

STARI, or Masters Disease: Lone Star Tick–Vectored Lyme-like Illness

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Lyme disease in the United States is now defined microbiologically as an infection caused exclusively by the spirochete *Borrelia burgdorferi* sensu stricto [1] and is vectored by ticks of the *Ixodes* complex, namely, *Ixodes scapularis* in the northeastern and north central states and *Ixodes pacificus* on the West coast. In the past, Lyme disease has been defined clinically, especially for surveillance purposes [2]. The most common characteristic feature is an expanding annular erythematous rash called erythema migrans, which was previously thought to be pathognomonic [3–6].

An enigma for the past 20 years has been the recognition and reporting of a condition in nonendemic states that is not primarily caused by *Borrelia burgdorferi* sensu stricto and is vectored by the Lone Star tick (*Amblyomma americanum*). The adult female, not the nymph or adult male, is characterized by a distinctive white dot on the middle of its back (Fig. 1). Having an expanding annular erythema migrans-like rash, this Lyme disease mimic is now being recognized as a separate disease. This feature, along with others, enables it to meet the clinical and surveillance criteria, but not the microbiologic definition, for Lyme disease [7].

The following discussion centers on this Lone Star tick–vectored Lyme-like illness (also known as southern tick–associated rash illness [STARI] or Masters disease [7–9]) and how it differs from Lyme disease caused by *Borrelia burgdorferi* sensu stricto. The appropriateness of the STARI moniker is now being questioned because of the expansion of the Lone Star tick territory (see Fig. 1). The semantics in this situation may remind one of the

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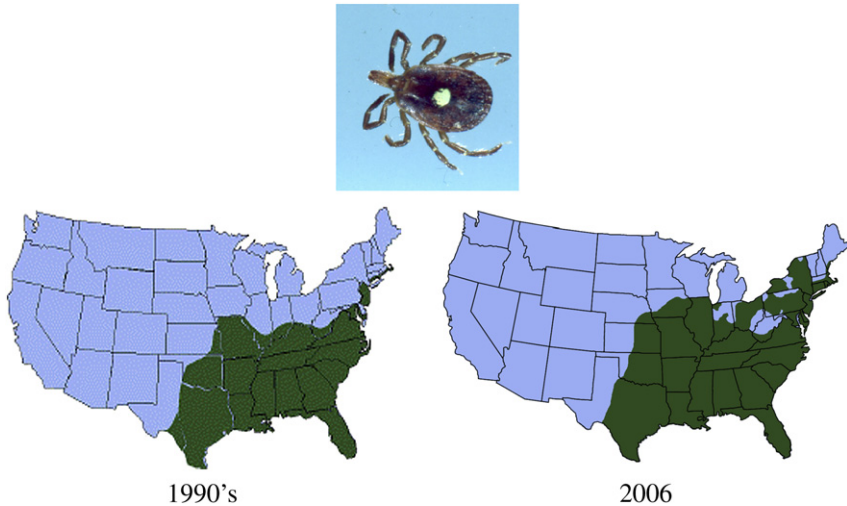


Fig. 1. Lone Star tick photograph (*inset*) and maps showing territory expansion. (Courtesy of J. Occi, White Station, NJ [*inset*], and M. Yabsley, Athens, GA [*maps*].)

problems that doctors encountered with the name and distribution of Rocky Mountain spotted fever (RMSF) [10].

Epidemiology

Lyme-like illness does not appear to be caused by *Borrelia burgdorferi* sensu stricto. The exact etiology or etiologies are still uncertain. One putative bacterial cause of Lyme-like illness is *Borrelia lonestari* found in *Amblyomma americanum* ticks [11,12]. One case implicating this bacterial species has been published [13]. In addition, *Borrelia lonestari* has been detected in Lone Star ticks removed from humans [14]. In one polymerase chain reaction (PCR) DNA screen of 312 southeastern Missouri *Amblyomma americanum* ticks, *Borrelia lonestari* evidence was not detected [15]; however, in a separate southeastern Missouri tick study in different but contiguous counties, 214 *Amblyomma americanum* ticks were examined, with 5.6% of them testing positive for *Borrelia lonestari* DNA [16]. In an attempt to verify the *Borrelia lonestari* association, 31 Missouri bull's-eye rash biopsies from Lyme-like illness patients were subjected to culture and PCR analyses. No evidence of *Borrelia lonestari* was detected [15].

