

## Review Article



# Rickettsial Diseases

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## Abstract

Rickettsiae are a rather diverse collection of organisms with several differences; this prohibits their description as a single homogenous group. Rickettsiae are maintained in nature through a cycle involving reservoir in mammals and arthropod vectors. The public health impact of these on lives or productivity lost is largely unmeasured, but suspected to be quite high worldwide. The diseases caused by *Rickettsia* and *Orientia* species are often collectively referred to as rickettsioses. *Coxiella burnetii*, the agent of Q fever is still frequently categorized as rickettsial disease. New or emerging rickettsial diseases; tickborne lymphadenopathy (TIBOLA) and *Dermacentor*-borne-necrosis-eschar- lymphadenopathy (DEBONEL) related to *Rickettsia slovaca* infection have been described. The rickettsial diseases were believed to have disappeared from India are reemerging and recently their presence has been documented in at least eleven states of our country. Many cases of rickettsial diseases go undiagnosed due to lack of diagnostic tools. Greater clinical awareness, a higher index of suspicion, better use of available diagnostic tools would increase the frequency with which rickettsial diseases are diagnosed.

## Introduction

Rickettsiae comprise a group of microorganisms that phylogenetically occupy a position between bacteria and viruses. The genus *Rickettsia* is included in the bacterial tribe Rickettsiae, family Rickettsiaceae, and order Rickettsiales. The taxonomy of Rickettsiales is complex and continues to be updated. The Rickettsiaceae family is maintained in nature through a cycle involving reservoir in mammals and arthropod vectors. The public health impact of these on lives or productivity lost is largely unmeasured, but suspected to be quite high worldwide. They are obligate intracellular gram-negative coccobacillary forms that multiply within eukaryotic cells. Rickettsiae do not stain well with Gram stain, but they take on a characteristic red color when stained by the Giemsa or Gimenez stain. Rickettsiae are a rather diverse collection of organisms with several differences; this prohibits their description as a single homogenous group. A general characteristic of rickettsiae is that mammals and arthropods are natural hosts. Rickettsioses usually are transmitted to humans by arthropods.<sup>1,2</sup> Eighteen rickettsioses, caused by organisms within the genus of rickettsiae, are recognized and can be divided into the following 3 biogroups:

**Typhus group:** causing classical epidemic typhus caused by *Rickettsia prowazekii* and *Rickettsia typhi* transmitted by human body louse and rat flea respectively.

**Spotted fever group:** containing a large number of species *Rickettsia rickettsii*, *Rickettsia conorii* etc. transmitted from rodents and other animals by ticks (except *Rickettsia akari*) Rocky Mountain spotted fever is prototype.

**Scrub typhus:** caused by *Orientia tsutsugamushi* and transmitted by larval trombiculid mites.

The diseases caused by *Rickettsia* and *Orientia* species are often collectively referred to as rickettsioses.

## Other Rickettsioses

The genus previously named Rochalimaea has been classified in the family Bartonellaceae, are organisms related to rickettsiae, which causes cat scratch disease, relapsing fever and trench fever. *Coxiella burnetii* causes Q fever and tribe Ehrlichia can cause fever in human and several equine and canine species. *Coxiella burnetii*, the agent of Q fever, and *Bartonella* spp. were recently removed from the order Rickettsiales, but Q fever and bartonellosis are still frequently categorized as rickettsial diseases. New or emerging rickettsioses have been described in last few decades, including tickborne lymphadenopathy (TIBOLA) and *Dermacentor*-borne-necrosis-eschar- lymphadenopathy (DEBONEL) related to *Rickettsia slovaca* infection, as well as lymphangitis-associated rickettsiosis attributed to *Rickettsia sibirica* infection.<sup>1-5</sup>

The symptoms, signs and laboratory data in Rocky Mountain Spotted Fever (RMSF), Boutonneuse Fever (BF) and African Tick Bite Fever (ATBF) are given in Table 1.

## Spotted Fever Group (SFG) Rickettsiae

The spotted fevers compose a large group (15 rickettsioses) of tick- and mite- borne zoonotic infections that are caused by closely related rickettsiae. They include Rocky Mountain spotted fever (RMSF), boutonuse fever, African tick bite fever, North Asian tick typhus, Queensland tick typhus, Finders Island spotted fever, Japanese spotted fever and rickettsial pox. These diseases have a broad spectrum of severity and Rocky Mountain spotted fever is most virulent. Even young and previously healthy people may die of RMSF. In recent years, the wide distribution and potentially severity of other spotted fevers have been recognized in southern Europe, Africa, Australia, China and Japan. Establishing an early diagnosis is deceptively difficult.

