Chapter 11

RICKETTSIAL DISEASES

VINCENT L. ANGELONI, M.D.*

Major, Medical Corps, U.S. Army; Staff Immunodermatologist, Dermatology Clinic, Brooke Army Medical Center, Fort Sam Houston, Texas 78234-6200

INTRODUCTION

Rickettsiae are pleomorphic, rod-to-coccoid–shaped organisms that stain poorly with Gram's stain but are morphologically typical of Gram-negative bacteria. They are unique in that, except for the genus *Rochalimaea*, they are obligate intracellular parasites. Living cells are required for the culture of all rickettsiae (with the exception of *Rochalimaea quintana*, the rickettsia that causes trench fever). This is a hazardous undertaking done by only a few specially equipped laboratories.

Within the family Rickettsiaceae, four genera—*Rickettsia, Coxiella, Rochalimaea,* and *Ehrlichia*—are capable of producing disease in humans. The rickettsiae are grouped by the clinical infections they induce, their etiologic agents, vectors, serologic reactions, and epidemiological factors. Their antigenic differences have allowed these organisms to be classified into genera, groups, and species. The pathogenic members of the family Rickettsiaceae can be divided into six serogroups: spotted fever, typhus, scrub typhus, trench fever, Q fever, and ehrlichiosis (Table 11-1). In the spotted fever group, the typhus group, and in scrub typhus, rickettsiae are found within the cytoplasm of the infected cell. Spotted fever serogroup organisms may also grow within the nucleoplasm of the cell.[1] *Ehrlichia* species exist within a phagosome in the host cell, and *Coxiella* within a phagolysosome; *Rochalimaea* species are epicellular parasites that cling to the exterior of cells.

The transmission of rickettsial diseases to humans usually requires an insect or arachnid vector, and rickettsiae survive only briefly outside the host or vector. Human infection is incidental (except for epidemic typhus) and is of no benefit to the infecting rickettsial organism. Rickettsiae do not penetrate intact skin but can cause infection in abraded skin or can be transferred by the fingers to mucosal surfaces, which are readily infected. In humans, rickettsial diseases can be mild or life threatening and are characterized by fever and skin rash. The genus *Coxiella,* however, is an exception to the above generalizations. *Coxiella* is extremely resistant to desiccation and survives for long periods outside the host; its spread does not involve a vector but occurs via inhalation of the organism, and it is usually not associated with a skin rash. Rocky Mountain spotted fever (RMSF), caused by *R rickettsii,* is the most common rickettsial disease in the United States[2] and carries the threat of significant morbidity and mortality if the diagnosis is not made promptly. Other rickettsial diseases that are indigenous to the United States include murine typhus, rickettsialpox, and *R prowazekii* infections associated with flying squirrels.[3,4] However, imported cases of boutonneuse fever[5] or scrub typhus[6] are not unusual.

SPOTTED FEVER SEROGROUP

Rickettsiae in the spotted fever serogroup are genetically related but differ in their surface antigens. There are several nonpathogenic members of this group. The spotted fever group organisms are maintained in nature in Ixodid ticks and animals. They induce a widespread vasculitis that involves both skin and internal organs, producing the clinical manifestations of rash and dysfunctions of brain, heart, lungs, and kidneys. The diseases produced by the spotted fever serogroup include RMSF, boutonneuse fever, and rickettsialpox. RMSF is generally the most severe infection of the group, although fatalities may also occur with infections of other spotted fever serogroup organisms. These other organisms produce diseases that induce headache, myalgia, fever, and maculopapular eruptions that may become petechial similar to RMSF, but the diseases are usually milder and may have an eschar at the site of tick attachment.

Rocky Mountain Spotted Fever

RMSF is an acute, severe, infectious disease. It is the most prevalent of the rickettsial diseases in the United States and is identical to Sao Paulo fever, Colombian spotted fever, *fiebre maculosa*, *fiebre petequial,* and *fiebre manchada* of Mexico. RMSF was first described in the 1890s, when a series of cases was described in the Bitterroot valley of Montana. The first published account was by a U.S. Army surgeon in 1896,[7] although the impact of RMSF on military campaigns has been insignificant. From 1942 through 1945, only 135 cases were reported among army personnel; all of these occurred in the

TABLE 11-1
RICKETTSIAL DISEASES OF MEDICAL IMPORTANCE

Serogroup	Disease	Organism	Vector	Reservoir	Geographical Location
Spotted Fever	Rocky Mountain Spotted Fever (Brazilian and Mexican spotted fevers)	*Rickettsia rickettsii*	Tick	Ticks, rodents, dogs	Western hemisphere
	Boutonneuse Fever (Mediterranean fever, South African Tick Bite fever, Kenya tick typhus, Indian tick typhus, Marseilles fever)	*R conorii*	Tick	Ticks, rodents, dogs	Europe, Africa, Asia
	Siberian Tick Typhus North Asian tick-borne rickettsial disease	*R sibirica*	Tick	Rodents, ticks	Siberia, Mongolia
	Queensland Tick Typhus	*R australis*	Tick	Rodents, marsupials	Australia
	Rickettsialpox	*R akari*	Mouse mite	House mouse	North America, Europe, former Soviet Union, Korea
Typhus	Epidemic Typhus	*R prowazekii*	Body louse	Human	Worldwide (war, famine associated), rare in the United States
	Recrudescent Typhus (Brill-Zinsser Disease)	*R prowazekii*	None	Human	Worldwide
	Endemic (Murine) Typhus	*R typhi*	Rat flea	Rat	Worldwide
Scrub Typhus	Scrub Typhus	*R tsutsugamushi*	Mite	Rodents, trombiculid mites	Asia, Australia, Pacific islands, Malaysia
Trench Fever	Trench Fever	*Rochalimaea quintana*	Body louse	Human	Europe, Africa, Central and South America (war associated)
Q Fever	Q Fever	*Coxiella burnetii*	None (airborne)	Ticks, sheep, goats, cattle	Worldwide
Ehrlichiosis	Ehrlichiosis	*Ehrlichia chaffeensis*	Tick?	Unknown	Southeastern, south-central United States
Sennetsu Fever	Sennetsu Fever	*E sennetsu*	Tick?	Unknown	Japan, Malaysia

continental United States.[8] Several large military bases (eg, Fort Sill, Oklahoma; Fort Bragg, North Carolina) are located in areas of the United States that have some of the highest rates reported for RMSF. Therefore, it is possible that medical officers in these areas will see patients with this disease.

Microbiology

R rickettsii is a small (0.3 x 1 μm), pleomorphic, coccobacillary organism and is an obligate intracellular, bacterial parasite. It may be stained with Geimsa, Machiavello's, or Castaneda's stains. Although *R rickettsii* stains poorly with the Gram's stain, it is Gram-negative. This fairly fragile organism is killed by drying, moist heat (50°C), formalin, and phenol. Freezing does not kill the organism, and it may remain viable in the frozen state for long periods. Because *R rickettsii* grows only in the cytoplasm or nucleoplasm of eukaryotic cells, culturing is done in guinea pigs and mice, yolk sacs of embryonated hen's eggs, or tissue culture. The organ-

isms grow directly in the cytoplasm of the host, without being surrounded by a host cell membrane. The outer membrane of the organism has a slime layer, which is thought to play a role in virulence. After the organism divides by binary fission a few times within the cell, some of the rickettsiae exit the cell to infect other cells. In contrast, *R prowazekii* replicates until the host cell finally bursts.[9] *Rickettsia* species proliferate best at temperatures of 32°C to 38°C, which may explain the accentuated rash on the extremities and scrotum.[10]

Various tick species serve as the primary reservoir, hosts, and vectors. Rickettsial growth in the tick's ovaries results in transovarial transmission to at least some of the female tick's offspring.[11] Whether the infection is obtained transovarially or through feeding on an infected mammal, the infection persists for the life of the tick. This may be several years. Tick species harboring *R rickettsii* are characterized by a life cycle with three stages: larva, nymph, and adult. Only the adult ticks feed on humans. When the tick is attached to and feeding on a human, a "reactivation" process occurs in the rickettsial organism and it transforms from a dormant, avirulent state to a highly pathogenic one. This reactivation requires several hours. A certain interval of time is also required for the organisms to be inoculated into human skin after their release from the tick's salivary gland.[12] In the tick, infection with the organism begins in the gut wall, which is eventually penetrated and a generalized infection is produced. Transstadial transmission (ie, transmission of the organism from the larva to the nymph and from the nymph to the adult) also occurs in these ticks.

In humans, inoculated rickettsiae spread via the blood and lymphatic system to infect endothelial cells in all parts of the body. The organisms proliferate within the endothelial cells with some of the organisms exiting the infected cells, causing infection in other endothelial cells or vascular smooth muscle cells. Infection in humans is a biological dead end for the organism.

Epidemiology and Vectors

Humans are only incidentally involved with *R rickettsii*. Transmission of disease occurs when an infected tick bites a human or the tick is crushed and contaminates the skin with rickettsiae. Rickettsiae are present in the hemolymph and feces of infected ticks. Aerosol spread of the disease is unlikely because the organism loses infectiousness rapidly in such material,[11] but this has been reported in laboratory accidents.[13] In one case, RMSF was acquired via blood transfusion when the infected donor was phlebotomized 3 days prior to the onset of illness.[14]

When the tick attaches for its first meal after hibernation, a reactivation process is initiated in the rickettsial organism, which adds several hours to the time needed for the transmission of the infection.[15] Later in the season, only 6 to 10 hours of attachment may be needed for transmission.[16,17] *Dermacentor andersoni* (the wood tick) requires 10 to 24 hours of feeding to transmit the infection.[11] In endemic areas, screening children for ticks twice a day is recommended to prevent infection.[18,19]

In the continental United States, several species of ticks have been identified as carriers of RMSF. *D andersoni* is the primary vector in the West, while *D variabilis* (the dog tick) is implicated in the South and the East. *Amblyomma americanum* (the Lone Star tick) has been implicated as a possible vector in the Southwest. In Brazil and Colombia, *Amblyomma cajennense* is the vector. *Rhipicephalus sanguineus* (brown dog tick) is a vector in southern regions of Mexico and the United States.[16,20] Most species of vector ticks appear to have a low rate of infection. The prevalence of *R rickettsii* infection among ticks has been estimated at 1 in 1,000.[12]

Several other ticks have been found to be infected with *R rickettsii* but, because they rarely attack humans, are not important as vectors. These are *Hemaphysalis leporispalustris*,[12] *Dermacentor parumapertus*, *Ixodes dentatus*, *I brunneus*, and *I texanus*. Several species can be considered potential vectors, however; they attack humans and have been found to contain *R rickettsii* or a closely related organism,[11] but they have not yet been documented as a cause of RMSF (Exhibit 11-1).

R rickettsii has also been found in numerous small mammals (eg, chipmunks, opossums, rabbits, squirrels, mice, and rats). This is due largely to the feeding habits of the various tick hosts. Some of these small mammals develop rickettsemia to a degree that would allow them to cause new infections in uninfected ticks that feed on them. These mammals probably play an important role in maintaining the organisms in nature. Infection in ticks tends to be limited in subsequent generations because the rickettsial infection may cause decreased viability and fecundity in tick offspring after several generations. Thus, the presence of small mammals provides a survival advantage for the organism by establishing new lines of infection, thereby overcoming the limitation of the infection that would be expected by the decreased reproductive ability or survival of future tick generations.[15,21]

EXHIBIT 11-1

VECTORS OF ROCKY MOUNTAIN SPOTTED FEVER

Known Vectors
Dermacentor andersoni
D variabilis
Amblyomma cajennense
Rhipicephalus sanguineus

Potential Vectors
Amblyomma americanum
D maculatum
D occidentalis
Ixodes scapularis
I pacificus

Data source: Burgdorfer W. Ecological and epidemiological considerations of Rocky Mountain spotted fever and scrub typhus. In: Walker DH, ed. *Biology of Rickettsial Diseases*. Vol 1. Boca Raton, Fla: CRC Press; 1988: 33–50.

Although the name RMSF persists, it has become a misnomer. Prior to the 1940s, most cases were reported from the western mountain states. Now, however, the most common sites in the United States are the eastern, southeastern, and south-central regions.[22] The incidence appears to be highest in areas characterized by eastern deciduous forests made up largely of pine, oak, or hickory trees.[18] The disease may also occur in urban areas and, rarely, urban endemic foci have been described.[23] All states in the United States except Maine, Alaska, and Hawaii are considered endemic areas.[24] States with the highest rates of infection are Oklahoma, North Carolina, and South Carolina.[12,18] High incidences are also seen in Maryland, Virginia, Georgia, Tennessee, Ohio, Missouri, Arkansas, Texas, and Kansas.

Human males and females of all ages are susceptible to RMSF. The age distribution and gender of patients tend to be related to the occupational or recreational activities in the area. Rural areas have higher incidences of disease and in the West, infection seems to occur more often in persons following outdoor occupations. Adults are primarily affected in the Rocky Mountain area, but in the southern United States, children make up a large number of cases, probably because the dog tick is the main vector in that area.

Seasonal variations in the number of reported cases are related to the responsible tick vector's periods of activity. Most cases occur between April and October although sporadic cases occur throughout the year, even in winter.[25] July is typically the month with the highest number of reported cases. Even with effective antibiotics available, the fatality rate for RMSF remains in the 3% to 7% range.[2,10,16,22,26]

Clinical Manifestations

The incubation period lasts 4 to 8 days (range 2–14 d). The prodromal period lasts 2 to 3 days and is characterized by headache, malaise, anorexia, photophobia, chills, fever, arthralgia, and myalgia. Symptoms may appear gradually or rather suddenly with rigors, prostration, and severe headache, backache, and abdominal pain. At this point, the observed symptoms are nonspecific and the disease is difficult to distinguish from more common illnesses. Asymptomatic infection has not been conclusively demonstrated.[12]

Because RMSF causes widespread capillary damage, the signs and symptoms of the disease are protean. Although the presence of the RMSF classic triad (fever, rash, history of tick bite) would seem to be very helpful, only 3% of patients will have these findings during the first 3 days of illness.[2]

Fever, rash, and edema are common clinical findings. The fever is characterized by morning remissions, may reach 106°F, and can last up to 3 weeks in severe cases. Restlessness, insomnia, and delirium can be seen when the fever peaks. The pulse rate usually parallels the temperature and a sudden elevation of pulse rate over a 24-hour period may herald the appearance of circulatory failure. Myalgia, hyperesthesia, slight nonproductive cough, and epistaxis are also seen frequently.

