Review

Journal of Cutaneous Medicine and Surgery
Incorporating *Medical and Surgical Dermatology*
DOI: 10.1007/s10227-005-0134-z
J Cutan Med Surg 2005; 105–115

Rickettsial Infections Around the World, Part 2: Rickettsialpox, the Typhus Group, and Bioterrorism

Jashin J. Wu,[1] David B. Huang,[2,3,4] Katie R. Pang,[5] and Stephen K. Tyring[6,7]

In this second part of our review of rickettsial infections, we discuss rickettsialpox, the typhus group, and factors that make this disease class a possible agent of bioterrorism.

Rickettsialpox

Epidemiology (Table I)

Rickettsialpox is caused by the organism *Rickettsia akari*, a small obligate intracellular bacteria with a cell wall similar to that of gram-negative bacteria. It has the same lipopolysaccharide antigens as others of the spotted fever rickettsial group.[1] The arthropod vector for rickettsialpox is *Liponyssoides sanguineus*, a bloodsucking mite that feeds on rodents.[2] The house mouse, *Mus musculus*, is the reservoir for rickettsialpox, and humans are infected only if mice or other preferred hosts are not accessible. *R. akari* is maintained by transovarial transmission in mites so human transmission is not essential for the life cycle.

Clinical Manifestations

The disease starts with a primary skin lesion at the site of inoculation by the mite and, after a usual incubation period of 9–14 days, progresses into a febrile illness, followed by a secondary papulovesicular eruption.[3] The systemic symptoms are self-limited, usually resolving in 1–2 weeks, and may be severe, but no fatalities have been reported.[4]

The primary lesion is typically a solitary papule, may be seen on any part of the body, and can appear as soon as 24–48 hours after the bite.[3] It can present with pruritus,[3] tenderness,[4] erythema, and induration of 1.0–2.5 cm in diameter, or be asymptomatic.[5] The papule transforms into a vesicle with cloudy or opaque fluid, which then ruptures and leaves a large area of induration that surrounds an eschar (Fig. 1). Regional tender adenopathy is frequently seen in the area draining the eschar, which resolves after approximately 4 weeks and can leave a small scar.[3]

Systemic symptoms, usually including fever and malaise, appear suddenly about 1 week after the primary lesion. Temperature can reach up to 106°F but usually peaks between 101°F and 104°F[6] and gradually defervesces after 7 days.[6] Patients can also have chills that precede the fever, followed by myalgias and drenching sweats. Other possible symptoms include anorexia, conjunctival injection, cough, photophobia, rhinorrhea, sore throat, generalized lymphadenopathy, nausea, or vomiting.[2]

The onset of the generalized cutaneous eruption usually occurs about 48–72 hours after the general symptoms begin but can follow several hours to 9 days after the systemic symptoms. There may be 20–40 asymptomatic lesions measuring 0.2–1.0 cm and consisting of erythematous macules, papules, and papulovesicles.[2] The rash may affect the face, trunk, and extremities, including the palms and soles (Fig. 2 and 3).[3] Characteristic lesions are round with a small central vesicle or pustule, and some vesiculate and form a crust. Scarring from these secondary lesions usually does not occur.[3] Some patients may also develop an enanthema, usually on the palate, which resembles the cutaneous lesions but lasts less than 48 hours.[5]

Diagnosis

Although there are no specific laboratory findings in rickertsialpox, a common finding is mild leukopenia

[1]Department of Dermatology, University of California, Irvine, California, USA
[2]Division of Infectious Diseases, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA
[3]University of Texas at Houston School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas, USA
[4]Division of Infectious Diseases, Department of Medicine, University of Texas Health Science Center at Houston, Houston, Texas, USA
[5]Department of Dermatology, Wayne State University School of Medicine, Detroit, Michigan, USA
[6]Department of Dermatology, University of Texas Health Science Center at Houston, Houston, Texas, USA
[7]Center for Clinical Studies, Houston, Texas, USA
Online publication: 22 December 2005
Correspondence to: Stephen K. Tyring, Center for Clinical Studies, 2060 Space Park Drive, Suite 200, Houston, TX, 77058, USA; E-mail: styring@ccst-exas.com

FIGURE 1 Eschar on posterior right calf of patient with rickettsialpox (see ref. 74). Available from http://www.cdc.gov/ncidod/eid/vol8no7/01-0501.htm.

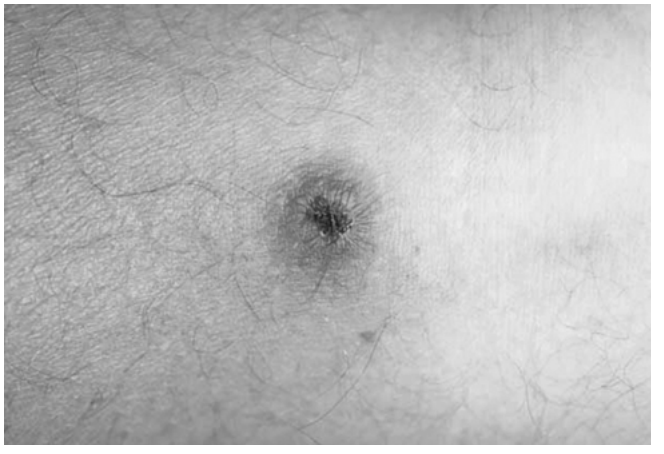
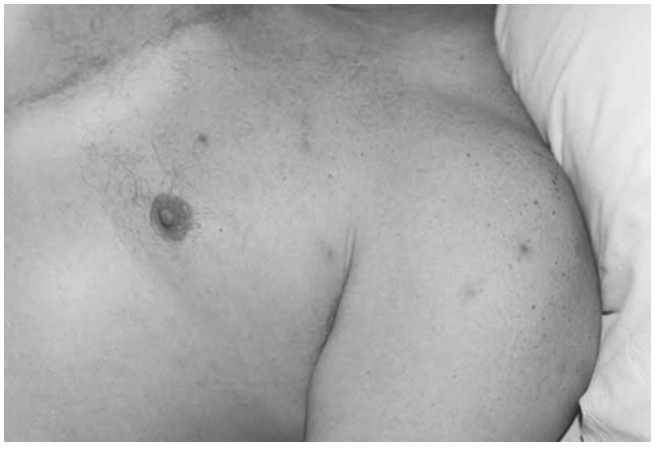


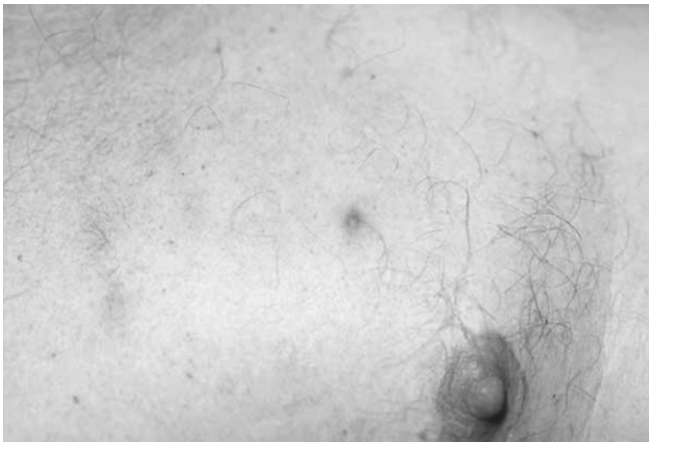
FIGURE 2 Multiple papulovesicles on the upper trunk of a patient with rickettsialpox (see ref. 74). Available from http://www.cdc.gov/ncidod/eid/vol8no7/01-0501.htm.



