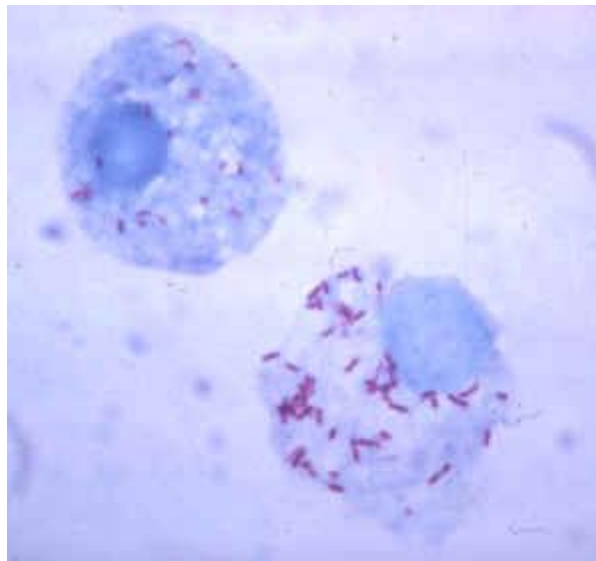


Rickettsia

Rickettsia is a genus of non-motile, Gram-negative, non-sporeforming, highly pleomorphic bacteria that can present as cocci (0.1 μm in diameter), rods (1–4 μm long) or thread-like (10 μm long). Being obligate intracellular parasites, the *Rickettsia* survival depends on entry, growth, and replication within the cytoplasm of eukaryotic host cells (typically endothelial cells) ^[1]. Because of this, *Rickettsia* cannot live in artificial nutrient environments and are grown either in tissue or embryo cultures (typically, chicken embryos are used). In the past they were positioned somewhere between viruses and true bacteria. The majority of *Rickettsia* bacteria are susceptible to antibiotics of the tetracycline group.



Rickettsia rickettsii

Despite the similar name, *Rickettsia* bacteria do not cause rickets, which is a result of vitamin D deficiency.

Rickettsia species are carried by many ticks, fleas, and lice, and cause diseases in humans such as typhus, rickettsialpox, Boutonneuse fever, African tick bite fever, Rocky Mountain spotted fever, Flinders Island spotted fever and Queensland tick typhus (Australian Tick Typhus) ^[2]. They have also been associated with a range of plant diseases. The name rickettsia is often used for any member of the Rickettsiales. They are one of closest living relatives to bacteria that were the origin of the mitochondria organelle that exists inside most eukaryotic cells.

Scientific classification

Domain: Bacteria

Phylum: Proteobacteria

Class: Alphaproteobacteria

Order: Rickettsiales

Family: Rickettsiaceae

Genus: *Rickettsia*

Virulence factors

R. rickettsii invades the endothelial cells that line the blood vessels. Endothelial cells are not phagocytic in nature; however, after attachment to the host cell surface, the pathogen causes changes in the host cell cytoskeleton that induces phagocytosis. They are able to avoid lysosomal fusion and oxidative burst by escaping from the phagosome into the cytoplasm where they multiply and spread.

Over the years, different virulence factors have been identified in *R. rickettsii*.

OmpA and OmpB

OmpA (rOmp) and Omp B (rOmp) have been identified as rickettsial outer surface proteins and are implicated in adherence of the bacterium to the host cell. The genes that encode these two surface proteins are designated as ompA and ompB, respectively.

rOmp B is the predominant surface membrane protein in *R. rickettsii*; Policastro et al, identified the rOmpA to rOmpB ratio to be 1:9 (1994). While the surface proteins of the bacterium have been identified, the host cell protein receptor(s) have not.

T4SS

Entry into the host cell is mediated by a 'Type 4 secretion system' (T4SS) which is found in all rickettsiae. The organization of the T4SS apparatus is a rather elaborate one; it is a tunnel-shaped structure that is embedded in the bacterial inner membrane and extends to the outer membrane. At least 12 or more proteins help form the tunnel-like apparatus. Once adherence to the host cell is established, the T4SS of rickettsiae recruits substrates to the bottom of the apparatus, activating the complex via an ATP-dependent process that results in the direct transfer of the bacterium's DNA and other proteins into the host cell.

Phospholipase A2

Invasion of the host endothelial cell immediately triggers phagocytosis, where the rickettsiae escape from the phagosome and into the cytosol where replication takes place. Although the escape from the phagosome is not well understood, it is thought to be mediated by phospholipase A2 activity.

