

Scrub Typhus in the Western Pacific Region

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Abstract

Scrub typhus is widely endemic in Asia. Man's behaviour and climatic changes greatly influenced the occurrence of the disease. Increasing prevalences of scrub typhus have been reported from some Asian countries and may coincide with the widespread use of beta-lactam antibiotics or to improve diagnostic facilities and/or more urbanisation into rural areas. Many cases acquired in Asia surfaced in Europe and America. The disease probably is overlooked among paediatric patients. Most patients with scrub typhus present with acute fever of unknown origin (acute FUO). Eschars are rare among Southeast Asian patients. Complications usually develop after the first week of illness. The complications include pneumonitis, meningoencephalitis, renal failure and jaundice. Improved serologic and molecular diagnostic tests are now available. Although drug-resistant strain of *Orientia tsutsugamushi* has been reported, the infection usually responds to simple but unpopular drugs such as doxycycline or chloramphenicol.

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Introduction

Scrub typhus is an acute febrile illness caused by a rickettsia *Orientia tsutsugamushi* (formerly called *Rickettsia tsutsugamushi*).¹ Description of scrub typhus was written in Chinese medical literature as early as AD 313.² The disease still prevails in the Western Pacific and many parts of Asia. Its boundary, forming a triangle, extends from Japan and far eastern Russia in the north to northern Australia in the south and to Pakistan and Afghanistan in the west.² Rodents survey also suggests the presence of this disease as far as Iran.³ At the present time, there is no convincing evidence for the occurrence in Africa although a Japanese visitor with proven disease may have been infected while in Congo.⁴

Transmission

Man acquires the rickettsiae from bites of chiggers (mite larvae). *Leptotrombidium deliense* is the most important vector species in Southeast Asia and southern China, while *L. akamushi*, *L. scutellare* and *L. pallidum* are the main vectors in Japan and Korea.⁵⁻⁸ Formerly, it was thought that rodents are the reservoirs of the rickettsiae. However, uninfected chiggers rarely acquire the rickettsiae while feeding on an infected rodent^{5,9} and if they do, transmission to other mammals is unlikely since chiggers usually do not reattach themselves to a second host. They feed on mammalian tissue-fluid only once in their lifetime.⁷ In addition, chiggers that acquire the rickettsiae in this way cannot pass the rickettsiae to their

offsprings.^{9,10} Only in the already infected female adult mite that carry the rickettsiae in their ovary, that such vertical transmission can occur.^{9,10} Thus, it is now believed that the chiggers with its efficient transovarian transmission are the major reservoirs of the rickettsiae and also act as vectors and rodents, like man, acquire the rickettsiae from the chiggers.^{5,7,9,10} Infection in rodents are usually mild or asymptomatic.¹¹

Epidemiological Highlights of Scrub Typhus

Infection by *R. tsutsugamushi* probably is one of the most common infections in indigenous populations of Asia. From serological survey in Malaysia, there are as many as 200 000 infections annually.¹² Seroprevalence rates vary from 2% in India,¹³ 10% in eastern Nepal,¹⁴ 11.9% in Indonesia,¹⁵ 1% to 16% in the Philippines,¹⁶ 2.8% to 11.2% in Korea,¹⁷ 20% in the Pescadores Islands of Taiwan to as high as 69% in some Thai villages.^{19,20} In Malaysia, the serological prevalence rates varied from 6% to 69% with an estimated overall prevalence of antibodies in 3% of the general population.²¹ A comprehensive study of 1629 hospitalised patients with febrile illnesses in rural Malaysia revealed that scrub typhus accounted for 19.3% of these fevers.²² A similar nationwide seroprevalence rates for scrub typhus among patients with acute febrile illnesses in Korea ranged from 1.8% to 19.3%¹⁷ and were even more prevalent than haemorrhagic fever with renal syndrome.²³ The disease was also a major cause of acute fevers in US soldiers

