] Neither secondary nor primary lesions are present on mucous membranes, palms,

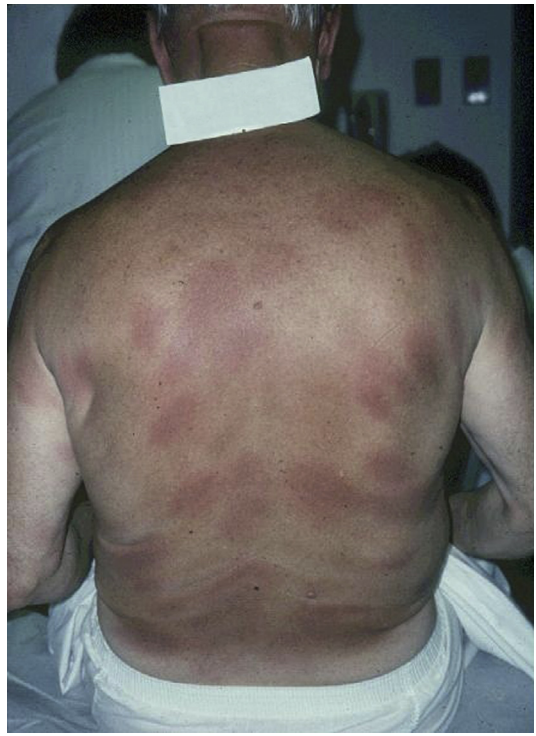

Fig. 6. Multiple EM lesions.

or soles. Secondary lesions are the result of hematogenous spread from the original tick bite and contain viable spirochetes.[23,37] However, secondary lesions lack a punctum because they do not occur at the site of tick inoculation; they also are not associated with local pruritus, tenderness, or vesiculation. Some secondary lesions may be transient, appearing and disappearing suddenly during examination.[5] These evanescent lesions may be observed for several weeks in untreated patients, even after resolution of primary and secondary lesions.[5]

Using high-volume ($\geq$9 mL) blood culture samples, using special media, it can be shown that as many as 50% of patients with EM from the United States have spirochetemia; multiple EM lesions are observed in more than 40% of patients with detectable spirochetemia (**Table 3**).[37] Spirochetemic patients are significantly more likely than those with negative blood cultures to have systemic symptoms, to have more symptoms, and to have a higher cumulative symptom severity score.[37] The presence of multiple EM lesions, regional lymphadenopathy, headaches, stiff neck, and chills (but not fever) are also significantly more likely to be associated with positive blood cultures.[37] However, no single characteristic or combination of variables had enough specificity and sensitivity (>80%) to predict spirochetemia.[37]

Influence of Strain Differences on Manifestations of Erythema Migrans

Hematogenous dissemination of *B burgdorferi* from the initial focus of infection at the site of tick bite and primary EM lesion is thought to account not only for multiple EM lesions but for objective extracutaneous manifestations of Lyme disease (eg, facial nerve palsy, meningitis, carditis, and arthritis). *B burgdorferi* can be classified into subtypes based on RNA intergenic spacer type (RST; also referred to as restriction fragment length polymorphism) at the 16S-23S ribosome of *B burgdorferi*,[38] genotyping of the outer surface protein (Osp) C gene,[39,40] or multilocus sequence typing.[41] Some subtypes of *B burgdorferi* are less likely to be associated with spirochetemia,[37–39,42] perhaps explaining why 20% of 55 untreated patients with EM remained symptom free after a mean of 6 years in one study.[43] In general, patients with RST types 1 and 2 and OspC types A, B, I, and K are more likely to have multiple EM lesions and spirochetemia.[37,38,42] In contrast, some patients with solitary EM lesions and less invasive subtypes have significant systemic symptoms, implying that other factors (eg, host factors or cytokines) may contribute to these symptoms.[44] In one report, patients with EM infected with RST 1 strains had more symptoms than those infected with other strains and greater cytokine levels, including interferon-gamma (IFN-γ), IFN-γ–inducible chemokines, CCL2, CXCL9, and CXCL10.[42] In addition, in

Table 3
Comparison of selected clinical and laboratory characteristics of 213 patients with EM with and without spirochetemia

Variable	Spirochetemia (93 Patients) No. (%)	No Spirochetemia (120 Patients) No. (%)	*P* Value
Multiple EM lesions	39 (41.9)	18 (15.0)	<.001
Symptomatic	83 (89.2)	89 (74.2)	.006
Regional lymphadenopathy	46 (49.5)	43 (35.8)	.05
Lymphocyte count <1.0 $\times$ 10^9 cells/L	26 of 91[a] (28.6)	10 of 116[a] (8.6)	<.001

[a] Number of patients for whom lymphocyte count was obtained.

From Wormser GP, McKenna D, Carlin J, et al. Brief communication: hematogenous dissemination in early Lyme disease. Ann Intern Med 2005;142(9):751–5; with permission.

this report, RST 1 strains stimulated peripheral blood mononuclear cells from healthy humans to secrete significantly higher levels of interferon-alfa (INF-α), IFN-γ, and CXCL10 than RST 2 or RST 3 strains.[42]

Epidemiology

It has been estimated by the CDC that approximately 300,000 cases of Lyme disease occur annually in the United States.[45] Of the approximately 25,000 confirmed cases reported in 2012, 13 states in New England, the Middle Atlantic (and Virginia), and North Central regions accounted for 95% of cases.[14,46] Although more than 70% of these patients had a reported history of EM, the incidence of EM is likely to be underestimated because this skin lesion may go unnoticed when it occurs at body sites that are not readily visualized by a patient (or even health care provider), or when minimal or no systemic or local symptoms are present.[1,2,7,8,16] In addition, case reporting is intrinsically biased toward later manifestations of Lyme disease, such as arthritis, because in many states positive serologic tests are reported (which are usually negative in EM but positive in late disease; discussed later).[15,47–49] There are 2 peaks in the age distribution for EM, at 5 to 14 years old and 45 to 54 years old. Because nymphal *I scapularis*, the stage most closely associated with transmission of *B burgdorferi*, are most active from May to July, the overwhelming majority of cases of EM occur in late spring or summer.[50–52] Nymphal ticks are more numerous than adult ticks and are also much smaller and thus less likely to be detected and removed before transmission of infection can occur.[16,19] Ticks are also more likely to be encountered during the warmer months, when people tend to increase outdoor activity.[52]