Exhaustive attempts to culture the causative agent or agents of Lyme-like illness have been unsuccessful. At least 14 different researchers have collaborated with the senior author in this quest. The following list summarizes the attempts that have been or are being made in the ongoing search for causes: Barbour-Stoenner-Kelly (BSK)-II media, BSK H, original BSK,

microgravity, Kelly's Relapsing Fever medium, fibroblasts, bovine vitreous added to culture, white-footed mice, sterilized and pulverized Lone Star ticks added to culture media, rabbits, severe combined immune-deficient mice, and embryonated chicken eggs.

Lyme-like illness appears to be vectored by the Lone Star tick (*Amblyomma americanum*). The first piece of evidence is that the usual vectors of Lyme disease do not vector Lyme-like illness. In a 1991 study, 165 consecutive embedded ticks were removed from humans in southeastern Missouri, and not one was an *Ixodes scapularis* deer tick [17]. The *Ixodes scapularis* deer tick is common in southeastern Missouri but infrequently bites humans during the warm months when Lyme-like illness is usually seen [18]. In the 1991 southeastern Missouri study, the most common tick removed was the Lone Star tick [17]. Other studies have shown that the Lone Star tick is aggressive and the tick that most commonly parasitizes humans in the South [19–21]. A study showing the association of Lone Star ticks with Lyme-like illness was published in 1998 [22]. A June peak for Lyme-like illness in southeastern Missouri was shown in the 1991 study [17] and in a later, 3-year study from 2000 to 2003 [7]. The June erythema migrans–like peak correlated nicely with the slightly earlier *Amblyomma americanum* tick bite incidence. This June peak for Lyme-like illness was significantly earlier than for Lyme erythema migrans rashes in New York [7].

For the past 20 years, the senior author has advised his patients to save (at least for 30 days) the embedded ticks they remove. Of the estimated 30 ticks saved by bull's-eye rash patients, 100% were *Amblyomma americanum* (nymph, adult male, or adult female).

Because Lyme-like illness meets the surveillance definition of Lyme disease, doctors are sometimes required by law to report these patients as having Lyme disease [23]. Lyme-like illness, however, does not meet the microbiologic definition of Lyme disease; physicians in nonendemic states may be told there is no Lyme disease in their area and that any Lyme disease diagnosis is in error. This confusion makes clinicians wonder about the significance of reporting a disease that officially does not exist in their area. The authors believe that Lyme-like illness is greatly under-reported, even when it meets the surveillance definition for Lyme disease. The senior author [24] has seen as many as four cases in a single day.

Appearance

The annular lesions in Lyme-like illness have many similarities to Lyme erythema migrans. This similarity is the primary basis for the term “Lyme-like” (Figs. 2–4). Although the lesions of each illness can differ clinically as a group—Lyme-like lesions tend to be smaller and more circular, have more central clearing, are more likely to have a patchy irregular border (see Fig. 2J, K), and are less commonly seen in multiples—it is difficult to