Actin polymerization

In the cytosol, another virulence factor, ActA, allows survival of the bacterium. ActA is a bacterial surface protein that is associated with actin nucleation and tail formation in *R. rickettsii*. After interacting with the host cytoskeletal proteins, the bacterium develops an actin tail. The actin-based motility of *R. rickettsii* allows swift, unidirectional movement across the cytoplasm into adjacent cells, promoting cell to cell spread.

Endothelial cell damage caused by *R. rickettsii* can lead to end organ failure, DIC, and even death.

Pathogenesis

R. prowazekii is most known for being the agent of epidemic, louse-borne typhus in humans. It has infected approximately 20-30 million humans during World War I and killed another few million after World War II ^[2]. Typhus ranks as one of the main epidemic diseases of human history, a truly apocalyptic pestilence that follows in the wake of wars, famine, and other human misfortune ^[3]. Rocky Mountain spotted fever, which is caused by infection with *R. rickettsii*, is the most severe rickettsial illness that is tickborne in the US. The primary ticks that carry it are the American dog tick (*Dermacentor variabilis*) and the Rocky Mountain wood tick (*Dermacentor andersoni*). Patients infected with *R. rickettsii* generally have nonspecific symptoms including

fever, nausea, vomiting, muscle pain, lack of appetite, and severe headache after an incubation period about 5-10 days following an infected tick bite. Later symptoms include rash, abdominal pain, joint pain, and diarrhea. Fever, rash, and a previous tick bite are usually the most common components of clinical diagnosis. Rocky Mountain spotted fever is treated by a tetracycline antibiotic like doxycycline; once a person has had the disease, they are thought to have long lasting immunity against re-infection (CDC).

Rickettsial illnesses, caused by organisms within the genus of *Rickettsiae*, are recognized and can be divided into the following 3 biogroups ^[4]:

Spotted Fever Group

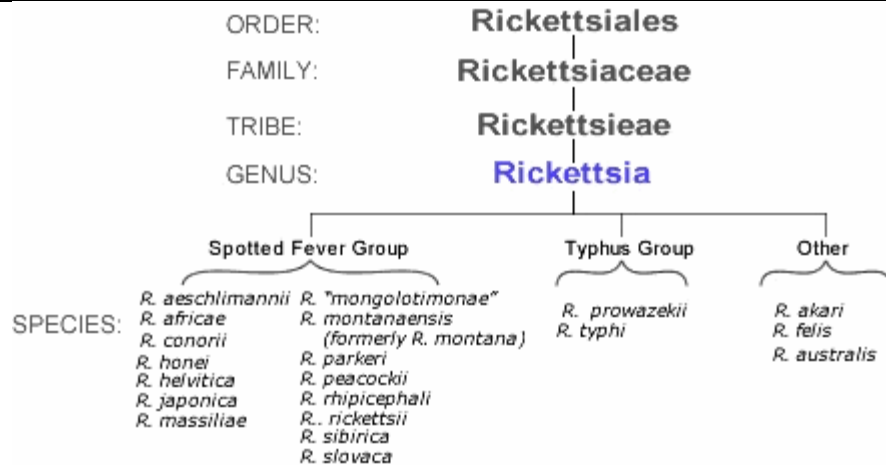
Organism	Disease	Distribution
<i>R. rickettsii</i>	Rocky Mountain spotted fever	Western hemisphere
<i>R. akari</i>	Rickettsialpox	USA, former Soviet Union
<i>R. conorii</i>	Boutonneuse fever	Mediterranean countries, Africa, India, Southwest Asia
<i>R. sibirica</i>	Siberian tick typhus	Siberia, Mongolia, northern China
<i>R. australis</i>	Australian tick typhus	Australia
<i>R. japonica</i>	Oriental spotted fever	Japan

Typhus Group

Organism	Disease	Distribution
<i>R. prowazekii</i>	Epidemic typhus Recrudescent typhus Sporadic typhus	South America and Africa Worldwide United States
<i>R. typhi</i>	Murine typhus	Worldwide

Scrub typhus group

<i>Organism</i>	<i>Disease</i>	<i>Distribution</i>
<i>R. tsutsugamushi</i>	Scrub typhus	Asia, northern Australia, Pacific Islands
PS: <i>R. tsutsugamushi</i> has been reclassified into the genus <i>Orientia</i>		



Taxonomic classification of the order Rickettsiales

Species

R. aeschlimannii
R. africae
R. akari
R. asiatica
R. australis
R. canadensis
R. conorii
R. cooleyi
R. felis
R. heilongjiangensis
R. helvetica
R. honei
R. hulinii
R. japonica

R. massiliae
R. montanensis
R. parkeri
R. peacockii
R. prowazekii
R. rhipicephali
R. rickettsii
R. sibirica
R. slovaca
R. tamurae
R. typhi ^[5]
etc.