EM has been reported, and *B burgdorferi* sensu lato has been isolated, from clinical specimens throughout Europe and parts of Asia (eg, Japan) where *B afzelii* and *B garinii* are the most common causal genospecies.[26,29–31,33,53–56] Reports of EM from regions (including in the United States) without prior culture isolation of *B burgdorferi* sensu lato from human specimens or vector ticks should be viewed with skepticism.[57]

Differential Diagnosis

One group of investigators attempted to examine the diagnostic value of clinical history and physical examination in the evaluation of rashes consistent with EM.[20] The investigators were unable to identify a single sign or symptom or any epidemiologic information diagnostic of EM. They commented on the need for an algorithm that combines specific signs or symptoms in order to improve diagnostic sensitivity.[20]

The diagnosis of EM should be considered in patients who present with nonspecific illnesses in endemic areas during the late spring and summer, even if a rash is initially not reported.[2,58] Health care providers should perform a complete skin examination with all clothing removed to evaluate areas poorly visualized by the patient. In this way, previously unrecognized EM may be identified. EM should also be considered (and searched for) when examining patients with unexplained atrioventricular heart block because carditis caused by *B burgdorferi* has been reported in 2% to 9% of untreated patients with EM, with the higher incidence seen in early studies before recognition of the value of antimicrobial therapy for this disorder.[5,59,60]

EM can usually be differentiated from other skin disorders. EM occurs infrequently from autumn to midspring (although this may vary with weather patterns and tick density and activity). Arthropod bites unassociated with *B burgdorferi* infection may resemble EM. Because it generally takes days for transmission of *B burgdorferi* to occur after a tick bite,[16,19] an erythematous lesion surrounding the bite site while a tick is still attached, or within 48 hours of detachment, is most likely a hypersensitivity reaction to the tick bite rather than an infection (**Fig. 7**, **Table 4**).[2,15–17] Such hypersensitivity

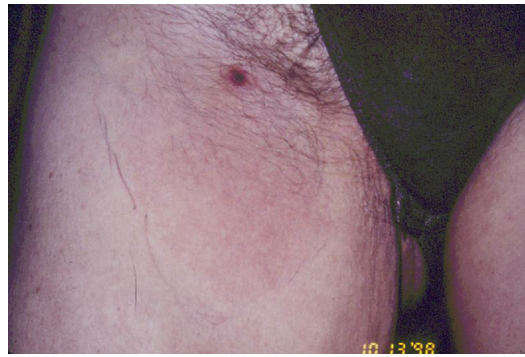

Fig. 7. A probable hypersensitivity reaction to a tick bite, mimicking EM. The rash (more than 5 cm and thus technically fulfilling CDC criteria for a diagnosis of EM) was noted at the time an adult *I scapularis* tick was removed, a few hours before taking this photograph. The patient experienced intense pruritus at the site, which she had noted in the past with tick bites. There were no associated systemic symptoms. The rash resolved within approximately 48 hours without treatment. The patient remained well and serology for antibodies to *B burgdorferi*, performed after approximately 3 months, was negative.

reactions are usually less than 5 cm in the largest diameter, may be associated with significant pruritus (atypical for EM), and tend to fade spontaneously within 24 to 48 hours. In contrast, an EM lesion typically increases progressively in size over days. Most patients with EM seen in the United States also have associated systemic

Table 4
Differentiating EM from hypersensitivity reaction to an arthropod bite

Characteristic	EM	Arthropod Bite Hypersensitivity Reaction
Recall of bite at site	~20%	Variable
Tick present at time of rash	No	Yes (or detached within prior 24 h); also may occur after other arthropod (eg, mosquito) bites
Time interval between bite and rash	Median 7–10 d (range, 1–36 d)[2,5,11,12]	Hours
Location	Intertriginous areas, border of tight-fitting clothing	Same; also can occur on exposed areas such as face or forearm
Local symptoms	Rare; minimal if present	Pruritus
Evolution	Expands over days to weeks	Expands over hours
Resolution	Days to weeks (median 4 wk if untreated[5])	<48 h
Size	≥5 cm (can be smaller)	<5 cm (can be larger)
Systemic symptoms	Up to 80%	Absent
Fever	16% documented, 39% subjective[12]	Absent

See Fig. 7.

From Nadelman RB, Wormser GP. Erythema migrans and early Lyme disease. Am J Med 1995;98(4A):15S–23S; with permission.

symptoms, in contrast to those with local tick bite hypersensitivity reactions. It may be helpful in some cases for the health care practitioner to demarcate the lesion with ink and observe evolution over 1 to 2 days without treatment. If the rash expands or systemic symptoms develop, antimicrobial treatment should be initiated, whereas if the rash resolves within 48 hours no treatment is necessary.[2,16] Factors that may be used to distinguish EM from arthropod bite reactions unassociated with *B burgdorferi* infection are listed in **Table 4**.

In contrast with EM, both staphylococcal and streptococcal cellulitis develop suddenly, evolving over hours with a bandlike rather than oval or circular shape, and are usually painful. Although fever may accompany both EM and pyogenic cellulitis, leukocytosis and a toxic-appearing patient may be observed in staphylococcal and streptococcal cellulitis but are rarely noted in patients with EM. The typical body sites at which skin manifestations occur also differ for these infections. Cellulitis caused by pyogenic organisms usually develops on the distal lower extremities, sometimes after trauma, and often in a person with underlying peripheral vascular disease (eg, venous stasis) or with a history of prior surgery affecting venous or lymphatic flow (eg, saphenous vein harvesting for coronary artery bypass surgery or mastectomy).[2] In contrast, EM tends to occur in the axillae, back, buttocks, popliteal fossae, and other sites where a tick may feed unnoticed for a sufficient period of time (2 days or more) to transmit infection (see **Table 1**).