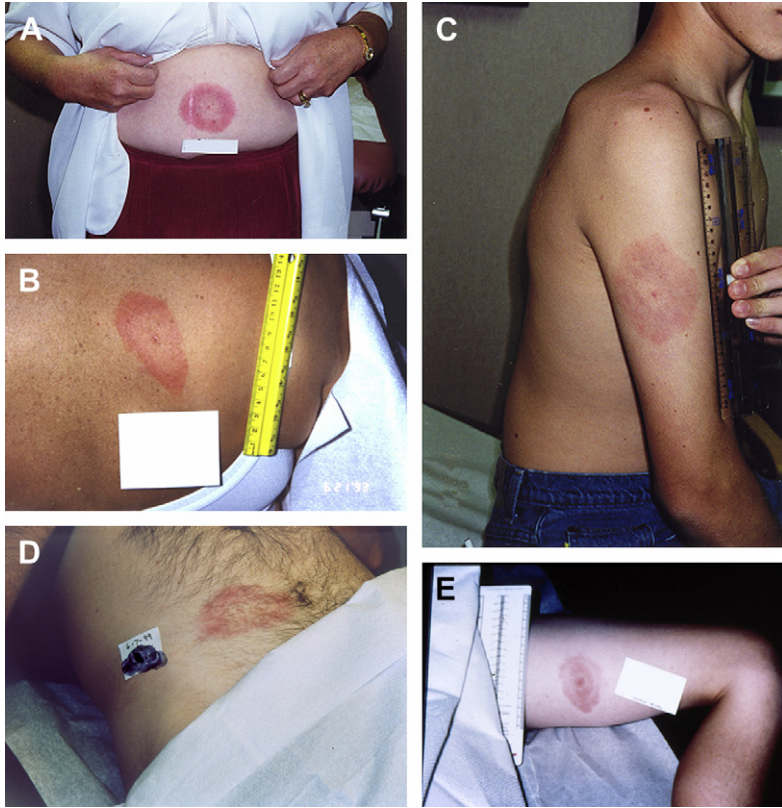


Fig. 2. (A–K) Missouri Lyme-like lesions.

use appearance to differentiate individual lesions because of the overlap and wide range of appearances in each group. In a 3-year comparative study [7], an almost perfect circular bull's-eye rash with good central clearing was four times as likely to be from Missouri as from New York. Other published photographs of Lyme-like lesions from nonendemic Lyme disease areas are available [3,7,22,24–30].

Clinical sequelae

With the etiology of Lyme-like illness still uncertain and with no definitive test available, it is impossible to absolutely prove rash sequelae; however, the authors' impressions are that Lyme-like illness results in far less severe arthritis than Lyme disease. In an early study, Missouri patient data were compared with national Lyme disease data, and the frequency of signs and symptoms was roughly comparable [26]. Although no long-term follow-up

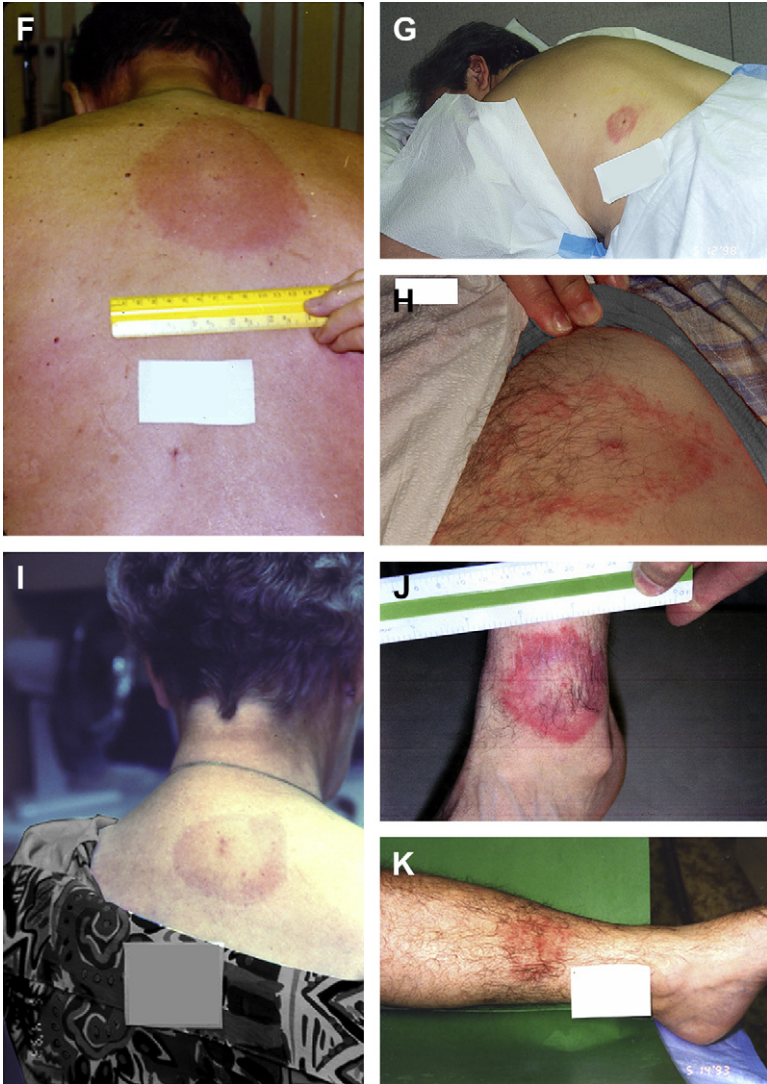


Fig. 2 (continued).

study of Lyme-like illness has been done, the authors believe that sequelae definitely occur.

