Scrub typhus: an underestimated endemic disease of Northwestern Himalayas, India

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Scrub typhus is a vector-borne rickettsial zoonotic disease, endemic to South Eastern and Far Eastern Asian countries and northern Australia. It is an acute febrile illness, associated with rash and often an eschar, a black crust-like skin lesion. *Orientia tsutsugamushi*, etiological agent of scrub typhus infects the endothelial cells causing vasculitis, multiple organ dysfunction, life threatening complications and mortalities. Scrub typhus is endemic in Himalayan/sub-Himalayan regions. This review summarizes the status of scrub typhus in mountainous states of India, i.e. Himachal Pradesh, Uttarakhand and Jammu and Kashmir, located in Northwestern Himalayas. Scrub typhus is a major cause of acute febrile illness, fever of unknown origin and febrile jaundice in this region. Disease has been reported both as mono-infection and co-infections with dengue, leptospirosis, malaria and hepatitis from these states. Pediatric scrub typhus cases with neurological complications are common in this region. Agricultural or farming activities are the primary risk factors for the occurrence of scrub typhus in both rural and urban population. Early presentation of the cases and timely diagnosis and treatment of patients is crucial to prevent life threatening complications and deaths. Scrub typhus mimics epidemiology and clinical course of commonly reported infectious diseases and requires differential diagnosis. Therefore, it is imperative to make health workers aware about its manifestations for early diagnosis and treatment and accurate prevalence estimations.

Keywords: Acute febrile illness, fever of unknown origin, Himachal Pradesh, meningitis, scrub typhus, Uttarakhand.

SCRUB typhus is a serious public health problem of Asia Pacific region affecting one million people each year[1]. The term 'scrub' is used because of the type of vegetation (terrain between woods and clearings) that harbours the vector involved in the transmission of the disease[2]. However, the name is not entirely correct as the disease has also been reported from sandy and semiarid areas[3]. Scrub typhus is among world's most under diagnosed/under-reported diseases[4]. It requires better understanding of its vectors, reservoirs, outbreaks, and pathogenesis of causative organism in endemic and non-endemic regions[4]. Scrub typhus is an acute febrile, arthropod borne infectious disease caused by *Orientia tsutsugamushi*. Mites act as both vectors and reservoirs of *O. tsutsugamushi*. At least 23 species of trombiculid mites belonging to genera, *Leptotrombidium*, *Guntheria*, *Ascoschoengastia*, *Eutrombicula*, *Odontacarus* and *Microtrombicula* were reported to harbour *O. tsutsugamushi*[5]. Mites remain infected throughout different stages (egg, larva, nymph and adult) of their life cycle[4].

Disease is transmitted to mammalian hosts including humans by the bite of larval stages of trombiculid mites, called as chiggers. *O. tsutsugamushi* is maintained in mites through sequential passage of chiggers from one life stage to the next stage(s) (transstadial transmission) and by infecting the ovarian germinal tissue (transovarial transmission)[4]. There are two major groups of vertebrate hosts involved in maintenance and dissemination of the chiggers. Maintenance hosts are small mammals such as rodents and shrews and ground-dwelling birds. Second group is of incidental hosts and plays a vital role in transporting chiggers to more distant areas and thereby setting up new foci of infection. This group comprises birds (migratory) and larger mammals including humans. Among vertebrates, only monkeys, gerbils, hamsters and humans suffer clinically with scrub typhus[5].

Rodents thriving in different types of habitats, such as *Rattus* species are often implicated in scrub typhus transmission. It is believed, scrub typhus distribution reflects the distribution of rodent hosts and mites[6]. Small terrestrial mammals and ground-dwelling birds are easily infested with chiggers than larger vertebrates. These hosts pick up chiggers from forage, burrows and nests[5].

Rodents in endemic areas can have 50% lifetime infection rates and are infected repeatedly with *O. tsutsugamushi* during their lifetime[7]. *O. tsutsugamushi* has been recovered from spleen, liver, kidney and lungs of the infected rodent hosts[5]. Birds play an important role in distribution of scrub typhus. Chiggers may be transported by birds in both local areas (ground-living birds) and over long distances (migrants). Ground-living birds have been reported to be heavily infested with chiggers of different species of mites. Domestic chicken from endemic areas, wild birds and house sparrows have been tested positive for *O. tsutsugamushi*[5].