The rash is an important, although not always a completely reliable, diagnostic sign (Figure 11-1). It may appear from 2 to 14 days after onset, occurring most often around the fourth day. An eschar is not typical of RMSF, although it has been described rarely.[27] The rash first appears on the cooler portions of the body such as the distal extremities or scrotum.[19] Initially, it is macular and blanches with pressure. In some cases, it may appear first on the trunk, but even in these patients it tends to become accentuated on the extremities.[18] The lesions spread in a centripetal fashion with involvement of the trunk, buttocks, neck, axilla, and face. Within 2 to 3 days, the rash assumes a petechial or purpuric character. At this time, while the rash is petechial, the Rumpel-Leede phenomenon may be seen: when a tourniquet or sphygmomanometer cuff is applied to the extremity for 3 to 5 minutes, petechiae can be seen below the site of compression. The Rumpel-Leede phenomenon is not specific for RMSF and

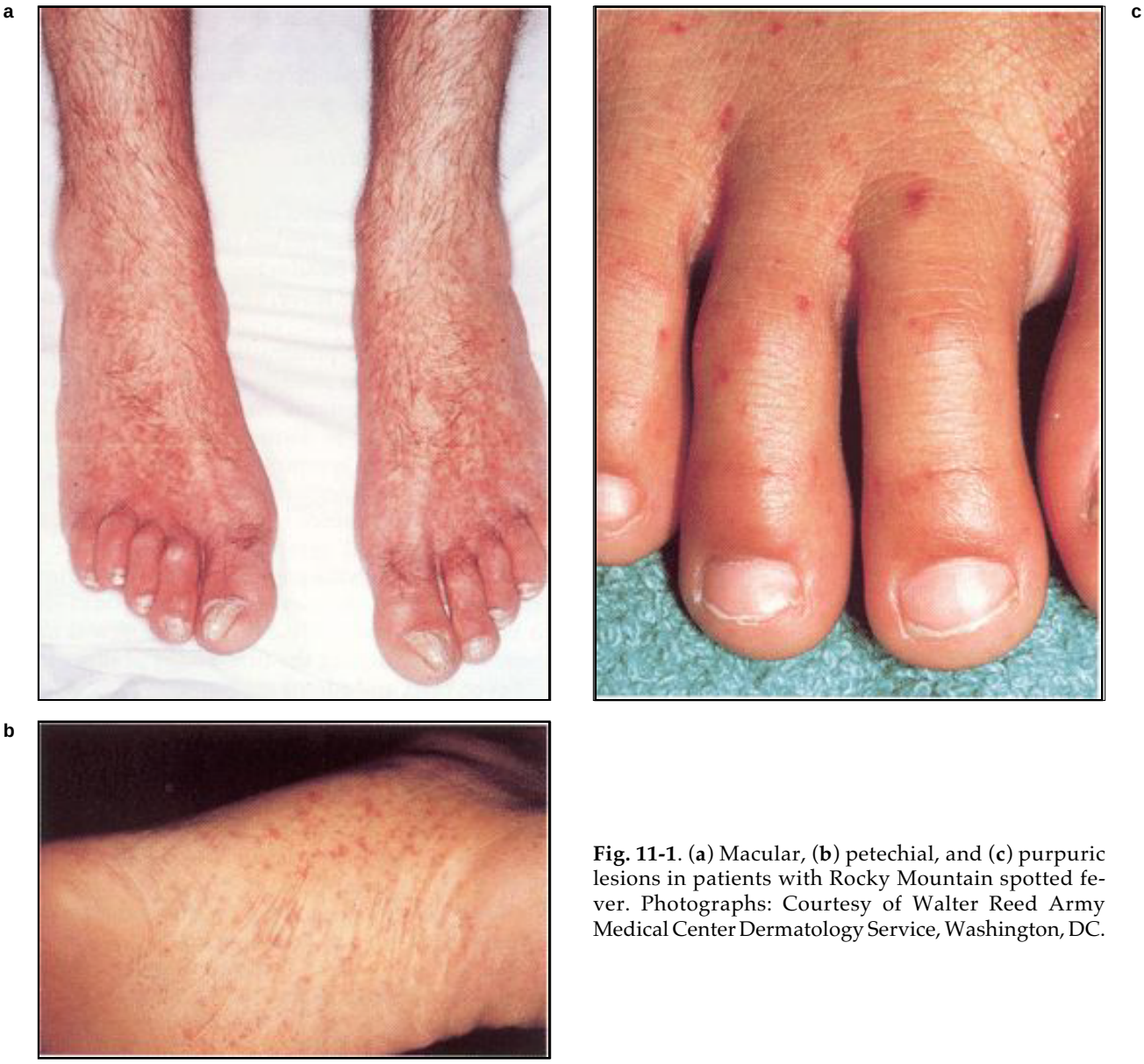

Fig. 11-1. (**a**) Macular, (**b**) petechial, and (**c**) purpuric lesions in patients with Rocky Mountain spotted fever. Photographs: Courtesy of Walter Reed Army Medical Center Dermatology Service, Washington, DC.

also can be seen in platelet disorders and sometimes scarlet fever. After the petechial stage, lesions may coalesce and form ecchymotic areas. Necrotic or gangrenous changes may follow, occurring over bony prominences, the scrotum, penis, vulva, ears, and, in severe cases, the extremities. In mild cases, the rash may never become petechial and the macules can disappear, especially after antibiotic treatment has been initiated. Estimates of the percentage of cases with petechial rashes are in the range of 40% to 60%. Only one third of patients will have fever, headache, and petechial skin lesions.[28] The rash may not involve the palms and soles in a substantial number of cases.[12,29]

Unfortunately, the late appearance of the rash often causes a delay in diagnosis that could have catastrophic consequences. In approximately 10% of patients, the rash may be completely absent.[22] "Spotless" spotted fever is seen more often in older patients, fatal cases, and black people whose heavy pigmentation obfuscates the rash.

Nonpitting edema occurs frequently. It may be generalized or strictly limited to the periorbital region, face, or extremities. This usually worsens as the disease progresses and is a direct result of the vascular damage caused by the organism.

Nonproductive cough may be noted. Chest radiography may reveal patchy interstitial infiltrates in

approximately one third of patients. The pulmonary edema seen in severe cases is due to increased permeability in the pulmonary vessels caused by rickettsial infection of the endothelial cells.[10] Severe pulmonary edema and development of adult respiratory distress syndrome is a life-threatening complication.

Eye findings include conjunctivitis (in 30%), photophobia, and sometimes petechial lesions. In severe disease, ocular palsy, hemorrhage, venous engorgement, vascular occlusion, and papilledema may occur. The latter is seen in 1.5% of patients, can occur with normal cerebrospinal fluid pressure,[2,29,30] and is thought to be due to vascular involvement of the optic nerve head.

Electrocardiographic findings are usually nonspecific; however, myocarditis occurs and can trigger arrhythmias in approximately 7% of patients.[2] There have also been isolated reports of creatine kinase–myocardial band elevations.[29] In general, the myocarditis is rather mild and often completely overshadowed by pulmonary problems.[29]

Abdominal pain is not unusual and could be severe enough to cause misdiagnosis and unnecessary laparotomy for suspected appendicitis,[31] ruptured diverticula, or acute cholecystitis.[12,32] Anorexia, nausea, vomiting, and diarrhea are the most frequent gastrointestinal complaints.[33] Probably the most common misdiagnosis is gastroenteritis. Guaiac-positive stools and vomitus can be seen in approximately 10% of patients.[34] Fatal gastrointestinal hemorrhages may occur.[9] Splenomegaly can occur later in the first week of illness. Jaundice is seen infrequently, and the liver is usually not severely damaged. Hypotension due to peripheral circulatory failure results in prerenal azotemia that sometimes progresses to acute oliguric renal failure.[29,35]

Neurological manifestations are common and can mimic encephalitis or meningitis. Mild nuchal rigidity and Kernig's sign may be present. Early in the disease, mental status changes consisting of confusion, dulling of the senses, and restlessness are possible. Lethargy, delirium, and coma may follow. Loss of sphincter control and transient deafness are rare complications. Abnormal neurological findings such as ankle clonus or a positive Babinski sign can appear as the condition worsens. Other neurological manifestations include tremor, rigidity, meningismus, opisthotonus, central blindness, convulsions, pyramidal tract signs, aphasia, dysarthria, ataxia, unilateral corticospinal signs, hemiplegia, paraplegia, neurogenic bladder, and cerebral hemorrhage.[18,28,29,36] Psychiatric symptoms may complicate the picture; hallucinations, paranoid behavior, and involuntary commitment have been reported.[28]

Initially, the illness appears nonspecific and is difficult to distinguish from other illnesses associated with fever, headache, and myalgia. In RMSF, however, symptoms usually progress. Overwhelming infections may result in death within a few days, especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. In fatal cases, patients are usually comatose and may show signs of neurological embarassment, circulatory collapse, and renal failure.

Severe disease may be associated with thrombocytopenia resulting in various hemorrhagic phenomena such as purpura or secondary hemorrhage in the brain or lungs. Necrotic gangrene may occur in dependent areas such as the fingers, toes, scrotum, and earlobes. Massive skin necrosis requiring skin grafts has also been reported.[37] Secondary bacterial infection may also complicate the picture: pneumonia, otitis media, and parotitis may occur.[16] Convalescence is usually rather slow, requiring weeks to months.

Most patients without complicated courses will have no sequelae.[28] Neurological sequelae include symptoms ranging from "nervousness" to convulsions. Abnormal electroencephalogram findings may persist. In children, the risk of learning disability is increased.[18] Deafness and impaired vision can be permanent. Severely ill patients may have impairment of fine motor control, hypotonia, hyperreflexia, ataxia, mental retardation, aphasia, paraplegia, neurogenic bladder, transverse myelitis, depression, learning disabilities, and decreased intelligence.[29]

Laboratory Findings

There are no diagnostic laboratory findings in RMSF. Early in the disease, leukopenia or a normal white blood cell count may be seen with increased band forms that later evolve into a leukocytosis.[18, 28] Mild, normocytic, normochromic anemia may also be found. Hemolysis occurs rarely, mainly in patients who are deficient in G6PD.[26,38] Thrombocytopenia may occur in 32% to 52% of patients[16] and may be related to an increased adherence and margination of platelets, to vascular endothelium at foci of infection.[39] Evidence of coagulation disturbances can be found. Hypofibrinogenemia, elevated fibrin degradation product levels, and prolonged prothrombin and partial thromboplastin times can occur and may not be associated with disseminated intravascular coagulation (DIC) or bleeding.[28] Al-

though laboratory findings are compatible with intravascular coagulation, true DIC in RMSF probably occurs only rarely. Normal or elevated plasma fibrinogen levels can be seen in RMSF, an exceptional finding in cases of DIC.[10] In true DIC, occlusive thrombi occur in normal blood vessels and heparin is effective therapy. In RMSF, heparin therapy may result in increased hemorrhage.[40] Thrombi in RMSF are found only in vessels where there is severe injury, and bleeding occurs more often without coagulopathy. The preferred treatment is with antirickettsial antibiotics.[9,12]

Hyponatremia is common. Abnormal liver function tests may be noted; aspartate aminotransferase, alanine aminotransferase, and bilirubin may be increased.[29,33] Blood urea nitrogen may be increased. The urine is usually normal except in cases where renal failure is developing. Inappropriate secretion of antidiuretic hormone has been reported[41]; however, inappropriate secretion cannot be diagnosed with certainty when hypotension, hypovolemia, or edema are present.[42] What appears to be elevated may actually be *appropriate* secretion of antidiuretic hormone followed by a dilutional hyponatremia.[29]

Cerebrospinal fluid findings are variable. Moderate lymphocytic pleocytosis is not uncommon although cells may be absent. Glucose is usually normal and protein may be normal to moderately elevated.[28]

In severe cases, elevation of creatine kinase and aldolase enzymes may be noted, reflecting muscle involvement.[29]

Prognostic Factors

Two important factors in the prognosis of RMSF are the rapidity with which the diagnosis is made or suspected and when treatment is started. Typically, patients who are treated before the fifth day of illness do well, whereas those who are not treated until the sixth day have a 25% mortality.[43] Factors that result in delayed diagnoses include the late appearance or absence of the rash, late reporting or lack of tick-bite history, and an initial diagnosis other than RMSF.

Age is also important: patients over 40 do significantly worse than younger patients. Mortality for patients younger than 40 years of age is approximately 13%, whereas patients older than 40 have a 41% mortality.[18] The presence of other underlying diseases complicates management and adversely affects prognosis. The infective burden and the virulence of the organisms also play a role. This is reflected by a short incubation period and increased severity of symptoms. Patients with G6PD deficiency can have particularly fulminant courses.[44]

The need for mechanical ventilation, the presence of coma, or acute renal failure portend a poor prognosis. In one study, 9 of 10 patients who needed mechanical ventilation died.[30] Of patients who lapse into coma, 86% have fatal outcomes.[12] Acute renal failure complicates fluid management and may require dialysis.[12]

Men tend to do worse than women. Black men also seem to have more severe illness, a finding that is unrelated to skin color or socioeconomic class.[29,38] When the role that dark pigmentation plays in delaying recognition of the RMSF rash, and therefore delaying treatment, is eliminated, black men are still found to have a significantly higher mortality. Thus, in a study comparing mortality data in black women to age-matched white women with RMSF, the mortality rates are very similar. However, when black men are compared to an age-matched white control population with RMSF, the black men have a strikingly higher mortality rate than their white counterparts.[38] Case fatality rates for blacks are more than 3-fold higher than for whites, with black men over the age of 40 at high risk for a fatal outcome.[22,26]

Diagnosis

Serologic Diagnosis. Serology is the principal diagnostic tool for rickettsial diseases used in most laboratories. It is, however, a retrospective method that compares acute titers of antibodies to convalescent titers obtained weeks later. Treatment should not be withheld while waiting for antibody titers. Because immunity to infection is lifelong, confirming the diagnosis of RMSF is important for both the physician and the patient. Samples should be collected as early as possible in the illness, during the second week, and again 4 to 6 weeks after the onset. Serologic studies should be repeated even after successful treatment, because negative results imply that the patient does not have immunity.[19]

Diagnostic testing for RMSF includes commercially available tests such as latex agglutination and Proteus OX-19 and OX-2 agglutination (the Weil-Felix test). Indirect fluorescent antibody, indirect hemagglutination, and complement fixation tests are available through reference laboratories. There is cross-reactivity of the antibodies identified by indirect hemagglutination, indirect fluorescent antibody, and latex agglutination among other mem-

bers of the spotted fever serogroup (*R akari*, *R conori*, *R sibirica*, and *R australis*), typhus serogroup (*R prowazekii*, *R typhi*), and scrub typhus serogroup (*R tsutsugamushi*). The indirect hemagglutination and indirect fluorescent antibody tests appear to be the most sensitive of those currently in use.[45]

The indirect fluorescent antibody test is the current standard for serologic tests, with a sensitivity of 94% to 100% and a specificity of 100%. Antibody titers of 1:64 or greater are considered to be diagnostic when detected 7 to 10 days after the onset of RMSF-like symptomatology.[10] Indirect fluorescent antibody titers tend to be more persistent, allowing the test to be used to screen for disease prevalence. In addition, the test can be used to quantitate the immunoglobulin M and immunoglobulin G response, which is necessary to distinguish epidemic typhus from recrudescent typhus (Brill-Zinsser disease, which is discussed later in this chapter).[16] The main disadvantages of the indirect fluorescent antibody test are that it is technically difficult to perform and requires a fluorescent microscope. Reproducibility can also be a problem due to variations induced by different fluorescent conjugates, light sources, and optical systems.

Complement fixation testing is used less often today, although previously it was the principal serologic test with fairly high specificity. However, low sensitivity in early disease was a major problem with this test. The Centers for Disease Control and Prevention have stopped providing rickettsial antigen for this test.[10] Complement fixation antibody titers can persist at low levels for years. Spotted fever group and typhus group cross-reactions are observed frequently.

The indirect hemagglutination test can detect antibodies earliest in the disease, showing a sharp rise in convalescent titers after days 7 through 9 of illness. However, few RMSF patients have diagnostic titers in the acute stages of illness.[12] Cross-reactions are seen with RMSF, rickettsialpox, and boutonneuse fever. Sensitivity in convalescent sera is very high but in the acute stages it is low.