Lyme-like patients are less likely to have regional lymphadenopathy and tender or pruritic rashes. They also seem to be less symptomatic at the time of rash appearance and recover at a more rapid rate after treatment with antibiotics. They are more likely to recall a tick bite than Lyme erythema migrans patients [7].



Fig. 3. Missouri Lyme-like lesion plus coinfection with Q fever. This Lyme-like lesion followed a witnessed adult female Lone Star tick bite, which also seroconverted for *Coxiella burnetii*.

Histology

In Fig. 5, the histologic differences between dermal cellular infiltrates of Lyme erythema migrans and Lyme-like illness rashes are shown. It is evident that when stained with hemotoxylin-eosin, the Lyme-like rashes have a predominantly lymphocytic infiltrate. In contrast, Lyme erythema migrans often shows an abundance of plasma cells [31].

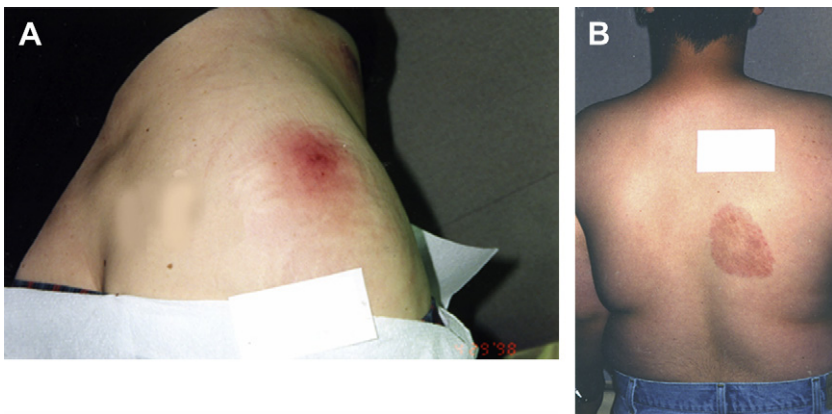


Fig. 4. Missouri Lyme-like lesion plus coinfection with human monocytic ehrlichiosis. (A) This patient had positive 16srRNA PCR for *Ehrlichia chaffeensis*. (B) This patient seroconverted for *Ehrlichia chaffeensis*.

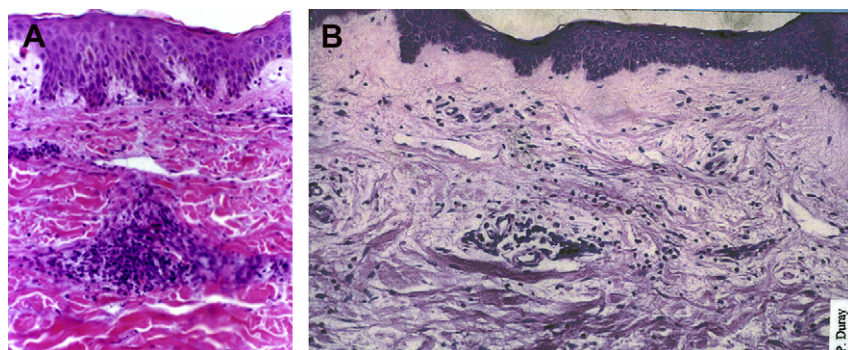


Fig. 5. (A) Hematoxylin-eosin stain ($\times 400$) of dermal biopsy of Lyme-like lesion following a witnessed adult female Lone Star tick bite. Note the lymphocytic infiltrate. (B) Hematoxylin-eosin stain of Lyme erythema migrans biopsy from the Northeast. Note the abundance of plasma cells. (Courtesy of P. Duray, Bethesda, MD.)

