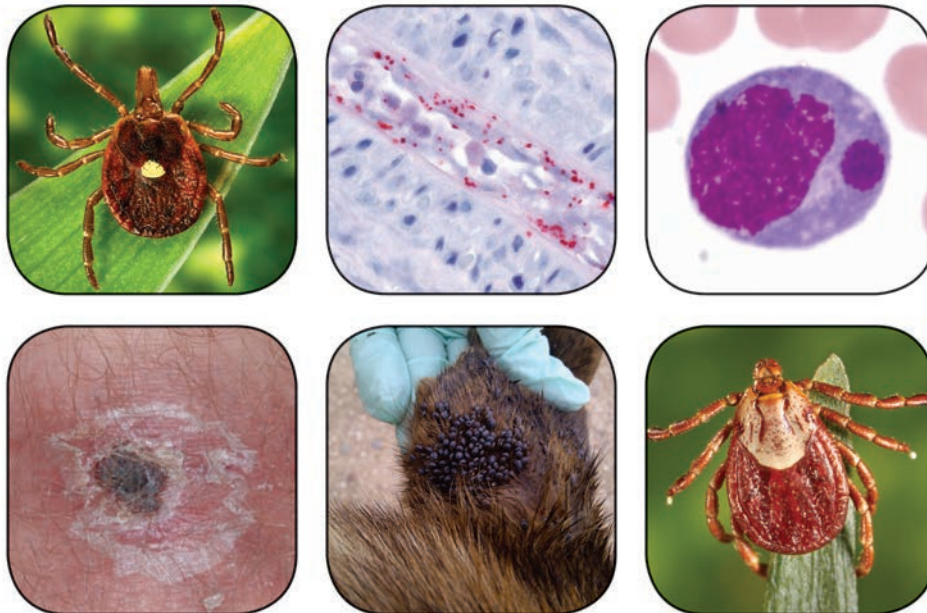


## Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever and Other Spotted Fever Group Rickettsioses, Ehrlichioses, and Anaplasmosis — United States

A Practical Guide for Health Care and Public Health Professionals



Continuing Education Examination available at <http://www.cdc.gov/mmwr/cme/conted.html>.



U.S. Department of Health and Human Services  
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J. Stephen Dumler, MD, receives a royalty from the University of Maryland School of Medicine for license of patent on in vitro growth of *Anaplasma phagocytophilum* for diagnostic antigen production. Bobbi S. Pritt, MD, is employed by Mayo Clinic, which performs reference laboratory testing for physicians throughout the United States. Planning committee reviewed content to ensure there is no bias.

Content will not include any discussion of the unlabeled use of a product or a product under investigational use.

**Front cover photos:** *Top row, left to right:* adult female *Amblyomma americanum* (lone star tick), immunohistochemical stain demonstrating *Rickettsia rickettsii* (red) in blood vessel endothelial cells, Wright stain of peripheral blood smear showing an intramonozytic morula associated with *Ehrlichia chaffeensis* infection. *Bottom row, left to right:* eschar associated with *Rickettsia parkeri* rickettsiosis, dog infested with *Rhipicephalus sanguineus* ticks, adult female *Dermacentor andersoni* (Rocky Mountain wood tick).

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# Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever and Other Spotted Fever Group Rickettsioses, Ehrlichioses, and Anaplasmosis — United States

## A Practical Guide for Health Care and Public Health Professionals

Holly M. Biggs, MD<sup>1</sup>; Casey Barton Behravesh, DVM, DrPH<sup>1</sup>; Kristy K. Bradley, DVM<sup>2</sup>; F. Scott Dahlgren, MSPH<sup>1</sup>; Naomi A. Drexler, MPH<sup>1</sup>; J. Stephen Dumler, MD<sup>3</sup>; Scott M. Folk, MD<sup>4</sup>; Cecilia Y. Kato, PhD<sup>1</sup>; R. Ryan Lash, MA<sup>1</sup>; Michael L. Levin, PhD<sup>1</sup>; Robert F. Massung, PhD<sup>1</sup>; Robert B. Nadelman, MD<sup>5</sup>; William L. Nicholson, PhD<sup>1</sup>; Christopher D. Paddock, MD<sup>1</sup>; Bobbi S. Pritt, MD<sup>6</sup>; Marc S. Traeger, MD<sup>7</sup>

<sup>1</sup>National Center for Emerging and Zoonotic Infectious Diseases, CDC, Atlanta, Georgia

<sup>2</sup>Oklahoma State Department of Health, Oklahoma City, Oklahoma

<sup>3</sup>University of Maryland School of Medicine, Baltimore, Maryland

<sup>4</sup>Mosaic Life Care, St. Joseph, Missouri

<sup>5</sup>New York Medical College, Valhalla, New York

<sup>6</sup>Mayo Clinic, Rochester, Minnesota

<sup>7</sup>Indian Health Service, Whiteriver, Arizona

### Summary

*Tickborne rickettsial diseases continue to cause severe illness and death in otherwise healthy adults and children, despite the availability of low-cost, effective antibacterial therapy. Recognition early in the clinical course is critical because this is the period when antibacterial therapy is most effective. Early signs and symptoms of these illnesses are nonspecific or mimic other illnesses, which can make diagnosis challenging. Previously undescribed tickborne rickettsial diseases continue to be recognized, and since 2004, three additional agents have been described as causes of human disease in the United States: Rickettsia parkeri, Ehrlichia muris-like agent, and Rickettsia species 364D. This report updates the 2006 CDC recommendations on the diagnosis and management of tickborne rickettsial diseases in the United States and includes information on the practical aspects of epidemiology, clinical assessment, treatment, laboratory diagnosis, and prevention of tickborne rickettsial diseases. The CDC Rickettsial Zoonoses Branch, in consultation with external clinical and academic specialists and public health professionals, developed this report to assist health care providers and public health professionals to 1) recognize key epidemiologic features and clinical manifestations of tickborne rickettsial diseases, 2) recognize that doxycycline is the treatment of choice for suspected tickborne rickettsial diseases in adults and children, 3) understand that early empiric antibacterial therapy can prevent severe disease and death, 4) request the appropriate confirmatory diagnostic tests and understand their usefulness and limitations, and 5) report probable and confirmed cases of tickborne rickettsial diseases to public health authorities.*

### Introduction

Ticks (Acari: Ixodidae and Argasidae) transmit multiple and diverse pathogens (including bacteria, protozoa, and viruses), which cause a wide range of human and animal diseases, including rickettsial diseases, caused by bacteria in the order Rickettsiales. Vertebrate animals play an integral role in the life cycle of tick species, whereas humans are incidental hosts. Awareness, diagnosis, and control of tickborne rickettsial diseases are most effectively addressed by considering the intersecting components of human, animal, and environmental health that collectively form the foundation of One Health (1),

an approach that integrates expertise from multiple disciplines and facilitates understanding of these complex zoonoses.

Tickborne rickettsial diseases in humans often share similar clinical features yet are epidemiologically and etiologically distinct. In the United States, these diseases include 1) Rocky Mountain spotted fever (RMSF) caused by *Rickettsia rickettsii*; 2) other spotted fever group (SFG) rickettsioses, caused by *Rickettsia parkeri* and *Rickettsia* species 364D; 3) *Ehrlichia chaffeensis* ehrlichiosis, also called human monocytic ehrlichiosis; 4) other ehrlichioses, caused by *Ehrlichia ewingii* and *Ehrlichia muris-like* (EML) agent; and 5) anaplasmosis, caused by *Anaplasma phagocytophilum* (2), also called human granulocytic anaplasmosis. Rickettsial pathogens transmitted by arthropods other than ticks, including fleas (*Rickettsia typhi*), lice (*Rickettsia prowazekii*), and mites (*Rickettsia akari*) are not included in this report. Imported tickborne rickettsial infections that might be diagnosed in returning

**Corresponding author:** Holly M. Biggs, National Center for Emerging and Zoonotic Infectious Diseases, CDC. Telephone: 404-639-1075; E-mail: Rzbepidiag@cdc.gov.

international travelers are summarized; however, tickborne and nontickborne rickettsial illnesses typically encountered outside the United States are not addressed in detail in this report.

The reported incidence of tickborne rickettsial diseases in the United States has increased during the past decade (3–5). Tickborne rickettsial diseases continue to cause severe illness and death in otherwise healthy adults and children, despite the availability of effective antibacterial therapy. Early signs and symptoms of tickborne rickettsial illnesses are nonspecific, and most cases of RMSF are misdiagnosed at the patient's first visit for medical care, even in areas where awareness of RMSF is high (6,7). To increase the likelihood of an early, accurate diagnosis, health care providers should be familiar with risk factors, signs, and symptoms consistent with tickborne rickettsial diseases.

This report provides practical information to help health care providers and public health professionals to

- recognize the epidemiology and clinical manifestations of tickborne rickettsial diseases;
- obtain an appropriate clinical history for suspected tickborne rickettsial diseases;
- recognize potential severe manifestations of tickborne rickettsial diseases;
- make treatment decisions on the basis of epidemiologic and clinical evidence;
- recognize that early and empiric treatment with doxycycline can prevent severe morbidity or death;
- recognize doxycycline as the treatment of choice for adults and children of all ages with suspected rickettsial disease;
- make treatment decisions for patients with certain conditions, such as a doxycycline allergy or pregnancy;
- recognize when to consider coinfection with other tickborne pathogens;
- determine appropriate confirmatory diagnostic tests for tickborne rickettsial diseases;
- understand the availability, limitations, and usefulness of confirmatory diagnostic tests;
- recognize unusual transmission routes, such as transfusion- or transplantation-associated transmission;
- recognize selected rickettsial diseases among returning travelers;
- advise patients regarding how to avoid tick bites; and
- report probable and confirmed cases to appropriate public health authorities to assist with surveillance, control measures, and public health education efforts.

Additional information concerning the tickborne rickettsial diseases described in this report is available from medical and veterinary specialists, various medical and veterinary societies, state and local health authorities, and CDC. The information and recommendations in this report are meant to serve as a source of general guidance for health care providers

and public health professionals; however, individual clinical circumstances should always be considered. This report is not intended to be a substitute for professional medical advice for individual patients, and persons should seek advice from their health care providers if they have concerns about tickborne rickettsial diseases.

## Methods

This report updates the 2006 CDC recommendations for the diagnosis and management of tickborne rickettsial diseases in the United States (8). Updated recommendations are needed to address the changing epidemiology of tickborne rickettsial diseases, provide current information about new and emerging tickborne rickettsial pathogens, and highlight advances in recommended diagnostic tests and updated treatment information.

The CDC Rickettsial Zoonoses Branch reviewed the 2006 report and determined which subject-matter areas required updates or revisions. Internal and external subject-matter experts in tickborne rickettsial diseases, representing a range of professional experiences and viewpoints, were identified by the CDC Rickettsial Zoonoses Branch to contribute to the revision. Contributors represented various areas of expertise within the field of tickborne rickettsioses and included practicing physicians specializing in internal medicine, family medicine, infectious diseases, and pathology; veterinarians with expertise in state, national, and international public health; epidemiologists; tick ecologists; microbiologists; and experts in rickettsial laboratory diagnostics. The peer-reviewed literature, published guidelines, and public health data were reviewed, with particular attention to new material available since preparation of the previous report. The scientific literature was searched through February 2016 using the MEDLINE database of the National Library of Medicine. The terms searched were *Rickettsia*, *Rickettsia* infections, *R. rickettsii*, RMSF, *Ehrlichia*, ehrlichiosis, *E. chaffeensis*, anaplasmosis, *Anaplasma*, and *A. phagocytophilum*. Text word searches were performed on multiple additional terms tailored to specific questions, which included epidemiology, treatment, diagnosis, and prevention. Titles of articles and abstracts extracted by the search were reviewed, and if considered potentially relevant, the full text of the article was retrieved. Reference lists of included articles were reviewed, and additional relevant citations were provided by contributors. In certain instances, textbook references were used to support statements considered general knowledge in the field. Articles selected were in English or had available translations. Peer-reviewed publications and published guidelines were used to support recommendations



when possible. Abstracts without a corresponding full-length publication, dissertations, or other non-peer-reviewed literature were not used to support recommendations. When possible, data were obtained from studies that determined the presence of tickborne rickettsial infection using confirmatory diagnostic methods. Additional criteria were applied on a per-question basis. For some questions, an insufficient number of studies was identified to support the development of a recommendation. In these instances, the report indicates that the evidence was insufficient for a recommendation, and when possible, general guidance is provided based on the available evidence and expert opinion of the CDC Rickettsial Zoonoses Branch. All contributors had the opportunity to review and provide input on multiple drafts of the report, including the final version. Future updates to this report will be dictated by new data in the field of tickborne rickettsial diseases.

## Epidemiology

### Overview

Tickborne rickettsial pathogens are maintained in natural cycles involving domestic or wild vertebrates and primarily hard-bodied ticks (Acari: Ixodidae). The epidemiology of each tickborne rickettsial disease reflects the geographic distribution and seasonal activities of the tick vectors and vertebrate hosts involved in the transmission of these pathogens, as well as the human behaviors that place persons at risk for tick exposure, tick attachment, and subsequent infection (Box 1). SFG rickettsiosis, ehrlichiosis, and anaplasmosis are nationally notifiable in the United States. Cases have been reported in each month of the year, although most cases are reported during April–September, coincident with peak levels of tick host-seeking activity (3–5,9–14). The distribution of tickborne rickettsial diseases varies geographically in the United States and approximates the primary tick vector distributions, making it important for health care providers to be familiar with the regions where tickborne rickettsial diseases are common. Travelers within the United States might be exposed to different tick vectors during travel, which can result in illness after they return home. Travelers outside of the United States might also be exposed to different tick vectors and rickettsial pathogens in other countries, which can result in illness after they return to the United States (see Travel Outside of the United States). Health care, public health, and veterinary professionals should be aware of changing vector distributions, emerging and newly identified human tickborne rickettsial pathogens, and increasing travel among persons and pets within and outside of the United States.

## Spotted Fever Group Rickettsiae

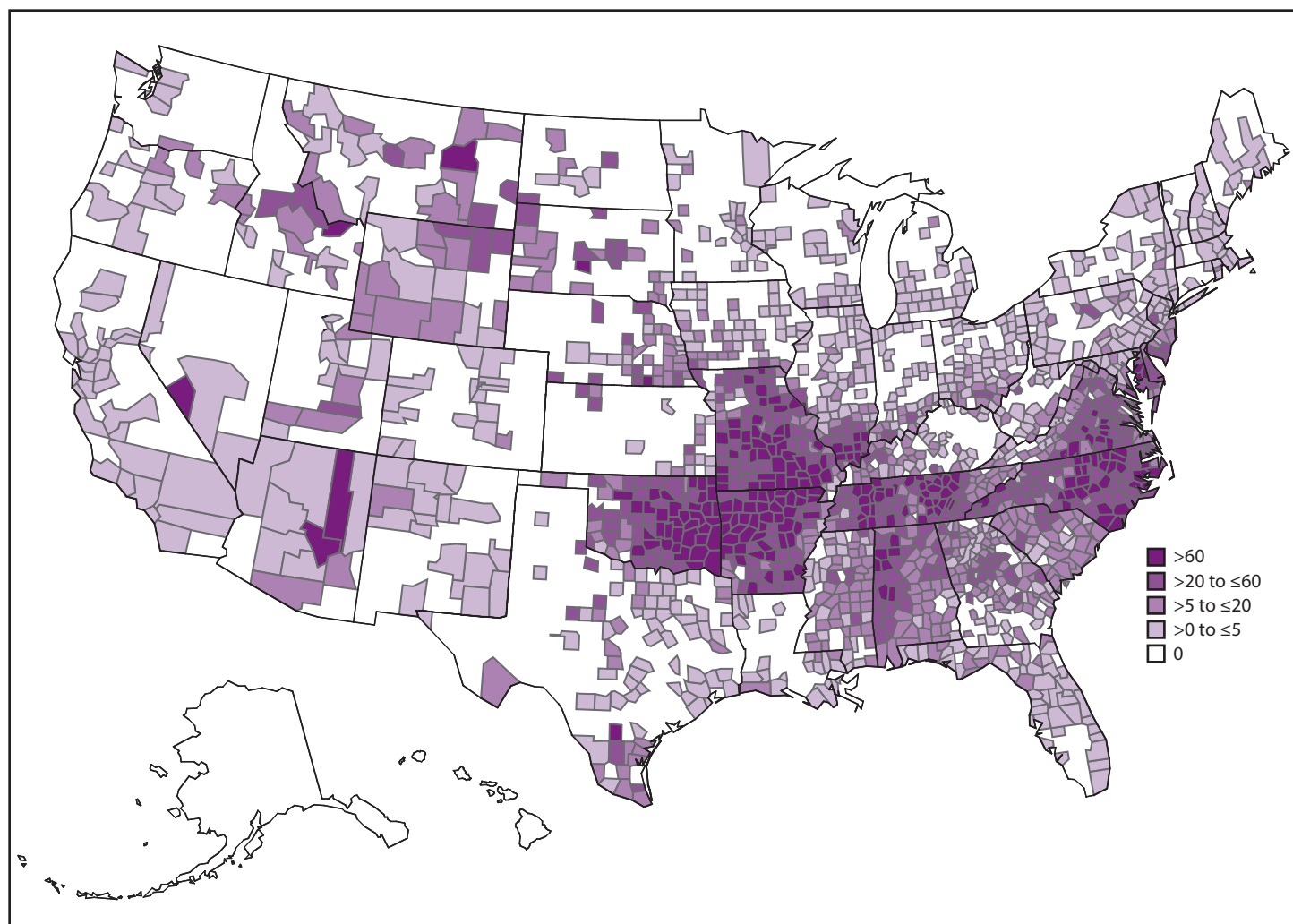
SFG rickettsiae are related closely by various genetic and antigenic characteristics and include *R. rickettsii* (the cause of RMSF), *R. parkeri*, and *Rickettsia* species 364D, as well as many other *Rickettsia* species of unknown pathogenicity. RMSF is the rickettsiosis in the United States that is associated with the highest rates of severe and fatal outcomes. During 2008–2012, passive surveillance indicated that the estimated average annual incidence of SFG rickettsiosis was 8.9 cases per million persons in the United States (4). The passive surveillance category in the United States for SFG rickettsiosis might not differentiate between RMSF and other SFG rickettsioses because of the limitations of submitted diagnostic evidence. Reported annual incidence of SFG rickettsiosis has increased substantially during the past 2 decades. The highest incidence occurs in persons aged 60–69 years, and the highest case-fatality rate is among children aged <10 years, although illness occurs in all age groups (4). Incidence varies considerably by geographic area (Figure 1). During 2008–2012, 63% of reported SFG rickettsiosis cases originated from five states: Arkansas, Missouri, North Carolina, Oklahoma, and Tennessee (4). However, SFG rickettsiosis cases have been reported from each of the contiguous 48 states and the District of Columbia (4,9,12,14).

