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

A Practical Guide for Physicians and Other Health-Care and Public Health Professionals

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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On the cover: First row: *Ixodes scapularis* (blacklegged tick) and *Dermacentor variabilis* (American dog tick). Second row: *Amblyomma americanum* (lone star tick) and *Rhipicephalus sanguineus* (brown dog tick). Photos/CDC.

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

A Practical Guide for Physicians and Other Health-Care and Public Health Professionals

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Summary

Tickborne rickettsial diseases (TBRD) continue to cause severe illness and death in otherwise healthy adults and children, despite the availability of low cost, effective antimicrobial therapy. The greatest challenge to clinicians is the difficult diagnostic dilemma posed by these infections early in their clinical course, when antibiotic therapy is most effective. Early signs and symptoms of these illnesses are notoriously nonspecific or mimic benign viral illnesses, making diagnosis difficult. In October 2004, CDC's Viral and Rickettsial Zoonoses Branch, in consultation with 11 clinical and academic specialists of Rocky Mountain spotted fever, human granulocytotropic anaplasmosis, and human monocytotropic ehrlichiosis, developed guidelines to address the need for a consolidated source for the diagnosis and management of TBRD. The preparers focused on the practical aspects of epidemiology, clinical assessment, treatment, and laboratory diagnosis of TBRD. This report will assist clinicians and other health-care and public health professionals to 1) recognize epidemiologic features and clinical manifestations of TBRD, 2) develop a differential diagnosis that includes and ranks TBRD, 3) understand that the recommendations for doxycycline are the treatment of choice for both adults and children, 4) understand that early empiric antibiotic therapy can prevent severe morbidity and death, and 5) report suspect or confirmed cases of TBRD to local public health authorities to assist them with control measures and public health education efforts.

Introduction

Tickborne rickettsial diseases (TBRD) are clinically similar, yet epidemiologically and etiologically distinct illnesses. In the United States, these diseases include 1) Rocky Mountain spotted fever (RMSF), 2) human monocytotropic (or monocytic) ehrlichiosis (HME), 3) human granulocytotropic (or granulocytic) anaplasmosis (HGA, formerly known as human granulocytotropic ehrlichiosis or HGE) (*1*), 4) *Ehrlichia ewingii* infection, and 5) other emerging TBRD. The reported incidence of these diseases has increased during the previous decade. Despite the availability of low-cost and effective antibiotic therapy, which may be used empirically for suspected cases, TBRD continue to cause severe illness and death in otherwise healthy adults and children. The greatest challenge to clinicians is diagnosing these infections early in their clinical course, when antibiotic therapy is most effective (*2,3*). The majority of patients with TBRD seek medical care within 2–4 days of onset of illness (*4–7*). In general, these patients are first evaluated by family practitioners, pediatricians, internists, emergency department (ED) physicians, or physician extenders. Early signs and symptoms of these illnesses are notoriously nonspecific, or they might mimic benign viral illnesses, making diagnosis difficult. For example, even in areas where awareness of RMSF is high, approximately 60%–75% of patients with this TBRD receive an alternate

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diagnosis on their first visit for medical care (*8*,*9*). Moreover, the earlier patients seek care in the course of their illness, the more likely an alternate diagnosis will be made (*4*). The lack of a specific initial syndrome, however, does not imply that the course of these diseases will be benign.

In October 2004, to address the need for a consolidated resource for the diagnosis and management of TBRD, CDC's Viral and Rickettsial Zoonoses Branch collaborated with 11 clinical and academic specialists of RMSF, HGA, and HME. These external contributors were invited by CDC subject matter specialists to participate among clinicians and researchers in the field of TBRD, based on direct working interactions related to case consultation and recognized expertise from peer-reviewed publications. In December 2004, the framework of this report was developed by CDC's Viral and Rickettsial Zoonoses Branch, based on a summary of the peer-reviewed published reports on the epidemiology and clinical aspects of TBRD. External contributors further developed recommendations for the diagnosis and treatment of TBRD based on their clinical research and experience. All work group collaborators reviewed and provided input and approved the final content of this report.

The primary goal of this report is to provide primary care physicians and physician extenders with practical information to assist with the diagnosis and care of patients with TBRD. This report provides a framework for recognizing suggestive symptoms, considering likely alternative diagnoses, eliciting relevant history, requesting appropriate diagnostic tests, and initiating prompt, effective treatment. Information in this guide is designed to assist clinicians to

- recognize common epidemiologic situations and clinical manifestations of TBRD;
- obtain appropriate history and diagnostic tests for TBRD;
- develop a differential diagnosis that includes and ranks TBRD;
- make treatment decisions based on epidemiologic and clinical evidence;
- recognize that doxycycline is the treatment of choice for both adults and children;
- recognize that early and empiric antibiotic therapy can prevent severe morbidity or death;
- identify the availability, limitations, and utility of confirmatory laboratory assays;
- recognize potential severe manifestations of TBRD; and
- report suspected and confirmed cases to appropriate public health authorities to assist with control measures and public health education efforts.

This report also provides resources on TBRD for healthcare and public health professionals. Clinical cases are included for self-evaluation and to reinforce the information presented in this guide. Additional information concerning TBRD in this report is available from medical specialists, various medical societies, CDC, and state and local health authorities.

Epidemiology of TBRD

RMSF, HME, and HGA are tickborne zoonoses caused by *Rickettsia rickettsii*, *Ehrlichia chaffeensis*, and *Anaplasma phagocytophilum*, respectively. These pathogens are maintained in natural cycles involving wild mammals and hard-bodied (ixodid) ticks. The epidemiologies of these diseases reflect the geographic distribution and seasonal activities of the vectors and reservoirs and the human behaviors that place persons at risk for tick attachment and subsequent infection. Selected epidemiologic and clinical features of TBRD have been summarized (Table 1). RMSF, HME, and HGA are reported each month of the year in the United States, although 90%–93% of reported cases occur during April–September (*6*,*10*–*12*), coincident with peak levels of tick feeding activity on humans. Travelers outside of the United States might also be exposed to other tick vectors in other countries that transmit related agents that result in disease after they return to the United States.

Males appear to be at higher risk for infection with all TBRD, possibly because of greater recreational or occupational exposures to tick habitats. Although previous studies have indicated that the highest incidences of RMSF have occurred in children aged <10 years, surveillance during 2003 demonstrates a higher age-specific incidence for RMSF among persons aged 40–64 years, compared with other age groups (*13*). For HME and HGA, the highest age-specific incidences occurred among persons aged ≥70 and 60–69 years, respectively (*14*). The higher frequency of disease reporting in adults might reflect greater susceptibility to recognizable disease rather than higher infection rates. Two recent cross-sectional studies in the southeastern and south central United States* have indicated that

* Mountain: Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada. East South Central: Kentucky, Tennessee, Alabama, Mississippi. East North Central: Ohio, Indiana, Illinois, Michigan, Wisconsin. West South Central: Arkansas, Louisiana, Oklahoma, Texas. West North Central: Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, Kansas. Pacific: Washington, Oregon, California. New England: Massachusetts, Connecticut, Rhode Island, New Hampshire. South Atlantic: Delaware, Maryland, Virginia, District of Columbia, West Virginia, North Carolina, South Carolina, Georgia, Florida. Mid-Atlantic: New York, New Jersey, Pennsylvania.

TABLE 1. Selected features of Rocky Mountain spotted fever,* human monocytotropic ehrlichiosis, human granulocytotropic anaplasmosis,† and *Ehrlichia ewingii* infection — United States§

Agent (disease)	Primary vector(s)	Approximate distribution¶	Incubation period (days)	Common initial signs and symptoms	Common laboratory abnormalities	Rash	Case-fatality rate
Rickettsia rickettsii (Rocky Mountain spotted fever)	*Dermacentor variabilis* (American dog tick), *Dermacentor andersoni* (Rocky Mountain wood tick), and *Rhipicephalus sanguineus* (brown dog tick) in AZ**	Widespread in the United States, especially South Atlantic and South Central states	2–14	Fever, nausea, vomiting, myalgia, anorexia, and headache	Thrombocytopenia, mild hyponatremia, and mildly elevated hepatic transaminase levels	Maculopapular rash approximately 2–4 days after fever onset in 50%–80% of adults (>90% in children); might involve palms and soles	5%–10%
Ehrlichia chaffeensis (human monocytotropic ehrlichiosis)	*Amblyomma americanum* (lone star tick)	South and Mid-Atlantic, North/South Central United States, and isolated areas of New England	5–14	Fever, headache, malaise, and myalgia	Leukopenia, thromobocytopenia, and elevated serum transaminase levels	Rash in <30% of adults and approximately 60% of children	2%–3%
Anaplasma phagocytophilum (human granulocytotropic anaplasmosis)	*Ixodes scapularis* and *Ixodes pacificus* (blacklegged tick) in the United States	New England, North Central and Pacific states	5–21	Fever, headache, malaise, myalgia, and vomiting	Leukopenia, thrombocytopenia, elevated serum transaminase levels	Rare	<1%
Ehrlichia ewingii infection	*Amblyomma americanum* (lone star tick)	South Atlantic and South Central United States to isolated areas of New England	5–14	Fever, headache, myalgia, nausea, and vomiting	Leukopenia, thromobocytopenia, and elevated serum transaminase levels	Rare	No documented fatalities

* **SOURCE:** Walker DH, Raoult D. *Rickettsia rickettsii* and other spotted fever group rickettsiae (Rocky Mountain spotted fever and other spotted fevers). In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:2287–95.

† **SOURCE:** Walker DH, Dumler JS. *Ehrlichia chaffeensis* (human monocytotropic ehrlichiosis), *Anaplasma phagocytophilum* (human granulocytotropic anaplasmosis) and other ehrlichiae. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:2310–8.

§ Treatment for each of these diseases is the same: adults, doxycycline 100 mg orally (PO) or intravenously (IV) twice daily; and children, doxycycline 2.2 mg/kg administered PO or IV twice daily.

¶ *Mountain:* Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada. *East South Central:* Kentucky, Tennessee, Alabama, Mississippi. *East North Central:* Ohio, Indiana, Illinois, Michigan, Wisconsin. *West South Central:* Arkansas, Louisiana, Oklahoma, Texas. *West North Central:* Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, Kansas. *Pacific:* Washington, Oregon, California. *New England:* Massachusetts, Connecticut, Rhode Island, New Hampshire. *South Atlantic:* Delaware, Maryland, Virginia, District of Columbia, West Virginia, North Carolina, South Carolina, Georgia, Florida. *Mid-Atlantic:* New York, New Jersey, Pennsylvania.

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

up to 22% of children have serologic evidence of previous exposure to antigens of both *E. chaffeensis* (*15*) and *R. rickettsii* (*16*), suggesting that rickettsial and ehrlichial infection might be more common than previously recognized.

RMSF

In the United States, *R. rickettsii* is transmitted to humans by several tick species. However, the species that transmit *R. rickettsii* most frequently include the American dog tick (*Dermacentor variabilis*; Figure 1) in the eastern, central, and Pacific coastal United States and the Rocky Mountain wood tick (*Dermacentor andersoni*; Figure 2) in the western United States. In 2005, the brown dog tick (*Rhipicephalus sanguineus*; Figure 3), a vector of RMSF in Mexico (*17*), was implicated as a vector of this disease in a confined geographic area in Arizona (*18*). The cayenne tick (*Amblyomma cajennense*; Figure 4) is a common vector for RMSF in Central and South America, and its range extends into the United States in Texas (*19*). During 1997–2002, the estimated average annual incidence of RMSF, based on passive surveillance, was 2.2 cases per million

FIGURE 1. An adult female *Dermacentor variabilis* (American dog tick)

Photo/CDC

persons. More than half (56%) of reported cases of RMSF were from only five states: North Carolina, South Carolina, Tennessee, Oklahoma, and Arkansas (CDC, unpublished data, 2005). However, cases have been reported from each of the contiguous 48 states, except Vermont and Maine (*10,11*). Average reported annual incidence of RMSF per 1 million population, based on cases reported to CDC during 1997–2002, has been reported (Figure 5). Incidence varies considerably by geographic area. RMSF is also

FIGURE 2. An adult female *Dermacentor andersoni* (Rocky Mountain wood tick)

Photo/CDC

FIGURE 3. An adult female *Rhipicephalus sanguineus* (brown dog tick)

Photo/CDC

FIGURE 4. An adult male (left) and female (right) *Amblyomma cajennense* (cayenne ticks)

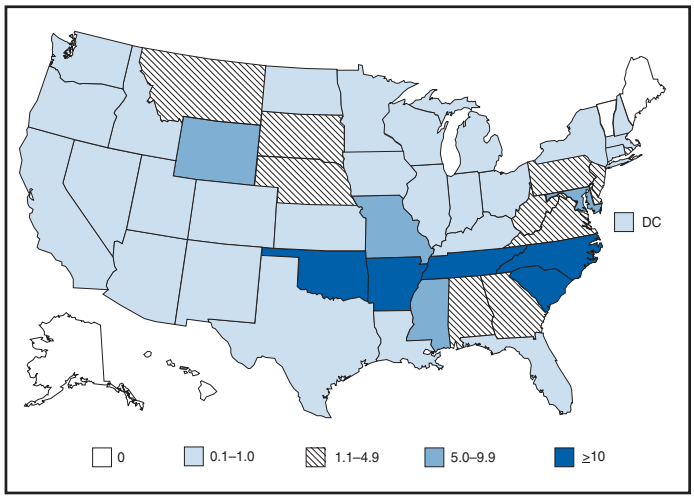
Photo/J. Occi, Forestry Images, Athens, GA

endemic throughout several countries in Central and South America, including Argentina, Brazil, Columbia, Costa Rica, Mexico, and Panama (*17,19,20*). Household clusters of disease and hyperendemic foci of infected ticks have been reported (*3,21*). Dogs are susceptible to RMSF, and they might frequently develop the disease concurrently with other household members in an endemic focus (*22,23*).

HME

E. chaffeensis is transmitted to humans by the lone star tick, *A. americanum* (Figure 6), and possibly other ticks. The white-tailed deer is a major host of all stages of lone star ticks and is an important natural reservoir for *E. chaffeensis.* Natural infections of coyotes, dogs, and goats

FIGURE 5. Average reported annual incidence* of Rocky Mountain spotted fever, by state — United States, 1997–2002



* Per 1,000,000 persons per year.

FIGURE 6. An adult female *Amblyomma americanum* (lone star tick)

Photo/CDC

have been documented. The lone star tick is among the most commonly encountered ticks in the southeastern United States, with range extensions into areas of the South Central and New England states (Figure 7). Cases of HME are most commonly reported to CDC from Missouri, Oklahoma, Tennessee, Arkansas, and Maryland, although the disease is found throughout the range of the lone star tick. The average reported annual incidence of HME was 0.7 cases per million population, but incidence varied by state, based on cases reported to CDC from 2001 to 2002 (Figure 8). In a prospective study among febrile patients with a history of a recent tick bite in central North Carolina, the incidence of ehrlichial infection was approximately twice that of RMSF (*24*). The reported incidence probably represents an underestimate of the true burden of disease in areas where *E. chaffeensis* is endemic (*24,25*). Clusters of HME have been reported, suggesting that foci of ticks infected with *E. chaffeensis* do occur (*21,26*).

