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A REVIEW ON SCRUB TYPHUS

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Abstract:
Scrub typhus is a zoonosis caused by the pathogen Orientia tsutsugamushi (O. tsutsugamushi). The disease has significant prevalence in eastern and Southeast Asia. Several methods are effectual for diagnosis of scrub typhus that includes ELISA, IFA, ICT, Weil–Felix, PCR. Moreover, issues related to diagnostic assays, treatment, and preventive measures are also enumerated and described. Scrub typhus is endemic to a geographically distinct region, the so-called tsutsugamushi triangle, which includes Japan, Taiwan, China, and South Korea. It also occurs in Nepal, Northern Pakistan, Papua New Guinea, and the Australian states of Queensland and Northern New South Wales. In India, the disease had occurred among troops during World War II in Assam and West Bengal, and in the 1965 Indo-Pak war.

Keywords: *Scrub typhus, Orientia tsutsugamushi, diagnosis, treatment, symptoms, epidemiology, pathogenesis.*

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INTRODUCTION:

Scrub typhus is a serious public health problem in the Asia-Pacific area (3). Scrub typhus is a vector borne zoonosis/ febrile illness caused by the O. tsutsugamushi (1). Scrub typhus, also known as tsutsugamushi disease, is caused by the arthropod-borne gram-negative obligately intracellular bacillus Orientia tsutsugamushi. Scrub typhus, transmitted by Leptotrombidium mites, is responsible for a potentially fatal tropical infection(3). Scrub typhus has re-emerged as one of the most common life-threatening rickettsial infections accounting for a million cases annually(10). However, it is a largely overlooked public health problem in India. This disease is known to occur in diverse ecological settings in India with large numbers of cases being reported from Tamil Nadu, Andhra Pradesh, Karnataka, and Kerala in the South, Himachal Pradesh, Uttaranchal, Jammu, and Kashmir in the North, Meghalaya, Assam, and Nagaland in the North-East, West Bengal and Bihar in the East, and Maharashtra and Rajasthan in the West(4). Globally, its endemic in South Asia, Southeast Asia, East Asia, the Pacific Islands, and Northern Australia (the "tsutsugamushi triangle"), with reports of similar infections from Africa, the Middle East, and South America(5). The term scrub means the type of vegetation (Terrain between woods and clearings) that harbors the vector and typhus means "fever with stupor" or smoke in Greek. "Tsutsugamushi" means small and dangerous, and "mushi" means insect or mite(10). Humans are accidental hosts. A billion people are at risk, and nearly a million cases are reported every year. The mortality of scrub typhus in untreated patients range from 0% to 30% and tends to vary with age and region of infection(9).

Transmission of scrub typhus disease occurs throughout the year in the tropical areas, whereas in the temperate zones, transmission is seasonal. However, outbreaks have been reported during the cooler season in southern parts of India. The vectors of scrub typhus are L. deliense and Leptotrombidium aka mushi which are present in most countries of the South-East Asian region(10). The infection is transmitted through the larval mites or "chiggers." A number of small rodents, particularly wild rats of subgenus Rattus, are the natural hosts for scrub typhus(10).

History_ Scrub typhus, first described in Japan in 1899, caused by Orientia tsutsugamushi (formerly Rickettsia)(10). Scrub typhus was recognized as a typhus-like fever in India in 1917(3). During the Second World War, scrub typhus emerged out to be the most dreaded disease among the soldiers of the Far East(10). It was a major cause of fever among military personnel along the Assam-India-Myanmar (formerly Burma) border during World War II, and the 1965 Indo-Pak war. However, scrub typhus is still an under-diagnosed disease in India(3). Other Clinicians and scientists in Indonesia, Philippines, Taiwan, Australia, Vietnam, Malaysia and India Reported on diseases most likely to have been scrub typhus in early 1900s. In India, scrub typhus broke out in an epidemic form in Assam and West Bengal during the Second World War. Gradually, the disease became prevalent in many parts of India. Scrub typhus is endemic and re-emerging in eastern and southern parts of Asia. There were reports of scrub typhus outbreaks in Himachal Pradesh, Sikkim, and Darjeeling (West Bengal) during 2003–2004 and 2007(10).

