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# Scrub Typhus in a Tertiary Care Hospital in North India

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*Abstract.* Scrub typhus, a zoonotic disease caused by the bacterium *Orientia tsutsugamushi*, has become endemic in many parts of India. We studied the clinical profile of this infection in 228 patients that reported to this tertiary care center from July 2013 to December 2014. The median age of patients was 35 years (interquartile range = 24.5–48.5 years), and 111 were males and 117 females. A high-grade fever occurred in 85%, breathlessness in 42%, jaundice in 32%, abdominal pain in 28%, renal failure in 11%, diarrhea in 10%, rashes in 9%, and seizures in 7%. Common laboratory abnormalities at presentation were a deranged hepatic function in 61%, anemia in 54%, leukopenia in 15%, and thrombocytopenia in 90% of our patients. Acute kidney injury (32%), acute respiratory distress syndrome (ARDS) (25%), and disseminated intravascular coagulation (DIC) (16%) were the commonest complications. A hepatorenal syndrome was seen in 38% and multiple organ dysfunction syndrome (MODS) in 20% patients. The overall case fatality rate was 13.6%. In univariate analysis, ARDS requiring mechanical ventilation, acute kidney injury requiring hemodialysis, hypotension requiring inotropic support, central nervous system dysfunction at presentation, and MODS were inversely associated with survival. Survival was significantly higher in patients that presented with a duration of fever < 10 days compared with those that presented ≥ 12 days ($P < 0.05$) after onset. In conclusion, scrub typhus has become a leading infectious disease in north India and an important cause of infectious fever. An increasing awareness of this disease coupled with prompt management will go a long way in reducing both morbidity and mortality from this disease.

## INTRODUCTION

Acute febrile illness (AFI) is the most common presenting complaint in the emergency and outpatient clinics in developing countries. Outbreaks of AFI occur usually in the rainy and post-rainy season in India. Malaria, dengue, typhoid, scrub typhus, and several viral infections have been classically responsible for such outbreaks.[1]

*Orientia tsutsugamushi* is an obligate intracellular, gram-negative bacteria causing scrub typhus. The chigger mites of the family Trombiculidae of genus *Leptotrombidium* are responsible for the disease transmission.[2] The so-called "tsutsugamushi triangle" region, which extends from northeast Asia to Papua New Guinea and northern Australia in the southeast, Pakistan and Afghanistan in the northwest, and the Maldives and Réunion Islands in the southwest, is endemic for scrub typhus with around 2 million of the population at risk.[3–5] The disease has become a significant occupational hazard in rural workers, adults involved in agriculture, forest occupation, soldiers in temporary camps, and in those living close to bushes and wood piles.[5]

In recent years, scrub typhus has rapidly remerged to become the major cause of AFI in many parts of India, especially during the monsoon and postmonsoon seasons. Of the 29 states in India, 23 have reported the presence of scrub typhus.[6–9] The clinical presentation of scrub typhus ranges from subclinical disease to multiorgan failure and death.[10] The disease usually presents with fever, diffuse lymphadenopathy, myalgia, rash, jaundice, thrombocytopenia, capillary leak syndrome, hepatomegaly, and splenomegaly.[11] The pathognomonic feature of scrub typhus is the necrotic eschar at the bite site. The disease can progress to severe complications like acute respiratory distress syndrome (ARDS), hepatitis, acute kidney injury, myocarditis leading to heart failure, and meningoencephalitis in different proportions of the patients. A late presentation, delay in diagnosis and treatment, and varying levels of antibiotic resistance exhibited by the organism are factors responsible for high mortality.[12]

With the changing epidemiology of scrub typhus, it is now among the commonest causes of AFI in India. It is important to get familiar with the clinical and diagnostic laboratory features of scrub typhus, so as to differentiate it from other etiologies of AFI. An early diagnosis and institution of specific treatment will reduce morbidity and mortality from this infectious disease. This study was carried out to document the clinical presentation and outcomes of adult patients with scrub typhus presenting to our tertiary care hospital in north India.