Serology

Because Lyme-like illness—by definition—is not caused by infection with *Borrelia burgdorferi* sensu stricto [1], it is not surprising that conventional serologic tests such as ELISAs and Western blots, which are based on *Borrelia burgdorferi* sensu stricto, are usually negative. Cross-reactivity can occur, however, and Lyme tests are known to have false-positive and false-negative results. A 3-year comparative study illustrates the different results. Using a baseline ELISA, none of the 25 Missouri patients tested positive. Of 143 Lyme patients tested in New York, 81 were positive. There were 4 Missouri patients and 1 New York patient who were tested serologically but did not undergo biopsy. Finally, 25 New York patients seroconverted, whereas none of the Missouri patients seroconverted at 3 months [7]. Lyme Western blots on Lyme-like illness patients are usually negative but frequently match poorly with a disease-free control population [29,32].

Missouri Lyme-like patients were tested using the C6 peptide Lyme serology [9]. All but 1 of the 72 Missouri patients tested negative, as did the only published case of a probable *Borrelia lonestari*-associated Lyme-like lesion. For this C6 peptide study [9], the blinded control subjects included those who had unusual diseases such as human monocytic ehrlichiosis (HME), MO-1 babesiosis, parvovirus B19, scleroderma, rheumatoid arthritis, chronic inflammatory demyelinating polyneuropathy, loxoscelism, infectious mononucleosis, among others. All of the control subjects were negative, whereas eight of nine culture-confirmed *Borrelia burgdorferi* sensu stricto Lyme patients tested positive.

Historically, it was not unusual for the old whole-cell sonicate ELISAs to be positive for Lyme-like patients. For example, when the Centers for

Disease Control and Prevention (CDC) used a whole-cell sonicate Lyme ELISA on 22 Missouri bull's-eye rash patients, 50% tested positive using a 3-SD cutoff [19,29,31]. These 22 patients were a subset of a total of 45 Lyme-like patients from multiple practices in Missouri who were enrolled in the CDC study. Of these 45 patients in this early 1990s CDC study, 40 had a total of 57 different positive Lyme serologies from seven other laboratories [29]. Of these seven other laboratories, one included Dr. Russell Johnson at the University of Minnesota who did the serologies for a national treatment study, in which some of these patients had been previously enrolled [33]. Because of specificity problems, some laboratories (including the CDC) started replacing the whole-cell sonicate-based ELISA with a flagellin-based ELISA. This change resulted in Lyme-like patients having far fewer positive test results [19]. Felz and colleagues [25] reported seven erythema migrans-like rash patients who had laboratory evidence suggestive of *Borrelia burgdorferi*. Multiple variants of *Borrelia burgdorferi* have been isolated from nature from the home sites of Missouri Lyme-like patients [34]. In addition to the very similar clinical picture, these findings and test results have caused some to suspect that other related *Borrelia* might be possible etiologic agents [29,30,34].

The authors believe that in areas in which *Amblyomma americanum* and *Ixodes scapularis* ticks are common (eg, New York and New Jersey), some of the seronegative and culture-negative cases in Lyme studies might be due to Lyme-like illness.

Incubation time

Of the physician-diagnosed Lyme-like illness cases published, the authors identified 128 in which the incubation times were able to be calculated [3,7,19,22,24,25,29]. Being careful to count patients only once, 45 Lyme-like illness patients had a mean incubation time of 9.2 days. Another 83 patients had a median incubation time of 6.6 days. The most recent 18 patients had a mean incubation time of 6.1 days [7].

The authors found no evidence that larger adult tick bites (with possible larger inoculums) had shorter incubation times compared with smaller nymphal tick bites. Another factor likely affecting incubation time is the duration of tick attachment; however, the authors were unable to acquire reliable data because patients were often uncertain about when the ticks became embedded [22].