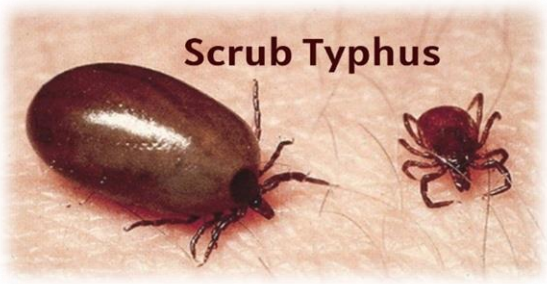
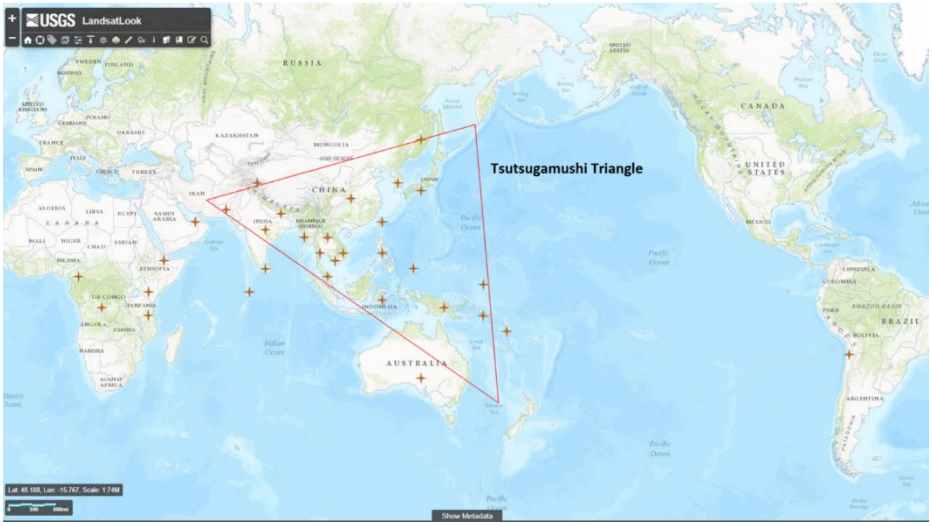


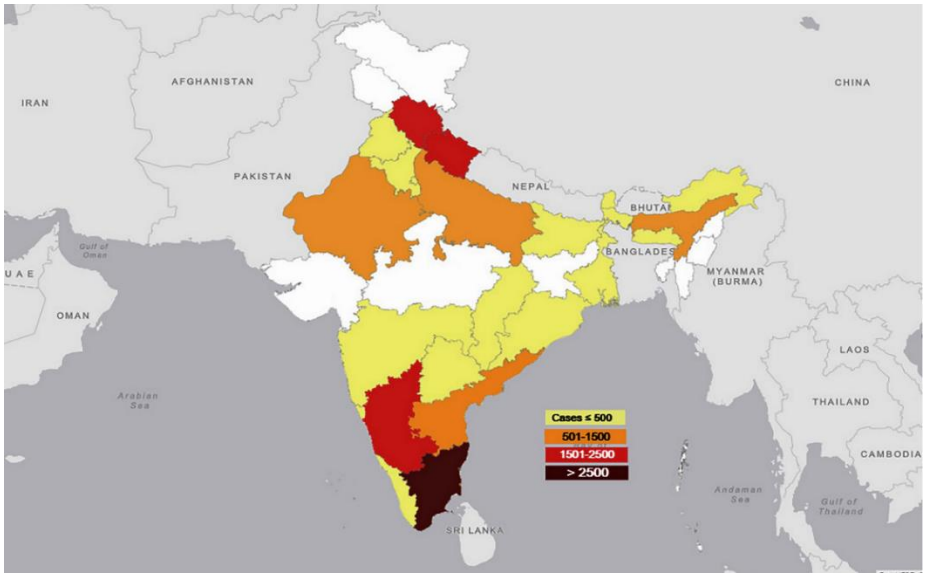
Fig 1. Mites

EPIDEMIOLOGY:

The traditional endemic area of scrub typhus is known as the "tsutsugamushi triangle". It is a region covering more than 7 million km^2, from the Russian Far East in the north, to Pakistan in the west, Australia in the south, and the Japan in the east(5). It also occurs in Nepal, Northern Pakistan, Papua New Guinea, and the Australian states of Queensland and Northern New South Wales. In India, the disease had occurred among troops during World War II in Assam and West Bengal, and in the 1965 Indo-Pak war(3). There was a resurgence of the disease in 1990 in a unit of an army deployed at the Pakistan border of India. It is known to occur all over India, including Southern India and Northern India(7). The disease is largely prevalent to south-eastern and eastern parts of Asia; India, Pakistan, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and other islands in the region. Several factors like the presence of scrub vegetation, woodpiles, and the cattle around the residences have been considered as major factors for the acquisition of scrub typhus(7). Better understanding of the epidemiology of scrub typhus will help efforts to prevent and control the disease(4).