ranging from 2400 to 4000 WBC/mm^3, with a relative lymphocytosis. There may be a slight increase in the sedimentation rate, and proteinuria, which is secondary to fever. Although blood cultures are negative, *R. akari* from the blood of infected patients can be found after intraperitoneal inoculation into susceptible mice.[7] Except for one reported case in which the serum of a 33-year-old man with rickettsialpox that showed a greater than fourfold increase in the titers of Proteus OX-2 and OX-19, the Weil–Felix test typically does not detect antibodies to *R. Akari*.[8] However, serum antibodies can be identified by complement fixation studies within 10 days of the start of generalized symptoms, with titers peaking after 3–4 weeks in untreated patients and after 6–8 weeks in patients treated with antibiotics.[3]

The histopathology of the primary lesions, or eschars, shows extensive inflammation and necrosis of the dermis and subcutaneous tissue, while papulovesicles show superficial edema and frank separation of the epidermal–dermal junction, which forms a subepidermal vesicle.

FIGURE 3 Closer view of papulovesicular lesions on patient with rickettsialpox (see ref. 74). Available from http://www.cdc.gov/ncidod/eid/vol8no7/01-0501.htm.



Perivascular infiltrate may be vasculitic or lymphohistiocytic, with fibrin in lumen and walls. [2] Direct immunofluorescence, using an anti-*R. rickettsii* globulin conjugated with fluorescein isothiocyanate, was reported by Kass et al.[2] to be positive in the eschars of five of seven patients but in only one papulovesicular lesion nine patients, likely because there is a higher number of organisms at the site of inoculation.

The differential diagnosis includes infectious mononucleosis, gonococcemia, echovirus (types 9 and 16), coxsackievirus A (types 9 and 16), coxsackievirus B (type 5), and varicella.[9] Rickettsialpox most resembles varicella but can be distinguished from it based on several factors: Vesicles of varicella are on an erythematous base, whereas those of rickettsialpox develop from papules; varicella does not present with eschars and will show multinucleate giant cells in a Tzanck smear while lesions of rickettsialpox will not.

Treatment

The treatment of choice is doxycycline 100 mg po q12h for 2–5 days.[1] Rickettsialpox also responds to chloramphenicol but its use is limited because of the self-limited nature of the disease and the serious idiosyncratic reactions to chloramphenicol. Treatment should be withheld in pediatric patients unless the symptoms are severe, when a 2-day course of doxycycline, which is brief and unlikely to cause tooth and bone deposition, may be used.[3] Finally, rodent control helps control outbreaks of rickettsialpox.

The Typhus Group (Table 1)

Epidemic Typhus (Louse-Borne Typhus, Classic Typhus, Sylvatic Typhus)

Epidemiology

Epidemic typhus is caused by *Rickettsia prowazekii*, which is spread by the body louse (*Pediculus humanus corporis*).

TABLE 1

Etiology and epidemiology of typhus group rickettsial disease

Geographic distribution	*Disease*	*Organism*	*Principal tick vectors*
Africa, Americas, Asia	Epidemic typhus	*Rickettsia prowazekii*	*Pediculus humanus corporis*
Worldwide	Murine (endemic) typhus	*Rickettsia typhi*	*Xenopsylla cheopis, Ctenocephalides felis*
Asia, Australia	Scrub typhus	*Rickettsia* (*Orientic*) *tsutsugamushi*	*Leptotrombidium*

FIGURE 4 Rose spots-like skin lesion on the trunk (day 4) (see ref. 75). Available from http://www.cdc.gov/ncidod/eid/vol5-no5/Niang.htm#Figure%203.

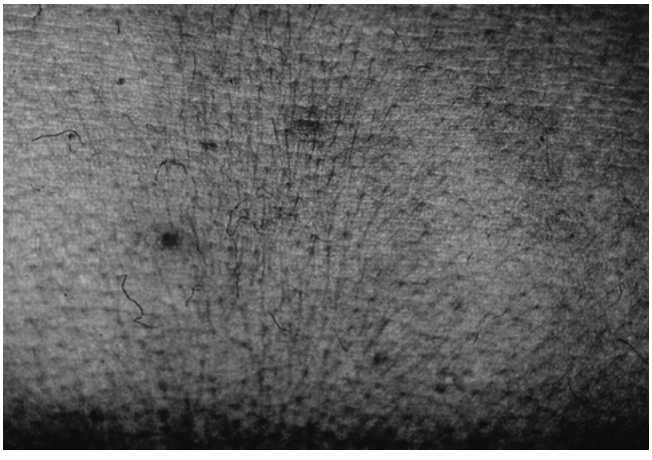
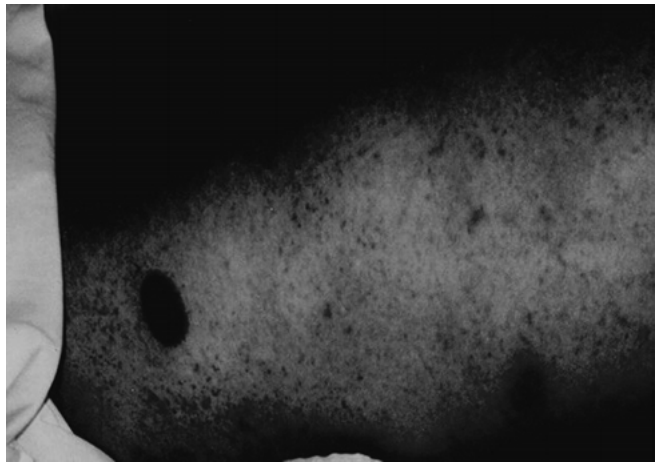


FIGURE 5 Diffuse petechial rash of epidemic typhus (day 7) (see ref. 75). Available from http://www.cdc.gov/ncidod/eid/vol5-no5/Niang.htm#Figure%203.



The life cycle begins when the body louse feeds on patient infected by primary epidemic typhus or by Brill–Zinsser disease, the recrudescent form of epidemic typhus. The organism replicates in the alimentary tract of the louse, begetting numerous progeny that wait for defecation of the louse. When the louse takes a blood meal, it defecates. When the host scratches the lesion, it contaminates the wound with *R. prowazekii*-infected feces. Close personal contact or sharing of clothes is required for person-to-person spread. Epidemic typhus is typically transmitted in the cold winter months since migration of populations and crowding allow proliferation of lice. Infected lice usually die within 1–3 weeks from obstruction of the alimentary tract, and they do not pass the rickettsia to their offspring.

The first epidemics caused by epidemic typhus happened in the late 15th century. It is estimated that between 1918 and 1922 in Eastern Europe 30 million cases occurred leading to 3 million deaths.[10] During World War II, cases occurred in the concentration camps of Eastern Europe and in North Africa. The most recent epidemics have been reported in Africa, Central America, and South America.