Herpes simplex and *Varicella zoster* may usually be distinguished from EM by their dermatomal distribution and tenderness, although vesicular EM lesions tend to be more painful than those without vesiculation. Patients with vesicular EM often present complaining of an unwitnessed spider bite. It is important to recognize that the range of the brown recluse spider (which extends southerly from southeastern Nebraska to southern Ohio) does not include most of the geographic region in which Lyme disease is endemic.[61,62]

An erythematous border and central clearing are characteristic of tinea infection, and thus may resemble EM. However, tinea rashes evolve much more slowly (weeks rather than days) compared with EM and are not associated with systemic symptoms. Scaling and thin, irregular, raised borders should suggest tinea. Characteristics of some skin disorders that may be confused with EM are summarized in **Table 5**.

Southern Tick-associated Rash Infection

An EM-like rash has been identified in many patients residing in regions of the United States (especially the South) where *B burgdorferi* infection has not been identified in humans.[63–66] This rash has some features reminiscent of EM, including peak summer incidence, similar incubation period after a tick bite, and a similar appearance to EM, including the occasional presence of multiple lesions. However, in contrast with patients with Lyme disease, *B burgdorferi* has failed to grow in Barbour-Stoenner-Kelly medium from biopsied skin lesions. Acute and convalescent phase serologic assays are almost always negative for antibodies to *B burgdorferi*.[65,66] In addition, *I scapularis* ticks, the usual vector for Lyme disease, are rarely infected with *B burgdorferi* in the southern United States (<0.5%) and infrequently bite humans.[67] The tick vector for this EM-like rash is *Amblyomma americanum*, which is not thought to be a competent vector for *B burgdorferi*.[68] Therefore it may be concluded that this rash does not represent Lyme disease; it has come to be known as southern tick-associated rash illness (STARI), or Masters disease (after a key investigator).[63,65,66] At one time, a new *Borrelia* genospecies, *Borrelia lonestarii*, was postulated to be the causal agent,[69] but a subsequent study of 19 patients with STARI failed to detect this organism.[66] A prospective clinical evaluation of patients from Missouri with STARI

Table 5
Differential diagnosis of EM

Diagnosis	Appearance	Body Site	Size	Progression	Seasonal Tendency	Miscellaneous
Tinea (ringworm)	Ring shape, with satellite lesions; scaling at periphery	Variable; exposed skin	1–10 cm	Days to weeks	No	Pruritus; pet exposure
Bacterial cellulitis	Homogenous erythema; bandlike appearance; warm and tender, lymphangitic streaking; tender regional lymphadenopathy	Distal extremities; site of prior trauma	Rarely large except on lower extremities	More rapid than EM (hours to days)	No	Pain, fever, leukocytosis; history of prior trauma, vascular disease, or surgery
Contact dermatitis	Shape related to contact; vesicles and bullae may be present	Variable	Variable	Variable (often slow progression)	No	Pruritus often severe; history of contact with inciting substance (eg, poison ivy)
Urticaria	Raised, multiple lesions	Variable	Variable	Waxes and wanes over hours	No	Pruritus
Fixed drug eruption	Deep, well-demarcated, violaceous plaque	Fixed, often involves genitals	Variable	Fixed in size	No	Burning
Brown recluse spider bite	Necrotic; red, white, and blue sign	Extremities	Variable	Spreads centrifugally	Yes (mates May to September)	May be painful; uncommon in northeastern United States
Herpes simplex / Varicella zoster	Vesicles on erythematous base	Dermatomal distribution	Variable	May progress rapidly (days)	No	Prodrome may occur; pain (sometimes severe); pruritus, fever

See Table 4 for distinguishing EM from a hypersensitivity reaction to an arthropod bite.

Adapted from Feder HM, Whitaker DL. Misdiagnosis of erythema migrans. Am J Med 1995;99(4):412–9, with permission; and Tibbles CD, Edlow JA. Does this patient have erythema migrans? JAMA 2007;297(23):2617–27.

and patients from New York with EM showed distinct differences in the clinical characteristics of patients from the two regions.[65] Missouri patients were significantly more likely to recall a preceding tick bite at the site of the lesion, and had a shorter time to onset of lesions than New York patients. New York patients with EM were more likely to be symptomatic and were more likely to have multiple skin lesions. Missouri patients tended to have skin lesions that were more circular and smaller in size, and were more likely to have central clearing. Missouri patients recovered more rapidly than New York patients after antibiotic treatment.[65]

Coinfection

I scapularis, the vector for *B burgdorferi*, is also known to transmit *Babesia microtia*, causing babesiosis, a malarialike infection,[8,16,70] and *Anaplasma phagocytophilum*, the agent of human granulocytic anaplasmosis (HGA; formerly known as human granulocytic ehrlichiosis).[16,58,70,71] The presence of these two organisms may confound the typical clinical picture of Lyme disease. The occurrence of leukopenia, thrombocytopenia, or anemia in a patient with Lyme disease should suggest coinfection, because cytopenias are not characteristic of Lyme disease.[58,71–73] Abnormal levels of transaminases and other liver enzymes are common in patients with HGA but may occur in patients with Lyme disease alone.[5,12] The lack of rapid response (48 hours) to amoxicillin or cefuroxime axetil, particularly the persistence of fever, should raise consideration of the diagnosis of coinfection.[15,16] A patient with EM who appears toxic or requires intensive care should prompt an evaluation for babesiosis, especially in an immunocompromised or asplenic patient,[74] or HGA.[75] Deer tick virus, a cause of meningoencephalitis, and *Borrelia miyamotoi*, which has been associated with viral-like syndromes as well as meningoencephalitis, are two recently described pathogens that have also been linked to *I scapularis* bites.[76–78]