Treatment

The causative agent or agents of Lyme-like illness are not definitively known. The authors believe that this Lyme-like illness deserves Lyme-like treatment, and that standard Lyme treatment recommendations apply [35]. Therefore, the authors prescribe 10 to 30 days of oral doxycycline at

3 mg/kg in divided doses, amoxicillin 500 mg three times daily, or cefuroxime 500 mg orally twice daily [3]. Because there is evidence that cephalexin is not efficacious for Lyme disease [36], the authors do not recommend its use in treating Lyme-like illness. If there is fever, a flulike illness, severe headache, lymphadenopathy, multiple lesions, or other evidence of dissemination beyond the rash, longer duration of treatment is recommended. Although much research still needs to be done, other arguments for treating Lyme-like illness include possible coinfection, possible sequelae, and the expanding tick pathogen spectrum. The clinician is also handicapped because of the limited usefulness of serologic tests. The treatment regimens mentioned earlier are supported by the limited data available [7,19,33]. It is unfortunate that long-term follow-up studies on these Lyme-like illness patients have not been done.

Coinfection

Our current appreciation of the Lone Star tick (*Amblyomma americanum*) as a vector of human pathogens is relatively recent [37]. Just as physicians in the northeastern United States should be aware of coinfections resulting from the *Ixodes scapularis* deer tick transmitting more than one pathogen [38], doctors should be aware that the Lone Star tick can similarly transmit more than one pathogen.

Three published cases of Lyme-like illness coinfection (two with HME due to *Ehrlichia chaffeensis* and one due to Q fever caused by *Coxiella burnetii*) are described in the following sections.

Lyme-like illness coinfection with Q fever

Coxiella burnetii, the agent of Q fever, has been identified in Lone Star ticks from Texas [39] and Mississippi [40].

Case 1

A 13-year-old Missouri boy had a 9-cm Lyme-like rash on his back following the removal of an adult female Lone Star tick from the rash site 2 weeks earlier (see Fig. 3). This well-documented case also included photographs of the rash. The patient was enrolled in a national double-blind study comparing azithromycin treatment with amoxicillin treatment [33]. Later, he was also enrolled in a CDC study of Missouri Lyme-like lesions. As part of this study, stored acute and convalescent sera were tested for multiple tick-borne illnesses. The patient showed seroconversion for *Coxiella burnetii*, with the acute-phase titer being less than 1:16 and the convalescent-phase titer being 1:256. With the prompt azithromycin treatment, he remained asymptomatic except for the Lyme-like rash. The other patients tested in this study were negative for *Coxiella burnetii* [19].

Lyme-like illness coinfection with Ehrlichia chaffeensis

Ehrlichia chaffeensis has previously been shown to be in Missouri Lone Star ticks. In 1993, 1% to 3% of Lone Star ticks from four states tested positive for *Ehrlichia chaffeensis*. Some of the positive ticks were from southeastern Missouri [41]. Case 2 and Case 3 are published HME cases [42]; these patients also had Lyme-like illness.

Case 2

A man who had a 10-cm erythema migrans-like lesion was *Ehrlichia chaffeensis* PCR positive using 16srRNA (see Fig. 4A) [42].

Case 3

A 15-year-old boy had a Lyme-like lesion and seroconverted for *Ehrlichia chaffeensis* (see Fig. 4B).

HME co-infection is more likely when elevated liver enzymes, thrombocytopenia, or leucopenia is present [42].

Potential coinfection with Ehrlichia ewingii

Ehrlichia ewingii was first described as a human pathogen in 1999 by researchers at Washington University School of Medicine in St. Louis, Missouri [43]. This rare ehrlichiosis is somewhat unique. Like anaplasmosis, formerly known as human granulocytic ehrlichiosis, it invades granulocytes; however, like *Ehrlichia chaffeensis* (HME), it is vectored by the Lone Star tick.

Coinfection with Francisella tularensis (tularemia or rabbit fever)

Although a case example is not presented here, tularemia caused by *Francisella tularensis* is also a candidate for coinfection with Lyme-like illness. Both illnesses are vectored by Lone Star ticks. There now appears to be more cases of tularemia caused by Lone Star tick bites than by contact with rabbits [37].

Arkansas physicians have been aware of tick transmission of *Francisella tularensis*, the agent causing tularemia, since the 1940s. Most cases occurred during summer months when rabbit hunting and direct contact with rabbits were infrequent but when tick bites were common [44]. In the early 1950s, *Francisella tularensis* was isolated from Arkansas Lone Star ticks [45]. From 1981 to 1987, 1026 cases of tularemia from Arkansas, Kansas, Missouri, Louisiana, Oklahoma, and Texas were examined. An attached tick was reported in 63% of the cases, but only 23% of cases had rabbit exposure. Lone Star tick bites are now recognized to be the main method of tularemia transmission [46].