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Scrub typhus is an occupational zoonosis and man is an accidental host[1]. The pathogen disseminates systemically from the site of inoculation, and infects the endothelial cells causing vascular damage, vasculitis and multiple organ dysfunction[4,8]. The disease is known as 'War disease' as outbreaks have been reported frequently among military personnel posted in endemic areas. In India, scrub typhus was reported among troops posted at Assam and Bengal during World War II and also during 1965 Indo-Pak war. Indian soldiers deployed at border with Pakistan had been reported to suffer from the disease[9]. Socioeconomic status and occupation are important risk factors for the occurrence of scrub typhus in human beings. In general, people from rural setting especially females involved in agricultural operations are at higher risk of acquiring the infection[10,11]. Earlier, scrub typhus was considered to be a disease of rural areas but outbreaks from the metropolitans have also been reported[12]. Globally, scrub typhus is endemic in a vast region which extends from Northern Japan and Far-Eastern Russia in the North, to Northern Australia in the South, and to Pakistan and Afghanistan in the West. This geographical territory is also called as the *tsutsugamushi triangle*[10]. However, the disease is no longer restricted to *tsutsugamushi triangle* and cases have been reported outside this geographical territory. In 2006, an individual case of scrub typhus was detected in Chiloé Island, Chile and *Orientia* species involved was closely related but not similar to *O. tsutsugamushi*[13]. In the same year, another case of scrub typhus was recorded in Dubai and etiological agent was identified as a new *Orientia* species, *O. chuto*[14]. Three cases of scrub typhus caused by *O. tsutsugamushi* were reported from Chiloé Island in 2016. This part of southern Chile, far away from 'tsutsugamushi triangle' is considered to be an endemic focus of the disease in South America[15].

Disease and clinical features

Approximately 6 to 21 days after being bitten by an infected vector, patients exhibit non-specific flu-like symptoms, fever, headache, myalgia, cough, generalized or regional lymphadenopathy, nausea, vomiting and abdominal pain[1,8]. In endemic regions, scrub typhus has been identified as one of the leading causes of fever of unknown origin (FUO) and acute febrile illness[16–21]. An eschar at the site of chigger bite is a classic clinical feature of scrub typhus. Presentation of eschar is highly variable in different regions of the world, ranging from 1% to 97% cases of the disease[1]. Eschar is produced as a part of immune response to the rickettsial antigens in the body[22]. It appears at front of the body in areas with thin, moist or wrinkled skin. Eschar usually single, develops below umbilicus, on lower extremities, anterior chest, axilla, genitalia, inguinal area, head and neck. Presence of an eschar is a valuable clinical clue in the diagnosis of scrub typhus; however its absence does not rule out the infection[1,23]. The occurrence of eschar is rare in Southeast Asian patients and indigenous people of endemic areas. In these regions, illness is less severe, often without rash or eschar[24,25]. Presentation of multiple eschars in an individual patient is rare and is reported only in 0.6–2.2% cases[26,27]. Eschar begins as a papule at the site of chigger feeding and then ulcerates and forms a black crust resembling a skin burn from a cigarette. Eschar if present develops prior to the onset of fever and other clinical symptoms[1].

In scrub typhus, initial flu-like symptoms are easily overlooked and delayed presentation of the cases result severe complications and mortalities[18,28]. Acute fever and headache are the most common presenting symptoms, are often associated with breathlessness, cough and myalgia[11,18,29]. Scrub typhus is classically described as acute febrile illness of short duration however; fever can last for more than seven days[11]. Complications due to scrub typhus appear from second week onwards after infection[8]. These include jaundice, acute renal failure, pneumonitis, acute respiratory distress syndrome (ARDS), myocarditis, septic shock, meningoencephalitis, pericarditis, disseminated intravascular coagulation, gastrointestinal (GI) bleeding and multiple organ failure. Majority of mortalities recorded in scrub typhus occur due to these complications[8,17]. Lungs are one of the main organs to be affected and interstitial pneumonia may occur in severe cases[1]. Approximately, 11% of scrub typhus patients develop ARDS with a mortality rate as high as 25% (ref. 30). Scrub typhus caused meningitis (aseptic or diffused) and/or encephalitis is a severe illness, causing patients to become agitated, delirious and seizures in some cases. Rarely, scrub typhus infection can cause psychiatric disturbances such as visual hallucinations[31]. Cranial nerve involvement is reported in approximately 25% cases of scrub typhus with or without meningitis[32]. Involvement of eighth cranial nerve causes acute hearing loss or hearing impairment[33,34]. Abducens (6th cranial nerve) nerve palsy, a rare complication to scrub typhus leads to sudden diplopia, esotropia and profound weakness of ocular muscles[35,36]. Haemorrhages and coagulation disorders occur among scrub typhus patients. GI bleeding is reported in severely ill patients with mucosal haemorrhages, multiple erosions and ulcers. Conjunctival hyperemia and haemorrhages can occur during the acute phase of the disease[1].