Worldwide map of countries with reported scrub typhus cases. The majority of scrub typhus cases occur in the "tsutsugamushi triangle" in the Asia-Pacific area. Countries with human cases are labelled with a star. [Modified from https://landsatlook.usgs.gov/viewer.html](3)



Mapping the regional distribution of scrub typhus in India. Number of scrub typhus cases less than or equal to 500 is represented as yellow, 501–1500 cases is represented as orange, 1501–2500 cases is represented as red and more than 2500 cases is represented as maroon.(4)

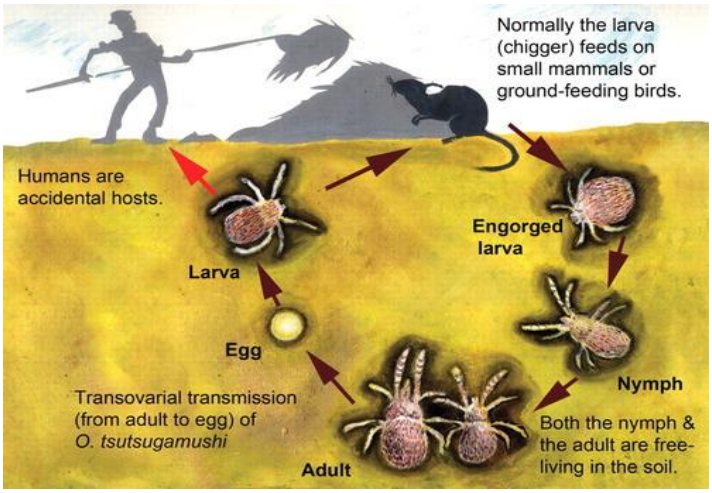


Fig 2. Transmission & life cycle

Fig 3. An Eschar

Fig 4. Rashes (Neck)

PATHOGENESIS:

Scrub typhus in humans is caused by the larval bite of mite that harvests the bacteria (O. tsutsugamushi) in its salivary gland(5). It invades endothelial cells to produce disseminated vasculitic and perivascular inflammatory lesions, which results in significant vascular leakage and ensuing end-organ injury of various organs such as lungs, heart, and kidney(10). Orientia tsutsugamushi aims a wide range of cells in host with cell types including dendritic cells and activated monocyte cells for completing its replicative cycles and acts as a vehicle for spreading orientia in the lymphatic system(5). It induces the formation of several cytokines such as granulocyte-colony-stimulating factor (CSF), macrophage-CSF, interferon γ, and tumor necrosis factor-α. The cytotoxic T-lymphocytes and the NK T-cells play an important role in destroying the infected host cells. The organism downregulates the host defence mechanism by downregulating the GP-96 on the macro- phages and the endothelial cells, which plays a prime role in antigen presentation, functioning of the dendritic cells, antibody production, and cross-priming of the immune system(10).

T-lymphocytes are involved in cell-mediated immunity against Orientia, producing interferon γ by mononuclear cells in the peripheral blood(10).

SYMPTOMS/ CLINICAL FEATURES:

The incubation period of O. tsutsugamushi in humans is around 10-12 d (can vary between 6-21 days) the onset of disease is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms. The

clinical manifestations vary in severity from a mild febrile illness to a severe potentially fatal disease with multi organ dysfunction syndrome (MODS)(1). The severity of the symptoms varies widely, depending on the susceptibility of the host, the virulence of the bacterial strain, or both. The first sign of scrub typhus disease in patients is a vesicular lesion at the site of mite feeding, which later becomes an eschar or an ulcer with regional lymphadenopathy. An eschar typically presenting with black necrotic center and an erythematous border is seen at the site of the chigger bite and is often found in the groin, axilla, genitalia, and neck. The prevalence of eschar in patients infected with scrub typhus ranges from 7% to 80%. It is the single most important clue for diagnosis and is a pathognomonic sign. Typically, eschar is formed at the time when symptoms are manifested(10). The eschar starts as a small papule that enlarges and subsequently undergoes central necrosis to turn black(1).