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

The etiological agent *Rickettsia rickettsii*, belong to the spotted fever group (SFG) rickettsiae and are obligate intracellular bacteria. The spotted fever rickettsiae have been found in every continent except Antarctica. The tick of *Dermacentor* species,

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*Rhipicephalus sanguineus* and *Amblyomma cajennense* are both vector and main reservoir. There is a variation in infection rates in population from time to time and the causes for the same are not very clear. Humidity, climatic variation, human activities altering the vegetation and fauna and use of insecticides are suspected to play a role in the fluctuation of the prevalence of human rickettsioses. *Rickettsia rickettsii*, is transmitted transstadially (stage to stage) and transovarially in tick and thus maintains infection in nature. The tick transmits the disease to human during a prolonged period of feeding that may last for 1-2 weeks. The bite is painless and usually unnoticed. Rickettsiae are injected from salivary glands of attached tick after 6-10 hours of feeding on human. Human may be infected by exposure to infected tick hemolymph while removing tick from person or animal especially if tick is crushed between fingers. The laboratory-acquired infection by aerosols or parenteral inoculation of Rickettsiae has been reported. The fluctuations in infection rate of RMSF has been attributed to an increase in the infected tick population or tick contact with human, an increase in interest of physician in the disease, and development of more sensitive, specific serological tools. The fall in incidence following the introduction of effective antibiotics, and the increased incidence coinciding with decline in the use of tetracycline as first-choice antibiotic for many other infections which implies occurrence of many undiagnosed cases.<sup>1,2,5,7</sup>

## Pathophysiology

Rickettsiae microorganisms appear to exert their pathologic effects by adhering to and then invading the endothelial lining of the vasculature within the various organs affected. The adhesions appear to be outer membrane proteins that allow the rickettsia to be phagocytosed into the host cell. Once inside, the rickettsial organisms escape from the cell, damaging its membrane and causing the influx of water. Rickettsiae rely on the cytosol of the host cells for growth. To avoid phagocytosis within the cells, they secrete phospholipase D and hemolysin C, which disrupt the phagosomal membrane, allowing for rapid escape. The most important pathophysiologic effect is increased vascular permeability with consequent edema, loss of blood volume, hypoalbuminemia, decreased osmotic pressure, and hypotension. On the other hand, disseminated intravascular coagulation is rare and does not seem to contribute to the pathophysiology of rickettsiae.<sup>2-5,7</sup> The consequent of cell-to-cell spread of rickettsiae in body in a focal network of hundreds of contiguous infected endothelial cells corresponding to the lesion and manifest as maculo-papular rash. The vascular injury and subsequent host lympho-histiocytic response correspond to distribution of rickettsiae and include interstitial pneumonia, interstitial myocarditis, perivascular glial nodules of central nervous system, and similar vascular lesions in skin, gastrointestinal tract, pancreas, liver, skeletal muscles and kidneys. Platelets are consumed locally.<sup>7</sup>

## Clinical Manifestations

The incubation period ranges from 2-14 days. The disease begins with fever, myalgia and headache. Headache is usually quite severe, young children may not complain of pain at all (Table 1). Onset of nausea, vomiting, pain abdomen, diarrhea and abdominal tenderness occur in substantial number of patients suggesting gastroenteritis or an acute surgical abdomen. The rash, the major diagnostic sign, appear in a small number of cases on first day and in about 50% cases by third day, usually appear after 3-5 days of onset of fever and occurring up to

91% of patients overall. The rash typically begins around the wrists and ankle but may start on the trunk or be diffuse at the onset. Rocky Mountain 'spotless' fever occur more often in older patients and in black patients. Focal neurological deficits, transient deafness, meningismus and photophobia may suggest meningitis or meningoencephalitis. The cerebrospinal fluid contains increase leukocytes (either lymphocytes of polymorphs) and increase proteins concentration in one third of patients. However cerebrospinal fluid sugar concentration is low in only in 8%, Fulminant RMSE is more often observed in black males with glucose-6-phosphatase dehydrogenase deficiency. Older age, male gender and possibly alcoholism are other risk factors associated with fatal outcome. In classic RMSF, death occurs 8 to 15 days after onset of symptoms when appropriate is not given in a timely manner. In fulminant RMSF, death occurs with in first 5 days. The highest age-specific incidence of RMSF is among children <10 yr of age and the disease is milder in children.<sup>2,4,7</sup>

## Other Spotted Fever Group Rickettsiae

Among eight other SFG rickettsial species known to be pathogenic for human *R. conorii*, *R. sibirica*, *R. japonica*, *R. australis*, *R. honei*, *R. africae* and *R. slovaca* are considered to be transmitted by tick bite. *R. conorii*, infection has been designated by many geographic names: Marseilles fever, Mediterranean spotted fever, Kenya tick typhus and Indian tick typhus. Flea-borne spotted fever is caused by *R. felis*, suspected to be endemic globally and is an incompletely defined emerging disease.<sup>3</sup> It causes a murine typhus-like illness in south Texas and is recognized increasingly worldwide. This new rickettsia, *R. felis*, is genetically a spotted fever group rickettsia and is capable of highly efficient transovarial transmission in cat fleas. This organism is found in cat fleas obtained from areas endemic for murine typhus in the United States. The antigenically different strains of *R. conorii* cause Israeli spotted fever and Astrakhan fever. *R. conorii* has been identified in India, Pakistan, Israel, Russia, Georgia, Ukraine, Ethiopia, Kenya, South Africa, Morocco and southern Europe.

