

## Revisiting the Overlooked Infection: Rickettsioses

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### ABSTRACT

The prevalence of human Rickettsioses cases in Indonesia is unknown and could probably be underestimated. The high prevalence of seropositive *Rickettsia* sp. was reported in small mammals (as vectors) and humans. In Indonesia, a recent study in patients with acute fever revealed that the prevalence of Rickettsioses is 10%. Many cases of Rickettsioses were often misdiagnosed with dengue fever, enteric fever, or leptospirosis due to their overlapping clinical manifestation. The limitation of point of care testing in Indonesia hindered the adequacy of diagnosis confirmation. Appropriate empirical or definitive treatment with macrolide, mainly doxycycline, is preferable compared to other broad-spectrum antibiotics, such as cephalosporin or quinolones. Moreover, when left untreated, Rickettsioses may deteriorate progressively to fatal outcomes, such as meningitis, sepsis, and even death. The awareness of health care practitioners, the availability of confirmatory rapid diagnostic tests and adequate treatment choices are important in eradicating this disease.

**Keywords:** infection, Rickettsioses, tropical disease.

### INTRODUCTION

Rickettsial diseases are a group of diseases caused by a genus of obligately intracellular, gram-negative coccobacilli and short bacilli, and non-spore-forming bacteria.<sup>1,2</sup> The family of Rickettsiaceae as the etiology of Rickettsial diseases were originally classified into six genera, i.e., *Rickettsia*, *Ehrlichia*, *Anaplasma*, *Neorickettsia*, *Candidatus Neoehrlichia*, and *Wolbachia*<sup>1</sup>. However, based on the antigenic and genetic data, it was further classified as *Rickettsia* spp. and *Orientia*, spp. These species are traditionally divided into three Rickettsioses disease groups, i.e., spotted fever group (SFG), typhus group and scrub typhus group.<sup>3,4</sup>

The acute presentations of Rickettsioses are often similar during the first 5 days, i.e., fever,

headache, myalgia, nausea, vomiting and cough. It is usually first presented as a fever that may subside without further clinical evolution or it may also evolve along one or more principal clinical lines, i.e., macular or maculopapular rash, eschar, vesicular rash, pneumonitis, meningoencephalitis, and even sepsis and toxic shock syndromes with hypotension and multiorgan failure.<sup>1,2</sup>

Regardless of its potentially fatal outcomes, Rickettsioses are often misdiagnosed in daily clinical practice because the initial signs and symptoms of the disease may overlap with other acute febrile illnesses clinical features, such as dengue fever, leptospirosis, or enteric fever disease.<sup>5,6</sup> Establishing a definitive diagnosis is also challenging as it requires more time to

examine serum samples during the acute and convalescent phases, whereas, the disease course may deteriorate rapidly if they are not promptly treated.<sup>1,2,4,7</sup>

## DEFINITION AND CLINICAL FEATURES

Rickettsioses were firstly described as exanthematic typhus in 1760, followed by the first report of scrub typhus in 1879 and the discovery of a pathogen for Rocky Mountain spotted fever (RMSF) by Howard Taylor Ricketts, whose name underlies the etymology of the disease.<sup>1,8,9</sup> In Indonesia, the term typhus (as included in Rickettsioses) or “tifus” (in Indonesian language) is commonly mistaken as typhoid fever or enteric fever which is caused by *Salmonella, sp.* and has a fecal-oral transmission.<sup>10</sup>

The earliest definition of the term “typhus” is difficult to be determined since it was applied to a broad range of infectious diseases before the 20<sup>th</sup> century. The new era of rickettsiology had been fastened by the discovery of typhus diagnostic test which was able to identify epidemic typhus caused by *Rickettsia spp.* and *Orientia spp.* With the rapid invention of antibiotics, however, the widespread epidemic could be suppressed and nowadays the prevalence rate of the infection has decreased.<sup>9</sup>

Centers for Disease Control and Prevention (CDC) categorized rickettsial diseases as travel-

related infectious diseases, in which all travellers from endemic areas are at risk of acquiring rickettsial infections. Since most rickettsial diseases incubate for 5-14 days, tourists may not experience symptoms during their trip and onset may coincide with their return home or within a week after returning.<sup>11</sup> The lists of endemic areas are diverse, for example, RMSF is endemic in south-central United States, Canada, Mexico, and South America; scrub typhus in Asia, Australia, Pacific; murine typhus spreads worldwide; and Mediterranean spotted fever in southern Europe, Africa and Asia.<sup>1,2,7</sup> Table 1 summarizes the groups of Rickettsioses and their features.