A notable regional increase in the reported incidence of SFG rickettsiosis occurred in Arizona during 2003–2013. Over this period, approximately 300 cases of RMSF and 20 deaths were reported from American Indian reservations in Arizona compared with three RMSF cases reported in the state during the previous decade (15). Since identification of the first case of locally transmitted RMSF in 2003 (16), RMSF has been found to be endemic in several American Indian communities in Arizona. On the three most affected reservations, the average annual incidence rate for 2009–2012 was approximately 1,360 cases per million persons (17). The 7%–10% case-fatality rate in these communities, which is the highest of any region in the United States, has been associated predominantly with delayed recognition and treatment (4,18).

### *Rickettsia rickettsii*

In the United States, the tick species that is most frequently associated with transmission of *R. rickettsii* is the American dog tick, *Dermacentor variabilis* (Figure 2). This tick is found primarily in the eastern, central, and Pacific coastal United States (Figure 3). The Rocky Mountain wood tick, *Dermacentor andersoni* (Figure 4), is associated with transmission in the western United States (Figure 5). More recently, the brown dog tick, *Rhipicephalus sanguineus* (Figure 6), which is located throughout the United States (Figure 7), has been

FIGURE 1. Reported incidence rate\* of spotted fever rickettsiosis,† by county — United States, 2000–2013



\* As reported through national surveillance, per 1,000,000 persons per year. Cases are reported by county of residence, which is not always where the infection was acquired.

† Includes Rocky Mountain spotted fever (RMSF) and other spotted fever group rickettsioses. In 2010, the name of the reporting category changed from RMSF to spotted fever rickettsiosis.

recognized as an important vector in parts of Arizona (16) and along the U.S.-Mexico border. Several tick species of the genus *Amblyomma* are vectors of *R. rickettsii* from Mexico to Argentina, including *A. cajennense*, *A. aureolatum*, *A. imitator*, and *A. sculptum* (19–22). Although the geographic ranges of *A. imitator* and *A. mixtum* (a species closely related to *A. cajennense*) extend into Texas, the role of *Amblyomma* ticks in transmission of *R. rickettsii* in the United States has not been established.

*D. variabilis* ticks often are encountered in wooded, shrubby, and grassy areas and tend to congregate along walkways and trails. These ticks also can be found in residential areas and city parks. Larval and nymphal stages of most *Dermacentor* spp. ticks in the United States usually do not bite humans. Although

adult *D. variabilis* and *D. andersoni* ticks bite humans, the principal hosts tend to be deer, dogs, and livestock. Adult *Dermacentor* ticks are active from spring through autumn, with maximum activity during late spring through early summer.

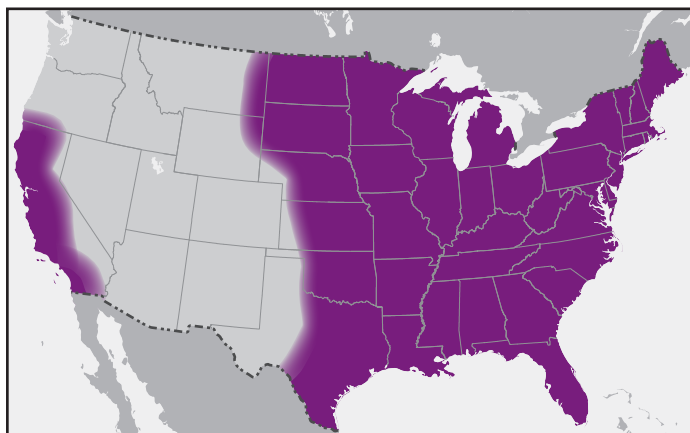
The brown dog tick, *Rh. sanguineus*, has been a recognized vector of *R. rickettsii* in Mexico since the 1940s (23); however, *Rhipicephalus*-transmitted *R. rickettsii* in the United States was not identified until 2003, when it was confirmed in a child on tribal lands in Arizona (16). Canids, especially domestic dogs, are the preferred hosts for the brown dog tick at all life stages. Humans are incidental hosts, bitten as a result of contact with tick-infested dogs or tick-infested environments. All active stages (larvae, nymphs, and adults) of *Rh. sanguineus* will bite humans and can transmit *R. rickettsii*. Heavily parasitized dogs

FIGURE 2. Adult female *Dermacentor variabilis* (American dog tick)



Photo/CDC

FIGURE 3. Approximate U.S. distribution of *Dermacentor variabilis* (American dog tick)



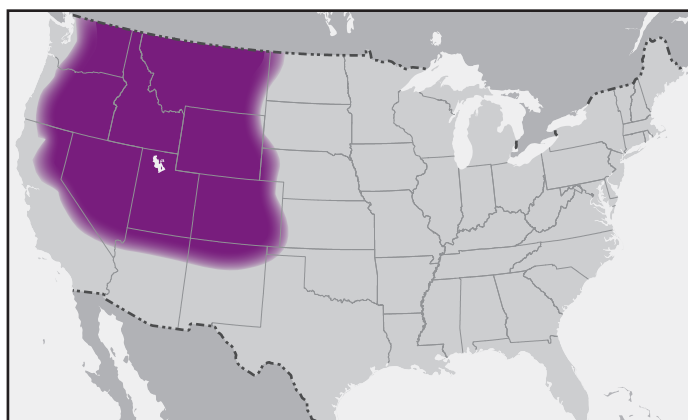
(Figure 8), as well as sizable infestations of brown dog ticks in and around homes, have been found in affected communities in Arizona (16,17,24). Free-roaming dogs can spread infected ticks among households within a neighborhood, resulting in community-level clusters of infection. Children aged <10 years represent more than half of reported cases in this region and are theorized to have higher rates of exposure to *Rh. sanguineus* ticks because of increased interaction with dogs and their habitats (16,25). On Arizona tribal lands, the warm climate and proximity of ticks to domiciles provide a suitable environment for *Rh. sanguineus* to remain active year-round (26). The majority of human cases of RMSF in Arizona occur during July–October after seasonal monsoon rains; however, cases have been reported every month of the year (25).

FIGURE 4. Adult female *Dermacentor andersoni* (Rocky Mountain wood tick)



Photo/CDC

FIGURE 5. Approximate U.S. distribution of *Dermacentor andersoni* (Rocky Mountain wood tick)



Similar epidemiologic characteristics and transmission dynamics have been reported in parts of Mexico (27–30). A high incidence of RMSF occurs in several northern Mexican states, including Baja California and Sonora, which border the United States. Persons infected with *R. rickettsii* in Mexico have sought health care across the U.S. border; health care providers should be aware of the risk for RMSF in persons traveling from areas where the disease incidence is high. *Rh. sanguineus* is found worldwide but is reported to transmit *R. rickettsii* in the southwestern United States, Mexico, and possibly some RMSF-endemic areas of South America (16,29–32). This species might contribute to the enzootic cycle more commonly than has been recognized (33,34).

### *Rickettsia parkeri*

The first confirmed case of human *R. parkeri* infection was reported in 2004 (35). During 2004–2015, at least 40 patients



FIGURE 6. Adult female *Rhipicephalus sanguineus* (brown dog tick)



Photo/CDC

FIGURE 7. Approximate U.S. distribution of *Rhipicephalus sanguineus* (brown dog tick)

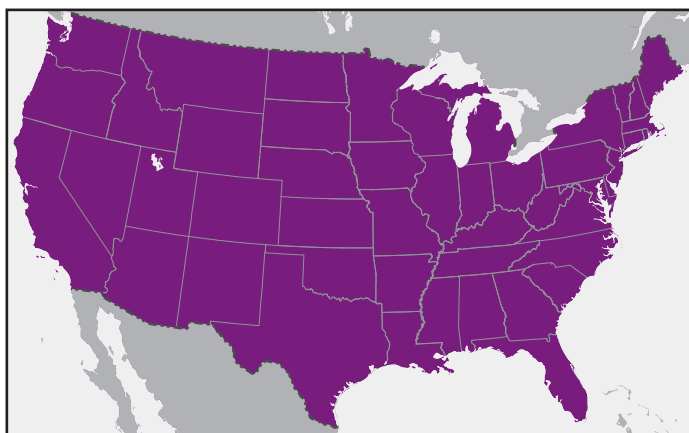


FIGURE 8. Dog infested with *Rhipicephalus sanguineus* ticks



Photo/CDC

and as far north as Kansas, Maryland, Oklahoma, and Virginia (Figure 10). The Gulf Coast tick is typically found in prairie grassland and coastal upland habitats (42). *R. parkeri* rickettsiosis cases have been documented during April–October, with most cases occurring during July–September.

### ***Rickettsia* Species 364D**

The first confirmed case of human disease associated with *Rickettsia* species 364D was described in 2010 from California and likely was transmitted by the Pacific Coast tick, *Dermacentor occidentalis* (43). Fewer than 10 cases of *Rickettsia* species 364D infection, all from California, have been reported in the literature (43,44). Cases have been documented in children and adults (44). The Pacific Coast tick is found in the coastal ranges of Oregon and California and in the states of Baja California and Sinaloa in Mexico. Principal hosts of adult ticks are horses, cattle, and black-tailed deer, whereas immature ticks feed on rodents and rabbits. The prevalence and distribution of *Rickettsia* species 364D in *D. occidentalis* ticks suggests that these infections in humans might be more common in California than currently recognized (45,46). Reported cases of *Rickettsia* species 364D rickettsiosis have occurred during July–September (43,44).

with *R. parkeri* rickettsiosis were identified from 10 states (35–41) (CDC, unpublished data, 2015). The median age of patients from case reports was 53 years (range: 23–83 years) (38); *R. parkeri* rickettsiosis has not been documented in children, and no fatal cases have been reported. *R. parkeri* is transmitted by the Gulf Coast tick, *Amblyomma maculatum* (Figure 9). The geographic range of *A. maculatum* extends across the southern United States from Texas to South Carolina

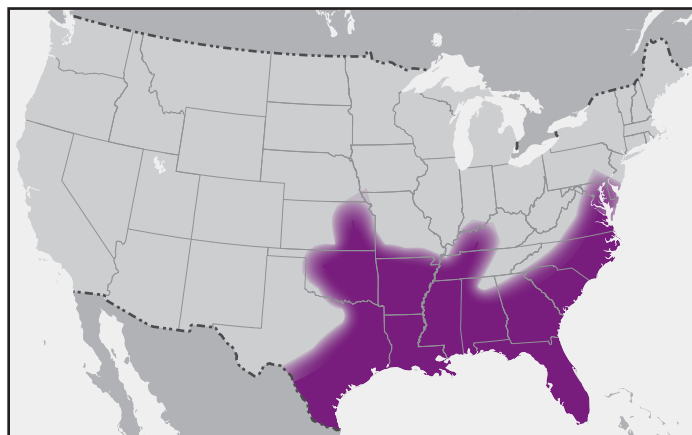
### **Ehrlichiae**

In the United States, three *Ehrlichia* species are known to cause symptomatic human infection. *E. chaffeensis*, the cause of human monocytic ehrlichiosis, was described first in 1987 and is the most common agent of human ehrlichiosis (47). *E. ewingii* was reported as a human pathogen in 1999 after



FIGURE 9. Adult female *Amblyomma maculatum* (Gulf Coast tick)

Photo/CDC

FIGURE 10. Approximate U.S. distribution of *Amblyomma maculatum* (Gulf Coast tick)

being detected in peripheral blood leukocytes of four patients with illness during 1996–1998 (48). EML agent ehrlichiosis, first described in 2011, is the most recently recognized form of human ehrlichiosis in the United States and was detected originally in the blood of four patients from Minnesota and Wisconsin in 2009 (49).

During 2008–2012, the average annual incidence of ehrlichiosis was 3.2 cases per million persons, which is more than twice the estimated incidence during 2000–2007 (5). Cases have been reported from an increasing number of counties (5) (Figure 11). Incidence generally increases with age, with the highest age-specific incidences occurring among persons aged 60–69 years (5,13,50). Case-fatality rates are highest among children aged <10 years and adults aged ≥70 years, and an increased risk for death has been documented among persons who are immunosuppressed (5,13). In areas where ehrlichiosis is endemic, the actual disease incidence is likely underrepresented in estimates that are based on passive surveillance (51–53).

### *Ehrlichia chaffeensis*

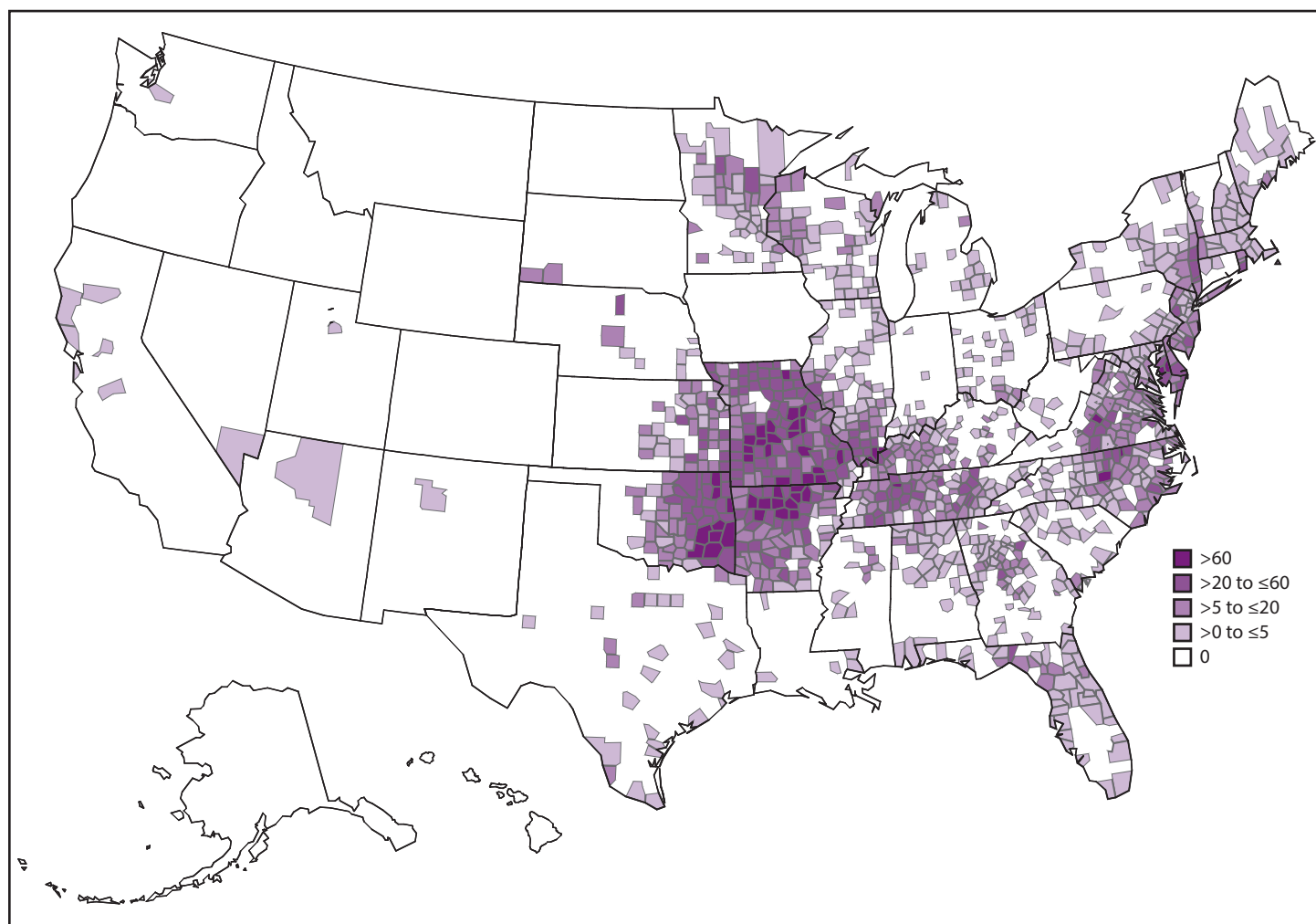
*E. chaffeensis* is transmitted to humans by the lone star tick, *Amblyomma americanum* (Figure 12). The lone star tick is among the most commonly encountered ticks in the southeastern United States, with a range that extends into areas of the Midwest and New England states (Figure 13). Ehrlichiosis cases have been reported throughout the range of the lone star tick; states with the highest reported incidence rates include Arkansas, Delaware, Missouri, Oklahoma, Tennessee, and Virginia (5). The white-tailed deer is a major host of all stages of lone star ticks and is thought to be an important natural reservoir for *E. chaffeensis* (54). Consequently, the lone star tick is found most commonly in woodland habitats that have white-tailed deer populations. The lone star tick feeds on a wide range of hosts, including humans, and has been implicated as the most common tick to bite humans in the southern United States (55,56). Although all stages of this tick feed on humans, only adult and nymphal ticks are known to be responsible for transmission of *E. chaffeensis* to humans. Most cases of *E. chaffeensis* ehrlichiosis occur during May–August.

### *Ehrlichia ewingii*

*E. ewingii* ehrlichiosis became a notifiable disease in 2008. During 2008–2012, cases were primarily reported from Missouri; however, cases also were reported from 10 other states within the distribution of the principal vector, the lone star tick, *A. americanum* (5,57) (Figure 13). Although *E. ewingii* ehrlichiosis initially was reported predominantly among persons who were immunosuppressed, passive surveillance data from 2008–2012 indicated that the majority of persons (74%) with reported *E. ewingii* infection did not report immunosuppression (5). No fatal cases of *E. ewingii* ehrlichiosis have been reported. The ecologic features of *E. ewingii* are not completely known; however, dogs, goats, and deer have been infected naturally and experimentally (58–60).

### *Ehrlichia muris*-Like Agent

In 2011, a new species of *Ehrlichia* referred to as the EML agent was described as a human pathogen after detection in the blood from four patients (three from Wisconsin and one from Minnesota) by using molecular testing techniques (49). The EML agent subsequently was identified in blood specimens from 69 symptomatic patients who lived in or were exposed to ticks in Minnesota or Wisconsin during 2007–2013 (61). The blacklegged tick, *Ixodes scapularis* (Figure 14), is an efficient vector for the EML agent in experimental studies (62,63), and DNA from the EML agent has been detected from *I. scapularis* collected in Minnesota and Wisconsin but has not been detected in *I. scapularis* from other states (64,65).

FIGURE 11. Reported incidence rate\* of *Ehrlichia chaffeensis* ehrlichiosis, by county — United States, 2000–2013

\* As reported through national surveillance, per 1,000,000 persons per year. Cases are reported by county of residence, which is not always where the infection was acquired.

### *Anaplasma phagocytophilum*

*A. phagocytophilum* causes human anaplasmosis, which is also known as human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis). Passive surveillance from 2008–2012 indicates that the average annual incidence of anaplasmosis was 6.3 cases per million persons (3). Incidence is highest in the northeastern and upper Midwestern states, and the geographic range of anaplasmosis appears to be expanding (3,66) (Figure 15). In Wisconsin, anaplasmosis has been identified as an important cause of nonspecific febrile illness during the tick season (67). Age-specific incidence of anaplasmosis is highest among those aged  $\geq 60$  years (3). The reported case-fatality rate during 2008–2012 was 0.3% and was higher among persons aged  $\geq 70$  years and those with immunosuppression (3).

