



Rickettsiae Infections - Classification

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Introduction

The Rickettsiae are a heterogenous group of small obligatory intracellular, gram negative coccobacilli and short bacilli, most of which are transmitted by a tick, mite, flea or louse vector. Except for louse borne typhus, humans are incidental hosts (1). The family Rickettsiaceae is named after Havard Taylor Ricketts who discovered spotted fever rickettsia (1906) and died of typhus fever contracted during his studies. The family currently comprises three genera- Rickettsia, Orientia and Ehrlichia which appear to have descended from a common ancestor (2). Former members of the family, Coxiella Burnetti, which causes Q fever and Rochalimaea Quintana causing Trench fever have been excluded because the former is not primarily a arthropod borne and later is not an obligate intracellular parasite being capable of growing in cell free media besides being different in genetic properties (3). The specific association between Rickettsiae and the vector are extensively studied, moreover Rickettsiae associated diseases are part of a continuously evolving field. Nevertheless some Rickettsiosis, such as epidemic typhus, have been described since the 16th century. Emerging diseases related to these bacteria are being investigated as well as new species, the implication of which is not always clear in human pathology when they are discovered. Some of these diseases are benign, others may be potentially fatal. Clinicians must therefore be aware of them (4).

Classification of Rickettsial Fever

Given the various etiological agents with varied mechanisms of transmission, geographical distribution and associated diseases, the consideration of rickettsial diseases as a single entity poses complex challenges (1). (Table-1)

Pathogenesis

The genus Rickettsia consists of the causative agents of two groups of diseases- Typhus fever and Spotted fever. The disease caused by Rickettsia vary from mild to severe clinical presentation with case fatality ranging from none to over 30%. Despite the variability in clinical presentations, many pathogenic Rickettsia cause debilitating diseases, any one of which could be used as a potential biological weapon (5). The Rickettsial diseases develop after infection through skin or respiratory tract. Ticks and mites transmit the agents of spotted fever and scrub typhus by inoculating the Rickettsia directly into the dermis during feeding. The

louse and flea which transmit epidemic and murine typhus respectively, deposit infected faeces on the skin and the infection occurs when organisms are rubbed into the puncture wound made by the arthropod (6). The Rickettsiae of Q fever gain entry through the respiratory tract when infected dust is inhaled. Although organisms probably multiply at the original site of entry in all instances, local lesions appear with regularity only in certain diseases such as scrub typhus etc. After multiplication at the local site these enter the blood stream, Rickettsiae multiply in endothelial cells of small blood vessels and produce vasculitis. The cells become swollen and necrotic, there is thrombosis of the vessel leading to rupture and necrosis. Vascular lesions are prominent in the skin but vasculitis occurs in many organs such as muscles, heart, lung and brain. In the brain aggregations of lymphocytes, polymorphonuclear lymphocytes and macrophages are associated with the blood vessels of the grey matter, these are called typhus nodules.

Typhus Fever Group

This group of diseases consists of epidemic typhus, recrudescent typhus (Brill -Zinsser disease) and endemic typhus. Epidemic typhus (Louse borne typhus, Classical typhus fever, Jail fever, Typhus exanthematicus) has been one of the great scourges of mankind, occurring in devastating epidemics during the times of war and famines, so vividly described by Hans Zinsser in his book "Rats Lice & History" (7). The disease has been reported from all parts of the world but particularly common in Russia with about three million deaths. In India, the epidemic spot is Kashmir.

The causative agents of Epidemic typhus is *R. prowazekii* named after von Prowazek, who died of typhus fever while investigating the disease. Humans are the only natural vertebrate hosts, infection being spread by the squirrel, louse and flea. The human body louse *Pediculus humanus corporis* is the vector. The head louse may also transmit the infection but not the pubic louse. The infection is transmitted when the contaminated louse faeces is rubbed through the minute abrasions caused by scratching. Occasionally infection may also be transmitted by aerosols of dried louse faeces through inhalation or through conjunctiva. The incubation period is 5-15 days. The disease

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Table 1. Features of Selected Rickettsial Infections

Disease	Organism	Transmission	Geographic Range	Incubation Period (Days)	Duration (Days)	Rash (%)	Eschar (%)	Lymphadenopathy ^a
Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i>	Tick bite: <i>Dermacentor andersoni</i> <i>D. variabilis</i> <i>Amblyomma cajennense</i> , <i>A. aureolatum</i> <i>Rhipicephalus sanguineus</i>	United States United States Central/South America	2-14	10-20	90	<1	+
Mediterranean spotted fever ^b	<i>R. conorii</i>	Tick bite: <i>R. sanguineus</i> , <i>R. pumilio</i>	Mexico, United States Southern Europe, Africa, Middle East, Central Asia	5-7	7-14	97	50	+
African tick-bite fever	<i>R. africae</i>	Tick bite: <i>A. hebraeum</i> , <i>A. variegatum</i>	Sub-Saharan Africa, West Indies	4-10	?	50	90	++++
Rickettsial pox	<i>R. akari</i>	Mite bite: <i>Liponyssoides sanguineus</i>	United States, Ukraine, Croatia	10-17	3-11	100	90	+++
Flea-borne spotted fever	<i>R. felis</i>	Flea (mechanism undetermined): <i>Ctenocephalides felis felis</i>	North and South America, Europe Worldwide	8-16	8-16	80	15	—
Epidemic typhus	<i>R. prowazekii</i>	Louse feces: <i>Pediculus humanus corporis</i> , fleas and lice of flying squirrels, or recrudescence	Worldwide	7-14	10-18	80	None	—
Tick-borne lymphadenopathy	<i>R. slovaca</i>	Tick bite: <i>Dermacentor marginatus</i> , <i>D. reticularis</i>	Europe	7-9	17-180	5	100	++++
Murine typhus	<i>R. typhi</i>	Flea feces: <i>Xenopsylla cheopis</i> , <i>C. felis</i> , others	Worldwide	8-16	8-16	80	None	—
Human monocytotropic ehrlichiosis	<i>Ehrlichia chaffeensis</i>	Tick bite: <i>Amblyomma americanum</i> , <i>D. variabilis</i>	United States	1-21	3-21	36	None	++
Human granulocytotropic anaplasmosis	<i>Anaplasma phagocytophilum</i>	Tick bite: <i>Ixodes scapularis</i> , <i>I. ricinus</i> , <i>I. pacificus</i>	United States, Europe, Asia	1-21	3-14	Rare	None	—
Scrub typhus	<i>Orientia tsutsugamushi</i>	Mite bite: <i>Leptotrombidium deliense</i> , others	Asia, Australia, New Guinea, Pacific Islands	9-18	6-21	50	35	+++
Q fever	<i>Coxiella burnetii</i>	Inhalation of aerosols of infected parturition material (sheep, dogs, others), ingestion of infected milk or milk products	Worldwide	3-30	5-57	<1	None	—