FIGURE 7. Approximate distribution of vector tick species for human monocytotropic ehrlichiosis and human granulocytotropic anaplasmosis

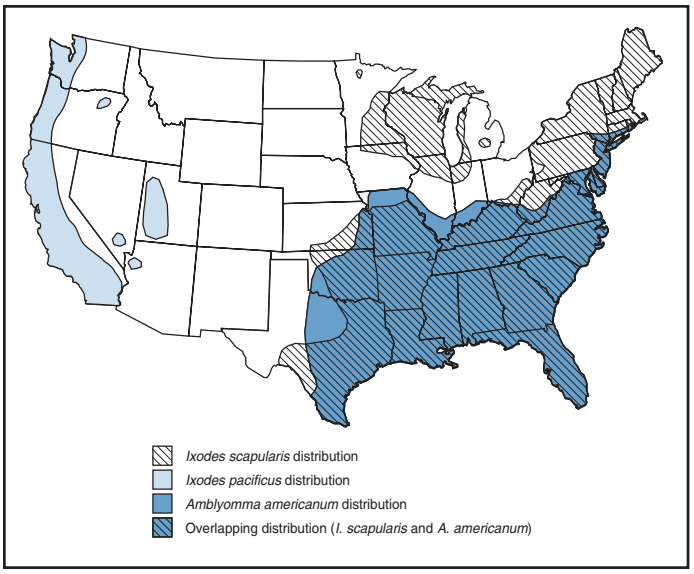
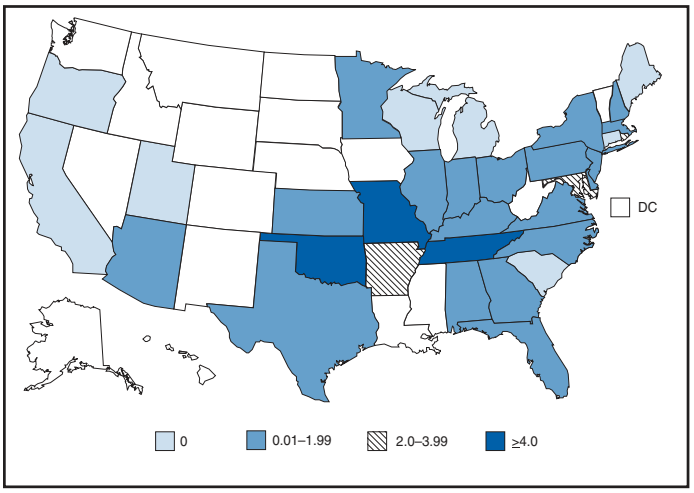


FIGURE 8. Average reported annual incidence* of human monocytotropic ehrlichiosis, by state — United States, 2001–2002†



SOURCE: Demma LJ, Holman RC, McQuiston JH, Krebs JW, Swerdlow DL. Epidemiology of human ehrlichiosis and anaplasmosis in the United States, 2001–2002. Am J Trop Med Hyg 2005;73:400–9.
* Per 1,000,000 persons per year.
† Nonreporting states do not have a value and appear white.

HGA

The blacklegged tick (*Ixodes scapularis;* Figure 9) is the vector of *A. phagocytophilum* in New England and North Central United States, whereas the western blacklegged tick (*Ixodes pacificus;* Figure 10) is the principal vector in northern California. Deer, elk, and wild rodents are thought to be reservoirs. HGA is more frequently reported than HME, resulting

FIGURE 9. An adult female *Ixodes scapularis* (blacklegged tick)

Photo/CDC

FIGURE 10. An adult female *Ixodes pacificus* (western blacklegged tick)

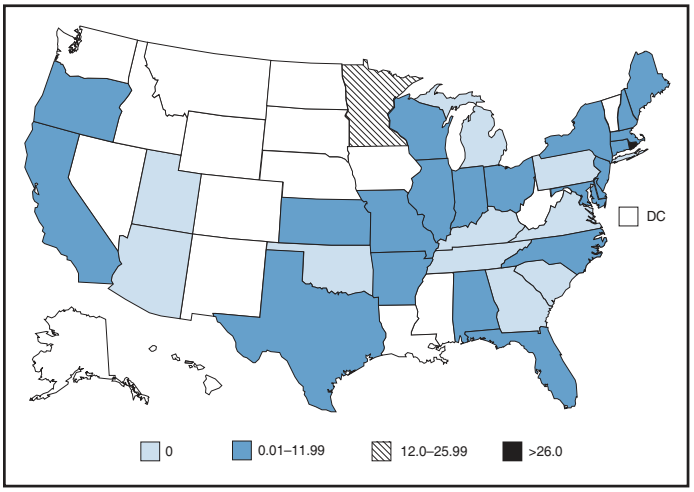
Photo/CDC

in an average reported annual incidence of 1.6 cases per million during 2001–2002. States that reported the highest incidence during this period were Rhode Island (36.5 cases per million), Minnesota (12.3 cases per million), Connecticut (8.1 cases per million), New York (2.3 cases per million), and Maryland (1.6 cases per million) (Figure 11). HGA has been identified as a substantial cause of unexplained fever during the tick season in Wisconsin (*27*). Evidence suggests that the incidence of HGA in Wisconsin might be much higher than that in Minnesota (*7*). Because these *Ixodes* species ticks also transmit *Borrelia burgdorferi* (the causative agent of Lyme disease) and various *Babesia* species (agents of human babesiosis), the preponderance of cases of HGA occur in the same states that report high incidences of Lyme disease and human babesiosis. Simultaneous infection with *A. phagocytophilum* and *B. burgdorferi* has been reported (*28*), and discerning such a mixed infection is vital because it might affect antimicrobial choice. For example, amoxicillin can be used to treat early stage Lyme disease, but it is not effective for HGA.

Ehrlichia ewingii Infection

Amblyomma americanum also is the principal vector of the ehrlichial pathogen, *E. ewingii*. The ecologic features of

FIGURE 11. Average reported annual incidence* of human granulocytotropic anaplasmosis, by state — United States, 2001–2002†



Adapted from: Demma LJ, Holman RC, McQuiston JH, Krebs JW, Swerdlow. Epidemiology of human ehrlichiosis and anaplasmosis in the United States, 2001–2002. Am J Trop Med Hyg 2005;73:400–9.
*Per 1,000,000 persons per year.
†Nonreporting states do not have a value and appear white.

E. ewingii are not completely known; however, dogs and deer have been naturally infected. Cases of granulocytotropic ehrlichiosis caused by *E. ewingii* have been reported primarily in immunocompromised patients from Missouri, Oklahoma, and Tennessee (*29,30*). *E. ewingii* infections in dogs or ticks also have been described in these states and in Arkansas, Texas, Florida, Georgia, Mississippi, North Carolina, and Virginia, suggesting that human infections with this pathogen might be expected to occur throughout the range of the lone star tick (*31,32*).

The following is a summary of the salient epidemiologic features of TBRD:

- Occurrence is seasonal, with the majority of illness onset during warmer spring and summer months, but cases might develop throughout the year.
- RMSF has been reported in all of the contiguous 48 states, except Vermont and Maine.
- RMSF and HME are most commonly reported in the southeastern and south central United States.
- HGA is reported most frequently in New England, the north central states, and in focal areas along the West Coast.

Pathogen Tropisms and Clinical Presentation

R. rickettsii, *E. chaffeensis*, *E. ewingii*, and *A. phagocytophilum* have specific and distinct cell tropisms. *R. rickettsii* infects endothelial cells and more rarely infects underlying smooth muscle cells, where rickettsiae multiply freely in the cytoplasm. The rickettsiae cause a small-vessel vasculitis, resulting in a maculopapular or petechial rash in the majority of patients. Vasculitis occurring in organs (e.g., the brain or lungs) can result in life-threatening complications. *R. rickettsii* does not stain with the majority of routine histopathologic stains and is not detected by blood smear evaluation because of limited numbers of circulating bacteria. Ehrlichioses and anaplasmosis are characterized by infection of leukocytes, where the causative agents multiply in cytoplasmic membrane-bound vacuoles as microcolonies called morulae. *E. chaffeensis* most frequently infects monocytes, whereas *A. phagocytophilum* and *E. ewingii* demonstrate a predilection for granulocytes. Morulae may be stained with conventional Wright or Giemsa stains and are occasionally observed in leukocytes in smears of peripheral blood, buffy coat preparations, or cerebrospinal fluid. In this context, a routine blood smear can provide a presumptive clue for early diagnosis; however, the visualization of morulae still requires confirmatory testing for *Ehrlichia* or *Anaplasma* species by serology, polymerase chain reaction (PCR), or immunostaining methods (*33*). The demonstration of morulae is also not sensitive, and a case of ehrlichiosis or anaplasmosis might be missed if the diagnosis relies solely on detection of morulae on blood smears. Although the diagnostic sensitivity of a blood smear is greater for HGA than for HME, blood smears might only be positive in up to 60% of patients with HGA (*34*).

The following is a summary of salient features of pathogen tropisms:

- *R. rickettsii* infects endothelial cells, causing vasculitis, which leads to rash and life-threatening damage to the brain, lungs, and other viscera.
- *R. rickettsii* is not evident in blood smears, and these bacteria and do not stain with the majority of conventional stains.
- *Ehrlichia* and *Anaplasma* species infect monocytes or granulocytes, respectively, and morulae might occasionally be observed on peripheral blood smears by using routine stains.

Clues from the Clinical History

A thorough clinical history that elicits recent tick exposure, specific recreational or occupational exposures to tick-infested habitats, recent travel to areas where TBRD might be endemic, or similar illnesses in family members, coworkers, or pet dogs can provide critical information that can be used to make a presumptive diagnosis of TBRD and help guide subsequent therapeutic actions. However, the absence of certain features does not exclude a diagnosis of TBRD.

These features include 1) history of tick bite or exposure, 2) recent travel to areas endemic for TBRD, and 3) similar illness in family members, coworkers, or pets.

History of Tick Bite or Exposure

A detailed medical history might reveal activities that suggest potential exposure to ticks. Outdoor activities during April–September, particularly in areas with high uncut grass, weeds, and low brush can increase the risk for tick bites (*35*). These activities include recreational pursuits (e.g., camping, hiking, fishing, hunting, gardening, and walking dogs) as well as occupational activities that involve persons being in brushy or grassy areas that might be inhabited by ticks. Vegetation that borders roads, trails, yards, or fields also are potential areas that might be inhabited by ticks. In endemic areas (where the agents causing TBRD are present at all times), even adults or children who play in grassy areas in their backyard are at risk. Queries concerning frequency of contact with family pets, especially dogs, and findings of tick attachment to animals or removal can be useful. The majority of patients will not recall or recognize an attached tick because the location of the tick might be obscure; the bite is typically painless; and bites from smaller immature stages of ticks (e.g., nymphs are approximately 1–2 mm or the size of the head of a pin; Figure 12) might not be readily detected but might still result in infection. A specific history of a tick bite within 14 days of illness onset is typically only reported in 60% of RMSF cases (*10,11*) and has been reported in only 68% of ehrlichiosis cases (*6*). Therefore, the absence of definite tick attachment should never dissuade a physician from considering the diagnosis of a TBRD. Finally, certain patients do not specifically recall tick exposure but might describe other pruritic, erythematous, or ulcerated cutaneous lesions that they call a mosquito bite, spider bite, chigger bite, or bug bite, which can be indistinguishable from an actual tick bite.

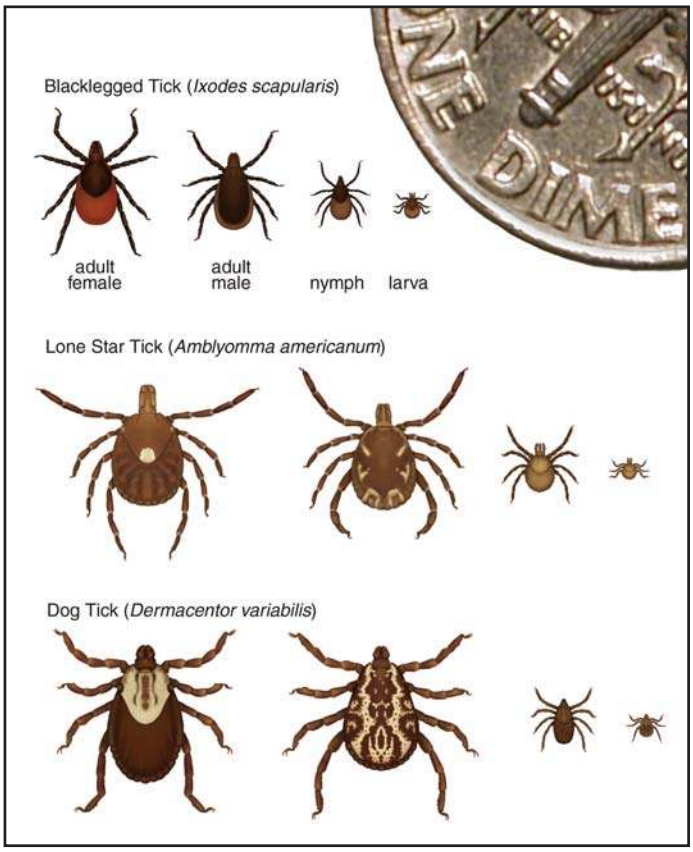
Recent Travel to Areas Endemic for TBRD

Clinicians in areas of the United States where the incidence of TBRD is historically low are typically at a disadvantage in distinguishing these diseases among multiple other infectious and noninfectious syndromes that they resemble. Because TBRD are typically sporadic, identifying these infections requires high clinical acumen, especially in an environment in which TBRD have not previously been recognized as occurring frequently.

Knowledge of the epidemiology of these illnesses, including regions of the country with a high incidence (number of reported cases per million persons per year) of TBRD (e.g., south Atlantic, north central, and south central and New England states), is important. A history of recent travel from an endemic area of TBRD (e.g., within 2 weeks preceding illness), especially if the patient had participated in an outdoor activity, might support a suspicion of tickborne illness. Physicians should also consider the possibility that changes in tick vector range can influence the distribution of TBRD. In addition, in 2004, a total of 13 cases of RMSF occurred in eastern Arizona, a state in which the disease was previously rarely diagnosed (*18*).

Clinicians should also consider that TBRD occur worldwide and might have epidemiologic, seasonal, and clinical features distinct from those observed in the United States. International travel to destinations (e.g., southern Mediterranean, Central and South America, Africa, Asia, and the Middle East) might result in tick vector exposure, particularly if the patient participated in rural or outdoor activities. For example, African tick-bite fever (ATBF), an increasingly reported travel-related rickettsiosis caused by

FIGURE 12. Comparison of *Ixodes scapularis* (blacklegged tick), *Amblyomma americanum* (lone star tick), and *Dermacentor variabilis* (American dog tick), by life stage*



Photo/CDC
* Ticks are shown in relative size to each other and to a dime.