Latex agglutination is a rapid, simple, commercially available test that requires no special equipment to perform.[46] Titers fall below levels of significance after approximately 2 months. Only active RMSF infections are detected and a single high titer (1:128) is usually diagnostic.[47,48] Specific latex agglutination tests for murine typhus, epidemic typhus,[49] and boutonneuse fever have also been developed.[50]

Proteus agglutination (Weil-Felix) tests were initially described in 1916 and depend on cross-reacting antigens present on *Proteus vulgaris* strains. These antibodies appear in the sera of patients 5 to 12 days after RMSF develops and cause agglutination with *Proteus* strains OX-19 and OX-2. The Weil-Felix test has also been used in the diagnosis of murine typhus, epidemic typhus, boutonneuse fever, and other rickettsial diseases. Patients with rickettsialpox and recrudescent typhus fever do not develop Weil-Felix antibodies. The sensitivity and specificity are low when compared to more current serologic tests that detect specific rickettsial antibodies. False-positive results have been reported in cases of leptospirosis, *Proteus* infections, brucellosis, tularemia, enteric, relapsing, and rat bite fevers,[16] atypical measles,[51] and healthy people.[12] Most people who are found to have positive Weil-Felix antibody titers early in the disease course are subsequently proven *not* to have RMSF.[12] Weil-Felix testing is no longer considered by the Centers for Disease Control and Prevention as a criterion for the laboratory diagnosis of RMSF, and some authorities have recommended its abandonment.[10,52]

The Centers for Disease Control and Prevention criteria for confirming the laboratory diagnosis of RMSF, which were established in 1981, are the following[45]:

- a 4-fold increase in serum antibody titers from the acute to the convalescent phase, as determined by complement fixation, indirect fluorescent antibody, indirect hemagglutination, latex agglutination, or microagglutination tests;
- a single, high, acute-phase titer using latex agglutination, which is confirmatory only when acute and convalescent titers are not available;
- a single convalescent titer of 1:16 or higher by complement fixation or 1:64 or higher by indirect fluorescent antibody testing in clinically compatible cases;
- isolation of rickettsiae; and
- fluorescent antibody staining of biopsy of autopsy specimens.

Notable is the absence of the Weil-Felix test in this diagnostic scheme. Weil-Felix positivity is only a probable indicator of disease, and should be confirmed with more-specific tests.

Rickettsial Isolation. Isolation of the rickettsial organism is not feasible in most situations, as this technique is practiced by only a few research laboratories. Rickettsiae may be grown in guinea

pigs and mice, cell culture, and yolk sacs of embryonated hen's eggs. Guinea pigs inoculated intraperitoneally develop fever, erythema, edema, and sometimes hemorrhagic necrosis of the scrotum. The animals are sacrificed on day 3 of fever, and diagnosis may be attempted by staining smears of tunica vaginalis, or frozen sections of epididymis or spleen, with fluorescein-conjugated antibody. Alternatively, specimens may be frozen at –70°C and sent to a reference laboratory for confirmation of diagnosis.[10]

Identification of Rickettsiae in Tissue. Attempts to visualize rickettsiae in tissue using standard or modified histochemical stains (eg, Giemsa, modified Brown-Hopps) have been made. However, because the number of organisms in tissue may be small, using these techniques to identify organisms is tedious and fraught with error.

A more-acceptable method is the use of 3-mm punch biopsies of lesional skin, followed by staining with specific immunofluorescent antibodies or indirect immunofluorescent techniques. Sensitivity of the direct immunofluorescent technique is 70% and specificity is 100%. The reliablility of the results may directly correlate with the experience of the pathologist. In any case, negative results do not rule out the diagnosis. Rickettsiae appear to be most numerous in endothelial cells at the center of the petechial lesion. Therefore, step sections through the middle of the frozen specimen are more likely to demonstrate the organisms. Antirickettsial antibiotic treatment appears to have little effect on the sensitivity of the biopsy if used for less than 24 hours. After 24 hours of antiobiotic therapy, the number of organisms in the tissue appears to be dramatically reduced, making the biopsy unreliable. Punch biopsy and immunofluorescence can also be used to diagnose boutonneuse fever, murine typhus, and epidemic typhus.[10] The disadvantages of the immunofluorescent technique are the following:

- this technique is not widely available,
- a fluorescent microscope is necessary,
- the results may depend on the experience of the pathologist, and
- a rash must be present and a biopsy of a petechial lesion is the preferred specimen.

Rickettsiae can be demonstrated in formalin-fixed, paraffin-embedded tissue. This technique can be employed to make a diagnosis the same day or the next day, but it has not been routinely used as of this time.[53–55]

Pathological Findings

There are no diagnostic histopathological findings in RMSF and the pathological findings are similar to those caused by other *Rickettsia* species. The major sites of involvement are the capillaries and venules. The arteriolar damage may be more prominent owing to the infiltration of the media by *R rickettsii*. Endothelial swelling and perivascular and interstitial infiltration of lymphocytes, macrophages, and a few neutrophils are seen. Although this may have the appearance of a leukocytoclastic vasculitis, it is not the result of immune complexes. Thrombi may be seen in a small number of vessels and microinfarcts are found infrequently.[10]

Similar histopathological patterns are seen in affected organs such as skin, kidney, heart, lung, liver, muscle, esophagus, stomach, intestines, pancreas, testis, and epididymis. The most characteristic lesion is the *glial* or *typhus nodule* that occurs in the central nervous system, where perivascular lymphocytes and macrophages infiltrate the subendothelium and neuropil. This lesion is not diagnostic of rickettsial infection, as it is seen in various encephalitides.[10]

Myocardial changes are typified by interstitial inflammation with occasional necrosis of myocardial cells. Conduction fibers involvement may result in electrocardiographic abnormalities.[56]

Differential Diagnosis

The presumptive diagnosis of RMSF should be entertained in a febrile patient with a recent history of a tick bite or having crushed a tick. Especially in endemic areas, the absence of this history should not decrease the medical officer's index of suspicion. Because in some areas more than 50% of the populace may have a history of tick bite, a positive history may not be particularly helpful either.[57] Problems arise when patients are initially misdiagnosed and are given an antibiotic that is ineffective against rickettsiae. When such patients return to the physician because their symptoms have progressed and a rash has developed, the diagnosis of drug eruption—rather than RMSF—is likely to be made, further delaying treatment. Inappropriate antibiotic therapy is associated with a mortality of 20%.[2] Within the first week of illness, finding a marked left shift in the differential count with a near-normal number of leukocytes should suggest consideration of the diagnosis. Biopsy of a skin lesion (preferably petechial) for immunofluorescent staining could help in making a rapid diagno-

sis if the results are positive but is not helpful if negative.[19]

The rash may be a helpful clinical sign, but it is not always classic or diagnostic in its presentation. Other illnesses that present with fever and petechial lesions must be considered: meningococcemia, murine and epidemic typhus, typhoid fever, measles (especially atypical measles), and enteroviral infection with an exanthem.

The rash of meningococcemia becomes purulent or necrotic within a day or two of onset. It is additionally distinguished by abnormal cerebrospinal fluid findings; positive culture of organisms from the cerebrospinal fluid, blood, or skin lesions; and positive countercurrent immunoelectrophoresis or latex agglutination of cerebrospinal fluid or urine.[43] If the diagnosis is in doubt, then treatment to cover both RMSF and meningococcus infection should be started using tetracycline with the addition of penicillin, or with chloramphenicol alone.

Measles usually has a distinctive prodrome with coryza, respiratory symptoms, photophobia, and Koplik's spots. Atypical measles can mimic RMSF more closely with fever, myalgia, and headache, followed by a rash and elevated Weil-Felix OX-19 titers.[51] The rash is maculopapular and petechial, starts on the extremities, and spreads centripetally. Urticarial or vesicular lesions may be noted, differing from RMSF. Koplik's spots are absent and pneumonia may occur. Atypical measles is a diagnostic consideration only in adults: it depends on the patient's having received the inactivated measles vaccine during the years 1963 through 1967.[18]

Enteroviral infections can be confusing owing to their seasonal occurrence and the faint maculopapular rash that may accompany them. These patients usually have a milder, self-limiting illness. The rash usually

- starts on the trunk,
- may be petechial on occasion, and
- can involve the palms and soles.

The occurrence of aseptic meningitis can further confuse the clinical picture. When the diagnosis is in doubt, treatment for RMSF is indicated.

Murine typhus, which is usually a milder disease, occurs more often during the winter and in urban areas, and is rarely purpuric. Epidemic typhus can produce many of the same findings as RMSF, but the rash is rarely seen on the palms, soles, and face, and usually is first seen on the trunk, spreading centrifugally to the arms and thighs. The individual lesions initially begin as pink, blanchable macules but as the exanthem progresses, petechiae are found. As in RMSF, skin lesions may progress to necrosis or gangrene. Cases of RMSF that occur during the winter should be scrutinized closely to rule out epidemic typhus, although therapy for these diseases is the same.[58]

In the western United States, Colorado tick fever is more common than RMSF. Caused by a virus that is transmitted by *D andersoni*, Colorado tick fever is characterized by fever, headache, backache, and leukopenia, but it does not produce an exanthem. Thus, it may be confused with RMSF early in the disease, before the rash is seen. Episodes of fever followed by 2 to 3 afebrile days, with subsequent return of fever, suggests Colorado tick fever. This is usually not a severe illness.[59]

Other diagnostic considerations include immune complex vasculitis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, disseminated gonococcal infection, secondary syphilis, leptospirosis, rubella, and drug eruptions.

Treatment

The antibiotics tetracycline and chloramphenicol are effective in treating RMSF. These agents are bacteriostatic, not bacteriocidal, and if administered late in the course of disease, the infection may still prove to be fatal. Most patients who are treated 4 to 5 days after the onset of symptoms will survive, with the exception of the rare patient with both G6PD deficiency and RMSF. Because G6PD deficiency predisposes to severe infection, patients with this history may require presumptive therapy with doxycycline as soon as they present with signs and symptoms even *slightly* suggestive of RMSF.[19] Results are usually seen within days of initiating treatment. Therapy is generally continued until 4 days after the patient becomes afebrile, or for a 7- to 10-day course. Sulfonamides are contraindicated if RMSF is suspected because they enhance the infection.

Antibiotic therapy for patients older than 9 years of age who are stable with mild disease and who do not have significant nausea or vomiting should consist of oral tetracycline or doxycycline. The dose of tetracycline should be 30 to 40 mg/kg/d, administered every 6 hours (the maximum dose is 2 g/d). Doxycycline should be administered with a loading dose of 4.4 mg/kg/d divided every 12 hours the first day, followed by a maintenance dose of 2.2 mg/kg/d divided every 12 hours. The maximum dose of doxycycline is 300 mg/d.[43] Doxycycline is the recommended tetracycline if azotemia is present.[60]

More severely ill patients who require hospital care should be given intravenous antibiotics. Tetracycline is the drug of choice, especially in patients with hematologic complications (ie, thrombocytopenia). The intravenous dose of tetracycline is also 20 to 30 mg/kg/d in divided doses administered every 12 hours. Chloramphenicol is administered intravenously or orally in a dose of 50 to 100 mg/kg/d, divided every 6 hours (the maximum dose is 3 g/d). Chloramphenicol has the advantage of also covering meningococcal disease and is the preferred drug for pregnant women. Hematologic parameters must be monitored with chloramphenicol therapy to screen for the development of blood dyscrasias.

Therapy for pediatric patients younger than 9 years of age is controversial. Some authorities prefer chloramphenicol because enamel hypoplasia can occur with tetracycline therapy in this age group.[61] However, the fact that chloramphenicol has been associated with bone marrow aplasia causes some experts to recommend tetracycline despite tooth discoloration.[61,62] Dental abnormalities associated with tetracycline are more likely with repeated or prolonged exposures to the drug. Doxycycline may be preferred over tetracycline because it binds less to calcium, decreasing its potential to affect the tooth enamel. Whichever antibiotic is chosen, adequate documentation should be included in the patient's record specifically addressing the discussion of the side effects with the patient's parents (Figure 11-2).[61]

Ancillary and supportive care can be difficult in some cases. Fluid management can be a troublesome problem due to the vascular damage sustained during the course of the illness. Albumin or plasma may be needed in addition to electrolyte solutions. Injudicious use of fluids may lead to circulatory overload, increasing edema and cardiopulmonary failure. Hematologic parameters, including platelets, should be monitored closely, and transfusions may be needed in some cases. Management of DIC is best handled by its prevention, using appropriate antibiotic treatment early to control the infection. Standard heparin therapy for DIC may be ineffective in patients with RMSF.[1,16,62]

Treatment with systemic corticosteroids is controversial but may be useful in patients with widespread vasculitis and encephalitis with cerebral edema.[24,62]

Prevention

Because a commercial vaccine for RMSF is not currently available, preventive efforts are aimed at avoiding or reducing contact with ticks. Insecticides such as dichlorodiphenyltrichloroethane (DDT), dieldrin, chlordane, toxophene, and malathion have been used succesfully in the past. However, environmental concerns have limited the use of residual insecticides such as chlordane or dieldrin for tick control in large areas. Dipping domestic animals, rodent control, and clearing brush may help control the tick population.

Avoidance of ticks is the primary personal preventive measure. Repellents such as *N,N*-diethyl-*m*-toluamide (DEET), dimethyl phthalate, or permethrin should be applied to clothing and exposed body parts and should be reapplied after swimming or perspiring heavily. Applying the repellant to clothing may produce longer periods of effectiveness.[59] The acaricide permanone (ie, a synthetic permethrin) is an effective repellent that may be applied to clothing and remains effective for several weeks, even after one or more washings.[60] Ticks may be easier to detect on lighter-colored apparel, and clothing should cover the legs and arms. Pants should remain tucked into socks. Even with these precautions, it is important to inspect the entire body for ticks every 4 hours.[63] It is not uncommon for people to be totally unaware of ticks crawling on their skin and biting. Because ticks must remain attached for several hours to transmit the infection, periodic examination and removal of attached ticks may prevent transmission.

Engorged ticks must be removed with care. The most successful method appears to be using fine-tipped forceps to grasp the tick near the insertion of the mouthparts into the skin. Steady, gentle traction with the forceps is then applied in an attempt to dislodge the tick.[64] The site should then be disinfected with soap and water or alcohol. Whether using forceps or fingers, it is important not to crush the tick since this could contaminate the skin with rickettsiae. A more-recent study suggests that a twisting motion with forceps held as close to the skin as possible is a more-effective and safer method for removing the tick.[65] If the fingers are used for deticking, the skin should be protected with gloves, cloth, or tissue that can be discarded. The hands should always be washed immediately after deticking.

Dogs should be deticked and wear tick-repellent collars. Treating the baseboards and cracks in human and dog quarters with a residual insecticide will help.