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during the Vietnam War.²⁴ A recent one-year nationwide study of acute fevers of unknown origin (acute FUO) in Thailand showed that 9.6% of these fevers were caused by scrub typhus (Leelarasmee A et al, unpublished data). This constitutes a significant public health problem for Thailand where 200 000 to 300 000 cases of acute FUO were reported to the Ministry of Public Health each year.²⁵

Most of endemic *O. tsutsugamushi* infections in the Asian populations are acquired through agricultural exposure such as in oil palm and rubber plantations in Malaysia² or in rice-fields in Thailand (Linthicum KJ et al, unpublished data). In Thailand, the prevalence of scrub typhus peaks during the rainy season, correlating with such activities and the presence of chigger populations which are more abundant during that time.²⁵⁻²⁷ Thus, man's behaviour and climatic changes which affect the chiggers and rodents ecology influenced the occurrence of the disease.^{2,7,28} It is interesting that increasing incidence of scrub typhus is being reported from Thailand²⁵ and Korea.²⁹ In addition, new and unsuspected focus of scrub typhus had been discovered in the suburb of greater Metropolitan Bangkok.³⁰ It is unclear whether these are due to increasing awareness, widespread availability of specific serodiagnostic tests or are related to increasing urbanisation into rural areas previously endemic for scrub typhus. A similar increase in the incidence of scrub typhus in Japan during 1975 to 1984⁹ might be related to the widespread use of beta-lactam antibiotics³¹ which, inherently, do not have any activity against the rickettsiae.³²

In addition to occupational activities, scrub typhus is also associated with recreational or travel activities such as camping, rafting, or trekking in the woods or mountainous areas. A new geographic focus of scrub typhus has recently been identified in a remote rain forest region in the Northern Territory of Australia after infection was diagnosed in tourists who had visited the area.³³ In the era of international air travel and the increasing popularity of "eco-tourism", cases of scrub typhus acquired in Asia have been increasingly reported in Europe³⁴⁻³⁷ and America^{38,39} (Table I). Delay in diagnosis despite typical clinical signs and the common practice of prescribing beta-lactam antibiotics as empiric therapy resulted in fatal or near fatal multiorgan complications or permanent disability in some of these patients.^{31,33,39} Thus, awareness of scrub typhus in febrile travellers returning from Asia is vital since prompt treatment with doxycycline or chloramphenicol may be life-saving even in a desperately-ill patient.⁴⁰ This is important in countries where physicians may be unfamiliar with the disease and where specific tests may not be available.

Scrub typhus has also been recognised as an infectious disease of military importance since World War II.⁴¹ This was confirmed during the 1950s campaign in Malaysia⁴²

TABLE I: "EXPORTED" SCRUB TYPHUS FROM ASIA

Case	Nationality	Acquired from	Complications
1	Canadian	India or Nepal	Hepatitis ³⁸
2	American	Thailand	Multiorgan failure ³⁹
3	American	India	Not stated ³⁸
4	Italian	Burma or Thailand	Not stated ³⁴
5	French	Thailand	Pericarditis, pneumonitis ³⁵
6	German	Thailand	Pericarditis, pleural effusion ³⁶
7	German	Malaysia	None ³⁶
8	German	Papua New Guinea	None ³⁶
9	Swiss	"Asia"	Not stated ³⁷

and during the Vietnam War.^{24,43} War-time scrub typhus often involves mass exposure of non-immune humans into the territory of *O. tsutsugamushi*. The occurrence of almost 18 000 cases among allied troops and more than 30 000 similarly afflicted Japanese soldiers in the Pacific Theatre during World War II⁴¹ dramatically demonstrated how important scrub typhus was to the military operations. During that war, with a 1% to 35% case fatality rate, scrub typhus was second only to malaria as a cause of medical casualties⁴¹ and because there was no specific treatment at that time, it was feared by the soldiers even more than malaria was.⁹ After the war, interest in scrub typhus waned. However, serosurveys and reports of outbreak of scrub typhus in soldiers performing military duties during peace time period in Thailand,⁴⁴ Malaysia⁴⁵ and Taiwan,⁴⁶ showed that scrub typhus is still a potential threat to military personnel in Southeast Asia. For example, one-fifth (20.8%) of the 185 Thai soldiers involved in a training exercise in secondary forest and lalang grass areas in central Thailand were hospitalised with classical scrub typhus.⁴⁴ A similar incident occurred in Taiwan⁴⁶ and 0.4% to 1.8% of British and New Zealand soldiers seroconverted during a six-week training exercise in Johor, Malaysia.⁴⁵ A recent serostudy in Thailand also demonstrated that field exercises simulating combat conditions significantly expose soldiers to infection by *O. tsutsugamushi*.⁴⁷