The fever caused by *R. africae* is frequently "spotless" but when rash is observed, it is often vesicular. It is only tick-transmitted rickettsioses of southern Africa which occurs in patients who have traveled or hunted in the bush and has multiple tache noire inoculation eschars. Boutonneuse fever occurs in Mediterranean locations mainly in warm months with peak incidence from July to September. The frequent absence of a history of tick bite is likely due to transmission of disease by immature larvae and nymphs, which often goes unnoticed. The pathogenic basis for tissue injury in spotted fever is well elucidated in eschar with dermal and epidermal necrosis and perivascular edema due to endothelial injury leading to disseminated vascular infection causing meningoencephalitis and vascular lesions of kidney, lungs, gastrointestinal tract, liver, pancreas, heart, spleen and skin. Boutonneuse fever is by no means is a uniformly a benign illness and causes death up to 5% in hospitalized patients. After a mean incubation period of 7 days, fever, myalgia and headache characterize the onset. A careful clinical examination may reveal an eschar also. Severe disease resembling RMSF occur in patients with underlying diabetes mellitus, cardiac insufficiency, alcoholism, old age and glucose-6-phosphatase deficiency.<sup>2,3,5,7</sup>

*Rickettsia akari* causes a non fatal febrile illness called rickettsial pox and has been recognized in urban area of USA, Korea and parts of Russia. After an incubation period of 9 to 14 days a painless papule ulcerates to form the eschar with painless regional lymphadenopathy. There is usually sudden onset of

fever with chills, headache, myalgia, especially backache and photophobia. A generalized maculo-papular rash appears after 2 to 3 days which begins as firm erythematous papule, form vesicles and heal with crust formation. The disease is mild, complications and death are rare. Untreated illness resolves in 2 to 3 weeks with residual headache and lassitude may persist for 1 to 2 weeks.<sup>2,5,11</sup>

Although Indian Tick Typhus (ITT) was clinically described at the beginning of the century, the etiologic agent has never been isolated from patients in India, nor has a case been diagnosed by strain-specific serologic testing. A spotted fever group rickettsia was isolated in 1950 from a brown dog tick, *Rhipicephalus sanguineus*, collected in India and assumed to be the agent causing ITT. It was designated as *Rickettsia conorii*, the agent of Mediterranean spotted fever, which occurs all around the Mediterranean and is transmitted by the same tick species. However, the disease as it appears in India differs from the common description of Mediterranean spotted fever. The rash is frequently purpuric, and an inoculation eschar at the bite site is rarely found. The disease as known in India is mild to moderately severe.<sup>12-13</sup>

## Typhus Group Rickettsiae

### Epidemic or Louse-Borne Typhus

'Typhus' is derived from *typhos*, the ancient Greek word for 'fever with stupor' or cognate with the Sanskrit word for 'smoke', dhupa. Louse-borne typhus is the prototype of the typhus group rickettsial diseases. The primary disease and its recrudescence form (Brill-Zinsser disease) are caused by *Rickettsia prowazekii*. It is known as epidemic typhus, classic typhus, typhus exanthematicus, tarbadillo, fleckfieber and jail fever. The occurrence of typhus parallels the history of war and famine. An astonishing 30 million cases occurred in Soviet Union and Eastern Europe during 1918-1922 with an estimated 3 million deaths. During World War II, typhus struck heavily in concentration camps in Eastern Europe and North Africa.<sup>2-6,14</sup> The etiological agent *Rickettsia prowazekii* is an intracellular coccobacillary bacteria with inconsistent morphology and reproduces by binary fission.<sup>2-6,14</sup> Louse borne typhus is transmitted from person to person by body louse. There is no evidence of head lice acting as vector in this infection.<sup>2</sup>

The cycle is thought to be initiated by a human case of recrudescence typhus or by a recently introduced case of primary louse-borne typhus. The louse is infected by feeding on a rickettsemic person. The organism in the louse infects its alimentary tract, resulting in large numbers of organisms in its feces within about 1 week. Close personal contact is required to transmit lice to others. When the louse takes a blood meal, it defecates. The irritation causes the host to scratch the site, thereby contaminating the bite wound with louse feces. Human infection might also occur by mucous membrane inoculation with contaminated feces. The infested louse dies of its infection due to obstruction of alimentary tract in 1 to 3 weeks and does not transmit the organism to offspring however can transmit rickettsiae to other lice through ingestion of feces. The air-borne infection may occur in crowded conditions by inhalation of dried louse feces. A reservoir of *R. prowazekii* other than human apparently exists in USA in the southern flying squirrel *Glaucomys volans*. The transmission among these rodents is suspected to be by squirrel lice or fleas, or both.<sup>2-6,14</sup> Chronic human carriage of *R. prowazekii* may result in later relapse of typhus fever called Brill-Zinsser disease. Such patients are thought to form a source

of potential infection when louse infestation becomes common in prisons and refugee camps or unsanitary conditions.<sup>2</sup>

## Pathophysiology

After proliferation at the site of the louse bite, the organism spreads hematogenously. *Rickettsia prowazekii*, like other most rickettsiae produces vasculitis by infecting the endothelial cells of capillaries, smaller arteries and veins resulting in fibrin and platelet deposition causing occlusion of blood vessel. The pathology is similar to that described for the spotted fever group of rickettsial diseases. However, typhus group rickettsiae extensively multiply and accumulate intracellularly until they burst the endothelial cell and disseminate into the bloodstream. The angiitis is most marked in the skin, heart, nervous system, skeletal muscle and kidneys. If local thrombosis is extensive, it can cause gangrene of skin and distal part of extremities.<sup>2-6,14</sup>