The last outbreak of epidemic typhus in the U.S. occurred in 1922. Since then, most of the U.S. cases were due to Brill–Zinsser disease in immigrants or concentration camp survivors from Eastern Europe.[11] Fleas or lice from flying squirrels are the vectors of infection in humans in the U.S. *R. prowazekii* was isolated from the southern flying squirrel (*Glaucomys volans*) in 1975.[12] Most cases of epidemic typhus from the southeastern U.S. have been associated with contact with flying squirrels.[13,14] Cases have been reported in Georgia, Tennessee, North Carolina, Massachusetts, Pennsylvania, Virginia, and West Virginia.[15]

Clinical Manifestations

The typical course of epidemic typhus is 1–3 days of malaise before myalgia, headeache, fevers, and chills set in.[16] In a study of 60 Ethiopian patients with epidemic typhus, all patients had headache and fever, 33% had a petechial rash, and 5% had a macular erythematous rash.[16] Around the fifth day, the rash begins in the axillary folds and upper trunk and spreads centrifugally to the extremities and occasionally to the soft palate and conjunctiva, but sparing the palms, soles, and face. This is in contrast to the rash of RMSF, which starts in the extremities and spreads centripetally. The epidemic typhus rash appears at first as nonconfluent erythematous macules that blanch on pressure (Fig. 4), but after several days it becomes maculopapular and petechial (Fig. 5).

In uncomplicated epidemic typhus, fever usually resolves after 2 weeks of illness if untreated, but recovery of strength usually takes 2–3 months. With appropriate antibiotics, fever resolves with 72 hours of the initiation of therapy. Headache resolves after 7 days of treatment. Aside from headache, other neurologic symptoms range from meningismus to coma.

The complications include vasculitis-induced cerebral thrombosis and gangrene, which affects symmetric fingers and toes. Although treatment is medical in most cases, severe gangrene may require amputation. Neurologic deficits from cerebral thrombosis may take 2–4 weeks to resolve, but residual deficits are infrequent. Mortality from epidemic typhus is variable, but highest rate is those over 60 years old.

Diagnosis

For many years, the Weil–Felix agglutination reaction was the standard for serologic diagnosis, but there is a considerable cross-reactivity among the members of the ricksettsiae and a lack of specificity.[17] More sensitive tests include the plate microagglutination and microimmunofluorescence tests.[16] Acute and convalescent serum can be used to demonstrate a four-fold rise in specific antibody titers. Also, in the past it was difficult to differentiate between *R. prowazekii* and *R. typhi* because of antigenic similarity; antibody absorption tests were required. However, now polymerase chain reaction (PCR)can correctly detect *R. prowazekii* and differentiate between the ricksettsiae.[18] A real-time PCR duplex assay has been recently developed that can distinguish *R. prowazekii* from eight of the spotted group ricksettsiae, *R. typhi*, and *R. Canada*.[19]

Laboratory abnormalities include increases in aspartate aminotransferase and lactate dehydrogenase in most patients and mild thrombocytopenia in about 40% of patients. These abnormalities resolve with 14 days of therapy. The white blood cell count is usually normal but may be high in a few patients.

Treatment

As with the other rickettsial infections, the most highly effective therapies are the tetracyclines and chloramphenicol. Although doxycycline has been shown to be effective in a single oral dose, the standard recommended treatment is 200 mg once a day for 5 days.[20,21] If the patient is too ill to take oral medication, the tetracyclines and chloramphenicol can be given intravenously. Delousing the patient is also crucial to prevent the cycle of reinfection.

Decreasing the population of the body louse by regular bathing, washing of infested clothes, and use of insecticides are ways to prevent epidemic typhus. Even after several washings, clothes should be treated with permethrin to eliminate lice. Doxycycline prophylaxis may offer some protection if taken in endemic areas and may also interrupt a typhus outbreak.[16]

Vaccine for R. prowazekii

In the 1970s, the first typhus vaccines were developed using crude antigen or formalin-killed rickettsia and/or killed *R. Prowazekii*.[22] Although they provided a limited level of protection, they were indicated only for those at the highest risk of acquiring epidemic typhus, and they had undesirable toxic reactions and difficulties in standardization.[22,23]

Because of the obligate intracellular existence of the rickettsial agents, a vaccine capable of eliciting a strong cell-mediated immunity is critical. DNA vaccination provides prolonged antigen expression, and immunization with recombinant plasmid DNA, consisting of a bacterial plasmid that includes the gene of interest, represents a hopeful method in DNA vaccine research, especially in rickettsiology. Furthermore, inducing an immune response to a single bacterial protein using a genetic vaccine allows the opportunity to develop diagnostic tests that could distinguish immune individuals from infected individuals and would aid in determining if *R. prowazekii* was intentionally spread within the population. A search for an effective vaccine against *R. prowazekii* is currently in progress. One laboratory has amplified 24 target genes using PCR to be transferred into DNA vaccine vectors, which will be tested in a rat model.[24]

Brill–Zinsser Disease

Until the start of the 19th century, no clear distinction could be made between typhoid and typhus. In 1896, Nathan Brill noted sporadic cases of a typhoid-like illness with negative blood cultures during an epidemic of typhoid fever in New York City.[25] His clinical summary of 221 cases distinguished the disease clearly from typhoid.[26] Since it was noncommunicable and did not have a deadly course, he believed it was not typhus.

In the early 1930s, Hans Zinsser used bacteriologic and epidemiologic methods to show that Brill's disease was an imported form of classical typhus representing recrudescence of infections initially acquired in Europe.[27,28] He believed that such a recurrence could produce a nidus for epidemic spread if the mouse–louse–man cycle could take place. *R. prowazekii* was isolated subsequently from ill patients with Brill–Zinsser disease; and these patients could infect lice feeding on them.[29] Brill–Zinsser disease was isolated from the lymph nodes of two Russian immigrants who had come to the United States more than 20 years earlier.[30,31]

It is believed that a weakening immune system or stress may reactivate the infection.[10] The clinical symptoms are usually milder than primary epidemic typhus and more closely resemble the symptoms of murine typhus.[15] Brill–Zinsser patients have elevated IgG antibody to *R. prowazekii* but do not have specific IgM antibody. Therapy is the same as with primary epidemic typhus.