R. africae, has an estimated incidence of 4%–5.3% among international travelers to sub-Saharan Africa and has been identified in clusters of infection among group travelers (e.g., game hunters, safari tourists [*36*], and humanitarian workers; *37*). A related rickettsial organism, *R. conorii*, endemic in the Mediterranean basin, Middle East, and parts of Africa and the Indian subcontinent causes Mediterranean spotted fever (MSF; *38*). ATBF and MSF are characterized by fever, malaise, headache, and myalgia, which are typical symptoms for other TBRD. However, a distinguishing clinical feature of both travel-related diseases is the development of one or more eschars (a dark, scab-like plaque overlying a shallow ulcer with surrounding erythema or scaling) at the site of tick attachment that is noted coincident with or shortly after the onset of fever in 30%–50% of patients (*36,39*).

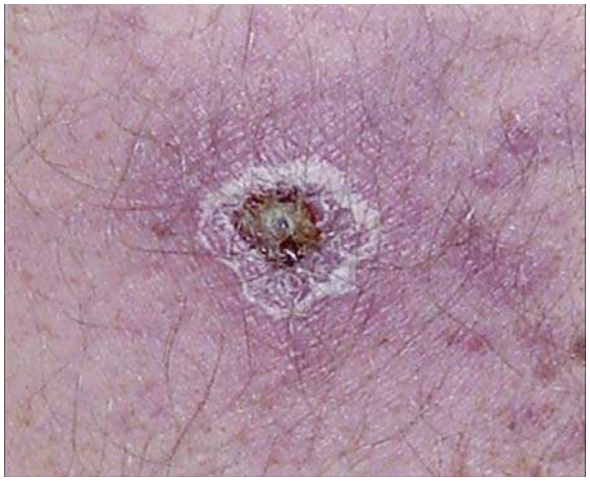
Emerging TBRD

Similarly, considering TBRD as a diagnosis is essential because of new, previously unrecognized rickettsial pathogens that have been observed in tick vectors in the United States. For example, in 2002, *R. parkeri* was identified as a new cause of spotted fever rickettsiosis in a patient living in the southeastern coastal United States (*40*). This agent is present in *A. maculatum* (the Gulf Coast tick; Figure 13), which is found in the southeastern United States. A clinical presentation, similar to ATBF and MSF (i.e., fever, headache, eschars, and regional lymphadenopathy), was observed in a patient with no substantial travel history (Figure 14). The diagnosis of spotted fever rickettsiosis was confirmed by using rickettsial culture from an eschar skin biopsy and serologic and molecular methods (*40*). Other spotted fever group rickettsiae might also cause mild febrile illness in certain persons exposed to ticks in highly endemic areas (*41*). The common observation of antibodies to rickettsiae and ehrlichiae in persons and dogs might indicate exposure to other rickettsial agents of varying pathogenicity (*15,16,24*).

FIGURE 13. An adult female *Amblyomma maculatum* (Gulf Coast tick)

Photo/CDC

FIGURE 14. Eschar associated with *Rickettsia parkeri* infection



Photo/C.A. Ohl, Wake Forest University School of Medicine, Winston-Salem, NC

Similar Illness in Family Members, Coworkers, or Pets

Clinicians might be inclined to offer diagnoses of a communicable viral infection when more than one family member is affected by an illness. However, clustering of certain TBRD is a well-recognized epidemiologic phenomenon and might occur after exposure to natural foci of infected ticks. Temporally and geographically related clusters occurring among family members, coworkers, or persons frequenting a particular common area have been observed. These clusters include family clusters of RMSF (*3*), clusters of ehrlichiosis among residents of a golfing community (*26*), and soldiers on field maneuvers (*21*). Common exposures to tick-infested habitats or outdoor activities might place certain or all members of a family or group, including pet dogs, at risk for TBRD. Concurrent infections with *R. rickettsii* and *Ehrlichia* species also have been observed in humans and dogs (*22,24,29*). Therefore, clinicians should query patients concerning similar illnesses among family members, close coworkers, or community residents, and even among household dogs.

The following is a summary of salient features of clues from the clinical history:

- A detailed history of recent recreational or occupational activities might reveal potential exposure to ticks.
- Exposure can occur in the patient's backyard or neighborhood.

- Familiarity with TBRD epidemiology will be helpful when querying patients regarding recent travel to endemic areas (domestic and international; *38,39*).
- Clustering of certain TBRD is well-recognized and has been reported among family members, coworkers, and other defined groups.

Clinical Assessment

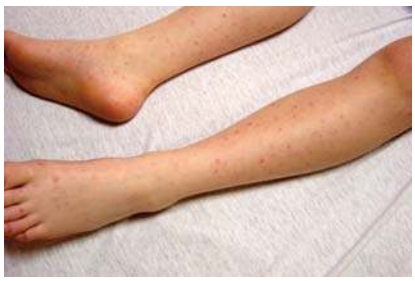
Signs and Symptoms

The early signs and symptoms of HME, HGA, RMSF, and *E. ewingii* infection might resemble nonspecific findings of other infectious and noninfectious diseases. The majority of patients with TBRD visit a physician during the first 2–4 days of illness, after an incubation period of approximately 5–10 days after a tick bite (*5*). Patients with HGA might seek medical care later (4–8 days after fever onset) (*7*). Substantial overlap occurs in the initial clinical presentation of the three diseases. Initial symptoms commonly include a sudden onset of fever, chills, and headache, commonly associated with malaise and myalgia. In adults, photophobia might be observed. Headache is nearly always reported by adults who seek medical care and can be severe. Patients also might report nausea, vomiting, and anorexia early in the course of their illness, especially with RMSF (*35*) and HME in children. Diarrhea might occasionally occur. Other frequently observed signs and symptoms in children with either RMSF or HME are abdominal pain, altered mental status, and conjunctival injection. Abdominal pain might be severe enough to mimic appendicitis or other causes of acute abdominal pain (*42*). Certain findings described in medical textbooks are less commonly observed by clinicians and include bilateral periorbital edema, edema of the dorsum of hands and feet, and calf pain and tenderness. Because the signs and symptoms that persons have when they first seek medical care are nonspecific, clinicians frequently must incorporate clues from the clinical and epidemiologic history and consider other features (e.g., the presence of rash or abnormalities of routine laboratory tests).

In RMSF, a rash typically appears 2–4 days after onset of fever; however, the majority of patients will seek medical care before this period. For adults and children with RMSF, rash frequently occurs earlier in children than in adults (*43*) and is eventually observed in approximately 90% of children. The exanthem typically begins as small, blanching, pink macules on the ankles, wrists, or forearms that evolve to maculopapules (Figure 15). In half of cases, the rash might evolve to petechiae over the next several days of illness. The classic centripetal spread of rash is typically not noticed by the patient and might be difficult to elicit from the clinical history. The rash can expand to involve the entire body, including the palms and soles, but its presence on the face is usually limited. Discerning the rash in darker-skinned persons might be difficult. The classic spotted or generalized petechial rash of RMSF is usually not apparent until the fifth or sixth day of the illness and signifies progression of the disease, although the progression is considerably variable (Figure 16). Patients with petechial rash are often severely ill, and although fever and organ dysfunction might resolve quickly with treatment, complete recovery can take longer to occur. The rash progression of RMSF includes several critical exceptions and considerations.

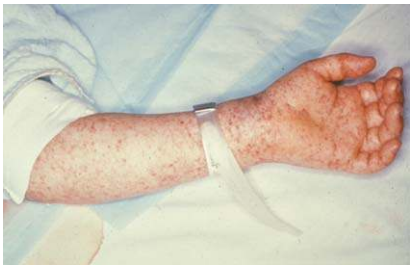
- A rash on the palms and soles is not pathognomonic and might occur in illnesses caused by drug hypersensitivity reactions, infective endocarditis, and a diverse group of other agents, including *Treponema pallidum*, *Neisseria meningitidis*, *Streptobacillus moniliformis*, *E. chaffeensis*, and certain enteroviruses.
- The rash might be evanescent or localized to a particular region of the body.

FIGURE 15. Maculopapular rash on the legs and feet of a patient with Rocky Mountain spotted fever



Photo/G.S. Marshall, University of Louisville School of Medicine, Louisville, KY

FIGURE 16. Late petechial rash on the forearm and hand of a patient with Rocky Mountain spotted fever



Photo/CDC

- A rash might be completely absent or atypical in up to 20% of RMSF cases (*4,43,44*).

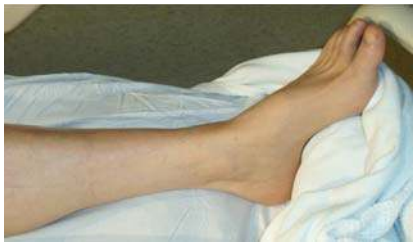
Rash is observed in approximately one third of all patients with HME (although rash is described in up to 66% of children) and is rare in patients with HGA or *E. ewingii* infection (*45,46*). For children with HME and a rash, distinguishing the condition from RMSF might be difficult. Rash patterns occasionally associated with HME vary in character from petechial or maculopapular (Figure 17; *47*) to diffuse erythema (*48*) and typically occur later in the course of disease (median: 5 days after onset; *6*).The rash patterns might involve the extremities, trunk, face or, rarely, the palms and soles (*49*).

In certain cases, patients with RMSF or ehrlichiosis might seek medical attention for a febrile illness that mimics viral meningoencephalitis. Focal neurologic deficits, including cranial or peripheral motor nerve paralysis or sudden transient deafness, might also be observed (*50*).

Differential Diagnosis of Febrile Patients with Rash

The differential diagnosis of febrile patients with rash is broad. The onset of TBRD is frequently rapid, and the majority of patients experience high fever, shaking chills, severe headache, and generalized myalgias, in contrast to other tickborne diseases (e.g., Lyme disease). Tickborne viral fevers (e.g., Colorado tick fever) infrequently cause rash but should be included in the differential diagnoses of TBRD, particularly when leukopenia and thrombocytopenia are present in a patient who has recently traveled to the western United States. Clinically, TBRD might be essentially indistinguishable from the majority of viral infections, particularly those in children. The dermatologic classification of the rash, its distribution, pattern of progression and timing relative to onset of fever, and other systemic signs provide clues that help the clinician rule out other exanthemata. Maculopapular rashes might occur in association with multiple conditions, including human herpesvirus 6 infection (i.e., roseola), human parvovirus B19, enteroviral infection (e.g., coxsackievirus and echovirus), Epstein-Barr virus infection, disseminated gonococcal infection, *Mycoplasma pneumoniae* infection, leptospirosis, secondary syphilis, Kawasaki disease, thrombotic thrombocytopenic purpura (TTP), drug reactions, and immune complex-mediated illness (*51*). A petechial rash can occur in association with meningococcal infection, enteroviral infection, immune thrombocytopenic purpura, and after group A streptococcal pharyngitis. *R. rickettsii* infection is noted for causing a rash on the soles and palms, although this distribution typically occurs late in RMSF and in only half of cases, whereas in the majority of other bacterial or viral infections rash has not been observed. Initially, clinicians might experience difficulty distinguishing *N. meningitidis* infection from RMSF because both can begin as a maculopapular rash and progress to a petechial rash, but the rash and other clinical features progress more rapidly in meningococcemia than in RMSF. Selected infectious causes and features of maculopapular and petechial rash illnesses have been reported (Table 2). Other exanthematous diseases that can occasionally be confused with TBRD include toxic-shock syndrome, erythema multiforme, and Stevens-Johnson syndrome.

FIGURE 17. Maculopapular rash associated with *Ehrlichia chaffeensis* infection



Photo/D.J. Sexton, Duke University Medical Center, Durham, NC

Laboratory Findings

Obtaining a complete blood cell count (CBC), comprehensive metabolic panel, and examination of peripheral blood smear are essential when considering a diagnosis of TBRD. The total white blood cell (WBC) count is typically normal in patients with RMSF, but increased numbers of immature bands are generally observed. Thrombocytopenia, mild elevations in hepatic transaminases, and hyponatremia might be observed with RMSF (*35*), whereas leukopenia (up to 53% of patients), thrombocytopenia (up to 94% of patients), and modest elevations of liver transaminase levels are particularly suggestive of HME and HGA (*52,53*). An inverse relation has been reported between the mean WBC and platelet count and the probability that HGA is the cause of nonspecific fever (*53*). Blood smears might be useful in identifying patients with HGA (*34*) or *E. ewingii* infection. Nonspecific changes in the concentrations of routine laboratory parameters that have been observed for patients infected with *E. chaffeensis* (*52*) or *A. phagocytophilum* have been reported (*53*; Table 3).

Cerebrospinal fluid (CSF) analysis might be a useful adjunct to laboratory diagnosis of TBRD. When CSF is evaluated in patients with RMSF or HME, a pleocytosis (usually <100 cells/microliter) is typically observed (with

TABLE 2. Selected causes of fever and maculopapular or petechial rash*

Disease	Agent	Season	Onset	Clinical features
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Spring to summer	Fever, headache, malaise, and sometimes gastrointestinal symptoms and rash after 2–4 days in ≥50% of patients	Rash usually starts peripherally and moves centrally; might involve soles and palms; progresses from maculopapular (MP†) to petechial (P§)
Murine typhus	*Rickettsia typhi*	Sporadic	Fever, malaise, headache, and rash after 4–5 days in approximately 50% of patients	MP rash frequently involving the trunk, with involvement of extremities as well
Monocytotropic ehrlichiosis	*Ehrlichia chaffeensis*	Spring to summer	Fever, malaise, headache, and rash in approximately 30% of patients	Erythematous, MP, or P rash substantially more common in children than in adults
Group A streptococcal pharyngitis	Group A *Streptococcus*	Fall to winter	Abrupt onset of fever and sore throat and malaise; rash follows acute illness	Cause of P rash in children who appear well
Meningococcal disease	*Neisseria meningitidis*	Year-round, but especially late winter to early spring	Fever and rash (if bacteremic) within 24 hours	MP and P rash usually begins on lower extremities and moves centrally; early rash might not have petechial component
Fifth disease (erythema infectiosum)	Human parvovirus B19	Late winter to early summer	Low fever and mild constitutional signs before rash onset	"Slapped cheek" appearance of rash; lacy-appearing rash on trunk
Roseola	Human herpesvirus 6	Year-round	Fever 3–5 days then rash; most common in children aged <2 years	MP rash begins on trunk and spreads elsewhere; fades rapidly
Enteroviral infection	Echoviruses, coxsackieviruses, and other nonpolio enteroviruses	Most common during summer to early fall, but occurs year-round	Nonspecific febrile illness, with or without rash	Fine MP rash appears at fever onset; begins on face and spreads to chest and extremities; might be P rash

* **SOURCE:** Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:1821–5, 1891–8, 2148–61, 2287–95, 2306–9, 2310–8, 2362–79, 2498–513.
† Maculopapular.
§ Petechial.