Selected species: *R. prowazekii*; *R. rickettsia*

1. Rickettsia prowazekii

Rickettsia prowazekii is a species of gram negative, Alpha Proteobacteria, obligate intracellular parasitic, aerobic bacteria that is the etiologic agent of epidemic typhus, transmitted in the feces of lice. In North America, the main reservoir for *R. prowazekii* is the flying squirrel. *R. prowazekii* is often surrounded by a protein microcapsular layer and slime layer; the natural life cycle of the bacterium generally involves a vertebrate and an invertebrate host, usually an arthropod, typically the human body louse. A form of *R. prowazekii* that exists in the feces of arthropods remains stably infective for months. *R. prowazekii* also appears to be the closest free-living relative of mitochondria, based on genome sequencing.

Infection Process

Infectious Dose: The minimum infectious dose is less than 10 organisms.

Description: After ingestion, *R. prowazekii* invades the midgut epithelium cells of the insect, in which they replicate, and a large number of infective organisms are released back into the gut. The organisms are then excreted with louse fecal matter and are thus transmitted to humans when a skin wound is scratched or scraped.

Transmission

The disease is transmitted through the bite of a rickettsia-infected louse. The bacteria contained in the contaminated feces of the louse enter the bloodstream at the site of the bite or of the injury caused when the person scratches himself. An infected person can then infect new lice, which can then continue to transmit the disease.

Pathogenesis

R. prowazekii is the cause of epidemic typhus in humans. The disease is passed to humans through the body louse, or lice. Because of this it primarily shows up in areas of overpopulation and poor economy ^[6].

Lice do not pass *R. prowazekii* onto humans directly through their bites. The lice will bite or scratch the human host until the skin is broken but then the bacteria are transferred via feces from the louse left in the wound. The lice may infect multiple human hosts in this manner but will die within 2 weeks of infecting the first host. Because the lice die, and thus the number of organisms that can pass on the disease decrease, *R. prowazekii* is able to survive in its human hosts for long periods of time and reinfect a "clean" louse so that the cycle will continue ^[7].

Epidemic Typhus will cause death in up to 40% of untreated cases. The Center for Disease Control classifies *R. prowazekii* as a class B bioterrorism agent due to its "ability to be acquired via aerosol (like anthrax another deadly pathogen), efficient anthropod transmission, and severe clinical outcome and death in untreated cases" ^[8].

Symptoms of epidemic typhus include early onset fever, nausea, muscle pain, and headaches. Also, after a few days after the fever comes, a pink rash will develop first on the extremities and will move to the stomach and buttocks. Eventually the pink will raise up and also become darker.

Symptoms

Early clinical manifestations include fever and severe headache, although recent observations suggest that abdominal pain is also frequent. Other manifestations occur variably and include chills, rash, myalgias, and arthralgias; central nervous system involvement often included delirium, coma, and seizures. Pulmonary manifestations can be rickettsial interstitial infection that leads to vascular leakage and noncardiogenic pulmonary edema or secondary infections of the airway. A nonproductive cough is observed in 38% to 70% of patients, and the frequent detection of infiltrates on chest radiographs underscores the prevalence of primary pulmonary involvement and secondary bacterial pneumonia.

Treatment

Antibiotic Therapy: Tetracyclines and chloramphenicol are highly effective in the treatment of epidemic typhus. Because of a long half-life, doxycycline has been shown to be effective against epidemic typhus when administered as a single oral dose; however, the standard recommended treatment is doxycycline 200 mg per day for 5 days. Doxycycline is a very active compound in the treatment of classic epidemic typhus at an oral dosage of only 200 mg in a single administration. With such a dosage, side effects are very unlikely and the cost of a complete treatment is minimal. This

is a particularly important factor when a large population has to be treated. In addition, one can assure that the drug is actually taken by personally administering the two capsules to the patient^[9].

Prevention

Vaccine

Production of very large doses of vaccine, which was very complicated and dangerous for laboratory technicians, presented tremendous difficulties. The problem was finally solved by Dr. H R Cox of the United States in 1938, who found that typhus Rickettsias will grow without difficulty in embryonated chicken eggs. This method made it possible to produce very large quantities of live Rickettsias. They can then be killed by the addition of one-half percent solution of phenol, to produce a sufficient vaccine against typhus. Large quantities of vaccine could thus be prepared and used. An attenuated, live *Rickettsia prowazekii* vaccine against epidemic typhus is now also available, although infrequently used^[10].