Another important but often-overlooked aspect of scrub typhus is their occurrence among children. In fact, as many as one-fourth⁵ to half⁶ of scrub typhus cases are children. A careful study in an endemic area of Japan has indicated that mite attacks on children are not uncommon.⁵ A serological survey in a rural Thai village has shown a 52% prevalence of antibody against *O. tsutsugamushi* among children below ten years of age.¹⁹ Infection in endemic area occurs very early in life^{5,19} but only approximately 10% are symptomatic.⁵ However, clinical manifestation of scrub typhus in Southeast Asian children often lacks the classical textbook descriptions and may be easily misdiagnosed unless specific diagnostic test is done. Eschar is rare and most children, like adults, present themselves with only fever and non-

specific signs (acute FUO). Our own study has indicated that scrub typhus accounted for at least 6% of these acute FUOs among children in southern Thailand.⁴⁸ Availability of specific diagnostic tests will enable physicians to recognise more of these paediatric scrub typhus cases.

Clinical Manifestations

Human infections with *O. tsutsugamushi* may or may not be symptomatic depending on the strains of the rickettsia, immune status and other host factors. Studies in some hyperendemic areas revealed that as high as 69% of normal healthy inhabitants had antibody against *O. tsutsugamushi*¹⁹ and abortive or mildly symptomatic infection was 10 times more common than overt cases.⁵ On the other extreme, exposure of non-immune persons may result in symptomatic disease in a significant percentage. A dramatic example occurred in Burma during World War II where 18% of a single British battalion became ill with scrub typhus during only a 2-month sojourn and, at that time, 5% of the battalion had died of it.⁴¹

For the symptomatic, incubation period is 6 to 21 days. The illness begins with fever, headache, and non-specific symptoms such as nausea, vomiting and myalgia. Some patients may complain of having frequent cough or transient loose stool. History of chigger bites are infrequently obtained because most patients are unaware of the bites.⁴⁹ The chiggers are very tiny (smaller than 1 mm in size) and their bites are usually painless and may be felt, at most, like a splinter prick. Because the chiggers usually attach themselves on the host for only 1 to 3 days and then fall off, they are absent from the patient's body when he seeks medical care. However, in some patients, the site of the bite may develop into an eschar or crusted black sore (about 1 cm in diameter) which is a cardinal sign of scrub typhus. The eschar usually is painless; the patient is often unaware of it and may have been there as early as 5 days before the onset of fever. The lesion is usually single but may be multiple.^{5,50} Since the chigger usually climbs up the host body (negative geotaxis) and prefers dark (negative phototaxis) and warm and moist area for attachment, the lesion is usually found in the perineum, in the axilla or in the belt area. Only one-third of them is on the sun-exposed extremities.⁵⁰ The eschar, although common among Caucasians, Japanese, Taiwanese and Korean patients with scrub typhus,^{2,5,23,43,50} is uncommon in Southeast Asian patients in Southeast Asia. In 1940, Lewthwaite and Savor⁵¹ observed that the proportion of patients who had an eschar versus those without the lesion was 10:1 among Europeans compared with 1:40 among native population of Malaysia. The rarity of eschar in Southeast Asians may be explained in various ways: 1) the difficulty in identifying the lesion on dark-skinned patients, 2) detection of an eschar requires a careful

search, especially in the axilla and perineum, 3) in these moist intertriginous areas, the lesion may not have a black crust characteristic of an eschar⁵⁰ and consequently, the lesion is often missed, 4) it has been shown in partially immune experimental animals that, unlike the primary exposure, intracutaneous reinoculation of the rickettsia did not result in an eschar formation.⁵¹ This situation is possible in Southeast Asia where multiple exposures to almost 30 different antigenic strains of *O. tsutsugamushi* are common.⁵²