Prophylaxis is not a routine practice even after a recognized tick bite. Only 2% to 5% of ticks carry rickettsiae,[21] and only 1%[12] of these rickettsiae are *R*

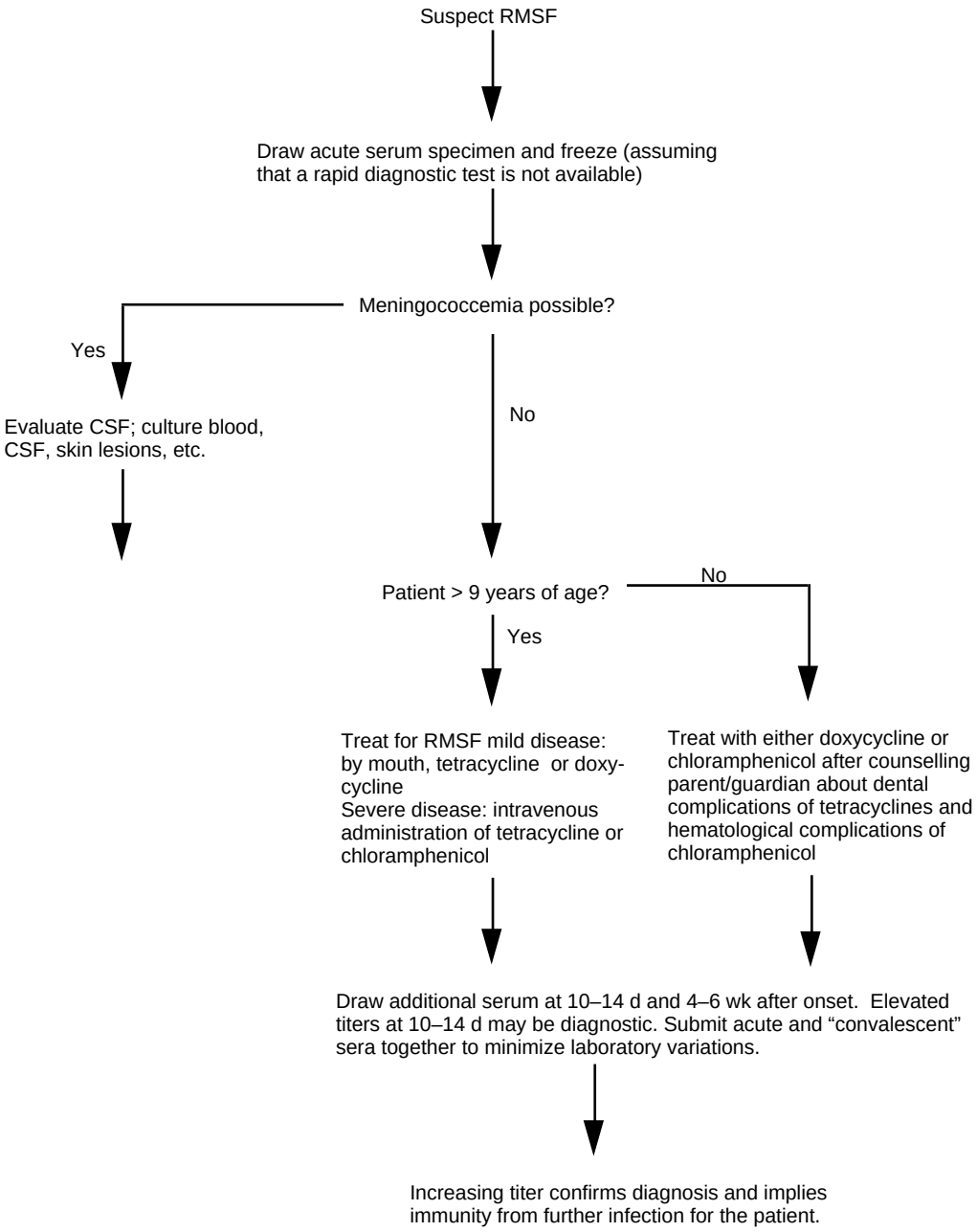

Fig. 11-2. Rocky Mountain spotted fever treatment algorithm. RMSF: Rocky Mountain spotted fever; CSF: cerebrospinal fluid.

rickettsii. Therefore, most patients with tick bites would be treated unnecessarily.[29] Experimental work with guinea pigs also does not support prophylaxis.[66]

Boutonneuse Fever

The boutonneuse group of spotted fevers (which have various names wherever they occur) are caused by *R conorii*. The rash becomes maculopapular and sometimes even nodular, resulting in the name boutonneuse (ie, buttonlike).

Microbiology

R conorii, the most ubiquitous of the spotted fever serogroup rickettsiae, is easily identified in ticks by means of (*a*) the light microscope and Giemsa and Stamp stains or (*b*) immunofluorescence. *R conorii* is antigenically distinct and is less virulent for ani-

mals and humans than *R rickettsii*. Growth in cell cultures is similar to other rickettsiae of the spotted fever group, and it is cultivated in the same ways as *R rickettsii*. The various strains of *R conorii* isolated throughout the world appear to be antigenically identical.

Epidemiology, Vectors, and Hosts

Varieties of boutonneuse fever are found in almost every country. The reservoirs are field rodents or dogs. The vector is the brown dog tick, *Rhipicephalus sanguineus*. African tick-bite fever is seen in every region of southern Africa except semidesert environments. The common veld ticks transmit the disease in rural areas, whereas the dog tick (*Hemaphysalis leachi*) transmits the disease in the suburbs. Other species may be more important in certain geographical areas (Table 11-2). The reservoirs are *Rhabdomys pumilio* (striped mouse), *Otomys irroratis* (vlei rat), and *Rattus rattus*.[67] Dogs and humans acquire the infection incidentally. Adult ticks rarely transmit the infection because they are (*a*) more host specific and (*b*) large enough to be felt crawling on the skin, making it likely that they will be removed before they have a chance to attach. Larval ticks are almost invisible and are the primary vectors of this disease, as they are not very host specific and are too small to be felt crawling on the skin. Transovarian transmission occurs in these ticks.[68]

Transmission to humans occurs either via a tick bite or contamination of the conjunctiva with tick juice or excretions. The tache noire is the characteristic lesion; it manifests as a raised red lesion with a black central crust, but is not seen when the mode of transmission is conjunctival contamination. Typically, the tache noire causes regional lymphadenopathy, systemic manifestations, and rash. The illness lasts approximately 1 to 2 weeks in untreated patients.

Patients can be from urban or rural areas and often have had contact with dogs.[69] In endemic areas such as Sicily, as many as 20% of the populace are serologically positive. However, many of these people do not have any history of boutonneuse fever, making it possible that asymptomatic illness is fairly common or that nonpathogenic strains of *R conorii* exist.[70] The peak period in which boutonneuse fever occurs is June through October.

Clinical Findings

Most patients report that they have been in tick-infested areas or that a tick may have been found in their clothing or bed linen within the last few weeks. After an incubation period of approximately 7 days, the tick bite becomes a red papule progressing to black and necrotic. This lesion is completely painless and only rarely pruritic; it may be seen in 30% to 90% of patients and is usually pathognomonic when found with a compatible rash and symptoms. Multiple taches noires have also been reported.[69,71] Some patients with the disease will have only a febrile illness lacking both the eschar and the rash, while others have the tache noire without other signs or symptoms.[70] In adults, the tache noire is usually found on the lower limbs,

TABLE 11-2

RICKETTSIAE OF SPOTTED FEVER GROUP DISEASES (EXCLUDING RMSF)

Organism	Disease	Tick
R australis	Queensland tick typhus	Ixodid ticks
R conorii	Boutonneuse fever (Marseilles fever, Mediterranean fever)	Ixodid: *Rhipicephalus sanguineus*
R conorii	East African tick typhus	*Rhipicephalus simus* or *Hemaphysalis leachi*
R conorii	Indian tick typhus	Ixodid ticks, especially *Hemaphysalis*
R conorii var *pyperi*	South African tick-bite fever	Ixodid: *Rhipicephalus* and *Amblyomma* spp, and *H leachi*
R sibirica	North Asian tick typhus	Various Ixodid ticks of *Hemaphysalis* and *Dermacentor* spp

RMSF: Rocky Mountain spotted fever. Data source: Gear JHS. Other spotted fever group rickettsial diseases: Clinical signs, symptoms, and pathophysiology. In: Walker DH, ed. *Biology of Rickettsial Diseases*. Vol 1. Boca Raton, Fla: CRC Press; 1988: 101–114.

groin, or lower abdomen. In infants, the scalp is a common site.[69] In patients who do not have a clinically obvious tache noire, close examination of the skin drained by enlarged nodes may reveal the lesion. Conjunctival transmission should be suspected in patients with severe unilateral conjunctivitis. Edema of the eyelid may be severe enough to cause chemosis. Shallow ulcers may be apparent on the conjunctiva, and the preauricular nodes on the affected side may be enlarged. One day after the bite, some patients will experience malaise; chills, anorexia, muscle and joint pain, headache, and fever follow. The fever peaks on day 2 or 3 and continues for approximately 10 days. In mild cases, fever may last only 1 to 7 days. The rash appears on days 3 through 5; it is first noted on the extremities, then spreads to the trunk. The rash appears in crops, with new macules and papules noted approximately every 1 to 3 days. The papules tend to be rather coarse and may feel like shotty nodules in the skin. The lesions are pink at first, and later become darker. Characteristically, the patient's palms, soles, and even face are involved.[68] The profuseness of the rash correlates to the severity of the illness. In more-severe cases, the rash may be petechial and dusky.

Usually, boutonneuse fever is a benign, uncomplicated disease with recovery the norm. On occasion it is severe—more often in elderly patients in whom complications are common—and may be fatal if untreated. Adverse prognostic indicators in addition to old age include chronic alcoholism, underlying disease, generalized purpuric exanthema, abnormalities of serum electrolytes, renal failure, and prolonged prothrombin time.[71,72] The most frequent complication is deep venous thrombosis that may or may not be accompanied by pulmonary embolus. Thrombosis may occur in other areas; vision changes may be due to involvement of the retinal veins. Myocarditis can occur, as can electrocardiographic abnormalities, pericarditis, and heart failure.[69] Gangrene of the fingers and toes may also be seen. Severely ill patients may have hypotension; a cyanotic, dusky appearance; and, rarely, may develop a hemorrhagic state. Epistaxis, hemoptysis, hematemesis, melena, and petechial hemorrhages in the skin may be manifestations of this coagulopathy. Jaundice can be seen in more-severe cases. Renal failure is more likely to occur in patients with preexisting renal disease. Death may be due to a combination of severely increased vascular permeability, shock, pulmonary embolism, uremia, and hemorrhage.[68]

As occurs in patients with RMSF (and also in murine typhus and scrub typhus, which are discussed later), G6PD deficiency may be associated with increased severity of disease.[73] The malignant form of boutonneuse fever bears a clinical resemblance to RMSF with a petechial rash and neurologic, renal, and cardiac involvement.[74]

In Israel, an endemic disease similar to boutonneuse fever is caused by *R sharonii*, which is antigenically distinct from *R conorii*. The Israeli variant is also characterized by fever and rash, but lacks a tache noire.[75]

North Asian tick typhus (also called tick-borne rickettsiosis) is caused by *R sibirica*. This disease is characterized by fever, eschar, regional adenitis, and a macular and papular rash. Some patients may have petechial lesions. Severe forms are uncommon.

Queensland tick typhus is caused by *R australis* and is found only in Australia. It is similar to boutonneuse fever with an eschar seen in most cases. This illness is usually benign, although fatalities have been reported.[76]

Laboratory Findings

In mild cases of boutonneuse fever and similar diseases, the hemoglobin and hematocrit are unaffected. Anemia can be seen in one third of patients and severe anemia may be seen in patients with underlying diseases or the malignant form of the disease. Leukocyte counts are usually near normal, but neutrophilia may be noticed more often in the elderly, and leukopenia with a relative lymphocytosis is common in adolescents and children. Platelets may be slightly to severely decreased with a decreased prothrombin time in some cases. More severely ill patients can have abnormal liver function tests, especially aspartate transferase and alanine transferase or increased bilirubin. Urinalysis may reveal proteinuria and hematuria. If renal failure ensues, increased creatinine and blood urea nitrogen, oliguria, and anuria may be found. Hyponatremia is seen in roughly one fourth of patients.[77]

Differential Diagnosis

Secondarily infected insect bites with local adenopathy can cause confusion in making the differential diagnosis. Diseases to be considered, depending on the geographical location, are anthrax, bubonic plague, sporotrichosis, trypanosomiasis, venereal disease (herpes simplex, lymphogranuloma venereum, chancroid, syphilis), coxsackie A or echovirus infections in children, and arborvirus infections.

Diagnostic Tests

The diagnosis of boutonneuse fever is usually made clinically. When available, direct immunofluorescence of skin biopsy specimens can be used.

Rickettsiae can be demonstrated in the skin, using tissue obtained from the periphery of the tache noire[70] or macular elements of the rash.[78] This provides the earliest diagnosis but is usually only available from reference labs. Isolation of the organism may be attempted in guinea pigs. Such testing is useful before antibiotics are administered, in more-severe cases, and in questionable cases that lack the tache noire.[79]

Serologic diagnosis is accomplished using specific tests such as complement fixation, latex agglutination,[80] indirect fluorescent antibody,[50] or microimmunofluorescence. Microimmunofluorescence is not readily available and is difficult and time consuming to perform. Antibody titers become positive after 10 days and may persist for years after the initial attack.[68,81,82]

Weil-Felix testing should be used for screening purposes only.[68] Equal titers of OX-19 and OX-2 are usually found. If OX-19 is found singly, or if the titer of OX-2 is much greater than that of OX-19, then the diagnosis of tick typhus is probable. If OX-19 titer is much higher than OX-2, then both epidemic and murine typhuses would be more likely considerations (epidemic and endemic typhuses are discussed later in this chapter). The Weil-Felix test is not specific and should *not* be relied on for diagnosis. Low titers are often seen in healthy people in areas where this infection is common.

Therapy

Quarantine of patients is unnecessary. Ironing all clothing and bed linens will kill any remaining larvae. Most patients will respond promptly to antibiotic therapy and show improvement within 48 hours. Tetracycline is the antibiotic of choice and chloramphenicol is a useful alternative. Treatment with two 200-mg doses of doxycycline may be as effective as the usual 10-day treatment with tetracycline.[72]

Prevention

Control measures for these tick-borne diseases are the same as those for RMSF. Infested dogs, cats, and rats should not be allowed inside dwellings. Tick repellents and proper clothing are also helpful. Vaccines have been developed and may be considered for military operations.

Rickettsialpox

Rickettsialpox is a febrile illness that is characterized by cutaneous eschar followed by a papulovesicular exanthem. This disease was not discovered until after World War II, so there are no figures regarding its occurrence among troops.[83]

Microbiology

R akari, which causes rickettsialpox, is a coccobacillary organism that is morphologically similar to *R rickettsii*. It is serologically cross-reactive with other spotted fever organisms due to the presence of a group-specific antigen. The *R akari* organism is a small, coccobacillary, obligate intracellular parasite that stains with Giemsa and Machiavello's stains. It is infective for mice and guinea pigs and grows in the developing chick embryo. The mouse is highly susceptible to infection and is considered to be the animal of choice for isolation.

Epidemiology, Vectors, and Hosts

The vector for rickettsialpox is the mouse mite, *Allodermanyssus sanguineus*. The host is the house mouse, *Mus musculus*. The disease is transmitted to humans by the bite of the mite. This illness is rarely seen outside cities in the United States, where improvements in housing have limited the scope of the house mouse and its mites. Rickettsialpox has become a disease of the inner city, with most cases now seen in New York City.[59] All ages and both sexes are equally susceptible to infection.

Clinical Findings

Estimates on the incubation period are difficult because the bite of the vector, *Allodermanyssus sanguineus*, is painless and the mite is microscopic, so it cannot be felt on the skin. Laboratory accidents and cases that have been well documented after exposure suggest that the incubation period is 7 to 14 days.[84]

A papule at the bite site may appear within 1 to 2 days. This lesion is usually asymptomatic although some patients will complain of pruritus. A vesicle develops over the papule, which subsequently dries and forms a crust or eschar. Induration surrounds the lesion and there is regional lymphadenopathy. The eschar can appear anywhere, but areas covered with clothing seem to be preferred by the mite.[84]

Fever and malaise are common, with temperature elevation as high as 106°F reported. Morning remissions are common. Headache, stiff neck, backache, myalgias, and photophobia may also be seen. Occasionally, cough, nausea, vomiting, and abdominal pain are reported.[84]

The rash usually appears 2 to 3 days after systemic symptoms are seen. The typical morphology of the early lesions is a firm, erythematous, nonpruritic papule. A small vesicle or pustule will be present in some of the lesions, although not all will vesiculate. Rarely, the lesions may resemble "rose spots" of typhoid, presenting as faint macules. The vesicular lesions resolve without scarring. The lesions are seen on the face, trunk, and extremities most commonly, but palms, soles, and mucous membranes may also be involved.[84]

Laboratory Findings

Routine laboratory findings are nonspecific in this disease. Leukopenia is common in the early stages.