With the continuing outbreaks of epidemic typhus in Russia and the immigration of eastern Europeans into North America over the last few decades, cases of Brill–Zinsser continue to be reported in the U.S.[32,33] and Canada.[34]

Murine Typhus (Endemic Typhus)

Epidemiology

R. typhi, an obligate intracellular bacterium, has been found worldwide and in the U.S., where most cases are in south Texas and southern California. These areas usually have inadequate vector and reservoir control. *R. typhi* causes murine typhus, also known as endemic typhus. The peak prevalence of murine typhus occurs during the summer and early fall, and in Texas, the peak prevalence is April through June.[35]

In 1926, *R. typhi* was discovered by Maxcy.[54] It is a zoonosis found most commonly in subtropical seaboard and temperate regions and responsible for epidemics. *R. typhi* causes a mild illness but occasionally it is fatal. *R. typhi* has been isolated in cat fleas and infected individuals with exposure to fleas.[36] Murine typhus is spread by the feces of infected fleas into the bite wounds of the flea. *R. typhi* and *R. felis* share some genetic and antigenic components present on the major protein antigen, the rickettsial outer membrane protein B.[37] However, genotypic characterization of the gene for a 17-kDa lipoprotein (citrate synthase) and 16S ribosomal RNA differentiates between these species.[37,38]

Clinical Manifestations

The clinical symptoms of *R. typhi* are nonspecific and usually occur 1–2 weeks after exposure to infected fleas. Symptoms may include fever (96%), headache (45%), chills (44%), nausea (33%), myalgia (33%), rash (18%–50%), and neurologic signs and symptoms (1%–45%).[35] When a rash is identified, the appearance is described as macular or maculopapular (78%), most often distributed on the trunk (88%), with involvement of the extremities (>45%) and infrequent involvement of the palms and soles.[35] The neurologic signs and symptoms may include ataxia, confusion, seizures, or stupor. Ten percent of infected patients require hospitalization and up to 4% of these patients expire.[35]

Diagnosis

The diagnosis of endemic typhus is based on clinical suspicion and supporting serologic laboratory confirmation. As with the other rickettsia species, serologic tests used for diagnosis of *R. typhi* based on its specific antigen include latex agglutination, indirect florescent antibody, or solids-phase immunoassay.[39] These tests are sensitive and specific within 1–2 weeks of onset of disease.[35] A shell vial assay can be used to verify infection during the acute phase of illness. This assay is not widely obtainable and is considered dangerous and difficult. Other tests available for laboratory confirmation of rickettsial infection include PCR amplification of rickettsial nucleic acids in peripheral blood and immunomagnetic retrieval of circulating endothelial cells together with immunocytologic demonstration of intraendothelial cell involvement.

Laboratory values may suggest involvement with *R. typi* infection. Mild thrombocytopenia and leukopenia are seen in 25%–50% of patients in the first 7 days of illness. The most common laboratory abnormality is an increased serum aspartate arninotransferase level (90%–92%).[35,41] Other hepatocellular enzymes (alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase) may be higher. Endothelial damage caused by *Rickettsia* infections can lead to hypoalbuminemia and serum electrolyte abnormalities such as hypocalcemia (79%) and hyponatremia (60%).

Treatment

The first-line treatment of mild-to-moderate *R. typhi* infection is doxycycline (200 mg/day) or tetracycline (25 mg/kg/day).[21] Other effective regimens are chloramphenicol (2 g/day for 7–10 days) or quinolones such as ofloxacin (400 mg/day for 5–7 days) and ciprofloxacin (1.5 g/day for 5–7 days).[42,43] In severe cases, intravenous doxycycline or chloramephenicol (50–75 mg/kg/day in four divided doses) is the preferred agent of treatment. These regimens should be continued at least 48–72 hours after defervescence before switching to oral treatment. After 72 hours of therapy, most patients become afebrile.

Scrub Typhus

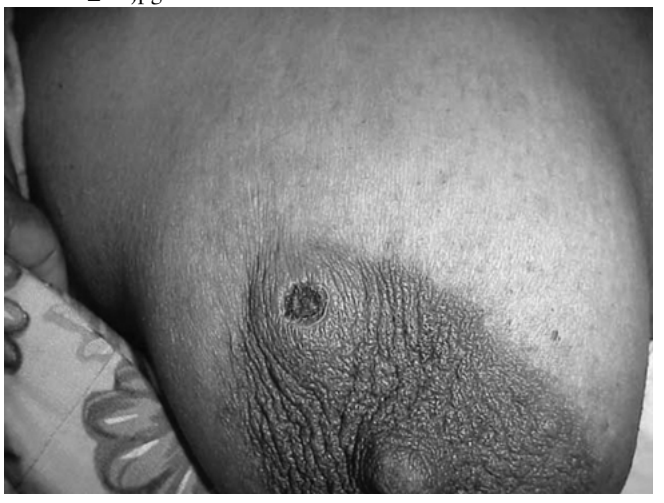
Epidemiology

Scrub typhus, a febrile disease caused by *Rickettsia* (*Orientia*) *tsutsugamushi*, is endemic to the area bounded on the west by Pakistan, on the north by northern Japan and southeastern Siberia, and on the south by Queensland, Australia.[44] First described in 1899, it was responsible for much morbidity in U.S. troops in World War II and the Vietnam War. The main reservoir of the organism and the vector for transmission of the infection to humans is chiggers of the species *Leptotrombidium* (*Trombicula*) *akamushi* and *L. deliense*, or larval trorniculid mites, which inhabit rural habitats like tall grasslands, scrub forests, or plantations.

Clinical Manifestations

R. tsutsugamushi, an obligate intracellular organism, is different from other rickettsia species because of its lack of peptidoglycan and lipopolysaccharide and its distinctive antigenic variants,[45] but there is enough cross-reactivity with antigens from other rickettsia such that serologic diagnosis can be made with the indirect fluorescent antibody test.[45,46] The disease is more widespread after periods of heavy rainfall when mites proliferate. As the infected chigger feeds on a human host, *R. tsutsugamushi* is inoculated and then multiplies at the wound, forming a painless small papule after approximately 2 days. The papule enlarges, vesiculates, then necroses in the center, forming a black crust, or eschar[44] (Fig. 6), and is associated with tender or suppurative regional ade-

FIGURE 6 Eschar on the breast of patient with scrub typhus during an outbreak on Darnley Island, Torres Strait (see ref. 76). Available from www.cdc.gov/ncidod/eid/vol9no4/images/02-0509_1b.jpg



nopathy. The rickettsia disseminate and cause vasculitis and perivasculitis of small blood vessels in multiple organs, particularly affecting the central nervous system and causing deafness, meningitis, and encephalitis.[47] It can also damage the liver, lungs, and kidneys. Because there are different infecting strains of *R. tsutsugamushi*, the severity of illness can vary with the strain's virulence,[46] and the mortality rate of untreated patients can range from 1% to 60%.

The incubation period for the disease is 6–18 days, and the presenting symptoms commonly include headache, fever up to 105°F, and chills. Patients can also have cough, myalgia, nausea, and anorexia.[48] The usual physical findings are generalized lymphadenopathy (85%), eschar (46%) most often in the calf area but also found in the axilla, groin, and inguinal area, splenomegaly (43%), and maculopapular rash (34%) that appears at day 3–8 of the febrile illness and persists for an average of 4.2 days. Some patients can also have deafness and tinnitus (in up to one third of cases), and conjunctival infection.[44]

The rash usually begins with macular lesions on the trunk that extend centripetally and can then become papular. Neuropsychiatric symptoms are common, including confusion, delirium, nuchal rigidity, and slurred speech; 9 of 72 patients presented with encephalitis or meningitis in one report.[47] CSF studies show results that resemble a tuberculous or viral meningitis picture.[47]

Treatment with appropriate antibiotics reduces the duration of illness and the risk of death.[46] Fever resolves after 48 hours in treated patients, while before antibiotics fever usually persisted an average of 14 days and up to half of patients died.[44] Patients that are untreated also can suffer complications such as acute respiratory distress syndrome, ataxia, coma, renal failure, hyperbilirubinemia, blindness, deafness, and cognitive defects.[44]

Diagnosis

Scrub typhus must be considered in febrile patients who have traveled, in endemic areas. Some patients may not have the classic rash and eschar but have lymphocytosis and generalized adenopathy that may confuse the diagnosis with infectious mononucleosis.[48] While serologic confirmation of the diagnosis is pending, therapy should be started empirically.

