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[EDITOR'S NOTE: This issue discusses the rash and skin manifestations associated with tick-borne infections. Physicians treating patients with other dermatological conditions are invited to visit our sister publication, [eMedical Dermatology Review](#), to access additional accredited programs.]

### In This Issue...

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In this audio interview Paul G. Auwaerter, MD of Johns Hopkins University School of Medicine will discuss tick-borne illnesses from a clinical perspective.

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### Common Tick-borne Infections in the United States

Since its initial description 30 years ago, Lyme disease (LD) has become the most commonly reported vector-borne disease in the United States. Due in part to this notoriety, healthcare professionals as well as the public have become increasingly aware of all tick-borne human infections. Although most cases respond well to antibiotic therapy, early diagnosis as well as determining appropriate therapy can be challenging.

In this issue, we discuss the recently released guidelines from the Infectious Disease Society of America (IDSA) and the American Association of Neurology (AAN) that address diagnostic and treatment recommendations for LD; other papers reviewed elucidate diagnosis of early LD, contrast the presentations of Southern Tick-associated Rash Illness (STARI) with LD, describe a new Rickettsial human infection, and detail changes in the expected areas endemic for another rickettsial infection, Rocky Mountain spotted fever (RMSF).

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### ***Guest Faculty Disclosures***

**Paul G. Auwaerter, MD**, has disclosed that he has served as a consultant for Novartis, Pfizer, Ortho-McNeil, Schering-Plough, and Genzyme. He is on the Speakers' Bureau for Schering-Plough and has also disclosed that he is a Stock Shareholder for Johnson and Johnson.

### ***Unlabeled / Unapproved Uses***

Dr. Auwaerter has indicated that his presentation will not contain any off-label information.

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## LEARNING OBJECTIVES

**At the conclusion of this activity, participants should be able to:**

- Discuss the new recommendations regarding the treatment of Lyme disease, Human Granulocytic Anaplasmosis, and Babesiosis
- Identify new diagnostic procedures and therapeutic options for tick-borne disease in the United States
- Describe reported changes in the range of tick-borne pathogens as well as newly described causes of tick-borne infection

## COMMENTARY

Clinicians face some daunting hurdles when diagnosing tick-borne infections. Astute knowledge of local tick populations and the diseases they carry is critical,



as is having a high index of suspicion in the differential diagnosis. Some infections such as RMSF and ehrlichiosis can start with non-specific flu-like symptoms before becoming more severe, with multi-organ system involvement that may result in death, even with appropriate initiation of antibiotics. LD has its own controversies; many internet-educated patients believe they suffer from active *Borrelia burgdorferi* infection as an explanation for chronic fatigue, musculoskeletal pain, and subjective neurocognitive complaints. A good resource for the basics of common tick-borne disease in the United States – including endemic range of infections, photographs of tick vectors, diagnosis, and treatment – can be found at the Centers for Disease Control website ([www.cdc.gov/ncidod/diseases/list\\_tickborne.htm](http://www.cdc.gov/ncidod/diseases/list_tickborne.htm)).

Recently, 2 societies (the IDSA and the AAN) have issued new guideline statements for LD diagnosis and treatment.<sup>1,2</sup> These 2 documents come at an important time, since a small group of physicians (often referring to themselves as "Lyme literate") advocate for a considerably more liberal diagnosis of LD in patients with chronic subjective problems such as fatigue, musculoskeletal complaints, and/or neurocognitive dysfunction who may not have any objective history of LD such as erythema migrans (EM) or validated Lyme serologic testing. Moreover, this group of physicians also believes that persistent *B. burgdorferi* infection is responsible for these chronic symptoms and that long-term antibiotic administration is helpful. They have even had a non-peer-reviewed guideline published outlining their policies.<sup>3</sup>

It is important to distinguish those patients with only subjective symptoms from those with objective evidence of late LD (such as monoarthritis, radiculitis, or true encephalopathy) who have evidence of active infection. Patients with such objective evidence should be termed "late Lyme disease," while those with subjective and persisting complaints should fall under the recently coined rubric "post-Lyme disease syndrome." The term "chronic Lyme disease," while favored by the so-called "Lyme literate" physicians, is not used by the IDSA or AAN organizations, who find "post-Lyme disease syndrome" a more accurate description of those patients in whom there is an inability to recover *B. burgdorferi* but who have persisting subjective complaints after appropriate antibiotic therapy for Lyme disease.