## Clinical Manifestations

After an incubation period of 7 to 12 days, an abrupt onset with intense headache, chills, fever and myalgia are characteristic. The fever worsens quickly and become unremitting and remains high until death or if untreated, resolution by crisis toward the end of the second week. The conjunctivae are suffused and face congested. There may be epistaxis, dry cough, delirium and splenomegaly is common. The typhus rash appears on the second to fourth day of fever, begins in axillary folds and upper part of trunk and spreads centrifugally to limbs. It consists of small irregular pink macules which rapidly darken to a mulberry or purple color and rarely become frank petechial, coalescence to a generalized patchy purple mottling under the skin may occur. There is no eschar. Meningoencephalitis may occur in 50% with meningism, tinnitus, hyperacusis followed by deafness, dysphagia, dysphoria, agitated delirium and coma. Survivors may suffer transverse myelitis, hemiparesis, peripheral neuropathy with hyperesthesia and prolonged psychiatric disturbances. Secondary infection leading to bronchopneumonia, suppurative parotitis, otitis media and peripheral blood vessels occlusion may occur. During recovery myocarditis may occur with or without specific treatment.<sup>2-6,14</sup> In untreated uncomplicated louse-borne typhus, fever lyses after 2 weeks of illness; recovery of normal mentation is rapid, but recovery of strength requires a prolonged convalescence of 2 to 3 months. In population at risk of epidemic typhus fever, nutrition and general immunity to infection are inadequate and illness is often severe with overall mortality rate up to 20% and >50% in the weak and aged. Louse-borne typhus is a mild disease in children.

## Brill-Zinsser Disease (i.e. relapsing louse-borne typhus)

Brill-Zinsser disease occurs as recrudescence of previous infection with *Rickettsia prowazekii*. Its pathogen is unknown but recrudescence is presumed to be precipitated by stress or a waning immune system. The pathology is similar to that described for the other rickettsial diseases. However, the organisms appear to lie dormant, most likely in the cells of the reticuloendothelial system, until they are reactivated by an unknown stressor, multiply and cause another acute but milder infection. The illness is similar to louse-borne typhus but it is usually milder and resembles more closely murine typhus.

## *Rickettsia typhi* (Murine Typhus)

Murine typhus has been recognized as a worldwide zoonosis and often unrecognized. The etiological agent of murine typhus is *Rickettsia typhi* (*Rickettsia mooseri*). It is also known as endemic and shop typhus. *Rickettsia typhi* is an obligate intracellular bacterium that infects endothelial cells in mammalian host and midgut epithelial cells of flea host. It is believed to be mild but illness may be severe and can cause death. It may occur in epidemics or with high prevalence in certain regions. Murine typhus is found worldwide and is especially prevalent in temperate and subtropical seaboard areas, where the most important rat reservoir (*Rattus* spp) and flea vector (*Xepopsylla cheopis*) are found. The residents or visitors of areas are at risk, where flea bearing animals bring infested fleas in to close proximity to human. A new rickettsial agent *Rickettsia felis* has been recognized to share some antigenic and genetic components of *R. typhi* and is associated with cat fleas. *Rickettsia felis* is now recognized to be more closely related with spotted fever group rickettsiae. The outbreaks of murine typhus are well documented around the World especially in areas with inadequate vector and reservoir control. The Khmers displaced to temporary shelters at Thai-Cambodian border, 70% of patients with unexplained fever had murine typhus. Human are infected by close contact with rodents and fleas in granaries, breweries, shops and food stores, and domestically in developing countries. Flea feces infected with rickettsiae contaminate the flea bite, which is then scratched, so inoculating the infection or may be inhaled when dried or rubbed into the conjunctiva. In flea vector predominantly gut epithelium are infected, a reservoir of infected flea is maintained mostly by horizontal transmission from flea to vertebral host to uninfected flea. Once infected, the flea maintains the infection for duration of life. *R. typhi* may also infect the flea reproductive organs and foregut tissues, which explains the low levels of transovarial (vertical) transmission and direct inoculation via a flea bite. The fleas remain uninfected from *R. typhi* infection.<sup>2-7,15</sup>

## Clinical Manifestations

A small proportion of patients will remember the history of flea exposure. After an incubation period of 1 to 2 weeks there is an abrupt onset of illness and the initial presentation is often nonspecific. Fever (92%), severe headache (45%), chills (44%), myalgia (33%), and nausea and vomiting (33%) are most common. The presence of hepatomegaly (24%) and splenomegaly (10%) has also been reported. Neurological signs and symptoms have been reported in 1-45% of patients including confusion, stupor, seizures and localizing sign such as ataxia. Rash is noted in 18% at presentation and will present in 50% (2-71%) over the course of illness. The rash is macular or maculo-papular in 78% and petechiae are noted in about 10%. These lesions are most often distributed on trunk (88%) but involvement of extremities (45%) is not infrequent. Occasionally the rash may also be present on the palm and soles. The clinical course of murine typhus is usually uncomplicated, and childhood murine typhus is often mild and some times only nighttime fever with normal day time activity. However about 10% patients may develop central nervous system abnormalities, renal insufficiency, hepatic insufficiency, reparatory failure and hematemesis requiring intensive care. About 4% of hospitalized patients will die of infection.<sup>2-7,15</sup>