During the first week of illness, fever persists and mild hepatomegaly may be detected. Although splenomegaly is common in Caucasians, it is uncommon in Asian patients. A maculopapular rash appears between the third and eighth day of fever and spreads peripherally from the trunk to the extremities, sparing the palms and soles. It rarely (<5%) becomes purpuric and in Caucasians, usually lasts 4 to 5 days. The skin rash in dark-skinned Asians is evanescent and is less prevalent (3% to 30%).

If left untreated, the disease has a prolonged course ranging from 5 to 36 days but usually is between 2 to 3 weeks⁵⁰ (scrub typhus was once called "twenty-day" fever in Japan⁵). Complications may develop during the second week of illness, usually among the elderly and non-immune patients.^{50,53,54} Pneumonitis, meningo-encephalitis and jaundice are the major complications.^{50,53,54} Acute renal failure is also not uncommon, especially in patients with glucose 6 phosphate dehydrogenase (G6PD) deficient⁵³⁻⁵⁵ Myocarditis, as evidenced on electrocardiogram⁵⁶ and by autopsy findings,⁵⁷ is common in protracted and fatal cases. However, the significance of myocarditis as a contributory factor to circulatory failure and death in scrub typhus is unknown.⁵⁶⁻⁵⁸

Pneumonitis is the most important complication and interstitial lung involvement is an almost universal histologic findings in those who died.^{57,59,60} The pulmonary pathology is indistinguishable from that of Q fever, mycoplasma and viral pneumonia.^{59,60} Not infrequently, the patient is diagnosed as having mycoplasma pneumonia.⁵³ Tachypnoea with minimal signs in chest auscultation is sometimes observed in pregnant patients and, particularly, in children who usually present with the triads of fever, tachypnoea and hepatosplenomegaly.⁴⁸ Arterial oxygen desaturation may be observed out of proportion to chest X-ray changes which may reveal just interstitial or minimal bronchopneumonia.⁵⁰ However, frank pneumonia and adult respiratory distress syndrome (ARDS) can occur and are the leading causes of death in scrub typhus.^{50,53}

Central nervous system (CNS) involvement is another major complication of scrub typhus, occurring in about 10% of patients with this infection.⁵⁴ This complication

ranges from aseptic meningitis to frank meningoencephalitis. In fact, the name "typhus" itself, is derived from the Greek word, "typhos", which means "stupor". This signifies the prominent involvement of the CNS by the disease. A recent prospective study of 117 children with aseptic meningitis and/or encephalitis syndromes in southern Thailand revealed that, next to Japanese encephalitis virus infection, scrub typhus was the second most common cause, accounting for 11% of these syndromes.⁶¹ Recognition of this presentation of scrub typhus is important because it is one of the "treatable" forms of viral-like meningoencephalitis.⁵⁴

It is noteworthy that, because of the vasculotropic nature of *O. tsutsugamushi* and the vasculitis it produces, simultaneous multi-organ (lungs, CNS and kidneys) complications are not unusual in the severe form.^{39,50,53,54,57} In addition, liver involvement with jaundice and abnormal liver function tests, sometimes in the "hepatitis" range, may be seen.⁶² The prevalence of jaundice in hospitalised patients with scrub typhus in some part of Thailand⁶³ and Taiwan⁶² is remarkably high (11% to 17%) compared to the figure of 1% reported among American patients during the Vietnam War.⁴³ These patients are not uncommonly misdiagnosed as viral hepatitis or leptospirosis.⁶²