## SITUATION IN INDONESIA

The epidemiology data of Rickettsioses vary according to geographic distribution and seasonal activities of tick vectors and vertebrate hosts, in addition to the human behaviors that increase the risk of tick exposure, tick attachment, and subsequent infection.<sup>7</sup> The exact prevalence of these diseases is often underestimated since the establishment of definitive diagnosis is still limited.

A study held in 1995 on rickettsial disease risk revealed that Indonesia was an endemic area for murine typhus, scrub typhus, and Q fever, whereas other typhus and SFG endemicity were unknown.<sup>10</sup> Evidence of rickettsial diseases or

**Table 1.** Group of Rickettsioses and their clinical features.<sup>1,2,11</sup>

Disease*	Organism	Transmission	Incubation (days)	Duration (days)	Rash %	Eschar %	Lymphadenopathy <sup>a</sup>
Spotted fever group (SFG)							
Rocky Mountain spotted fever	<i>R. rickettsii</i>	Tick	2-14	2-10	90%	<1	+
Flea-borne spotted fever	<i>R. felis</i>	Flea	8-16	8-16	80	15	-
Rickettsialpox	<i>R. akari</i>	Mite bite	10-17	3-11	100	90	+++
Mediterranean spotted fever	<i>R. conori</i>	Tick bite	5-7	7-14	97	50	+
Typhus group							
Murine typhus	<i>R. typhi</i>	Flea feces	8-16	9-18	80	None	-
Epidemic typhus	<i>R. prowazekii</i>	Louse feces, fleas, lice	7-14	10-18	80	None	-
Scrub typhus group							
Scrub typhus	<i>Orientia tsutsugamushi</i>	Mite bite	9-18	6-21	50	35	+++

\*The diseases are not limited to what is listed on the table, however, it conveys the list of the most common diseases.

<sup>a</sup> +++++, severe; +++, marked; ++, moderate; +, present in a small proportion of cases; —, not a noted feature.

Rickettsioses in Indonesia have been described since the early 1900s in western Indonesia (Sumatra and Java) to eastern Indonesia (Papua)<sup>10,12–14</sup> Several cases of underdiagnosed yet fatal clinical features of Rickettsioses also had been reported among travellers returning from Indonesia.<sup>15,16</sup> Another study on ectoparasite and small mammals in Indonesia also showed a high rate of typhus group rickettsiae-specific antibodies, which indicated the high risk for rickettsia infection and the existence of various hosts and vectors across the country.<sup>14,17</sup> This data indicated the potential Rickettsioses endemicity in Indonesia.

In the last decade, many studies have highlighted the importance of Rickettsioses as one important differential diagnosis of fever.<sup>5,6,18–21</sup> In 2020, observational research showed that Rickettsioses were the third most prevalent cause of acute febrile illness in Indonesia. All the cases were misdiagnosed by the standard of care examination.<sup>6</sup> Furthermore, Rickettsioses were also the third most common cause of sepsis in a multinational study held in southeast Asia, therefore, our awareness of this disease is mandatory.<sup>22</sup>

## THE EMERGING PROBLEM OF RICKETTSIOSES IN INDONESIA

In the upcoming text, we will elaborate on the emerging problem of Rickettsioses in Indonesia.