Laboratory Diagnosis

EM is a clinical diagnosis that is based on the characteristic appearance of the skin lesion in a patient with the appropriate epidemiologic and exposure history. Results of routine laboratory tests, such as complete blood counts, liver enzyme assays, and sedimentation rate, are generally not helpful in the diagnosis of Lyme disease and are usually normal (except in the case of coinfection with *A phagocytophilum* or *B microtia*; discussed earlier). However, the clinical diagnosis can be confirmed through laboratory testing, with isolation of *B burgdorferi* in culture being the gold standard for accurate identification. Laboratory validation is important primarily in the investigational setting (ie, treatment trials or epidemiologic studies). The diagnosis of infection with *B burgdorferi* may be supported by serology (acute and convalescent phase), culture of clinical specimens (skin and blood), and polymerase chain reaction (PCR; nested and quantitative reverse transcription PCR from skin). These tests were compared in 47 patients with EM in Westchester County, New York (**Table 6**).[79] In a more recent report, the sensitivity of quantitative PCR of blood culture and plasma, and nested PCR of plasma and skin, were compared with skin culture (61.5% sensitivity) in Westchester patients with EM.[80] Using quantitative PCR blood culture, 39 of 52 (75%) untreated patients with EM tested positive; 48 of 52 (92.3%) patients tested positive using at least 1 of the 5 methods.[80] Culture methods have in general been restricted to specialty and/or research laboratories; as with PCR (which has recently become more readily available), they are not useful in routine patient care.

The most practical laboratory method available to clinicians is serologic testing for antibodies to *B burgdorferi*. For many years, a 2-tier system has been recommended, usually polyvalent enzyme-linked immunosorbent assay (ELISA) followed by

Table 6
Comparison of diagnostic tests for 47 adult patients with EM

Diagnostic Method	No. (%) Positive Result
Skin culture	24 (51.1)
Blood culture (18 mL)	21 (44.7)
Any culture	31 (66)
Nested PCR	30 (63.8)
Quantitative PCR	38 (80.9)
Any PCR	38 (80.9)
Acute phase serology	19 (40.4)
Convalescent phase serology	31 (66)
Any serology	32 (68.1)
Any test positive	44 (93.6)
All tests negative	3 (6.4)

From Nowakowski J, Schwartz I, Liveris D, et al. Laboratory diagnostic techniques for patients with early Lyme disease associated with erythema migrans: a comparison of different techniques. Clin Infect Dis 2001;33(12):2023–7; with permission.

immunoglobulin (Ig) M and IgG immunoblots if the first step test is positive or equivocal.[16,48,81] However, serology is insensitive in early Lyme disease, with half of patients with EM having negative serology on presentation.[47,48,79] The probability of seroreactivity has been directly linked to the duration of EM,[47,48] with all 14 of the patients presenting with EM duration of greater than or equal to 2 weeks in one study having positive ELISA and IgM immunoblot at presentation.[47] Convalescent phase testing can be used to increase the sensitivity of serologic assays.[16,48] Two-tiered testing has the disadvantages of increased cost, time, and labor, and subjectivity in the interpretation of immunoblots.[82] More recently, testing using a C6 ELISA (based on the highly conserved 25-amino-acid C6 peptide of the VlsE protein) was significantly more sensitive than 2-tier testing, with sensitivities of 66.5% (95% confidence interval [CI], 61.7–71.1) and 35.2% (95% CI, 30.6–40.1), respectively ($P<.001$) in sera from 403 patients with EM.[82] Specificity of the C6 ELISA assay was slightly decreased compared with 2-tier testing.[82] However, because the diagnosis of EM is usually straightforward and because all available diagnostic assays frequently yield false-negative results, the routine use of serology or any other diagnostic test (eg, PCR) cannot be recommended at present for patients with EM.[16] Diagnostic tests in patients with EM should be reserved for those in whom there is a doubt about the diagnosis (eg, difficulty in distinguishing between EM and a hypersensitivity reaction to an arthropod, or an EM-like rash in a nonendemic region), or for those in clinical trials or epidemiologic studies.

TREATMENT

Long-term Outcome of Untreated Patients with Erythema Migrans

Although EM lesions resolve spontaneously within a median of 4 weeks, most untreated patients at some point develop clinical manifestations that may cause considerable morbidity.[5,43] Of 314 patients with EM diagnosed between 1976 and 1982, 55 who did not receive antibiotics were followed prospectively (after enrollment from 1976 to 1978) for a mean duration of 6 years. Although all EM lesions resolved spontaneously, within 1 to 14 months, 9% developed recurrent EM at the site of the primary lesion, 5% had recurrence of secondary lesions, and 7% had recurrence of

both, whereas 5% had recurrent evanescent lesions. Two children experienced frequent evanescent lesions for more than 3 years. Other manifestations of Lyme disease were experienced by 12 patients with recurrent skin lesions.[5] Eighty percent of all those observed without treatment developed joint symptoms ranging from arthralgias to intermittent episodes of arthritis to chronic synovitis. Of these 80%, 11% also developed neurologic abnormalities and 4% had cardiac involvement. The most typical course for Lyme arthritis, occurring in 51% of patients, was intermittent attacks of monoarticular or oligoarticular arthritis of large joints (almost invariably involving the knee), beginning months after the initial infection.[43] Although some patients experienced recurrent attacks of arthritis for many years, the number of recurrences decreased by 10% to 20% each year.[43] Severity of symptoms at onset of illness was predictive of development of late disease (arthritis).[43] However, 20% of untreated patients had no subsequent manifestations of Lyme disease over a median of 6 years (range, 3–8 years) after the resolution of their EM lesions.