*I. scapularis* (Figure 14) is the vector for *A. phagocytophilum* in the northeastern and Midwestern United States (68) (Figure 16),

whereas the western blacklegged tick, *Ixodes pacificus* (Figure 17), is the principal vector along the West Coast (Figure 18). The bites of nymphal and adult ticks can transmit *A. phagocytophilum* to humans. The relative roles of particular animal species as reservoirs of *A. phagocytophilum* strains that cause human illness are not fully understood and likely vary geographically; however, mice, squirrels, woodrats, and other wild rodents are thought to be important in the enzootic cycle. Most anaplasmosis cases occur during June–November. The seasonality of anaplasmosis is bimodal, with the first peak during June–July and a smaller peak during October, which corresponds to the emergence of the adult stage of *I. scapularis* (13).

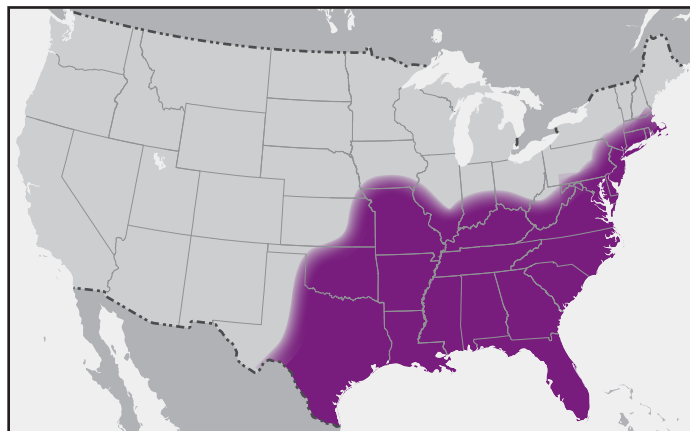
The blacklegged tick also transmits nonrickettsial pathogens in certain geographic areas, including *Borrelia burgdorferi* (the cause of Lyme disease), *Babesia microti* (the primary cause of human babesiosis in the United States), *Borrelia miyamotoi*, (a cause of tickborne relapsing fever), and deer tick virus

FIGURE 12. Adult female *Amblyomma americanum* (lone star tick)



Photo/CDC

FIGURE 13. Approximate U.S. distribution of *Amblyomma americanum* (lone star tick)



(Powassan virus, lineage II; a cause of tickborne encephalitis). The preponderance of cases of human anaplasmosis occur in the same states that report high incidences of Lyme disease and human babesiosis. Simultaneous infections with *A. phagocytophilum* and *B. burgdorferi* or *B. microti* have been described (69–73), and discerning such a mixed infection is important because it might affect antimicrobial choice (see Coinfections of *Anaplasma* with Other Tickborne Pathogens).

BOX 1. Summary of epidemiologic features of tickborne rickettsial diseases

- Incidence varies geographically in the United States, thus it is important for health care providers to know the regions in which particular tickborne rickettsial diseases typically occur.
- Occurrence is seasonal and corresponds with the feeding period for the life stage of the primary tick vector; the majority of illness occurs during the spring and summer months but might occur throughout the year, especially in geographic regions with warmer climates.
- In the past decade, *Rickettsia parkeri*, *Rickettsia* species 364D, and EML agent were newly recognized as agents of tickborne rickettsial disease in the United States.
- SFG rickettsioses, including RMSF, are reported from all of the contiguous 48 states and the District of Columbia.
- RMSF and *Ehrlichia chaffeensis* ehrlichiosis most commonly are reported in states from Missouri and Oklahoma east to North Carolina and Virginia.
- RMSF has emerged in parts of Arizona where it is associated with a different tick vector, *Rhipicephalus sanguineus*. RMSF in this area is characterized by unusually high incidence and case-fatality rates (particularly among children) and associated with prolonged periods of seasonal tick exposure and increased domestic and peridomestic exposures.
- Cases of RMSF have been reported in persons who acquire infection in areas of Mexico where disease incidence is high and subsequently seek health care across the U.S.-Mexico border.
- *R. parkeri* rickettsiosis first was described in 2004, and cases most commonly are reported along the Gulf Coast and the eastern seaboard.
- *Rickettsia* species 364D rickettsiosis first was described in 2010, and all reported cases are from California.
- Although recognized human cases of *Ehrlichia ewingii* ehrlichiosis are uncommon, cases increasingly are recognized and reported over a wider geographic range.
- EML agent ehrlichiosis first was described in 2011, and cases have been identified in persons exposed to ticks in Minnesota and Wisconsin.
- Anaplasmosis is reported predominantly from the northeastern United States, Minnesota, and Wisconsin.

**Abbreviations:** EML = *Ehrlichia muris*-like; RMSF = Rocky Mountain spotted fever; SFG = spotted fever group.



## Epidemiologic Clues from the Clinical History

Obtaining a thorough clinical history that includes questions about recent 1) tick exposure, 2) recreational or occupational exposure to tick-infested habitats, 3) travel to areas where tickborne rickettsial diseases are endemic, and 4) occurrence of similar illness in family members, coworkers, or pet dogs can provide critical information to make a presumptive diagnosis of tickborne rickettsial disease. However, the absence of one or more of these factors does not exclude a diagnosis of tickborne rickettsial disease. Health care providers should be familiar with the epidemiologic clues that support the diagnosis of tickborne rickettsial disease but recognize that classic epidemiologic features are not reported in many instances (Box 2).

### History of Tick Bite or Exposure

A detailed history should be taken to elicit information about known tick bites or activities that might be associated with exposure to ticks. Although the recognition of a tick bite is helpful, unrecognized tick bites are common in patients who are later confirmed to have a tickborne rickettsial disease. A history of a tick bite within 14 days of illness onset is reported in only 55%–60% of RMSF cases (9,12,25) and 68% of ehrlichiosis cases (10). Therefore, absence of a recognized tick bite should never dissuade health care providers from considering tickborne rickettsial disease in the appropriate clinical context. In fact, the absence of classic features, such as a reported tick bite, has been associated with delays in RMSF diagnosis and increased risk for death (9,18,74,75). The location of the tick bite might be obscure, and the bite is typically painless. Bites from immature stages of ticks (e.g., nymphs, which are 1–2 mm, or the size of a pinhead) (Figure 19) might be even less apparent. Some patients who do not report tick exposure might describe other pruritic, erythematous, or ulcerated cutaneous lesions that they refer to as mosquito, spider, chigger, or bug bites, all of which might be indistinguishable from a recent tick bite.

A thorough recreational and occupational history can help reveal potential exposures to tick habitats. In areas endemic for ticks, activities as commonplace as playing in a backyard, visiting a neighborhood park, gardening, or walking dogs are potential sources of tick exposure. Many types of environments serve as tick habitats, depending on the specific tick vector species. Areas with high uncut grass, weeds, and low brush might pose a high risk for certain vector species; however, these tick species also seek hosts in well-maintained grass lawns around suburban homes (76). Moreover, certain species can withstand drier conditions and might be found in vegetation-free areas or forest floors covered with only leaf litter or pine needles. Additional areas that might be inhabited by ticks

FIGURE 14. Adult female *Ixodes scapularis* (blacklegged tick)



Photo/CDC

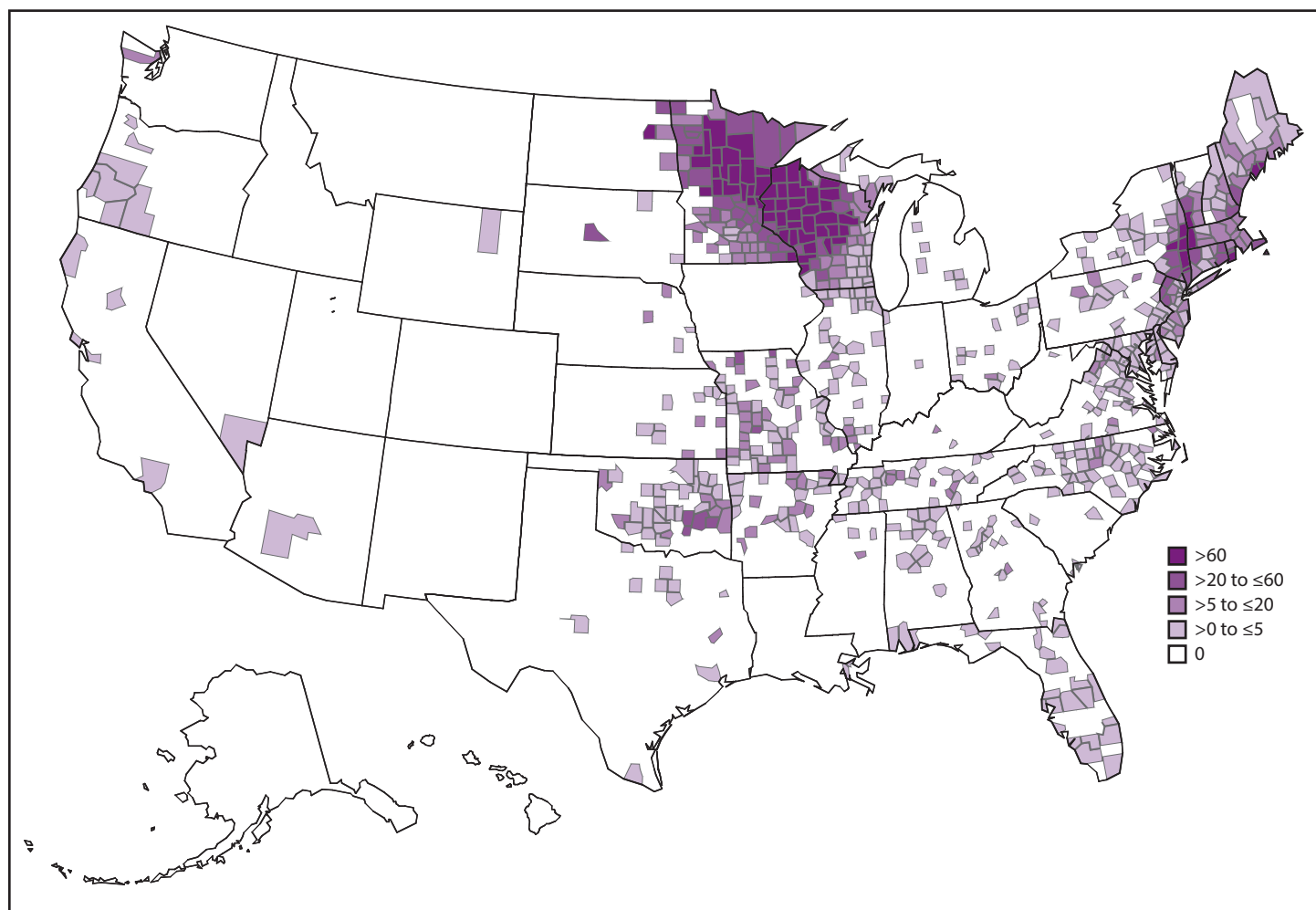
include vegetation bordering roads, trails, yards, or fields; urban and suburban recreational parks; golf courses; and debris piles or refuse around homes (24,77–80). Activities that commonly result in contact with potential tick habitats include recreational pursuits (e.g., camping, hiking, fishing, hunting, gardening, and golfing) and occupational activities (e.g., forestry work, farming, landscaping, and military exercises). Although peak tick season is an important consideration, health care providers should remain aware that tickborne rickettsial illnesses have been reported in every month of the year, including winter (3–5,25,81). Climate differences and seasonal weather patterns can influence the duration and peak of tick season in a given geographic region and a given year.

Queries about contact with pets, especially dogs, and a history of tick attachment or recent tick removal from pets might be useful in assessing potential human tick exposure. Pet dogs with attached ticks can serve as useful indicators of peridomestic tick infestation (17,82,83). Tick-infested dogs can transfer ticks directly to humans during interactions and serve as transport hosts, carrying ticks in and around dwellings where the ticks can then transfer to the human occupants (84) (see Similar Illness in Household Members, Coworkers, or Pets).

### Recent Travel to Areas Known To Be Endemic for Tickborne Rickettsial Diseases

Health care providers practicing in areas where the incidence of tickborne rickettsial disease is historically low might be less likely to distinguish these diseases from other clinically similar and more commonly encountered infectious and noninfectious syndromes. Tickborne rickettsial diseases typically are sporadic, and identifying these infections requires a high index of clinical suspicion, especially in environments in which the infections

FIGURE 15. Reported incidence rate\* of anaplasmosis, by county — United States, 2000–2013



\* As reported through national surveillance, per 1,000,000 persons per year. Cases are reported by county of residence, which is not always where the infection was acquired.

have not been recognized previously as occurring frequently. Knowledge of the epidemiology of tickborne rickettsial diseases, including the regions of the United States with a high incidence, is important. The distribution of tickborne rickettsial diseases is influenced by the geographic range of the tick vector, which can change over time. Distribution maps of tick vectors and disease incidence can serve as guides; however, the distribution borders are not fixed in space or over time, and the ranges for many tick species might be expanding.

Travel history within and outside of the United States can provide an important clue in considering the diagnosis of a tickborne rickettsial disease. Travel from an area where tickborne rickettsial diseases are endemic within 2 weeks of the onset of a clinically compatible illness could support a presumptive diagnosis of tickborne illness, especially if travel activities that might result in tick exposure are reported. Tickborne rickettsial diseases occur worldwide, and the

FIGURE 16. Approximate U.S. distribution of *Ixodes scapularis* (blacklegged tick)

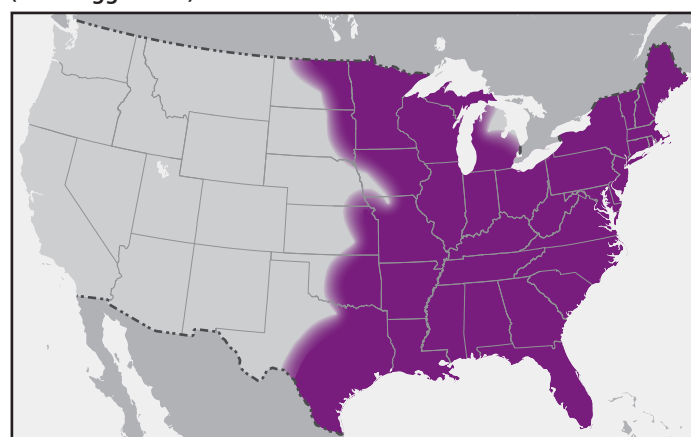
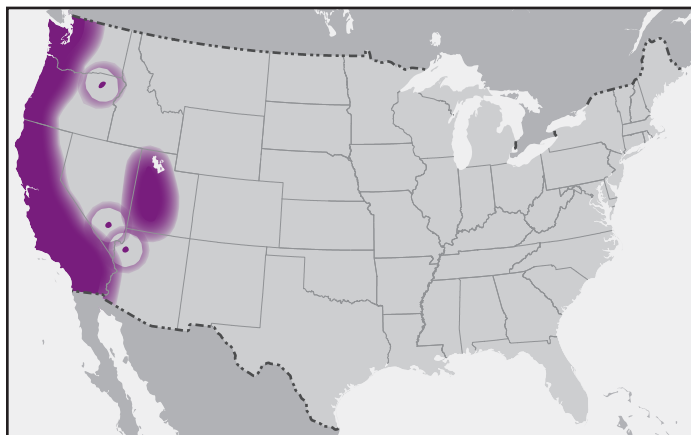


FIGURE 17. Adult female *Ixodes pacificus* (western blacklegged tick)



Photo/CDC

FIGURE 18. Approximate U.S. distribution of *Ixodes pacificus* (western blacklegged tick)



imported diseases might have epidemiologic, seasonal, and clinical features that differ from those in the United States. Selected additional tickborne rickettsial diseases that might be considered in returning international travelers are presented (see Travel Outside of the United States and Appendix A).

### Similar Illness in Household Members, Coworkers, or Pets

Clustering of certain tickborne rickettsial diseases is a well-recognized epidemiologic occurrence, particularly after common exposures to natural foci of infected ticks. Temporally and geographically related clusters of illness have occurred among family members (including their pet dogs), coworkers,

FIGURE 19. Sizes of the larva, nymph, and adult stages of *Rhipicephalus sanguineus* (brown dog tick) compared with a human finger



Photo/CDC

or persons frequenting a particular common area. Described clusters include ehrlichiosis among residents of a golfing community (80), ehrlichiosis and RMSF among soldiers on field maneuvers (85,86), and RMSF among family members (87–89). Infections with *R. rickettsii* and *Ehrlichia* species have been observed concurrently in humans and their pet dogs (48,83,90). Recognition of a dog's death from RMSF has even prompted recognition and appropriate treatment of RMSF in the sick owner (90). Health care providers should ask ill patients about similar illnesses among family members, coworkers, community residents, and pet dogs.

Dogs are frequently exposed to ticks and are susceptible to infections with many of the same tickborne rickettsial pathogens as humans, including *R. rickettsii*, *E. chaffeensis*, *E. ewingii*, and *A. phagocytophilum* (82). Evidence of current or past rickettsial infection in dogs might be useful in determining the presence of human risk for tickborne rickettsial diseases in a given geographic area (82). Tickborne rickettsial infection in dogs can range from inapparent to severe. RMSF in dogs manifests with fever, lethargy, decreased appetite, tremors, scleral injection, maculopapular rash on ears and exposed skin, and petechial lesions on mucous membranes (91–93). A veterinarian should be consulted when tickborne rickettsial disease is suspected in dogs or other animals (see Protecting Pets from Tick Bites). Documentation of a tickborne rickettsial disease in a dog should prompt veterinary professionals to warn pet owners about the risk for acquiring human tickborne disease. Cases of RMSF in dogs preceding illness in their owners (83) illustrate the value of communication between veterinarians and human health care providers when zoonotic diseases are suspected and emphasize the importance of a One Health approach to address zoonotic diseases.



**BOX 2. Summary of epidemiologic clues from the clinical history**

- The absence of known tick attachment should never dissuade a health care provider from considering the diagnosis of tickborne rickettsial disease.
- A detailed history of recent recreational and occupational activities and travel might reveal potential exposure to ticks or tick habitats.
- Familiarity with tickborne rickettsial disease epidemiology is helpful when asking patients about recent travel to areas (domestic and international) where these diseases are endemic.
- Clustering of certain tickborne rickettsial diseases is well recognized and has been reported among family members, pet dogs, coworkers, military personnel, and other groups.
- Dogs and humans are susceptible to infection with many of the same tickborne rickettsial pathogens, including *Rickettsia rickettsii*, *Ehrlichia chaffeensis*, *Ehrlichia ewingii*, and *Anaplasma phagocytophilum*; in some instances, pet dogs might serve as sentinels for tickborne rickettsial disease in humans.