Differential Diagnosis

For clinicians, scrub typhus is easy to diagnose if the patient presents with fever and an eschar because of the narrow differential diagnoses of this lesion which include scrub typhus, Thai tick typhus and anthrax. However, most Southeast Asian patients with scrub typhus do not have an eschar and present just only with "acute FUO", the syndrome of which includes scrub and murine typhus, leptospirosis, dengue and chikungunya infections. In Thailand, scrub typhus is commonly misdiagnosed as typhoid fever.⁴⁸ This is not surprising because the word typhoid means "resembles typhus" and scrub typhus itself was once called "pseudo-typhoid" in Indonesia.⁶⁴ However, a careful interrogation with regards to age of the patient, the season of occurrence, the duration of fever, the occupational and the work area together with careful physical examination, often will enable a physician to make the best guess and direct the empirical therapy for this syndrome.

Diagnosis

O. tsutsugamushi cannot be cultivated on artificial bacterial media. It needs mice or chicken embryo inoculation and/or cell culture systems for isolation. Because these techniques are hazardous, complex, and time-consuming, the definitive diagnosis of scrub typhus relies mainly on serological methods. The first serological reaction used was the Weil-Felix OX-K agglutination test which depended upon cross-reactivity between *Pro-*

teus mirabilis and *O. tsutsugamushi*. Although the test is quite specific at the frequently quoted titre of 1:320, it is grossly insensitive with an overall sensitivity of 33% to 44%.^{65,66} This may be due to the relatively late appearance of the Weil-Felix antibodies,⁵⁰ the suppression of antibodies production by prior antibiotic treatment⁶⁷ and the absence of OX-K antibodies in re-infection type of scrub typhus,^{51,68} which is common in hyperendemic areas of Asia.⁶⁹ The standard reference test for scrub typhus is either the indirect fluorescent antibody (IFA) or the indirect immunoperoxidase (IIP) test using yolk sac-propagated or cell culture-derived *O. tsutsugamushi* antigens.^{66,70} The latter test is a modification of the IFA assay in which fluorochrome is replaced by peroxidase, thus, enabling the test slide to be read with ordinary light microscope. Although, the World Health Organization (WHO) has recommended it as the test of choice for serodiagnosis of scrub typhus,⁷¹ the IIP test is not commercially available. Recently, a commercial dot-blot enzyme-linked immunosorbent assay (dot-ELISA) test kit for scrub typhus has been developed⁷² and found to be sensitive and specific.^{65,72} The test is a solid phase immunoassay using *O. tsutsugamushi* antigens absorbed on a nitrocellulose paper. After successive inoculation with the patient's serum and enzyme-conjugated anti-antibody, the addition of a precipitable, chromogenic substrate causes the formation of a coloured dot on the paper which can be read with the naked eye. The assay is simple and does not require a microscope and the result is available within one hour of testing which may be suitable for use in rural hospitals.⁶⁵

Another major development for serodiagnosis of scrub typhus is the production of recombinant polypeptide antigens which can substitute for antigens prepared from potentially hazardous living rickettsiae through the yolk sac or cell culture methods. The genes encoding the 56 kDa polypeptides which are immunodominant antigens on the surface of *O. tsutsugamushi*, have been cloned and expressed in *Escherichia coli*.^{73,74} These recombinant 56 kDa antigens have been purified and successfully applied as a passive haemagglutination (PHA)⁷⁵ and ELISA.⁷⁶

More sophisticated molecular diagnostic polymerase chain reaction (PCR) tests have also been developed for detecting *O. tsutsugamushi* DNA in blood⁷⁷⁻⁸¹ and in tissues.⁷⁷ Some tests are strain-specific⁸² and may be useful for epidemiological investigation. All these tests have been shown to be specific and can detect *O. tsutsugamushi* DNA as early as day 2 of fever,^{79,81} even before the appearance of specific antibody in the blood.^{79,81} This may be an advantage over serological method if patients present themselves very early in the course of their illness. However, in Thailand, where patients usually seek medical help relatively late, we found that the sensitivity of the PCR assay was comparable to that of

the IFA (unpublished data). The PCR test, however, may replace the hazardous and cumbersome mouse isolation method since both tests showed identical sensitivity in a study from northern Thailand.⁸³