Treatment Trials of Patients with Erythema Migrans

There have been several randomized prospective trials in the United States to evaluate treatment of EM. From 1980 to 1981, the first randomized trial was conducted in Connecticut in 112 patients with EM, comparing erythromycin, tetracycline, and penicillin for 10 days.[10] EM and associated symptoms resolved more rapidly in patients receiving penicillin or tetracycline compared with those receiving erythromycin. An intensification of fever, rash, or pain, noted in 15% of patients during the first 24 hours after initiation of antimicrobial therapy, was thought to represent a Jarisch-Herxheimer–like reaction. Complications such as meningitis, carditis, and arthritis were observed less frequently in patients receiving tetracycline or penicillin than in those receiving erythromycin.[10] No additional benefit was noted when the duration of treatment with tetracycline was extended from 10 to 20 days.[10] Two subsequent smaller studies evaluated amoxicillin (to which probenecid was added to increase drug levels) and doxycycline and showed efficacy of these medications with rapid resolution of rash and associated symptoms and a favorable outcome at 6 months in nearly all patients.[83,84] A similar satisfactory outcome was reported in patients receiving azithromycin in a third treatment arm in 1 of these studies.[84]

The efficacy of oral cefuroxime axetil 500 mg twice daily and doxycycline 100 mg 3 times daily were compared in a total of 364 patients (from New York, New Jersey, and Connecticut) with early Lyme disease characterized by EM in 2 subsequent randomized, multicenter, investigator-blinded, prospective, controlled studies.[85,86] A satisfactory clinical outcome (defined as resolution of EM and associated signs and symptoms by day 5 posttreatment, or improvement of these findings by day 5 and complete resolution at 1 month posttreatment) was observed in 93% and 90% of the cefuroxime axetil group and in 88% and 95% of the doxycycline group, respectively.[85,86] The two drugs seemed to be equally effective in treatment of early Lyme disease and prevention of extracutaneous disease at 1 year of follow-up.[85,86] Patients receiving cefuroxime axetil more frequently experienced diarrhea, whereas those treated with doxycycline were significantly more likely to have photosensitivity reactions; most adverse effects were mild and did not require discontinuation of treatment.[85,86]

Another prospective (but unblinded) controlled study addressed intravenous (IV) versus oral treatment of those with disseminated Lyme disease (not involving the central nervous system).[87] Of 140 patients with EM and disseminated disease, 133 had multiple EM lesions and 81 had fever. Resolution of symptoms and the prevention of complications did not differ between those patients receiving oral doxycycline 100 mg twice daily for 21 days versus ceftriaxone 2 g IV daily for 14 days.[87]

Because a significant minority of patients have allergies or are otherwise intolerant of β-lactam antimicrobials, and because tetracyclines may be associated with photosensitivity reactions during the late spring and summer months when EM is most common and also are contraindicated in pregnant women and young children, much interest has focused on the well-tolerated macrolide azithromycin for treatment of patients with EM. This drug was associated with excellent in vitro activity against *B burgdorferi* and was predicted to attain therapeutic levels in skin.[88] In a multicenter prospective controlled study 246 patients (from Westchester County and Long Island [NY], Connecticut, Missouri, Wisconsin, New Jersey, Minnesota, California, and Rhode Island) were randomized to receive either azithromycin 500 mg daily for 7 days or amoxicillin 500 mg 3 times daily for 20 days.[88] Azithromycin was significantly less effective than amoxicillin for the resolution of EM and associated symptoms, and in the prevention of objective relapse at 6 months[88] (in retrospect, the patients from Missouri, a nonendemic area for Lyme disease, probably had STARI rather than EM). However, in European studies, azithromycin seems to be more successful in treating early Lyme disease. Azithromycin was compared with phenoxymethylpenicillin and with doxycycline in prospective randomized trials from Germany and Slovenia, and showed comparable efficacy with possible earlier resolution of symptoms.[89–91] Another macrolide, oral clarithromycin (500 mg twice daily for 21 days), was studied in an open-labeled pilot trial in 41 patients with EM in Long Island, NewYork.[92] Symptoms resolved in 91% of the 33 evaluable patients by the end of treatment, and all 28 evaluable patients were well at 6 months.[92] However, although a semisynthetic macrolide, roxithromycin, showed good in vitro activity against *B burgdorferi*, a European trial comparing this drug with phenoxymethylpenicillin was interrupted because of failure in 5 of 19 enrolled patients, all of whom were receiving roxithromycin.[93]

Shorter, 10-day courses of tetracyclines have been shown to be as effective as longer courses.[10,94–97] Ten days of oral doxycycline twice daily, with or without a single 2-g IV dose of ceftriaxone, was compared with 20 days of oral doxycycline twice daily in a prospective, randomized, double-blind controlled trial.[94] All 3 treatment groups had similar rates of complete response at all assessment times over 30 months. Objective evidence of treatment failure was extremely rare regardless of the regimen.[94] It was concluded that extending the course of doxycycline from 10 to 20 days, or adding 1 dose of IV ceftriaxone at the beginning of a 10-day course of doxycycline did not enhance therapeutic efficiency in patients with EM.[94]

Doxycycline is not routinely recommended in children less than 8 years of age, which limits antibiotic options for children who are intolerant of amoxicillin. In a prospective, randomized, unblinded study in 43 children aged 6 months to 12 years, 2 different doses (20 mg/kg/d and 30 mg/kg/d) of cefuroxime axetil were compared with amoxicillin (50 mg/kg/d). All patients had good outcomes with resolution of EM and no long-term problems attributable to Lyme disease.[98] Minimal adverse effects were observed in all 3 groups.[98] Both amoxicillin and cefuroxime axetil have been recommended as the preferred regimen for pediatric patients less than 8 years old.[16]

Unlike other agents used to treat Lyme disease, doxycycline has excellent activity against *A phagocytophilum*, the causal agent of HGA, which may be transmitted together with *B burgdorferi* or separately after *I scapularis* tick bites.[16,58,75] Cephalexin, fluoroquinolones, metronidazole, and sulfonamides have no appreciable activity against *B burgdorferi* and should not be used to treat patients with Lyme disease.[16,99]

A low incidence of serious adverse effects has been observed in treatment trials for early Lyme disease. Doxycycline may cause phototoxicity, a potential concern because EM usually occurs in late spring or summer. Patients should be counseled regarding avoiding strong sunlight and using sun block. To prevent esophagitis

associated with doxycycline, patients should be advised to drink a full 240 mL (8 oz) of fluid with this medication, and should avoid a recumbent position for 1 hour afterward. Doxycycline is relatively contraindicated in children less than 8 years old and in pregnant or breastfeeding women. Amoxicillin and cefuroxime axetil have been associated with rash, diarrhea, and other adverse effects. Guidelines from the Infectious Diseases Society of America (IDSA) for the treatment of EM are summarized in **Table 7**.