Both guidelines (reviewed herein) present the best available evidence that outlines diagnostic and treatment recommendations for LD, including strong statements that LD is misdiagnosed by many in the "Lyme literate" group and that long-term antibiotics offer no important benefit to patients with persisting subjective symptoms. Recommendations regarding occasional co-pathogens (*Anaplasma phagocytophilum* and *Babesia microti*) are also reviewed.

Although EM is often considered to specifically indicate LD, some patients, especially in southern regions of the US, present with such lesions after a tick bite, yet do not have evidence of *B. burgdorferi* infection. Wormser et al compare and contrast early LD seen in New York with EM lesions identified in Missouri.<sup>4</sup> The Missouri patients appear to have a milder illness than those with LD, without any of the persisting symptoms of fatigue and musculoskeletal pain seen in a minority of LD patients even after antibiotic treatment. This non-*Bb* EM illness should be referred to as STARI, and not reported as LD to public health authorities.

The reports of community outbreaks of RMSF in arid regions of Arizona – an area outside traditional endemic boundaries – point to a tick vector heretofore never implicated in transmission.<sup>5</sup> Clinicians therefore need to be aware of potential RMSF even in previously non-endemic regions.

## UPDATED GUIDELINES FOR LYME DISEASE, HGA AND BABESIOSIS

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.

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Halperin JJ, Shapiro ED, Logigian E, et al. **Practice Parameter: Treatment of nervous system Lyme disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology.** *Neurology.* 2007; 69(1):91-102. Epub 2007 May 23.

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The IDSA Guideline Paper represents an evidence-based review of over 400 articles, providing comprehensive diagnostic and treatment recommendations from a group of scientific and clinical experts in tick-borne diseases. The AAN appropriately focuses upon central nervous system involvement by LD in a similar evidenced-based fashion.

LD, caused by *B. burgdorferi*, most commonly causes an ovoid, enlarging erythematous rash called erythema migrans (EM), which may be accompanied by systemic symptoms such as fever, headache, neck stiffness, arthralgia, myalgia, and fatigue. Other manifestations include certain neurologic, arthritic and cardiac disorders. The tick-borne infection is most commonly seen in temperate coastal and riparian environs in Northeast, Mid-Atlantic and Upper Midwest states, which account for over 85% of recent reports. The IDSA Guideline updates recommendations first published in 2000, and uses the best available evidence to guide diagnostic assessment, antibiotic selection, and treatment duration, and offers a comprehensive look at all forms of LD.

The document also discusses other tick-borne disorders that are transmitted by the *B. burgdorferi* vector *Ixodes scapularis* (black-legged deer tick), including Human Granulocytic Anaplasmosis (HGA due to *Anaplasma phagocytophilum*) and Babesiosis. HGA may cause a flu-like syndrome with fever, often along with leukopenia/neutropenia, thrombocytopenia, and transaminase elevations. Diagnosis may be delayed if dependent on serology or polymerase chain reaction (PCR), so a high index of suspicion should prompt rapid empiric initiation of doxycycline. HGA usually responds promptly to administration of doxycycline within 48-72 hours, and no chronic infection has been described. *Babesia microti* is a parasite that causes a malaria-like illness infecting red blood cells, capable of producing a severe illness, especially in patients without spleens or who are immune-compromised.

While space limitations in this forum do not allow for a thorough discussion of the wealth of data presented, new information includes:

- Early LD may be treated with a 10-day oral course of doxycycline, 100mg twice daily, although either doxycycline or amoxicillin (500mg three times daily) also remain recommended in a range of 14-21 days.<sup>6</sup>
- Primary prophylaxis with a single dose of doxycycline 200mg may be offered to certain patients meeting important criteria: bite by *Ixodes* tick,

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attachment for  $\geq 36$  hours in a child over 8 years of age or an adult and engorgement, and/or local rate of tick infection by *B. burgdorferi* surpassing 20%.<sup>7</sup>