2. *Rickettsia rickettsii*

Rickettsia rickettsii is a unicellular, gram-negative coccobacillus that is native to the New World. It belongs to the spotted fever group (SFG) of *Rickettsia* and is most commonly known as the causative agent of Rocky Mountain spotted fever (RMSF). By nature, *R. rickettsii* is an obligate intracellular parasite that survives by an endosymbiotic relationship with other cells.

Pathogenesis

Typical symptoms of RMSF can appear 2 to 14 days after exposure and include fever, headache, depression, nausea, vomiting, and gradually may develop a skin rash called purpura or petechiae. Sometimes the rash occurs 2 to 5 days after the onset of the fever. Serious cases of RMSF can include central nervous system, pulmonary, or hepatic injuries. Patients that have compromised immune systems often have an increased susceptibility to other infections. If Rocky Mountain spotted fever is left untreated, there is a high mortality rate ^[11]. *Rickettsia rickettsii* can infect endothelial cells within the human body through the vascular smooth muscle cells and tissues ^[12]. In addition, it is an intracellular pathogen that can infect and multiply

within the nucleus or cytosol of endothelial cells of the blood vessels ^[13].

Rocky Mountain spotted fever is prevalent more commonly among children in the southeast and southcentral United States. The most incidences of RMSF occur in children 5 to 9 years old. Success in treatment of RMSF increases with initial diagnosis and treatment and reported tick bites or tick attachments prior to major symptoms ^[14].

Rickettsia rickettsii strains can vary in the extent of virulence in experimental animals. In Montana scientists used guinea pigs to isolate the different virulence strains. The guinea pigs were divided into four groups: R,S,T, and U. The R type strains produced the most virulent strains, which caused severe infections, fevers, and mortality in 30% of the guinea pigs. The S and T type strains caused milder symptoms and shorter fevers. The U type strains did not produce any symptoms of Rickettsia. There were only minor differences in the structure of the *Rickettsia rickettsii* organism such as the lipopolysaccharide, proteins, and antigenic properties ^[15].

Symptoms

The Centers for Disease Control and Prevention states that the diagnosis of RMSF must be made based on the clinical signs and symptoms of the patient and later confirmed using specialized laboratory tests. However, the diagnosis of RMSF is often missed due to its non-specific onset. The clinical signs and symptoms that a patient may experience could appear and may be misdiagnosed as other diseases even by the most experienced physician.

Initial signs and symptoms

During the initial stages of the disease, the patient will experience fever, nausea, vomiting, and loss of appetite ^[16].

Rash

The classic RMSF rash occurs in about 90% of patients and develops 2 to 5 days after the onset of fever. The characteristic rash appear as small, flat pink macules that develop peripherally on the patient's body, such as the wrists, forearms, ankles, and feet. During the course of the disease, the rash will take on a more darkened red to purple spotted appearance and a more generalized distribution.

Late signs and symptoms

Diarrhea, abdominal and joint pain, and pinpoint reddish lesions (petechiae) are observed during the late stages of the disease^[16].

Long-term implications

Patients with severe infections may require hospitalization. They may become thrombocytopenic, hyponatremic, experience elevated liver enzymes, and other more pronounced symptoms. It is not uncommon for severe cases to involve the respiratory system, central nervous system, gastrointestinal system or the renal system. This disease is worst for elderly patients, males, African-Americans, alcoholics, and patients with G6PD deficiency.

Diagnosis and treatment

Physician diagnosis

A proper physician's diagnosis is crucial during the early stages of RMSF. However, due to the fact that the signs and symptoms are very non-specific at onset, RMSF can often be misdiagnosed. For this reason, it is vital for a physician to treat the patient based on suspicion alone.

Laboratory confirmation

Rocky Mountain Spotted Fever is often diagnosed using an indirect immunofluorescence assay (IFA), which is considered the reference standard by the Centers for Disease Control and Prevention (CDC). The IFA will detect an increase in IgG or IgM antibodies.

A more specific lab test used in diagnosing RMSF is polymerase chain reaction or PCR which can detect the presence of rickettiae DNA.

Immunohistochemical (IHC) staining is another diagnostic approach where a skin biopsy is taken of the spotted rash; however, sensitivity is only 70% ^[17].

Antibiotics

Doxycycline and Chloramphenicol are the most common drugs of choice for reducing the symptoms associated with RMSF. When it is suspected that a patient may have RMSF, it is crucial that antibiotic therapy be administered promptly. Failure to receive antibiotic therapy, especially during the initial stages of the disease, may lead to end-organ failure (heart, kidney, lungs, meningitis, brain damage, shock, and even death ^[17]).

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