

## Management of scrub typhus

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### Introduction

Scrub typhus is an acute febrile illness of variable severity that is caused by *Orientia* [formerly *Rickettsia*] *tsutsugamushi*. It is transmitted to humans by an arthropod vector of the trombiculidae family. *Tsutsu* means small and dangerous and *mushi* means insect or mite<sup>(1)</sup>. Humans are accidental host in this zoonotic disease. Scrub typhus was described from Japan in 1899.

The term scrub is used because of the type of vegetation (terrain between wood and clearing) that harbours the vector, however the name is not entirely correct because certain endemic areas can be sandy, semi arid and mountain desert. The public health importance of this disease is underestimated because of difficulties with clinical diagnosis and lack of laboratory methods in many geographical areas.

### Epidemiology

Scrub typhus is endemic to the part of world known as the “*tsutsugamushi triangle*” which extends from northern Japan and far eastern Russia in the north to northern Australia in the South and to Pakistan in the West. (Figure 1)

In 1999 WHO stated that “scrub typhus” is probably one of the most under diagnosed and under reported febrile illness<sup>(2)</sup>. One million case of scrub typhus occur each year with an estimated fatality of 10% unless treated appropriately and can result in more deaths than dengue<sup>(3)</sup>

The burden of disease is more in rural Asia, with studies showing scrub typhus causing up to 20% of febrile hospital admissions<sup>(4)</sup>. Scrub typhus is prevalent in many parts of India but exact data is not available. It is under diagnosed in India due to its non specific clinical presentation, limited awareness and low index of suspicion among clinicians, and lack of diagnostic facilities. The rickettsial diseases once thought to have been eradicated from India are re emerging and has been reported from various parts of India<sup>(5-8)</sup>.

The recent isolation of *O. chuto* in Dubai<sup>(9)</sup> and detection of another divergent *Orientia* transmitted to a patient in Chile<sup>(10)</sup> indicate that geographic distribution and genetic diversity of the genus should be investigated.

### Etiopathogenesis

Scrub typhus is caused by *Orientia tsutsugamushi* (a gram negative obligate intracellular bacterium). This pathogen does not have a membrane and hence grows freely in cytoplasm of infected cell. It has a different genetic composition and cell wall structure than that of other rickettsiae. It includes six major heterogeneous serotypes Karp, Kato, Kawasaki, Boryon, Gilliam, and Kuroki<sup>(11)</sup>. Many new strains and genotypes are being identified.

The disease in humans results from the introduction of *O. tsutsugamushi* through the skin by the bite of larval stage of chigger (trombiculid) mite. Humans get infected accidentally when the occupational or recreational behavior brings them in contact with mite infected habitat.

*Orientia* inoculated in chigger's saliva infects mainly dendritic cells and macrophage in the dermis underlying the eschar at the site of inoculation. The early development of lymphadenopathy in the regional drainage of the eschar suggests lymphogenous spread<sup>(12)</sup>. Subsequently hematogenous disseminated infection involves predominantly endothelial cells, and to a lesser degree, macrophages, both of which release cell specific adhesion molecules, suggesting that these cells play key role in systemic inflammation.

After internalization in macrophages it escapes from phagosomes by unknown mechanism and proliferates in cytoplasm. Compared with other rickettsiae, *O. tsutsugamushi* is more frequently found in circulating mononuclear cells during naturally acquired infection in humans. The mechanism of cellular invasion is not known, but binding of phagocytes may involve interaction between cell surface heparin sulphate, proteoglycans and bacterial lectins. Invasion of endothelial cells leads to disseminated vasculitis and perivascular inflammatory cells in various organs which result in significant vascular leakage and end organ injury<sup>(1)</sup>.

The exact mechanism of cell injury by *O. tsutsugamushi* and its pathophysiological effects are still unresolved issues<sup>(13)</sup>. The factors which allow for persistent *Orientia* infection are others areas not understood<sup>(14)</sup>.

### Clinical features

The clinical manifestations of scrub typhus range from mild to fatal illness. The incubation period is 5 to 21 days after the initial bite. The early manifestations are an eschar, representing localized cutaneous necrosis at the site of mite feeding (which is not always present) and regional lymphadenopathy followed by fever, headache, myalgia, generalised lymphadenopathy, cough, gastrointestinal symptoms, rash, transient hearing loss and conjunctival injection<sup>(15)</sup>. The eschar is seen at the site of chigger bite and is often found in groin, axilla, genitalia and neck<sup>(16)</sup>. (Figure 2). It is seen in about half of the cases of primary infection whereas in secondary infection it occurs only in minority of cases<sup>(17)</sup>. The eschar is usually seen in Caucasians and east Asian patients but is seen less frequently in south Asian patients, especially those who are dark skinned, hence a thorough examination is required. A maculopapular rash may be seen after one week on trunk and may spread to extremities. The other clinical sign may be hepatosplenomegaly. The immunity to homologous strain is good but short lived for heterogenous strain, thus new episode of disease occur from different serotypes of *O. tsutsugamushi* in the area.