At the end of the 1st week, there appears a maculopapular rash starting from the trunk and spreading to the limbs.
At the end of the 2nd week, systemic symptoms ensue mostly involving the central nervous system, cardiovascular system, renal, respiratory, and gastrointestinal systems. Seriou's complication in the form of myocarditis, pneumonia, meningoencephalitis, acute renal failure, and gastrointestinal bleeding may occur. The chances of developing acute respiratory distress syndrome are more in patients of scrub typhus who have higher white blood cell (WBC) counts, lower haematocrit, higher bilirubin levels, and delayed treatment with antibiotics. Deafness, dysarthria, and dysphagia may occur, but are usually transient, although deafness can last for several months(10). Due to the wide variation in the clinical manifestations, the diagnosis of scrub typhus is often missed or made late(1).

Indirect Methods of Diagnosis:

- ICT (Immunofluorescence assay)
- Weil-felix test
- ELISA (Enzyme linked immunosorbent assay)
- IFA (Immunofluorescence assay)

Direct Methods of Diagnosis_

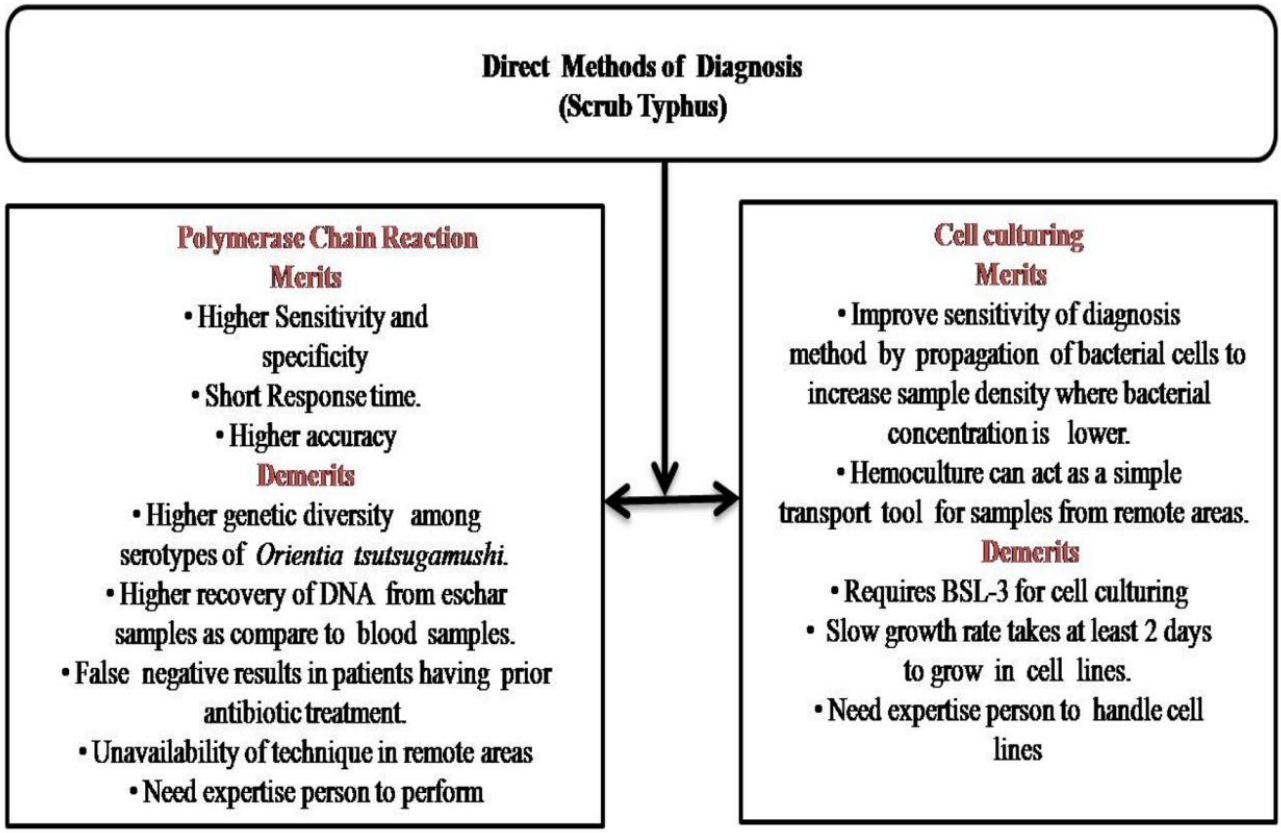
- PCR (Polymerase chain reaction)
- Cell Culturing