a++++, severe; +++, marked; ++, moderate; +, present in a small portion of cases; - not a noted feature. bEschar is usually present at the bite site



starts with fever and chills. A characteristic rash appears on the fourth or fifth day starting on the trunk and spreading over the limbs but sparing the face, palms and soles. Towards the second week, the patient becomes stuporose and delirious. The case fatality may reach 40% and increase with age. In some patients who recover from the disease, the Rickettsiae may remain latent in the lymphoid tissue or organs for years. Such latent infection may at times be reactivated leading to recrudescent typhus (Brill Zinsser disease).

Endemic Typhus

Murine or flea borne typhus is a mild form of disease caused by *R. typhi* (*R. mooseri*) which is maintained in nature as mild infection of rats, transmitted by flea *Xenopsylla cheopis*. The flea remains uninfected but remains infectious for the rest of its natural span of life. A related species *R. felis*, maintained in a cycle involving opossums and the cat flea (*Ctenocephalus felis*) has been found to cause endemic typhus in USA. In Kashmir and China, lice have been known to transmit endemic typhus in humans beings producing smouldering outbreaks. Humans acquire the disease usually through the bite of infected fleas, when their saliva or feces is rubbed in or through aerosols of dried feces. Human infection is a dead end. *R. typhi* and *R. prowazekii* are closely associated but may be differentiated by biological and immunological tests. Endemic typhus is worldwide in prevalence but not of much public health importance as the disease is mild and sporadic and can be easily controlled now.

Spotted Fever Group

Divisions have also been identified in the Spotted fever group and it has been suggested that this should be divided into two clades (8). Rickettsiae of this group possess a common soluble antigen and multiply in the nucleus as well as in the cytoplasm of the host cells. They are all transmitted by ticks except *R. akari*, which is mite borne.

Rocky Mountain Spotted Fever (*New World Spotted Fever*, *Tick Borne Typhus Fever*, *Sao Paulo Fever*)

Many species have been recognized in this group, the causative agent of Rocky Mountain Spotted Fever, discovered by Ricketts in 1906, was the first insect transmitted bacterial pathogen to be recognized. The rickettsiae are transmitted transovarially in ticks, which therefore act as both vectors and reservoirs. The rickettsiae are shed in tick feces but transmission to human beings is primarily by bite. Rocky Mountain Spotted Fever is the most serious type of spotted fever and is the first to have been described. It is prevalent in many parts of north and South America and is transmitted by *Dermacentor andersoni* and related species of ticks. In Rocky Mountain Spotted fever rapid recognition of the causative agent and the immediate start of appropriate antibiotic therapy are important because this is associated with relevant morbidity & mortality (9).

Rickettsial Pox

The mildest rickettsial disease of humans is a self limited, nonfatal, vesicular exanthema first observed in New

York (1946). The causative agent is *R. akari* (from akari meaning mite). The reservoir of infection is the domestic mouse, *Mus musculus* and the vector is the mite, *Liponyssoides sanguineus* in which transovarial transmission occurs. *R. akari* has also been isolated from wild rodents in Korea.

Scrub Typhus (Chigger Borne Typhus)

Scrub Typhus is a mite borne disease caused by *Orientia tsutsugamushi* (formerly *R. tsutsugamushi*, *R. orientalis*) characterized by fever, headache, rash and an eschar at the site of the inoculating chigger bite. It is endemic in Southern and Eastern Asia, Northern Australia and the Western Pacific Islands. The infected Chigger while feeding deposits rickettsiae into the tissue of the human host. The incubation period is 1-3 weeks. The disease assumes great importance in military medicine especially during jungle warfare as was recognized in the Indo Burmese theatre in the second world war.

As newly recognized rickettsial diseases and rickettsial pathogens increase in scope and magnitude, several elements related to the concept of emerging rickettsioses deserve consideration. Close inspection of mild or atypical forms of historically recognized rickettsioses and a greater emphasis on culture- and molecular-based diagnostic techniques are the keys to identifying future rickettsial agents of disease (10).

Conclusion

Species of the genus *Rickettsia* are small, obligate intracellular, gram-negative bacteria, many of which are considered nowadays a paradigm of emergent pathogens. Knowledge of Rickettsial group of diseases shall go long way in understanding this less studied disease.

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