Long-term Outcome of Treated Patients with Erythema Migrans

Long-term outcomes are excellent for patients treated appropriately for EM.[15,18,25,85,86,94,100,101] In an observational study evaluating 118 patients (recruited in the LYMErix vaccine trial[102]), seen in 10 endemic states with culture-confirmed EM, who were mostly treated with oral doxycycline, 11% had persistent signs and symptoms for more than 30 days after treatment, decreasing to 4% at 60 days.[18] However, these symptoms were mainly subjective, including headache, fatigue, and arthralgias, or represented residual neurologic symptoms of facial numbness or weakness in the 2 patients who had experienced seventh cranial nerve palsy. At 20 months' follow-up, all but 1 of the patients had completely recovered.[18]

In another prospective study conducted in Westchester County, New York, 99 patients with EM confirmed by culture of blood or skin biopsy specimens (5 additional

Table 7
IDSA recommendations for treatment of patients with EM

Drug	Dosage for Adults	Dosage for Children
Preferred[a]		
Amoxicillin	500 mg 3 times per day	50 mg/kg per day in 3 divided doses (maximum 500 mg per dose)
Doxycycline	100 mg twice per day Relatively contraindicated in pregnant or lactating women	Not recommended for children aged <8 y For children aged ≥8 y, 4 mg/kg per day, in 2 divided doses (maximum 100 mg per dose)
Cefuroxime axetil	500 mg twice per day	30 mg/kg per day in 2 divided doses (maximum 500 mg per dose)
Alternative[b]		
Azithromycin	500 mg per day for 7–10 d	10 mg/kg per day (maximum 500 mg per day)
Clarithromycin	500 mg twice per day for 14–21 d Relatively contraindicated in pregnant women	7.5 mg/kg twice per day (maximum 500 mg per dose)
Erythromycin	500 mg 4 times per day for 14–21 d	12.5 mg/kg 4 times per day (maximum 500 mg per dose)

In patients suspected of having coinfection with HGA, doxycycline is preferred if not contraindicated.

[a] Recommended duration is 14 days (10–21 days for doxycycline or 14–21 days for amoxicillin and cefuroxime axetil).

[b] Because of their lower efficacy, macrolides are reserved for patients who are unable to take, or who are intolerant of, tetracyclines, penicillins, and cephalosporins; patients treated with macrolides should be closely observe to ensure resolution of clinical symptoms.

From Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006;43(9):1089–134. [Erratum appears in Clin Infect Dis 2007;45(7):941].

patients who participated in a Lyme disease vaccine study[102] were excluded) were followed for a mean of 4.9 ± 2.9 years after treatment with first-line antibiotic regimens at baseline.[25] EM resolved within 3 weeks in all cases, and no patient developed extracutaneous manifestation of late Lyme disease. Within 3 months, 84% to 92% of patients were asymptomatic. Of those followed for more than 1 year, 10% were symptomatic at their last visit; symptoms were mild and intermittent. Of note, 47% of patients experienced subsequent tick bites, and 15% of patients had repeated episodes of EM (discussed later) after initial enrollment, highlighting the need for education on tick bite prevention for those persons who live, work, or have recreation in endemic areas. The number and severity of symptoms at baseline, and presentation with multiple EMs, were associated with the presence of symptoms at follow-up.[25]

A similar favorable outcome after antibiotic treatment has been observed in multiple studies from Europe. In a prospective study of French patients treated for EM, complete resolution of EM was observed with regression of associated symptoms at 6-week follow-up (except in those with preexisting rheumatologic disorders).[30] No patients developed arthritis or neurologic or cardiac manifestations of Lyme disease at 3-year follow-up.[30] Studies from other European countries showed similar excellent outcomes in patients treated for EM after 6 weeks, and at long-term follow-up (up to 27 months).[29,35,89–91,103] In one novel study, symptoms in 230 Slovenian patients with EM were compared, at baseline and at 6 and 12 months after standard antibiotic treatment of EM, with those of controls (spouse, family member, or friend within 5 years of age) without a prior history of Lyme disease.[100] Based on identical questionnaires administered to both groups, patients were less likely than controls to have subjective symptoms; none of the symptoms were severe enough to be disabling. The findings suggest that some symptoms experienced after treatment of EM may be unrelated to infection. However, this conclusion must be tempered by the fact that patients with multiple EM lesions (who may be more likely to develop symptoms after treatment) were excluded from participation.[100] The applicability to US patients of findings in European studies is uncertain because of clinical differences associated with *B burgdorferi* sensu stricto infection in the United States versus infection caused by *B afzelii* and *B garinii* in Europe.

Objective evidence of late disease almost never develops after patients with EM are treated with currently recommended regimens.[16,85–88,94,100,101] In some of the rare patients who have developed objective neurologic findings, subtle symptoms suggestive of central nervous system involvement had been present in retrospect at initiation of oral antimicrobial therapy.[84] However, approximately 10% of patients with EM experience subjective symptoms such as fatigue, myalgias, and arthralgias, and vague neurologic symptoms after treatment.[25,85,86,88,94,104] There is no evidence that ongoing infection causes these symptoms and prolonged antimicrobial treatment of these patients does not result in sustained improvement and can be harmful.[16,105–112]