TABLE 3. Changes in the concentrations of routine laboratory parameters observed in patients infected with *Ehrlichia chaffeensis or *Anaplasma phagocytophilum*†**

Laboratory parameter	Days 1–7	Days 8–14	Days 15–28
Total white blood cells (absolute)	Reduced	Reduced to normal	Normal
Segmented neutrophils (%)	Increased	Increased to normal	Normal
Band neutrophils (%)	Increased	Increased to normal	Normal
Lymphocytes (%)	Reduced	Normal to increased	Increased to normal
Monocytes/eosinophils (%)	Reduced	Reduced to normal	Normal
Platelets	Reduced	Reduced to increased	Normal
C-reactive protein	Increased	Increased to normal	Normal
Hepatic transaminases	2- to 4-fold increase	Normal to mildly increased	Normal

* **SOURCE:** Fishbein DB, Dennis DT. Tick-borne disease—a growing risk. N Engl J Med 1995;333:452–3.
† **SOURCE:** Bakken JS, Aguero-Rosenfeld ME, Tilden RL, et al. Serial measurements of hematologic counts during the active phase of human granulocytic ehrlichiosis. Clin Infect Dis 2001;32:862–70.

either a polymorphonuclear or lymphocytic predominance), whereas CSF evaluated in *E. ewingii* infection is characterized by a neutrophilic pleocytosis (*29*). Moderately elevated protein (100–200 mg/dL) and normal glucose levels also are commonly observed in patients with RMSF (*54,55*). A Gram stain indicating gram-negative diplococci, very low glucose (i.e., <20–30 mg/dL), or neutrophilic pleocytosis is more suggestive of meningococcal meningitis. Clinicians should distinguish TBRD-related CNS involvement from other infections (e.g., *N. meningitidis*); however, in the majority of patients, reliably distinguishing between RMSF, HME, and meningococcal infection based on laboratory testing is difficult (unless a pathogen is cultured). Therefore, empiric treatment for both TBRD and meningococcemia is necessary for ill patients with fever and rash and for patients in whom neither disease can be ruled out.

The following is a summary of salient clinical assessment features:

- Early clinical presentations of HME, HGA, RMSF, and *E. ewingii* infection include fever, headache, myalgia, and malaise and are difficult to distinguish from other infectious and noninfectious diseases.

- Patients with RMSF typically do not have a spotted or petechial rash when they initially seek medical care during the first 2–4 days of illness.
- A CBC, metabolic panel, and peripheral blood smear examination are helpful in developing both a differential diagnosis and treatment approach to TBRD.
- CSF analysis might reveal neutrophilic or lymphocytic pleocytosis and elevated protein but might not reliably distinguish TBRD and meningococcal disease, necessitating empiric antibiotic therapy for both conditions when indicated.
- Leukopenia, thrombocytopenia, mild hyponatremia, and mildly elevated hepatic transaminase levels are common and particularly useful clinical features of TBRD, although the absence of these features does not exclude a diagnosis of TBRD.
- Infrequent features of TBRD include severe abdominal pain and meningoencephalitis.
- Rash is observed frequently in RMSF, occasionally in HME, and rarely in HGA or *E. ewingii* infection.

Treatment and Management

An assessment of clinical signs and symptoms, along with laboratory diagnostic tests and a thorough clinical history, will help guide clinicians in developing a differential diagnosis and treatment plan. At least 50% of patients with TBRD might need to be hospitalized. Patients with evidence of organ dysfunction and severe thrombocytopenia, mental status changes, and the need for supportive therapy should be hospitalized. Essential considerations include social factors, the likelihood that the patient can and will take oral medications, and existing comorbidities. For example, a patient who appears well, has acute febrile illness and an unrevealing history and physical examination, and whose laboratory indices are within normal limits might warrant a "wait and watch" approach for 24 hours with reassessment if the patient fails to improve. If laboratory testing of a patient with a history compatible with TBRD reveals leukopenia or thrombocytopenia, or metabolic abnormalities, the clinician should consider obtaining blood cultures for other likely pathogens and specific laboratory tests and initiating empiric oral antimicrobial therapy that will effectively treat TBRD. Certain patients with TBRD can be treated on an outpatient basis with oral medication, particularly if a reliable caregiver is available in the home and the patient is compliant with follow-up medical care. When other diagnoses are under consideration, empiric treatment for these conditions can be incorporated into the therapeutic plan. For example, for a patient's condition in which meningococcal disease cannot be ruled out, intramuscular ceftriaxone should be administered in addition to oral doxycycline to provide activity against possible meningococcal infection, pending culture results. Inpatient observation and assessment of the blood cultures after 24 hours of incubation should be considered for such patients. A critical step is for clinicians to keep in close contact with patients who are treated in the outpatient setting to ensure that they are responding to therapy as expected.

Appropriate antibiotic treatment should be initiated immediately when a clinician suspects that the diagnosis could be RMSF, HME, HGA, or *E. ewingii* infection, based on clinical, laboratory, or epidemiologic findings. Delay in treatment can lead to severe disease and fatal outcome for TBRD (*2–4*). Because each of the agents causing TBRD is susceptible to tetracycline-class antibiotics, these drugs, particularly doxycycline, are considered the therapy of choice in nearly all clinical situations. Fever typically subsides within 24–48 hours after treatment when the patient receives doxycycline or another tetracycline during the first 4–5 days of illness. If a patient fails to respond to early treatment with a tetracycline antibiotic (i.e., within 48 hours), this response might be an indication that their condition is not a TBRD. Severely ill patients might require longer periods before clinical improvement is noted, especially if they have multiple organ dysfunction.

Doxycycline is the drug of choice for treatment of all TBRD in children and adults. This drug is bacteriostatic in its activity against rickettsial organisms. The recommended dose is 100 mg per dose administered twice daily (orally or intravenously) for adults or 2.2 mg/kg body weight per dose administered twice daily (orally or intravenously) for children weighing <100 lbs. (45.4 kg). Intravenous therapy is frequently indicated for hospitalized patients, and oral therapy is acceptable for patients considered to be early in the disease and who can be managed as outpatients. Oral therapy also can be used for inpatients who are not vomiting or obtunded. The optimal duration of therapy has not been established, but current recommendations for RMSF and HME are for treatment for at least 3 days after the fever subsides and until evidence of clinical improvement is noted, which is typically for a minimum total course of 5–7 days. Severe or complicated disease might require longer treatment courses. Patients with HGA should be treated with doxycycline for 10–14 days to provide appropriate length of therapy for possible incubating coinfection with Lyme disease (*45*).

The use of tetracyclines to treat children with TBRD is no longer a subject of controversy (*56–58*). Concerns regarding dental staining after tetracycline therapy have

been based primarily on studies conducted during the 1960s that involved children receiving multiple courses of the drug for recurrent otitis media (*59,60*). The propensity of tetracyclines to bind calcium can lead to darkening of the teeth if the antibiotic is ingested during the period of tooth crown formation. More recent studies in 1971 and 1998, however, have demonstrated that although multiple exposures to tetracycline increase the risk for tooth staining, limited use of this drug in children during the first 6–7 years of life has a negligible effect on the color of permanent incisors (*56,57*). Beyond ages 6–7 years, the risk for tetracycline staining is of minimal consequence because visible tooth formation is complete. Moreover, a prospective study of children treated with doxycycline for RMSF demonstrated that these children did not have substantial discoloration of permanent teeth compared with those who had never received the drug (*56*). Because TBRD can be life-threatening and limited courses of therapy with tetracycline-class antibiotics do not pose a substantial risk for tooth staining, the American Academy of Pediatrics Committee on Infectious Diseases revised its recommendations in 1997 and has identified doxycycline as the drug of choice for treating presumed or confirmed RMSF and ehrlichial infections in children of any age (*61,62*).

Chloramphenicol is an alternative drug that has been used to treat RMSF (*50*); however, this drug is associated with various side effects and might require monitoring of blood indices. Chloramphenicol is no longer available in the oral form in the United States. Moreover, epidemiologic studies in which CDC case report data have been used suggested that patients with RMSF treated with chloramphenicol have a higher risk of dying than persons who received a tetracycline (*11,63*). In vitro evidence also indicates that chloramphenicol might not be an effective antibiotic for HME or HGA (*64,65*). Clinicians who suspect a TBRD and are considering empiric antibiotic therapy before laboratory confirmation should be aware that doxycycline provides therapeutic coverage for RMSF, HME, HGA, and *E. ewingii* infection.

Tetracyclines are generally contraindicated for use in pregnant women because of risks associated with malformation of teeth and bones in the fetus and hepatotoxicity and pancreatitis in the mother (*66*). However, tetracycline has been used successfully to treat HME in pregnant women (*67*), and the use of tetracyclines might be warranted during pregnancy in life-threatening situations where clinical suspicion of TBRD is high. Whereas chloramphenicol is typically the preferred treatment for RMSF during pregnancy, care must be used when administering chloramphenicol late during the third trimester of pregnancy because of risks associated with grey baby syndrome (*66*). Substantially limited clinical data exist that support the use of other antimicrobials during pregnancy, although rifampin has been used successfully in several pregnant women with HGA (*68*). In vitro studies have demonstrated that rifamycins provide effective activity against *Ehrlichia* and *Anaplasma* species (*64,65*), and therapy with rifampin may be considered for patients with HGA who are unsuited for tetracycline treatment because of pregnancy or a history of drug allergy (*45*). Clinicians should use caution, however, in ensuring that RMSF can be ruled out because the clinical presentations of RMSF and anaplasmosis are similar, and the comparative effectiveness of rifampin and doxycycline is unknown at this time.

Because certain patients with TBRD might initially receive an alternative diagnosis, they might be empirically treated with antibiotics inactive against rickettsiae, including penicillins, cephalosporins, aminoglycosides, erythromycin, or sulfonamides. This situation presents both diagnostic and therapeutic challenges. In certain cases, patients treated with beta-lactam antibiotics or sulfa-containing drugs are mistakenly thought to have drug eruptions when they later manifest a rash (*66*), further postponing a correct diagnosis and appropriate treatment. Because the physician might conclude that the prescribed treatment will take time to work, a delay in obtaining critical additional laboratory or clinical information also might be a result. In addition, sulfa-containing antimicrobials have been associated with increased severity of TBRD, although whether disease severity is directly related to the use of sulfa-containing drugs or the delayed administration of more effective antimicrobials is not clear. Cases of severe ehrlichiosis complicated by acute respiratory distress syndrome have been associated with the use of trimethoprim-sulfamethoxazole (*69,70*).

In addition, clinicians should note the overlap between early symptoms of invasive meningococcal infection and TBRD. These conditions are difficult to distinguish early in the course of illness. In patients for whom both conditions are included in the initial differential diagnoses, after performing blood cultures and a lumbar puncture, empirically treating for both diseases is appropriate. This treatment can be accomplished by adding an appropriate parenteral penicillin or cephalosporin that has activity against *N. meningitidis* to doxycycline therapy.

Preventive antibiotic therapy for rickettsial infection is not indicated for patients who have had recent tick bites and are not ill. Limited numbers of ticks in areas where tickborne diseases are endemic are infected with pathogenic rickettsiae. Approximately 1%–3% of vector ticks are infected with spotted fever group rickettsiae (*71*). How-

ever, less than 1% of these rickettsiae usually have been confirmed to be *R. rickettsii* (*72,73*). Approximately 5%–15% of lone star ticks are infected with *E. chaffeensis* (*47*), and 10%–50% of *I. scapularis* ticks are reported to be infected with *A. phagocytophilum* (*74,75*) in endemic areas. Therefore, the risk for such infection after a tick bite is low. Moreover, for RMSF, preventive therapy has been demonstrated to delay but not prevent the onset of symptoms (*76*).

The following is a summary of salient features of treatment and management:

- Clinical history, symptoms, and physical and laboratory findings should guide the clinician's approach to patient management and treatment.
- Not all patients with TBRD will require hospitalization.
- Clinicians may consider a wait and watch approach for 24–48 hours for patients early in the course of illness and who have nonsupporting history, nonspecific clinical signs, and normal laboratory findings.
- Doxycycline is the drug of choice for the treatment of presumptive or confirmed TBRD in both adults and children.
- Limited courses of tetracycline-class antibiotics (e.g., doxycycline) do not pose a substantial threat of tooth staining in children.
- Tetracyclines typically are contraindicated for use during pregnancy but might be warranted in life-threatening situations where clinical suspicion of TBRD is high.
- Delay in treatment can lead to severe disease and fatal outcome of TBRD.
- In evaluating for TBRD, when early invasive meningococcal infection cannot be ruled out, providing treatment for both conditions by adding an antimicrobial that has activity against *N. meningitidis* is appropriate.
- Prophylactic use of antibotics after a tick bite is not recommended.

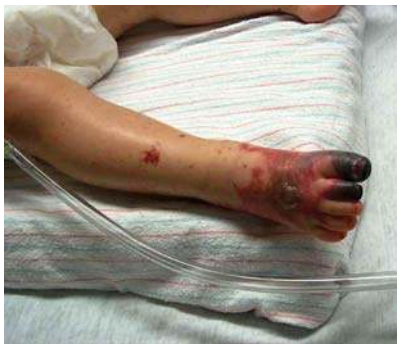
Considerations for Management of Patients with Severe Manifestations of TBRD

A substantial number of patients with TBRD require hospitalization (*6,7,10*). Severe manifestations of TBRD might include prolonged fever, renal failure, disseminated intravascular coagulopathy (DIC), hemophagocytic syndrome, meningoencephalitis, and acute respiratory distress syndrome. A notable exception is that HGA has not been associated with meningoencephalitis.

RMSF is frequently a severe illness, and patients commonly require hospitalization. Up to 20% of untreated cases and 5% of treated cases have fatal outcome, making RMSF the most commonly fatal rickettsial disease in the United States (*5,10*). However, assessment of passive reporting of RMSF-associated death has suggested that only one third of fatal cases of RMSF were reported to CDC during 1983–1998 (*77*). Therefore, the actual case-fatality rate of RMSF might be closer to 5%–10%. Host factors associated with severe or fatal RMSF include advanced age, male gender, black race, chronic alcohol abuse, and glucose-6-phosphate-dehydrogenase (G6PD) deficiency (*50*). Deficiency of G6PD is a sex-linked genetic condition affecting approximately 12% of the U.S. black male population; deficiency of this enzyme is associated with a high proportion of fulminant cases of RMSF (*50,78*). Fulminant cases follow a clinical course that is fatal within 5 days of onset. Long-term health effects persisting for >1 year after acute RMSF infection include partial paralysis of the lower extremities; gangrene requiring amputation of fingers, toes, arms, or legs; hearing loss; blindness; loss of bowel or bladder control; movement disorders; and speech disorders (*79*). These complications are observed most frequently in persons recovering from severe, life-threatening disease, often after lengthy hospitalizations. Digital necrosis in a patient occurring late in the course of RMSF has been illustrated (Figure 18).