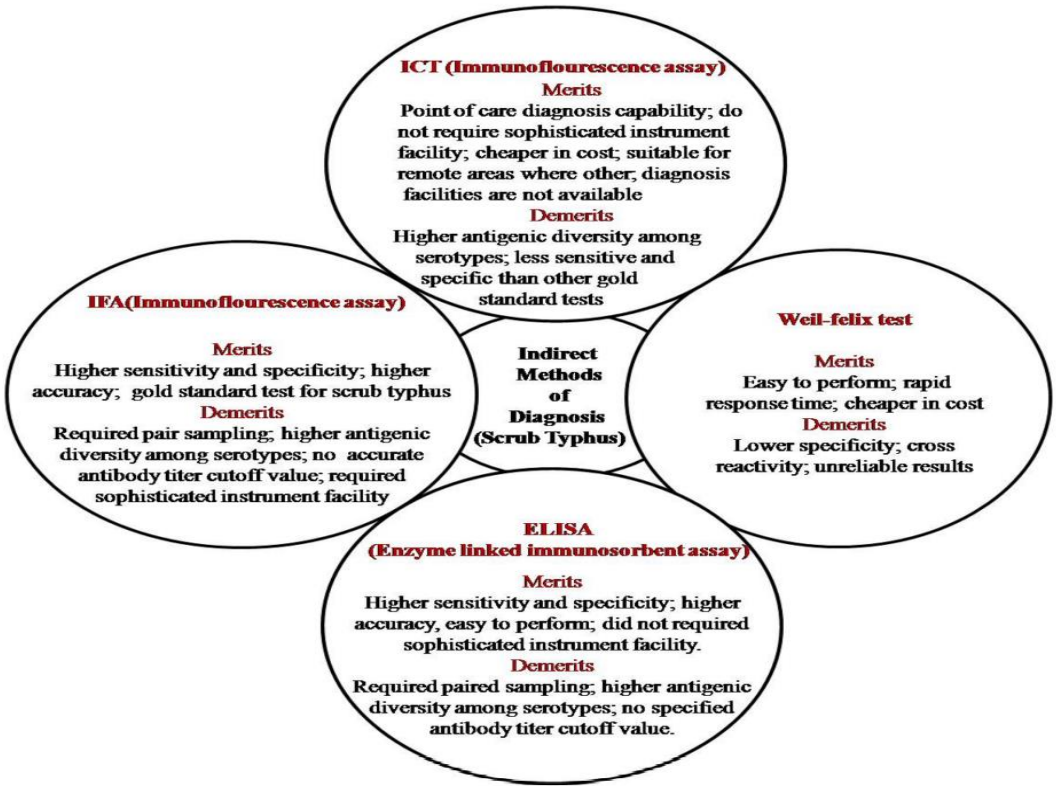
DIAGNOSIS:

Early diagnosis is important because there is usually an excellent response to treatment and timely anti-microbial therapy may help prevent complications(7). In developing countries with limited diagnostic facilities, it is prudent to recommend empiric therapy in patients with undifferentiated febrile illness having evidence of multiple system involvement(7). Laboratory methods for diagnosing rickettsial diseases including scrub typhus are mainly based on serological tests and molecular assays. Cross-reactivity of Orientia with other rickettsia is rare. Presence of eschar in patients aids in the clinical diagnosis of scrub typhus with higher specificity (98.9%), but lack its applicability due to a wide variation in its distribution (7.0–97%) among patients(5). In the past, the clinical diagnosis of scrub typhus was dependent on detecting eschar and rash and on the history of outdoor activity. Immunohistochemical staining of skin biopsy specimens, particularly that of eschars, is sensitive and specific, and this technique can be reliable for confirming the diagnosis of scrub typhus(7). Indirect methods of diagnosis include serological assays such as Weil–Felix test, immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA) and rapid diagnostic assays(5).

