REVIEW

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Rickettsia as an agent of neglected Rickettsia infection

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ABSTRACT

Rickettsia is an obligate parasite of certain arthropods (especially ticks, mites, and ticks) and can cause serious diseases. OmpA dan OmpB is a surface protein that facilitates *Rickettsia's* fast attachment and entry into the endothelium. Clinical symptoms are usually characterized by self-limited acute fever in both humans and other animals. Diseases caused by *Rickettsia* are endemic in almost all around the world, including Indonesia. *Rickettsia* diseases include epidemic typhus, murine typhus, scrub typhus, and spotted fever. Culture, nucleic acid amplification, and serological tests can be used as diagnostic examinations. The serological test is the gold standard of Rickettsial diagnostic, even though molecular tests have been developed. Diagnostic limitations mean that rickettsiosis is often overlooked as a cause of infection. *Rickettsia* eradication was carried out by giving tetracycline, chloramphenicol, and rifampin. Vaccines are not yet available so prevention and appropriate use of antibiotics based on the diagnostic examination will determine the success of eradication.

Keywords: *Rickettsia, Diagnostic test, Virulence Factors*.
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INTRODUCTION

Rickettsiae are a group of microorganisms that phylogenetically occupy a position between bacteria and viruses. The genus Rickettsia belongs to the family Rickettsiaceae, and the Rickettsiales.[1] These bacteria are obligate parasites of certain arthropods (ticks, mites, and ticks) and can cause serious illness, usually characterized by self-limited acute fever in both humans and other animals.[2] OmpA and OmpB are surface proteins that facilitate *Rickettsia* bacteria to attach and enter the endothelium, commonly known as endocytosis.[3] The immune system plays an important role in the pathogenesis of rickettsiosis. Based on various studies conducted on humans and animals, it is shown that components of the immune system play an important role in controlling Rickettsia infection, mainly through mechanisms that support Rickettsia elimination.[1]

Rickettsia disease is epidemic typhus, murine typhus, scrub typhus, and spotted fever.[4] Everyone who travels to endemic areas is at risk of contracting the rickettsial infection. If the disease continues to progress but is not treated immediately, it can result in organ damage associated with severe morbidity.[5] Therefore, treatment of patients with suspected pending confirmatory test results, because the certain infection can progress rapidly and result in fatality. In conducting the diagnostic test for diseases caused by *Rickettsia*, the main modalities are culture, nucleic acid amplification, and serological tests.[6]

Diseases caused by *Rickettsia* are endemic in almost all parts of the world, including Indonesia. The incidence of rickettsiosis in humans in Indonesia is underreported. Limited reports in the past have found murine typhus in some tourists returning from Indonesia. In 2002, more than 450 travel-related cases were reported worldwide; significant proportions are R. typhi from the tropics and sub-tropics, R. conorii from South Asia, and O. tsutsugamushi from Asia-Pacific. An active surveillance study of children in Asia shows that 7.6% of cases in Indonesia are caused by Rickettsia. Another fever study revealed the prevalence of murine typhus, spotted fever, and scrub typhus in Northeast Papua to be around 1-5%, while the prevalence of murine typhus in central Jawa was 7%.[6,7] This shows that the incidence of rickettsia infection in Indonesia does exist, but limited diagnostic laboratory facilities for rickettsiosis cause this infectious disease to be underreported.

Currently, research on Rickettsia has developed, thanks to advances in technology, these bacteria have been successfully identified using a molecular approach, namely the PCR method.[8] Based on this, to prevent and treat the occurrence of Rickettsia infection, it is important to recognize *Rickettsia* as an agent of Ricketts infection. Therefore, this literature review discusses Rickettsia bacteria, starting from their characteristic, and how to treat and prevent them.