Similarly, HME and HGA can cause serious or fatal disease as well, although at lower rates than are observed for RMSF. At least 50% of patients with HGA and HME are hospitalized to rule out other potentially life-threatening conditions and to manage the illness (*34,47*). Clinical indications for admission might include immunocompromised state, pain management (i.e., headache and myalgias), mental confusion, cough, infiltrate in chest radiograph, abnormal spinal fluid findings, or specific acute organ failure. Approximately 3% of HME patients and less than 1% of HGA patients with symptoms severe enough to seek

FIGURE 18. Digital necrosis affecting the toes of a patient, occurring late in the course of Rocky Mountain spotted fever



Photo/G.S. Marshall, University of Louisville School of Medicine, Louisville, KY

medical attention will die from the infection (*25,34,47*). The severity of ehrlichiosis might be related, in part, to the immune status of the patient. Persons with compromised immune systems caused by immunosuppressive therapies (e.g., corticosteroids or cancer chemotherapy), human immunodeficiency virus (HIV) infection, organ transplantation, or splenectomy appear to develop more severe disease from *E. chaffeenis* infection, and case-fatality rates for these persons are characteristically higher than case-fatality rates reported for the general population (*30*). Although the case fatality rate for HGA (0.5%–1.0%) is lower than that for HME, notable complications, including respiratory failure, a toxic-shock–like syndrome, rhabdomyolysis, pancreatitis, acute renal failure, and invasive infections caused by opportunistic viral or fungal agents can occur, especially among patients who have co-morbid illnesses or who are actively immunosuppressed (*45*). In addition, advanced patient age and delay in diagnosis and the onset of specific antibiotic therapy are predictors of a more severe course of HGA (*53*).

Management of severely ill patients with TBRD should include careful assessment of fluid and electrolyte balance. Vasopressors and rigorous fluid management might be needed, especially when the illness is complicated by renal failure or hypotension. Patients might have pulmonary infiltrates because of vasculitis that are erroneously thought to be caused by cardiac failure or pneumonia. Seizures might require aggressive treatment, and arrhythmias (e.g., atrial fibrillation or flutter) will frequently respond to treatment of the patient's underlying disease. Consultation with an intensivist or an infectious disease subspecialist might be helpful in managing these complications.

The following is a summary of salient features of severe manifestations:

- TBRD can be life-threatening.
- Severe manifestations of TBRD include prolonged fever, renal failure, myocarditis, meningoencephalitis, hypotension, acute respiratory distress syndrome, and multiple organ failure.

Confirmatory Diagnostic Tests

Rickettsial infections pose difficult diagnostic challenges to both clinicians and laboratorians. Rapid confirmatory assays are not commonly available to guide treatment decisions of acutely ill patients. However, confirmatory assays provide the physician with vital information that retrospectively validates the accuracy of the clinical diagnosis. Laboratory confirmation of infection is also vital to understanding the epidemiology and public health impact of TBRD.

Several laboratory methods are available to diagnose TBRD. However, they vary in the time required to obtain results and in the type of information they provide the clinician. Therefore, treatment decisions should be based on epidemiologic and clinical clues and should never be delayed while waiting for laboratory confirmation of a diagnosis. Similarly, test results should be interpreted in the context of the patient's illness and the epidemiologic setting. Misuse of specialized tests for patients with a low probability of the disease and in areas with a low prevalence of disease might result in confusion. A fundamental understanding of the signs, symptoms, and epidemiology of the disease is critical in guiding requests for tests and interpretation of test results for ehrlichioses, anaplasmosis, and RMSF. Studies have suggested that antibiotic therapy might diminish the development of convalescent antibodies in RMSF (CDC, unpublished data, 2005). However, the degree to which doxycycline might cause this occurrence is uncertain. If molecular or culture diagnostic methods are conducted, obtaining blood for testing before antibiotics are administered is essential to obtain the best results.

Blood-Smear Microscopy

Microscopic examination of blood smears stained with eosin-azure type dyes (e.g., Wright-Giemsa stain) might reveal morulae in the cytoplasm of infected circulating leukocytes (1%– 20%) of patients with HME and 20%–80% of patients with HGA (*45,47*) during the first week of infection, which is highly suggestive of ehrlichial or anaplasma infection. However, blood smear examination is insensitive and should be performed by an experienced microscopist. In addition, a negative blood smear examination should not dissuade the caregiver from initiating treatment with doxycycline if the clinical presentation and routine laboratory findings support the diagnosis of ehrlichiosis or anaplasmosis. Blood smear examination is not useful for diagnosis of RMSF.

Serologic Testing

Serologic assays for RMSF, HME, and HGA are commonly available through multiple commercial and state public health laboratories. Serologic evaluations are commonly conducted by using the indirect immunofluorescence antibody (IFA) assay. Antibodies in the serum bind to fixed antigens on a slide and are detected by a fluorescein-labeled conjugate. Although IFA remains the principle diagnostic tool for the diagnosis of rickettsial and ehrlichial infections, no standardized antigens, conjugates, or agreement on what consti-

tutes a positive result among the various laboratories providing these tests exist. Individual laboratories should be consulted regarding their test threshold levels. Enzyme-linked immunosorbent assay (ELISA) is becoming a more frequently used assay. Similar to IFA, the accuracy of ELISA depends on the laboratory conducting the test, the quality and specificity of the antigen, and the threshold levels at which a positive result is considered. Available ELISA tests are qualitative and cannot be used effectively to monitor increases or decreases in antibody titer.

The sensitivity of the IFA assay is substantially dependent on the timing of collection of the sample. Early in any TBRD, a majority of serologic tests will be negative. Clinical illness nearly always precedes laboratory diagnosis by any method. As the illness progresses to 7–10 days, the sensitivity of IFA serology increases. The IFA is estimated to be 94%–100% sensitive after 14 days, and that sensitivity is increased if paired samples are tested (*80*). The IFA is considered to be the gold standard of serologic testing for rickettsial diseases, and other serologic tests have not been developed that surpass the sensitivity and specificity of these assays. Testing two sequential serum or plasma samples together to demonstrate a rising IgG or IgM antibody level is essential to confirm acute infection. Paired serum specimens taken early (i.e., acute) and later (i.e., convalescent) in the disease course represent the preferred specimens for evaluation. Typically, these specimens should be taken at least 2–3 weeks apart to examine for a four-fold or greater increase in antibody titer (*33*).

The majority of patients demonstrate increased IgM or IgG titers by the second week of the illness (patients infected with certain imported rickettsiae might not demonstrate increased titers until 4 weeks after illness onset). However, patients might lack diagnostic IgG and IgM antibody titers in the first 7 days of illness, a period when the majority of patients initially seek medical care and laboratory testing is performed. The duration of time that antibodies will persist after recovery from the infection is variable. In certain persons, high titers of antibodies against *A. phagocytophilum* have been observed for 3½ years after the acute illness (*81*). For RMSF, IgG and IgM titers increase concurrently by the second week of illness, and IgM antibodies wane after 3–4 months, whereas IgG titers persist for 7–8 months (*82*). The majority of commercial reference laboratories conduct testing for IgG and IgM antibodies.

Cross-reactivity of antigens results in antibody responses that are typically group-specific, but not necessarily species-specific, after infections with these pathogens. For example, serologic tests that detect antibodies reactive with *R. rickettsii* might have resulted from previous infections with other spotted fever group rickettsial species. Similarly, antibodies reactive with *E. chaffeensis* or *A. phagocytophilum* occasionally react with the other ehrlichial species, which might impede epidemiologic distinction between the ehrlichial infections (*83*). Most patients with *E. ewingii* infections develop antibodies that react with *E. chaffeensis* antigens. Little cross-reactivity of *Rickettsia* with *Ehrlichia* or *Anaplasma* species exists. Certain serologically confirmed cases of infection thought to be RMSF, HME, or HGA might represent infections with the other agent or with another antigenically related species. The predominance of non-*R. rickettsii* species in tick vectors collected in RMSF-endemic areas suggests that related organisms of undetermined pathogenicity might play a role in human illness (*84*). This occurrence is especially true for persons who are infected with rickettsial organisms from endemic areas outside of the United States.

Nucleic Acid Detection

Amplification of specific DNA by PCR provides a rapid method for detecting TBRD infections. These tests are available from CDC, certain state health laboratories, and a limited number of research and commercial laboratories (Box). Conventional PCR tests have no specified standard, and diagnostic sensitivity and specificity might vary among individual assays (*80*). Doxycyline treatment, in particular, can also decrease the sensitivity of PCR (*45*). In studies of *A. phagocytophilum* infection, PCR was estimated as 60%–70% sensitive (*53*), and for diagnosis of infection with *E. chaffeensis*, PCR was estimated to be 52%–56% sensitive (*25*) to 87% sensitive (*85*). For RMSF, PCR is probably more useful for detecting the etiologic agent in a skin biopsy or autopsy tissue specimen than it is in an acute blood sample because, typically, low numbers of rickettsiae circulate in the blood in the absence of advanced disease or fulminant infection (*18*). PCR testing of skin biopsies alone does not offer ideal sensitivity, and a negative result does not exclude the diagnosis because of focality of vessel involvement. Laboratory confirmation of RMSF in the acute stage is improved when PCR is used in conjunction with IHC staining. PCR of whole blood specimens is more useful for confirming HME, HGA, and *E. ewingii* infection because of the tropism of these pathogens for circulating WBC. However, no optimal time frame has been established that is ideal for sample collection to ensure the highest sensitivity for diagnosing ehrlichioses or anaplasmosis. New techniques (e.g., real-time PCR) might offer the advantages of speed, reproducibility, quantitative

BOX. Websites of organizations that provide tickborne rickettsial disease (TBRD) testing, laboratory safety, and general information

CDC	
Viral and Rickettsial Zoonoses Branch	http://www.cdc.gov/ncidod/dvrd/ehrlichia/index.htm
National Center for Infectious Diseases	http://www.cdc.gov/ncidod/dvrd/rmsf/index.htm
Laboratories Performing Diagnostic Assays	
Association of Public Health Laboratories	http://www.aphl.org/about_aphl/state_laboratory_listing.cfm
Laboratory Safety	
CDC Select Agent Program	http://www.cdc.gov/od/sap
Biosafety in Microbiological and Biomedical Laboratories	http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm
General Information Regarding TBRD	
Council of State and Territorial Epidemiologists	http://www.cste.org
The American Society for Rickettsiology	http://www.cas.umt.edu/rickettsiology

capability, and low risk for contamination, compared with conventional PCR (*86*).

IHC Staining

Another approach to diagnosing TBRD is immunohistochemical (IHC) staining of antigens in formalin-fixed, paraffin-embedded biopsy or autopsy tissues. This test can be particularly useful to diagnose fatal TBRD in those patients for whom diagnostic levels of antibodies have not developed before death. For patients with a rash, IHC or immunofluorescence staining of a skin biopsy can be a critical diagnostic technique for RMSF. Immunostaining of skin biopsy specimens has been reported to be 100% specific and 70% sensitive in diagnosing RMSF (*35*). This method has been used to diagnose fatal and nonfatal cases of RMSF (*18,87–89*). Because rickettsiae might be focally distributed in tissue, this test might not always detect the agent. Autopsy tissues also are appropriate for evaluation and include the liver, spleen, lung, heart, kidney, and brain. The IHC method is most useful in documenting the presence of organisms in patients before initiation of antibiotic therapy or within the first 48 hours after antibiotic therapy has been initiated. IHC techniques also are available for diagnosing cases of ehrlichioses and anaplasmosis from bone marrow biopsies and tissue obtained at autopsy of fatal cases, including the spleen, lymph nodes, liver, and lung (*90–92*). Immunostaining for spotted fever group rickettsiae, *E. chaffeensis*, and *A. phagocytophilum* is offered by CDC and certain university-based hospitals and commercial laboratories in the United States (Box).

Culture

Because the agents that cause TBRD are obligate intracellular pathogens, they must be isolated by using cell culture techniques that are typically more labor-intensive and time-consuming than serologic, molecular, or IHC assays. Theoretically, any laboratory capable of performing routine viral isolations might have 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 to handle BSL-3 pathogens (*93*). Laboratories attempting culture of *R. rickettsii* bacteria need to comply completely with federal regulations (42 C.F.R. [2004]) regarding the registration and use of select agents (*93*). As a result, culture is rarely used for diagnosis, and other methods (e.g., serology, PCR, or immunostaining) are used to confirm infection.

The following is a summary of salient features of diagnostic testing:

- Blood smear microscopy might reveal presence of morulae in infected leukocytes, which is highly suggestive of HGA or, less commonly, HME.
- Blood smears are not useful to diagnose RMSF.
- Examination of paired serum samples obtained 2–3 weeks apart that demonstrate a rise in antibody titer is the most appropriate approach to confirm TBRD.
- Patients usually do not have diagnostic serum antibody titers during the first week of illness; therefore, an inability to detect antibodies (IgG or IgM) in acute-phase serum does not exclude TBRD.
- Immunohistochemistry of a biopsied skin lesion or autopsy tissues is useful for RMSF diagnosis in patients for whom diagnostic titers of antibodies have not yet developed.

- Whole blood specimens might be useful for a PCR confirmation of HME, HGA, and *E. ewingii* infection; however, a negative result does not rule out the diagnosis.

Surveillance and Reporting

National reporting requirements are determined collaboratively by the Council of State and Territorial Epidemiologists and CDC. RMSF, anaplasmosis, and all forms of ehrlichiosis are nationally notifiable diseases. RMSF became nationally notifiable in 1989 and anaplasmosis and ehrlichiosis, in 1998. When health-care providers identify a potential case of TBRD, they should notify the local health department. The local health department, in cooperation with the state health department, can assist the health-care provider in obtaining appropriate diagnostic testing to confirm the diagnosis. All confirmed or probable cases of RMSF, HME, HGA, and *E. ewingii* infection should be reported to the state health department. The case definitions for confirmed and probable cases of RMSF, HME, and HGA have been reported (Table 4; *33,94*). Each state health department compiles case reports and submits them to CDC, where data are compared and disseminated via the *MMWR Weekly* and annual *Surveillance Summaries*.