The diagnosis of scrub typhus can be made through multiple serologic methods. The indirect fluorescent antibody test is more sensitive and specific than the more widely available Weil–Felix agglutination test,[47] and a peak in antibody titer after the second week of disease is seen. With the immunoperoxidase assay, which is easier to perform than the indirect fluorescent antibody test and just as sensitive and specific,[47,49] a fourfold increase in convalescent titers verifies the diagnosis of scrub typhus. Polymerase chain reaction can also be used to detect the DNA of *R. tsutsugamushi* from skin biopsy specimens and peripheral blood.[50] The gold standard for diagnosing scrub typhus is the immunofluorescent antibody assay, but it requires specialized training and equipment and is done in only a few reference laboratories. Thus, a sensitive, rapid lateral flow assay that identifies Orientia tsutsugamushi-specific IgG/IgM antibodies is being developed.[51]

Patients typically have a normal white blood cell count, with lymphocytosis in the majority of cases. About half of the patients have elevated aspartate aminotransferase and 20% have proteinuria.[48]

Other diagnoses that must be considered include other rickettsial diseases, typhoid fever, brucellosis, infectious mononucleosis, leptospirosis, toxoplasmosis, and dengue fever.[46]

Treatment

Appropriate antibiotic therapy is either tetracyclines or chloramphenicol. Tetracyclines were found to reduce fever and other symptoms more quickly in one comparative study.[52] Fourteen days of tetracycline 2 mg/day or doxycycline 200 mg/day, the recommended course of treatment,[53] is also effective at reducing relapses of scrub typhus, which are more common if patients are started on shorter courses of therapy during the first five days of the illness.[52] Ciprofloxacin was found in an animal model to be as effective as chloramphenicol,[54] and it successfully treated a patient in one case report.[53]

Infection with a particular strain of *R. tsutsusamushi* provides immunity to that strain only; patients can have later episodes of scrub typhus if exposed to a heterologous serotype.[46] Because of the multiple antigenic strains of *R. tsutsugamushi*, a prophylactic vaccine for scrub typhus has not been developed. Individuals that will travel in endemic areas can prevent scrub typhus by taking doxycycline 200 mg/week,[55,56] using insect and mite repellent, and refraining from sitting or lying on the ground.

Rickettsial Infections and Bioterrorism

In 1996, a law was enacted in the United States to thwart terrorists from gaining access to dangerous infectious agents.[57] *R. priwazekii* and *R. rickettsii*, along with 10 other bacteria, were listed as hazardous agents with severe restrictions on their study and transfer to other laboratories. A committee with expertise in infectious diseases, microbiology, and public health gathered to categorize infectious diseases into levels of potential threats of bioterrorism.[58] CDC category A was considered the most dangerous group; *R. prowazekii* was placed in category B, and *R. rickettsii* was placed in category C.[59,60] However, it has been argued that *R. prowazekii* belongs in category A and that *R. typhi* and *R. rickettsii* also belong in category A, or at least in category B.[59]

There is a real threat of the rickettsiae being used as bioweapons. In the 1930s the USSR developed *R. prowazekii* as a biologic weapon, and in the late 1930s to 1940s Japan carried out field and human testing of typhus as a biologic weapon in northeastern China.[61,62] Further, *R. prowazekii* was the subject of active bioweapon research in the USSR during the 1970s and afterward.

There are several characteristics of potential biologic agents used for terrorism: high and stable infectivity, especially by small-particle aerosol; high level of virulence; low minimum infectious dose; clinical similarity of the bioterrorism agent to more common diseases; difficulty in distinguishing between bioterrorism and natural transmission; low level of immunity in the target population; easy person-to-person communicability; the diagnosis strikes terror in the population; and difficulty of therapy.[59]

R. prowazekii in dried louse feces and *R. typhi* in dried flea feces are highly infectious and stable for long periods of time.[63,64] Furthermore, aerosols containing *R. prowazekii*, *R. typhi*, *R. conori*, and *R. rickettsii* have resulted many laboratory infections.[65,66] *Rickettsia* can also be preserved stably in a lyophilized state, milled to 1–5-μm particles, and treated to prevent electrostatic clumping for aerosol dispersal. The minimum infectious dose (ID_{50}) for some pathogenic rickettsiae is only one or two organisms.[67]

Similar to the severe viral hemorrhagic fevers, epidemic typhus (10%–60% mortality) and Rocky Mountain spotted fever (20%–15% mortality) are among the most severe infectious diseases in humans. *R. conorii* and *R. typhi* may cause life-threatening illness in special populations (e.g., elderly, those with G6PD deficiency, which is common in African–American men).[68–70] Since the National Institutes of Health has stated that no population will be left behind, these special populations are at an increased risk of bioterrorism and should be observed closely.

The clinical manifestations of the rickettsial diseases may resemble other more common diseases, leading to delayed accurate diagnosis and therapy. Furthermore, with the exception of *R. prowazekii*, the enzootic nature of many rickettsial diseases obscures the distinction between an act of bioterrorism and natural transmission. Since rickettsial diseases are endemic in numerous areas of the world, identification of the infectious source would be difficult. However, the unexpected occurrence of a few human cases of typhus in nonendemic areas or an epidemic should set off the alarm for bioterrorism.

In developed countries there is a very low level of immunity to all rickettsial diseases. Very high levels of susceptibility exist in these nations, and a high attack rate would be anticipated in populations exposed to an infectious aerosol. However, with the exception of *R. prowazekii*, these diseases are not transmissible from person to person. The introduction of *R. prowazekii* to an indigent population infested with human body lice (*Pediculus humanus corporis*) could result in overwhelming spread.

The level of fear generated by a particular infectious disease depends more upon media presentation and public perception rather than on scientific truth. Media hype regarding September 11, 2001, anthrax, and the subsequent tainted mailings created great terror of the disease. The panic over ebola and other hemorrhagic fevers was depicted in several recent movies. Nonetheless, anthrax and the hemorrhagic fevers are not very communicable. The name of the disease itself may instill alarm in the public [such as monkeypox, West Nile disease, severe acute respiratory syndrome (SARS), smallpox, and plague], but several diseases are virtually unheard of (such as brucellosis, tularemia, and leishmaniasis). It is likely that an epidemic of any of the rickettsial diseases would not cause mass terror even though they have the potential for exceptionally high morbidity and mortality.

Successful therapy of the rickettsial diseases is dependent upon a quick and accurate diagnosis and use of an antimicrobial agent to which the *Rickettsia* is susceptible. Even now, patients with Rocky Mountain spotted fever or epidemic typhus are misdiagnosed and treated with an empiric antibiotic that is not rickettsiostatic or rickettsiocidal.[71–73] Popular, empiric, first-line drugs against febrile illnesses (e.g., β-lactams and aminoglycosides) have no effect on rickettsial diseases. There is no evidence that fluoroquinolones, rifampin, and the newer macrolides are effective against Rocky Mountain spotted fever and epidemic typhus.