Persistent fatigue was rare in patients followed prospectively for a mean of 15.4 years (range, 11–20 years) after treatment of culture-confirmed EM in Westchester County, New York.[113] Patients were evaluated using an 11-item fatigue severity scale (FSS-11) that has been used in studies of posttreatment Lyme disease syndrome[113] in which a score of greater than or equal to 4 is considered to indicate severe fatigue. Only 3 of 100 subjects (3%) were thought to have had persistent fatigue that might be attributable to Lyme disease, and the FSS-11 scores for these individuals was less than 4, averaging 2.27, with no person having functional impairment.[113] Although fibromyalgia has been postulated to be triggered by *B burgdorferi* infection, it was also exceedingly rare in this same cohort, observed in only 1 of 100 study participants.[114] The presence of chronic symptoms following treatment of EM must be interpreted in

the context of similar symptoms in the general population.[115,116] Ninety percent of the general population have 1 or more somatic symptoms in a given 2-week to 4-week period and 30% report current musculoskeletal symptoms.[115] Significant fatigue is experienced by 20% of adults, and more than 75% of healthy college students report at least 1 symptom in a 3-day period.[115] Thus, outcome studies that include controls without Lyme disease may be best suited to identify sequelae that may be related to infection with *B burgdorferi* as opposed to coincidental.[100]

Outcome in Special Patient Groups: Pregnant and Immunocompromised Hosts

Pregnant women have been excluded from enrollment in prospective treatment studies. However, there is no reason to think that this group of patients requires different antimicrobial therapy from others, other than avoiding doxycycline in pregnancy. Epidemiologic studies of outcomes following Lyme disease during pregnancy[117–119] have been unable to corroborate an early uncontrolled report that described adverse fetal outcomes in 19 patients with EM during pregnancy.[120] Furthermore, a survey of 162 pediatric neurologists in Connecticut (the state with the second highest incidence of Lyme disease[14]) failed to identify a single child with a neurologic problem thought to be related to Lyme disease during pregnancy.[121]

Several investigations of pregnancy outcomes from Europe have been conducted.[122–124] In a retrospective study from Hungary, untreated patients with EM had worse pregnancy outcomes than women treated orally, whereas those treated with IV therapy had the best outcomes.[123] However, no consistent adverse outcome was noted and the investigators concluded that a specific congenital Lyme borreliosis syndrome was unlikely. The findings of a prospective study of 105 pregnant women with EM from Slovenia were consistent with this conclusion.[122] Excellent outcomes were achieved after antibiotic treatment in 93 (88.6%) pregnancies, and adverse outcomes (abortion, preterm birth, syndactyly, and urologic anomalies) were not clearly linked to Lyme disease.[122] Good outcomes were also reported after treatment with IV ceftriaxone in 7 pregnant women with documented spirochetemia.[124] However, in European studies of EM during pregnancy, most patients have presumably been infected with *B afzelii* rather than *B burgdorferi* sensu stricto; thus it may not be possible to generalize conclusions to the United States.

Several studies have been published in Europe regarding the response to treatment of immunocompromised patients with EM.[125–127] In a Slovenian study (again, presumably dominated by *B afzelii* infection), more frequent early disseminated disease and more treatment failures requiring retreatment were noted in 67 patients with a variety of causes of immunosuppression compared with the control group.[127] However, both groups had a similarly favorable outcome at 1-year follow-up.[127] A favorable outcome was also observed in a retrospective study of 33 immunosuppressed patients from Austria with EM.[126] Initial clinical presentation, response to therapy, and production of anti-*Borrelia* antibodies were similar in immunosuppressed patients compared with controls.[126] Excellent outcomes after treatment of EM were also noted in 6 Slovenian patients with a prior history of organ transplant.[125]

Early Borrelia burgdorferi Infection Without Erythema Migrans

Some patients from endemic areas present with nonspecific systemic symptoms without EM during tick season. Some have EM lesions that are not recognized because of an inadequate physical examination that did not include visualization of the entire body. In others, an EM rash may have come and gone. In others, EM may become noticeable some days after systemic symptoms appear. However, there is evidence that some patients with Lyme disease present with nonspecific symptoms

without EM.[128] A Lyme disease vaccine trial offered a unique opportunity to study this topic because participants were followed prospectively by experts in tick-borne diseases who were familiar with the diagnosis of EM, and all patients had baseline blood samples stored that could be run in parallel after an acute illness to check for seroconversion. Of nearly 11,000 study participants in 10 states, 269 met predetermined criteria for definite, possible, or asymptomatic Lyme disease. Of these, 42 persons (16%) had systemic symptoms associated with IgM and/or IgG seroconversion but no EM. The 14 patients with only IgM seroconversions were considered to have possible Lyme disease, whereas 28 patients with IgG seroconversions on either the VlsE peptide ELISA or on sonicate Western blot were considered to be definite cases. A few patients were thought to have coinfection (ie, HGA [termed ehrlichiosis in the study] or babesiosis). Patient symptoms are summarized in **Table 8**. Symptoms resolved in a median of 3 to 7 days for almost all patients after treatment with doxycycline (34 patients) or amoxicillin (6 patients) (2 patients declined any treatment), although arthralgias or fatigue persisted for weeks to months in 7 patients. No patient developed objective manifestations (eg, arthritis or neurologic signs) of Lyme disease during the study.[128]

Reinfection

Patients may sustain a second, and occasionally more, episodes of Lyme disease after the first episode has resolved. These subsequent occurrences of Lyme disease are almost invariably associated with EM.[24] Reinfection may be defined as a new infection that occurs after successful antimicrobial treatment of a prior episode of Lyme disease.[24] In various prospective US series, the rate of reinfection ranged from 1.2% to 14.6 % over 1 to 5 years (averaging 1.2%–3.1% per year).[18,25,94] In 100

Table 8
Characteristics of systemic symptoms in patients with early Lyme disease without EM

	Definite Lyme Disease (n = 24) Number (%) or Median (Range)	Possible Lyme Disease (n = 7) Number (%) or Median (Range)
Age	53 (27–72)	48 (37–62)
Male sex	14 (58)	5 (72)
Fever	15 (63)	7 (100)
Chills	12 (50)	4 (57)
Malaise	17 (71)	7 (100)
Headache	13 (54)	6 (86)
Stiff neck	10 (42)	2 (29)
Paresthesia	7 (29)	0
Arthralgia	17 (71)	2 (29)
Myalgia	11 (46)	5 (71)
Sore throat	2 (8)	0
Dry cough	1 (4)	0
Number of symptoms per patient	4 (1–7)	5 (4–7)

Definite Lyme disease indicates seroconversion by IgG or C6 ELISA testing; possible Lyme disease indicates seroconversion only by IgM testing; patients thought to have coinfection with anaplasmosis (ehrlichiosis) or babesiosis were excluded.