## Clinical Signs and Symptoms and Pathophysiology of Disease

Tickborne rickettsial diseases commonly have nonspecific clinical signs and symptoms early in the course of disease. Although the clinical presentations of tickborne rickettsial disease overlap, the frequency of certain associated signs and symptoms (e.g., rash and other cutaneous findings), typical laboratory findings, and case-fatality rates differ by pathogen (Table 1). Familiarity with the clinical signs and symptoms and pathophysiology of tickborne rickettsial diseases, including RMSF and other SFG rickettsioses (Box 3), ehrlichioses (Box 4), and anaplasmosis (Box 5) will assist health care providers in developing a differential diagnosis, prescribing appropriate antibacterial treatment, and ordering appropriate confirmatory diagnostic tests.

### Rocky Mountain Spotted Fever and Other Spotted Fever Group Rickettsioses

#### Rocky Mountain Spotted Fever

##### Pathophysiology

*R. rickettsii* is an obligate intracellular pathogen that primarily infects vascular endothelial cells, and, less commonly, underlying smooth muscle cells of small and medium vessels (Figure 20). Infection with *R. rickettsii* leads to systemic

vasculitis that manifests externally as characteristic petechial skin lesions. If disease progresses untreated, it can result in end-organ damage associated with severe morbidity and death. Pathogen-mediated injury to the vascular endothelium results in increased capillary permeability, microhemorrhage, and platelet consumption (94). Late-stage manifestations, such as noncardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]) and cerebral edema, are consequences of microvascular leakage. Hyponatremia occurs as a result of appropriate secretion of antidiuretic hormone in response to hypovolemia (95).

##### Signs and Symptoms

Symptoms of RMSF typically appear 3–12 days after the bite of an infected tick or between the fourth and eighth day after discovery of an attached tick (96). The incubation period is generally shorter (5 days or less) in patients who develop severe disease (97). Initial symptoms include sudden onset of fever, headache, chills, malaise, and myalgia. Other early symptoms might include nausea or vomiting, abdominal pain, anorexia, and photophobia. A rash typically appears 2–4 days after the onset of fever; however, most patients initially seek health care before appearance of a rash (25,74,98). The classic triad of fever, rash, and reported tick bite is present in only a minority of patients during initial presentation to health care (6,25); therefore, health care providers should not wait for development of this triad before considering a diagnosis of RMSF.

The RMSF rash classically begins as small (1–5 mm in diameter), blanching, pink macules on the ankles, wrists, or forearms that subsequently spread to the palms, soles, arms, legs, and trunk, usually sparing the face. Over the next several days of illness, the rash typically becomes maculopapular, sometimes with central petechiae (Figures 21 and 22). The classic spotted or generalized petechial rash, including involvement of the palms and soles, usually appears by day 5 or 6 and is indicative of advanced disease. Absence of rash should not preclude consideration of RMSF; <50% of patients have a rash in the first 3 days of illness, and a smaller percentage of patients never develop a rash (6,25). The rash might be atypical, localized, faint, or evanescent (99). In some persons, skin pigmentation might make the rash difficult to recognize. The rash might resemble those of other infectious and noninfectious etiologies (see Differential Diagnosis of Fever and Rash). Children aged <15 years more frequently have a rash than older patients and develop the rash earlier in the course of illness (6–8). Lack of rash or late-onset rash in RMSF has been associated with delays in diagnosis and increased mortality (6,18,74). Unlike some SFG rickettsioses, an inoculation eschar is rarely present with RMSF (100,101). Other clinical

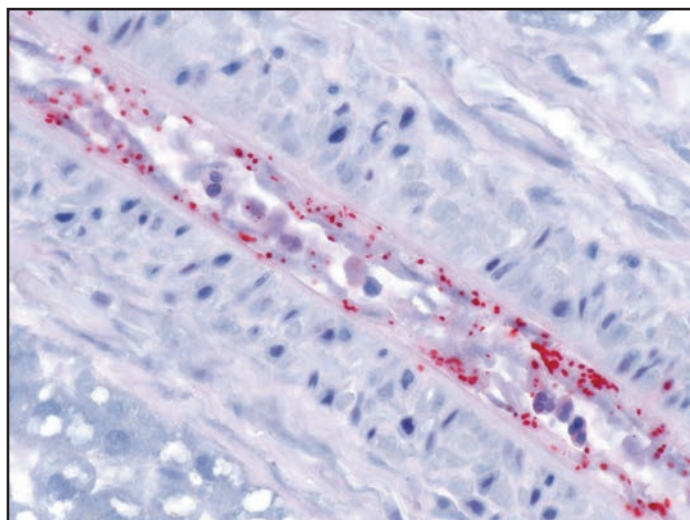
**TABLE 1. Selected clinical features of tickborne rickettsial diseases — United States**

Disease	Incubation period	Common initial signs and symptoms	Cutaneous signs	Common laboratory findings	Estimated case-fatality rate
Rocky Mountain spotted fever	3–12 days	Fever, headache, chills, malaise, myalgia, nausea, vomiting, abdominal pain, photophobia, anorexia	Maculopapular rash approximately 2–4 days after fever onset in most, might become petechial and involve palms and soles	Thrombocytopenia, slightly increased hepatic transaminase levels, normal or slightly increased white blood cell count with increased immature neutrophils, hyponatremia	5%–10%
<i>Rickettsia parkeri</i> rickettsiosis	2–10 days	Fever, myalgia, headache	Eschar, sparse maculopapular or vesiculopapular rash that might involve palms and soles	Mild thrombocytopenia, mild leukopenia, increased hepatic transaminase levels	—*
<i>Rickettsia</i> species 364D rickettsiosis	—†	Fever, headache, myalgia, fatigue	Eschar or ulcerative lesion with regional lymphadenopathy	—†	—*
<i>Ehrlichia chaffeensis</i> ehrlichiosis (human monocytic ehrlichiosis)	5–14 days	Fever, headache, malaise, myalgia, nausea, diarrhea, vomiting	Rash in approximately 30% of adults and 60% of children, variable rash pattern that might involve palms and soles, appears a median of 5 days after illness onset	Leukopenia, thrombocytopenia, increased hepatic transaminase levels, hyponatremia, anemia	3%
<i>Ehrlichia ewingii</i> ehrlichiosis	—†	Fever, headache, malaise, myalgia	Rash rare	Leukopenia, thrombocytopenia, increased hepatic transaminase levels	—*
<i>Ehrlichia muris</i> -like agent ehrlichiosis	—†	Fever, headache, malaise, myalgia	Rash in approximately 12%	Thrombocytopenia, lymphopenia, leukopenia, increased hepatic transaminase levels, anemia	—*
Human anaplasmosis (human granulocytic anaplasmosis)	5–14 days	Fever, headache, malaise, myalgia, chills	Rash rare, in <10%	Thrombocytopenia, leukopenia, mild anemia, increased hepatic transaminase levels, increased numbers of immature neutrophils	<1%

\* No known deaths.

† Not documented.

**FIGURE 20. Immunohistochemical stain demonstrating *Rickettsia rickettsii* (red) in blood vessel endothelial cells**



Photo/CDC

features that have been observed in association with RMSF include abdominal pain that mimics acute appendicitis (102), cholecystitis (103), or gastroenteritis; diarrhea; conjunctival suffusion; periorbital and peripheral edema (more common in children); calf pain; acute transient hearing loss; hepatomegaly; and splenomegaly (6,104).

Severe, late-stage manifestations of RMSF include meningoencephalitis, acute renal failure, ARDS, cutaneous necrosis, shock, arrhythmia, and seizure. Features of late illness might be confused with other diseases or syndromes. For example, RMSF-associated cutaneous necrosis and gangrene might be difficult to distinguish clinically from purpura fulminans associated with meningococcemia (105). RMSF-associated neurologic manifestations, renal failure, and thrombocytopenia have led to confusion with the diagnosis of thrombotic thrombocytopenic purpura (TTP) (106–108). RMSF-associated vasculitis has been confused with idiopathic, acute vasculitides, such as Kawasaki disease in pediatric patients. RMSF might also mimic bacterial or viral meningoencephalitis (109). Focal neurologic deficits, including cranial or peripheral motor nerve paralysis, or sudden transient hearing loss can occur (110–112).

**FIGURE 21.** Maculopapular rash with central petechiae associated with Rocky Mountain spotted fever



Photo/CDC

### Clinical Course

Clinical suspicion for RMSF should be maintained in cases of nonspecific febrile illness and sepsis of unclear etiology, particularly during spring and summer months. Delay in diagnosis and treatment is the most important factor associated with increased likelihood of death, and early empiric therapy is the best way to prevent RMSF progression. Without treatment, RMSF progresses rapidly. Patients treated after the fifth day of illness are more likely to die than those treated earlier in the course of illness (9,18,74,75). The frequency of hospital admission, intensive care unit admission, and death increases with time from symptom onset to initiation of appropriate antibacterial treatment (18) (Table 2). Delays in diagnosis and initiation of antirickettsial therapy have been associated with seeking health care early in the course of the illness (7,74), late-onset or absence of rash (6,18), and nonspecific or atypical early manifestations, such as gastrointestinal symptoms (18,98) or absence of headache (75). Epidemiologic factors associated with increased risk for death include disease that occurs early or late in the typical tick season (74) and the lack of a report of a tick bite (9,75,98). Although knowledge of the epidemiology might help guide diagnosis, the absence of epidemiologic clues can be misleading.

RMSF is the most frequently fatal rickettsial illness in the United States; the case-fatality rate in the preantibiotic era was approximately 25% (113–115). Present-day case-fatality rates, estimated at 5%–10% overall, depend in part on the timing of initiation of appropriate treatment; case-fatality rates of 40%–50% among patients treated on days 8 or 9 of illness

**FIGURE 22.** Late-stage petechial purpuric rash involving the sole of the foot in a patient with Rocky Mountain spotted fever



Photo/CDC

have been described recently (18) (Table 2). Additional risk factors for fatal RMSF include age  $\geq 40$  years, age  $< 10$  years, and alcohol abuse (18,75,116,117). Glucose-6-phosphate dehydrogenase deficiency is a risk factor for fulminant RMSF, with death occurring in  $\leq 5$  days (118). Experimental and accumulated anecdotal clinical data suggest that treatment of patients with RMSF using a sulfonamide antimicrobial can result in increased disease severity and death (119,120).

Long-term neurologic sequelae of RMSF include cognitive impairment; paraparesis; hearing loss; blindness; peripheral neuropathy; bowel and bladder incontinence; cerebellar, vestibular, and motor dysfunction; and speech disorders (7,110,121–124). These complications are observed most frequently in persons recovering from severe, life-threatening disease, often after lengthy hospitalizations, and are most likely the result of *R. rickettsii*-induced vasculopathy. Cutaneous necrosis and gangrene (Figure 23) might result in amputation of digits or limbs (105). Long-term or persistent disease caused by *R. rickettsii* has not been observed.

### Laboratory Findings

The total white blood cell count is typically normal or slightly increased in patients with RMSF, and increased numbers of immature neutrophils often are observed. Thrombocytopenia, slight elevations in hepatic transaminases (aspartate transaminase and alanine transaminase), and hyponatremia might be present, particularly as the disease advances (25,77); however, laboratory values cannot be relied on to guide early treatment decisions because they are often within or slightly deviated from the reference range early in the course of illness (25). Indicators of diffuse tissue injury, such as elevated levels of creatine kinase or serum lactate dehydrogenase, might be present later in the course



**TABLE 2. Outcome for confirmed cases of Rocky Mountain spotted fever, by day of illness that treatment with doxycycline was started — two tribal communities in eastern Arizona, 2002–2011**

Day (no. of patients)*	Outpatient No. (%)	Hospitalized No. (%)	ICU patients among those hospitalized No. (%)	Deaths among hospitalized and ICU patients No. (%)
Day 1 (6)	5 (83)	1 (17)	0 (0)	0 (0)
Day 2 (11)	8 (73)	3 (27)	0 (0)	0 (0)
Day 3 (9)	4 (44)	5 (56)	1 (11)	0 (0)
Day 4 (7)	3 (43)	4 (57)	1 (14)	0 (0)
Day 5 (8)	2 (25)	6 (75)	4 (50)	0 (0)
Day 6 (9)	0 (0)	9 (100)	5 (55)	3 (33)
Day 7 (11)	0 (0)	11 (100)	4 (36)	3 (27)
Day 8 (5)	1 (20)	4 (80)	2 (40)	2 (40)
Day 9 (4)	0 (0)	4 (100)	4 (100)	2 (50)

Source: Adapted from Regan JJ, Traeger MS, Humpherys D, et al. Risk factors for fatal outcome from Rocky Mountain spotted fever in a highly endemic area—Arizona, 2002–2011. *Clin Infect Dis* 2015;60:1659–66.

Abbreviation: ICU = intensive care unit.

\* Day of illness that treatment was started and the total number of confirmed patients treated on that day.

**FIGURE 23. Gangrene of the digits in a patient with late-stage Rocky Mountain spotted fever**



Photo/CDC

of illness. Disseminated intravascular coagulation (DIC) is rare (125,126). When cerebrospinal fluid (CSF) is evaluated, a lymphocytic (or less commonly, neutrophilic) pleocytosis (usually <100 cells/ $\mu$ L) can be observed (122). CSF protein might be moderately elevated (100–200 mg/dL), and the glucose level is typically within normal range (111,127).

### ***Rickettsia parkeri* Rickettsiosis**

Compared with RMSF, *R. parkeri* rickettsiosis is less severe. Symptoms develop a median of 5 days (range: 2–10 days) after the bite of an infected tick (39). The first manifestation in nearly all patients is an inoculation eschar (a dark, scabbed plaque overlying a shallow ulcer, typically 0.5–2 cm in diameter), which generally is nonpruritic, nontender or mildly tender, and surrounded by an indurated, erythematous halo and occasionally a few petechiae (Figure 24). The presence of more than one eschar has been described (39). Fever typically develops within a few days of the eschar. Shortly

after the onset of fever (approximately 0.5–4 days later), a nonpruritic maculopapular or vesiculopapular rash commonly develops (90%) (Figure 25). The rash primarily involves the trunk and extremities and might involve the palms and soles in approximately half of patients and the face in <20% of patients (39). Other common symptoms include myalgia (76%) and headache (86%). Regional lymphadenopathy is detected in approximately 25% of patients. Gastrointestinal manifestations, such as nausea or vomiting, are rare (38,39). Mild thrombocytopenia has been observed in 40%, mild leukopenia in 50%, and modest elevation of hepatic transaminase levels in 78% of cases (39). Hospitalization from *R. parkeri* rickettsiosis occurs in less than one third of patients; no severe manifestations or deaths have been reported. Because the clinical description of *R. parkeri* infection is based on observations from a limited number of cases, the full clinical spectrum of illness is likely incomplete.

### ***Rickettsia* Species 364D Rickettsiosis**

The first clinical description of a confirmed case of *Rickettsia* species 364D infection was published in 2010 (43). Although the full spectrum of illness has yet to be described, 364D infection appears to be characterized by an eschar (Figure 26) or ulcerative skin lesion with regional lymphadenopathy (43,44). Fever, headache, myalgia, and fatigue have occurred among persons with confirmed infection. Rash has not been a notable feature of this illness. Illnesses among the few described patients have been relatively mild and have readily responded to appropriate antimicrobial therapy.

**BOX 3. Summary of clinical features of Rocky Mountain spotted fever and other spotted fever group rickettsioses**

- RMSF is the most severe rickettsial illness in the United States.
- Delay in recognition and treatment is the most important factor associated with risk for death from RMSF.
- Early empiric therapy is the best way to prevent RMSF progression and resultant morbidity and mortality.
- The classic triad of fever, rash, and reported tick bite is rarely present when patients with RMSF first seek care.
- Rash is present in most patients during the course of RMSF, although it can appear late or be atypical, localized, faint, evanescent, and difficult to recognize in persons with darker pigmented skin.
- Thrombocytopenia, increased immature neutrophils, elevations in hepatic transaminase levels, and hyponatremia might be present in patients with RMSF; however, laboratory findings are often within or slightly deviated from the reference ranges early in the course of illness.
- *Rickettsia parkeri* rickettsiosis is typically milder than RMSF, and the first manifestation in nearly all patients is an inoculation eschar.
- The few described cases of *Rickettsia* species 364D rickettsiosis have involved a relatively mild illness characterized by eschar and regional lymphadenopathy.

**Abbreviation:** RMSF = Rocky Mountain spotted fever.

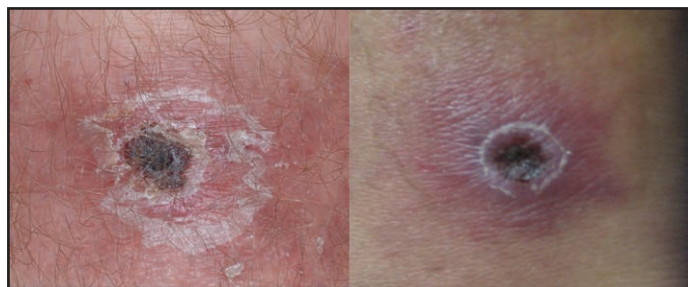
## Ehrlichioses

### *Ehrlichia chaffeensis* Ehrlichiosis (Human Monocytic Ehrlichiosis)

#### Pathophysiology

Ehrlichiae are obligate intracellular bacteria that infect peripheral blood leukocytes. *E. chaffeensis*, the pathogen that causes human monocytic ehrlichiosis, predominantly infects monocytes and tissue macrophages (Figure 27). The organisms multiply in cytoplasmic membrane-bound vacuoles, forming tightly packed clusters of bacteria called morulae. In patients with fatal *E. chaffeensis* ehrlichiosis, systemic, multiorgan involvement has been described with the greatest distribution of bacteria in the spleen, lymph nodes, and bone marrow (128). Unlike in RMSF, direct vasculitis and endothelial injury are rare in ehrlichiosis. The host systemic inflammatory response, rather than direct effects of the pathogen, is likely to be largely responsible for many of the clinical manifestations of ehrlichiosis (129).

**FIGURE 24.** Various appearances of eschars associated with *Rickettsia parkeri* rickettsiosis



Photos/CDC

**FIGURE 25.** Vesiculopapular rash associated with *Rickettsia parkeri* rickettsiosis



Photo/CDC

### Signs and Symptoms

Symptoms of *E. chaffeensis* ehrlichiosis typically appear a median of 9 days (range: 5–14 days) after the bite of an infected tick (128). Fever (96%), headache (72%), malaise (77%), and myalgia (68%) are common signs and symptoms. Gastrointestinal manifestations can be prominent, including nausea (57%), vomiting (47%), and diarrhea (25%) (129–131). Abdominal pain, vomiting, and diarrhea might be more common among children (132). Approximately one-third of patients develop a skin rash during the course of illness; rash occurs more frequently in children than in adults. Rash patterns vary in character from petechial or maculopapular (128,132) to diffuse erythema (133) and typically occur a median of 5 days after illness onset (10). The rash typically involves the extremities and trunk but can affect the palms, soles, or face (134). Cough or respiratory symptoms are reported in approximately 28% of patients and are more common among adults (10,51,129). Central nervous system involvement, such as meningitis or meningoencephalitis, is present in approximately 20% of patients (135).