It would be relatively simple in theory for any bioterror lab to transform any *Rickettsia* to be resistant to chloramphenicol and tetracyclines by electroporation of resistance genes and selection of transformants under antimicrobial pressure. Regrettably, it is likely that this has already been done somewhere in the world. It is thought that a tetracycline-resistant strain of *R. prowazekii* has already been developed in the USSR.[59] This leads to the possibility that *R. prowazekii* bioweapon has

been already developed that is resistant to all antimicrobial therapy.

The most hazardous of the genus is *R. prowazekii*, followed by *R. rickettsii* and *R. typhi*. Except for no person-to-person communicability, *R. prowazekii* engineered to antimicrobial resistance meets all of the criteria of the most dangerous infectious diseases. However, the needs for biodefense against rickettsial infections are the same as the needs for public health measures against these diseases throughout the world. The most urgently required innovations would be acute and effective diagnostics and therapies for typhus group and spotted fever group rickettsioses and a cross-protective typhus group vaccine.

Conclusion

The Rickettsiaceae family is very prevalent and maintained in nature through reservoirs of mammals and arthropod vectors. This family of microbes is a significant cause of morbidity and mortality, and these infections are likely unrecognized and underdiagnosed. The impact of the Rickettsiaceae family on global public health is likely extremely significant. Numerous rickettsial strains have been isolated from fleas, ticks, and other vectors from many countries, and it is likely that many other strains will be identified in the future. Prevention methods are crucial in controlling flea and tick vectors and potential flea hosts, especially in persons who spend extended periods of time outdoors or work with animals (e.g., hunters, farmers, veterinarians, forestry work, military training). Local public health authorities should be notified in all rickettsial cases. Current effective therapies include the tetracyclines, chloramphenicol, and quinolones. Unfortunately, no vaccine of proven effectiveness exists currently, but once infected by natural transmission, recovery will confer a solid, long-lasting immunity to reinfection.

CME Questions

1. Which of the following is the etiologic agent of Boutonneuse fever?

   a. *R. australis*
   b. *R. conorii*
   c. *R. sibirica*
   d. *R rickettsii*
   e. *R. akari*

2. Which of the following is an effective therapy against Rocky Mountain spotted fever?

   a. Aminoglycosides
   b. Erythromycin
   c. Trimethoprim-sulfamethoxazole
   d. Doxycycline
   e. Cephalosporins

3. All of the following are caused by *Rickettsia prowazekii* EXCEPT:

   a. Brill–Zinsser disease
   b. Epidemic typhus
   c. Murine typhus
   d. Classic typhus

4. All of the following are characteristics of potential biologic agents used for terrorism EXCEPT:

   a. High level of immunity in the target population
   b. Clinical similarity of the bioterrorism agent to more common diseases
   c. High level of virulence
   d. Low minimum infectious dose
   e. High and stable infectivity

5. In which of the following diseases can a patient's temperature reach up to 106°F?

   a. Scrub typhus
   b. Oriental spotted fever
   c. Epidemic typhus
   d. Rocky Mountain spotted fever
   e. Rickettsialpox

6. *R. prowazekii* can be found on all of these continents EXCEPT:

   a. Australia
   b. North America
   c. South America
   d. Asia
   e. Africa

7. A *tacke noire*, an eschar at the site of the bite, is very suggestive of which of the following?

   a. Scrub typhus
   b. Boutonneuse fever
   c. Rickettsialpox
   d. Oriental spotted fever
   e. Murine typhus

8. All of these rickettsiae are considered to be potential agents used in bioterrorism EXCEPT:

   a. *R. prowazekii*
   b. *R. typhi*
   c. *R. rickettsii*
   d. *R. tsutsugamushi*

9. All of the following are effective treatments for Queensland tick typhus EXCEPT:

   a. Rifampin
   b. Chloramphenicol
   c. Ofloxacin
   d. Ciprofloxacin
   e. Tetracycline

10. Which of the following is the animal vector of *R. prowazekii?*

    a. Rabbit
    b. Mouse
    c. Groundhog
    d. Raccoon
    e. Flying squirrel

11. Which of the following is a known rickettsial virulence factor?

    a. Cell wall
    b. Cilia
    c. Adhesins
    d. Iron binding
    e. Flagella

12. Which of the following is primarily spread by the feces of infected fleas?

    a. Rocky Mountain spotted fever
    b. Murine typhus
    c. Boutonneuse fever
    d. North Asian tick typhus
    e. Scrub typhus

13. In the United States, which population is the most likely to be affected by Brill–Zinsser disease?

    a. Infants
    b. Farmers
    c. Homosexual men
    d. Post-menopausal women
    e. Eastern Europeans immigrants

14. Which of the following is the etioiogic agent of scrub typhus?

    a. *R. prowazekii*
    b. *R. australis*
    c. *R. japonica*
    d. *R. tsutsugamushi*
    e. *R. typhi*

15. Which of the following is another name for Brazilian spotted fever?

    a. Boutonneuse fever
    b. Classic sported fever
    c. Queensland spotted fever
    d. Oriental spotted fever
    e. Rocky mountain spotted fever

16. Into which category of potential use in bioterrorism did the CDC place *R. prowazekii*?

    a. A
    b. B
    c. C
    d. D
    e. X

17. *R. sibirica* is the etiologic agent for which of the following?

    a. North Asian tick typhus
    b. Queensland tick typhus
    c. Epidemic typhus
    d. Scrub typhus
    e. Endemic typhus

18. *R. akari* is the etiologic agent for which of the following?

    a. Rocky Mountain spotted fever
    b. Epidemic typhus
    c. Rickettsialpox
    d. Scrub typhus
    e. Queensland tick typhus

19. Which of the following is the etiologic agent of Queensland tick typhus?

    a. *R. sibirica*
    b. *R. japonica*
    c. *R. australis*
    d. *R. rickettsii*
    e. *R. prowazekii*

20. Into which category of potential use in bioterrorism did the CDC place *R. rickettsii*?

    a. A
    b. B
    c. C
    d. D
    e. X

21. Epidemic typhus is typically transmitted in which season, of the year?

    a. Spring
    b. Summer
    c. Fall
    d. Winter

22. *Leptotrombidium* is the primary tick vector for which of the following?

    a. Rickettsialpox
    b. Epidemic typhus
    c. Rocky Mountain spotted fever
    d. Scrub typhus
    e. Endemic typhus

23. *Ixodes holocyclus* is the primary tick vector for which of the following?

    a. Boutonneuse fever
    b. Queensland tick typhus
    c. North Asian tick typhus
    d. Murine typhus
    e. Sylvatic typhus

24. All of the following are symptoms of the classic triad for Rocky Mountain spotted fever EXCEPT:

    a. Fever
    b. Headache
    c. Nausea/vomiting
    d. Rash

25. All of the following may decrease the risk of an outbreak of epidemic typhus EXCEPT:

    a. Use of insecticides
    b. Doxycycline prophylaxis
    c. Washing of infested clothes
    d. Drinking herbal tea
    e. Regular bathing

26. Which of the following is the etiologic agent of murine typhus?

    a. *R. typhi*
    b. *R. tsutsugamushi*
    c. *R. rickettsii*
    d. *R. japonica*
    e. *R. akari*

27. Which of the following is the primary insect vector for Oriental spotted fever?

    a. *Pediculus homanus corporis*
    b. *Ctenocephalides felis*
    c. *Dermacentor*
    d. *Haemaphysalis*
    e. It has yet to be determined.