### 1. Undiscovered facts that Rickettsiosis cases are prevalent

During 2013–2016, the Indonesia Research Partnership on Infectious Disease (INA-RESPOND) conducted an observational cohort study (Acute Fever Requiring Hospitalization/AFIRE) on acute febrile illness at eight tertiary healthcare facilities in Indonesia. Among 1,488 enrolled subjects with fever and 1,003 pediatric and adult subjects with identified etiology of disease, Rickettsioses ranked as the third most prevalent infection (103 subjects, 10.3%), following dengue and typhoid fever.<sup>6</sup> The confirmed Rickettsioses were established by one of these examinations: enzyme-linked immunosorbent assay (ELISA) and/or

indirect immunofluorescence assay (IFA) for serology examination, followed by polymerase chain reaction (PCR) of bacterial DNA 17-kD outer membrane protein (17-kD *omp*) gene of *Rickettsia sp.*, 47-kD *omp* gene of *O. tsutsugamushi*, and 743-bp sequence of *Rickettsia sp. ompB* gene.<sup>5</sup> In this study, IgG of *R. typhi* was detected among 30.8% of total subjects, followed by IgG detection of spotted fever and *O. tsutsugamushi*. Although mere single serology detection is not sufficient in diagnosing Rickettsioses, this high rate of seropositivity reflects the high exposure of *Rickettsia, spp.* in Indonesia, which is higher<sup>13,23–26</sup> or similar<sup>12</sup> compared to the previous studies. One systematic review by Wangdi et al.<sup>20</sup> studied undifferentiated febrile illness cases in south and southeast Asia and revealed that the prevalence of Rickettsioses reached 4%, which comprised of scrub typhus, murine typhus, and spotted fever disease. Compared to this systematic review, data on the prevalence of Rickettsioses in Indonesia is significantly higher and demands further attention.

Rickettsioses are also one of the most common etiologies of community-acquired sepsis from a multinational multicentre observational study in southeast Asian countries, including Indonesia, together with dengue and leptospiral infection. The prevalence rate of Rickettsioses as the cause of sepsis and severe sepsis reached 6%, comprised of *R. typhi*, *O. tsutsugamushi*, and spotted fever group.<sup>22</sup>

Although these studies showed that the prevalence of Rickettsioses was high, all identified cases were initially suspected as leptospirosis, typhoid fever, chikungunya, or dengue fever – none were diagnosed as Rickettsioses.<sup>22</sup> This data may also portray the unawareness of healthcare practitioners to suspect Rickettsioses in the first instance on a patient with acute febrile illness. By reflecting on the rate of misdiagnosis of this disease, healthcare providers need to be conscious and thorough in diagnosing acute febrile illness, and hence can consider Rickettsioses as a differential diagnosis.

## 2. Inadequacy of diagnostic modalities

One of the possible reasons why Rickettsioses was often misdiagnosed as another disease was because the accompanying symptoms of Rickettsioses, such as fever, nausea, headache, vomiting, lethargy, anorexia, arthralgia, myalgia, chills, and epigastric pain, may overlap with dengue, typhoid, and leptospiral infection.<sup>1,2</sup> The AFIRE study showed that Rickettsioses mostly affected gastrointestinal, lower respiratory tract and systemic organs, and therefore, its manifestation is similar to other differential diagnoses. Signs and symptoms are also often not specific for Rickettsioses, as the Rickettsia Triad (fever, headache, and rash) were only developed in 10% of subjects.<sup>5,6</sup> On 815 adult patients with community-acquired sepsis, Rickettsioses were presented as acute respiratory infection, acute systemic infection, acute diarrhea and acute central nervous system (CNS) infection which overlapped with symptoms of influenza, rhinovirus, hantavirus, leptospirosis, *S. aureus* infection, dengue fever, *E. coli* infection, *Streptococcus*, spp. infection, and other bacterial infection.<sup>22</sup>

A presumptive clinical diagnosis of Rickettsioses can be confirmed by immunohistochemical (IHC) assays in tissue, detection of antibodies by IFA with concomitant seroconversion or a fourfold or greater rise in antibody titre between acute and convalescent samples, or PCR of blood or tissue.<sup>1,2,4</sup> Whilst having high diagnostic value, those examinations are not widely available as point-of-care testing (POCT), expensive, and may cause a delay in empirical treatment (e.g., waiting for the serum convalescent testing). Detection of antibody and antigen for Rickettsioses in Indonesia is still limited for research purposes. The isolation of *Rickettsia*, spp. requires suitable techniques and must be handled as highly pathogenic in a biosafety level 3 laboratory, hence its use for prompt diagnosis is also limited.<sup>4</sup> This lack of diagnostic modalities is concerning because