## Scrub Typhus

Scrub typhus, a dreaded disease in pre-antibiotic era, is an

important military disease which caused thousands of cases in the Far East during Second World War. Scrub typhus, a zoonosis, was known in Japanese folklore to be associated with the jungle mite or chigger which was named "dangerous bug" (tsutsugamushi). The illness was described by Hashimoto in 1810. In 1916, Weil and Felix, described heterophile antibody agglutination of *Proteus mirabilis* OX-K variant by sera of patients suffering from scrub typhus. Ogata in 1931 isolated the organism and named it *Rickettsia tsutsugamushi*. Now it has been reclassified as *Orientia tsutsugamushi*. An estimated one billion people are at risk for scrub typhus and one million cases occur annually. Man's behavior and climatic changes greatly influence the occurrence of the disease. Interest in this infection is re-emerging because of descriptions of strains of *O. tsutsugamushi* with reduced susceptibility to antibiotics and because of the surprising interactions between scrub typhus and the human immunodeficiency virus. Increasing prevalence of the scrub typhus has been reported from some Asian countries and may coincide with the widespread use of betalactam antibiotics or to urbanization into rural areas. Scrub typhus is a zoonosis and is a widespread disease in Asia and Pacific Islands. It also occurs in Japan, South Korea, Nepal, Northern Pakistan, South China, Papua New Guinea, Queensland and Northern New South Wales. Scrub typhus is known to occur all over India including the hills of North India. It is particularly important to consider scrub typhus when working in developing countries and travelers returning from areas endemic for this disease.<sup>2-5,16-20</sup>

## Clinical Manifestations

The clinical manifestations of this disease range from sub-clinical disease to organ failure to fatal disease. Deaths are attributable to late presentation, delayed diagnosis, and drug resistance. Clinical picture of scrub typhus is typically associated with fever, rash, myalgia and diffuses lymphadenopathy. A necrotic eschar at the inoculating site of the mite is pathognomic of scrub typhus. The eschar resembles the skin burn of a cigarette butt.<sup>4</sup> Fever, chills, cough, headache, diarrhea, eschar, adenopathy and rash are common presenting features in scrub typhus. However occurrence of eschar is rare in South-East Asian patients moreover indigenous peoples of endemic areas commonly have a less severe illness, often without any rash or eschar.<sup>21-22</sup> Cough sometimes accompanied by infiltrates on the chest radiograph is one of the commonest presentations of scrub typhus infection. In severe cases, tachypnea progresses to dyspnea, the patient becomes cyanotic, and full-blown adult respiratory distress syndrome may develop.<sup>3</sup> The unusual presentation with acute abdomen is also known to occur, especially in patients coming from hyper endemic areas.<sup>23</sup> The vertical transmission from transplacental infection in acute febrile illness during pregnancy and perinatal blood borne infection during labour can cause scrub typhus in neonates also.<sup>24</sup>

## Rickettsioses in India

The rickettsial diseases once thought to have been eradicated from India are reemerging in many parts of our country. The presence of rickettsial diseases in India has been documented in Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Pondichery, Kerala and Tamilnadu. There are many reports of occurrence of rickettsial diseases from hills of north and eastern parts of India as well from southern plateau in last few years. Recently both scrub typhus and SFG rickettsioses have been reported from Haryana, which is situated in plains of north India.<sup>13,25-31</sup>

## *Coxiella Burnetii* (Q fever)

Q fever was so named by Derrick in 1937 as 'query fever' caused by *Coxiella burnetii* and occurs worldwide. It is a very small rickettsia-like organism which is a zoonosis of rodents, rabbits and birds that is particularly resistant to heating and drying. It is transmitted to domestic goats and cattle by ticks and to human by direct infection through milk, placental products and dried feces in dust. Workers who handle livestock (e.g., cattle, sheep, goats), especially at the time of slaughter or parturition, are at an increased risk of infection. It causes an intracytoplasmic infection in which organism multiplies, especially in splenic histiocytes and Kupffer cells of the liver.<sup>2,4,5,32</sup>

### Clinical Manifestations

After incubation period ranges from 2-6 weeks. Acute Q fever infection usually has an abrupt onset, with fever, intractable headache, chills, myalgia, cough, and chest pain. Characteristically, rash is absent. Chronic Q fever infection is less common. It may be manifested as endocarditis, chronic or relapsing multifocal osteomyelitis, chronic hepatitis, chronic vascular infection, pericarditis, or myocarditis. Humans contract the disease by inhaling contaminated aerosols when they come in contact with infected animals or materials contaminated by them. The acute illness may subside spontaneously and complicating endocarditis may occur after a few months in 10% patients. Pneumonitis occurs in more than half of patients. Physical findings may not be pronounced; however, radiographs may demonstrate a wide variety of pathologic findings ranging from multiple segmental opacities to pleural effusion, lobar consolidation, or linear atelectasis. Hepatosplenomegaly is a common finding; it usually is accompanied with elevation of liver enzymes. Chronic Q fever infection must be excluded in patients with multifocal osteomyelitis, especially if a history of exposure to farm animals is noted.<sup>2,4,5,32</sup>