It is hypothesized that hyperactive immune response involved in eschar formation results in renal, respiratory, haematological/circulatory disorders and development of severe illness[22,37]. Hepatic and renal dysfunction occurring due to vasculitis, are common in scrub typhus. Liver injury can range from mild transaminitis to acute liver failure. In endemic areas, scrub typhus (followed by dengue, viral hepatitis, malaria and amoebic liver abscess) is an important infectious cause of acute liver failure[38]. Mild transaminitis is the most consistent laboratory finding in scrub typhus, being reported in as high as 90% of

Table 1. Major studies reporting occurrence of scrub typhus in Northwestern Himalayas

Reporting year	Cases reported	Diagnostic tests used	State	Reference
2004	113	Weil-Felix	Himachal Pradesh	55
2005	52	Weil-Felix	Himachal Pradesh	14
2006	21	MIF[1] assay, Weil-Felix, PCR[2]	Himachal Pradesh	15
2008	05 (children)	MIF assay, Weil-Felix	Himachal Pradesh	22
2014	77	IgM ELISA[3]	Uttarakhand	17
2014	66 (children)	IgM ELISA	Uttarakhand	20
2015	367	IgM ELISA	Uttarakhand	16
2016	330	IgM ELISA	Himachal Pradesh	26
2016	253	IgM ELISA	Himachal Pradesh	11
2016	170	IgM ELISA	Uttarakhand	38
2016	37	Weil-Felix, IgG ELISA, IgM ELISA	Kashmir valley	50
2016	61 (children)	IgM ELISA	Himachal Pradesh	64
2016	96 (children)	IgM ELISA	Uttarakhand	45
2016	105	IgM ELISA	Uttarakhand	37
2017	323	IgM ELISA	Himachal Pradesh	56
2017	61	IgM ELISA	Himachal Pradesh	34
2017	170	IgM ELISA	Himachal Pradesh	62
2018	168	IgG IFA[4], IgM IFA, Real Time PCR	Uttarakhand	66
2019	106	IgM ELISA	Himachal Pradesh	25
2019	92	IFA	Himachal Pradesh	48
2019	54	IgM ELISA	Uttarakhand	40

[1]Microimmunofluorescence; [2]Polymerase chain reaction; [3]Enzyme linked immunosorbent assay; [4]Immunofluorescence assay.

the cases[18,29,38–45]. Renal dysfunction occurs in 10–20% of scrub typhus cases[42]. Acute kidney injury can also be a secondary complication and may require renal replacement therapy[12]. Patients with fever presented with varying degree of renal failure, eschar and having a history of environmental exposure should be suspected for scrub typhus[11,46]. Thrombocytopenia is another important laboratory finding in scrub typhus patients[23,41,45]. Elevated transaminases, thrombocytopenia and leukocytosis, together can be an important diagnostic marker for scrub typhus infection[45].

Scrub typhus is a life threatening disease in children. In some regions, half of the total reported cases of scrub typhus are of paediatric origin[23]. Eschar is reported in up to two thirds (7–68%) of paediatric cases of scrub typhus[47]. Meningitis/meningoencephalitis is one of the most common complications of scrub typhus in paediatric patients[25,45,48]. Children presented with acute febrile illness, maculopapular rash, hepatosplenomegaly, lymphadenopathy, thrombocytopenia and features suggestive of capillary leak syndrome, must be suspected for scrub typhus[23].