Other severe manifestations include ARDS, toxic shock-like or septic shock-like syndromes, renal failure, hepatic failure, coagulopathies, and occasionally, hemorrhagic

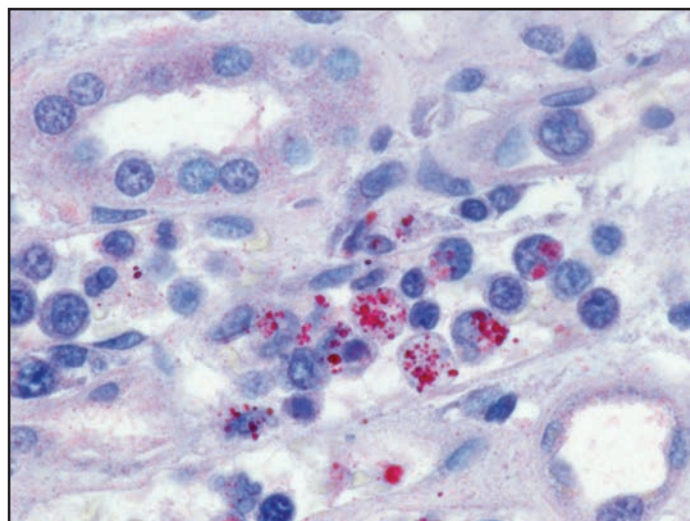
FIGURE 26. Eschar on a patient with *Rickettsia* species 364D rickettsiosis

Photo/Samantha H. Johnston, Children's Hospital & Research Center Oakland

manifestations (133). *E. chaffeensis* infection might rarely trigger hemophagocytic lymphohistiocytosis (136–140). Severe cases have been mistaken for TTP (141), appendicitis (142), or fulminant viral hepatitis (143). Heartland virus disease, a recently identified tickborne viral infection transmitted by the lone star tick, can closely resemble ehrlichiosis (144).

### Clinical Course

*E. chaffeensis* ehrlichiosis can cause severe disease or death, although at lower rates than have been observed for RMSF. Approximately 3% of patients with symptoms severe enough to seek medical attention die from the infection (51,128). The severity of ehrlichiosis could be related, in part, to host factors such as age and the immune status of the patient. Persons who have compromised immune systems as a result of immunosuppressive therapies, human immunodeficiency virus (HIV) infection (145,146), organ transplantation (147,148), or splenectomy more frequently have severe symptoms of ehrlichiosis and are hospitalized more often (13). Case-fatality rates among persons who are immunosuppressed are higher than those among the general population, on the basis of U.S. passive surveillance and some case series (5,13,145); delays in recognition and initiation of appropriate antibacterial treatment in this population might contribute to increased mortality (149). Although older age ( $\geq 60$  years) and immunosuppression are risk factors for severe ehrlichiosis (5,10,13), many cases of severe or fatal ehrlichiosis have been described in previously healthy children and young adults (128). Pediatric patients frequently have an asymptomatic or a mild infection (51,128,132); however, children aged  $<10$  years

FIGURE 27. Immunohistochemical stain demonstrating *Ehrlichia chaffeensis* morulae (red) within monocytes in the kidney of a patient with ehrlichiosis

Photo/CDC

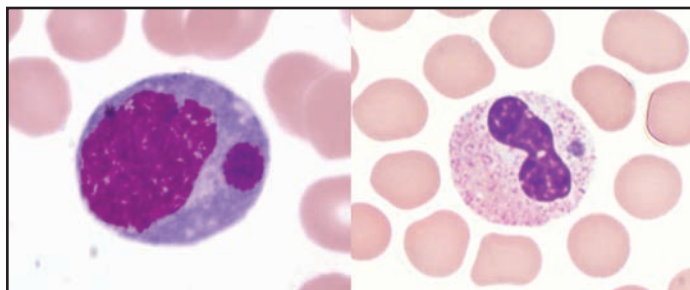
have the highest case-fatality rate among passively reported cases (5,13). Receiving a sulfonamide antimicrobial agent might also predispose to severe ehrlichial illness (150–153). Confirmed reinfection with *E. chaffeensis* has been described in an immunosuppressed patient; however, the frequency of reinfection in immunocompetent persons is unknown (154).

### Laboratory Findings

Characteristic laboratory findings in the first week of *E. chaffeensis* ehrlichiosis include leukopenia (nadir usually 1,300–4,000 cells/ $\mu$ L) (129), thrombocytopenia (nadir usually 50,000–140,000 platelets/ $\mu$ L, although occasionally  $<20,000$  platelets/ $\mu$ L), and mildly or moderately elevated levels of hepatic transaminases. Anemia occurs later in clinical illness and is reported in 50% of patients (129). Mild-to-moderate hyponatremia might also be present (128). During the recovery period, a relative and absolute lymphocytosis is seen in most patients (155). In some cases, pancytopenia due to ehrlichiosis has prompted bone marrow aspirate and biopsy, which typically reveals normocellular or hypercellular marrow (128,156). In some patients, morulae might be observed in monocytes in peripheral blood (157) (Figure 28) and occasionally in CSF (158,159) or bone marrow. In this context, a routine blood smear can provide a presumptive clue for early diagnosis; however, the visualization of morulae still requires confirmatory diagnostic testing (see Confirmatory Diagnostic Tests). When CSF is evaluated, a lymphocytic pleocytosis is most commonly observed, although neutrophilic pleocytosis also can occur (128,135). CSF white blood cell counts are typically



**FIGURE 28.** Wright stain of peripheral blood smears showing an intramonocytic morula associated with *Ehrlichia chaffeensis* infection (left) and an intragranulocytic morula (right), such as associated with *Ehrlichia ewingii* or *Anaplasma phagocytophilum* infection



Photos/J. Stephen Dumler, University of Maryland (left); Bobbi S. Pritt, Mayo Clinic (right)

<250 cells/ $\mu$ L but can be higher in children (128,135,158). Elevated CSF protein levels are common (135).

### *Ehrlichia ewingii* Ehrlichiosis

Clinical manifestations of *E. ewingii* ehrlichiosis are similar to *E. chaffeensis* ehrlichiosis and include fever, headache, malaise, and myalgia. Gastrointestinal symptoms have been described less commonly in *E. ewingii* ehrlichiosis, and rash is rare. Fewer severe manifestations have been reported with *E. ewingii* than with *E. chaffeensis* ehrlichiosis (145), and no deaths have been described. Although *E. ewingii* infection has been considered more common in persons who are immunosuppressed (149), recent passive surveillance data indicated that most (74%) reported cases were not in persons with documented immunosuppression (5). Similar to *E. chaffeensis* ehrlichiosis, patients with *E. ewingii* ehrlichiosis commonly have leukopenia, thrombocytopenia, and elevated hepatic transaminase levels. *E. ewingii* has a predilection for granulocytes, and morulae might be observed in granulocytes during examination of a blood smear, bone marrow, or CSF (48,160) (Figure 28).

### *Ehrlichia muris*-Like Agent Ehrlichiosis

EML agent ehrlichiosis is associated with fever (87%), malaise (76%), headache (67%), and myalgia (60%) (49,61). Rash is reported in 12% of described cases (61). Symptomatic EML agent ehrlichiosis might be more common among persons who are immunosuppressed. No fatal cases have been reported to date. Thrombocytopenia (67%), lymphopenia (53%), leukopenia (39%), elevated levels of hepatic transaminases (78%), and anemia (36%) are described (61). Morulae have not been observed yet in peripheral blood cells of patients infected with the EML agent.

### BOX 4. Summary of clinical features of ehrlichioses

- Symptoms of *Ehrlichia chaffeensis* ehrlichiosis typically include fever, headache, malaise, myalgia, and gastrointestinal symptoms.
- With *E. chaffeensis* ehrlichiosis, rash is present in approximately one third of patients but is more common among children than among adults.
- Neurologic manifestations are reported for approximately 20% of patients with *E. chaffeensis* ehrlichiosis.
- Increased severity of *E. chaffeensis* ehrlichiosis has been associated with increased age ( $\geq 60$  years) and immunosuppression.
- Leukopenia, thrombocytopenia, and elevated hepatic transaminase levels are characteristic laboratory findings in the first week of *E. chaffeensis* ehrlichiosis.
- *E. chaffeensis* has a predilection for mononuclear phagocytic cells, and morulae might be observed in monocytes of the blood, CSF, or bone marrow phagocytes.
- *Ehrlichia ewingii* ehrlichiosis has similar clinical features as *E. chaffeensis* ehrlichiosis; however, rash and gastrointestinal symptoms are less common.
- *E. ewingii* has a predilection for granulocytes, and morulae might be observed in granulocytes of the blood, CSF, or bone marrow.
- Signs and symptoms of EML agent ehrlichiosis are similar to those of *E. ewingii* ehrlichiosis.
- EML agent ehrlichiosis has recently been described, and the target cell type is not known.
- The case-fatality rate for *E. chaffeensis* ehrlichiosis is approximately 3%; no deaths from *E. ewingii* or EML agent ehrlichiosis have been reported.

**Abbreviations:** CSF = cerebrospinal fluid; EML = *Ehrlichia muris*-like.

## Anaplasmosis

### *Anaplasma phagocytophilum* (Human Granulocytic Anaplasmosis)

#### Pathophysiology

*A. phagocytophilum* is an obligate, intracellular bacterium that is found predominantly within granulocytes. Similar to ehrlichiae, anaplasmae multiply in cytoplasmic membrane-bound vacuoles as microcolonies called morulae. Infection with *A. phagocytophilum* induces a systemic inflammatory response, which is thought to be the mechanism for tissue damage in anaplasmosis (161). Altered host neutrophil function occurs with *A. phagocytophilum* infection

and could result in host neutrophils being ineffective at regulating inflammation or microbicidal activity (161).

### Signs and Symptoms

Symptoms of anaplasmosis typically appear 5–14 days after the bite of an infected tick and usually include fever (92%–100%), headache (82%), malaise (97%), myalgia (77%), and shaking chills (129). Rash is present in <10% of patients, and compared with *E. chaffeensis* ehrlichiosis and RMSF, gastrointestinal symptoms are less frequent and central nervous system involvement is rare (129,162). Patients with anaplasmosis typically seek medical care later in the course of illness (4–8 days after onset) than patients with other tickborne rickettsial diseases (2–4 days after onset) (8,163).

### Clinical Course

In most cases, anaplasmosis is a self-limiting illness. Severe or life-threatening manifestations are less frequent with anaplasmosis than with RMSF or *E. chaffeensis* ehrlichiosis; however, ARDS, peripheral neuropathies, DIC-like coagulopathies, hemorrhagic manifestations, rhabdomyolysis, pancreatitis, and acute renal failure have been reported. Severe anaplasmosis can also resemble toxic shock syndrome, TTP (164), or hemophagocytic syndromes (165). Serious and fatal opportunistic viral and fungal infections during the course of anaplasmosis infection have been described (166,167). Although the case-fatality rate among patients who seek health care for anaplasmosis is <1%, approximately 7% of hospitalized patients require admission to the intensive care unit (13,166,168). Predictors of a more severe course of anaplasmosis include advanced patient age, immunosuppression, comorbid medical conditions such as diabetes, and delay in diagnosis and treatment (13,168).

### Laboratory Findings

Characteristic laboratory findings in anaplasmosis include thrombocytopenia, leukopenia, elevated hepatic transaminase levels, increased numbers of immature neutrophils, and mild anemia (169). Similar to ehrlichiosis, lymphocytosis can be present during the recovery period (170). CSF evaluation typically does not reveal any abnormalities (168). Blood smear examination might reveal morulae within granulocytes (Figure 28) (see Confirmatory Diagnostic Tests). Bone marrow is usually normocellular or hypercellular in acute anaplasmosis, and morulae might be observed (161,166,171).

### Coinfections of *Anaplasma* with Other Tickborne Pathogens

The tick vector responsible for *A. phagocytophilum* transmission in the eastern United States, *I. scapularis*, also transmits nonrickettsial pathogens in certain geographic areas, including

*Borrelia burgdorferi*, *Babesia microti*, *Borrelia miyamotoi*, and deer tick virus (Powassan virus, lineage II). Simultaneous infections with *A. phagocytophilum* and *B. burgdorferi* or *B. microti* have occurred (69–71,172). Confirmed *Anaplasma* coinfection has been reported in <10% of patients with Lyme disease (69,70,172).

Response to treatment can provide clues to possible coinfection. For example, anaplasmosis should respond readily to treatment with doxycycline. If the clinical response is delayed, coinfection or an alternative infection might be considered in the appropriate epidemiologic setting (173–175). Conversely, if Lyme disease is treated with a beta-lactam antibacterial drug in a patient with unrecognized *A. phagocytophilum* coinfection, symptoms of anaplasmosis could persist (70,173). Leukopenia or thrombocytopenia in a patient with Lyme disease should raise clinical suspicion for possible coinfection with *A. phagocytophilum* (173).

#### BOX 5. Summary of clinical features of anaplasmosis

- Patients with anaplasmosis typically have fever, headache, and myalgia; rash is rare.
- The case-fatality rate for anaplasmosis is <1%.
- Serious and fatal opportunistic viral and fungal infections have occurred during the course of anaplasmosis.
- Leukopenia, thrombocytopenia, elevated hepatic transaminase levels, and mild anemia are characteristic laboratory findings in anaplasmosis.
- *Anaplasma phagocytophilum* has a predilection for granulocytes, and blood smear or bone marrow examination might reveal morulae within these cells.
- The tick vector that transmits *A. phagocytophilum* also transmits other pathogens, and coinfections with *Borrelia burgdorferi* or *Babesia microti* have been described.

### Differential Diagnosis of Fever and Rash

The differential diagnosis of fever and rash is broad (176,177) (Box 6), and during the early stages of illness, tickborne rickettsial diseases can be clinically indistinguishable from many viral exanthemas and other illnesses, particularly in children. Tickborne rickettsial diseases can be mistaken for viral gastroenteritis, upper respiratory tract infection, pneumonia, urinary tract infection, nonrickettsial bacterial sepsis, TTP, idiopathic vasculitides, or viral or bacterial meningoencephalitides (104,129). Despite nonspecific initial symptoms of tickborne rickettsial diseases (e.g., fever, malaise, and headache), early consideration in the differential diagnosis and empiric treatment is critical in preventing poor outcomes, especially for RMSF, which progresses rapidly without treatment. The dermatologic classification of the rash,

its distribution, pattern of progression, and timing relative to onset of fever, and other systemic signs provide clues to help guide the differential diagnosis. A complete blood count, peripheral blood smear, and routine chemistry and hepatic function panels also can be helpful in guiding the differential diagnosis. Epidemiologic clues (e.g., season, tick bite history, travel, outdoor activities, exposure to pets or other animals, and exposures or risk factors relevant to diagnoses other than tickborne rickettsial diseases) might prove useful. Other life-threatening illnesses that can have signs and symptoms that are similar to those of tickborne rickettsial diseases, such as meningococcemia, are important to recognize, consider in the initial differential diagnosis, and treat empirically pending further diagnostic evaluation.

## Treatment and Management

Doxycycline is the drug of choice for treatment of all tickborne rickettsial diseases in patients of all ages, including children aged <8 years, and should be initiated immediately in persons with signs and symptoms suggestive of rickettsial disease (8,178–180) (Box 7). Diagnostic tests for rickettsial diseases, particularly for RMSF, are usually not helpful in making a timely diagnosis during the initial stages of illness. Treatment decisions for rickettsial pathogens should never be delayed while awaiting laboratory confirmation. Delay in

treatment can lead to severe disease and long-term sequelae or death (74,116,181).

A thorough clinical history, physical examination, and laboratory results (e.g., complete blood count with differential leukocyte count, hepatic transaminase levels, and serum sodium level) collectively guide clinicians in developing a differential diagnosis and treatment plan. Because of the nonspecific signs and symptoms of tickborne rickettsial diseases, early empiric treatment for rickettsial diseases often needs to be administered concomitantly with empiric treatment for other conditions in the differential diagnosis. For example, for a patient in whom meningococcal disease and tickborne rickettsial disease are being considered, administering antibacterial therapy to treat potential *Neisseria meningitidis* infection in addition to administering doxycycline to treat rickettsial agents is appropriate while awaiting additional diagnostic information.

The recommended dose of doxycycline for the treatment of tickborne rickettsial diseases is 100 mg twice daily (orally or intravenously) for adults and 2.2 mg/kg body weight twice daily (orally or intravenously) for children weighing <100 lbs (45 kg) (8) (Table 3). Oral therapy is appropriate for patients with early stage disease who can be treated as outpatients. Intravenous therapy might be indicated for more severely ill patients who require hospitalization, particularly in patients who are vomiting or obtunded. The recommended duration of therapy for RMSF and ehrlichiosis is at least 3 days after subsidence of fever and until evidence of clinical improvement

**BOX 6. Selected conditions other than tickborne rickettsial diseases that can result in acute illness with fever and rash**

<b>Bacterial infections</b>	<b>Viral infections</b>	<b>Other conditions</b>
Meningococcemia*	Hand, foot, and mouth disease*	Drug eruptions*
Secondary syphilis*	Roseola	Kawasaki disease*
Disseminated gonococcal infection*	Measles	Thrombotic thrombocytopenic purpura
Bacterial endocarditis*	Rubella	Immune thrombocytopenic purpura
Scarlet fever	Mononucleosis	Immune complex vasculitis
Rat bite fever*	Acute (primary) HIV infection	Toxic shock syndrome*
Lyme disease	Cytomegalovirus infection	Erythema multiforme*
Relapsing fever	Human parvovirus B19 infection	Stevens-Johnson syndrome*
Leptospirosis	Chickenpox	
Murine typhus	Colorado tick fever	
Rickettsialpox	West Nile virus disease	
Sylvatic and epidemic typhus	Chikungunya virus disease	
Scrub typhus	Dengue fever	
<i>Capnocytophaga canimorsus</i> infection	Zika virus disease	
<i>Mycoplasma pneumoniae</i> infection	Viral hemorrhagic fevers	
Typhoid and paratyphoid fevers		

**Abbreviation:** HIV = human immunodeficiency virus.  
 \* Might cause rash or skin lesions involving the palms of the hands and soles of the feet.



