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

Health Professionals

Diagnosis and Management of Tickborne Rickettsial

Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis

--- United States

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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 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

 This report also provides resources on TBRD for health-care 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 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 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

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 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).

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 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 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

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occurred in children aged <10 years, surveillance during 2003 demonstrates a higher

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

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:

 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

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).

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:

Clinical Assessment

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.

 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.

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 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

 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.

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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:

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). However, 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:

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 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:

  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 constitutes 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 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

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 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:

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

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

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:

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:

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 (40.6ºC) and a

maculopapular rash on her legs, including the soles of her feet.

Possible causes of fever and rash in this child

include meningococcemia, RMSF, HME, enteroviral

infections, Kawasaki disease, drug reactions, and streptococcal disease with exanthem.

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, 16.2×10^9 cells/L (normal: $4.5\text{--}11.0 \times 10^9$ cells/L); platelet count, 46×10^9 platelets/L (normal: $150\text{--}350 \times 10^9$ 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 103.5ºF (39.7ºC) 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 109 cells/L (normal: 4.5--11.0 x

109 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

109 cells/L (normal: 150--350 x

109 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

100.4ºF (38ºC).

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
100.4ºF (38ºC), 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 109 cells/L (normal: 4.5--11.0 x 109 cells/L); a platelet count of 99 x 109 cells/L (normal: 150--350 x 109 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 illness 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 (39.7ºC); 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 109 cells/L (normal: 4.5--11.0 x

109 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 109 cells/L (normal: 150--350 x

109 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

100.6ºF (38.1ºC). 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,

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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,

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not have diagnostic serum antibody levels during the first week of illness; therefore, an inability to detect antibodies (IgG or

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diagnosis; rather, they should empirically provide treatment if they suspect TBRD. Doxycycline is the drug of choice for the treatment

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

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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.

References Physical examination revealed an acutely ill man; the patient had a fever of

103.5ºF (39.7ºC) 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 109 cells/L (normal: 4.5--11.0 x

109 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

109 cells/L (normal: 150--350 x

109 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

100.4ºF (38ºC).

 Laboratory tests obtained on the previous day revealed

a WBC count of 3.8 x 109 cells/L (normal: 4.5--11.0 x

109 cells/L); a platelet count of 99 x

109 cells/L (normal: 150--350 x

109 cells/L); and a hemoglobin concentration of

12.7 g/dL (normal: 12--16 g/dL).   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 illness 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. 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

100.6ºF (38.1ºC). 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).

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