Mortality due to scrub typhus varies between 7% and 30%, but can be more (up to 70%) if cases are presented late and diagnosis and treatment are delayed[1,11,49]. High in-hospital mortality in scrub typhus patients is significantly associated with clinical factors such as altered sensorium, low serum albumin, hepatic dysfunction, renal dysfunction, septic shock, multiple organ dysfunction, ARDS, duration of fever >7 days and day of receiving treatment >7 days at the time of presentation[50]. Laboratory findings such as leucocytosis, hyperbilirubinemia, high aspartate aminotransferase (AST) levels, hypoalbuminemia, high urea levels and high creatinine levels are indicators of severe disease involving organ failure. Failure of one or more organs is significantly associated with mortality in scrub typhus[51]. Among various complications observed in scrub typhus, renal failure and altered sensorium were reported to be significantly associated with risk of death in scrub typhus patients[11].

Scrub typhus in Northwestern Himalayan region

Scrub typhus is regarded as an under-diagnosed disease in India[52]. It occurs in mountainous states of Himachal Pradesh, Uttarakhand and Jammu and Kashmir, located in Himalayan/sub-Himalayan region (Table 1). This region is endemic for scrub typhus and majority of cases are recorded during monsoon and post-monsoon season (July to November). During this period, the region receives heavy rainfall and climate remains warm (15–30°C) and humid (humidity 65–85%), conditions conducive for vector multiplication and spread of scrub typhus[11,23,29]. Participation in agricultural or farming activities is an important risk factor for occurrence of scrub typhus in both rural and urban populations of the region[29]. Presence of bushes around the houses, rodents at home, open air defecation and travel to the forest were also reported as the risk factors associated with the occurrence of scrub typhus[41]. Females are at higher risk of acquiring the infection than males. Among women, incidence of the disease was significantly higher in those associated with outdoor agricultural and farming activities[11,29,43]. Many studies have identified scrub typhus as one of the leading

causes of FUO or acute febrile illness in this region[17–21,40,53,54]. Disease has been reported both as mono-infection and as co-infection(s) with dengue, leptospirosis and malaria and hepatitis[21,39,55]. This region has witnessed massive deforestation and clearing of forests due to growing human population and developmental works such as roads and hydroelectric projects. It is suggested that the deforestation-induced secondary growth of scrub vegetation may increase the densities of mites and rodents, a potential risk for the occurrence of scrub typhus[56].

Himachal Pradesh

Himachal Pradesh is well known for the endemicity of scrub typhus and its life threatening complications. First reported cases of scrub typhus in India in 1934, were from Himachal Pradesh[32]. An outbreak of the disease was reported from Sabathu and Simla hills in 1957 (ref. 57). Scrub typhus cases have been reported regularly from the state since early 2000 (refs 11, 16–18, 25, 29, 49, 58). In 2003, Shimla, Solan and Sirmour were reported as the worst affected districts of the state with scrub typhus[58]. *Leptotrombidium deliense* and *Gahrliepia* (schoengastilla) sp., vector species involved in transmission of the disease have been reported from Himachal Pradesh[58]. Scrub typhus case-fatality rate in the state is between 4% and 17.3% (refs 51, 58). Fever was the most common presenting complaint and eschar was present in 9.5–40.6% patients[12,18,29,59].

In Himachal Pradesh, the highest incidence of scrub typhus was recorded among age group of 18–29 years with a range of 18–78 years[11,29]. More than 2/3rd of the patients were below 50 years of age and a significantly higher incidence of the disease was recorded in farmers compared to other persons indirectly involved in agricultural activities. More than 70% of the patients in these studies were females. Apart from flu-like symptoms, other clinical signs noted at the time of admission were temperature >100°F, tachycardia, hypotension, congested eyes, tachypnea, pallor, icterus, eschar, lymphadenopathy and skin rashes. Eschars were present in less than 50% of the patients and lymphadenopathy was recorded in less than 20% of the patients. Some (3.3%) patients complained of decreased hearing/hearing loss at the time of presentation. Liver function abnormalities were the most common biochemical findings. ARDS was observed between 1.6% and 18.2% of patients[11,29]. On the analysis of system wise manifestations, abdominal pain involving GI tract/hepatobiliary system was the most common symptom followed by icterus and splenomegaly[29].