Characteristics and properties of growth

Microbiologically, *Rickettsia* does not stain well with Gram stain but has a characteristic red color when stained with Giemsa or Gimenez stain. *Rickettsia* has a typical Gram-negative cell wall and lacks flagella. Their genome is very small, consisting of 1-1.5 million bases.[1]

Rickettsia are rod-shaped or spherical-variety bacteria, these bacteria cannot be filtered, and most of the species are

negative Gram.[2] This genus consists of two antigenically determined groups, namely the spotted fever group and the typhus group, which are related to scrub typhus rickettsiae. Ass for the separate genus Orientia, they differ in their lack of lipopolysaccharide, peptidoglycan, and a mucus layer. *Rickettsia* can reside in the cytoplasm or in the nucleus of the cells they invade, carrying out binary fission and metabolizing host-derived glutamate via aerobic respiration and the acid citrate cycle.[2]

Rickettsiaceae are approximately 0.3 to 0.5 micrometers in size. Most rickettsiae only grow in animal cells, transmitted to humans through carrier and arthropod bites. Some species are resistant to drought because transmission of rickettsia can also occur when inhaling arthropod feces or penetrating the skin through abrasion. Another rickettsia can either occur in animals or humans, which serve as a reservoir for blood-sucking arthropods carrying rickettsia bacteria which will transmit it to other animals and humans.[2]

Epidemiology dan Transmision

Rickettsia is an intracellular bacterium whose life cycle involves arthropods as a vector and vertebrates as hosts (Figure 1). *Rickettsia* organisms have been found on all continents except Antarctica. The existence of rickettsia species is generally based on the area caused by climatic conditions and constraints that affect vectors and their natural hosts. However, *Rickettsia felis* and *Rickettsia typhi* spread by a tick. Other vectors known to harbor and transmit rickettsia are mites (*Rickettsia akari*) and ticks (*Rickettsia prowazekii*).[2] Several reports that *Rickettsia felis* has been found in nonhematophagous arthropods, such as booklice, and also in mosquitoes.[9–11]

Everyone who travels to an endemic area is at risk of contracting Ricketts. Throughout the year there is the transmission of rickettsial infections, but increases during outdoor activities. A Most traveler who experiences Ricketts have no symptoms during their journey, and the onset may coincide with their return within a week, this condition happens because the Rickettsia bacteria incubation period is 5-14 days. The

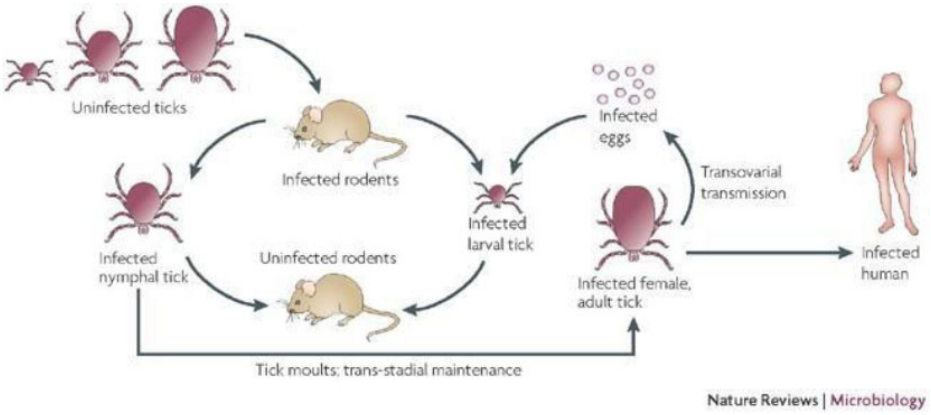

Figure 1. Rickettsia life cycle and transmission pathways.[11]