- The term "chronic Lyme disease" is not favored: it is indistinct in discriminating between late LD (monoarthritis, neuroborreliosis typified by objective manifestations) and persisting symptoms after appropriate antibiotic treatment for LD (subjective symptoms such as fatigue, memory complaints, musculoskeletal pains). The terms "late Lyme disease" and "post-Lyme disease syndrome" are preferred. Post-Lyme disease syndrome may be an appropriate label for patients with 6 months or more of persisting symptoms after diagnosis and treatment of LD. Since fatigue and musculoskeletal pains are common in so-called "normal" populations, it is difficult to precisely define how often LD truly precipitates these symptoms.
- Diagnosis of LD based solely on chronic, subjective symptoms is inappropriate, as is the use of unvalidated tests as performed in so-called "Lyme specialty research laboratories." Administration of long-term antibiotics for these patients—often in combination and by oral or parenteral routes—has shown no substantial benefit in the 2 randomized, double-blinded trials published to date.<sup>8,9</sup>
- The weight of *in vitro*, animal, and human data does not support the concept that *B. burgdorferi* establishes a latent infection after antibiotic therapy—or that the organism suppresses the immune system and therefore results in frequently seronegative testing.
- Since antibiotics do not appear to help patients with chronic, subjective symptoms of LD, their use cannot be justified. More research is needed to understand the etiology of patients with subjective complaints, to determine how often they are truly induced by *B. burgdorferi*, as well as to develop therapies that may have utility.

A completely new section deals with patients who have persistent symptoms such as fatigue, neurocognitive dysfunction, and musculoskeletal pain after appropriate treatment for LD. A proposed case description is outlined as below:



## Proposed Definition of Post-Lyme Disease Syndrome

### INCLUSION CRITERIA

- An adult or child with a documented episode of early or late Lyme disease fulfilling the case definition of the Centers for Disease Control and Prevention. If based on erythema migrans, the diagnosis must be made and documented by an experienced health care practitioner.
- After treatment of the episode of Lyme disease with a generally accepted treatment regimen, there is resolution or stabilization of the objective manifestation(s) of Lyme disease.
- Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6 month period after completion of antibiotic therapy:
  - Fatigue
  - Widespread musculoskeletal pain
  - Complaints of cognitive difficulties
  - Subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social, or personal activities.

### EXCLUSION CRITERIA

- An active, untreated, well-documented co-infection, such as babesiosis.
- The presence of objective abnormalities on physical examination or on neuropsychologic testing that may explain the patient's complaints. For example, a patient with antibiotic refractory Lyme arthritis would be excluded. A patient with late neuroborreliosis associated with encephalopathy, who has recurrent or refractory objective cognitive dysfunction, would be excluded.
- A diagnosis of fibromyalgia or chronic fatigue syndrome before the onset of Lyme disease.
- A prolonged history of undiagnosed or unexplained somatic complaints, such as musculoskeletal pains or fatigue, before the onset of Lyme disease.
- A diagnosis of an underlying disease or condition that might explain the patient's symptoms (eg morbid obesity); sleep apnea and narcolepsy; side effects of medications; autoimmune diseases; uncontrolled cardiopulmonary or endocrine disorders; malignant conditions within 2 years, except for uncomplicated skin cancer; known current liver disease; any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa or bulimia nervosa; and active drug abuse or alcoholism at present or within 2 years.
- Laboratory or imaging abnormalities that might suggest an undiagnosed process distinct from post-Lyme disease syndrome, such as a highly elevated erythrocyte sedimentation rate (>50 mm/h); abnormal thyroid function; a hematologic abnormality; abnormal levels of serum albumin, total protein, globulin, calcium, phosphorus, glucose, urea nitrogen, electrolytes, or creatinine; significant abnormalities on urine analysis; elevated liver enzyme levels; or a test result suggestive of the presence of a collagen vascular disease.

The description further notes that although testing by either culture or PCR for evidence of *B. burgdorferi* infection is not required, should such testing be done, it should be performed by reliable methods. A positive result should also be considered an exclusion

The role of long-term antibiotic therapy is also addressed in the Guidelines published by Halperin et al, with the similar conclusion that long-term antibiotics have no compelling role in patients with post-Lyme disease syndrome and in treating the subjective neuro-cognitive complaints believed attributable to LD.

Two independent panels have therefore reached similar conclusions on this topic, which should mitigate an oft-cited criticism by "Lyme-literate" physicians that the IDSA guidelines reflect the view of only a small group of academic physicians.

## CAN HISTORY OR EXAMINATION FINDINGS BE DEPENDED UPON FOR THE DIAGNOSIS OF ERYTHEMA MIGRANS?

Tibbles CD, Edlow JA. **Does this patient have erythema migrans?** *JAMA*. 2007;297(23):2617-27.