Prognosis and Treatment

Figures from the pre-antibiotic era during World War II showed that case fatality rates among untreated scrub typhus ranged from 1% to 35%.² Severity of the disease is dependent upon the virulence of the infecting strain, age and immune status of the patient. Variations in virulence of different strains of *O. tsutsugamushi* are well documented both in animals⁸⁴⁻⁸⁶ and in human.^{5,87} In addition, genetic variation of the host also determines the severity of the infection.^{88,89} It is interesting, however, that a study from northern Thailand reported that severity of scrub typhus was not enhanced by co-infection with human immunodeficiency virus (HIV), an agent-causing profound immunosuppression.⁹⁰

The rickettsiae *O. tsutsugamushi* is resistant to aminoglycosides, penicillins and other beta-lactam antibiotics.³² Sulfonamide drugs may potentiate the severity of rickettsial infection and thus should be avoided.⁹¹ In 1949, chloramphenicol was first shown to be effective in scrub typhus by shortening the duration of fever and reduced mortality from 5% to 0%.⁴⁰ Later, tetracycline, in a non-randomised clinical trial, was found to eliminate fever of scrub typhus slightly more rapidly than chloramphenicol.⁹² A single-dose (200 mg) or a 3-day course of doxycycline was shown to be as effective as a seven-day course of tetracycline.^{93,94} However, a 6% to 9% relapse rate may occur if treatment was initiated early (before day 5) in the course of illness.⁹⁵ The relapse, however, usually responds to another single dose or another course of doxycycline. Generally, the responses in the above-mentioned clinical trials of chloramphenicol or tetracycline group of drugs are rapid with 79% to 97% of patients becoming afebrile within 48 hours of treatment.⁹²⁻⁹⁵ However, it is noteworthy that, except in one trial⁹⁴ the subjects of these studies are generally young^{92,93,95} and many are soldiers.^{92,95} The severity of scrub typhus in these patients are either mild^{92,94} or not mentioned.^{93,95} The response in severely ill patient, especially in those who are older and have multiple organ dysfunction is usually slower. It is prudent, however, not to use single-dose or short course treatment in this type of patients but rather to continue the drug until fever has subsided for at least 3 to 5 days. The patient who receives doxycycline or minocycline should also be instructed to take the medication in the upright position and with sufficient water to prevent medication-induced esophagitis.⁹⁶

Besides chloramphenicol and tetracyclines, there are limited data regarding alternative therapy in scrub typhus. Ciprofloxacin was successfully used to treat a

patient in Nepal⁹⁷ despite its poor *in-vitro* activity against *O. tsutsugamushi*.³² Macrolide antibiotics such as erythromycin and azithromycin are active *in-vitro*^{32,98} and three patients in Japan were successfully treated with clarithromycin.⁹⁹ However, more studies are needed to justify the general use of these drugs for treatment of scrub typhus.

Recently, strains of *O. tsutsugamushi* resistant to doxycycline have been isolated from patients with scrub typhus in northern Thailand.⁸⁷ The geographic extent and the optimal treatment for these antibiotic-resistant strains are still unknown.

Prevention

The immunity against scrub typhus is not absolute. Specific immunity to reinfection with homologous strain of *O. tsutsugamushi* persists for at least 15 months but resistance to reinfection with heterologous strains waned after only 2 months.¹⁰⁰ An effective vaccine for human has not been developed.² The main obstacles are that there are too many (almost 30) different strains of *O. tsutsugamushi* that exist in Asia⁵² and failure to identify epitope that confers general group-specific immunity.

Chemoprophylaxis with chloramphenicol is not practical and incurs the risk of bone marrow toxicity.² A weekly (200 mg) dose of doxycycline given three days before exposure and continued for six weeks after exposure, has been shown to protect (89% efficacy) against experimental infection with *O. tsutsugamushi*.¹⁰¹ Mass chemoprophylaxis with doxycycline once weekly in soldiers has also been shown to prevent scrub typhus.¹⁰²

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