Histological examination of the eschar will show swollen endothelial cells, capillary fibrin thrombi, and a dense perivascular infiltrate of lymphocytes, mononuclear cells, and a few polymorphonuclear cells. Rickettsial organisms have not been identified in cutaneous lesions. Histologically, the vesicles show a mononuclear infiltrate along the subepidermal region, with vacuolar changes in the basal cells. The vesicle seems to form subepidermally,[9] but intraepidermal locations have been described.[84]

Differential Diagnosis and Treatment

Other rickettsial diseases with eschars (taches noires) should be considered; scrub typhus, tick typhus (Siberian or Queensland), and boutonneuse fever may have eschars that cannot be distinguished from that of rickettsialpox. Chickenpox is commonly confused, but the lack of an eschar and the finding of multinucleated giant cells on the Tzanck preparation should make this diagnosis. Direct fluorescent antibody staining for varicella-zoster virus could also be used to confirm varicella.

Complement fixation or indirect fluorescent antibody testing can be used to identify this infection. Cross-reactions with other spotted fever group rickettsiae occur. A cross-absorption technique using *R rickettsii* and *R akari* antigens can be performed to allow more-accurate diagnosis.[85] In most cases, the clinical syndrome and a rise in group-specific indirect fluorescent antibody titers will make the diagnosis. Weil-Felix antibodies do not develop in this disease.

This is a mild illness from which even untreated patients recover without difficulty. Treatment with tetracycline will speed defervescence and recovery.

TYPHUS SEROGROUP

Typhus serogroup organisms are responsible for epidemic typhus, the recrudescent form of epidemic typhus called Brill-Zinsser disease, and endemic (murine) typhus. The organisms are characterized by a common, group-specific antigen and intracytoplasmic growth. The pathology of these diseases is also that of a vasculitis, as in spotted fever group infections. Both epidemic and endemic typhuses have a rash that begins on the trunk and spreads to the extremities, in contrast to the rash of RMSF, which is found first on the extremities.

Epidemic Typhus

Epidemic typhus has many common names: louse-borne typhus, classic typhus, typhus exanthematicus, tarbardillo, fleckfieber, and jail fever. Both the primary disease and its recrudescent form (Brill-Zinsser disease) are caused by *R prowazekii*. Clinically, epidemic typhus is quite similar to murine typhus except that it tends to be more severe. Epidemic typhus can also be similar to RMSF, except that the truncal distribution of the rash characterizes epidemic typhus. Mortality rates for this disease vary from 10% to 40% in untreated patients.[86] Epidemic typhus associated with flying squirrels (ie, sylvatic typhus) generally tends to be a milder disease.

Several important investigators perished while studying this disease, the most notable being Howard T. Ricketts, who died in 1910 while studying typhus in Mexico,[87,88] and Stanislaus von Prowazek, who died in 1915 while studying typhus in Siberia and Turkey.[86,89]

Military Significance

Although typhus infections have played an important role in every major European military campaign since the 16th century, epidemic typhus has never been a serious problem for the U.S. military.[90] Early accounts of the disease are difficult to classify

definitively as typhus. In 1492, a malignant spotted fever in Spain killed 17,000 troops during the conquest of Granada. This number is roughly 5-fold greater than the number of battlefield casualties. Typhus was also a major factor in Napoleon I's invasion of Russia in 1812. In a period of approximately 7 weeks, more than 60,000 Russian troops died, mostly from typhus. The disease was then spread throughout Europe by French and Russian prisoners of war. In Germany during 1813 and 1814, 2 million people are estimated to have contracted the disease and 250,000 died.[88]

During the American revolution, a typhuslike illness forced continental forces in New York to retreat from the British, prolonging the war by an estimated 2 years.[91] There was little typhus noted among the soldiers in the Civil War; however, well-described cases underscore the difficulties of medical practice in the preantibiotic era. The commonly used medications included quinine, turpentine emulsion, brandy, whiskey, tannin, and beef soup.[92]

The toll extracted by typhus during World War I was great. An epidemic of typhus in Serbia claimed an estimated 180,000 to 210,000 lives in 1915, including one third of the Serbian physicians.[93] In 1909, the body louse was discovered to be the vector of the disease.[88] This discovery led to the quarantine of louse-infested patients and the burning of infested clothing. However, 3 million deaths and 25 million cases of typhus were reported in Russia from 1917 through 1925.[88] Surprisingly, little or no typhus was reported among U.S. military personnel despite widespread lousiness (pediculosis) among the troops.[83]

Significant advances were made in the control of rickettsial diseases, especially epidemic typhus, during World War II. (The mild, recrudescent form of typhus, Brill-Zinsser disease, had no effect on military operations.[83]) DDT was first used as a dusting agent on the clothes of infested persons during the winter of 1943 and 1944, when an epidemic in Naples, Italy, was suppressed with its use.[83] Scrub typhus was similarly controlled in the Pacific using miticidal dusting agents.[18] Much of this progress resulted from investigations done under the auspices of the U.S. Typhus Commission, which was established in 1942. Contributions made by this commission led to a better understanding of the disease and resulted in improved louse control, personal hygiene, treatment, and vaccines. U.S. Army research played a key role in these accomplishments, especially in the development of the vaccine and purifying the antigen, which allowed the diagnostic serologic test to be developed.[94] Vaccinations started in January of 1942.[83] During 1942 alone, there were 23,000 civilian cases of typhus in Egypt and 77,000 cases in French North Africa. From 1942 through 1945, U.S. troops had only 30 cases, none of which was fatal.[88,93,95] These numbers are truly amazing, considering that when the Allied forces undertook the North African invasion, there were estimates that the unreported cases of typhus may have totalled over 500,000.[83]

During World War II, Polish physicians used their knowledge of immunology to keep German authorities away from several villages. Knowing that the Germans did not wish to have their personnel in an epidemic area, the Polish physicians administered Proteus OX-19 antigen to persons in these villages who showed symptoms that might be compatible with typhus. German health authorities were then given sera from these patients to test, and they found high titers against OX-19, suggesting louse-borne typhus. Due to the number of positive sera the Germans tested, they considered the villages to be epidemic areas. Fortunately for the Poles, the Germans never examined any of the patients, nor were they suspicious of the uniformly high initial titers in all the patients.[96,97]

German concentration camps reportedly had thousands of cases of typhus. When camps were liberated, extensive delousing efforts were necessary to prevent spread of the infection throughout Europe. These efforts were complicated by the fact that many of the prisoners fled the camps and scattered throughout the countryside.[83]

The U.S. Army was not affected by typhus during the Korean and Vietnam conflicts.[93]

Microbiology

R prowazekii is an obligate intracellular bacterium that appears antigenically to be closely related to *R typhi*. It is classically described as a coccobacillary form measuring approximately 0.25 x 0.35 μm, although it is the most pleomorphic of the rickettsiae. It also stains with Geimsa and Machiavello's stains. The organism is infective for mice, guinea pigs, and embryonated eggs. Stored at –70°C, *R prowazekii* may remain viable for years, but it is destroyed by phenol, formalin, merthiolate, and other antiseptics.[98]

Epidemiology, Hosts, and Vectors

Epidemic typhus is a disease of the colder months, poor sanitation, wars, and times of social upheaval. These conditions favor poor hygiene and crowding,

factors conducive to the spread of louse infestation. The last reported epidemic of louse-borne typhus occurred in the United States in 1922. Sporadic cases of the disease have occurred since then, as have cases of the recrudescent type (Brill-Zinsser disease) or typhus associated with flying squirrels.[99]

Hosts for *R prowazekii* include humans, the flying squirrel (*Glaucomys volans*),[3] and the body louse (*Pediculus humanus corporis)*.

Lice are very host specific; usually they remain on the same host and do not leave voluntarily unless the host's temperature changes significantly. Thus, lice tend to leave hosts who are febrile and those who have died. Transfer between humans occurs during conditions of close contact, poor sanitation, and overcrowding. Both the human body louse (*Pediculus humanus humanus*) and the head louse (*P humanus capitis*) can be infected with *R prowazekii*. The head louse has not been implicated in the transmission of typhus, leaving the body louse as the main vector for humans. The louse acquires the infection from feeding on an infected human and becomes infective itself in 5 to 7 days. The infected louse then feeds on an uninfected human, defecating while feeding. Transmission to humans occurs by contamination of the bite site with the infected feces, not from the bite itself. Transmission may also occur when infective louse feces contaminate the conjunctiva or mucous membranes or when the louse is crushed. Aerosolized spread is possible if infected louse feces become airborne when clothing is shaken.[100]

Lice feed approximately every 5 hours. They will acquire *R prowazekii* 60% to 80% of the time after a single feeding, so the ultimate rate of acquisition of infection is near 100%. However, patients with Brill-Zinsser disease will infect lice with *R prowazekii* only 1% to 5% of the time.[101]

Once *R prowazekii* enters the louse, infection is limited to the gut epithelial cells, which eventually become full of rickettsiae and rupture, discharging the organisms into the feces. The feces remain infective for up to 100 days. Infected lice die within 14 days.[101]

In the flying squirrel, the infection is transmitted by the squirrel louse, *Neohaematopinus sciuropteri* and, to a lesser degree, by the squirrel flea, *Orchopeas howardii*. Most cases of human infection occur in the eastern United States when flying squirrels enter attics in the winter months. The exact mechanism of transmission of the disease is unknown but could involve the squirrel flea, which has been reported to parasitize humans.[99] The squirrel louse does not feed on humans and is unlikely to be involved. Ground squirrels (eg, chipmunks, prairie dogs) or tree squirrels (ie, gray squirrels) are not hosts for *R prowazekii*. When infections due to flying squirrels are encountered, they are not associated with human-to-human spread, because pediculosis is not a major health problem in the eastern United States.[4,99] Several cases of epidemic typhus thought to involve the flying squirrel have been reported.[4,102,103]

Clinical Findings

The incubation period is usually approximately 7 days (range 3–11 d). Compared with murine typhus (which is discussed later), the onset of epidemic typhus is more dramatic; prostration occurs early with more-severe symptoms noted. The temperature rises rapidly over the next 1 to 2 days, and the rash may appear on approximately day 5 of the illness. The rash is first seen on the trunk and axillary folds as erythematous macules (Figure 11-3). These become petechial in a day or so. During the second week of illness, the lesions tend to become confluent, hemorrhagic, and occasionally necrotic. The lesions spread in a centrifugal pattern from the trunk to the extremities, but they are only rarely seen on the palms, soles, or face. As in RMSF, the eruption may be absent in 10% of patients.[98]

Neurological involvement can be significant. Severe delirium, maniacal episodes, or coma can occur. Respiratory involvement is fairly common, with a hacking, nonproductive cough. Hemoptysis may occur secondary to bronchial erosion. Rales

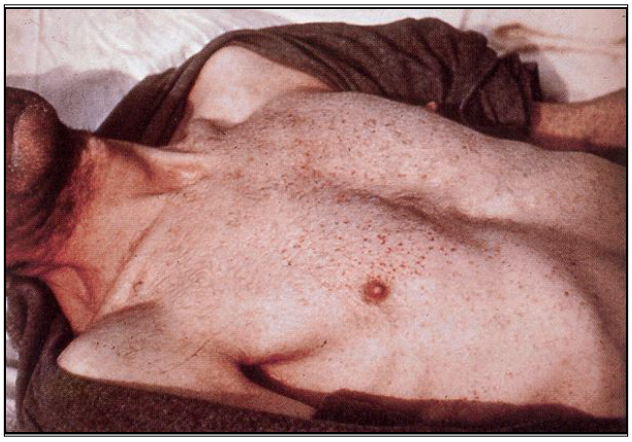

Fig. 11-3. The petechial lesions seen on the trunk are characteristic of epidemic typhus, which developed in this patient during World War II. Photographs: Courtesy of Walter Reed Army Medical Center Dermatology Service, Washington, DC.

may be appreciated in the lower lung fields, usually during the second week of illness. Cardiovascular involvement characteristically produces hypotension with a weak, rapid pulse. Peripheral cyanosis and cold sweats occur, as they do in murine typhus. Abnormalities may be found on the electrocardiogram. Photophobia, eye suffusion, conjunctival injection, and deep eye pain may be present. Transient partial deafness is common in patients with epidemic typhus. Gastrointestinal findings include nausea, vomiting, abdominal pain, constipation, and splenomegaly. The liver is usually not enlarged.[104]

Otitis media, parotitis, and pneumonia can occur due to secondary bacterial infections. In addition, bronchiolitis, vascular collapse and shock, gangrene, and azotemia may be observed in untreated individuals. With treatment, mortality from epidemic typhus is essentially zero.[105]

Laboratory Findings

Leukopenia can be found early in the illness; the leukoyte count is normal late in the disease. Urinalysis findings include albuminuria and, rarely, hematuria. Serum chemistry may be remarkable for hypochloridemia and hypoalbuminemia. Azotemia may also be noted.

Differential Diagnosis

Typhoid, meningococcemia, boutonneuse fever (without eschar), malaria, measles, yellow fever, relapsing fever, and epidemic typhus acquired from flying squirrels all may need to be considered in the differential diagnosis. Suspicion regarding epidemic typhus should be raised when medical officers encounter patients who seem to have atypical cases of RMSF or murine typhus. When diseases resembling RMSF occur during an unusual season (ie, winter) or in an area with an extremely low incidence of RMSF, serologic data should be closely scrutinized. Additionally, patients (*a*) with compatible symptoms who lack a history of tick bite or exposure, (*b*) without a rash, or (*c*) who have a centrifugally spreading rash should also be suspected of having epidemic typhus.[4]

Laboratory Diagnosis

Immunofluorescent staining can detect *R prowazekii* in the gut of lice that have been collected from patients suspected of having classic epidemic typhus. This could allow the diagnosis to be made within a matter of hours.[106]

Serologic testing using either complement fixation or the indirect immunofluorescent test will also confirm this diagnosis. Note that cross-reactions with murine typhus and spotted fever serogroup organisms are possible; the toxin neutralization test can help distinguish cross-reactions to murine typhus.[4] Titers for *R rickettsii* are usually much lower than those to *R prowazekii*. The same tests are also used for diagnosing epidemic typhus associated with flying squirrels.

Weil-Felix testing shows positive titers for only OX-19, usually after 10 to 14 days. False-positive reactions may make interpretation difficult in certain areas (see the previous discussion of the serologic diagnosis of RMSF).

Isolation of the organism should be attempted only by experienced personnel with the proper facilities. Storing clotted blood from an infected patient at –70°C will maintain the viability of the organisms for years. Refrigerated clots must be used for isolation attempts within a few days.

Treatment

Tetracycline or chloramphenicol in appropriate doses should be continued until the patient is afebrile for more than 24 to 48 hours. Relapses may occur, especially when treatment is started early in the course. Because antibiotic resistance does not develop, relapses usually respond to continuation of the antibiotic. In some situations (eg, natural disasters, refugee populations), single-dose therapy with doxycycline (100–200 mg) is an effective therapy that may be preferable if medical supplies are limited. The severe headache does not respond to the usual drugs. Severely toxic patients may require treatment with systemic steroids.[107]

Control Measures

Where conditions favor lousiness, an effective residual insecticide should be applied to the body and clothing. Personal hygiene should be maintained at adequate levels. Typhus vaccine that prevents or attenuates the disease is available but is not routinely administered to military personnel.[105,107]

Epidemic typhus is a reportable illness and local health authorities must be notified. Isolation of patients is not necessary; however, the patient should be deloused as should the patient's clothing, quarters, and close contacts. Disinfection should include insecticide powder and treatment of nits using pyrethrin shampoo or lindane. Even the

corpses of patients who die before delousing should be deloused appropriately.