**TABLE 3. Recommended treatment for tickborne rickettsial diseases**

Age category	Drug	Dosage	Maximum	Duration
Adults*	Doxycycline	100 mg twice per day, orally or IV	100 mg per dose	At least 3 days after fever subsides and until evidence of clinical improvement is noted; minimum treatment course of 5–7 days†
Children weighing <100 lbs (45 kg)	Doxycycline	2.2 mg/kg of body weight per dose twice per day, orally or IV	100 mg per dose	

**Source:** CDC, Division of Vector-Borne Diseases. Tickborne diseases of the United States, a reference manual for health care providers. 3rd ed. Atlanta, GA: US Department of Health and Human Services, CDC; 2015. <http://www.cdc.gov/lyme/resources/tickbornediseases.pdf>

**Abbreviation:** IV = intravenously.

\* Guidance is available for the treatment of suspected tickborne rickettsial disease during pregnancy (see Pregnancy and Lactation).

† Treatment for patients with anaplasmosis should be extended to 10 days if concurrent Lyme disease is suspected, or alternatively, another antimicrobial with efficacy against *Borrelia burgdorferi* should be included.

is noted (8,180,182,183); typically the minimum total course of treatment is 5–7 days. Severe or complicated disease could require longer treatment courses. Patients with anaplasmosis should be treated with doxycycline for 10 days to provide appropriate length of therapy for possible coinfection with *B. burgdorferi* (173). Children aged <8 years with anaplasmosis in whom concurrent Lyme disease is not suspected can be treated for a duration similar to that for other tickborne rickettsial diseases (173,183).

Fever typically subsides within 24–48 hours after treatment when the patient receives doxycycline in the first 4–5 days of illness. Lack of a clinical response within 48 hours of early treatment with doxycycline could be an indication that the condition is not a tickborne rickettsial disease, and alternative diagnoses or coinfection should be considered. Severely ill patients might require >48 hours of treatment before clinical improvement is noted, especially if they have multiple organ dysfunction.

Patients with evidence of organ dysfunction, severe thrombocytopenia, mental status changes, or the need for supportive therapy should be hospitalized. Other important considerations for hospitalization include social factors, the likelihood that the patient can and will take oral medications, and existing comorbid conditions, including the patient's immune status. Certain patients with tickborne rickettsial disease can be treated on an outpatient basis with oral medication, particularly if a reliable caregiver is available in the home and the patient adheres to follow-up medical care. A critical step is for clinicians to keep in close contact with patients who are treated as outpatients to ensure that they are responding to therapy as expected. Similarly, if a 24-hour watch-and-wait approach is taken with a febrile patient who otherwise appears well and has no obvious history of tick bite or exposure, a normal physical examination, and laboratory findings within reference ranges, ensuring close patient follow-up is essential. Patients should be monitored closely because of the potential for rapid decline in untreated

patients with tickborne rickettsial diseases, especially among those with RMSF.

Management of severely ill patients with tickborne rickettsial disease should include assessment of fluid and electrolyte balance. Vasopressors and careful fluid management might be needed when the illness is complicated by hypotension or renal failure. Patients with RMSF can develop ARDS or pulmonary infiltrates related to microvascular leakage that might be erroneously attributed to cardiac failure or pneumonia (184). Consultation with an intensive care or infectious disease specialist could be helpful in managing these complications.

## Doxycycline in Children

The American Academy of Pediatrics and CDC recommend doxycycline as the treatment of choice for children of all ages with suspected tickborne rickettsial disease (8,178). Previous concerns about tooth staining in children aged <8 years stem from experience with older tetracycline-class drugs that bind more readily to calcium than newer members of the drug class, such as doxycycline (185). Doxycycline used at the dose and duration recommended for treatment of RMSF in children aged <8 years, even after multiple courses, did not result in tooth staining or enamel hypoplasia in a 2013 retrospective cohort study of 58 children who received doxycycline before the age of 8 years, compared with 213 children who had not received doxycycline (186). These results support the findings of a study published in 2007 reporting no evidence of tooth staining among 31 children with asthma exacerbation who were treated with doxycycline (187). Combined data from these two studies indicate a tooth staining prevalence rate of 0% (none of the 89 patients; 95% confidence interval [CI]: 0%–3%) among those treated with short courses of doxycycline before age 8 (186).

The use of doxycycline to treat children with suspected tickborne rickettsial disease should no longer be a subject of controversy (186–188). Nonetheless, recent surveys of health care providers revealed that most (61%–65%) practicing

primary care providers did not recognize doxycycline as the appropriate treatment for suspected RMSF in children aged <8 years (189–191). During 1999–2012, children aged <10 years were five times more likely than older children and adults to die from RMSF (4,116). A similar finding also has been observed among children aged <5 years with ehrlichiosis (5). These data suggest that inappropriate or delayed RMSF treatment decisions might be contributing to disproportionately high RMSF case-fatality rates among young children.

## Alternative Antibacterial Agents to Doxycycline

Tetracyclines, including doxycycline, are the only antibacterial agents recommended for treatment of all tickborne rickettsial diseases. Chloramphenicol is the only alternative drug that has been used to treat RMSF; however, epidemiologic studies using CDC case report data suggest that patients with RMSF treated with chloramphenicol are at higher risk for death than persons who received a tetracycline (9,75). Chloramphenicol is no longer available in the oral form in the United States, and the intravenous form is not readily available at all institutions. Chloramphenicol is associated with adverse hematologic effects, which have resulted in its limited use in the United States, and monitoring of blood indices is required if this drug is used (192,193). In vitro evidence indicates that chloramphenicol is not effective in the treatment of ehrlichiosis or anaplasmosis (194,195). Therefore, if chloramphenicol is substituted for doxycycline in the empiric treatment of tickborne rickettsial diseases, ehrlichiosis and anaplasmosis will not be covered and RMSF treatment might be suboptimal.

Rifamycins demonstrate in vitro activity against *E. chaffeensis* and *A. phagocytophilum* (194,195). Case reports document favorable maternal and pregnancy outcomes in small numbers of pregnant women treated with rifampin for anaplasmosis (196–198). Small numbers of children also have been treated successfully for anaplasmosis using rifampin (199); however, no clinical trials demonstrating in vivo efficacy of rifampin in the treatment of anaplasmosis or ehrlichiosis have been conducted. Rifampin could be an alternative for the treatment of mild illness due to anaplasmosis in the case of pregnancy or documented allergy to tetracycline-class drugs (173). The dose of rifampin is 300 mg orally twice daily for adults or 10 mg/kg of body weight for children (not to exceed 300 mg/dose) (162,173). Before considering treatment with rifampin, clinicians should use caution and ensure that RMSF can be ruled out because the early signs and symptoms of RMSF and anaplasmosis are similar, and rifampin is not considered an acceptable treatment for RMSF. In addition, rifampin does

not effectively treat potential coinfection of *A. phagocytophilum* with *B. burgdorferi* (173).

Many classes of broad-spectrum antibacterial agents that are used empirically to treat febrile patients, such as beta-lactams, macrolides, aminoglycosides, and sulfonamides, are not effective against tickborne rickettsial diseases (18,77). Although some fluoroquinolones have in vitro activity against rickettsiae (200), their use for treatment of certain rickettsial infections has been associated with delayed subsidence of fever, increased disease severity, and longer hospital stay (201,202). No human efficacy data on fluoroquinolone use in RMSF exist, and fluoroquinolones are not recommended for treatment of RMSF (77). *E. chaffeensis* exhibits in vitro resistance to levofloxacin in vitro (195,203), relapse of infection after treatment with levofloxacin has been reported (204), and, as with the other tickborne rickettsial diseases, fluoroquinolones are not recommended for treatment of anaplasmosis (173).

Sulfonamide antimicrobials are associated with increased severity of tickborne rickettsial diseases. Experimental and accumulated anecdotal clinical data suggest that treatment of patients with RMSF with a sulfonamide drug can result in increased disease severity and death (119,120). Cases of severe ehrlichiosis also have been associated with the use of trimethoprim-sulfamethoxazole (150–153). In some patients treated with sulfonamide or beta-lactam drugs, diagnosis and appropriate treatment of tickborne rickettsial illness was delayed because the development of a rash was mistaken for a drug eruption rather than recognized as a manifestation of rickettsial illness (205).

## Doxycycline Allergy

Severe doxycycline or tetracycline allergy in a patient with a suspected tickborne rickettsial disease poses a challenge because of the lack of equally effective alternative antimicrobial agents. In a patient reporting an allergy to a tetracycline-class drug, determining the type of adverse drug reaction and whether it is potentially life threatening (e.g., anaphylaxis or Stevens-Johnson syndrome) by history or medical documentation is important. Consultation with an allergy and immunology specialist could be helpful in making this determination. In patients with non-life-threatening tetracycline-class drug reactions, administering doxycycline in an observed setting is an option; however, the risks and benefits should be evaluated on a case-by-case basis. In patients with a life-threatening tetracycline allergy, options include use of alternative antibacterial agents discussed in the preceding section or, possibly for immediate hypersensitivity reactions, rapid doxycycline desensitization in consultation with an

allergy and immunology specialist. Anaphylactic reactions to tetracycline-class drugs, although rare, have been reported (206,207). Rapid doxycycline desensitization accomplished within several hours in an inpatient intensive care setting in patients with a history of immediate hypersensitivity reactions (including anaphylaxis) has been described (206,208); however, data are limited to individual case reports.

## Pregnancy and Lactation

Use of tetracycline-class drugs has generally been contraindicated during pregnancy because of concerns about potential risk to the musculoskeletal development of the fetus, cosmetic staining of primary dentition in fetuses exposed during the second or third trimester, and development of acute fatty liver of pregnancy in the mother (209–213). Although these adverse effects were observed in association with the use of tetracycline and older tetracycline derivatives, the contraindication for use during pregnancy has been applied across the class of tetracyclines, which includes newer derivatives, such as doxycycline. Controlled studies to assess the safety of doxycycline use in pregnant women have not been conducted, and available data are primarily observational. An expert review on doxycycline use during pregnancy concluded that therapeutic doses were unlikely to pose a substantial teratogenic risk; however, the data were insufficient to conclude that no risk exists (214,215). The risk for cosmetic staining of the primary teeth by doxycycline could not be determined because of limited data (214). A recent systematic review reported no evidence of teratogenicity associated with doxycycline use during pregnancy; however, limited data and a lack of controlled studies were limitations (216). No reports of maternal hepatic toxicity associated with doxycycline use have been published (215–217). Rarely, fatty liver of pregnancy has occurred in patients who received high-dose intravenous tetracycline (215,218); however, the dosages administered in these cases exceeded what is recommended for the treatment of tickborne rickettsial disease.

Only limited clinical data exist that support the use of antibacterial agents other than doxycycline in the treatment of tickborne rickettsial disease during pregnancy. Doxycycline has been used successfully to treat tickborne rickettsial diseases in several pregnant women without adverse effects to the mother; however, follow-up to address adverse effects to the fetus was limited (142,197). Chloramphenicol is a potential alternative treatment for RMSF during pregnancy; however, care must be used when administering the drug late during the third trimester of pregnancy because of the theoretical risk for gray baby syndrome (193,217).

Chloramphenicol is not an alternative for the treatment of ehrlichiosis or anaplasmosis (194,195). Limited case report data suggest that rifampin could be considered an alternative to doxycycline for the treatment of mild anaplasmosis during pregnancy (173,196,197). Patient counseling and discussion of potential risks versus benefits with the pregnant woman by the health care provider are important components in treatment decision-making during pregnancy; nonetheless, for potentially life-threatening illnesses, such as RMSF and *E. chaffeensis* ehrlichiosis, consideration of disease-related risks for the mother and fetus is of paramount importance.

Doxycycline is excreted into breast milk at low levels; however, the extent of absorption by nursing infants is unknown. Short-term use of doxycycline as recommended for the treatment of tickborne rickettsial disease is considered probably safe during lactation on the basis of available literature and expert opinion (219). Although doxycycline is not specifically addressed, tetracycline is listed by the American Academy of Pediatrics Committee on Drugs as “usually compatible with breastfeeding” (220).

## Preventive Therapy After Tick Bite

Studies of preventive antibacterial therapy for rickettsial infection in humans are limited. Available data (221) do not support prophylactic treatment for rickettsial diseases in persons who have had recent tick bites and are not ill.

## Treatment of Asymptomatic Persons Seropositive for Tickborne Rickettsial Diseases

Treatment of asymptomatic persons seropositive for tickborne rickettsial diseases is not recommended regardless of past treatment status. Antirickettsial antibodies can persist in the absence of clinical disease for months to years after primary infection; therefore, serologic tests cannot be used to monitor response to treatment for tickborne rickettsial diseases (222–224).



**BOX 7. Summary of the treatment and management of tickborne rickettsial diseases**

- Doxycycline is the drug of choice for treatment of all tickborne rickettsial diseases in children and adults; empiric therapy should be initiated promptly in patients with a clinical presentation suggestive of a rickettsial disease.
- Tickborne rickettsial diseases respond rapidly to doxycycline, and fever persisting for >48 hours after initiation of therapy should prompt consideration of an alternative or additional diagnosis, including the possibility of coinfection.
- Doxycycline is recommended by the American Academy of Pediatrics and CDC as the treatment of choice for patients of all ages, including children aged <8 years, with a suspected tickborne rickettsial disease.
- Delay in treatment of tickborne rickettsial diseases can lead to severe disease and death.
- In persons with severe doxycycline allergy or who are pregnant, chloramphenicol may be an alternative treatment for Rocky Mountain spotted fever; however, persons treated with chloramphenicol have a greater risk for death compared with those treated with doxycycline.
- Chloramphenicol is not an acceptable alternative for the treatment of ehrlichiosis or anaplasmosis.
- For mild cases of anaplasmosis, rifampin might be an alternative to doxycycline for patients with a severe drug allergy or who are pregnant.
- Data on the risks of doxycycline use during pregnancy suggest that treatment at the recommended dose and duration for tickborne rickettsial diseases is unlikely to pose a substantial teratogenic risk; however, data are insufficient to state that no risk exists.
- Prophylactic use of doxycycline after a tick bite is not recommended for the prevention of tickborne rickettsial diseases.
- Treatment of asymptomatic persons seropositive for tickborne rickettsial disease is not recommended, regardless of past treatment status, because antibodies can persist for months to years after infection.

## Special Considerations

### Transfusion- and Transplant-Associated Transmission

#### Blood Product Transfusion

Transmission of *R. rickettsii*, *A. phagocytophilum*, and *E. ewingii* via transfusion of infected blood products has

been reported infrequently. *E. chaffeensis*, EML agent, *R. parkeri*, and *Rickettsia* species 364D transmission via infected blood products has not been documented in the United States. Infected donors who are asymptomatic or in the presymptomatic period, defined as the period of rickettsemia before the onset of symptoms, pose the greatest risk to the blood supply (225). For example, in the single documented transfusion-acquired case of *R. rickettsii*, the blood donation occurred 3 days before the onset of symptoms in the donor (226). Potential donors with symptomatic rickettsial disease pose less risk because they are likely to be identified by the routine screening for symptomatic infections that is already in place as part of the blood donation process.

Among tickborne rickettsial diseases, anaplasmosis is the most frequently associated with transfusion-acquired infection, with eight published reports from the United States (198,227–232). Transmission of *A. phagocytophilum* despite leukoreduction of red blood cells and platelets has occurred (227,228,231,232). Transmission of *E. ewingii* infection via leukoreduced, irradiated platelet transfusion also has been reported (233). Although the risk for transmission of certain rickettsial pathogens might be reduced by leukoreduction of blood products (234), the risk for transfusion-acquired infection is not eliminated (227,228,231,233,235). In vitro studies demonstrate that *A. phagocytophilum* and *E. chaffeensis* survive in refrigerated packed erythrocytes for up to 18 and 11 days, respectively (236,237). Transfusion-acquired *R. rickettsii* infection, reported in 1978, was transmitted in whole blood stored for 9 days (226).

Transfusion-associated transmission is of special concern for persons who are immune suppressed, such as those undergoing chemotherapy, solid organ transplantation, or stem cell transplantation; these persons are at greater risk for severe or fatal outcomes from tickborne rickettsial diseases. No practical screening method has been identified to prevent asymptomatic donors infected with tickborne rickettsiae from donating blood products. Suspected transfusion-associated transmission of a rickettsial disease should be reported as early as possible to the blood product supplier and public health authorities. Early reporting is essential in facilitating timely tracking and quarantining of potentially infectious co-components and notification of the infected donor and blood product recipients. In addition, if a recent blood donor develops symptoms of a tickborne rickettsial disease, the blood bank should be notified so that donated blood can be appropriately quarantined or recalled.

#### Solid Organ Transplantation

Two cases of transplant-acquired ehrlichiosis associated with a common deceased donor have been reported (238). Both renal allograft recipients, 20–22 days after transplantation,

developed an acute febrile illness with rapid clinical deterioration characterized by delirium, new or progressive cytopenias, and renal failure. An extensive infectious disease workup in one recipient led to detection by polymerase chain reaction (PCR) amplification of *E. chaffeensis* DNA in peripheral blood. Ehrlichiosis was suspected in the second renal allograft recipient after communication with the care team of the other recipient. Transmission of tickborne rickettsial infections through solid organ transplantation is possible (238) and is important to consider during the assessment of early transplant recipients with undifferentiated febrile illness or sepsis syndromes characterized by thrombocytopenia or leukopenia. In this context, a donor from a region highly endemic for tickborne rickettsial diseases with an appropriate epidemiologic history could support clinical suspicion for a donor-transmitted tickborne rickettsial disease.

### Travel Outside of the United States

International travel can pose a risk for infection with rickettsial pathogens not encountered in the United States (Appendix A). SFG rickettsioses are the most commonly diagnosed tickborne rickettsial diseases among returning travelers (239). The most frequently occurring among these are African tick bite fever, caused by *Rickettsia africae*, and Mediterranean spotted fever (also known as boutonneuse fever), caused by *Rickettsia conorii* (240,241). Approximately 90% of imported SFG rickettsioses occur among travelers returning from sub-Saharan Africa (239,242), and nearly all of these represent African tick bite fever (241,243).

Patients with African tick bite fever typically have fever, headache, myalgia, one or more inoculation eschars, regional lymphadenopathy, and sometimes maculopapular or vesicular rash (241,244). The incubation period is typically 5–7 days but can be up to 10 days after the bite of an infected *Amblyomma hebraeum* or *Amblyomma variegatum* tick (241,244). The course of illness usually is mild. African tick bite fever can occur in clusters among game hunters, safari tourists, deployed troops, and humanitarian workers (243,245,246). Travel for tourism has been identified as a risk factor (239,241), and African tick bite fever is the second most common cause of febrile illness after malaria among travelers returning from sub-Saharan Africa (247,248).