28. *R. prowazekii* is the etiologic agent for which of the following?

    a. South African tick fever
    b. Siberian tick typhus
    c. Sylvatic typhus
    d. Endemic typhus
    e. Kenya tick typhus

29. Approximately what percent of patients with Rocky Mountain spotted fever do not have a rash?

    a. 5%
    b. 10%
    c. 15%
    d. 20%
    e. 30%

30. All of the following are populations in which Rocky Mountain "spotless" fever are more likely to occur EXCEPT:

    a. African–Americans
    b. Immigrants
    c. Men
    d. Elderly patients

CME Answers

1. b; 2. d; 3. c; 4. a; 5. e; 6. a; 7. b; 8. d; 9. a; 10. e; 11. c; 12. b; 13. e; 14. d; 15. e; 16. b; 17. a; 18.c; 19. c; 20. c; 21.d; 22. d; 23. b; 24. c; 25. d; 26. a; 27. e; 28. c; 29. b; 30. b;

References

1. Walker D, Dumler J, Radulvis S. Spotted fevers and rickettsialpox In: Ronald A, Infectious disease: A treatise on infectious processes Philadelphia: JB Lippincott, 1994; pp 969–978.
2. Kass EM, Szaniawski WK, Levy H, et al. Rickettsialpox in a New York City hospital, 1980 to 1989. N Engl J Med 1994; 331:1612–1617.
3. Brettman LR, Lewin S, Hozman RS, et al. Rickettsialpox: Report of an outbreak and a contemporary review. Medicine 1981; 60:363–372.
4. Rose H. The clinical manifestations and laboratory diagnosis of rickettsialpox. Ann Intern Med 1949; 31:871–883.
5. Sussman L. Kew Gardens' spotted fever. N Y Med 1946; 2:27–28.
6. Greenberg M, Pellitteri O. Rickettsialpox. Bull NY Acad Med 1947; 23:338–351.
7. Huebner R, Stamps P, Armstrong C. Rickettsialpox—A newly recognized rickettsial disease: I. Isolation of the etiological agent. Public Health Rep 1946; 61:1605–1614.
8. Jacobson J, Desmond E, Kornblee L, et al. Positive Weil–Felix reactions in a case of rickettsialpox. Int J Dermatol 1989; 28:271–272.
9. Feigin R, Snider R, Edwards M. Rickettsial disease In: Cherry J, Textbook of pediatric infectious diseases Philadelphia: WB Saunders, 1992; pp 1847–1865.
10. Saah AJ. *Rickettsia prowazekii* In: Mandell GL, Bennett JE, Dolin R, Principles and practice of infectious diseases 4th ed. New York: Churchill Livingstone, 1995; pp 1735–1737.
11. McDads JE, Shepard CC, Redus MA, et al. Evidence of *Rickettsia prowazekii* infections in the United States. Am J Trop Med Hyg 1980; 29:277–284.
12. Bozeman FM, Masiello SA, Williams MS, et al. Epidemic typhus rickettsiae isolated from flying squirrels. Nature 1975; 255:545–547.
13. Sonenshine DE, Bozeman FM, Williams MS, et al. Epizootiology of epidemic typhus (Rickettsia prowazekii) in flying squirrels. Am J Trop Med Hyg 1978; 27:339–349.
14. Duma RJ, Sonenshine DE, Bozeman FM, et al. Epidemic typhus in the United States associated with flying squirrels. JAMA 1981; 245:2318–2323.
15. Baxter JD. The typhus group. Clin Dermatol 1996; 14:271–278.
16. Perine PL, Chandler BP, Krause DK, et al. A clinico-epidemiological study of epidemic typhus in Africa. Clin Infect Dis 1992; 14:1149–1158.
17. Kaplan JE, Schonberger LB. The sensitivity of various serologic tests in the diagnosis of Rocky Mountain spotted fever. Am J Trop Med Hyg 1986; 35:840–844.
18. Carl M, Tibbs CW, Dobson ME, et al. Diagnosis of acute typhus infection using the polymerase chain reaction. J Infect Dis 1990; 161:791–793.
19. Jiang J, Temenak JJ, Richards AL. Real-time PCR duplex assay for *Rickettsia prowazekii* and *Borrelia recurrentis*. Ann N Y Acad Sci 2003; 990:302–310.
20. Perine PL, Krause DW, Awoke S, et al. Single-dose doxycycline treatment of louse-borne relapsing fever and epidemic typhus. Lancet 1974; 2:742–744.
21. Raoult D, Drancourt M. Antimicrobial therapy of rickettsial diseases. Antimicrob Agents Chemother 1991; 35:2457–2462.
22. Walker DH Biology of Rickettsial Diseases. Early VaccinesCRC Press, Boca Raton, FL 1988.
23. Centers for Disease Control (CDC). Typhus vaccine. MMWR Morb Mortal Wkly Rep 1978; 27:189.
24. Coker C, Majid M, Radulovic S. Development of *Rickettsia prowazekii* DNA vaccine: cloning strategies. Ann NY Acad Sci 2003; 990:757–764.
25. Lutwick LI. Brill–Zinsser disease. Lancet 2001; 357:1198–1200.

