



# Risk Factors Leading to Fatal Outcome in Scrub Typhus

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## Introduction

Scrub typhus induced by the intracellular organism *Orientia tsutsugamushi* (*O. tsutsugamushi*) is an acute febrile illness characterized by a typical eschar, generalized lymphadenopathy, skin rashes, and vague non-specific symptoms such as myalgia, headache, and cough (1,2). An estimated one billion people are at risk for scrub typhus, and one million cases occur annually with 50% increase in case fatality rate in pre-antibiotic area (3). Scrub typhus is characterized by focal or disseminated vasculitis and perivasculitis, which may involve the lung, heart, liver, spleen, and central nervous system (1,4). Acute respiratory distress syndrome (ARDS) is a serious complication of scrub typhus (5). In addition, encephalitis, interstitial pneumonia, myocarditis and pericarditis, acute renal failure, acute hepatic failure, and acute hearing loss can also occur in patients with scrub typhus (6-9). Despite the availability of efficient and effective treatment, scrub typhus is still considered as a potentially fatal infectious disease.

## Risk Factors Leading to Fatal Clinical Outcomes

### 1. Pathophysiology

*O. tsutsugamushi*, an obligatory intracellular organism, causes the widespread infectious vasculitis or perivasculitis of multiple organs due to multiplication of the organisms in the endothelial cells lining the small blood vessels (10,11). The organisms proliferate in the endothelium of small blood vessels, inducing release of cytokines which damage endothelial integrity, causing fluid and protein leakage, platelet aggregation, polymorphs, and monocyte proliferation, leading to focal occlusive end-angiitis causing microinfarcts. This process especially affects skeletal muscles, skin, lungs, kidneys, brain and cardiac muscles (3). In mice infected lethally with *O. tsutsugamushi*, prominent apoptotic changes occurred in lymphocytes in the regional lymph nodes and spleens (12). Autopsy studies in persons who had died of sepsis showed a profound, progressive, apoptosis-induced loss of cells of the adaptive immune system (13). Such apoptotic changes in lymphocytes drive anti-inflammatory responses and anergy and attenuate the function of Th1 that is critical for cell-mediated immunity (13). Although no loss of CD8+ T cells,

natural killer cells, or macrophages occurred, sepsis markedly decreased the levels of B cells, CD4+ T cells, and follicular dendritic cells. The loss of lymphocytes and dendritic cells is especially important, because it occurs during life-threatening infection (13). The potential importance of the depletion of lymphocytes was illustrated by studies in animals, showing that prevention of lymphocyte apoptosis improves the likelihood of survival (13). Therefore, an apoptotic process in lymphocytes may explain immunosuppression in scrub typhus with clinical fatal outcomes (12).

### 2. Bacterial Factor

Bacterial virulence and pathogenicity can be considered as a risk factor for clinical fatal outcomes. A relationship between size of bacteremia and severity of clinical picture has been reported for a range of bacterial infections in both adults and children, based on quantitative bacterial culture and more recently, molecular biology techniques (14). A study that demonstrates a relationship between bacterial load and disease severity in adults with scrub typhus showing that the patients with severe clinical features have high *O. tsutsugamushi* DNA level in blood (14). In a study with mice, the lethal mice developed rickettsemias sooner and sustained higher rickettsemia levels before death than their nonlethally infected counterparts (15). The rickettsemias observed in the lethal scrub typhus infections resulted from more rapid growth of the organisms, a decreased host immune response, immunosuppression or inhibition of T-lymphocyte functions, or a combination of these factors (15). In order to cause high bacteremia rapidly, the invasion of *O. tsutsugamushi* into endocelial cells of microvasculature of tissue and organ involved is thought to be important. *O. tsutsugamushi* is also usually detected in the mesothelial cells, macrophages, and other inflammatory cells (16). Pathologic finding of scrub typhus in ARDS showed the direct invasion of *O. tsutsugamushi* into endothelial cells of the lung (17). Because *O. tsutsugamushi* is an obligate intracellular pathogen, it adheres on the surface of host cells, enters, and internalizes into host cells. Bacterial infection of host cells is attributable

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mainly to the interactions between bacterial surface components, complementary host cell receptors and extracellular matrix molecules. Fibronectin is considered most important extracellular matrix protein involved in the adherence and entry of bacteria into host cells. Among the components on the surface of *O. tsutsugamushi*, 56-kDa type-specific antigen (TSA 56) was identified as the bacterial ligand responsible for the interaction with fibronectin. Furthermore, the invasion of the pathogen was enhanced by the addition of purified recombinant peptides derived from TSA 56 (18). These findings indicate that TSA 56 plays an important role in the invasion of *O. tsutsugamushi*.