Mediterranean spotted fever is endemic in the Mediterranean basin, Middle East, parts of Africa, and the Indian subcontinent (240). This infection can be severe or fatal; in Portugal, a case-fatality rate of 21% among hospitalized adults has been described (249). Onset of Mediterranean spotted fever typically occurs abruptly with fever, myalgia, headache, eschar (usually singular), and maculopapular or petechial rash

that can involve the palms and soles. Severe manifestations including neurologic, cardiac, and renal complications have been described. The mean incubation period is 6 days (range: 1–16 days) after being bitten by an infected tick (250). *Rh. sanguineus* is the principal tick vector in Europe, Israel, and North Africa. Dogs can serve as reservoir hosts for *R. conorii* (251), and infected *Rh. sanguineus* ticks can transfer from dogs to humans during interactions. Other tick vectors might play a role in transmission in sub-Saharan Africa (250,252). Like other tickborne rickettsial diseases, Mediterranean spotted fever and African tick bite fever respond readily to antibacterial treatment with doxycycline.

Tickborne rickettsial pathogens found in the United States can also be encountered abroad. For example, *R. rickettsii* infection can be acquired in Canada and Mexico, as well as in Central America and South America, where cases are reported from Costa Rica, Panama, Brazil, Colombia, and Argentina (253–260). *R. parkeri* infections have been described in Uruguay, Brazil, and Argentina (38,253,261,262). Human anaplasmosis has been reported from several countries throughout Europe (263), as well as from several Asian countries, including China, Korea, Russia, and Japan (264–267).

### Confirmatory Diagnostic Tests

Several categories of laboratory methods are used to diagnose tickborne rickettsial diseases; these vary in availability, time to obtain results, performance characteristics, and the type of information each provides. Rapid confirmatory assays are rarely available to guide treatment decisions for acutely ill patients; therefore, it is imperative that therapeutic interventions are based on clinical suspicion. Because of the rapidly progressive nature of certain rickettsial diseases, antibacterial treatment should never be delayed while awaiting laboratory confirmation of a rickettsial illness (268), nor should treatment be discontinued solely on the basis of a negative test result on an acute phase specimen. Nonetheless, these laboratory assays provide vital information that validates the accuracy of the clinical diagnosis (268–270) and are crucial for defining the changing epidemiology and public health impact of tickborne rickettsial diseases (3–5).

Determining the most appropriate diagnostic assays to request for suspected tickborne rickettsial illness requires consideration of several factors (Box 8). These include the suspected pathogen, the timing relative to symptom onset, and the type of specimens available for testing (Appendix B) (Table 4). Diagnostic assays should always be ordered and interpreted in the context of a compatible illness

and appropriate epidemiologic setting to obtain optimal positive and negative predictive values (271). Misuse of specialized assays for patients with a low pretest probability of a rickettsial disease can result in confusion. For example, antirickettsial antibodies can remain detectable for months to years after infection (222,223,272,273); however, in the absence of a clinically compatible acute illness, detectable antibodies are not an indication for treatment for tickborne rickettsial disease.

### Serologic Assays

Indirect immunofluorescence antibody (IFA) assays using paired acute and convalescent sera are the reference standard for serologic confirmation of rickettsial infection (269,270). The IFA assay consists of rickettsial antigens fixed on a slide that are detected by specific antibodies in patient serum, which can then be identified by a fluorescein-labeled conjugate. IFA assays for immunoglobulin G (IgG) antibodies reactive against many types of tickborne rickettsial pathogens are commercially available and are the recommended serologic method for confirming tickborne rickettsial disease in the United States (274,275). However, IFA assays are insensitive during the first week of rickettsial infection, which is the period during which most patients seek medical attention and when the majority of specimens are collected for evaluation (268). As the illness progresses past 7 days, the sensitivity of most IFA assays increases in tandem with pathogen-specific antibody production (268). IFA assays are highly sensitive at detecting antibody 2–3 weeks after illness onset, and assay results are best interpreted if serum samples collected in the acute and convalescent phases of illness are tested in tandem (222,276). Clinical observations have suggested that very early therapy with a tetracycline-class drug can sometimes diminish or delay

the development of antibodies in RMSF (277,278); however, this should not dissuade appropriate serologic testing.

For serologic confirmation of SFG rickettsioses, ehrlichioses, or anaplasmosis, IgG IFA testing of at least two serum samples collected, ideally, 2–4 weeks apart, during acute and convalescent phases of illness, is recommended (271,274,275,279). A diagnosis of tickborne rickettsial disease is confirmed with a fourfold or greater increase in antibody titer in samples collected at appropriately timed intervals in patients with a clinically compatible acute illness (274,275). A diagnosis of tickborne rickettsial disease is supported but not confirmed by one or more samples with an IgG antibody reciprocal titer  $\geq 64$  in patients with a clinically compatible acute illness (274,275). A single elevated antibody titer is never sufficient to confirm acute infection with a rickettsial pathogen.

Although the majority of persons have increased IgG titers by the second week of the illness, persons infected with certain *Rickettsia* species might have delayed development of significant antibody titers. For example, patients infected with *R. africae* might not show seroconversion until 4 weeks after illness onset (280). Antigen-specific assays are not available commercially in the United States for *R. africae*; however, commercially available tests that use *R. conorii* or *R. rickettsii* antigens can often be useful diagnostically because of the frequent cross-reactions among the spotted fever group rickettsiae (271). Alternatively, pathogen-specific testing may be submitted to CDC through the state public health laboratories.

The duration that antibodies persist after recovery from the infection varies and depends on the pathogen and host factors. The serologic diagnosis of rickettsioses is often confounded by the occurrence of preexisting antibodies that are reactive with a particular pathogen although unrelated entirely to the disease under investigation (272). In certain persons high titers of antibodies against *A. phagocytophilum* have

TABLE 4. Recommended diagnostic tests for tickborne rickettsial diseases

Disease	PCR			Microscopy for morulae detection	IFA assay for IgG antibodies (acute and convalescent)*
	Whole blood	Eschar biopsy or swab	Rash biopsy		
Rocky Mountain spotted fever	Yes <sup>†</sup>	—	Yes	—	Yes
<i>Rickettsia parkeri</i> rickettsiosis	—	Yes	Yes	—	Yes
<i>Rickettsia</i> species 364D rickettsiosis	—	Yes	—	—	Yes
<i>Ehrlichia chaffeensis</i> ehrlichiosis (human monocytic ehrlichiosis)	Yes	—	—	Yes	Yes
<i>Ehrlichia ewingii</i> ehrlichiosis	Yes	—	—	Yes	Yes
<i>Ehrlichia muris</i> -like agent ehrlichiosis	Yes	—	—	—	Yes
Human anaplasmosis (human granulocytic anaplasmosis)	Yes	—	—	Yes	Yes

**Abbreviations:** IFA = indirect immunofluorescence antibody; IgG = immunoglobulin G; PCR = polymerase chain reaction.

\* IFA assay is insensitive during the first week of illness for most tickborne rickettsial diseases; a sample should be collected during this interval (acute specimen), and a second sample should be collected 2–4 weeks later (convalescent specimen) for comparison. Elevated titers alone are not sufficient to diagnose infection with tickborne rickettsial diseases; serial titers are needed for confirmation. Demonstration of at least a fourfold rise in antibody titer is considered confirmatory evidence of acute infection.

<sup>†</sup> PCR of whole blood samples for *Rickettsia rickettsii* has low sensitivity; sensitivity increases in patients with severe disease.



been observed for over 4 years after the acute illness (223). For *R. rickettsii*, detectable IgG titers can persist for >1 year after primary infection in some patients (222). In the United States, IgG antibodies reactive with antigens of *R. rickettsii* at reciprocal titers  $\geq 64$  can be found in 5%–10% of the population (273,281–283) and might be higher in certain regions. Misinterpretation of serologic data based on single or inappropriately timed samples is problematic and should be avoided, particularly when no other diagnostic techniques are included in patient assessments (279,284).

The majority of commercial reference laboratories that conduct testing for rickettsial pathogens test for IgG antibodies. Some commercial laboratories also perform IFA assays and other serologic testing for IgM antibodies. However, IgM antibodies reactive with *R. rickettsii* are frequently detected in patients for whom no other supportive evidence of a recent rickettsiosis exists (285). IgM antibodies against ehrlichiae and *A. phagocytophilum* also might have lower specificity than IgG antibodies (286,287). In this context, IgM antibody titers should be interpreted carefully and should not be used as a stand-alone method for diagnosis and public health reporting of tickborne rickettsial diseases.

Cross-reactive immune responses to rickettsial antigens result in antibodies that are typically group-specific, although perhaps not species-specific, for tickborne rickettsial pathogens (269). For example, antibodies reactive with *R. rickettsii* detected by a serologic test could result from infection with other SFG rickettsiae (288). Similarly, antibodies reactive with *E. chaffeensis* or *A. phagocytophilum* can react with the other species, which can impede epidemiologic distinction between the infections (286,289). Patients with *E. ewingii* or EML agent infections might develop antibodies that react with *E. chaffeensis* and, less commonly, *A. phagocytophilum* antigens (49,145).

Some rickettsial serologic testing is available in the enzyme-linked immunosorbent assay (ELISA) format. Commercial laboratories might offer ELISA because of the ease in reading and higher throughput. Unfortunately, the currently marketed ELISA kits offer only qualitative results (i.e., antibody presence or absence relative to a threshold value) and do not provide a quantitative method of demonstrating increases or decreases in antibody levels. Confirmation of an acute infection by documenting the rise in antibody titer between the acute and convalescent serum samples is the most useful serologic strategy for evaluating etiology of an acute illness.

## Nucleic Acid Detection

Amplification of species-specific DNA by conventional and real-time PCR assays provides a useful method for detecting tickborne rickettsial infections and identifying the infecting agent (269,270). PCR amplification of DNA extracted from

whole blood specimens collected during the acute stage of illness is particularly useful for confirming *E. chaffeensis*, *A. phagocytophilum*, *E. ewingii*, and EML agent infections because of the tropism of these pathogens for circulating cells. PCR detection of *R. rickettsii* in whole blood is possible but less sensitive because low numbers of rickettsiae typically circulate in the blood in the absence of advanced disease (16,269,290). Tissue specimens are a more useful source of SFG rickettsial DNA than acute blood samples (8). No optimal time frame for blood collection during the acute phase of infection has been established to ensure the highest sensitivity for diagnosing ehrlichioses, anaplasmosis, or RMSF using PCR, and this likely varies among the diseases. Doxycycline treatment decreases the sensitivity of PCR (51,167); therefore, obtaining blood for molecular testing before antibacterial agents are administered is recommended to minimize the likelihood of a false-negative result. PCR tests for tickborne rickettsial diseases are available at CDC, certain state health laboratories, and certain research and commercial laboratories. These tests are laboratory developed, target differing genes, and vary in sensitivity and specificity.

Diagnostic molecular methods for tickborne rickettsial diseases have incorporated new technologies such as real-time PCR assays that offer the advantages of speed, reproducibility, quantitative capability, and reduced risk for contamination compared with conventional PCR assays (291). The acquisition and evaluation of clinical samples previously believed suboptimal for a particular molecular method are now more frequently being considered as important sources of diagnostic information. For example, improved nucleic acid extraction technology has facilitated recovery of rickettsial DNA from some types of formalin-fixed, paraffin-embedded skin biopsies or autopsy tissues to allow species-specific PCR and sequence analysis (292,293). Testing of CSF by PCR assays has successfully identified *E. chaffeensis* (135,159,294). For eschar-producing tickborne rickettsial diseases, including *R. parkeri*, *Rickettsia* species 364D, and *R. africae*, an eschar biopsy, a swab of eschar exudate, or scab material from the eschar surface can provide suitable specimens for molecular confirmation of SFG rickettsial DNA (41,44,292,295).

## Immunostaining of Biopsy or Autopsy Tissue

Another approach to diagnosing tickborne rickettsial diseases is immunostaining, including immunohistochemistry and immunofluorescence of antigens in formalin-fixed, paraffin-embedded biopsy or autopsy tissues (Figure 29). For patients with a rash or eschar, immunohistochemical staining of a skin punch biopsy is a useful diagnostic technique for SFG

rickettsioses (296–298). Immunostaining of skin biopsy specimens is 100% specific and 70% sensitive in diagnosing RMSF (290,299). Sensitivities might be higher for tests using eschars than for those using rash lesions (269) because of the higher concentration of organisms in eschars compared with rash lesions. In cases of ehrlichiosis or anaplasmosis in which bone marrow biopsies are performed as part of the investigation of cytopenias, immunostaining of bone marrow biopsy specimens can reveal the diagnosis (156,160). Immunostaining can be particularly useful for diagnosing fatal tickborne rickettsial diseases in tissue specimens from patients who had not developed diagnostic levels of antibodies before death (16,141,293,300). Immunostaining methods are most likely to reveal organisms in patients before or within the first 48 hours after initiating appropriate antibacterial therapy. Immunostaining for SFG rickettsiae, *E. chaffeensis*, and *A. phagocytophilum* is offered by CDC and certain academic hospitals in the United States.

### Blood-Smear Microscopy

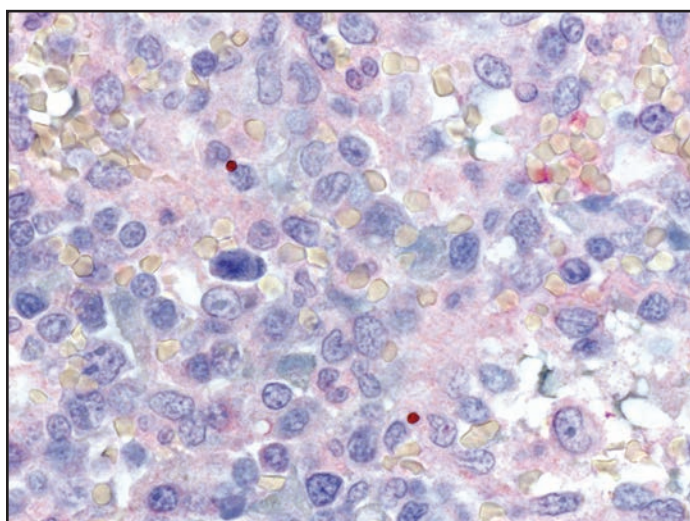
Careful microscopic examination of blood smears or buffy-coat preparations stained with eosin-azure–type dyes (e.g., Wright-Giemsa stains) during the first week of illness might reveal morulae in the cytoplasm of infected circulating leukocytes of patients with *E. chaffeensis* ehrlichiosis (157) or anaplasmosis (166). Observation of morulae is highly suggestive of infection by ehrlichiae or anaplasmae (Figure 28). However, blood-smear examination is a relatively insensitive and inconsistent technique and should be performed by experienced microscopists who must distinguish morulae from other intraleukocytic structures

including overlying platelets, Döhle bodies, phagocytosed bacteria, toxic granulations, and other cytoplasmic inclusions. A concentrated buffy-coat smear might improve the yield of morulae evaluation compared with a standard blood smear (270,301). Blood-smear examination is not useful for diagnosis of RMSF, other SFG rickettsioses, or EML agent infection.

### Culture

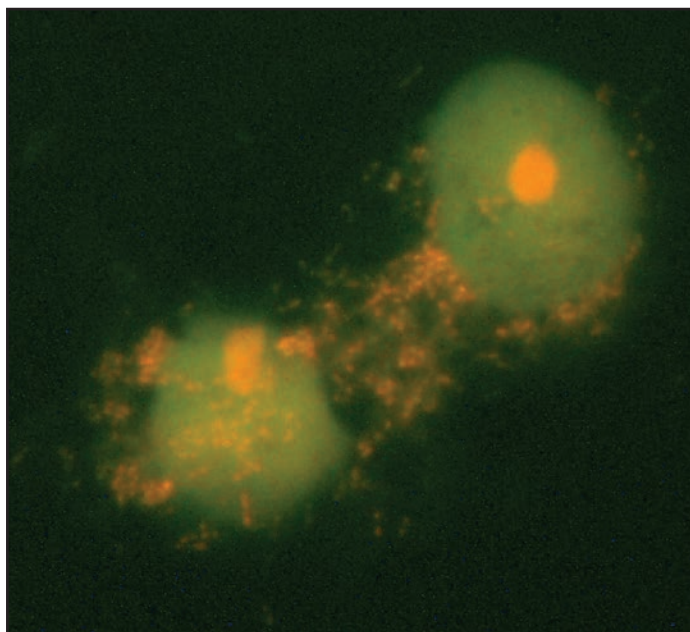
Culture represents the reference standard for microbiological diagnosis (302) (Figure 30); however, the agents that cause tickborne rickettsial diseases are obligate intracellular pathogens and must be isolated from patient samples using cell culture techniques that are not widely available. Depending on the agent and the expertise of the diagnostic laboratory, the sensitivity of detection by culture can be lower than molecular or serologic techniques (303,304). Clinical specimens used to inoculate cell cultures should be collected before the start of appropriate antibacterial therapy and preferably not frozen. Theoretically, any laboratory capable of performing routine viral isolations has the expertise to isolate these pathogens; however, *R. rickettsii* is classified as a biosafety level 3 (BSL-3) agent, and attempts to isolate this agent should be made only in laboratories equipped for and with laboratorians trained to work with BSL-3 pathogens (305).

FIGURE 29. Immunohistochemical stain demonstrating *Anaplasma phagocytophilum* morulae (red) in the spleen of a patient with splenic rupture associated with anaplasmosis



Photo/CDC

FIGURE 30. Acridine orange stain of *Rickettsia africae* isolated in Vero E6 cells from an eschar biopsy specimen from a patient with African tick bite fever



Photo/CDC

**BOX 8. Summary of confirmatory diagnostic tests**

- Antibacterial treatment should never be delayed while awaiting laboratory confirmation of rickettsial illness, nor should treatment be discontinued solely on the basis of a negative test result with an acute phase specimen.
- The reference standard for diagnosis of tickborne rickettsial diseases is the IFA assay using paired serum samples obtained soon after illness onset and 2–4 weeks later. Demonstration of at least a fourfold rise in antibody titer is considered confirmatory evidence of acute infection.
- Patients usually do not have diagnostic serum antibody titers during the first week of illness, and a negative result by IFA assay or ELISA during this period does not exclude the diagnosis of tickborne rickettsial diseases.
- For ehrlichioses and anaplasmosis, diagnosis during the acute stage can be made using PCR amplification of DNA extracted from whole blood.
- PCR assay of whole blood is less sensitive for diagnosis of RMSF than it is for ehrlichiosis or anaplasmosis; however, sensitivity increases in patients with severe disease.
- For SFG rickettsioses, immunostaining of skin rash or eschar biopsy specimens or a PCR assay using DNA extracted from these specimens can help provide a pathogen-specific diagnosis.
- Immunostaining of autopsy specimens can be particularly useful for diagnosing fatal tickborne rickettsial infections.
- Blood-smear or buffy-coat preparation microscopy might reveal the presence of morulae in infected leukocytes, which is highly suggestive of anaplasmosis or ehrlichiosis. Blood-smear microscopy is not useful for RMSF, other SFG rickettsioses, or EML agent ehrlichiosis.
- Rickettsiae cannot be isolated with standard blood culture techniques because they are obligate intracellular pathogens; specialized cell culture methods are required. Because of limitations in availability and facilities, culture is not often used as a routine confirmatory diagnostic method for tickborne rickettsial diseases.