Other possible coinfections

Other bacteria found in Lone Star ticks include *Rickettsia amblyommii*, which at this time is thought to possibly cause a mild spotted fever

rickettsiosis. There is also one case in which Rickettsi amblyomma DNA was identified in the patients STARI rash; the adult female *Amblyomma americanum* tick was temporally associated with the rash [47]. *Rickettsia rickettsii* has some circumstantial evidence implicating the Lone Star tick in the epidemiology of RMSF in humans. *Dermacentor* ticks are the main vectors of RMSF. Other spotted fever group rickettsia have been isolated from Lone Star ticks, but determining whether these agents cause human disease requires more investigation [37].

Our ability to identify previously unknown pathogens is greatly increasing. The likelihood of finding even more tick-vectored diseases is high. In a 3-year prospective study of 102 patients who had fever following a tick bite, Olano and colleagues [42] were able to establish a diagnosis in only 29 patients, leaving a very important unanswered question: “What did the other 73 patients have?” Although the causative agent is unknown, ticks were associated. Statistically, most of these patients were bitten by Lone Star ticks [17]; therefore, they are candidates for coinfection with Lyme-like illness. Just because an illness cannot be identified, it does not mean it is nonexistent. Absence of proof is not proof of absence. The need to be vigilant for new tick-borne diseases is self-evident.

An example of a possible future human pathogen vectored by Lone Star ticks is *Ehrlichia ruminantium*. To date there are no published human cases in the United States; it was first described in North America in 2006 as an infection of goats in Georgia, vectored by Lone Star ticks [48]. In an unpublished southeastern Missouri Lone Star tick survey, however, *Ehrlichia ruminantium* was identified in Lone Star ticks in areas where goats were not being raised (Susan E. Little, DVM, PhD, EVPC, personal communication, 2007). The combination of undiagnosed sick tick-bite victims [42], the prevalence of Lone Star tick bites [17], and *Ehrlichia ruminantium* being newly identified in southeastern Missouri *Amblyomma americanum* ticks (Susan E. Little, DVM, PhD, EVPC, personal communication, 2007), makes this organism, if it turns out to be a human pathogen, a future candidate for possible coinfection.

Clinical differentiation

Although Lyme-like rashes can have mild pruritis, the common presence of intense pruritis in hypersensitivity reactions can help distinguish them. Many patients present with an asymptomatic Lyme-like bull’s-eye rash on their back. Due to patients’ infrequent examination of their own back, they may be unaware of the rash until a family member calls it to their attention. Similarly, the absence or presence of any prior rash reaction to tick bites is helpful in differentiation (eg, a person has long history of multiple, yearly tick bites and then suddenly presents with a tick bite that resulted in a Lyme or Lyme-like rash). This situation is less likely to be a hypersensitivity. In the authors’ experience, most hypersensitivity reactions begin

within 2 days, whereas the average onset of a Lyme-like rash is about 1 week.

There have been reports of diagnostic confusion regarding the dermal manifestations of tick bites, spider bites, and cutaneous anthrax [49]. We call this “ticks versus spiders versus spores” (Table 1). Brown recluse spider bites (*Loxosceles reclusa*) and tick bites that have erythema migrans or Lyme-like lesions are associated with a skin rash; however, they can be differentiated clinically [28].

In areas in which ticks and brown recluse spiders exist, diagnostic confusion during the early dermal stages is common. In the New York anthrax outbreak in 2001, most of the cutaneous cases were initially misdiagnosed as spider bites [50]. Cutaneous anthrax is characterized by a lack of pain and, often, marked local edema and swelling.

Pain (often severe) is common with brown recluse spider bites, as is a gravity-dependent rash and the “red, white, and blue” sign. The red, white, and blue sign consists of concentric zones of erythema, eschemia, and cyanosis and usually occurs before the formation of an eschar [28].