### TIBOLA and DEBONEL

New or reemerging rickettsioses have been described in the last few decades, including tickborne lymphadenopathy (TIBOLA) and *Dermacentor*-borne-necrosis-eschar-lymphadenopathy (DEBONEL) related to *Rickettsia slovaca* infection, as well as lymphangitis-associated rickettsiosis attributed to *Rickettsia sibirica* infection. Patients may develop persistent asthenia and alopecia at the site of the eschar.<sup>5</sup> The first proven case of *R. slovaca* infection was reported only in 1997 in France and is called tickborne lymphadenopathy (TIBOLA). In Spain the same condition is called *Dermacentor*-borne-necrosis-erythema lymphadenopathy (DEBONEL).<sup>33</sup> The tick (*Dermacentor* spp.) bite is commonly located on the scalp region with a characteristic local reaction (eschar) which can be surrounded by a circular erythema. The other main symptoms are the enlarged and sometimes painful lymph nodes in the region of the tick bite, characteristically in the occipital region and/or behind the sternocleidomastoideal muscle. The most frequent general symptoms were low-grade fever, fatigue, dizziness, headache, sweat, myalgia, arthralgia, and loss of appetite. Without treatment, the symptoms were seen to persist for as long as 18 months. Doxycycline treatment can shorten the usually benign illness.<sup>34</sup>

### Diagnosis of Rickettsial Diseases

The diagnosis of rickettsial diseases is clinical and epidemiological. The differential diagnosis include typhoid

fever, measles, rubella, respiratory tract infection, gastroenteritis, acute surgical abdomen, enteroviral infection, meningococemia, disseminated gonococcal infection, secondary syphilis, leptospirosis, immune complex vasculitis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, infectious mononucleosis and drug reaction. Rickettsiae are not evident on blood smear findings and do not stain with most conventional stains. Serologic assays that demonstrate antibodies to rickettsial antigens (eg, indirect immunofluorescence, complement fixation, indirect hemagglutination, latex fixation, enzyme immunoassay, microagglutination) are preferable to the nonspecific and insensitive Weil-Felix test based on the cross-reactive antigens of *Proteus vulgaris* strains. Serologic findings usually take 10-12 days to become positive. In Weil Felix test, cells of *Proteus vulgaris* OX-2 react strongly with sera from persons infected with *SFG rickettsiae* with the exception of those with *Rocky Mountain Spotted Fever (RMSF)*, and whole cells of *P. vulgaris* OX-19 react with sera from persons infected with typhus group rickettsiae as well as with *RMSF*. However *Proteus vulgaris* OXK will react in patients suffering from scrub typhus. The value of testing 2 sequential serum or plasma samples together to show a rising antibody level is considerably more important in confirming acute infection with rickettsial agents because antibody titers may persist in some patients for years after the original exposure. Immunofluorescence assay (IFA) is currently considered to be the reference serological method. However, it cannot determine the causative agent to the species level. Polymerase chain reaction (PCR) to detect rickettsiae in blood or tissue provides promise for early diagnosis. PCR testing and immunohistochemical staining of skin specimen obtained by performing a biopsy may help confirm the clinical diagnosis in patients with rash (high expertise is usually needed to interpret the biopsy result). However, serology remains the mainstay of diagnosis because these other tests are expensive and less available to clinicians. Rickettsial isolation in culture is unnecessary, laborious, and hazardous to laboratory personnel.<sup>6,7</sup> In developing countries like India where definitive diagnostic investigations are not available, Weil-Felix test is still not entirely obsolete but has to be interpreted in the correct clinical context.<sup>25</sup>

**Q fever:** It is best diagnosed serologically by a four fold rise in antibody titer in two complement fixation test separated by 10 to 14 days. ELISA and IFAT are also available. PCR may be used.<sup>5,32</sup>

### Complications

**Rocky Mountain spotted fever (RMSF):** Complications are uncommon, especially if patients receive proper treatment. Acute complications may include a superimposed bronchopneumonia and congestive heart failure (caused by fluid overload). Long-term health problems following acute RMSF infection include partial paralysis of the lower extremities; gangrene requiring amputation of fingers, toes, arms, or legs; hearing loss; loss of bowel or bladder control; movement disorders; and language disorders. These rare complications are usually seen in severely affected individuals. Rickettsialpox is usually a self-limited disease with no complications. Boutonneuse fever occasionally may follow a malignant and rapidly fatal course with multiorgan failure, encephalopathy, and coagulopathy.<sup>2,7</sup>

**Louse-borne (epidemic) typhus and Murine Typhus:** Complications are uncommon but include gangrene, parotitis, otitis, myopericarditis, pneumonia, and pleurisy. In Brill-Zinsser disease, the complications are similar to the primary illness; however, relapses usually are less severe.<sup>2,6,14</sup>

**Scrub Typhus:** The complications of scrub typhus usually develop after the first week of illness. Jaundice, renal failure, pneumonitis, ARDS, septic shock, myocarditis and meningo-encephalitis are various complications known with this disease.<sup>2-6,25-28</sup>

**Q fever:** Complications include chronic Q fever, endocarditis, myocarditis, meningoencephalitis, glomerulonephritis, and syndrome of inappropriate antidiuretic hormone (SIADH).<sup>32</sup>