The efficiency with which *O. tsutsugamushi* can enter, survive and grow within cells of the human host, disseminate to other sites and seed into the bloodstream could also be influenced by characteristics of the invading strain. This possibility assumes that the genetic complements of *O. tsutsugamushi* vary between strains. Scrub typhus severity and clinical presentation of scrub typhus appear to be strain dependent, varying tremendously from extremely mild or unapparent disease to frequently fatal disease in both humans and laboratory animals (2). The general course of the disease and the prognosis vary considerably depending on the character of the endemic strain (16). In mice experimental models, T-cell response to native and recombinant protein antigens of *O. tsutsugamushi* was differentiated by each surface antigen; some antigens give rise to responses of T-cell immunity, but others not, depending on surface antigens of *O. tsutsugamushi* (19). T-cell immunologic responses in early course of scrub typhus have been known to play a key role in both natural resistance and acquired immunity determining the fate of the *O. tsutsugamushi* infected host (16). Therefore, the difference of surface antigen molecules depending on strains of *O. tsutsugamushi* is one of the factors that determine protective immunologic responses for scrub typhus. Although very limited, there is evidence for strain differences indicated by variation in sensitivity to antibiotics or antibiograms (2). The clinical outcomes such as alleviation of fever, median fever clearance time, and conjunctival suffusion in antibiotic resistant strain found in Thailand is worse than in prototype strains (20); nalidixic acid resistant *Salmonella typhi* in typhoid fever showed more aggravated course than that with susceptible to nalidixic acid (21). Antibiotics prevented death in mice infected by the strains with poor antibiotic response less often than after infection by the prototype strains (20). These observations suggest that it would be necessary to examine whether *O. tsutsugamushi* is resistant to antibiotics in patients with a severe clinical course of scrub typhus.

### 3. Host Factor

As the risk factors of fatal outcomes of scrub typhus, host factor has not been studied, sufficiently. The virulence of *O. tsutsugamushi* presents differently in every genetic

**Table 1. Risk Factors Leading to Fatal Outcomes in Scrub Typhus**

Risk Category	Risk Factor
<b>Bacterial Factor</b>	Size of bacteremia Surface molecules(ex: TSA 56) involved in invasion of host cell Strains of <i>O. tsutsugamushi</i> Antibiotics resistance
<b>Host Factor</b>	Genetic factor CMI(Cell Mediated Immunity) Underlying diseases(ex: LC, COPD)
<b>Other Factor</b>	Delay in drug administration

difference of host mouse strains (16). Though, the same *O. tsutsugamushi* strain causes infection in each different host, host mouse strain influences whether the result is non-healing disease that leads to the death or survival. Genetic factors of host, therefore, are known to be meaningful determinants of susceptibility to death from infectious disease (13). In an animal experiment, early T-lymphocyte activation-1(Eta-1)/osteopontine (OP) gene has been thought to enhance resistance to oriental infection by affecting the ability of macrophages to migrate to sites of infection and to express bactericidal activity. In fact, mice deficient in Eta-1/OP gene expression severely impaired cell-mediated immunity to viral and bacterial infection (16).

In addition, as a factor associated with fatal outcomes from host infected by a pathogen inducing sepsis, single base-pair alterations (single-nucleotide polymorphisms) in genes controlling the host response to microbes have been studied. Known alterations of them include polymorphisms in TNF receptors, interleukin-1 receptors, Fc gamma receptors, and Toll-like receptors. Polymorphisms in cytokine genes may determine the concentrations of inflammatory and antiinflammatory cytokines produced and may influence whether persons show marked hyperinflammatory or hypoinflammatory responses to infection. Genetic polymorphisms of TNF- alpha and TNF-beta are associated with the risk of fatal outcomes of infected patients (13,22). These genetic factors may, in the future, be used to identify patients at high risk for the development of fatal outcomes during infection (13). Cell-mediated immunity has been shown to be a major factor in resistance against intracellular parasites, including facultative intracellular bacteria such as *Listeria monocytogenes* and obligate intracellular rickettsiae (23). In host-rickettsiae mice experimental models that led to lethal infection, delayed-type hypersensitivity (DTH) response was the greatest by 5 to 7 days after infection and then waned rapidly during the terminal stages of infection. The host-rickettsiae models that led to a chronic, immunizing infection resulted in a slightly delayed maximum response at 7 to 9 days postinfection, followed by a gradual decline in reactivity



(23). In two models, DTH was observed early in the course of infection. The duration of DTH, however, was different each other. These observations suggest that DTH determines antirickettsial immunity and resistance to lethal challenge. Th1 cells play important roles in DTH, and therefore an imbalance of dichotomy of Th1/Th2 is thought to affect the progress of pathogenesis (16). Among the patients infected with scrub typhus and with severe clinical outcomes, a detailed study on the functions of DTH is in need. Underlying diseases of patients appear to corrupt the progress of scrub typhus. According to recent studies reported by Lee and his colleagues, among the patients on admission by scrub typhus in hospital, those having underlying diseases such as liver cirrhosis and COPD showed statistically meaningful high ratio of fatal case compared to those no underlying diseases (24,25). The patients with liver cirrhosis had longer duration of hospital stay and higher APACHE II score than those without liver cirrhosis (24). On the other hand, a previous study reported that the clinical manifestations of *O. tsutsugamushi* infection, unlike those due to some other intracellular pathogens, are not unusually severe in immunocompromised patients with AIDS and that there are no significant differences between HIV-infected patients and non-HIV-infected patients in severity of scrub typhus (26).

#### 4. Other Factors

Early treatment shows better outcomes and faster resolution than delayed treatment (3). When clinical symptoms begin or a patient is taken to hospital, prompt administration of antibiotics is crucial. In patients with serious complications of scrub typhus, treatment interval of fatal case was marginally significantly longer than that of the non-fatal case (25). In other rickettsial infection, delayed administration of antibiotics was also independently associated with major organ dysfunction (27).

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