**Abbreviations:** ELISA = enzyme-linked immunosorbent assay; IFA = indirect immunofluorescence antibody; PCR = polymerase chain reaction; RMSF = Rocky Mountain spotted fever; SFG = spotted fever group.

## Prevention of Tickborne Rickettsial Diseases

No vaccine is licensed for the prevention of tickborne rickettsial diseases in the United States. Avoiding tick bites and promptly removing attached ticks remain the best disease prevention strategies. General tick bite prevention strategies include various personal protective measures and behavior change components (Box 9).

### Regular Tick Checks on Humans and Pets

After spending time with tick-infested animals or in tick-infested habitats, persons should inspect themselves, their children, and their pets for ticks. Sites where ticks commonly attach to humans include, but are not limited to, the scalp, abdomen, axillae, and groin, as well as under socks and along the belt line (306). Using a mirror, or having someone assist for hard-to-see areas, might be helpful. Bathing soon after spending recreational time or working in tick-infested habitats also can be an effective method of locating attached or crawling ticks and has been shown to be an important personal protective measure for other tickborne diseases (307). Several hours might elapse before ticks attach and transmit pathogens; therefore, timely tick checks increase the likelihood of finding and removing ticks before they can transmit an infectious agent. Dogs and other pets should be checked routinely for ticks because they can carry ticks back to their home, which increases the risk for human exposure. Ticks on dogs are commonly found around and inside the ears, between the toes, and in the axillae and groin.

The duration of tick attachment necessary to transmit rickettsial organisms varies and has been reported to range from 2 to 20 hours for *R. rickettsii* (308,309). Limited data exist regarding the interval of transmission after tick attachment for *A. phagocytophilum*; however, animal studies indicate that 24–48 hours might elapse before pathogen transmission occurs (310,311). No comparable data exist for *E. chaffeensis*. Removing a tick as soon as possible is critical because longer periods of attachment considerably increase the probability of transmission of tickborne pathogens.

### Use of Repellents and Protective Clothing

Repellents can reduce the risk for tick bites from numerous tick species (312–320). Various repellent products registered with the Environmental Protection Agency (EPA) are available and can be applied to exposed skin and clothing to repel ticks and prevent tick bites. Repellents labeled for use against mosquitoes, fleas, or other arthropods might not be effective tick repellents, and repellency varies by tick species. All commercial products should be used according to the label instructions, and persons should pay particular attention to frequency of application.



*N,N*-diethyl-*m*-toluamide (DEET) effectively repels ticks and can be applied directly to the skin. Products with 20%–30% DEET are considered optimal for protection against most tick species (321), and concentrations >50% do not confer additional protection (320). IR3535 (3-[*N*-Butyl-*N*-acetyl]-aminopropionic acid, ethyl ester) and picaridin (1-piperidinecarboxylic acid, 2-[2-hydroxyethyl], 1-methylpropyl ester) at concentrations >15% can repel as well as DEET when applied to skin (315,322–325) and are considered effective DEET alternatives. Products containing permethrin should be applied to outer clothing (e.g., shirts and pants) and not directly to skin (314). Permethrin-impregnated clothing can reduce tick bites by >80% among outdoor workers (326,327). Repellents, including plant-derived repellents, have a wide range of efficacy, periods of use, and safety (328,329); check listed EPA-registered products for efficacy against ticks (<http://cfpub.epa.gov/oppref/insect>). To help prevent ticks from reaching the skin and attaching, protective clothing should be worn when outdoors, including long-sleeved shirts, pants, socks, and closed-toe shoes (330). Tucking pants into socks and shirt into pants could prevent ticks from crawling inside clothing.

## Protecting Pets from Tick Bites

Various domestic animals are susceptible to tickborne rickettsial diseases and can increase the likelihood of human exposure (1,82,331,332). For example, dogs serve as the primary host for *Rh. sanguineus*, which is known to transmit *R. rickettsii* both to humans and dogs in certain geographic areas. Regular use of pet ectoparasite control products (e.g., monthly topical acaricide products, acaricidal tick collars, oral acaricidal products, and acaricidal shampoos) can help reduce the risk for human exposure to ticks on pets.

## Limiting Exposure to Tick-Infested Habitats

The habitats of humans, pets, and ticks overlap. Understanding the habitats where ticks might be encountered is important for preventing tickborne disease in persons and pets. The preferred habitats of ticks can vary widely on the basis of the biology of the tick and that of their hosts. Ticks have varying abilities to withstand desiccation. *Ixodes* spp. ticks require damper environments, whereas *Rhipicephalus sanguineus* ticks can survive high heat and low humidity. *Dermacentor variabilis* is found along wooded meadows, whereas *Amblyomma americanum* can be in dry woodlands. *Rh. sanguineus* ticks are well adapted for domestic infestation and are commonly found in and around homes (24,26). Certain ticks seek their hosts from grass or other leafy vegetation, whereas others are found in leaf litter or pine needles. Some ticks actively move toward their

hosts, and others lie in wait for their host to pass nearby. The wide diversity of habitats makes avoiding tick-suitable habitats difficult; however, knowing this allows preventive measures to be taken before and after time spent outdoors. Walking on cleared trails, sidestepping vegetation, and creating tick-safe zones in yards can all help reduce the risk for tick bites (333).

## Tick Removal

Attached ticks should be removed immediately. The preferred method of removal is to grasp the tick close to the skin with tweezers or fine-tipped forceps and gently pull back and upward with constant pressure (334). The application of gasoline, kerosene, petroleum jelly, fingernail polish, or lit matches should never be used to remove ticks (334). A wide array of devices has been marketed to help assist in the removal of attached ticks; however, their efficacy has not been proven to exceed that of regular forceps or tweezers. If possible, removing ticks with bare fingers should be avoided because fluids from the tick's body might contain infectious organisms; however, prompt removal of the tick is the primary consideration. Removed ticks should not be crushed with fingers. After removing a tick, the bite area should be cleaned thoroughly with soap and water, alcohol, or an iodine scrub (321). The hands of persons who might have touched the tick also should be thoroughly washed, especially before touching their face or eyes.

### BOX 9. Summary of prevention of tickborne rickettsial diseases

- Perform regular tick checks on persons and pets and remove ticks immediately. Use tweezers or forceps, rather than bare fingers, to remove attached ticks when possible.
- Use tick repellents containing DEET, IR3535, picaridin (1-piperidinecarboxylic acid, 2-[2-hydroxyethyl], 1-methylpropyl ester), or other EPA-registered products when outdoors. Follow package label instructions for application.
- Wear protective clothing, including long-sleeved shirts, pants, socks, and closed-toe shoes.
- Permethrin-treated or impregnated clothing can significantly reduce the number of tick bites when working outdoors.
- Protect pets from tick bites by regularly applying veterinarian-approved ectoparasite control products, such as monthly topical acaricide products, acaricidal tick collars, oral acaricidal products, and acaricidal shampoos.
- Limit exposure to tick-infested habitats and tick-infested animals when possible.

**Abbreviations:** DEET = *N,N*-diethyl-*m*-toluamide; EPA = Environmental Protection Agency; IR3535 = 3-[*N*-Butyl-*N*-acetyl]-aminopropionic acid, ethyl ester.

## Surveillance and Reporting

SFG rickettsioses (including RMSF), ehrlichioses, and anaplasmosis are nationally notifiable diseases in the United States (Box 10). RMSF has been nationally notifiable since 1920 (335) and anaplasmosis and ehrlichiosis since 1999 (336). In 2010, the reporting category of RMSF was changed to spotted fever rickettsiosis to reflect the limitations of serology specificity, which does not readily distinguish RMSF from other SFG rickettsioses (274).

When health care providers identify a potential case of tickborne rickettsial disease, they should notify the state or local health department according to the respective public health jurisdiction's disease reporting requirements. The health department can assist the health care provider in obtaining appropriate laboratory testing to confirm the diagnosis of a tickborne rickettsial disease. Although many state laboratories have systems that automatically report specific diseases on the basis of positive confirmatory diagnostic tests, these vary by state. As part of the standard case identification of tickborne rickettsial diseases, health department staff might contact health care providers and the patient to collect demographic, clinical, laboratory, and exposure information to determine the surveillance case classification. The national surveillance case definitions of notifiable tickborne rickettsial diseases are maintained collaboratively by the Council of

State and Territorial Epidemiologists and the CDC National Notifiable Disease Surveillance System (NNDSS) (Box 10). Surveillance case definitions are used for standardization of national reporting and as a public health surveillance tool but are not intended to supplant clinical diagnoses on which treatment decisions are based.

Surveillance systems are critical for studying the changing epidemiology of tickborne rickettsial diseases and for developing effective prevention strategies and public health outreach activities. CDC collects and analyzes surveillance data on tickborne rickettsial diseases by using two complementary systems. As part of NNDSS, states submit standardized reports electronically, which include diagnosis, date of onset, basic demographics, and geographic data related to the case (Box 10). Data from NNDSS are published by CDC. A supplementary case report form system was designed to capture additional epidemiologic variables, including diagnostic tests used, clinical presentation, and illness outcome. Data in the case report form system is collected by CDC from local and state health departments most often using a standardized supplemental case report form. Data collected on the case report form are useful for guiding public health interventions and for identifying risk factors for hospitalization and death, changing trends in diagnostic test use, and emerging trends.

### BOX 10. Summary of surveillance and reporting for tickborne rickettsial diseases, with surveillance websites

- Spotted fever group rickettsiosis, ehrlichiosis, and anaplasmosis are nationally notifiable diseases in the United States.
- Health care providers who identify a potential case of tickborne rickettsial disease should notify their state or local health department, which can assist with obtaining diagnostic testing to confirm the diagnosis.
- Surveillance and reporting of tickborne rickettsial diseases inform public health practice and guide disease prevention efforts.

**CSTE case definition for spotted fever rickettsiosis:** <http://wwwn.cdc.gov/nndss/conditions/spotted-fever-rickettsiosis>

**CSTE case definition for ehrlichiosis and anaplasmosis:** <http://wwwn.cdc.gov/nndss/conditions/ehrlichiosis-and-anaplasmosis>

**CSTE suggested timelines for reporting:** [http://wwwn.cdc.gov/nndss/document/NNC\\_2014\\_Notification\\_Requirements\\_By\\_Category.pdf](http://wwwn.cdc.gov/nndss/document/NNC_2014_Notification_Requirements_By_Category.pdf)

**Tickborne rickettsial disease case report form:** [http://www.cdc.gov/ticks/forms/2010\\_tbrd\\_crf.pdf](http://www.cdc.gov/ticks/forms/2010_tbrd_crf.pdf)

**Abbreviation:** CSTE = Council of State and Territorial Epidemiologists.

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## Appendix A

### Selected Tickborne Rickettsioses Outside of the United States

Tickborne rickettsial diseases are found worldwide. This appendix highlights some of the more common tickborne rickettsial pathogens typically transmitted outside the United States and known to cause disease in humans.

Disease	Geographic distribution of human cases	Pathogen	Signs and symptoms
African tick bite fever	Sub-Saharan Africa, Caribbean (French West Indies), and Oceania	<i>Rickettsia africae</i>	Fever, headache, myalgia, eschar (sometimes multiple), regional lymphadenopathy, rash (maculopapular or vesicular); typically mild illness with benign course
Mediterranean spotted fever (also known as boutonniere fever)	Europe (Mediterranean basin), Middle East, Indian subcontinent, and Africa	<i>Rickettsia conorii</i>	Fever, headache, myalgia, eschar (usually singular), and rash (maculopapular or petechial, sometimes involving palms and soles); typically moderately severe illness, can be severe or fatal
Queensland tick typhus	Eastern Australia, including Tasmania	<i>Rickettsia australis</i>	Fever, headache, myalgia, eschar, regional lymphadenopathy, and rash (maculopapular or vesicular); typically mild illness, can be severe or fatal
Flinders Island spotted fever	Australia and southeast Asia	<i>Rickettsia honei</i>	Fever, headache, myalgia, eschar (in a minority of patients), and rash; typically mild illness
Japanese spotted fever	Japan and South Korea	<i>Rickettsia japonica</i>	Fever, headache, eschar, and rash; can be severe or fatal
Siberian tick typhus (also known as North Asian tick typhus)	North Asia	<i>Rickettsia sibirica</i>	Fever, eschar, regional lymphadenopathy, and rash (maculopapular); typically mild illness
Lymphangitis associated rickettsiosis*	Southern Europe and Africa	<i>Rickettsia sibirica mongolitimonae</i>	Fever, eschar (single or multiple), regional lymphadenitis, lymphangitis, and rash (maculopapular); typically mild illness, can have severe complications
Tickborne lymphadenopathy (also known as <i>Dermacentor</i> -borne necrosis and lymphadenopathy or scalp eschar and neck lymphadenopathy after tick bite)	Europe	<i>Rickettsia slovaca</i> and <i>Rickettsia raoultii</i>	Eschar (typically on the scalp), painful regional lymphadenopathy, alopecia surrounding eschar, low fever (<50%), rash (rare), and asthenia; typically mild illness with benign course
<i>Rickettsia massiliae</i> spotted fever*	Europe and South America	<i>Rickettsia massiliae</i>	Fever, eschar, and rash; typically mild to moderately severe illness

\* Few human cases are described in the peer-reviewed literature, and the clinical picture and geographic distribution might be incomplete.

## Appendix B

### Diagnostic Assays for Tickborne Rickettsial Diseases

Stage of illness	Specimen	Optimal specimen characteristics	Pathogen	Assay	Test advantages and limitations	
Acute (active signs and symptoms of disease)	Whole blood	<ul style="list-style-type: none"> <li>• EDTA-anticoagulated blood</li> <li>• Preferred volume of 3–5 mL</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Anaplasma</i> and <i>Ehrlichia</i> spp.</li> <li>• SFG rickettsiae</li> </ul>	PCR	<ul style="list-style-type: none"> <li>• Test is most sensitive during the first week of illness and before or within 48 hours of beginning therapy with doxycycline.</li> <li>• Sensitivity diminishes within 1 week after the collection date.</li> </ul>	
				Blood smear	<ul style="list-style-type: none"> <li>• A blood smear can provide a rapid presumptive diagnosis.</li> <li>• Sensitivity is low.</li> <li>• An experienced microscopist is required.</li> </ul>	
				Culture	<ul style="list-style-type: none"> <li>• <i>Anaplasma</i> and <i>Ehrlichia</i> spp.</li> <li>• SFG rickettsiae</li> </ul> <ul style="list-style-type: none"> <li>• Culture is the microbiological reference standard.</li> <li>• Confirmation of diagnosis might require ≥10 days, and propagation requires BSL-3 facilities.</li> <li>• Test is most sensitive during the first week of illness and before beginning therapy with doxycycline.</li> <li>• Availability is restricted to reference centers or research laboratories.</li> </ul>	
	Serum	Preferred volume of 3–5 mL		<ul style="list-style-type: none"> <li>• <i>Anaplasma</i> and <i>Ehrlichia</i> spp.</li> <li>• SFG rickettsiae</li> </ul>	PCR	<ul style="list-style-type: none"> <li>• Molecular assessment of serum is generally less sensitive than evaluation of whole blood.</li> <li>• Serum can be used if whole blood is not available.</li> </ul>
					IFA	<ul style="list-style-type: none"> <li>• Antibodies are often absent during the first week of illness.</li> <li>• Antibodies are usually specific to the genus rather than the species of pathogen.</li> <li>• Confirmation requires a fourfold or greater increase in titer between acute and convalescent serum specimens (see below for convalescent serum).</li> </ul>
	Eschar	Swab of unroofed eschar		SFG rickettsiae	PCR	<ul style="list-style-type: none"> <li>• Swab is less invasive than skin biopsy.</li> <li>• Assessment of swab might be less sensitive than evaluation of eschar biopsy and does not allow for culture or IHC.</li> </ul>
	Fresh tissue	Punch biopsy specimens (≥4 mm) of eschar or rash		SFG rickettsiae	PCR	<ul style="list-style-type: none"> <li>• Eschars contain abundant numbers of SFG rickettsiae relative to blood; when present, they represent the best clinical sample for a specific diagnosis.</li> <li>• Test is most sensitive during the first week of illness and before or within 48 hours of beginning therapy with doxycycline.</li> </ul>
					Culture	<ul style="list-style-type: none"> <li>• Isolation is more effective from tissue than from blood for SFG rickettsiae.</li> <li>• Collect specimen before beginning therapy with doxycycline.</li> <li>• Availability is restricted to reference centers or research laboratories.</li> </ul>
		Autopsy specimens might include representative samples of all major organs		<ul style="list-style-type: none"> <li>• <i>Anaplasma</i> and <i>Ehrlichia</i> spp.</li> <li>• SFG rickettsiae</li> </ul>	PCR	<ul style="list-style-type: none"> <li>• Test is most sensitive during the first week of illness and before or within 48 hours of beginning therapy with doxycycline.</li> </ul>
					Culture	<ul style="list-style-type: none"> <li>• Isolation is more effective from tissue than from blood for SFG rickettsiae.</li> <li>• Isolation is most effective from spleen, lymph node, liver, or bone marrow for <i>Anaplasma</i> and <i>Ehrlichia</i> spp.</li> <li>• Collect specimen before beginning therapy with doxycycline.</li> <li>• Availability is restricted to reference centers or research laboratories.</li> </ul>
IHC					<ul style="list-style-type: none"> <li>• Availability is restricted to reference centers or research laboratories.</li> </ul>	
Formalin-fixed tissue	<ul style="list-style-type: none"> <li>• Biopsy specimens might include skin, bone marrow, or lymph node</li> <li>• Autopsy specimens might include representative samples of all major organs</li> </ul>		<ul style="list-style-type: none"> <li>• <i>Anaplasma</i> and <i>Ehrlichia</i> spp.</li> <li>• SFG rickettsiae</li> </ul>	PCR	<ul style="list-style-type: none"> <li>• Formalin fixation results in cross-linking and fragmentation of DNA, which might limit sensitivity of nucleic acid detection methods.</li> </ul>	
				IHC	<ul style="list-style-type: none"> <li>• Availability is restricted to reference centers or research laboratories.</li> </ul>	
Convalescent (2–4 weeks after resolution of illness)	Serum	Preferred volume of 3–5 mL	<ul style="list-style-type: none"> <li>• <i>Anaplasma</i> and <i>Ehrlichia</i> spp.</li> <li>• SFG rickettsiae</li> </ul>	IFA	<ul style="list-style-type: none"> <li>• Antibodies are usually specific to the genus rather than the species of pathogen.</li> <li>• Confirmation of acute infection requires a fourfold or greater increase in titer between acute and convalescent serum specimens.</li> </ul>	

**Abbreviations:** BSL-3 = biosafety level 3; DNA = deoxyribonucleic acid; EDTA = ethylenediaminetetraacetic acid; IFA = indirect immunofluorescence antibody; IHC = immunohistochemical stain; PCR = polymerase chain reaction; SFG = spotted fever group.





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