Louse-infested persons who are both susceptible and exposed to typhus fever should be deloused with residual insecticides and observed for 15 days. All immediate contacts should be deloused, if necessary, and observed for 2 weeks.[63,98]

Recrudescent Typhus (Brill-Zinsser Disease)

Brill-Zinsser disease, the recurrent form of epidemic typhus, appears years after the original infection. Brill-Zinsser disease is not related to louse infestation and has been reported only sporadically in the United States. It should be suspected in patients with a previous history of epidemic typhus, especially among survivors of concentration camps or immigrants from eastern Europe.[108] The disease is caused by the reactivation of *R prowazekii* that remains in the lymphoid tissue of previously infected persons. Thus, humans act as a reservoir for epidemic typhus, since infected patients may be responsible for transmitting the infection to uninfected body lice. Clinically, Brill-Zinsser disease is much milder than the original illness and the rash is usually absent. Serologic testing will reveal extremely high immunoglobulin G titers for *R prowazekii* because the recrudescence is an amnestic antibody response. Titers of immunoglobulin M antibody will be low or absent. Weil-Felix testing is negative in patients who have Brill-Zinsser disease.

Endemic (Murine) Typhus

Murine typhus is a phylogenetically older and milder disease than epidemic typhus. Both the vector (the rat flea) and the reservoir (the rat) survive the infection by *R typhi* without ill effects, whereas infection with *R prowazekii* causes the death of the louse and more severe illness in humans.

Murine typhus usually occurs sporadically rather than in epidemics. Prior to 1940, all forms of typhus were considered together in U.S. Army medical statistics. During World War II, 787 cases of typhus were reported, with 15 deaths.[93,109] Troops on maneuvers in the southern United States at this time accounted for 497 of these patients. Troops stationed in the Hawaiian Islands accounted for 123 cases during 1942 through 1945.[83]

Data on the incidence of murine typhus during the Korean conflict are not available, but murine typhus was the second-most-common cause of febrile illness in U.S. Army personnel in Vietnam.[110]

Murine typhus can also be a major cause of febrile illnesses in refugee camps. One study of adults in a camp in Thailand for displaced Khmers (Cambodians) found the 1-month attack rate for adults to be 185 per 100,000.[111]

Microbiology

R typhi (*R mooseri*) measures 0.4 by 1.3 μm, and is a Gram-negative, obligate intracellular parasite. It is less pleomorphic than *R prowazekii* and shares common soluble antigens with that organism. *R typhi* is destroyed by formalin, phenol, and temperatures greater than 56°C for 30 minutes. *R typhi* is infective for rats, mice, guinea pigs, and yolk sacs of embryonated eggs[98] and is more virulent than *R prowazekii* for guinea pigs and mice.

Epidemiology, Vectors, and Hosts

Murine typhus is common in the United States, and this disease has the highest worldwide prevalence of all the rickettsial diseases. It is seen on every continent except Antarctica.[110]

The hosts in this disease include a large spectrum of animals. Rats (*Rattus norvegicus* and *Rattus rattus*) are the animal reservoir. Shrews, skunks, opossums, mice, and cats are fed on by various arthropod vectors and can serve as hosts.[110,112] In rats, infection is nonfatal and rickettsemia lasts only 1 to 2 weeks.[101] The infection is spread when fleas feed on infected rats. *R typhi* infects the gut epithelial cells and is excreted in the feces. Infection is not fatal for the flea and persists for life without affecting life span. Transmission to humans occurs when the skin, respiratory tract, or conjunctiva are contaminated with infected flea feces. *Xenopsylla cheopis* (the oriental rat flea) is the major vector. *Leptopsylla segnis* (the mouse flea), *Ctenocephalide felis* (the cat flea), and *Pulex irritans* (the human flea) are also implicated as potential vectors based on laboratory data. *L segnis* fleas are not thought to be an important vector in the United States, owing to their semisessile nature, but they may be more important in locations where *X cheopis* fleas are absent.[101] Transmission is thought to occur when infected feces are rubbed into the bite, but recent investigators have shown that the organism can be transmitted by flea bites alone.[110] Infection via inhalation of dust from rat-infested buildings may occur.[110] In the wild, however, fecal contamination remains the most important means of transmission. The infection may be transmitted transovarially in fleas, suggesting that fleas may also serve as reservoirs for the disease.[113]

Most cases are reported between late spring and early autumn when *X cheopis* is abundant. Endemic areas are primarily urban settings associated with commensal rats and their fleas. Rural areas may also be affected, however. Sea ports and coastal areas are favored. People whose occupation or living conditions bring them into close contact with rats or rat runs are primarily affected, especially in food-storage areas or granaries. Most human cases are acquired indoors where rats are present. Areas with higher incidences of this disease include South America, Mexico, Ethiopia, Malaya, Australia,[98] Thailand, India, Pakistan, and the southern United States.[112]

Clinical Manifestations

The typical incubation period is approximately 11 days (range 8–16 d). Prodromal symptoms begin with frontal headache, severe backache, and arthralgias approximately 4 to 6 days after exposure.[104] Usually, the patient notes a sudden, shaking chill but may have only a chilly sensation. Headache, fever, nausea, and vomiting are seen in nearly all patients. The patient's temperature increases steadily over the first few days and may become intermittent when the rash appears, with the morning temperature tending to be normal. Children may have fevers as high as 106°F, while that of adults peaks at 103°F to 104°F. Fever usually lasts approximately 12 days.

The rash makes its appearance after approximately 5 days of illness. It is seen first in the axillae and inner arms. Dull, red macules develop rapidly on the abdomen, shoulders, chest, arms, and thighs. The earlier lesions tend to be macular while older lesions are slightly raised. Approximately 20% of patients will lack the rash.[104] The spread of this rash is from trunk to extremities, the opposite of that seen in patients with RMSF. Only rarely will the rash involve the palms, soles, or face. Petechiae may develop in some cases, and the lesions may become hemorrhagic.[114]

Of the neurological findings, headache usually predominates. Patients with more severe illness may progress to stupor, prostration, and lethargy. Some may have neck stiffness, but Kernig's sign is usually not present. Transient, partial deafness and weakness have been reported.[104]

A hacking, nonproductive cough is not uncommon. Rales may be appreciated in the lower lung fields. Hypotension occurs, especially in the early stages. Clinical evidence of cardiac failure is unusual, however. Minimal electrocardiographic abnormalities, peripheral cyanosis, and cold sweating can be seen. Nausea, vomiting, abdominal pain, constipation, and splenomegaly are fairly common findings.

Although secondary bacterial infections leading to otitis media, parotitis, and pneumonia can complicate the illness, murine typhus is a benign disease for most, with complete recovery the norm.

Laboratory Findings

Laboratory findings are nonspecific for murine typhus. Moderate leukopenia may be noted initially, with a normal leukocyte count later in the illness (except when secondary bacterial infection occurs). Urinalysis may show albuminuria and, rarely, hematuria. Hypochloridemia and azotemia can occur.

Differential Diagnosis

Other diseases to be considered are typhoid, meningococcemia, boutonneuse fever (when lacking an eschar), mild epidemic typhus, flying squirrel–associated epidemic typhus, RMSF, and scrub typhus.

Diagnosis

Indirect fluorescent antibody can be used to diagnose murine typhus, but it requires cross-absorption with homologous and heterologous antigens to distinguish murine from epidemic typhus. Patients who have been previously vaccinated against epidemic typhus respond to murine typhus with antibodies that react in higher titers with *R prowazekii*.[50] Clotted blood obtained prior to antibiotic therapy can be used for attempted isolation of the organism. After the blood has clotted and the serum has been removed, the clot may be stored at –70°C.[115]

Treatment

Tetracycline or chloramphenicol are administered in appropriate doses until the patient is afebrile for longer than 24 hours. For critically ill patients who do not present until late in the illness, systemic steroids administered for 2 or 3 days may be a useful additional therapy; however, this regimen is not recommended for mild or moderately ill patients.[104] After recovery, permanent immunity to murine typhus exists, with cross-immunity to epidemic typhus.

Control Measures

Flea populations should be reduced, using insecticides to prevent additional exposure to fleas. After this is accomplished, insecticide powders with residual action should be used on rat runs and burrows. Attempts to treat rat-infested areas before the flea population is controlled will result in additional cases of disease when hungry fleas turn to humans in the absence of their usual host.[112] Isolation or quarantine are not necessary for the patient or his or her contacts.[63]

SCRUB TYPHUS, TRENCH FEVER, AND Q FEVER SEROGROUPS

Scrub typhus, trench fever, and Q fever each comprise a separate serogroup. These diseases are distinct from each other and from other rickettsial diseases; they are grouped together in this chapter for convenience only.

Scrub Typhus

Scrub typhus, caused by *R tsutsugamushi*, is in a distinct serogroup separate from the typhus and spotted fever serogroups. The disease is also known as tsutsugamushi disease, tropical typhus, rural typhus, Japanese river fever, and Kendani fever.[95] The mortality rate varies in untreated patients, ranging from 1% to 60%; with treatment, however, the mortality is less than 5%.[98] Aside from the antigenic differences that were discussed earlier in this chapter, this organism possesses a distinctive cell wall structure when compared to other rickettsiae. In addition, scrub typhus is transmitted by the larval form of trombiculid mites, which are commonly called chiggers. Trombiculid mites also serve as a reservoir for this disease.

Military Significance

Scrub typhus affects not only military personnel but also indigenous rural populations. The chigger that is the vector for this disease is found in southeast Asia, Japan, Malaysia, China, eastern Russia, Australia, Sri Lanka, Indonesia, Korea, India, and the Philippines. The term "scrub typhus" was used by Allied troops to describe the vegetation where the mites are usually found. Scrub typhus was feared by military personnel during World War II because there was no effective therapy and death was possible. Full convalescence often took more than 2 months and had significant impact on affected units.

Among Allied troops in World War II, 18,000 cases of this disease were reported, with a fatality rate that varied from 1% to 35%. According to U.S. Army statistics, 5,718 cases occurred in the southwest Pacific area.[90] In some areas the attack rate was quite high, with 25% to 33% of two U.S. Army Air Force squadrons in this region hospitalized in 1944.[88] Cases of scrub typhus were also reported from the Philippines and the India-Burma theater.[95] During this time, scientists from the United States and Britain investigated this disease and advanced our knowledge of the epidemiology and treatment of scrub typhus. In 1948, a U.S. Army–sponsored investigative team working at Walter Reed Army Institute of Research (WRAIR), Washington, D. C., and Kuala Lampur, Malaya, discovered that chloramphenicol was an effective treatment for scrub typhus. Joseph E. Smadel and his colleagues at WRAIR and the University of Maryland showed that this drug also cured murine typhus and RMSF.[94]

Scrub typhus had little effect on military operations in Korea.[93] During the Vietnam conflict, the incidence of scrub typhus was dwarfed by the incidence of malaria and diarrheal illnesses in this region.[116] Still, a 6% incidence of scrub typhus was found in patients hospitalized for malaria.[90] The actual number of reported cases is probably underestimated because the Weil-Felix test was positive only half the time with scrub typhus, and many cases were diagnosed and treated without serologic confirmation or even hospitalization. No deaths were reported from this disease.[90] The use of a repellent seems to have helped prevent chigger infestation, but sometimes soldiers did not use repellents for fear that the enemy would detect the odor.[117]

Microbiology

Several strains of *R tsutsugamushi* are antigenically similar, producing short-lived cross-immunity. Three major serotypes (ie, Karp, Gilliam, and Kato) have a sufficient degree of cross-reactivity with other strains to allow the indirect microimmunofluorescent test to be used diagnostically. This obligate intracellular parasite is distinguished from other rickettsiae by its growth in the cytoplasm without a surrounding vacuolar membrane. In

addition, the outer layers of *R tsutsugamushi* are significantly different from those of other rickettsiae. The outer leaflet is very thick with a thin inner layer, the opposite of other rickettsiae. *R tsutsugamushi* can be stained with Giemsa's stain or by using the modified Gimenez procedure that is used for other rickettsiae.

Epidemiology and Vectors

Several mites of the genus *Leptotrombidium* are vectors of scrub typhus: *L akamushi*, *L arenicola*, *L deliense*, *L fletcheri*, *L pallidum*, *L pavlovskyi*, and *L scutellare.* The mites are parasitic for humans only as larvae. They do not exhibit specific host-seeking behavior. Instead, they wait patiently on grass stems or leaves for a host to walk by. They tend to congregate in small areas, creating "mite islands." Shrubs or transitional vegetation are their preferred environment. In particular, overgrown fields, border areas at the edges of forests, and margins of streams are areas where the mites may be found in great numbers. Two days after hatching, the mites feed on tissue juices of the host for 2 to 12 days, then drop off the host and enter a pupalike stage that lasts for 5 to 7 days. Then they become nymphs and enter a second pupalike stage, after which they emerge as adults. The nymphs and adults are scavengers of the forest floor and do not feed on humans.[11]

The host for *R tsutsugamushi* is the genus *Rattus*, in which long-lasting infection is produced. Chiggers also feed on pigs, rabbits, shrews, and birds; these animals can also carry the organism.

Infection in the larva is acquired as an egg in the infected female; the larval is the only stage capable of transmission, and the larva feeds on a host only once. Transovarial transmission seems to be the only mechanism for the maintenance of the the organism in nature.

Scrub typhus is a disease of the Far East that has not been found in the western hemisphere. People whose occupations place them in contact with infected mites remain the most susceptible group for this infection.

Clinical Findings

An eschar, which is seen in scrub typhus, tick typhus, and rickettsialpox, begins as a red papule and becomes a punched-out ulcer that develops a hard crust (Figure 11-4). The crust may be lacking in moist intertriginous areas.[116] This lesion is painless and is seen in 95% of patients with rickettsialpox but only in approximately 50% of patients with scrub typhus.[104]

The rash—a maculopapular eruption that is neither hemorrhagic nor petechial—may be prominent or completely absent; it was reported in fewer than 40% of Americans in Vietnam.[117] However, the rash is uncommon when the disease occurs in the indigenous population.

A prodrome of headache, chills, and anorexia begins insidiously. Later, fever, cough, and generalized lymphadenopathy are seen. Characteristic clinical findings in patients without eschars are lacking, making this disease difficult to diagnose in such cases.[118]

Laboratory Findings

Routine laboratory findings are not helpful diagnostically. Lymphocytosis is common, with atypical lymphocytes seen somewhat frequently. There may be mild elevations of the liver function tests.

Differential Diagnosis

Other diseases to be considered and ruled out are murine typhus, leptospirosis, arborviral infection, typhoid, and malaria. When the rash is absent, generalized lymphadenopathy and the presence of atypical lymphocytes may suggest the diagnosis of infectious mononucleosis.[116]

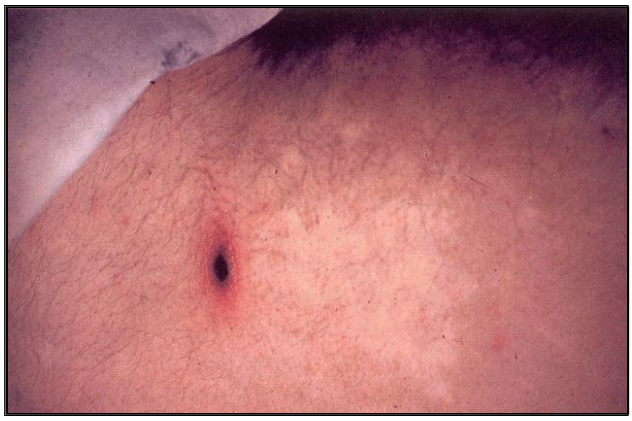

Fig. 11-4. Characteristic eschar (tache noire) of scrub typhus. Similar lesions are seen in tick typhus, boutonneuse fever, and rickettsialpox. Photographs: Courtesy of Walter Reed Army Medical Center Dermatology Service, Washington, DC.