Other serological tests include the indirect immunoperoxidase assay (IIP), Weil-Felix test (W-F), enzyme-linked immunoassays (ELISAs), and various commercially available immunochromatographic tests (ICT). The W-F agglutination test has been commercially available for many years. This test using the Proteus mirabilis OXK strain lacks both specificity and sensitivity, especially the latter, for routine diagnosis. Studies have shown that the sensitivity is only 50% during the second week of illness(10).

Other than this Polymerase Chain Reaction (PCR) and Sample Culturing is also conducted for diagnosis. The molecular method to diagnose scrub typhus is detecting the bacteria with PCR assays. PCRs usually target the genes of the outer membrane proteins of 56 kDa, 47 kDa, and groEL genes. This molecular biologic method can detect Orientia DNA in blood even during the persistent phase of the infection, when no obvious clinical symptoms are observed(7).


Direct Methods of Diagnosis
(Scrub Typhus)
Polymerase Chain Reaction
Merits
• Higher Sensitivity and specificity
• Short Response time.
• Higher accuracy
Demerits
• Higher genetic diversity among serotypes of Orientia tsutsugamushi.
• Higher recovery of DNA from eschar samples as compare to blood samples.
• False negative results in patients having prior antibiotic treatment.
• Unavailability of technique in remote areas
• Need expertise person to perform
Cell culturing
Merits
• Improve sensitivity of diagnosis method by propagation of bacterial cells to increase sample density where bacterial concentration is lower.
• Hemoculture can act as a simple transport tool for samples from remote areas.
Demerits
• Requires BSL-3 for cell culturing
• Slow growth rate takes at least 2 days to grow in cell lines.
• Need expertise person to handle cell lines


ICT (Immunoflourescence assay)
Merits
Point of care diagnosis capability; do not require sophisticated instrument facility; cheaper in cost; suitable for remote areas where other; diagnosis facilities are not available
Demerits
Higher antigenic diversity among serotypes; less sensitive and specific than other gold standard tests
IFA(Immunoflourescence assay)
Merits
Higher sensitivity and specificity; higher accuracy; gold standard test for scrub typhus
Demerits
Required pair sampling; higher antigenic diversity among serotypes; no accurate antibody titer cutoff value; required sophisticated instrument facility
Indirect Methods of Diagnosis (Scrub Typhus)
Weil-felix test
Merits
Easy to perform; rapid response time; cheaper in cost
Demerits
Lower specificity; cross reactivity; unreliable results
ELISA
(Enzyme linked immunosorbent assay)
Merits
Higher sensitivity and specificity; higher accuracy, easy to perform; did not required sophisticated instrument facility.
Demerits
Required paired sampling; higher antigenic diversity among serotypes; no specified antibody titer cutoff value.

Images(5)

Laboratory analysis & clinical profiles_

Symptoms	Patients No. (%)
Fever less than 1 week	1 (7.1)
Fever of 1 to 2 weeks	7 (50.0)
Fever of 2 to 3 weeks	4 (28.6)
Fever more than 3 weeks	2 (14.3)
Headache	6 (42.9)
Nausea / vomiting	5 (35.7)
Weakness	5 (35.7)
Gastrointestinal symptoms	4 (28.6)
Shortness of breath	4 (28.6)
Urinary symptoms	3 (21.4)

Characteristic	Number of patients (%)
Sex	
Male	10 (71.4)
Female	4 (28.6)
Age groups	
Below 10 years	2 (14.3)
10-19 years	1 (7.1)
20-29 years	4 (28.6)
30-39 years	2 (14.3)
40-49 years	3 (21.4)
50 years and above	2 (14.3)

Socio-demographic profiles_

Laboratory findings	Patients No. (%)
Leucocytosis (>11000/cmm)	5 (35.7)
Thrombocytopaenia (<150000/cmm)	1 (7.1)
Raised ESR (>40 mm in1st hr)	12 (85.7)
Raised AST (>50 IU/l)	14 (100)
Raised ALT (>50 IU/l)	13 (92.9)
Decreased serum albumin (<3 g/dl)	6 (42.9)
Increased serum bilirubin (>2 mg/dl)	3 (21.4)
Serum creatinine (>1.5 mg/dl)	1 (7.1)
Urinary albumin (1+ or more)	5 (35.7)
Presence of RBC in urine	1 (7.1)
Presence of pus cells in urine (>4/hpf)	4 (28.6)
Serum IgM for scrub typhus	14 (100)