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Seeking to determine how sensitive history or physical examination may be for the diagnosis of EM, Tibbles and Edlow performed a Medline search for English written studies containing at least 15 consecutive patients with a diagnosis of EM where historical and physical exam characteristics were descriptive enough to contribute to a sensitivity assessment. The authors found a total of 53 studies representing 8493 patients for analysis, with 32 from Europe and the balance from the United States. In the US studies, the sensitivity of systemic symptoms overall was 0.65 (95% CI 0.52-0.76), while individual historical variables were all less, including headache 0.36 (0.27-0.46), myalgia or arthralgia ~0.35 (0.25-0.46), fever 0.33 (0.23-0.46), and history of tick bite 0.26 (0.18-0.37). While a solitary cutaneous lesion yielded a summary sensitivity of 0.81 (95% CI 0.72-0.87), the typical "bull's eye" central clearing was only 0.19 (0.11-0.32).

EM has been a characteristic finding of LD transmitted by *Ixodes scapularis* (black-legged deer tick). In recent years, similar lesions have been described as a consequence of *Amblyomma americanum* (Lone star tick) bites. This new apparent infection has been coined STARI, and does not appear to be due to *B. burgdorferi*, the agent of LD.<sup>10,11</sup> The authors report one such patient with an EM-like rash had *B. lonestari* isolated, but this has not been found as yet in other patients.<sup>12</sup> Since LD remains a clinical diagnosis, concern arises whether a specific constellation could yield a definitive diagnosis of EM. The case definition used by the Centers for Disease Control defines EM as an expanding skin lesion of at least 5 cm, often accompanied by fatigue, fever, headache, mild stiff neck, arthralgia and myalgia.<sup>13</sup>

Reviewing and summarizing the data, the authors looked for variables that might precisely define EM; without surprise, they conclude that no single component of the history or physical is sufficient enough to secure the diagnosis of EM. Rather, physicians must depend upon synthesizing information from endemic LD acquisition risks and other historical or exam elements—all of which can increase diagnostic probability over single or few variables. Moreover, Lyme disease serology is often negative early in the infection. Equivocal lesions are more likely to be EM if the suspect process expands rather than diminishes. In such instances, convalescent Lyme serology may prove useful.

Observed skin rashes of any type rarely are sufficient alone to be completely pathognomic for any process, much less an infectious one. Tibbles and Edlow also emphasize the well-described but under-acknowledged fact that only a minority of EM rashes are with central clearing, representing a "bull's eye" rash. While this may be classically described lesion of LD, the more common EM rash is a solitary, ovoid homogeneously erythematous lesion without central clearing.<sup>14</sup>

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Ultimately, LD remains a clinical diagnosis whereby a variable presentation of EM must be factored into a full picture of history and endemic risks, physical exam findings and possibly laboratory data. Since prospective studies of rash, generally, have not been carried out, the true diagnostic accuracy of EM remains unknown.

## SOUTHERN TICK-ASSOCIATED RASH ILLNESS VERSUS LYME DISEASE

Wormser GP, Masters E, Nowakowski J, et al. **Prospective clinical evaluation of patients from Missouri and New York with erythema migrans-like skin lesions.** *Clin Infect Dis.* 2005;41(7):958-65.

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STARI, also sometimes referred to as Master's disease, describes patients in the Southeast and Southcentral parts of the US who have an EM-like rash. Although these lesions resemble those of typical LD, evidence of *B. burgdorferi* infection has not typically been found by serology in these patients.<sup>15-18</sup> Moreover, the tick known to transmit LD, *Ixodes scapularis*, is rarely infected with the spirochete *B. burgdorferi* in the southern US.<sup>19</sup> Further, the lone star tick (*A. americanum*), the most common agent of human tick bites in this region, is not capable of supporting *B. burgdorferi*.<sup>20</sup> While the agent of STARI is not conclusively known, a single patient in whom an EM-rash developed after a bite by *A. americanum* was found by PCR techniques to be infected with a novel but closely related organism: *B. lonestari*.<sup>21</sup> Despite this report in 2001, this organism has never been described in another STARI patient.<sup>22</sup>

This 2005 prospective study by Wormser et al was designed to compare the clinical characteristics of early Lyme disease with those of patients with suspected STARI, and examined 21 cases of EM-like lesions in patients from Missouri (STARI patients) compared to 101 cases of EM in patients in New York (Lyme disease). The comparison of the 2 patient populations yielded significant differences, some of which are selected below:

Selected Findings			
	Missouri cases n=21, New York cases n=101		p
Peak Months	May/June	June/July	
Tick bite at lesion	18 (86%)	20 (20%)	<0.001
Symptomatic	4 (19%)	77 (76%)	<0.001
Regional lymphadenopathy	1 (5%)	37 (27%)	0.042
3-month Follow-up Visit: Report of fatigue & arthralgia	0/17 (0%)	17/80 (21.3%)	0.037

These comparison data show that patients from Missouri with STARI had their illness earlier in the season, and that they more often recollected a tick bite, a common historical consequence as *A. americanum* bites are often painful as opposed to the usually innocuous bite of *I. scapularis*. Generally, the illness associated with the EM-like lesions in Missouri was milder than cases described in New York. The Missouri patients were less likely to have constitutional and subjective complaints such as fatigue, joint pain, headache, and neck stiffness, as

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well as fewer objective findings such as multiple EM lesions or regional lymphadenopathy. The skin lesions of the Missouri EM-like cases often had central clearing (bull's eye) at a small diameter, whereas in the New York cases, this "bull's eye" was more often seen in older, maturing lesions. Although the rashes resolved with antibiotic therapy, persisting symptoms were much more common in New York patients than Missouri patients at a 3 month assessment. None of the Missouri patients had serological evidence of *B. burgdorferi* infection.

Many of the Lyme disease cases reported outside of the usual endemic region (Northeast, Mid-atlantic, and Upper Midwest US) may be due to STARI, and clinicians should consider the STARI diagnosis for EM-like lesions in the Southeast, Gulf Coast, and Western states. It is also likely, given the extensive range of *A. americanum*, that some cases of Lyme disease in endemic states may actually be due to STARI. Although the clinical finding of EM is the most common way Lyme disease is diagnosed, it is clearly not the only cause of EM-like lesions.

Some patients who are diagnosed with "chronic" LD in non-endemic states and subject to long-term antibiotic therapy may indeed have had a history of STARI, but their persisting symptoms are likely due to other causes. Although the actual pathogen of STARI remains unknown in most cases, once discovered and commercial test assays developed, the STARI diagnosis will be helpful to reassure patients about the more benign nature of this infection as opposed to *B. burgdorferi*.

## ROCKY MOUNTAIN SPOTTED FEVER RANGE EXPANDS DUE TO A NEWLY IMPLICATED TICK VECTOR

Demma LJ, Traeger MS, Nicholson WL, et al. **Rocky Mountain spotted fever from an unexpected tick vector in Arizona.** *N Engl J Med.* 2005;353(6):587-94.

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RMSF, although first discovered in the northern states associated with that mountain range, is now most commonly described in the central and southeastern United States, especially the Carolinas. This tick-borne infection is transmitted in the east by *Dermacentor variabilis* (American dog tick) and in the west by *D. andersoni* (Rocky Mountain wood tick). The number of RMSF cases has increased in recent years, leading to calls for a heightened awareness of this potentially fatal infection that commonly causes fever, myalgia, headache and rash in its earlier stages.<sup>23,24</sup>

In this 2005 report, Demma et al present a case series describing RMSF in rural eastern Arizona – a region heretofore not considered part of the usual range of infection. These patients appeared to have acquired the infection from the common brown dog tick (*Rhipicephalus sanguineus*), which has not been thought to be a vector for the *Rickettsia rickettsii*, the organism responsible for RMSF.

Sixteen RMSF patients from rural eastern Arizona were identified in 2003-2004 through active surveillance of regional hospitals as well as through anecdotal reporting. Verification of infection was accomplished through traditional serology (IgM or IgG), immunohistochemical staining, or PCR. Thirteen (81%) of these patients were under 12 years of age. Most (15) patients were hospitalized (64%) and 2 died (12%). None of the ill patients had traveled outside of their local



communities recently. All patients had a history of contact with tick-ridden dogs, and 25% recollected a history of a recent tick bite. One patient was found to have a *R. sanguineus* nymph attached.

Additional investigations were performed at the patients' homesites to collect ticks for analysis. No *Dermacentor* ticks (the usual vector for RMSF) were found. Although over 1000 *R. sanguineus* ticks were collected, only 2 were found to be positive for *R. rickettsii*. Serum obtained from 4 dogs owned by infected patients also showed high titers to *R. rickettsii*; one dog yielded an engorged *R. sanguineus* tick that was both culture and PCR positive for *R. rickettsii*.