## Treatment

Adequate antibiotic therapy initiated early in the first week of illness is highly effective. Fever usually subsides within 24-72 hours after starting antibiotic therapy. If fever fails to subside with the use of a suitable antibiotic, the diagnosis of rickettsial disease should be reconsidered. Treatment may be terminated 2-3 days after the patient is afebrile. Doxycycline, 200 mg/d PO/IV divided bid, is the drug of choice. In Louse-borne (epidemic) typhus, Single oral dose of 200 mg. and repeat once later if necessary or in a short course of 100-200 mg daily for 3 days. Chloramphenicol, 500 mg 6 hourly orally or intravenously for 7 days, may be used as an alternative. However, it is not widely used in the because of its potential bone marrow toxicity. It may not be as effective against rickettsiae as doxycycline. Tetracycline can also be used in dosage of 500 mg 6 hourly orally or intravenously for 7 day. Infected pregnant patients must be evaluated individually, and either chloramphenicol (early trimester) or doxycycline (late trimester) may be used. Recently treatment with macrolide compounds clarithromycin and azithromycin, because of the lack of adverse effects and a good compliance, can be considered a valid alternative therapy to tetracyclines or chloramphenicol in the treatment for children aged < 8 years and pregnant females. Single dose of azithromycin 500 mg was successfully used in pregnant women suffering from scrub typhus without relapse and with favorable pregnancy outcomes.<sup>35</sup> Azithromycin seems to be an effective agent against scrub typhus because it efficiently penetrates polymorphonuclear leukocytes and macrophages, which are target cells for *O. tsutsugamushi*.<sup>36</sup> In addition, a long tissue half life and the long lasting post-antibiotic effects of azithromycin may explain no relapse despite the use of a single dose.<sup>37</sup> However there are reports of treatment failure and relapse after azithromycin therapy.<sup>38,39</sup> Recently telithromycin 800 mg was administered twice on first day then once daily from next day and was continued till two to three days after fever disappeared. It could be considered as promising new antibacterial agent in treatment of scrub typhus.<sup>40</sup> Rickettsiae are also sensitive to rifampicin and quinolones.<sup>2</sup> Recent data from Europe suggest that fluoroquinolones, such as ciprofloxacin, ofloxacin, and pefloxacin, may be effective in the treatment of certain rickettsioses. However, quinolones have been associated with clinical failures despite good in vitro activity. Sulfonamides were found to have a harmful effect either by delaying the institution of proper antimicrobial therapy or by directly stimulating growth of the organisms and are contraindicated in rickettsial infections.<sup>5</sup>

## Q-fever

Acute disease responds to tetracyclines or chloramphenicol; relapses are rare. In general, chronic Q fever infections require prolonged courses of antimicrobial therapy. In cases of endocarditis caused by chronic Q fever, the appropriate drug and duration of therapy is unknown. Additionally, combination therapy (eg, quinolones, tetracyclines, doxycycline,

chloramphenicol, lincomycin, rifampin) has produced variable results.<sup>2,4,5,32</sup>

## Prognosis

**Rocky Mountain spotted fever (RMSF):** The overall mortality rate without specific therapy is approximately 25%; however, the mortality rates are higher for men, elderly persons, and black men with G-6-PD deficiency. In the United States, the overall mortality rate currently is 5-7%. Fatalities are mainly caused by delay in diagnosis and treatment. Solid immunity usually follows recovery from RMSF. Rickettsialpox is usually self-limited. Deaths have not been reported. Boutonneuse fever generally runs a benign course. Very rarely, it may follow a rapidly fatal course in otherwise healthy children.

**Louse-borne (epidemic) typhus:** The mortality rate in untreated cases correlates with the patient's age. Mortality may be uncommon in children younger than 12 years, but rates rise to as high as 60-70% in individuals older than 50 years. Most patients who recover develop immunity. Brill-Zinsser disease (i.e., relapsing louse-borne typhus): This is analogous to primary louse-borne epidemic typhus, except that patients who recover do not develop immunity. Murine typhus although considered a mild illness, may prove fatal or severe illness if misdiagnosed or inadequately treated.

**Scrub Typhus:** Fatalities are rare with use of antibiotics. The heterogeneity of scrub typhus strains accounts for the frequent reinfections. Mortality from this disease is 7-30%

**Q fever:** Patients with uncomplicated Q fever recover within 1-2 months without sequelae. The mortality rate is less than 1%. On the other hand, complicated cases have a higher rate of permanent disabilities and fatalities.

## Prevention

Personal avoidance of ticks (wearing proper clothing and use of repellants) remains an integral part of protection against rickettsial infections. In case of bites, prompt removal of ticks might prove extremely beneficial in prevention of infection. Attempting to control the tick reservoir is not usually feasible. Use of antibiotics following tick exposure is not currently indicated to prevent rickettsial infection.

**Rocky Mountain spotted fever:** A recently improved killed chicken embryo vaccine has shown that it may provide partial protection against RMSF and ameliorate the illness when it occurs. Rickettsialpox: Avoidance of contact with and control of house mouse infestations is important to prevent acquisition of infection. Boutonneuse fever: Natural immunity occurs following infection. Effective vaccines are not yet available.

**Louse-borne (epidemic) typhus:** Delousing of individuals and use of insecticides to treat clothing are effective preventive measures against the spread of louse-borne typhus. Killed vaccines were shown to reduce mortality rates but were not effective in prevention of disease. Brill-Zinsser disease is analogous to primary louse-borne epidemic typhus. Murine Typhus: Prevention is primarily by controlling the flea and rat populations. Insecticides should be used before rodenticides to prevent rat fleas from seeking alternate hosts if rats are no longer available.