Characteristic	Number of patients (%)
Residence	
Rural	11 (78.6)
Urban	3 (21.4)
Religion	
Hinduism	9 (64.3)
Muslim	5 (35.7)
Occupation	
Agricultural and other workers	5 (35.7)
Housewife and unemployed	4 (28.6)
Having a business	3 (21.4)
Student	2 (14.3)

CHALLENGES & RISK FACTORS:

The abundance of the chigger of the trombiculid mite, which is the vector for scrub typhus, determines the chance of acquiring scrub typhus, which in turn determines the prevalence of scrub typhus in a given region. Chiggers are abundant in locales with high relative humidity (60%–85%), low temperature (20°C–30°C), low incidence of sunlight, and a dense substrate-vegetative canopy. They are found in great numbers in forest clearings, riverbanks, and grassy regions. Humans acquire scrub typhus on exposure to infected larvae (chiggers). In south India, scrub-typhus cases occur mostly in the cooler months (August–January), while in Southeast Asia scrub-typhus cases are highest in July-November. Occupational risk is higher in farmers (aged 50–69 years), females, and those working in vegetable fields, harvesting in autumn, and rural highlands(6).

Atypical clinical features and absence of eschars may result in delayed diagnosis, complications, or death. Data on scrub typhus(6)_

In pregnancy are scanty. Among the 82 cases reviewed from the literature till 2014 by McGready et al, 2.5% were associated with maternal mortality. Miscarriage occurred in 17%, and poor neonatal outcomes (stillbirth, preterm labor, and low birth weight) were documented in 42%. There have been reports of vertical transmission from transplacental

infection and transmission in perinatal blood-borne infection during labor, causing neonatal scrub typhus in mothers with acute febrile illness during pregnancy. It may be associated with increased foetal loss, preterm delivery, and small-for-gestational-age infants(6).

In children, scrub typhus may be mild or severe. Most patients present with fever and regional/generalized lymphadenopathy. A single painless eschar, maculopapular rash hepatomegaly, splenomegaly, and gastrointestinal symptoms (abdominal pain, vomiting, and diarrhoea) may be present. Case fatality rate in untreated patients may be as high as 30%, although deaths in children are infrequent(2).

MANAGEMENT & TREATMENT:

Early treatment results in better outcomes, i.e., shortening the disease course and reducing fatalities. Oral treatment is effective for mild cases, but the parenteral route is often necessary for severely ill patients(3). As a gram-negative bacterium, Orientia infection can be effectively treated with the appropriate antibiotics(3). Empirical therapy with doxycycline is to be encouraged in regions or locales where scrub typhus is endemic or re-emerging. This will lead to a reduction in complications, with a corresponding decrease in morbidity and mortality(6). Doxycycline is useful as an empirical treatment, because of its high cost-effectiveness and wide spectrum of activity, and is considered safe in children(6). Prophylaxis for scrub typhus with doxycycline has shown promising results when started before exposure to infection. Tetracycline or chloramphenicol remains the main stay of therapy in patients in whom scrub typhus is suspected. The recommended treatment regimen is as follows(10)_

DRUG	DOSE & DURATION	ROUTE
Doxycycline	Maximum 200 mg/day for 7–15 days	PO or intravenous
Tetracycline	25–50 mg/day divided every 6 hr	PO
Chloramphenicol	50–100 mg/day divided every 6 hr	IV

If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 µg/mL. Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3–4 days to avoid relapse. Chloramphenicol is best avoided during pregnancy and reduced doses should be given in hepatic impairment(10).

Clinicians should monitor the progress of patients in the light of reports of drug resistance(10).

Rifampicin is seen to be more effective than doxycycline in areas where scrub typhus appears to respond poorly to standard anti-rickettsia drugs. At present there is insufficient evidence from trials of comparative effects of different broad-spectrum antibiotics in scrub typhus(7). Further research is required to evaluate antibiotics usage in scrub typhus. Trials would be more easily interpreted if reliable diagnostic tests were available. Such research could examine whether a single dose of doxycycline is as effective as a three to five days course of treatment(7).