Diagnosis

An indirect fluorescent antibody titer of 1 to 400 or greater is 96% specific and 48% sensitive for the diagnosis of scrub typhus.[50] In poorer regions that lack funds for fluorescent microscopes, an alternative test, the indirect immunoperoxidase kit, is available. This kit has been in use in the Malaysian region since 1986 and has been shown to have acceptable sensitivity and specificity as well as a long shelf life.[119] The indirect immunoperoxidase kit and the indirect fluorescent antibody test were the recommended tests endorsed by the World Health Organization, which specifically advised against the use of the Weil-Felix reaction when other, more sensitive tests are available.[120]

Weil-Felix tests in patients with scrub typhus will reveal positive OX-K agglutinins in some, but in general, the sensitivity is rather low; positive results are seen in only 40% to 60% of patients.[6,116] However, because it is a simple test to perform, the Weil-Felix test is still the main test used in some areas of the world.

Treatment

Chloramphenicol can be given in a dose of 500 mg every 6 hours for 7 days, and has the advantage of covering both typhoid and meningococcus infections. Tetracycline seems to be more efficacious and is given in a dose of 500 mg every 6 hours for 7 days. Doxycycline has been used successfully as a single, oral dose in treating both louse-borne and scrub typhus.[121,122]

Recrudescence is likely when the patient is treated within the first 3 days of illness; a second course of antibiotics may be required. Recrudescence may also occur with single-dose therapy under similar circumstances.[63,116,123]

Control Measures

Effective chigger repellents that can be applied to the body include diethyltoluamide and dimethylphthalate. Clothing and bed linen should be impregnated with permethrin and benzyl benzoate, which are miticidal. Mite-infested areas may be treated with lindane, dieldrin, or chlordane.[63] Experimental evidence indicates that chiggers may need to remain attached to humans for 6 to 8 hours before *R tsutsugamushi* is transmitted.[124] Therefore, bathing after exposure may be helpful in preventing the disease. Chemoprophylaxis against scrub typhus and leptospirosis is possible using doxycycline in weekly doses of 200 mg. This prophylactic regimen is not used routinely for indigenous populations but would be beneficial for soldiers engaged in military operations.[124] Due to the existence of numerous antigenically different strains of *R tsutsugamushi*, an effective vaccine is not yet available.

Trench Fever

Except during outbreaks associated with wars, trench fever is a rarely reported disease. It has also been known as Wolhynian fever, Meuse fever, His-Werner disease, shin bone fever, shank fever, and quintan or 5-day fever.[125] *Rochalimaea quintana*, the rickettsia that is the causative agent, has also been identified as one of the etiologic agents in bacillary angiomatosis, a disease that was first described in patients with acquired immunodeficiency syndrome.[126]

In modern times, this disease was first recognized and described in 1915 as "trench fever" and "5-day fever." Epidemics were seen among soldiers of all armies along the western, eastern, and Balkan fronts with at least 1 million men stricken in western Europe.[127] Although the disease is relatively mild, trench fever accounted for more lost man-days for the U.S. armed forces than any other disease except influenza.[125] Each affected person was unfit for duty an average of 60 to 70 days. Fatalities were low, but many individuals experienced one or several relapses of the disease.[93] In peacetime, the disease is reported only sporadically in minor outbreaks. During World War II, epidemics again appeared with 80,000 cases in eastern Europe.[127]

Microbiology

Rochalimaea quintana is a short rod (0.5–1.5 μm) that resembles other rickettsiae in morphology and staining properties. It is unusual in that it can be cultured in host cell-free media. The organism can be cultured in axenic media and the yolk sac of chicken embryos. Laboratory animals are not susceptible to infection.

Epidemiology, Vectors, and Host

Rochalimaea quintana is still considered to be a member of the family Rickettsiaceae, although it is now classified in the genus *Rochalimaea*. Trench fever is distributed worldwide, although it is pri-

marily associated with wars, overcrowded conditions, and poor sanitation. Humans are the reservoir and body lice are the vectors. As with epidemic typhus, when the gut epithelium of the louse is infected, *R quintana* are excreted in the louse's feces. Humans acquire the organism when the feces are scratched into the bite wound.

Clinical Findings

The onset of trench fever is often sudden and a prodromal period is usually lacking. The incubation period varies from 3 to 38 days and the illness begins with chills followed by fever. The fever has three clinical forms: abortive, periodic, and continuous. Some patients will lack fever or show only rudimentary febrile episodes. Abortive fever is typified by continuous fever for approximately 4 to 5 days. Periodic fever is typified by paroxysms of fever alternating with normal temperatures at intervals of 5 days. There may be 3 to 8 cycles of this pattern, which is the characteristic febrile pattern for the disease. Continuous fever is uninterrupted for 2 to 3 weeks or longer. This type is associated with more severe symptoms.[127]

Chills, tachycardia, headache, retroorbital pain, vertigo, nystagmus, myalgia, exanthem, and hepatosplenomegaly can be seen. The rash is composed of erythematous macules and papules that are seen on the chest, abdomen, and back.[125] Characteristically, the disease will relapse days, weeks, months, or even years after the initial infection. Symptoms during these relapses are generally milder than those previously experienced. Leukocytosis and albuminuria may be present during the relapse.

Diagnosis and Treatment

Influenza, malaria, relapsing fever, typhus, rat bite fever, enteric fever, brucellosis, and other diseases may need to be considered. The characteristic fever pattern is helpful in making the diagnosis. Serologic testing using complement fixation, microagglutination, or indirect immunofluorescence are helpful in confirming the clinical diagnosis. An indirect hemagglutination test has also been developed that has a specificity greater than 99% and does not cross-react with other rickettsiae.[50]

Tetracycline and doxycycline are effective drugs for treatment of trench fever. As with other rickettsial diseases, chloramphenicol is an acceptable alternative.

Prevention and Control

Residual insecticides should be dusted on clothing and bedding. In areas where DDT resistance is encountered, lindane or malathion is recommended; however, these chemicals will not kill organisms in louse feces. Clothing and bedding should be sterilized at 100°C for at least 30 minutes.[127] Sputum and urine have been reported to contain viable organisms and should be disposed of as infective waste.[98]

Q Fever

Q fever, the sole member of the Q fever serogroup, was first described in 1937 and was designated "Q" for query.[128] At that time, the infectious particle was tentatively identified as a rickettsial organism, which is now known as *Coxiella burnetii*.[129] This is the only rickettsial disease that does not typically produce a rash. Most commonly, Q fever is a self-limited, mild, febrile illness. Other manifestations, in descending order of frequency, are pneumonia, endocarditis, and granulomatous hepatitis. Rarely, the disease may present with unusual manifestations (Exhibit 11-2).[130]

Q fever was called "Balkan grippe" when it occurred in British paratroops in Greece during World War II.[93] The disease occurred during the winter of 1944 and spring of 1945 in the North Apennine region of Italy, which is endemic for the disease.[131,132] An epidemic also affected five squadrons of the 449th Bomb Group in Italy; troops returning home to the United States from Italy had an attack rate of 38%.[133] In the process of isolating the organism from these soldiers, outbreaks of the disease occurred among laboratory personnel.[134]

Microbiology

C burnetii is a well-adapted organism that grows within the phagolysosome of the cell, requiring an acid pH. A sporelike form has been described, which accounts for the organism's longevity after dessication.[135] *C burnetii* is a highly infectious organism; a single organism may initiate the disease in humans. It is well adapted to survive harsh conditions, remaining viable after dessication on wool at 15°C to 20°C for 7 to 10 months, cold storage on fresh meat for 1 month, and after 40 months in skim milk at room temperature. The organism can be isolated from infected tissues stored in formaldehyde after 4 to 5 months and even from fixed paraffin-embedded tissue, although it is destroyed by 2%

formaldehyde.[136] There is no genotypic relationship and very little phenotypic similarity between *Rickettsia* and *Coxiella*. Essentially, *Coxiella* remains in the genus as a matter of history and convenience.

Epidemiology

Q fever is a zoonosis whose reservoirs are primarily cattle, sheep, and goats. The organism is shed in the animals' urine, feces, milk, and birth products and is extremely resistant to dessication. Evidence of *C burnetii* infection has also been found in horses, swine, water buffalo, dogs, camels, pigeons, chickens, ducks, geese, turkey, and several species of wild birds.[136] Cats and rabbits may be the most important vectors in some areas. Squirrels, meadow mice, deer mice, harvest mice, and deer may also harbor the organism. Infected domestic animals rarely show signs of infection. *C burnetii* is a hearty, widespread organism that has been isolated in 39 species and 10 genera of Ixodidae (hard ticks) and Argasidae (soft ticks). Q fever has been reported in 51 countries on five continents.[136] Arthropods maintain the organism in nature.

The placenta of infected animals is heavily contaminated with *C burnetii*, and after the placenta dessicates, the organisms are aerosolized. Viable organisms can be detected in the soil for 150 days. Humans are infected when they inhale the aerosolized organism, ingest raw milk, or handle contaminated straw or manure. Contaminated clothing may also be a source of exposure.[130] This disease usually affects those who are in contact with infected animals such as farmers, veterinarians, and abattoir workers. However, outbreaks may be seen in others through ingestion of contaminated raw milk, skinning infected wild animals, blood transfusion, or exposure to parturient cats,[136] Outbreaks of infection among laboratory workers are not unusual with this organism.[33] Rarely, cases of human-to-human transmission have been reported.[98]

EXHIBIT 11-2

RARE PRESENTATIONS OF Q FEVER

Arteritis
Arthritis
Aseptic meningitis
Dementia
Encephalitis
Epididymitis
Extrapyramidal disease
Fetal infection
Manic psychosis
Myocarditis
Nephritis
Orchitis
Osteomyelitis
Parotitis
Pericarditis
Thrombophlebitis
Thyroiditis
Toxic confusional states

Data source: Marrie TJ. Q fever: Clinical signs, symptoms, and pathophysiology. In: Walker DH, ed. *Biology of Rickettsial Diseases*. Vol 2. Boca Raton, Fla: CRC Press; 1988: 1–16.

Clinical Findings

The self-limited form of Q fever is similar to influenza with fever, myalgia, anorexia, headache, and retroorbital pain. The pneumonic form can present as an atypical pneumonia, a rapidly progressive pneumonia, or a febrile illness with pneumonia found only incidentally. Included in the differential diagnosis of atypical pneumonias are *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia psittaci*, pneumonic tularemia, and cytomegalovirus and other viral pneumonias, as well as Q fever. The incubation period is 9 to 17 days.

A clue to the diagnosis is often the severe headache, which may be overrepresented as a symptom. Cough, fatigue, nausea, anorexia, myalgia, sweats, retroorbital pain, and pleuritic chest pain are common findings. One third of patients have vomiting and diarrhea. Rarely, sore throat may be a complaint. The physical exam may reveal inspiratory rales or may lack auscultatory findings completely. Although Q fever characteristically produces no rash, an erythematous macular eruption on the trunk has been described in a few patients.[137]

Hepatomegaly or splenomegaly may affect approximately 5% of patients. Nuchal rigidity or confusion is reported in a small number of patients. Rapidly progressive pneumonia is seen in approximately 20% of patients. These patients are usually extremely ill and hypoxemic. The chest radiograph may show multiple round opacities, pleural effu-

sions, or increased interstitial markings. The erythrocyte count may be elevated in one third of patients, but most are normal. Hepatic transaminases increase in almost all patients and the syndrome of inappropriate antidiuretic hormone secretion may occur.[130]

Some patients with Q fever present with an illness resembling typical hepatitis, or possibly with a fever of unknown origin with mild liver function test elevations. Hypercalcemia may be seen. Liver biopsy reveals a "doughnut granuloma" (a dense fibrin ring surrounding a central lipid vacuole), which can also be seen in patients with Hodgkin's disease or infectious mononucleosis.

Endocarditis usually involves previously abnormal valves and patients may present with a fever of unknown origin or with culture-negative endocarditis. This very serious manifestation of Q fever is the most common manifestation of chronic Q fever. Fever, clubbing (50%), cardiac murmur, purpuric rash (22%), and arterial emboli (35%) occur.[130] Histologically, the rash is a leukocytoclastic vasculitis, which is thought to be due to the extremely high levels of circulating immune complexes that characterize the disease. Prosthetic valves and the aortic and mitral valves are the usual sites of Q fever endocarditis. Thrombocytopenia and increased hepatic transferases and alkaline phosphatase are common.[130]

Definitive Diagnosis

Coxiella undergoes a phase variation. In the natural state and in the laboratory, it exists in what is called phase I, in which *C burnetii* cells react strongly with late (45-d) convalescent guinea pig sera and weakly with early (21-d) guinea pig convalescent sera. Phase II organisms are produced when the organism is passed repeatedly in embryonated chicken eggs. The phase II form is avirulent and differs from the phase I organism in the sugar composition of its lipopolysaccharide and several other characteristics.[136] The diagnosis of chronic Q fever culture-negative endocarditis is made when phase I titers are markedly higher than phase II titers.[136,138] This is the opposite of what one would see in acute Q fever infections.

Various serologic tests such as complement fixation, microimmunofluorescence, and the enzyme-linked immunosorbent assay are used to diagnose Q fever.[138] As it has in other diseases where organisms are difficult or dangerous to isolate, the polymerase chain reaction may find future application in the diagnosis of Q fever.[139]

Treatment

Tetracycline is the drug of choice, although trimethoprim-sulfamethoxazole and rifampin have been used successfully. Erythromycin with rifampin is the preferred regimen for patients in whom the diagnosis of atypical pneumonia caused by Q fever is considered.[140] Patients with rapidly progressive pneumonia should be treated with tetracycline.

For endocarditis, the combination of tetracycline and clotrimazole is effective. Rifampin is also useful. Some authorities recommend indefinite treatment because relapses are common and replacement of the valve may be necessary.[136] If and when treatment is discontinued, the patient's complement fixation titers should be followed carefully every 6 months.[130]

Q fever hepatitis usually responds to a 2-week course of therapy with tetracycline.

Prevention

Australian abattoirs have long had problems with Q fever. Trials there have proven a vaccine effective in preventing disease with a minimum of adverse reactions.[141–143] A purified preparation of *C burnetii* is currently being tested by U.S. Army researchers.[140]

EHRLICHIOSIS SEROGROUP

Ehrlichiae are bacteria grouped within the family Rickettsiaceae; ehrlichial diseases are categorized in the ehrlichiosis serogroup. Ehrlichiae are presumed to be tick-borne and are well known as veterinary pathogens. Until recently, *Ehrlichia sennetsu* and *E canis* were thought to be the only species of *Ehrlichia* causing human disease; however, *E chaffeensis* has recently been identified as the sole etiologic agent of ehrlichiosis in the United States (Table 11-3). Other species cause infections in horses, dogs, sheep, cattle, bison, and deer. Ehrlichiae differ from other rickettsiae antigenically and in their preference for infecting leukocytes over vascular endothelial cells. They also grow and replicate within a phagosomal vacuole in the host cell. With the exception of *Coxiella* and *Ehrlichia*, rickettsiae grow in the cell without a surrounding membrane or vacuole.