In Himachal Pradesh, many studies have reported scrub typhus with potentially life-threatening complications such as meningoencephalitis along with variable neurological manifestations (altered sensorium, cerebellitis and myelitis, nerve palsy, seizures and paraparesis with acute transverse myelitis and bilateral papilledema), septic shock, ARDS, hepatic dysfunction/failure, renal dysfunction/failure, acute kidney injury, GI bleeding, multiple organ failure, congestive heart failure, severe thrombocytopenia and elevated transaminases[11,29,38,51,59–62]. The disease has also been reported with other rare clinical presentations such as acute reversible hearing loss, acute abdomen, abducens nerve (sixth cranial nerve) palsy, diplopia, esotropia, visual hallucinations, ptosis and facial deviation[34,59,62–64]. Scrub typhus meningitis complicated with multiple cranial palsies and cerebellitis has also been reported[62]. Rana *et al.*[59] reported 11.5% confirmed cases of scrub typhus with neurological manifestations. Molecular analysis of spinal fluid showed that CNS invasion of *O. tsutsugamushi* is more common compared to actual nervous manifestations of the disease.

Patients with GI symptoms progressing to ARDS without pathognomic eschars and rashes have been diagnosed as scrub typhus[42]. Scrub typhus was the leading (60.6%) cause of the febrile jaundice in the state followed by hepatitis E (21.2%), leptospirosis (5.3%), malaria (4.7%), hepatitis A (4.1%), dengue (2.4%) and hepatitis B (1.8%)[65]. In a study conducted in the region of Shivalik and lower hills of Himachal Pradesh, scrub typhus was reported in 22.5% patients suffering with acute undifferentiated fever. Incidence of scrub typhus in these patients was higher compared to dengue (7.8%), leptospirosis (0.6%), chikungunya (0.6%) and vivax malaria (0.1%)[21]. Scrub typhus co-infections with dengue, leptospirosis and malaria have also been recorded in the state[21,55]. Scrub typhus have been identified as the leading etiology of the sepsis associated acute kidney injury in Himachal Pradesh[66]. Cases of paediatric scrub typhus have also been reported from the state and need to be differentiated from other febrile illnesses of children[25]. Sood *et al.*[67] reported 7.4% of scrub typhus cases with neurological involvement with meningoencephalitis and multiple organ dysfunction syndrome among children with acute febrile illness and fever of 5–21 days duration.

Uttarakhand

Scrub typhus was first reported in the Kumaon hills (now Uttarakhand) in 1938 (ref. 41). In recent years, many cases of scrub typhus were reported both from Kumaon and Garhwal regions of the Uttarakhand. In 2010, nine cases of scrub typhus were reported from Garhwal region of Uttarakhand with symptoms of fever, pain, vomiting, GI complaints and respiratory distress[3]. In retrospective studies conducted in tertiary health facilities of Uttarakhand, scrub typhus was detected in 6–14.42% of patients suffering from acute febrile illness[20,54,68]. Pathania *et al.*[43] reported a higher incidence of disease in housewives compared to students and farmers. After fever, headache and myalgia, the most common clinical manifestation was upper eyelid oedema followed by abdominal pain, cough, vomiting

and altered sensorium. An eschar was found in 12.96% of patients whereas 74.07% had elevated liver transaminases[43]. Scrub typhus case with multiple eschars, a rare clinical presentation along with other characteristic manifestations of the disease have been reported from the state[26].

Many studies reported on occurrence of paediatric scrub typhus in Uttarakhand[23,44]. In a prospective observational study, 66 (39 males and 27 females) children from the hilly Garhwal division of Uttarakhand and adjoining non-hilly districts of western Uttar Pradesh were diagnosed with scrub typhus[23]. These were presented with fever (>5 days) and flu-like symptoms, and suffered from hepatomegaly, splenomegaly, oedema, tender lymphadenopathy and hypotension. Only 20% of the patients had an eschar or a maculopapular rash[23]. In a prospective study in scrub typhus affected children, fever (100%) was the most common presenting clinical symptom followed by meningeal signs (66.6%), nausea and vomiting (56.3%) and seizures (55.5%). Altered sensorium (51.8%) was the most commonly observed nervous symptom[48].