Since 1981, CDC has collected and analyzed surveillance data on RMSF by using two complementary systems. States submit reports electronically via the National Electronic Telecommunications System for Surveillance (NETSS) as part of the National Notifiable Disease Surveillance System. NETSS reports capture diagnosis, date of onset, and basic demographic and geographic data related to the case. In addition, physicians are encouraged to complete a standardized case report form (CRF; Appendix) and forward it to the state health department, where it is compiled with similar reports and forwarded to CDC. The CRF summarizes demographic, epidemiologic, and outcome data that are not reported in NETSS. Data collected on the CRF are useful in summarizing the epidemiologic characteristics of

TABLE 4. Case definitions for Rocky Mountain spotted fever,* human monocytotropic ehrlichiosis (HME), human granulocytotropic anaplasmosis (HGA), and unspecified ehrlichiosis†

	Rocky Mountain spotted fever	Ehrlichiosis and anaplasmosis		
Clinical description	Tickborne illness characterized by acute onset of fever and possible headache, malaise, myalgia, and nausea/vomiting or neurologic signs. A macular or maculopapular rash is reported in the majority of patients and is frequently observed on the palms and soles.	Tickborne illness characterized by acute onset of fever, headache, myalgia, and possible malaise. Nausea, vomiting, or rash might be observed in certain cases. Clinical laboratory findings might include thrombocytopenia, leukopenia, and possibly elevated liver enzymes. Intracytoplasmic morulae might be visible in the leukocytes of certain patients.		
		HME	**HGA**	**Unspecified ehrlichiosis**
Laboratory criteria	Serologic evidence of 4-fold change in serum antibody titer against *Rickettsia rickettsii* antigens between paired serum samples, as determined by IFA§ or ELISA¶; or demonstration of *R. rickettsii* antigen in a clinical specimen by IHC** methods; or detection of *R. rickettsii* DNA in a clinical specimen by PCR assay; or isolation of *R. rickettsii* from a clinical specimen in cell culture.	Demonstration of 4-fold change in antibody titer to *Ehrlichia chaffeensis* antigen by IFA in paired serum samples; or positive PCR†† assay and confirmation of *E. chaffeensis* DNA; or identification of morulae in leukocytes and a positive IFA titer to *E. chaffeensis* antigen; or immunostaining of *E. chaffeensis* antigen in a biopsy or autopsy sample; or culture of *E. chaffeensis* from a clinical specimen.	Demonstration of 4-fold change in antibody titer to *Anaplasma phagocytophilum* antigen by IFA in paired serum samples; or positive PCR assay and confirmation of *A. phagocytophilum* DNA; or identification of morulae in leukocytes, and a positive IFA titer to *A. phagocytophilum* antigen; or immunostaining of *A. phagocytophilum* antigen in a biopsy or autopsy sample; or culture of *A. phagocytophilum* from a clinical specimen.	Demonstration of 4-fold change in antibody titer to more than one *Ehrlichia* species in which a dominant reactivity cannot be established; or Identification of a species other than *E. chaffeensis* or *A. phagocytophilum* by PCR, immunostaining, or culture.
Case classification	**Probable case:** Identified in a person with a clinically compatible illness and serologic evidence of antibody reactive with *R. rickettsii* in a single serum sample at a titer considered indicative of current or previous infection (cutoff titers are determined by individual laboratories).	**Probable case:** Identified in a person with a clinically compatible illness with either a single positive IFA titer (based on cutoff titers established by the laboratory performing the test) or the visualization of morulae in leukocytes.		
	Confirmed case: Identified in a person with a clinically compatible illness that is laboratory confirmed by a 4-fold change in serum antibody titer, as determined by IFA or ELISA or positive PCR or positive IHC, or isolation in culture.			

* **SOURCE:** CDC. Rocky Mountain spotted fever (*Rickettsia rickettsii*): 2004 case definition. Atlanta, GA: US Department of Health and Human Services, CDC, Epidemiology Program Office, Division of Public Health Surveillance and Informatics; 2004.
† **SOURCE:** CDC. Ehrlichiosis (HGE, HME, other or unspecified): 2000 case definition. Atlanta, GA: US Department of Health and Human Services. CDC, Epidemiology Program Office, Division of Public Health Surveillance and Informatics; 2000.
§ Indirect immunofluorescence antibody.
¶ Enzyme-linked immunosorbent assay.
** Immunohistochemical.
†† Polymerase chain reaction.

disease and focusing on prevention and treatment. This process includes examining lesser understood aspects of these conditions (e.g., the role of immunosuppression as a risk factor for disease; the prevalence of severe outcomes of infection, including death; and hospitalization trends). In 2001, the form was expanded to include reporting of other common TBRD, including HGA and HME, in addition to RMSF.

A surveillance system is critical for studying the changing epidemiology of TBRD and for developing effective prevention strategies and public health education programs. The detection of a cluster of RMSF cases in a region of Arizona where the disease was not known to occur and subsequent prevention and control initiatives underscore the vital role of surveillance and reporting in protecting the public's health. By the end of 2004, the highest number of RMSF cases was reported to CDC (n = 1,514), suggesting potential increased activity. However, underreporting of TBRD is probably common.

The following is a summary of salient features of surveillance and reporting:

- RMSF, HME, HGA, and other ehrlichioses are reportable diseases in the United States.
- Physicians who identify a potential case of TBRD should notify the local health department, which can assist with obtaining diagnostic testing to confirm the diagnosis.
- Surveillance and reporting of TBRD are key components of public health education and disease prevention efforts.

Prevention

No licensed vaccines for TBRD exist. Avoiding tick bites and promptly removing attached ticks remain the best disease prevention strategies. Persons should limit their exposure to tick-infested habitats, including wooded or grassy areas. Persons should walk on cleared trails and avoid brushing against tall grass and other vegetation. This practice is particularly essential during periods of peak tick activity (i.e., late spring and summer) but should be observed, regardless of the season. Protective clothing, including a hat, long-sleeved shirts, pants, socks, and closed-toe shoes are helpful in preventing ticks from reaching the skin and attaching. Wearing light-colored clothing is preferred because crawling ticks can be seen easily.

Various over-the-counter products containing DEET (*N,N*-diethyl-*m*-toluamide) are available for application on exposed skin and clothing to repel ticks. The higher the concentration of DEET, the longer the duration of protection per application. Products with DEET concentrations as low as 10% and those containing 25%–35% concentrations are considered optimal. No evidence exists that concentrations >50% are more efficacious or provide longer duration of protection (*95*). The American Academy of Pediatrics has recommended that DEET concentrations no greater than 20%–30% should be used for children (*96*). Products containing permethrin (e.g., permanone) can be used to treat outer clothing (e.g., shirts and pants) and should not be applied to skin. Permethrin is available commercially as a spray-on preparation. It should be applied evenly to outer clothing, according to label directions in a well-ventilated area. Clothing should be allowed to completely dry before being worn. Pre-treated clothing is available and remains effective for multiple launderings. The use of DEET and permethrin should be considered by persons who enter heavily infested tick habitats where the risk for being bitten is high and the potential for TBRD infection exists.

Adults entering wooded or grassy areas should inspect themselves and their children frequently for ticks. Because several hours might elapse before ticks attach and inject pathogens, frequent checks increase the likelihood of finding ticks before they transmit an infectious agent. The duration of tick attachment necessary to transmit rickettsial organisms is substantially variable and has been reported to be as little as 2–10 hours (*97*) to 10–20 hours (*98*) for *R. rickettsii.* Limited data exist regarding the interval of transmission after tick attachment for *A. phagocytophilum*, but animal studies indicate that 24–48 hours might elapse before pathogen transmission (*99,100*). No comparable data exists for *E. chaffeensis*. Sites where ticks commonly attach include, but are not limited to, the scalp, waist, armpits, groin, and under socks and the beltline. Pets should also be checked for ticks because they can carry ticks back to their homes and human companions. Regular application of ectoparasite control on pets helps to reduce the risk for human exposure to ticks.

If an attached tick is found, it should be removed by grasping with tweezers or fine-tipped forceps close to the skin and gently pulling with constant pressure. Folk remedies, including gasoline, kerosene, petroleum jelly, fingernail polish, or lit matches should never be used to extract ticks (*101*). Removing the tick with bare hands should be avoided because fluids containing infectious organisms might be present in the tick's body and at the wound site. Ticks that have been removed should not be crushed between the fingers to prevent contamination, and hands should be washed to avoid potential conjunctival inoculation. The bite wound should then be disinfected.

The following is a summary of salient features of prevention:

- Avoid tick bites, which is key to the prevention of TBRD.
- Limit exposure to tick habitats, including grassy and wooded areas.
- Inspect the body carefully for ticks after being in a tick habitat.
- Remove attached ticks immediately by grasping with tweezers close to skin and pulling gently with steady pressure.

TBRD Cases

The following TBRD cases were observed in health-care settings. Information from the cases can be used to reinforce medical management information related to TBRD (*3,22,102*) and are intended to illustrate certain common pitfalls in the diagnosis and treatment of TBRD. The case reports include a description of the case and salient features that can be considered when dealing with a potential case of TBRD.

Case 1

In June 2001, a girl aged 5 years was taken to an ED in Missouri with a 3-day history of intermittent fever, headache, mild nausea, and a sore throat. On physical examination, the patient had a fever of 105°F (40.6°C) and a maculopapular rash on her legs, including the soles of her feet.

- **What should be included in the differential diagnosis?**

  Possible causes of fever and rash in this child include meningococcemia, RMSF, HME, enteroviral infections, Kawasaki disease, drug reactions, and streptococcal disease with exanthem.

- **What additional information would assist with the diagnosis?**

  Determine how long the rash has been present and when and where it appeared relative to onset of fever. The parent should be queried concerning medication use, immunocompromising conditions, and recent activities that could have led to animal exposures (including dogs), sick contacts, recent travel, outdoor activities (e.g., hiking, camping, and playing in brushy areas or backyard), and real or potential tick exposures.

  The parent noticed the rash, which began on the arms and legs, on the same day that the child was taken to the ED. They did not own a dog, and no history of recent travel out of the local area and no history of a tick bite were noted, although the parent said that ticks were in the area around their house.

- **What laboratory tests might be useful?**

  A CBC, comprehensive metabolic panel, blood culture, and a rapid *Streptococcus* pharyngitis screen should be performed. An acute serum should be obtained for IgG and IgM antibodies to *R. rickettsii*, *E. chaffeensis*, and *A. phagocytophilum*, but subsequent management of the patient should not depend on results. PCR for *E. chaffeensis* and *A. phagocytophilum* using EDTA whole blood might be useful if these tests are available from a reference laboratory.

  Laboratory results included a WBC count of 8,800 x 10^9 cells/L (normal: 4.5–11.0 x 10^9 cells/L), with 5% bands (normal: 0%–5%), 70% neutrophils (normal: 45%–75%), 17% lymphocytes (normal: 16%–46%), and 8% monocytes (normal: 4%–11%). The platelet count was 50 x 10^9 cells/L (normal: 150–350 x 10^9 cells/L). Serology results were not available for 3 days.

- **How does this information assist with the diagnosis?**

  The time of year for these clinical signs should raise suspicion for TBRD. A normal WBC is frequently observed in patients with viral infections and with RMSF. Patients with RMSF will commonly develop moderate to severe thrombocytopenia as the disease progresses, although a normal platelet count is frequently observed early in the course of illness. If serologic results are not immediately available, the clinician should not be dissuaded from initiating therapy if it is clinically indicated.

- **What actions, including treatment, should be taken?**

  On the basis of history, clinical signs, geographic location, and time of year, suspicion of a TBRD is reasonable. An appropriate course of action would include treatment with doxycycline (2.2 mg/kg body weight administered orally twice daily for a minimum of 5 days) and close follow-up to ascertain clinical response to therapy while continuing to rule out other possible causes. Appropriate antimicrobial therapy for other suspected etiologies should be considered until they can be reasonably excluded. For example, certain experts recommend administering an intramuscular dose of ceftriaxone, pending blood culture results, because meningococcal disease cannot be reliably distinguished from TBRD on clinical grounds alone. Convalescent-phase serology for RMSF, HGA, and HME should be performed 2–4 weeks later to confirm the diagnosis.

- **What preventive measures can the patient and her family take to prevent infection in the future?**

  The most effective preventive measure is to 1) limit exposure to ticks during peak periods of activity (prima-

rily April–September), 2) inspect body and clothing thoroughly for ticks after being in wooded or grassy areas, 3) remove attached ticks immediately by grasping with tweezers or forceps close to the skin and pulling gently with steady pressure, and 4) apply insect repellant (e.g., DEET) when exposure to grassy or wooded areas is anticipated.

Case 1 synopsis. This patient's clinical history suggested exposure to ticks, although no definitive indication of a tick bite was reported. Ticks are small (particularly in their nymphal and larval stages), and bites frequently go unnoticed because ticks might attach in places that are difficult to observe (e.g., the scalp, axillae, and inguinal regions). Up to 40% of patients with RMSF report no history of a tick bite (*10,11*). Therefore, the clinician should not be dissuaded from making a diagnosis of RMSF when no report of a tick bite is made. The clinical signs and laboratory values and a history that are compatible with tick exposure should guide the diagnosis and therapeutic actions. Serum samples collected on days 7 and 35 of illness demonstrated rising IgG antibody titers to *R. rickettsii* at 32 and 2,048, respectively.

Case 2

In mid-August 2003, a male child aged 14 months was taken to a community health clinic in Arizona after 1 day of fever 103.7°F (39.8°C). On physical examination, the child had a maculopapular rash that involved his palms and soles. On auscultation, abnormal breath sounds were detected in the right lower lung. The parent stated that they had not traveled out of the local area recently. No one else in the family was ill, and the child was up-to-date on vaccinations. Chest radiographic evaluation revealed a possible right lower lobe infiltrate. On the basis of clinical and radiographic findings, pneumonia and roseola infantum were diagnosed. The child was administered an intramuscular injection of ceftriaxone and sent home with a prescription for oral amoxicillin/clavulanate.

The next day, the child was taken back to the clinic with vomiting and rash that was petechial. His fever was 105.7°F (41°C). He was admitted to the hospital, and antibiotic treatment for pneumonia was continued. On day 3 of hospitalization, the child developed DIC. Remarkable laboratory findings included: WBC count, 16.2 x 10^9 cells/L (normal: 4.5–11.0 x 10^9 cells/L); platelet count, 46 x 10^9 platelets/L (normal: 150–350 x 10^9 cells/L); aspartate aminotransferase (AST), 291 U/L (normal: 10–40 U/L); and alanine aminotransferase (ALT), 99 U/L (normal: 10–55 U/L). The child's condition worsened, and 7 days after the onset of illness, he died of pulmonary hemorrhage.

Case 2 synopsis. A serum sample collected 5 days before the child's death tested negative by IFA for IgM and IgG antibodies reactive with *R. rickettsii*. However, *R. rickettsii* DNA was detected in serum by PCR assay. RMSF can have a rapid course; 50% of RMSF deaths occur within 9 days of illness onset (*10,11*). IgM and IgG antibodies are typically not detectable before the second week of illness; therefore, serology will be not useful in diagnosing the infection in its earliest stages. Fever and rash in a young child can be caused by various enteroviruses, human herpesvirus 6, *N. meningitidis*, measles virus, *R. rickettsii*, and *E. chaffeensis*, among other agents. Common causes of bacterial pneumonia in a child this age might include *Streptococcus pneumoniae, Staphylococcus aureus, Streptococcus pyogenes*, and, less commonly, *M. pneumoniae.* Although this child lived in an area where RMSF is not common (e.g., Arizona), the diagnosis should not be excluded because of geography. Although RMSF is more common in the south central and south Atlantic states, it should be considered endemic throughout the contiguous United States (*10*). TBRD are seldom treated with the appropriate antibiotic, unless they are suspected. In this context, the majority of broad spectrum antimicrobials, including penicillins, cephalosporins, aminoglycosides, erythromycin, and sulfa-containing drugs are not effective against rickettsiae, ehrlichiae, or anaplasmae.

