Rickettsiae as Emerging Infectious Agents

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KEYWORDS

- Rickettsiae • Taxonomy • Rickettsioses • Pathogenesis • Transmission
- Epidemiology • Clinical manifestations • Laboratory diagnosis

KEY POINTS

- Since first discovered by Howard Ricketts in 1906, 27 species of rickettsiae have emerged, of which at least 17 are pathogenic to humans.
- Pathogenic rickettsiae are introduced into a person's skin in association with arthropod vectors, spread via lymphatics to draining lymph nodes, and disseminate hematogenously to infect microvascular endothelial cells, which leads to severe illness.
- Clinical manifestations of rickettsial diseases usually include fever, headache, and rash. Severe cases develop interstitial pneumonia, meningoencephalitis, and multiorgan failure.
- Although serology confirms the diagnosis, detection of rickettsial antigen by immunohistochemistry or DNA by polymerase chain reaction in skin samples serves as a reliable assay for early diagnosis.
- Tetracyclines are the drug class of choice for the treatment of all spotted fever group and typhus group rickettsioses, with doxycycline being the preferred agent.

Rickettsia are obligately intracellular, small (0.3–0.5 × 0.8–2.0 μm) bacilli with a gram-negative cell wall that has typical bilayer inner and outer membranes separated by a periplasmic layer. Rickettsiae reside free in the cytosol where they replicate by binary fission. Owing to reductive evolution, rickettsiae have small genomes (1.1–1.5 Mb), reflecting the ability of these organisms to survive without some biosynthetic pathways by obtaining these molecules from the host cell.[1] This article presents the history, taxonomy, and microbiology of these intracellular bacteria. It also includes the

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pathogenesis, transmission, clinical manifestations, and laboratory diagnosis of rickettsial diseases.

DISCOVERY OF RICKETTSIAL SPECIES

In the sense of discovery, all infectious agents have been identified since the demonstration in 1876 that *Bacillus anthracis* causes anthrax. The first discovery of a *Rickettsia* was achieved by Howard Ricketts in the Bitterroot Valley of Montana in 1906 when he isolated the organisms from the blood of patients by inoculation of guinea pigs, which developed a febrile illness with distinctive scrotal swelling and hemorrhagic necrosis.[2] He also visualized the organisms and detected them in ticks, a model elucidation of an emerging infectious disease.[3] Von Prowazek and da Rochalima in Europe and Ricketts in Mexico identified the causative agent of louse-borne typhus by feeding clean lice on infected patients, observing the development of rickettsial infection in the louse gut, infecting monkeys, and observing the organisms microscopically.[4] This scientific tour de force resulted in the deaths of the investigators from infection with the agent named in their honor, *Rickettsia prowazekii*.

Each subsequent discovery began as a cluster of cases, such as in an apartment building in New York City (*Rickettsia akari*)[5,6]; application of archaic serologic methods (Weil-Felix *Proteus vulgaris* OX-2 and OX-19 strains agglutination) in patients with unknown diseases in Japan and on Flinders Island, Australia (leading to isolation of *Rickettsia japonica*[7] and *Rickettsia honei*,[8] respectively); molecular studies of old isolates (*Rickettsia massiliae*) or patient specimens *(Rickettsia parkeri* and *Candidatus* Rickettsia philippii)[9,10]; or investigation of unusual clinical manifestations, such as lymphangitis in *Rickettsia sibirica* mongolotimonae strain infections[11] and afebrile cervical lymphadenopathy and scalp ulcer in *Rickettsia slovaca* infections.[12] At present, polymerase chain reaction (PCR) studies are leading to the detection of DNA sequences of *Rickettsia* for which a causal role is proposed. Only time, rickettsial isolates from human specimens, detection of a specific immune response, and pursuit of fulfilling Koch postulates will reveal which are truly additional emerging rickettsial diseases.

TAXONOMY

The genus *Rickettsia* comprises an ever-increasing number of named species and agents detected by molecular methods for which taxonomic names have been proposed. Because of their historic association with human diseases and arthropod vectors, scientists have focused on investigation of human diseases and potential vectors such as ticks, mites, fleas, and lice that transmit rickettsiae during feeding in their saliva or through passing *Rickettsia*-infected feces. However, molecular methods have fostered broader searches and discovery of rickettsiae in other sources, such as herbivorous insects, leeches, and amoebas.[13] Phylogenetically these organisms are basal, more closely related to the common ancestor of the genus.

The *List of Prokaryotic Names with Standing in Nomenclature* (Available at: http://www.bacterio.net/. Accessed March 9, 2017) contains 27 species that currently are considered members of the genus *Rickettsia*, of which there is evidence that at least 17 are capable of infecting humans (**Table 1**). Some, such as *Rickettsia peacockii* and *Rickettsia buchneri*, are symbionts of ticks and very unlikely to cause human infections.[14,15] Others, such as *R parkeri*, *R slovaca*, and *R massilliae*, which were in the past considered to be nonpathogenic, are now recognized as agents of human disease.[9,12,16] Other cultivated organisms that have not been formally proposed as unique species, such as strain 364D (proposed name *R philippii*) and *Rickettsia amblyommatis*, are directly and indirectly associated with human infections.[10,17,18]