Adapted from Steere AC, Dhar A, Hernandez J, et al. Systemic symptoms without erythema migrans as the presenting picture of early Lyme disease. Am J Med 2003;114(1):58–62.

patients with EM confirmed by culture and followed for 15.4 years (range, 11–20 years) after treatment, 24% reported a second episode of EM during this time, and one-third of these individuals experienced at least 2 subsequent episodes.[113] For patients with a prior history of EM, the rate of recurrent EM can exceed the incidence of Lyme disease in the general population living in the same community by a factor of 20 to 50.[24]

The most likely cause of recurrent EM is repeat tick bite. In one prospective study on the use of prophylactic doxycycline after a recognized tick bite in Westchester County, New York, 17% of 335 subjects sustained new tick bites over the 6 weeks following enrollment, despite receiving oral and written instructions on ways to reduce the risk of tick bites.[19] In addition, the human immune response is not fully protective against reinfection. Strain variability of *B burgdorferi* is possibly a factor; there are at least 19 OspC types causing infection in the United States.[129] Data from 17 patients with 22 paired consecutive episodes of culture-confirmed EM indicate that all second episodes were associated with an OspC type different from that of the first episode, indicating reinfection rather than a relapse.[129] Based on these findings as well as data from other patients with EM in the northeastern United States, probabilistic and simulation models suggest that strain-specific immunity develops in humans after EM and that it lasts at least 6 years.[130] Consistent with this finding is an experimental model of infection in which mice immunized with one OspC type were immune to reinfection with that strain but susceptible to infection with a different OspC type.[131] Humans with late Lyme disease (eg, arthritis) are extremely unlikely to develop reinfection as a result of an expanded immune response.[24]

Limited data are available regarding the clinical features of reinfected patients. Recurrent EM in 28 patients seen on Rhode Island was evenly divided among men and women; was unassociated with any immunodeficiency; and was almost exclusively seen in June, July, and August.[51] Preliminary experience from Westchester County, New York, indicated no differences in the occurrence of a variety of clinical signs and symptoms or in EM size in 11 men and 11 women experiencing reinfection a mean of 3.25 ± 2.65 years apart.[132] However, patients with second episodes of EM seemed less likely (3 of 11 [14%] vs 7 of 11 [32%]; $P = .15$) than those with first episodes to have multiple EM lesions (although this did not achieve statistical significance). This finding is consistent with the development of partial immunity preventing hematogenous spread during the second episode.[24] Supporting this concept is the observation in another study that patients with a prior episode of Lyme disease seemed less likely than those with first episodes to have spirochetemia (odds ratio, 2.5; 95% CI, 1.1–5.6; $P = .02$).[37]

In contrast with reinfection, relapse has not been well documented in patients receiving recommended treatment courses.[24,51] However, relapse has been well documented in patients treated with antibiotics not recommended for Lyme disease (eg, cephalexin)[99] and has been reported in patients receiving second-line agents,[16] such as macrolides.[88]

Prevention of Infection

Avoiding ticks can be difficult for people who live, work, or have recreational activities in tick-infested environments. Covering up the skin and applying acaricides or insect repellants to clothing and skin have been recommended to decrease risk.[16,133] Daily skin inspection with prompt removal of attached ticks is also recommended in order to interrupt transmission of tick-borne infection.[16,133] The chance of developing Lyme disease after a recognized bite from an *I scapularis* tick can be further decreased with the appropriate prophylactic use of doxycycline. In a randomized placebo-controlled trial of 503 subjects who removed attached *I scapularis* ticks, the risk of

EM was reduced from 3.2% to 0.4%, an 87% risk reduction, with the use of a single 200-mg dose of doxycycline, given within 3 days of a tick bite.[19] In highly endemic areas, people bitten by nymphal or adult *I scapularis* ticks that are estimated to have been attached for longer than 36 hours should be offered doxycycline prophylaxis if there are no contraindications.[16] Duration of tick attachment can be estimated when the tick is available by measuring the degree of engorgement of the tick.[16] Other preventative methods have been recommended, including application of acaricides to property and modifying the environment to exclude deer (fences) or inhibit tick movement (placing wood chip borders on property).[15,133] Vaccination was shown to be 80% effective in preventing Lyme disease but is no longer available.[15,102]

SUMMARY

In the United States, EM has only been associated with infection with *B burgdorferi* sensu stricto but, in Europe and Asia, other genospecies more commonly cause Lyme disease (often referred to in Europe as Lyme borreliosis).[26,27,29–31,33,53–55] Although distinctive in appearance, EM-like lesions should not be considered pathognomonic for Lyme disease, in part because localized arthropod bite reactions without infection may appear similar, as may STARI, which occurs in regions of the United States that are not endemic for *B burgdorferi* infection.[6,20,63,65,66]

Because appropriate treatment with oral antibiotics at this early stage of infection with *B burgdorferi* results in excellent outcomes, with objective treatment failures being exceedingly rare, it is important to recognize EM lesions.[15,16,18,83–91,94,95,98,100,113,114] Clinicians should be aware that some patients with EM may also be coinfected with the bacterium that causes HGA (which is sensitive to doxycycline, but not amoxicillin) or the parasitic causal agent of babesiosis, which may require additional specific treatment. The gold standard for the diagnosis of EM is the isolation in culture of *B burgdorferi* from a biopsy taken from a sample of the skin lesion but this is neither routinely obtainable nor necessary.[12,18,26,29,31,33,42,54,134] Serologic testing is readily available, and consists of either a 2-tier serologic testing protocol or the C6 peptide ELISA; however, although both methods are useful in the diagnosis of extracutaneous manifestations of Lyme disease, they have limited value in patients presenting with EM, in part because of poor sensitivity in this early stage of infection.[16,47,48,82] For practitioners, EM remains a clinical diagnosis.[6,16]

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