Case 3

In early June 1996, a man aged 52 years who was HIV-seropositive sought medical care at a hospital in Florida. He had a 4-day history of fever, headache, myalgias, nausea, and vomiting. The patient had been previously healthy, with no known previous opportunistic infections. An absolute CD4+ lymphocyte count of 164 cells/μl was documented 2 months before this visit. Physical examination revealed an acutely ill man; the patient had a fever of 103.5°F (39.7°C) and experienced dizziness and low blood pressure when he stood up (orthostatic hypotension). He reported that 2 weeks before admission, he had been bitten by a tick while hiking in central Georgia.

A CBC and chemistry panel and, because of the history of a tick bite, serologic tests for *E. chaffeensis* were ordered. Remarkable laboratory findings included hemoglobin 11.5 g/dL (normal: 13–18 g/dL); WBC count, 2.0 x 10^9 cells/L (normal: 4.5–11.0 x 10^9 cells/L), with 66% neutrophils (normal: 45%–75%), 18% bands (normal: 0%–5%), 8% lymphocytes (normal: 16%–46%), and 8% monocytes (normal: 4%–11%); and platelet count, 16 x 10^9 cells/L (normal: 150–350 x 10^9 cells/L). Peripheral blood smears revealed ehrlichial morulae in 2.5% of all leukocytes, including monocytes, lymphocytes, atypical

lymphocytes, neutrophils, and metamyelocytes. ALT was 73 U/L (normal: 10–55 U/L), and AST was 358 U/L (normal: 10–40 U/L).

On the basis of laboratory and clinical findings, a diagnosis of HME was made, and intravenous doxycycline (100 mg every 12 hours) was initiated. Despite doxycycline therapy, the patient remained febrile, severely thrombocytopenic, and continued to have elevated liver enzymes. He developed right lower lobe pneumonia and renal failure and died 6 days after hospitalization.

Case 3 synopsis. Patient sera obtained on days 1 and 5 of hospitalization were negative for IgG and IgM antibodies reactive with *E. chaffeensis*. However, the correct diagnosis was revealed on admission by a finding of morulae in leukocytes, and this diagnosis was subsequently confirmed when *E. chaffeensis* DNA was detected by using PCR in whole blood specimens from the patient, and the agent was isolated in cell culture. HME can be a severe disease, particularly in immunosuppressed persons. HME does not commonly cause rash in adults; therefore, history of tick exposure and characteristic leukopenia and thrombocytopenia were most useful in arriving at a diagnosis. Although morulae were observed in the patient's peripheral blood, microscopy is generally insensitive, and morulae are reported to be observed in only 1%–20% of patients with HME (*45,47*). Therefore, a diagnosis of HME would need to be confirmed by PCR, serology, or immunostaining, or culture isolation.

Case 4

In mid-May 1999, a female aged 69 years went to her physician in upstate New York. She had a 3-day history of nausea, vomiting, fatigue, and fever. She said that her dog had died 2 days earlier after a brief illness characterized by signs similar to her own. Physical examination revealed no abnormalities. Her temperature was 100.4°F (38°C).

- **What should be included in the differential diagnosis?**

  Possible diagnoses that should be considered include viral syndrome, foodborne illness, and urinary tract infection.
- **What additional information would assist with the diagnosis?**

  Patient should be queried regarding other signs and symptoms, recent activities and travel, exposure to other ill persons, foods consumed, and contact with ticks. The patient had no other symptoms to report and reported no unusual activities or recent travel.
- **What diagnostic tests, if any, are needed?**

  Because the patient's symptoms were nonspecific, a CBC should be ordered. Results will not be available until the next day.

On the basis of the signs present when the patient first went to her physician, she was diagnosed with gastroenteritis and instructed to return within 24–48 hours, if her symptoms did not improve. The patient would be contacted regarding her laboratory test results. The next day, the patient returned with continued fever and changes in mental status. Her temperature remained at 100.4°F (38°C), but she was notably confused and lethargic. Her physical examination was unremarkable and did not reveal the presence of a rash.

Laboratory tests obtained on the previous day revealed a WBC count of 3.8 x 10^9 cells/L (normal: 4.5–11.0 x 10^9 cells/L); a platelet count of 99 x 10^9 cells/L (normal: 150–350 x 10^9 cells/L); and a hemoglobin concentration of 12.7 g/dL (normal: 12–16 g/dL).

- **How does this information assist with the diagnosis?**

  On the basis of the patient's thrombocytopenia, leukopenia, and worsening clinical condition, encephalitis and sepsis should be included in the differential diagnosis.
- **What actions, including treatment, should be taken?**

  On the basis of presenting signs and laboratory tests, the patient was hospitalized and intravenous levofloxacin therapy was initiated for fever of unknown cause. Blood, urine, and stool cultures were ordered as well as serologic assays for *B. burgdorferi*, *E. chaffeensis*, and *A. phagocytophilum*, and PCR for *E. chaffeensis* and *A. phagocytophilum*.

  The patient's temperature returned to normal within 48 hours, her nausea and vomiting resolved, and her blood counts returned to normal. She was discharged after 3 days. Blood, urine, and stool cultures revealed no specific pathogens, and serologic assays were negative for antibodies reactive with *B. burgdorferi*, *E. chaffeensis*, and *A. phagocytophilum*.

Case 4 synopsis. IHC staining of tissues from the patient's dog, submitted by the veterinarian to CDC, demonstrated abundant spotted fever group rickettsial antigens, and rickettsiae were identified within and around blood vessels in multiple tissues, including brain and testes. The cause of the dog's illness was identified as RMSF. This information was communicated to the patient's physician. When the physician contacted the patient, she reported that her fatigue and headache had persisted after discharge from the hospital. The patient was treated with oral doxycycline, and all symptoms resolved within 1 week. Subsequent testing of the patient's sera for early and late convalescent-phase antibody titer confirmed a diagnosis of RMSF. Titers of IgM and IgG antibodies were 1,024 and 512, respectively, on day 17 and declined to 256 and 256, respectively, on day 89 after ill-

ness onset. The patient did not recall a tick bite and had not seen or removed ticks from her dog, although her dog roamed freely in wooded areas before its illness. Dogs can serve as sentinels for RMSF in human populations, and infections in canines have been associated with increased risk for infection in their owners (*22*).

Case 5

In May 2001, a man aged 38 years sought medical attention in Tennessee with complaints of headache, fever, sore throat, and vomiting. He was treated 3 days previously by his primary care physician who diagnosed pneumonia and prescribed azithromycin and levofloxacin, but his fevers persisted. He was taken to the ED by his wife, and she said that he had new onset of confusion. He had no pets or animal exposures. He worked as a construction manager and was frequently outdoors in wooded areas but did not recall a tick bite.

- **What should be included in the differential diagnosis?**

  The initial signs and symptoms were nonspecific, but the patient's confused state raised concern for possible involvement of the CNS. During the summer months, the differential diagnosis included viral meningitis (particularly enteroviral), arboviral meningoencephalitis (West Nile virus and others), TTP, and TBRD. Bacterial meningitis and herpes simplex virus (HSV) encephalitis do not have confined seasonality but also could cause this presentation. Sepsis and other multisystem illnesses are associated with encephalopathy, however, so the differential diagnosis remained broad.

  The patient had an oral temperature of 103.4°F (39.7°C); blood pressure, 100/60 mmHg; and heart rate, 120 beats/minute. The skin examination revealed diffuse erythema with a several scabs on the lower legs. Examination of the abdomen revealed moderate epigastric tenderness with deep palpation but no rebound tenderness or organomegaly. Neurologic examination was nonfocal, except for altered mentation (i.e., Glasgow coma score: 13).

  Laboratory testing revealed the following: WBC, 11.9 x 10^9 cells/L (normal: 4.5–11.0 x 10^9 cells/L); 84% segmented neutrophils (normal: 45%–75%); 8% band neutrophils (normal: 0%–5%); 3% lymphocytes (normal: 16%–46%); 5% monocytes (normal: 4%–11%); platelets, 50 x 10^9 cells/L (normal: 150–350 x 10^9 cells/L); total bilirubin, 3.5 mg/dL (normal: 0–1.0 mg/dL); AST, 439 U/L (normal: 10–40 U/L); ALT, 471 U/L (normal: 10–55 U/L); and alkaline phosphatase, 236 U/L (normal: 45–115 U/L). Lumbar puncture revealed a WBC of 0, RBC of 1 with normal glucose of 55 mg/dL and normal protein of 20 mg/dL. Creatinine was elevated at 3.9 mg/dL (normal: 0.6–1.5 mg/dL). Computed tomography scan of the head did not demonstrate an acute abnormality.

- **How does the physical examination and laboratory information change the differential diagnosis?**

Because of the normal lumbar puncture, meningitis (i.e., viral or bacterial) was a less likely diagnosis. However, examination of the CSF might be unremarkable in patients with encephalitis. The presence of thrombocytopenia and elevated transaminases was suggestive of TBRD. Additional considerations included acute cholecystitis, sepsis (possibly associated with DIC), toxic-shock syndrome (rash with multiple organ failure), and TTP (i.e., acute renal failure with fever, altered mental status, and thrombocytopenia).

- **What additional tests should be performed?**

  Appropriate diagnostic studies should include blood culture, serologic testing for RMSF and HME (and PCR for these if available), prothrombin time and partial thromboplastin time, examination of the peripheral blood smear (with particular attention for schistocytes or intracellular morulae), and ultrasound of the gallbladder to evaluate for inflammation.

  The coagulation studies were within normal limits, and no schistocytes or morulae were observed on smear. Abdominal ultrasound revealed a normal gallbladder but mild splenomegaly. Therapy was initiated with ceftriaxone and vancomycin. Approximately 6 hours later, the patient developed seizures, and acyclovir and doxycycline were added to the course of medicine to effectively treat herpesvirus infection and TBRD. A magnetic resonance imaging scan of the brain was normal, and electroencephalography revealed nonspecific slowing. Antibodies to *R. rickettsii* and *E. chaffeensis* were not detected in acute sera. HSV PCR on CSF was negative. Blood cultures did not grow bacteria. The patient defervesced, and mental status normalized over the next 3 days.

Case 5 synopsis. Serum obtained 31 days after the initial signs and symptoms contained no antibodies to *R. rickettsii* but had an IgG titer of 256 to *E. chaffeensis*, retrospectively confirming the diagnosis of HME. Whereas headache is a nearly universal complaint among patients with HME, altered sensorium might be observed in up to 20% of cases (*6*). Other CNS manifestations include seizures, meningismus, cranial nerve palsies, focal weakness, and coma. A lymphocytic pleocytosis can be observed in the CSF in approximately 50% of patients with HME who undergo lumbar puncture (*103*). Neutrophilic pleocytosis can be observed early in the course of the illness.

Neuroimaging studies are usually normal or nonspecific. TBRD should be included in the differential diagnosis of patients presenting with clinical evidence of CNS infection or CSF findings suggestive of aseptic meningitis.

Case 6

In July 1994, a man aged 44 years went to see his physician in central Minnesota. He complained of a 1-week history of fever, chills, generalized myalgias, and right temporomandibular joint pain. When he became ill, he treated himself empirically with ampicillin, which was available at home, for 2 days. Because the patient experienced no clinical improvement, he sought medical care. The patient worked outdoors and was frequently in wooded areas. Fourteen days before he went to his physician, he removed two deer ticks that had been attached to his skin for an unknown period.

Physical examination findings. The patient had a low-grade fever of 100.6°F (38.1°C). Examination of heart, lungs, and abdomen were normal. No lymphadenopathy, hepatosplenomegaly, or skin rash were noted. Cardiovascular, pulmonary, gastrointestinal, or neurological symptoms were not present. Overall, physical examination was unremarkable, except for fever.

Laboratory findings. No laboratory evaluations were performed during the visit. A presumptive diagnosis of acute Lyme disease was made, and empirical treatment with amoxicillin and probenecid was initiated; a 1-week follow-up visit was scheduled. Five days after the outpatient visit, the patient died suddenly at home. He had complained of shortness of breath the day before his death.

Case 6 synopsis. Histopathologic examination of the patient's heart revealed widespread transmural myocarditis with neutrophilic and lymphocytic infiltrates. Postmortem serum specimens were evaluated initially for presumptive carditis as a result of *B. burgdorferi* infection. Serum titers of IgG and IgM antibodies to *B. burgdorferi* were not detected by ELISA and western blotting. PCR assays of serum and whole blood for *B. burgdorferi* also were negative. However, antibody titers to *A. phagocytophilum* (formerly known as *E. equi*) were significantly elevated at titer >256 by IFA methods. Detection of DNA extracted by PCR from whole blood and positive IHC staining of cardiac tissue confirmed a diagnosis of anaplasmosis. Although infection with *A. phagocytophilum* was demonstrated in this case, the pathogenesis of the associated carditis was less clear (*104*).

The diagnosis of HGA can be difficult because of the nonspecific nature of the febrile illness frequently observed when the patient first seeks medical care. In regions where both Lyme disease and HGA are known to occur, distinguishing between the diseases in the early stages of illness might be difficult. Because treatment should be initiated before a definitive diagnosis is made, selection of an antimicrobial effective against both rickettsial organisms and *B. burgdorferi* (e.g., doxycycline) is recommended. This case also underscores the importance of close follow-up of patients treated for TBRD on an outpatient basis. Because these diseases can rapidly progress, clinicians should emphasize to patients the need to return for reevaluation if substantial improvement is not observed within 24–48 hours of initiation of treatment.

Conclusion

TBRD continue to cause severe illness and death in otherwise healthy adults and children, despite the availability of low cost, effective antimicrobial therapy. The greatest challenge to clinicians is the difficult diagnostic dilemma posed by these infections early in their clinical course when antibiotic therapy is most effective.

Early clinical presentations of HME, HGA, RMSF, and *E. ewingii* infection include fever, headache, myalgia, and malaise and are difficult to distinguish from other infectious and noninfectious diseases. Rash is observed frequently in RMSF, occasionally in HME, and rarely in HGA. TBRD tend to occur seasonally, with the majority of cases occurring during the warmer spring and summer months. However, cases might develop year-round. A detailed history of recent recreational or occupational activities might reveal potential exposure to ticks, although the absence of a history of a recent tick bite should not dissuade clinicians from considering a diagnosis of TBRD.