TABLE 11-3

EHRLICHIOSES OF MEDICAL AND VETERINARY IMPORTANCE

Organism	Host	Vector	Disease
E equi	Horse	Unknown	Equine ehrlichiosis
E canis	Dog	*Rhipicephalus sanguineus*	Canine ehrlichiosis (tropical canine pancytopenia)
E chaffeensis	Unknown	Tick*	Human ehrlichiosis
E phagocytophila	Sheep, cattle, bison, deer	*Ixodes ricinus*	Tick-borne fever
E risticii	Cat,* horse	Unknown	Potomac horse fever
E sennetsu	Human*	Tick*	Sennetsu fever

*Not proven

Ehrlichiosis

Clinically, ehrlichial diseases range from asymptomatic or mild to severe or fatal. Diagnosis presently relies on detection of antibodies, which takes weeks. In the future, more rapid diagnosis of ehrlichial infections may be accomplished through the use of the polymerase chain reaction once appropriate probes are sequenced. Although still only a research procedure, this has already been done for *E risticii*, the agent of Potomac horse fever.[144]

Ehrlichiae have not been reported to have a significant impact on military campaigns. However, in 1968, sentry dogs used by U.S. troops in Vietnam developed an epizootic of a fatal disease called tropical canine pancytopenia.[145,146] This was characterized by debilitation, fever, anemia, and leukopenia, and hemorrhage. The disease is more severe in German shepherds; 200 to 300 dogs were lost to this disease during the war.[147] The cost of the dogs alone was estimated to be a minimum of $1 million.[147] Military units that relied on these animals were also compromised. During 1969, many units (usually military police) had more than one-half their dogs classified as possibly infected, resulting in loss of the units' operational capabilities.[147] The etiologic agent was postulated by investigators at WRAIR to be an ehrlichia-like organism,[148,149] and the organism was subsequently proven to be *E canis*.[150] The illness was responsive to tetracycline therapy.[151]

Microbiology

Ehrlichiae are obligate intracellular, bacterial parasites. They are small, Gram-negative organisms that preferentially infect mononuclear cells or polymorphonuclear leukocytes and grow within a phagosome in the cell cytoplasm. Their development within the cell is similar to that of chlamydiae, with three stages described (Figure 11-5).

Based on serologic testing of infected patients, *E canis* was originally believed to be the pathogen causing human ehrlichiosis. Because serology does not specifically identify the causative agent because of the possibility of cross-reactions with an antigenically related organsim, *E canis* was characterized as a tentative etiologic agent. However, *E chaffeensis*, a newly described ehrlichia that is closely related to *E canis*, was identified in 1991 as the causative agent of human erhlichiosis in the United States. The organism was named for Fort Chaffee, Arkansas, where it was isolated from a U.S. Army recruit with human erhlichiosis.[152]

Vectors and Reservoirs

Rhipicephalus sanguineus, the brown dog tick, is the vector of canine ehrlichiosis, but it is not a reservoir for the organism. Larval and nymph forms of the tick acquire the infection after feeding on chronically infected dogs and later, as adults, transmit the infection to uninfected dogs. Recent studies have failed to document transovarial transmission.[153,154] The most likely reservoir for canine ehrlichiosis would seem to be chronically infected canids, although this has not been proven. Other vertebrates or ticks may eventually be shown to be reservoirs.[153]

No specific tick has been identified as the vector for human ehrlichiosis. Epidemiological data that were generated when *E canis* was the suspected pathogen indicate that the disease is not acquired from dogs directly. In the United States, serologic

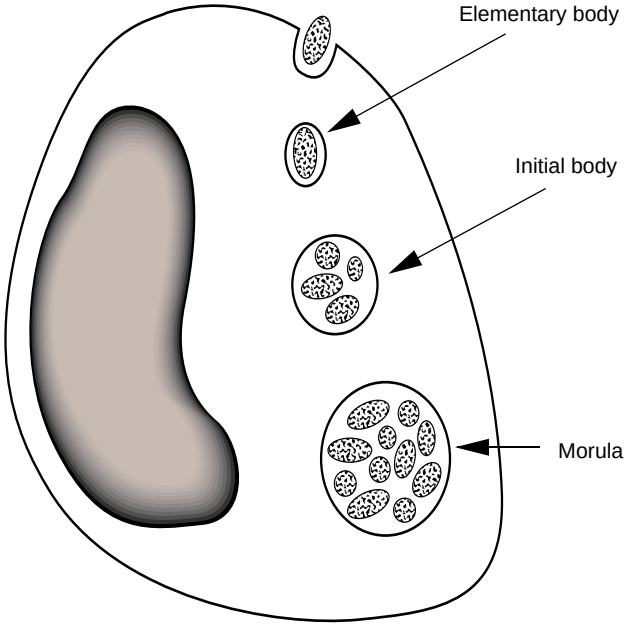

Fig. 11-5. In the first stage of the development of erlichia, *elementary bodies* (individual organisms) are phagocytized by host monocytes. Fusion of the phagosome with a lysosome does not occur, however. Elementary bodies grow within the phagosome and replicate by binary fission. After 3 to 5 days, the elementary bodies packed into the phagosome are (*a*) approximately 1.0 to 2.5 mμ in size, (*b*) recognizable as pleomorphic inclusions within the cell, and (*c*) called *initial bodies*. With additional growth over the next 7 to 12 days, *morulae* (mature inclusions) form and can be visualized via light microscopy. Each infected monocyte contains several morulae, which break up into initial bodies when the cell ruptures, allowing the infectious cycle to be repeated. Illustration source: Adapted from McDade JE. Ehrlichiosis—a disease of animals and humans. *J Infect Dis.* 1990;161(4):609–617. Legend source: Nyindo MBA, Ristic M, Huxsoll DL, Smith AR. Tropical canine pancytopenia: In vitro cultivation of the causative agent—*Ehrlichia canis*. *Am J Vet Res.* 1971;32:1651–1658.

evidence of *E canis* infection has been found in dogs in all geographical areas.[155,156] The geographical distribution of human cases corresponds to the distribution of the Lone Star tick, *Amblyomma americanum*. Additionally, the onset of cases in spring and early summer corresponds to the time of greatest activity for *A americanum* and for the dog tick, *Dermacentor variabilis*.[157] *R sanguineus* is more widely distributed than *A americanum* and bites humans less often.[158] However, evidence of *R sanguineus* bites have been documented in Texas, suggesting the possibility of an increasing anthropophilicity in these ticks.[159] The vector and reservoir for *E chaffeensis* are yet to be definitively determined; however, *E chaffeensis* has been found in a single *D variabilis* tick from an opossum. This evidence awaits confirmation and studies to document that *D variabilis* can transmit the infection.[152]

Epidemiology

Most cases of human ehrlichiosis are reported in rural areas from the spring to fall. As a group, patients tend to be older than those with RMSF. Cases appear to be most common in the months of May through June. Most patients report either an actual tick bite or exposure to ticks within a few weeks of infection.[160,161]

This may be a disease that is actually more common than would be suspected from the number of cases reported. In some areas, the incidence of ehrlichiosis may match or exceed that of RMSF.[161] Approximately 10% to 12% of specimens submitted with the tentative diagnosis of RMSF and that tested negatively for RMSF were found to be positive for *E canis* (the agent implicated serologically when these studies were done).[160,162] In a study of hospitalized, febrile patients in southeast Georgia, 10.7% of the patients were found to have a 4-fold rise or fall in titers to *E canis*.[161]

Currently, the predominant regions where ehrlichiosis has been reported include the south-central, southeastern, and mid-Atlantic states. States with high incidences are Oklahoma, Arkansas, Missouri, Virginia, and Tennessee.[158]

People in older age groups are at higher risk for ehrlichial infections in general and also have higher rates of serious complications and hospitalization.[158] Human ehrlichiosis can be rather mild in many cases. Of 74 U.S. Army reservists who were exposed to ticks, 12% had serologic evidence of ehrlichial infection. None required hospitalization and most experienced only mild symptoms. Two patients were asymptomatic.[163] Investigation of ehrlichiosis in Oklahoma revealed that fewer than half the patients required hospitalization[160]; however, hospitalization rates of up to 88% have been reported.[164] In cases reported in 1988, 6% of patients died.[164]

Ehrlichial infections in dogs appear to be widespread in both the size of the population affected (11%-58%)[165] and the geographical area. Cats have also been found to have infections with ehrlichia-like organisms.[166]

Clinical Findings

More than 80% of patients will recall exposure to ticks during the 3-week period before the onset of illness.[158] The incubation period averages approximately 9 days (range 4–33 d).[164]

Clinical manifestations tend to be nonspecific. Fever, chills, headache, myalgias, anorexia, and nausea and vomiting may appear abruptly or subacutely. A rash may occur 4 to 13 days after the onset of illness but is seen within the first week in only a minority of patients. The rash may be maculopapular or petechial and may involve various aspects of the body. Most children will develop the rash, whereas only one third of adult patients do. The rash does not appear to be a reliable marker for this disease because it is so variable in location and appearance.[158,167]

Serious complications may occur. Meningitis was reported in a pediatric patient.[168] Pulmonary complications may necessitate intubation and mechanical ventilation. Encephalopathy, mental status changes, coma, and acute renal failure can occur. Death may occur, especially in those with preexisting medical problems.[158]

Laboratory Findings

In studies of hospitalized patients, lymphocytopenia, leukopenia, and thrombocytopenia were fairly common. Although the hematologic findings may be characterized as a transient pancytopenia, leukopenia is noted first because of the shorter life span of these cells. Over one half the patients developed anemia at some time during their hospitalization, but usually not within the first week.[158,161,162] Various abnormalities of the bone marrow have been described[158,162,169,170] but the marrow of many patients is normal. The findings of normal bone marrows suggest sequestration or peripheral destruction as etiologies for the hematologic abnormalities.[171] Studies of dogs reveal a paucity of infected cells in the marrow, supporting this contention.[172]

Inclusion bodies may rarely be noted in the patients' leukocytes. Animals infected with *E canis* usually lack leukocyte inclusions.[162] Geimsa-stained, buffy-coat preparations may be helpful in finding inclusions, which can be found in lymphocytes, atypical lymphocytes, band neutrophils, segmented neutrophils, and monocytes. However, only 1% to 2% of cells will contain inclusions. The inclusions are purple, round, or ovoid structures 2 to 5 μm in size. Usually only one inclusion is seen, although up to four may be present in the cell. With electron microscopy, the inclusions are seen to be made up of numerous electron-dense organisms surrounded by a vacuolar membrane.[173] Because demonstrating inclusions is not dependable, serologic testing is more important in confirming this diagnosis.

Serum transaminase levels are elevated in most patients during the acute phase of the illness. Elevations of alkaline phosphatase, bilirubin, creatinine, and blood urea nitrogen are less common. Cerebrospinal fluid pleocytosis, with predominant lymphocytes and elevated protein, has been reported.[158,174]

Differential Diagnosis

Other febrile illnesses associated with ticks should be considered. These include Lyme disease, tularemia, babesiosis, and RMSF. Babesiosis is distinguished by the presence of parasites in erythrocytes on blood-smear examinations. Tularemia and Lyme disease should be distinguishable on a clinical basis. RMSF can be difficult to distinguish in early cases, especially those without a rash.

Diagnostic Testing

An indirect fluorescent antibody test for detecting *E canis* in dogs has been adapted for use in humans.[160] Positive results are indicated by at least a 4-fold rise or fall in acute and convalescent titers. In one series, 24% of patients with positive tests for *E canis* had confirmed diagnoses which were inconsistent with ehrlichiosis. False-positive results were seen in patients with streptococcal pharyngitis, mononucleosis, hepatic cirrhosis, urosepsis, tularemia,[160] and hepatitis A.[175] The CDC no longer uses *E canis* as the antigen for the indirect immunofluorescent antibody assay, but now uses *E chaffeensis* instead.[176]

Antibody titers rise sharply during the first 3 weeks of illness and peak at approximately 6 weeks. Acute-phase samples should be collected as early as possible in the course of the illness and convalescent titers should be drawn 3 to 4 weeks later. If the initial serum sample is not obtained until after the third week of illness, attempts to demonstrate a 4-fold decrease in titer can provide confirmatory evidence of infection. Serum must be collected during weeks 4 through 7 after onset of illness and again 6 weeks later. Other tick-borne illnesses should also be excluded serologically to confirm the diagnosis of ehrlichiosis. Most patients will seroconvert only to *E canis*, but some will show cross-reactions with

other rickettsiae (*R typhi, R rickettsii, C burnetii*).[177] Simultaneous infection with other tick-borne illness is possible, as exemplified by patients with ehrlichiosis and Lyme disease.[178,179]

Treatment

Therapy for human erlichiosis is similar to that for RMSF, with tetracycline being the drug of choice. It has proven efficacy in ehrlichiosis in dogs[151] and appears to be efficacious in humans also. Although no formal controlled studies have been done, some patients treated with chloramphenicol appear to do as well as those treated with doxycycline, but some adult patients have gotten worse or died with chloramphenicol.[173,180] A recent in vitro study showed that *E chaffeensis* is resistant to chloramphenicol, bringing into question the usefulness of this agent.[181] This same study found that *E chaffeensis* was susceptible in vitro to rifampin, which offers a possible alternative therapy. Confirmatory studies are needed to define the role of chloramphenicol and rifampin in the treatment of this infection. In patients who have prominent thrombocytopenia and leukopenia, tetracycline is a better alternative. Treatment should be instituted as early as possible. As it is in the treatment of children with RMSF, the use of these antibiotics in children under 9 years of age who have erlichiosis is controversial.

Sennetsu Fever

The causative agent of Sennetsu fever, *Ehrlichia sennetsu*, was originally isolated in 1953 from the peripheral blood, lymph nodes, and bone marrow of a patient with infectious mononucleosis–like symptoms. At the time, it was thought to be a new rickettsia. Subsequent studies revealed it to be related to *E canis* both antigenically and morphologically. A significant difference is that *E sennetsu* is readily propagated in mice, primary cell cultures, and several continous cell lines, whereas *E canis* propagates in canine monocytic cell lines only.[153] *E sennetsu* seems to grow in human monocytes in a manner similar to that of *E canis* in canine monocytes. Morulae and individual organisms are observed within cells in membrane-lined vacuoles.[182]

Western Japan and Malaysia are the most commonly reported areas affected by Sennetsu fever.[183,184] The actual geographical area involved may be more extensive than this, as serologic testing for this agent is usually not attempted elsewhere in the world. The vector of Sennetsu fever is presumed to be a tick, although this has not been conclusively proven.

Senettsu fever appears to be a rather mild, mononucleosis-like disease. Patients may present with fever, postauricular and posterior cervical lymphadenopathy, malaise, and anorexia. An exanthem is rarely seen, but generalized erythematous or localized petechial lesions have been described. Hepatosplenomegaly is seen in one third of patients. Fatalities have not been reported.[183]

Leukopenia with increased numbers of neutrophils is reported early in the disease. Later, lymphocytosis and atypical lymphocytes are seen.

The diagnosis may be confirmed using the complement fixation or indirect fluorescent antibody tests.

Sennetsu fever is treated with tetracycline. Improvement is prompt, with defervescence noted in 2 to 3 days and resolution of other symptoms shortly thereafter.

SUMMARY

The rickettsiae are grouped taxonomically in a unique family of bacteria that can cause diseases with a spectrum of effects ranging from rather benign to rapidly fatal. Because military personnel may be deployed to parts of the world that are endemic for some rickettsial diseases, these diseases pose particular challenges for medical officers. Diseases such as epidemic typhus have played crucial roles in military history. Although most military physicians have had no previous experience with this disease, it is one that is commonly associated with wartime conditions so we must be familiar with its presentation, treatment, prevention, and control. Some military bases are located in regions of the world where rickettsial diseases that are not seen in the United States (eg, boutonneuse fever and scrub typhus) are endemic. RMSF and ehrlichiosis are threats to soldiers who are training at bases in the continental United States that are in areas endemic for these diseases. In-depth knowledge and understanding of the diagnosis, treatment, and prevention of rickettsial diseases will allow medical officers to deal competently with these illnesses.

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