Clearly more research on scrub typhus in the Indian context is required, particularly regarding diagnosis and treatment of this condition(7).

During Pregnancy_ World Health Organization (WHO) recommends that pregnant women or children can use azithromycin or chloramphenicol(3). Macrolide antibiotics, such as azithromycin, are safe in pregnancy, but doxycycline, which is cheaper, can also be used if the former is not available. The aim of therapy is to save both mother and child, and the benefits of therapy with doxycycline outweigh the risks. doxycycline treatment should be used in children and pregnant women for treating scrub typhus, as the infection associated risks are too large(7).

PREVENTIVE MEASURES:

- Wearing protective clothing- Persons should wear long-sleeved shirts, long pants, boots and hats to reduce exposure. Persons should tuck in shirts and pants, and wear closed shoes(10).
- Following personal prophylaxis against the mite vector by impregnating clothes with miticidal chemicals (permethrin and benzyl benzoate) and the application of mite repellents (diethyltoluamide) to exposed skin surfaces.
- Avoid exposure conditions. Chiggers reside in grass, woodlands, and other vegetated areas. Persons are encouraged to avoid the outdoors or

take preventive actions. Do not sit or lie on bare ground or grass; use a sheet or a cover on the ground instead(10).

- Mites from sites should be eliminated by application of chlorinated hydrocarbons (lindane, dieldrin, and chlordane) to the ground and vegetation in camps and other populated zones in endemic areas.
- Insect and spatial repellents. Persons should apply insect repellent containing dibutyl phthalate, benzyl benzoate, diethyl toluamide or other chemicals to their skin and permethrin to their clothing, to prevent chigger bites(3).
- Insecticides and habitat modification. Farmers and field workers can improve sanitation, clear vegetation, control rodents, use insecticides and chemically treat the soil. These steps can impede the propagation of chiggers and the transmission cycle.
- WHO recommends prophylactic treatment under special circumstances in the endemic areas(10).
- Those people working in infested areas should consider impregnating clothing with permethrin. When sitting around or camping, groundcovers and tents with closed floors should be used. Lathering with soap in a hot bath or shower will remove both attached and unattached chiggers.
- Rodent control and habitat modification are helpful for disease control and prevention. Different rodent control strategies can be employed, from trapping, to poisoning, and use of natural predators.
- To make these measures work, public education on case recognition and personal protection is the priority. WHO recommends that advocacy, awareness, and educational activities should be targeted at school children, teachers, and women in endemic areas(3).
- **VACCINE_** There is no vaccine available for any rickettsial infections including scrub typhus. Initial efforts of preparation of vaccines with killed O. tsutsugamushi were disappointing, be- cause results of animal studies did not prove to be equally successful in human studies. This has been also been attributed to the diversity of the strains, lack of tolerability of live vaccines in volunteers due to absence of natural attenuated strains of the organism, and lack of achieving long-term heterologous protection even with irradiated strains(10).
- The different types of vaccines which were attempted to develop immunoprophylaxis were killed vaccines, live vaccines, live vaccines with antibiotics, attenuated vaccines, and subunit vaccines. The killed vaccines were developed as formalin-treated strains such as Karp and Gilliam strains(10).

CONCLUSION:

Scrub typhus is an important infectious disease with a potentially fatal outcome. Apart from the classical presentation as an acute febrile illness, many other unusual clinical manifestations are reported(4). Compared to present diagnosis methods like Weil–Felix, ICT, ELISA, and IFA, the molecular assays are very rapid, specific, and sensitive and can be used as a rapid point of care system. The present review summarizes the advancement in the detection of Orientia tsutsugamushi in different biological samples so far. Treatment with doxycycline; Tetracycline; Chloramphenicol; Rifampicin; in these patients can help to reduce mortality(10).

Experience with the disease in pregnancy is limited to a few case reports but vertical transmission has been demonstrated(3). Delay in initiating treatment owing to this may lead to untoward fatality. More widespread ac- cess to medical care, close suspicion of the disease along with the increased use of affordable and ac- curate rapid tests, is mandatory to improve diagnosis and treatment of this condition which can be easily treated with antibiotics(7).

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