TBRD can be life-threatening. Severe manifestations of TBRD include prolonged fever, renal failure, myocarditis, meningoencephalitis, hypotension, acute respiratory distress syndrome, and multiple organ failure. Patients usually do not have diagnostic serum antibody levels during the first week of illness; therefore, an inability to detect antibodies (IgG or IgM) in acute-phase serum does not exclude TBRD. Health-care providers should not delay treatment while waiting for a diagnosis; rather, they should empirically provide treatment if they suspect TBRD. Doxycycline is the drug of choice for the treatment of presumptive or confirmed TBRD in both adults and children.

Examination of paired serum samples obtained during acute illness and 2–3 weeks later that demonstrate a rise in antibody titer is the most appropriate approach to confirm TBRD. Physicians who identify a potential case of TBRD

should notify the local health department, which can assist with obtaining diagnostic testing to confirm the diagnosis.

No licensed vaccines for TBRD are available. Avoiding tick bites and promptly removing attached ticks remain the best disease prevention strategies.

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Appendix

Tickborne Rickettsial Disease Case Report Form

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, Georgia 30333

Tick-Borne Rickettsial Disease Case Report

CDC# (1-4)

Use for: *Rocky Mountain spotted fever (RMSF), ehrlichiosis (human monocytic ehrlichiosis [HME]), and human granulocytic ehrlichiosis [HGE]).*

Form Approved
OMB 0920-0009

– PATIENT/PHYSICIAN INFORMATION –

Patient's name: _____
Address: _____ (number, street)
City: _____

Date submitted: ___/___/___ (5-6) (7-8) (9-12) (mm/dd/yyyy)
Physician's name: _____ Phone no.: _____

NETSS ID No.: (if reported) Case ID (13-18) — Site (19-21) — State (22-23)

– DEMOGRAPHICS –

1. State of residence: Postal abrv: (24-25)

2. County of residence: (26-50) ☐ Check, if history of travel outside county of residence within 30 days of onset of symptoms

3. Zip code: (51-59) _____-____

4. Sex: (60) 1☐ Male 2☐ Female

5. Date of birth: ___/___/___ (61-62) (63-64) (65-68) (mm/dd/yyyy)

6. Race: (69) 1☐ White 2☐ Black 3☐ American Indian Alaskan Native 4☐ Asian 5☐ Pacific Islander 9☐ Not specified

7. Hispanic ethnicity: (70) 1☐ Yes 2☐ No

8. INDICATE DISEASE TO BE REPORTED: (71) 1☐ RMSF 2☐ HME 3☐ HGE 4☐ Ehrlichiosis (unspecified, or other agent)

– CLINICAL SIGNS,SYMPTOMS, AND OUTCOMES –

9. Was a clinically compatible illness present? (72)
(fever or rash, plus one or more of the following signs: headache, myalgia, anemia, thrombocytopenia, leukopenia, or elevated hepatic transaminases) 1☐ YES 2☐ NO 9☐ Unk

10. Date of Onset of Symptoms: ___/___/___ (73-74) (75-76) (77-80) (mm/dd/yyyy)

11. Was an underlying immunosuppressive condition present? (81)
1☐ YES 2☐ NO 9☐ Unk
Specify condition(s): _____

12. Specify any life-threatening complications in the clinical course of illness: (82)
1☐ Adult respiratory distress syndrome (ARDS) 3☐ Meningitis/encephalitis
2☐ Disseminated intravascular coagulopathy (DIC) 4☐ Renal failure 9☐ None
8☐ Other: _____

13. Was the patient hospitalized because of this illness? (83) (If yes, date)
1☐ YES 2☐ NO 9☐ Unk ___/___/___ (84-85) (86-87) (88-91) (mm/dd/yyyy)

14. Did the patient die because of this illness? (92) (If yes, date)
1☐ YES 2☐ NO 9☐ Unk ___/___/___ (93-94) (95-96) (97-100) (mm/dd/yyyy)

– LABORATORY DATA –

15. Name of laboratory: _____ **City:** _____ **State:** __ __ **Zip:** _____-____

Below, indicate Y (Yes) or N (No), **ONLY** if the test or procedure was performed. **Lack of selection** indicates that the test or procedure was not performed.

16. Serologic Tests	Serology 1 COLLECTION DATE (mm/dd/yyyy) (101-2) (103-4) (105-8) Titer	Positive?	Serology 2* COLLECTION DATE (mm/dd/yyyy) (109-10) (111-12) (113-16) Titer	Positive?
IFA - IgG	(_____)	1☐ YES 2☐ NO (117)	(_____)	1☐ YES 2☐ NO (118)
IFA - IgM	(_____)	1☐ YES 2☐ NO (119)	(_____)	1☐ YES 2☐ NO (120)
Other test: (121-130) _____	(_____)	1☐ YES 2☐ NO (131)	(_____)	1☐ YES 2☐ NO (132)

* Was there a fourfold change in antibody titer between the two serum specimens? 1☐ YES 2☐ NO (137)

17. Other Diagnostic Tests ?	Positive?
PCR	1☐ YES 2☐ NO (133)
Morulae visualization*	1☐ YES 2☐ NO (134)
Immunostain	1☐ YES 2☐ NO (135)
Culture	1☐ YES 2☐ NO (136)

* Visualization of morulae not applicable for RMSF.

– FINAL DIAGNOSIS –

18. Classify case based on the CDC case definition (see criteria below): (138)
1☐ RMSF 2☐ HME 3☐ HGE
4☐ Ehrlichiosis (unspecified, or other agent): _____ (139-148)

(149) 1☐ CONFIRMED 2☐ PROBABLE

State Health Department Official who reviewed this report:
Name: _____
Title: _____ Date: ___/___/___ (mm/dd/yyyy)

COMMENTS:

CDC CASE DEFINITION

Confirmed RMSF: A clinically compatible case with 1) a fourfold change in antibody titer to *Rickettsia rickettsii* antigen by IFA, CF, latex agglutination, microagglutination, or indirect hemagglutination antibody test in two serum samples, or 2) a positive PCR assay, or 3) immunostaining of antigen in a skin biopsy or autopsy sample, or 4) isolation and culture of *R. rickettsii* from a clinical specimen.

Probable RMSF: A clinically compatible case with 1) a single positive antibody titer by IFA (≥1:64 if IgG); or 2) a single CF titer ≥1:16; or 3) a single titer ≥1:128 by a latex agglutination, indirect hemagglutination antibody, or microagglutination test; or 4) a fourfold rise in titer or a single titer >1:320, by Proteus OX-19 or OX-2 test.

Confirmed Ehrlichiosis: A clinically compatible case with 1) a fourfold change in antibody titer to antigen from an *Ehrlichia* species by IFA in two serum samples, or 2) a positive PCR assay, or 3) the visualization of morulae in white blood cells with a single serum positive antibody titer by IFA, or 4) immunostaining of antigen in a skin biopsy or autopsy sample, or 5) isolation and culture of an *Ehrlichia* species from a clinical specimen.

Probable Ehrlichiosis: A clinically compatible case with 1) a single positive antibody titer by IFA, or 2) the visualization of morulae in white blood cells.

CDC 55.1 Rev. 01/2001 **1st COPY STATE HEALTH DEPARTMENT**

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports March 31, 2006 / Vol. 55 / No. RR-4

Continuing Education Activity Sponsored by CDC

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

A Practical Guide for Physicians and Other Health-Care and Public Health Professionals

EXPIRATION — March 31, 2008

You must complete and return the response form electronically or by mail by **March 31, 2008**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 2.0 hours Continuing Medical Education (CME) credit; 0.2 Continuing Education Units (CEUs); or 2.4 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 55, RR-4), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at http://www.cdc.gov/mmwr/cme/conted.html.
3. Select which exam you want to take and select whether you want to register for CME, CEU, or CNE credit.
4. Fill out and submit the registration form.
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6. Submit your answers no later than **March 31, 2008**.
7. Immediately print your Certificate of Completion for your records.

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1. Read this *MMWR* (Vol. 55, RR-4), which contains the correct answers to the questions beginning on the next page.
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   Coordinating Center for Health Information and Service, MS K-95
   Centers for Disease Control and Prevention
   1600 Clifton Rd, N.E.
   Atlanta, GA 30333
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

This report provides practical information on the diagnosis, treatment, and reporting of tickborne rickettsial diseases (TBRD). This report represents a collaborative effort by a work group comprised of general practitioners, adult and pediatric infectious disease specialists, clinical laboratorians, and epidemiologists from clinical practice, academic centers, and CDC. The goal of this report is to present a framework to assist clinicians in recognizing the symptoms of TBRD, obtaining appropriate diagnostic tests, and initiating prompt and effective treatment. Upon completion of this educational activity, the reader should be able to 1) describe common epidemiologic manifestations of TBRD; 2) describe common clinical manifestations of TBRD; 3) list a differential diagnosis that ranks TBRD; 4) identify treatment decisions based on epidemiologic clues; 5) identify treatment decisions based on clinical clues; 6) identify the utility of confirmatory laboratory assay for TBRD; and 7) identify doxycycline treatment for patients with suspected TBRD.

To receive continuing education credit, please answer all of the following questions.

1. During the first 4–5 days of one or more of TBRD, which of the following signs or laboratory results could be reasonably expected?
- A. Presence of maculopapular rash.
- B. Evidence of leukopenia or thrombocytopenia.
- C. Demonstration of serum antibodies against one of the agents of TBRD.
- D. All of the above.
- E. A and B only.

2. Which etiologic agent(s) of TBRD can be occasionally observed on peripheral blood smears by using routine stains?
- A. *Rickettsia rickettsii.*
- B. *Ehrlichia chaffeensis.*
- C. *Anaplasma phagocytophilum.*
- D. All of the above.
- E. B and C only.

3. Concerning the epidemiology of TBRD...(*Indicate all that apply.*)
- A. clustering of cases within families or communities is well-described.
- B. the majority of cases occur during April–September.
- C. Rocky Mountain spotted fever (RMSF) is endemic throughout the majority of the United States.
- D. all of the above.
- E. A and B only.

4. Concerning the rash of RMSF…(*Indicate all that apply.*)
- A. it typically begins as pink macules.
- B. it generally appears on the same day as onset of fever.
- C. it generally appears 2–4 days after onset of illness.
- D. A and C only.
- E. A and B only.

5. Treatment of TBRD using doxycycline should only be initiated after laboratory confirmation of infection is obtained.
- A. True.
- B. False.

6. Which of the following antimicrobial agents is the drug of choice for a child aged 4 years with suspected RMSF?
- A. Chloramphenicol.
- B. Trimethoprim-sulfamethoxazole.
- C. Doxycycline.
- D. Amoxicillin/clavulanate.

7. Which of the following are considered appropriate for tick removal? (*Indicate all that apply.*)
- A. Kerosene.
- B. Fingernail polish.
- C. Lit matches.
- D. Fine-tipped forceps.
- E. All of the above.

8. Serologic tests are requested on a patient with onset of febrile illness and maculopapular rash 3 days ago. Serum IgG and IgM antibodies to *R. rickettsii* are negative. What can you conclude concerning the etiology of the patient's condition?
- A. The absence of antibodies indicates that the person does not have RMSF.
- B. Antibodies might not be present during the first week of illness; absence of antibodies does not rule out RMSF.
- C. Tests for other TBRD should be ordered because rash is more commonly observed with human monocytotropic (or monocytic) ehrlichiosis (HME) or human granulocytotropic (or granulocytic) anaplasmosis than with RMSF.

9. When considering a diagnosis of TBRD, important questions to identify during the patient interview include...(*Indicate all that apply.*)
- A. recent history of crawling or attached tick on person.
- B. recent history of crawling or attached ticks on pet animals (i.e., dogs).
- C. recent history of outdoor recreational activity (e.g., camping, hiking, or walking a dog).
- D. recent foreign or domestic travel to a TBRD-endemic region.
- E. all of the above.

10. Which of the following laboratory results meet the case definition of a confirmed case of HME? (*Indicate all that apply.*)
- A. Demonstration of 4-fold change in antibody titer against *E. chaffeensis.*
- B. Single positive antibody titer against *E. chaffeensis.*
- C. Detection of *E. chaffeensis* DNA in a clinical specimen by using polymerase chain reaction assay.
- D. Identification of morulae in leukocytes.
- E. A and C only.

11. Which best describes your professional activities?
- A. Physician.
- B. Nurse.
- C. Health educator.
- D. Office staff.
- E. Other.

12. I plan to use these recommendations as the basis for…(*Indicate all that apply.*)
- A. health education materials.
- B. insurance reimbursement policies.
- C. local practice guidelines.
- D. public policy.
- E. other.

13. Overall, the length of the journal report was…
- A. much too long.
- B. a little too long.
- C. just right.
- D. a little too short.
- E. much too short.

14. After reading this report, I am confident I can describe common epidemiologic manifestations of TBRD.
- A. Strongly agree.
- B. Agree.
- C. Undecided.
- D. Disagree.
- E. Strongly disagree.

15. After reading this report, I am confident I can describe common clinical manifestations of TBRD.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can list a differential diagnosis that ranks TBRD.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can identify treatment decisions based on epidemiologic clues.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can identify treatment decisions based on clinical clues.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can identify the utility of confirmatory laboratory assay for TBRD.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

20. After reading this report, I am confident I can identify doxycycline treatment for patients with suspected TBRD.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

21. The learning outcomes (objectives) were relevant to the goals of this report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

22. The instructional strategies used in this report (text, figures, tables, box, and appendix) helped me learn the material.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

***MMWR* Response Form for Continuing Education Credit**
March 31, 2006/Vol. 55/No. RR-4

Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis — United States
A Practical Guide for Physicians and Other Health-Care and Public Health Professionals

To receive continuing education credit, you must
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Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	16.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
2.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	17.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
3.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	18.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
4.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	19.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
5.	[ ]A	[ ]B				20.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
6.	[ ]A	[ ]B	[ ]C	[ ]D		21.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
7.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	22.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
8.	[ ]A	[ ]B	[ ]C			23.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
9.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	24.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
10.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	25.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
11.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	26.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
12.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	27.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
13.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	28.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E
14.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	29.	[ ]A	[ ]B			
15.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	30.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E [ ]F

Signature ***Date I Completed Exam***

23. The content was appropriate given the stated objectives of the report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

24. The content expert(s) demonstrated expertise in the subject matter.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

25. Overall, the quality of the journal report was excellent.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

26. These recommendations will improve the quality of my practice.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

27. The availability of continuing education credit influenced my decision to read this report.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

28. The *MMWR* format was conducive to learning this content.
A. Strongly agree.
B. Agree.
C. Undecided.
D. Disagree.
E. Strongly disagree.

29. Do you feel this course was commercially biased? (*Indicate yes or no; if yes, please explain in the space provided.*)
A. Yes.
B. No.

30. How did you learn about the continuing education activity?
A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–10.
1. E; 2. E; 3. D; 4. D; 5. B; 6. C; 7. D; 8. B; 9. E; 10. E.

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