26. Brill NE. An acute infectious disease of unknown origin: a clinical study based on 221 cases. Am J Med Sci 1910; 139:484–502.
27. Zinsser H, Castaneda MR. On the isolation from a case of Brill's disease of a typhus strain resembling the European type. N Engl J Med 1933; 209:815–819.
28. Zinsser H. Varieties of typhus virus and the epidemiology of the American form of European typhus fever (Brill's disease). Am J Hyg 1934; 20:513–532.
29. Murray ES, Snyder JC. Brill's disease: II, etiology. Am J Hyg 1951; 53:22–32.
30. Price WH. Studies on the interepidemic survival of louse borne epidemic typhus fever. J Bacteriol 1955; 69:106–107.
31. Price WH, Emerson H, Nagel H, et al. Ecologic studies on the interepidemic survival of louse-borne epidemic typhus fever. Am J Hyg 1958; 67:154–178.
32. Reilly PJ, Kalinske RW. Brill–Zinsser disease in North America. West J Med 1980; 133:338–340.
33. Green CR, Fishbein D, Gleiberman I. Brill–Zinsser: still with us. JAMA 1990; 264:1811–1812.
34. Portnoy J, Mendelson J, Clecner B. Brill–Zinsser disease: report of a case in Canada. Can Med Assoc J 1974; 111:166.
35. Dumler JS, Taylor JP, Walker DH, Dumler JS, Taylor JP, Walker DH. Clinical and laboratory features of murine typhus in south Texas, 1980 through 1987. JAMA 1991; 266:1365–1370.
36. Azad AF, Sacci JB Jr, Nelson WM, et al. Genetic characterization and transovarial transmission of a typhus-like rickettsia found in cat fleas. Proc Natl Acad Sci USA 1992; 89:43–46.
37. Radulovic S, Higgins JA, Jaworski DC, et al. Isolation, cultivation, and partial characterization of the ELB agent associated with cat fleas. Infect Immun 1995; 63:4826–4829.
38. Azad AF, Radulovic S, Higgins JA, et al. Flea-borne rickettsioses: ecologic considerations. Emerg Infect Dis 1997; 3:319–327.
39. Kelly DJ, Chan CT, Paxton H, et al. Comparative evaluation of a commercial enzyme immunoassay for the detection of human antibody to Rickettsia typhi. Clin Diagn Lab Immunol 1995; 2:356–360.
40. Drancourt M, George F, Brouqui P, Sampol J, Raoult D. Diagnosis of Mediterranean spotted fever by indirect immunofluorescence of Rickettsia conorii in circulating endothelial cells isolated with monoclonal antibody-coated immunomagnetic beads. J Infect Dis 1992; 166:660–663.
41. Silpapojakul K, Mitarnun W, Ovartlarnporn B, et al. Liver involvement in murine typhus. QJM 1996; 89:623–629.
42. Raoult D, Gallais H, DeMicco P, et al. Ciprofioxacin therapy for Mediterranean spotted fever. Antimicrob Agents Chemother 1986; 30:606–607.
43. Ruiz Beltran R, Herrero JI. Evaluation of ciprofioxacin and doxycycline in the treatment of Mediterranean spotted fever. Eur J Clin Microbiol Infect Dis 1992; 11:427–431.
44. Watt G, Strickman D. Life-threatening scrub typhus in a traveler returning from Thailand. Clin Infect Dis 1994; 18:624–626.
45. Ohashi N, Tamura A, Sakurai H, et al. Characterization of a new antigenic type, Kuroki, of Rickettsia tsutsugamushi isolated from a patient in Japan. J Clin Microbiol 1990; 28:2111–2113.
46. Saah A. *Rickettsia tsutsugamushi* In: Dolin R, ed. Principles and practice of infectious diseases 4th ed. New York: Church Livingstone, 1995; pp 1740–1741.
47. Silpapojakul K, Ukkachoke C, Krisanapan S, et al. Rickettsial meningitis and encephalitis. Arch Intern Med 1991; 151:1753–1757.
48. Berman S, Kundin W. Scrub typhus in South Vietnam, a study of 87 cases. Ann Intern Med 1973; 79:26–30.
49. Kelly DL, Wong PW, Gan E, et al. Comparative evaluation of the serodiagnosis of rickettsial disease. Am J Trop Med 1988; 38:400–406.
50. Sugita Y, Nagatani T, Okuda K, et al. Diagnosis of typhus infection with *Rickettsia tsutsugamushi* by polymerase chain reaction. J Med Microbiol 1992; 37:357–360.
51. Wilkinson R, Rowland D, Ching WM. Development of an improved rapid lateral flow assay for the detection of *Orientia tsutsugamushi*-specific IgG/IgM antibodies. Ann N Y Acad Sci 2003; 990:386–390.
52. Sheehy T, Hazlett D, Turk R. Scrub typhus, a comparison of chloramphenicol and tetracycline in its treatment. Arch Intern Med 1973; 132:77–80.
53. Raoult D, Drancourt M. Antimicrobial therapy of rickettsial diseases. Antimicrob Agents Chemother 1991; 35:2457–2462.
54. McClain J, Joshi B, Rice R. Chloramphenicol, gentamicin, and ciprofloxacin against murine scrub typhus. Antimicrob Agents Chemother 1988; 32:285–286.
55. Twartz JC, Shirai A, Selvaraju G, et al. Doxycycline prophylaxis for human scrub typhus. J Infect Dis 1982; 146:811–818.
56. Olson JG, Bourgeois AL, Fang RC, et al. Prevention of scrub typhus: Prophylactic administration of doxycycline in a randomized double blind trial. Am J Trop Med 1980; 29:989–997.
57. Atlas RM. Biological weapons pose challenge for microbiology community. ASM News 1998; 64:383–389.
58. Rotz LD, Khan AS, Lillibridge SR, et al. Public health assessment of potential biological terrorism agents. Emerg Infect Dis 2002; 8:225–230.
59. Walker DH. Principles of the malicious use of infectious agents to create terror: reasons for concern for organisms of the genus Rickettsia. Ann N Y Acad Sci 2003; 990:739–742.
60. Azad AF, Radulovic S. Pathogenic rickettsiae as bioterrorism agents. Ann N Y Acad Sci 2003; 990:734–738.
61. Alibek K. BiohazardRandom House, New York 1999.
62. Harris S. Japanese biological warfare research on humans: a case study of microbiology and ethics. Ann N Y Acad Sci 1992; 666:21–49.
63. Silverman DJ, Boese JL, Wisseman CL. Ultrastructural studies of *Rickettsia prowazekii* from louse midgut cells to feces: search for "dormant" forms. Infect Immun 1974; 10:257–263.
64. Traub R, Wisseman CL, Farhang–Azad A. The ecology of murine typhus–a critical review. Trop Dis Bull 1978; 75:237–317.
65. Johnson JE, Kadull PJ. Rocky Mountain spotted fever acquired in a laboratory. N Engl J Med 1967; 277:842–847.
66. Pike RM. Laboratory-associated infection: summary and analysis of 3921 cases. Health Lab Sci 1976; 13:105–114.
67. Azad AF, Traub R. Experimental transmission of murine typhus by *Xenopsylla cheopis* flea bites. Med Vet Entomol 1989; 3:429–433.
68. Whelton A, Donadio JV, Elisberg BL. Acute renal failure complicating rickettsial infections in glucose-6-phosphate dehydrogenase-deficient individuals. Ann Intern Med 1968; 69:323–328.
69. Raoult D, Lena D, Perrimont H, et al. Haemolysis with Mediterranean spotted fever and glucose-6-phosphate dehydrogenase deficiency. Trans R Soc Trop Med Hyg 1986; 80:961–962.
70. Raoult D, Zuchelli P, Weiller PJ, et al. Incidence, clinical observations and risk factors in the severe form of Mediterranean spotted fever among patients admitted to hospital in Marseilles 1983–1984. J Infect 1986; 12:111–116.
71. Dalton MJ, Clarke MJ, Holman RC, et al. National surveillance for Rocky Mountain spotted fever, 1981–1992: epidemiologic summary and evaluation of risk factors for fatal outcome. Am J Trop Med Hyg 1995; 52:405–413.
72. Raoult D, Roux V, Ndihokubwayo JB, et al. Jail fever (epidemic typhus) outbreak in Burundi. Emerg Infect Dis 1997; 3:357–360.
73. Raoult D, Maurin M. Rickettsia species In: Yu VL, Merigan TC, Barriere SL, Antimicrobial Therapy and Vaccines Baltimore: Williams and Wilkins Co, 2001; pp 568–574.
74. Krusell A, Cower JA, Sexton DJ. Rickettsialpox in North Carolina: a case report. Emerg Infec Dis 2002; 7:727–728.
75. Niang M, Brouqui P, Raoult D. Epidemic typhus imported from Algeria. Emerg Infec Dis 1999; 5:716–718.
76. Faa AG, McBride WJ, Garstone G, et al. Scrub typhus in the Torres Strait Islands of North Queensland, Australia. Emerg Infec Dis 2003; 9:480–482.