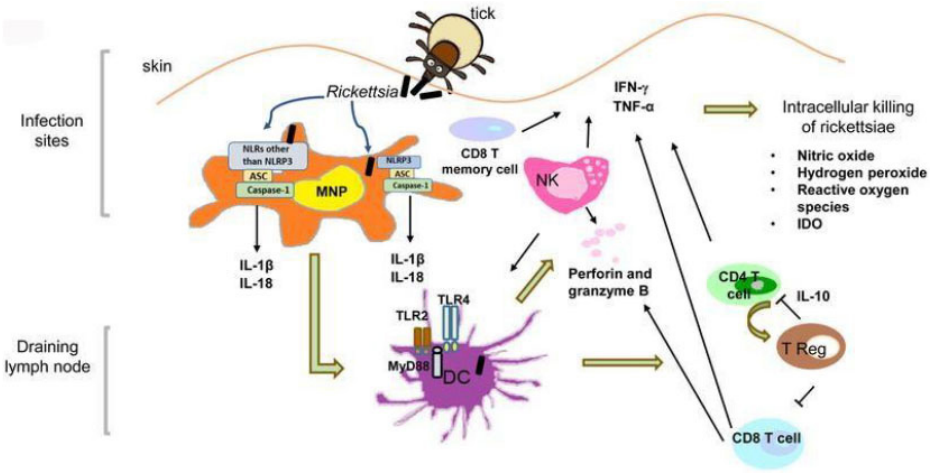

Figure 2. Schematic diagram of the interaction of spotted fever group rickettsia with various components of the host's immune system.[1]

most frequently diagnosed of rickettsia among tourists is based on the fever and typhus group, but the tourist can also be infected but not detected by many health care providers.[12] *Rickettsia conorii* subsp. *conorii* the etiology of *Mediterranean Spotted fever* (MSF) is the most common rickettsiosis in Europe, Southern Europe endemic, but sporadic cases have been reported on all continents. The first cases have been reported in 1909 in Tunisia. *Rhipicephalus sanguineus* is a potential vector and reservoir for *Rickettsia conorii* subsp. *Conorii* in Mediterania continent. MSF cases generally occur in summer, and climatic conditions are thought to be an important factor in increasing tick aggressiveness of *Rhipicephalus sanguineus* to bite humans.[6]

Rickettsia sibirica subsp. *mongolitimonae*, the cause of *lymphangitis-associated rickettsiosis* (LAR), for the first time was isolated in China from the *Hyalomma asiaticum* tick collected in Mongolia in 1991. *Rickettsia sibirica* subsp. *mongolitimonae* was detected on the *Hyalomma anatolicum excavatumt* tick in Greece and Cyprus, for *Rhipicephalus pusillus* tick in France, Portugal, and Spain. First human infection with *Rickettsia sibirica* subsp. *mongolitimonae* was reported in France in 1996.[13,14]

There are studies conducted in Japan regarding two endemic diseases of rickettsia, *Scrub Typhus* (ST) and *Japanese Spotted Fever* (JSF). The study explained that during 10 years, 4185 ST and 1765 JSF cases were reported; 20 (0.48%) ST cases and 16 (0.91%) JSF cases were reported as fatal cases. Older people have a higher mortality rate. Seasonal cases of ST vary depending on the region and are more common during spring or summer in the North and autumn or winter in the South; 78% of cases occur during autumn or winter, mainly in the South and the most fatal ST cases occur in Spring or summer in North.[15]