The clinical manifestations of scrub typhus in pregnant women are similar to those of non pregnant adult. There are few reports of vertical transmission from transplacental infection and transmission in perinatal blood borne infection during labor. Still birth and abortion are mainly observed in mothers whose illness is not controlled and treatment is delayed<sup>(18)</sup>.

Complications are usually seen in patients after first week of presentation. Patient with delay in presentation and treatment are more likely to develop complication and high mortality. Complications manifest as interstitial pneumonia, ARDS, renal failure, meningoencephalitis, myocarditis, gastrointestinal bleed, jaundice, septic shock and multiorgan dysfunction syndrome<sup>(11)</sup>. The reasons for wide variation of eschar, rash, increased severity of illness, ARDS and CNS complications are not clear. Similarly the bacterial virulence and host determined mechanisms that affect the severity are not clear<sup>(13)</sup>.



**FIGURE 1: Photograph showing “Tsutsugamushi’ triangle.**



**Figure 2 : Showing eschar**

## Diagnosis

Differentiating scrub typhus from other form of rickettsial infection, dengue, leptospirosis, typhoid fever, infectious mononucleosis, malaria and meningococcal infection may be difficult in early stages. The most common symptom and signs are similar. The clinical features of organ dysfunction may vary depending on severity of illness. The exact diagnosis is made by serology and classification of organism by smear or culture depending on the disease.

The presence of eschar and rash supports the diagnosis but is variably present. However eschar and rash are also seen in other rickettsial infection which needs to be differentiated.(Table1) Diagnosis therefore depends on clinical suspicion based on geographical history, prompting clinician for appropriate laboratory investigation. Diagnosis and surveillance of this disease can be challenging, particularly in the absence of advanced laboratory diagnostic techniques. Scrub typhus may pose a serious public health problem when patients are not diagnosed or misdiagnosed. Dual infection of scrub typhus with leptospirosis or dengue although reported are uncommon.

Serological tests are main tools for diagnosis. Indirect immunofluorescence assay, latex agglutination, indirect haemagglutination, indirect immunoperoxidase assay [IIP], and enzyme linked immunosorbent assay are various serological tests available. The serological tests are available in selected centers only.

Weil-Felix test is widely used due to lack of availability of specific tests. It is cheap, easy to perform and results are available overnight. It detects cross reacting antibodies to *Proteus mirabilis* OXK. Agglutinating antibodies IgM are detectable after 5 to 10 days following onset of symptoms. Diagnostic Weil-Felix agglutination shows greater than four times rise in titer to proteus OXK in paired serum. Single titer of >1:320 is also diagnostic. Fifty percent of patients have positive test in second week. However this test lacks sensitivity and specificity<sup>(19)</sup>.

Indirect immunofluorescence assay (IFA) uses fluorescent antihuman antibody to detect specific antibody from patients serum bound to a smear of scrub typhus antigen and is currently the gold standard<sup>(20)</sup>. The test is more sensitive and faster but costly and antigenic variation is common. Indirect immunoperoxidase is a modification of standard IFA method. It eliminates the expense of fluorescent microscope by substituting peroxidase for fluorescein. The results are comparable to IFA.

Qualitative enzyme linked immunosorbent assay (ELISA ) for detection of IgM antibodies (In Bios International, Inc)<sup>(21)</sup> is now currently available and is used for diagnosis in India by few centres. This test makes use of an *O.tsutsugamushi* derived recombinant antigen. Due to lack of seroprevalence studies in India antibody cut off titers put forward by the manufactures in western countries may be a limiting factor. This requires validation. Further this qualitative ELISA kit has not been validated for HIV/*O.tsutsugamushi* coinfecting population.