Though RMSF is unusual in Arizona – due to the hot and arid climate, the region does not host *D. variabilis* or *D. andersoni* – evidence collected from this investigation suggests that the local tick *R. sanguineus* (common brown dog tick) was the responsible vector, as *R. rickettsii* was found in such ticks as well as in dogs living in the involved communities. Although *R. sanguineus* is well-known to transmit infection, it is known mostly for infecting humans with *R. conorii*, the agent of Mediterranean or Boutonneuse spotted fever, a usually mild infection found in Asia, Africa and Europe. Why this tick is now carrying *R. rickettsii* and what may be the usual animal reservoirs in Arizona are unknown; however, the population attack rate for children is approximately 300 times the national average, leading the investigators to speculate that these children may have been frequently playing with tick-infested dogs.

Because of the wide-ranging distribution of *R. sanguineus*, this tick vector may be capable of causing RMSF in areas not previously thought to be endemic for this infection. Evidence supporting this concern was recently published using a serosurvey of banked blood from 1996.<sup>25</sup> In 1996, only 5% of canine blood samples had *R. rickettsii* antibodies, while samples from 2003-2004 found positive serologies in 70% of dogs and 16% of children in the outbreak community, as well as 57% of dogs in a neighboring community. Further, a recent report describes *R. rickettsii* isolates from Arizona carried by *R. sanguineus* as distinct from organisms retrieved from Montana in the traditional range of RMSF.<sup>26</sup>

At least for this area of eastern Arizona, *R. rickettsii* has clearly expanded its range through the common brown dog tick and is now endemic. Whether climatic changes or facile geographic relocation of infected ticks is responsible is unknown, but clinicians need to be aware of potential RMSF even in previously non-endemic regions.

## RICKETTSIA PARKERI: A NEW HUMAN PATHOGEN IN THE UNITED STATES

Whitman TJ, Richards AL, Paddock CD, et al. **Rickettsia parkeri infection after tick bite, Virginia.** *Emerg Infect Dis.* 2007;13(2):334-6.

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Although there are many members of the spotted fever group rickettsiae family worldwide, there are only three well known in the US: *R. rickettsii*, the cause of RMSF; *R. felis*, responsible for the recently described fleaborne spotted fever; and *R. akari*, which causes rickettsialpox.<sup>27</sup> In 2002, a patient from Virginia was described with fever and multiple eschars from which *R. parkeri* was cultured. This organism was first isolated in the 1930s from the Gulf Coast tick (*Amblyomma maculatum*), and while thought to be a possible pathogen of cattle,



had not been implicated as an agent of human disease.<sup>28</sup> A second case of human infection with this rickettsial organism identified in Mississippi has been presented in 2006 at the International Conference on Emerging Infectious Diseases Conference (Atlanta, Georgia).

This 2007 case report describes an illness similar to the 2002 case also diagnosed in the same Tidewater region of Virginia (around the southern portion of the Chesapeake Bay). A 53-year-old service man presented with a 2-day illness consisting of fever to 39°C, night sweats, and a rash that consisted of an eschar on his right leg along with papules arising over his thorax and limbs. The patient had a mild leukopenia (3400 cells/ml). A skin biopsy performed at the site of the eschar yielded PCR amplicons representing *R. parkeri*, although PCR of blood and serum samples were negative. The patient was placed on doxycycline 100mg twice daily, with fever quickly resolving within one day, and the rash disappearing by day 4 of treatment.

Knowledge of *R. parkeri* may be important since some cases of what may have been diagnosed as mild RMSF in southeastern states could, in fact, be due to this organism. Research examining serology has suggested that *R. parkeri* may crossreact with antigens used for *R. rickettsii* assays. The eschar may be the clinical distinguishing feature of *R. parkeri* infection – although if only fever and maculopapular rash are detected, RMSF may be diagnosed instead (which may be supported by serological studies). Clinicians should therefore consider *R. parkeri* as part of their differential diagnosis of mild, febrile illness with rash, especially if one or more eschars are present. There are no commercial assays currently available, so diagnosis is best made by cell culture techniques or PCR of skin biopsy specimens.

While the extent of *R. parkeri* infection is unknown, with greater knowledge of the organism and better diagnostic techniques, it may turn out to be a frequent infection in the southeastern United States.<sup>29</sup> Moreover, the number of rickettsial infections affecting humans is growing – with focused research efforts and use of PCR technology,<sup>30</sup> *R. parkeri* is unlikely to be the last newly described tick-borne pathogen.

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