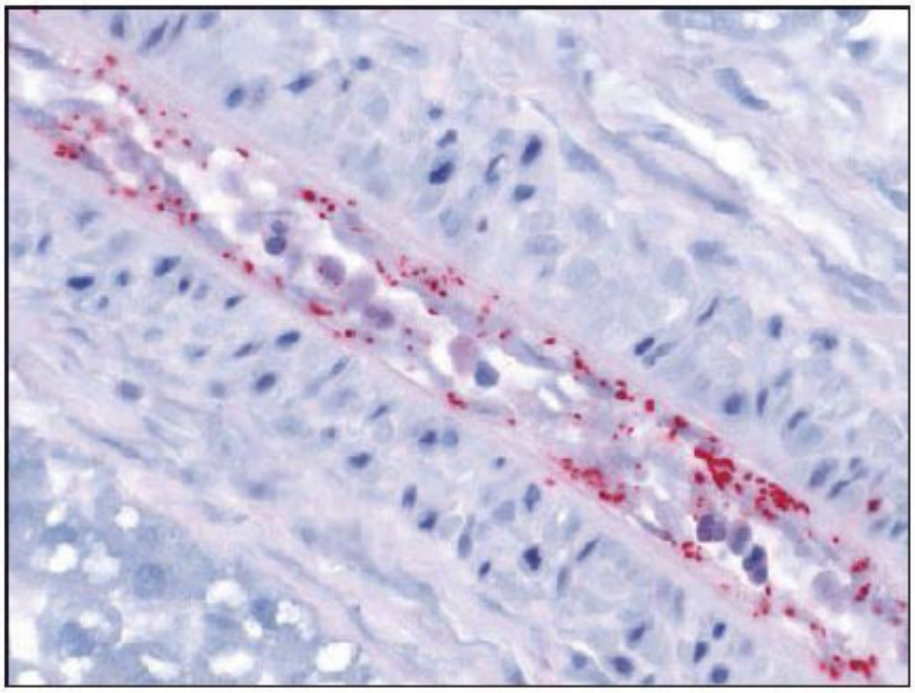

Figure 3. Immunohistochemical staining shows *Rickettsia rickettsii* (red) in vascular endothelial cell infection.[6]

Virulence Factor

The occurrence of endothelial infection by Rickettsia ricktettsii is due to the presence of surface proteins, there is OmpA and OmpB which facilitate bacteria to attach and enter faster the endothelium or commonly known as the endocytosis process. The surface protein will attract macrophage cells, which will phagocytize bacteria. After phagocytosed by macrophages, bacteria carry out a secretion system called type IV secretion system (T4ASS) to inject the substance into macrophages, thus avoiding the elimination process carried out by macrophages.[3,16]

Furthermore, the bacteria will come out of the macrophages and live freely in the cytosol of epithelial cells. The bacteria then obtain nutrients from the host cell, multiply, and take the host's actin protein. The actin protein is commonly found in mammalian host cells and can be combined for a long-chain form. The actin chains will act as tails between the endothelial cells. The movement between cells helps *Rickettsia* bacteria obtain as much nutrition as possible from the host to replicate and then infect neighboring cells. The actin protein also facilitates the movement of *Rickettsia* bacteria thereby helping the bacteria escape from immune cells, such as macrophages.[16]

Pathogenesis dan Pathophysiology

Rickettsia and *Orientia spe*cies are transmitted by flea or mite bite with infected excrement of an infected flea or tick. *Rickettsia* through the skin as a port of entry will spread through the bloodstream and infect the endothelium and sometimes infect vascular smooth muscle cells. *Rickettsia* species enter target cells, reproduce binary in the cytosol, and cause damage to cells.[2]

The immune system plays an important role in the pathogenesis of rickettsiosis. Based on various studies conducted in humans and animals, show that components of the immune system, such as dendritic cells, innate immune signaling, macrophages, NK cells, CD8+ T cells, CD4+ T cells, endothelial cells, antibodies, cytokines, inflammatory chemokines, play an important role in controlling Rickettsia infection, through mechanisms that support rickettsia elimination. However, when these protective immune components do not work effectively in the host response, or rickettsia modifies or manipulates the response of the immune system, it will result in the development of a disease with a high degree of severity and is fatal. In other companies, mutants of the immune systems, such as inducible regulatory (TR) T cells, play a role in the development and pathogenesis of rickettsia.[1]