Discussion

The current definition of Lyme disease in the United States is an infection caused exclusively by *Borrelia burgdorferi* sensu stricto [1]. Even though the precise etiology of Lyme-like illness is unknown, there is overwhelming evidence that it is not caused by *Borrelia burgdorferi* sensu stricto. This fact mandates that Lyme-like illness be classified as a separate condition or disease.

Borrelia burgdorferi sensu stricto has been documented in nature in areas nonendemic for Lyme disease [51–53]. According to Dr. James Oliver, *Borrelia burgdorferi* sensu stricto is common in the southern United States: he has 52 isolates of *Borrelia burgdorferi* sensu stricto from nature, including 15 strains that are typical of the reference strain B-31 (James H. Oliver, Jr., PhD, personal communication, 2007). It is theoretically possible that some cases of apparent Lyme-like illness in these areas might be caused by *Borrelia burgdorferi* sensu stricto. By definition, patients infected with *Borrelia burgdorferi* sensu stricto would have true Lyme disease, not Lyme-like illness.

Table 1
Dermal manifestations: ticks versus spiders versus spores

Organism	Pain	Necrosis or eschar	Marked edema	Gravity rash	Red, white, & blue sign
Tick bite	–	–	–	–	–
Spider bite	+	+	–	+	+
Anthrax	–	+	+	–	–

Amblyomma americanum ticks are generally considered to be incompetent vectors of Lyme disease [54,55]. One factor is that the *Amblyomma americanum* tick saliva can be borreliacidal. Ledin and colleagues [56] showed that after 48 hours of exposure to *Amblyomma americanum* saliva, 87% of the *Borrelia* spirochetes died. This finding shows the possibility of live *Borrelia burgdorferi* sensu stricto beyond the 24 hours of attachment, after which the likelihood of transmission increases significantly.

It has been shown that when *Dermacentor* ticks (also not considered a vector of Lyme disease) feed in conjunction with *Ixodes scapularis* ticks, the *Dermacentor* ticks can acquire and transmit *Borrelia burgdorferi* sensu stricto [57]. Although *Amblyomma americanum* ticks were not tested in this manner (and because *Dermacentor* ticks can obtain the ability to acquire and transmit *Borrelia burgdorferi* sensu stricto by feeding in close proximity to an *Ixodes scapularis* tick on the same infected host), there is a theoretic possibility that combining different tick salivary factors could result in the ability of *Amblyomma americanum* ticks, like *Dermacentor* ticks, to obtain this ability.

While working on a southeastern Missouri tick study, Oliver and colleagues [34] captured a cottontail rabbit that had over 1100 attached ticks comprising four different species. Two of the species were *Amblyomma americanum* and *Ixodes scapularis*. They were feeding on the same host at the same time and in close proximity to each other.

In a laboratory setting, a Lone Star tick experiment using *Borrelia burgdorferi* sensu stricto showed a transstadial transmission rate of 1.6% [58]. This finding caused Ryder and colleagues [58] to posit that *Amblyomma americanum* ticks might be involved in occasional human cases of Lyme disease.

Summary

The Lone Star tick (*Amblyomma americanum*) is the vector of Lyme-like illness, also known as STARI or Masters disease. The spread of this aggressive tick through the Northeast [59], even into Maine [60], has caused some to reconsider calling this STARI (see Fig. 1). There is concern that this acronym might cause problems similar to those caused by the Rocky Mountain spotted fever misnomer. The authors anticipate that as the *Amblyomma americanum* tick expands its territory, the Lyme-like illness will follow. In addition, the authors believe that Lyme-like illness is not caused by just any tick, but only by the *Amblyomma americanum* tick. We associate Lyme-like illness only with the Lone star tick (*Amblyomma americanum*) [61].

In August 2006, President Bush was treated for a Lyme erythema migrans rash on his leg. Although he had some limited exposure in Maryland, he spent most of that month in Texas, causing some discussion that he might have had Lyme-like illness [62]. The Lone Star tick is found throughout the

southeastern and south central United States, including Texas. It is the most common human-biting tick in those areas.

Physicians need to be aware of this newly recognized zoonosis. The authors do not recommend trying to differentiate the Lyme-like illness on rash appearance alone. Although there are group differences between Lyme and Lyme-like appearances, there are also tremendous overlaps and similarities when comparing individual lesions (see Figs. 2–4).

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