All currently available serological tests for scrub typhus have limitations. The clinicians should be aware of this despite their widespread use. Although there is agreement that an equal to or more than fourfold increase in antibodies titer between two consecutive samples

is diagnostic, such a diagnosis is retrospective and cannot guide initial treatment. Diagnosis based on a single titre requires cut off antibody titer. Cut off ranges are often quoted, without establishing titres in healthy local population, necessary to distinguish background immunity from acute infection<sup>(19)</sup>. These values are used for all patients, irrespective of whether or not they come from a scrub typhus endemic environment. Therefore for tests based on single titre local robust population data should be determined for appropriate cut off for diagnosis.

Real time and nested PCR can detect diverse antigenic types of *O. tsutsugamushi*. Nested PCR targeting gene encoding for the 56-kDa antigen of *O. tsutsugamushi* has shown high sensitivity and specificity in recent study<sup>(22)</sup>. The most appropriate specimen to be tested whether blood, buffy coat, or eschar remains unclear. PCR based assays will detect disease till bacteremia persists, before antibody response occurs in early phase of disease and overcome the problem of high background titer in endemic areas before antibody response starts appearing. However the high resource cost and training required for these PCR assays make them impractical in many areas of scrub endemicity. Because of the rural epidemiology of scrub typhus, delayed presentation, high cost, non availability and expertise, it seems unlikely that PCR based assays would replace serology completely. Combined antigen or DNA and antibody detection testing could provide strong diagnostic advantage.

Isolation of organism requires BSL3 reference laboratory. Median time to positivity is more and it provides retrospective diagnosis. Current methods of isolation are not appropriate for routine diagnosis. Although immunohistochemical staining of biopsy from eschar and skin lesions are sensitive and specific for diagnosis of scrub typhus, but these lesions are variably present.

Recently a panel of scrub typhus infection criteria was proposed for diagnostic accuracy evaluation, in which one or more of the following criteria have to be fulfilled 1] cell culture isolate, 2] a single admission immunoglobulin M [IgM] titre > 1:12,800 using the gold standard IFA, 3] a fourfold increase in IgM IFA titre and or 4] detection of *O. tsutsugamushi* DNA in at least two of three different PCR assays<sup>(23)</sup>.

The other investigations like haematology, biochemistry, radiology and endoscopy although not specific for scrub typhus may show abnormalities.

**Blood Counts**—normal WBC, or leukocytosis may be seen. Thrombocytopenia may occur.

**Liver Function Tests**—Elevated transaminases may be seen in 75-95% patients. Hyperbilirubinemia and raised alkaline phosphatase may occur. Hypoalbuminemia occurs in about 50% patients.

**Renal Function Tests**—Raised creatinine and abnormal urine sediments may be seen.

**Chest X ray**—Abnormalities are seen in 50—72%. The abnormalities seen are bilateral or unilateral reticulonodular opacities, minimal pleural effusion, hilar adenopathy, nonhomogenous opacities, unilateral or bilateral.

CT Scan Chest--- Axial interstitial thickening, centrilobular nodules, interlobular septal thickening, ground glass opacities, mediastinal and hilar lymphadenopathy and pleural effusion may be seen .

CT Scan Abdomen---may show splenomegaly, periportal areas of low attenuation, inhomogeneous enhancement of liver, gall bladder wall thickening, lymphadenopathy, ascites and splenic infarct.

CT Scan Brain-Multiple low attenuation lesions at corpus callosum and periventricular white matter.

MRI Brain -Small ring enhancing lesions with multiple areas of hyper-intensities at periventricular and deep white matter, cerebral haemorrhages and infarcts.

Ultrasound Abdomen---may show splenomegaly, ascites, lymphadenopathy, thickening of gall bladder.

UGI Endoscopy---may show superficial mucosal haemorrhage, multiple erosion, ulcers without preferred site and unusual vascular bleeding.

CSF--May show lymphocytic pleocytosis and increased protein and normal sugar. Uncommonly CSF sugar may be low. ADA is usually less than 10IU.

EKG---may show nonspecific ST and T wave changes, arrhythmias and heart block.

Table 1: Synopsis of Epidemiological and Clinical features of Typhus and Spotted Fever Group Rickettsioses