Rickettsia is an obligate intracellular pathogen that primarily infects vascular endothelial cells and occasionally, smooth muscle cells underlying small and medium vessels (Figure 3). Rickettsia infection causes a systemic vasculitis that manifests externally as a skin lesion with characteristic petechiae. If left untreated, it can cause organ damage with severe morbidity. Pathogen-mediated injury to the vascular endothelium will result in increased capillary permeability, microbleeding, and consumption of platelets. Late-stage manifestations, such as noncardiogenic pulmonary edema (ARDS) and cerebral edema, are a consequence of microvascular leakage. Hyponatremia occurs as a result of inappropriate secretion of antidiuretic hormones in response to hypovolemia.[5]

The resulting study by Lokita *et al* (2020) has found 30.8% for *R. typhi*, 5.7%, for *R. rickettsia,* and 3.8% for *O. tsutsugamushi* antibodies. In 103 of 975 (10.6%) non-dengue patients diagnosed with an acute rickettsial infection, symptoms included nausea (72%), headache (69%), vomiting (43%), lethargy (33%), anorexia (32%), arthralgia (30%), myalgia (28%), chills (28%), epigastric pain (28%), dan rush (17%). Rickettsia was identified as the etiology of febrile illness in 103 of 975 (10.6%). On clinical examination, none of these patients have been diagnosed with Rickettsia.[7] The result of this study confirms that rickettsia infection is an important and often overlooked cause of fever in hospitalized patients in Indonesia.

Diagnosis Test

The main modalities for carrying out diagnostic tests for *Rickettsia* are culture, nucleic acid amplification, and serological tests. Serological tests that can be performed are the rapid diagnostic test (RDT), indirect immunofluorescence assay (IFA), and ELISA. Performing antigen detection in biopsies, eschar, or skin can be useful during the acute phase of infection, and performing

cultures for definitive identification and characterization.[17]

1. Nucleic acid amplification test for scrub typhus
   To get accurate detection results, it is recommended to do it in the early phase of infection up to 10 days of fever, followed by a serological test to diagnose scrub typhus. Common target genes are htrA (47-kDa periplasmic serine protease), 56-kDa type-specific antigen, rrs (16S rRNA), and groEL (heat shock protein Hsp60). The 56-kDa type antigen is only specific for Orientia spp. Positive PCR and/or product sequencing provides strong evidence for the presence of pathogenic DNA.[17,18]
   The RT-PCR test can be performed for the diagnosis of scrub typhus, but high cost and needs to be done by a trained person, which is an obstacle if it is carried out in rural areas. The appropriate PCR test depends on the samples used, bacterial load, and time point of diseases. Samples taken from noninvasive eschar or eschar biopsies are excellent for PCR testing but are only performed in areas with high eschar levels such as Korea and China.[17]
2. Rapid diagnostic test for scrub typhus
   The availability of an affordable and accurate rapid diagnostic test (RDT) at the point of care can promote targeted treatment and its widespread use can increase awareness of scrub typhus. Comparison RDTs show increased diagnostic accuracy when using IgM versus total antibody. Anti-*O. tsutsugamushi* IgG can lead to high RDT false positive rates in endemic areas, which may require testing adjustment.[17]
3. Serology test for scrub typhus using indirect immunofluorescence assay
   For decades indirect immunofluorescence assays have been a mainstay of the diagnostic test for scrub typhus. However, attention still needs to be paid to standardization, cut-off variable titers used in endemic areas, and relatively high costs. The accuracy of the results is that if there is a four-fold increase in antibody titers in paired serum, it increases confidence, but confounding factors such as pre-existing antibodies and cross-reactivity are still present.[17,18]
4. Serology test for scrub typhus using the ELISA method
   The advantages of the ELISA test compared to the immunofluorescence assay are that it is simpler, standardized, and has high objectivity. However, the determination of validated diagnostic limits in endemic areas is often neglected.[15] Based on the ELISA evaluation conducted, it was found that there is a strong relationship between optical density (OD) and immunofluorescence assay titers. This allows the determination of a positive optical density cutoff ELISA corresponding to a single immunofluorescence assay titer of at least 1600 with a sensitivity of 93% and specificity of 91% and corresponding to enhanced scrub typhus infection criteria (STIC) composite indicator.[19]
5. Nucleic acid amplification test for murine typhus and spotted fever group
   The nucleic acid amplification tests method is used to diagnose Murine typhus and spotted fever group. The most frequently used genes are 16S rRNA (rrs), citrate synthase (gltA), 17-kDa lipoprotein, and other conservation genes. Diagnosis is made for treatment by combining Rickettsia genus-specific real-time PCR. Unique gene regions are targeted for species identification and subspecies level, or long-range PCR amplification can be sequenced because real-time PCR has target sequences of 75-150 nucleotides providing only limited taxonomy information.[17] Good samples for PCR include whole blood, buffy coat, skin or eschar/crust biopsy, or swab.[20]
6. Serodiagnosis typhus dan spotted fever group rickettsioses
   In diagnosing typhus and spotted fever group rickettsioses, serodiagnosis is the gold standard with the use of seroconversions and a four-fold increase in antibody titers. The serodiagnosis test has good specificity, but there are exceptions to the potential for IgM. The disadvantages are poor sensitivity occurs in acute infection, antibodies are difficult to detect within the first 10-14 days of infection, indirect diagnostic evidence (detection of host response), and the possibility of cross-reaction with other Rickettsiae. In serodiagnosis for typhus and spotted fever group rickettsioses, immuflouresence assay remains the preferred method.[17]