Rickettsioses are most misdiagnosed and potentially lethal, even though they are an easily treatable disease.<sup>6</sup>

In the AFIRE study, less than 50% of microbial etiologies were identified by standard-of-care testing, 23.6% were identified by INA-RESPOND laboratory, while the remaining 32.5% were unidentified. *Rickettsia* spp. (*R. typhi* and *R. felis*) is one of three infectious etiologies which was not captured by standard-of-care examinations.<sup>5</sup>

The previous studies and data highlight the need for a better and more widely accessible POCT for Rickettsioses, preferably based on antigen detection over antibody response to be able to rapidly diagnose and treat Rickettsioses.

## 3. Choice of therapy is widely available and simple, however, the administration is often delayed

Macrolide, mainly doxycycline, is the drug of choice for the treatment of all tickborne rickettsial diseases in patients of all ages. It should be initiated immediately in persons suggestive of Rickettsioses without waiting for the confirmatory laboratory examination. The drug is given orally or intravenously at a dose of 100 mg twice daily (adult) or 2.2 mg/kg of body weight twice daily (children), until at least 3 days after fever subsides and the patient is clinically improved.<sup>7</sup>

Prior to hospitalization, many patients with Rickettsioses have already consumed antibiotics, including amoxicillin, cefadroxil, cotrimoxazole, or cefixime – none of which are the empiric treatment for Rickettsioses.<sup>6</sup> During hospitalization, broad-spectrum antibiotics, such as ceftriaxone and ciprofloxacin, are effective empiric treatments; however, the routine broad-spectrum administration should be discouraged in the context of antimicrobial stewardship. In cases of acute fever unresponsive to empirical treatment of other acute febrile illnesses, administration of doxycycline should be considered.

#### 4. Fatal cases (sepsis, mortality) in Rickettsioses

The spectrum of Rickettsioses varies from self-limited febrile illnesses to the involvement of CNS, liver, lung, and even death. Among Rickettsioses, *R. prowazekii* and *R. typhi* are known to be able to survive for an extended period outside the reservoir or vector and they are extremely infectious. Due to their high level of infectivity and severe illness after inhalation, *R. prowazekii*, *R. rickettsii*, *R. typhi*, *R. conorii*, and *Coxiella burnetii* are known for bioterrorism threats.<sup>2,5,19,27</sup>

According to the AFIRE study, the overall mortality of patients with acute febrile illnesses reached 5.9% and the most common microbiologic etiologies included *R. typhi*, with mortality rate of 6.8%, markedly higher than the previous studies.<sup>5,6</sup> A study in Australia also observed that among 135 cases, 13% required ICU admission, mostly caused by spotted fever group and scrub typhus.<sup>28,29</sup> Another study in India reported a higher fatality rate of 12.2% with evidence of acute respiratory distress syndrome and aseptic meningitis among patients. One retrospective study on acute meningoencephalitis patients also identified *Rickettsia sp.* on cerebrospinal fluid examination, depicting the wide variety of its clinical manifestations. In fact, this underdiagnosed disease can lead to fatal outcomes even though the empirical treatment with doxycycline is relatively simple and widely available. An improvement in presumptive and confirmed diagnosis is important, as it will lead to more appropriate management and reduction of fatal cases and death.

#### CONCLUSION

Rickettsioses are a group of diseases that are common in Indonesia but often overlooked as a differential diagnosis of acute febrile illness. Previous studies have demonstrated that Rickettsioses are often misdiagnosed as dengue fever, leptospirosis, typhoid fever, and chikungunya due to some possible reasons, i.e.,

unspecific and overlapping signs and symptoms with other diseases, inadequate modalities of point of care examination to establish the confirmed diagnosis, and unfamiliarity of health care providers and system in suspecting Rickettsioses on patients with acute febrile illness. Therefore, awareness and understanding of the diseases, the adequate point of care diagnosis modalities, and treatment of Rickettsioses in Indonesia need to be established to reduce morbidity and mortality.

#### COMPETING INTERESTS

The authors declared no conflict of interest.

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