**Scrub Typhus:** The disease is best prevented by the use of personal protective measures including repellents. People entering an exposed area wear closed in footwear such as boots with socks, and long trousers. Exposed areas of skin and

**Table 1: Symptoms, signs and laboratory data in Rocky Mountain Spotted Fever (RMSF), Boutonneuse Fever (BF) and African Tick Bite Fever (ATBF)**

Fever	RMSF (%)	BF (%)	ATBF (%)
Fever	99-100	100	100
Headache	79-91	56	
Rash	88-90	97	30
Tache noire (Eschar)	<1	72	100
Multiple eschars	0	0	60
Myalgia	72-83	36	60
Nausea and/or vomiting	56-60		
Abdominal Pain	34-52		
Petechial Rash	45-49	10	
Conjunctivitis	30	9	
Lymphadenopathy	27	90	
Stupor	21-26	10	
Diarrhea	19-20		
Edema	18-20		
Ataxia	5-18		
Meningismus	18	11	
Splenomegaly	14-16	6	
Hepatomegaly	12-15	13	
Jaundice	8-9	2	
Pneumonitis	12-17		
Cough	33	10	
Dyspnea		21	
Coma	9-10		
Seizure	8		
Shock and/ or Hypotension	7-17		
Decreased Hearing	7		
Arrhythmia	7-16		
Myocarditis	5-26	11	
Death	4-8	2.5	
Increased Aspartate Aminotranferase	36-62	39	
Thrombocytopenia	32-52	35	
Anemia	5-24		
Hyponatremia	19-56	25	
Azotemia	12-14	6	

Data from references<sup>8,9,10</sup>

clothing itself should be treated with mite repellents. Those people working in infested areas should consider impregnating clothing with permethrin. Prophylactic treatment usually consist oral chloramphenicol or tetracycline given once every 5 days for thirty-five days or weekly doses of doxycycline during and for 6 weeks after exposure have both been shown to be effective regimes. No effective vaccine has been developed for scrub typhus.

**Q fever:** Q fever vaccines are under development and not yet available for clinical use. Control of disease in domestic animal population has been difficult because animals that have no detectable antibodies to *C burnetii* still shed the organism at parturition. Q fever outbreaks in research laboratories using animals (especially sheep) can be prevented by instituting proper control measures designed to protect the environment from fomite and aerosol transmission.<sup>2,4,5,32</sup>

## Guidelines for Management of Suspected Rickettsial Infections

As per recommendations of **Tick-borne Rickettsial Diseases Working Group**<sup>41</sup> of Centre for Disease Control (CDC), Atlanta for management of Rickettsial infections

- An assessment of clinical signs and symptoms, along with laboratory diagnostic tests and a thorough clinical history, will help guide clinicians in developing a differential diagnosis and treatment plan. Patients with evidence of organ dysfunction and severe thrombocytopenia, mental status changes, and the need for supportive therapy should be hospitalized.
- A patient, who appears well, has acute febrile illness and an unrevealing history and physical examination, and whose laboratory indices are within normal limits might warrant a “wait and watch” approach for 24 hours with reassessment if the patient fails to improve.
- If laboratory testing of a patient with a history compatible with rickettsial diseases reveals leukopenia or thrombocytopenia, or metabolic abnormalities, the clinician should consider obtaining blood cultures for other likely pathogens and specific laboratory tests and initiating empiric oral antimicrobial therapy that will effectively treat rickettsial diseases. Delay in treatment can lead to severe disease and fatal outcome for rickettsial infection. Because each of the agents causing rickettsial diseases is susceptible to tetracycline-class antibiotics, these drugs, particularly doxycycline, are considered the therapy of choice in nearly all clinical situations. Fever typically subsides within 24–48 hours after treatment when the patient receives doxycycline or another tetracycline during the first 4–5 days of illness.
- If a patient fails to respond to early treatment with a tetracycline antibiotic (i.e., within 48 hours), this response might be an indication that their condition is not a rickettsial diseases. Severely ill patients might require longer periods before clinical improvement is noted, especially if they have multiple organ dysfunction.
- Because certain patients with rickettsial diseases might initially receive an alternative diagnosis, they might be empirically treated with antibiotics inactive against rickettsiae, including penicillins, cephalosporins, aminoglycosides, erythromycin, or sulfonamides. This situation presents both diagnostic and therapeutic challenges. In certain cases, patients treated with beta-lactam antibiotics or sulfa-containing drugs are mistakenly thought to have drug eruptions when they later manifest a rash, further postponing a correct diagnosis and appropriate treatment. Because the physician might conclude that the prescribed treatment will take time to work, a delay in obtaining critical additional laboratory or clinical information also might be a result. In addition, sulfa-containing antimicrobials have been associated with increased severity of rickettsial diseases, although whether disease severity is directly related to the use of sulfa-containing drugs or the delayed administration of more effective antimicrobials is not clear.
- In addition, clinicians should note the overlap between early symptoms of invasive meningococcal infection and rickettsial diseases. These conditions are difficult to distinguish early in the course of illness. In patients for whom both conditions are included in the initial

differential diagnoses, after performing blood cultures and a lumbar puncture, empirically treating for both diseases is appropriate. This treatment can be accomplished by adding an appropriate parenteral penicillin or cephalosporin that has activity against *N. meningitidis* to doxycycline therapy.

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