Control and prevention

Treatment of patients with suspected rickets infection should be undertaken when the disease is suspected pending confirmatory test results because certain infections can progress rapidly and be fatal. Immediate empiric treatment with tetracycline is recommended for all ages, but doxycycline is used most often. Chloramphenicol can also be used as an alternative in some cases. However, compared with the use of tetracyclines, the use of chloramphenicol is associated with an increased risk of death, especially from *R. rickettsii* infection. In some areas, it has been reported that scrub typhus is resistant to tetracyclines, in this case, azithromycin can be an effective alternative. Limited clinical experience has shown that *A. phagocytophilum* and *R. africae* infections respond to treatment with rifampicin, which is considered an alternative drug for some patients who are pregnant or who are intolerant of doxycycline. However, expert advice should still be sought when considering alternative agents.[12]

Until now there is no vaccine available to prevent rickettsia infection. Antibiotics are not recommended for rickettsia prophylaxis and should not be given to asymptomatic people. Travelers in particular traveling to endemic areas should be instructed to minimize exposure during travel to infectious arthropods (including ticks, fleas, and mites) and animal reservoirs, especially dogs. The risk of transmission can be reduced by using appropriate insect repellent or tick hygiene on the skin or clothing, self-examination after visiting vector-infested areas, and wearing protective clothing. This precaution is especially important for people with underlying conditions that could compromise their immune system, because these people may be more susceptible to severe disease.[12]

The strength of this article is that discusses *Rickettsia* as an agent of neglect in a comprehensive and in-depth manner related to virulence factors, pathogenesis, and pathophysiology which can provide knowledge about the course of disease caused by *Rickettsia*. Meanwhile, the limitation of this article is that it has not discussed in detail the diagnostic test that has currently been developed, namely the molecular test using the PCR method.

CONCLUSION

The genus Rickettsia belongs to the family Rickettsiaceae, order Rickettsiales. OmpA and OmpB are surface proteins that facilitate Rickettsia bacteria to attach and enter the endothelium quickly, commonly known as the process of endocytosis. Diseases caused by Rickettsia include epidemic typhus, murine typhus, scrub typhus, and spotted fever. Diagnostic tests that can be used are culture, nucleic acid amplification, and serological tests. This disease can be prevented by proper use of insect or tick repellent on the skin or clothing, self-examination after visits to vector-infested areas, and wearing protective clothing.

CONFLICT OF INTEREST

All authors declared no conflict of interest regarding this manuscript

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AUTHOR CONTRIBUTION

All authors contributed equally to this study.

ETHICAL STATEMENT

N/A.

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