SPOTTED FEVER GROUP	ORGANISM	GEOGRAPHIC AREA	ARTHIPODS	VERTEBRATES	RASH DISTRIBUTION	ESCHAR
Rocky mountain spotted fever	R.rickettsii	Western hemisphere	ticks	Wild rodents, dogs	Extremities to trunk	no
Boutonneuse	R.conorii	Africa, Mediterranean, India	ticks	Wild rodents ,dogs	Trunk extremities, face	yes
Queensland tick typhus	R.australis	Australia	ticks	Wild rodents, marsupials	Trunk extremities, face	yes
North Asian tick typhus	R.sibirica	Siberia, Mongolia	ticks	Wild rodents	Trunk, extremities, face	yes
Rickettsialpox	R.akari	United States, former Soviet Union, Korea, Africa	Mite	Mouse	Vesicular, trunk, extremities, face	yes
TYPHUS GROUP						
Epidemic typhus	R.prowazekii	Highland areas of South America, Africa, Asia & United States	Body louse	Humans, flying squirrel	Trunk to extremities	No
Brill-Zinsser disease	R.prowazekii	Worldwide based on immigration	none	Humans(recurrence years after primary attack)	Trunk to extremities	no
Murine typhus	R.typhi	Worldwide in pockets	Fleas	Small rodents	Trunk to extremities	no

## Treatment

At present the data from clinical trials comparing the effects of different antimicrobial drugs are insufficient to determine the optimal drug and duration of treatment. The treatment of scrub typhus must be initiated early in course of disease, based on presumptive diagnosis to reduce mortality and morbidity. Meticulous supportive management is necessary to prevent progression to DIC and septic shock.

Rapid defervescence after antibiotic is so characteristic that in past it was used as a diagnostic test for *O. tsutsugamushi* <sup>(26)</sup>. Doxycycline 200 mg daily or tetracycline 500 mg 6 hrly is treatment of choice. The duration of treatment is 7- 14 days. Treatment of less than a week is initially curative but may be followed by relapse. Chloramphenicol 500mg qid is an alternative. Telithromycin has also been shown to be effective in the treatment of scrub typhus<sup>(24)</sup>. These antibiotics are bacteriostatic and they merely slow the multiplication of the organism while patient develop protective immune response. Resistance to tetracycline has been noted in some areas and rifampicin should be used in areas where there is poor response to doxycycline alone<sup>(25)</sup>.

Azithromycin has been shown to be effective in the treatment of scrub typhus in pregnancy and has shown favorable outcome in pregnancy. The exact duration and dose is not clear although 500 mg has been used as single dose or for three to five days<sup>(18)</sup>. Early and effective treatment has been advocated in pregnancy to avoid poor outcome. Doxycycline and chloramphenicol are not indicated in pregnancy being class D and class C drugs respectively.

Cochrane review on treatment of scrub typhus has concluded that there is insufficient evidence from trials to compare the efficacy of broad spectrum antibiotics. Rifampicin should be used in areas where doxycycline resistance is suspected, and more research is needed to evaluate the duration of treatment, alternative antibiotics in areas of resistance and regimens for severe disease.<sup>(26)</sup>

A recent meta analysis of drug treatment of scrub typhus in Asia <sup>(27)</sup> has evaluated the efficacy of treatment with different antibiotic regimens. Doxycycline was found to act more quickly and clearance of symptoms time was shorter, compared to regimens using azithromycin and chloramphenicol, but more adverse effects were seen with doxycycline. Doxycycline and azithromycin were equally effective. The symptom clearance time was more rapid with rifampicin than doxycycline, however it is only recommended where doxycycline resistance is suspected.

## Prevention

Case detection, public education, rodent control and habitat modification are aimed at controlling the infection of scrub typhus in human population. The disease can be prevented by avoiding the mite infected areas. People entering an exposed area should wear footwear such as boots with socks and clothes impregnated with miticidal chemicals and application of mite repellants to exposed skin surface. Lathering with soap in a hot bath or shower will



remove both attached and unattached chiggers. Clearing of vegetation and chemical treatment of soil may help to break cycle of transmission from chiggers and humans to other chiggers.

Control of the rodent and marsupial reservoirs may also assist to prevent chigger coming into areas where humans are living or working. Involvement of community based organisation in prevention and control of scrub typhus is important.

Chemoprophylaxis is recommended under special circumstances in certain areas where disease is endemic. Oral chloramphenicol or tetracycline given once every five days for 35 days, or weekly dose of doxycycline 200mg have both been shown to be effective regimens. There is no effective vaccine for scrub typhus due to enormous antigenic variation in *O. tsutsugamushi* strains and immunity to one strain does not confer immunity to another.

## Conclusion

Scrub typhus is important cause of acute undifferentiated febrile illness in India. It is under diagnosed, due to non specific clinical presentation, limited awareness, low index of clinical suspicion, and lack of diagnostic facilities. It should always be considered as cause of febrile illness in patient with history of exposure in geographical area and particular season. Early diagnosis and treatment helps to reduce mortality and complications associated with disease.

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