Bhat *et al.*[47] reported eschar hidden in the umbilicus of a girl child presented with fever, vomiting and abdominal pain[47]. She was diagnosed with scrub typhus and had ascites, hepatosplenomegaly, anaemia, thrombocytopaenia and elevated hepatic transaminases. Scrub typhus mono-infection and co-infections with dengue, malaria and hepatitis A and E have been reported from Uttarakhand and adjoining districts of Uttar Pradesh. Higher mortalities were recorded among patients suffering with scrub typhus compared to other disease[40]. Patients suffering from scrub typhus mono-infection had a significantly longer mean duration of fever and higher white cell and platelet counts and alkaline phosphatase levels as compared to dengue, malaria and hepatitis A and E[40]. Bhargava *et al.*[41] reported scrub typhus incidence of 11.2% among patients suffering from acute febrile illness. A non-productive cough appearing a few days after the onset of fever and shortness of breath was the most common systemic symptom. On clinical examination, the most frequent abnormality was found to be hepatomegaly, followed by cervical and/or axillary adenopathy and conjunctival icterus. Presence of eschars was significantly associated with the ARDS. The most common laboratory findings observed were elevated transaminases and thrombocytopenia. ARDS and acute kidney injury were significantly associated with death of the patients[41]. Meningitis/meningoencephalitis, hepatomegaly, splenomegaly, multi-organ failure and pneumonia were reported as the major complications among confirmed scrub typhus cases suffering with acute febrile illness[69]. Co-infections of leptospirosis and scrub typhus have also been reported from Uttrakhand[70].

Jammu & Kashmir

Not many studies have reported on incidence of scrub typhus in Jammu and Kasmir, although climate, vegetation and terrain are quite similar to those of Himachal Pradesh and Uttarakhand. Menon and co-workers[71] detected 3.3% prevalence of the *R. tsutsugamushi* among human beings in Jammu and Kashmir. FUO cases (22.8%) were found positive for scrub typhus in a tertiary medical facility at Srinagar[53].

Conclusion

Himalayan/sub-Himalayan regions are endemic for scrub typhus. It is believed that because of non-specific flu-like presentation of the disease, absence of pathognomic eschar/rash and paucity of confirmatory diagnostic tests, scrub typhus remains a grossly under-diagnosed disease in the region[42,65]. Scrub typhus has been identified as a major cause of FUO/acute febrile illness in Himalayan areas. Therefore, such cases even in absence of eschar or rash, should be suspected for this disease[42]. It is suggested that rural women below 50 years of age presenting with high grade fever with or without eschar should be strongly suspected for scrub typhus infection in northwestern Himalayas[11]. Early presentations and timely diagnosis and treatment of scrub typhus patients can prevent the life threatening complications and mortalities and improves the prognosis[17,23,28].

Many infectious diseases have epidemiology, i.e. seasonal patterns and reservoirs/vectors similar to scrub typhus and mimic its clinical manifestations. Hence, physicians should keep in mind possibility of occurrence of such diseases as dual infections/co-infections with scrub typhus especially in endemic regions[21,40,70,72]. Patients presented with symptoms such as acute febrile illness in endemic areas should not be presumed to be suffering from single infection alone[19,20]. Scrub typhus needs to be differentiated from diseases such as dengue, malaria, acute viral hepatitis, leptospirosis, typhoid, enteric fever, measles, meningococcal infection, tubercle meningitis, viral meningoencephalitis and other tropical infections[12,17,20,40,59]. Paediatric scrub typhus cases are frequent in Himalayan and sub-Himalayan areas. Therefore, children suffering with febrile illness and nervous disorders must be suspected from scrub typhus. In spite of endemicity of scrub typhus in the Northwestern Himalayas, no systematic study has been conducted to ascertain the status of infection and occurrence of its vectors, i.e. chiggers of trombiculid mites in animals/birds of the region. Such studies can contribute immensely for better understanding the dynamics of scrub typhus in the region. As observed by Park *et al.*[56], in sub-Himalayan regions also, forest conservation can play a crucial role in the control of disease by suppressing growth of scrub type vegetation, habitats for mites.

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