## PATIENTS AND METHODS

Patients above the age group of 12 years with an acute undiagnosed febrile illness (body temperature > 38.2°C) presenting to the outpatient or inpatient services of this hospital, between July 1, 2013 and December 31, 2014 (18 months) were prospectively included. A detailed history was collected and a thorough physical examination was carried out. All patients were managed according to the standard protocols as advocated by the Surviving Sepsis Campaign Guidelines. The patients with bilateral chest infiltrates on a chest X-ray, a ratio of partial pressure of arterial oxygen and fraction of inspired oxygen ($PaO_2/FIO_2$) < 300 in the absence of heart failure were defined as ARDS.[13] Multiple organ dysfunction syndrome (MODS) was confined to acutely ill patients presenting with features of two or more altered organ system functioning.[14] Laboratory tests carried out were a complete hemogram, renal function tests, liver function tests, coagulation tests including international normalized ratio and activated partial thromboplastin time, serum electrolytes, calcium, and phosphorous. Tests carried out as a workup for infectious diseases were blood culture, urine examination and culture, rapid tests for dengue, rapid antigen test and

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smear examination for malaria, and Widal test. IgM serology using commercial enzyme-linked immunosorbent assays (ELISAs) were performed for leptospirosis.

For scrub typhus, ELISA for IgM antibody was put up using Scrub Typhus Detect IgM ELISA (InBios International Inc., Seattle, WA) following the manufacturer's instructions. The antigen used to coat the wells was a recombinant 56-kDa type-specific antigen. The absorbance was read at 450 nm and an optical density of > 0.5 was considered positive. A nested polymerase chain reaction (PCR) was also performed for scrub typhus. DNA was extracted from the whole blood, blood clot, or eschar material by the phenol–chloroform method, and was amplified to detect scrub typhus according to nested PCR protocol.[15] The oligonucleotide primers used were based on the nucleotide sequences of a gene encoding for the 56-kDa antigen of a Gilliam strain of *O. tsutsugamushi*. The specific PCR products of size 484 base pairs were sequenced in a few representative samples to confirm the diagnosis. The sequences obtained were identified by comparison with sequences in GenBank by using the Basic Local Alignment Search Tool (http://blast.ncbi.nlm.nih. gov). Of the 228 cases, 198 were positive by ELISA alone, 84 by PCR alone, and 54 by both. All PCR products were sequenced and verified to be *O. tsutsugamushi* (GenBank accession numbers KT630272–KT630275, KT727932–KT727943, KT735173–KT735177, and KT957812–KT957872).

Descriptive statistics including frequency, mean, median, interquartile range (IQR), and standard deviation were calculated for the demographic data and laboratory parameters. Categorical variables were presented as percentage, and continuous variables were presented as mean/median along with 95% confidence limit and IQR. The associations of disease complications and laboratory features with the outcome were analyzed by univariate analysis. For all tests, a two-sided *P* value of 0.05 or less was considered statistically significant. All statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL).

## RESULTS

A total of 228 adult patients (111 males and 117 females) with median age of 35 years (IQR = 24.5–48.5 years) were diagnosed to have scrub typhus. Most cases presented during the month of September (31%) followed by October (26%) and August (24%). Three patients had a history of chigger bite and 58 (25%) patients had traveled to hilly area before this illness. Of the entire group, 44% were farmers and 40% were housewives. The adjoining states of Haryana and Punjab contributed to 56% of all cases followed by Himachal Pradesh (23%). The mean duration of fever before hospital presentation was 10 ± 5.3 days and the median hospital stay was 6 days (IQR = 4–10 days).

High-grade fever associated with chills and rigor was the most common presenting symptom in 85% (median duration of 10 days [IQR = 7–15 days]; Table 1). Breathlessness was the presenting feature in 42%, jaundice in 32%, abdominal pain in 28%, renal failure in 11%, diarrhea in 10%, rashes in 9%, and seizures in 7%. The most common laboratory finding was a deranged hepatic function in 61% and thrombocytopenia in 90% of our patients (Table 2). Acute kidney injury (32%), ARDS (25%), and DIC (16%) were the commonest complications. A hepatorenal syndrome was seen in 38% and MODS was seen in 20% patients.

TABLE 1
Clinical symptoms and signs in 228 adult patients of scrub typhus

| | No. of patients (%) |
|---|---|
| Symptoms | |
| High-grade fever with chills and rigor | 194 (85) |
| Shortness of breath | 95 (42) |
| Jaundice | 72 (32) |
| Abdominal pain | 63 (28) |
| Altered sensorium | 55 (24) |
| Vomiting | 52 (23) |
| Cough | 34 (15) |
| Myalgia | 16 (11) |
| Diarrhea | 22 (10) |
| Rash | 20 (9) |
| Generalized body swelling | 16 (7) |
| Seizure | 15 (7) |
| Signs | |
| Hepatomegaly | 138 (61) |
| Splenomegaly | 102 (45) |
| Pneumonitis | 72 (32) |
| Hypotension | 62 (27) |
| Pallor | 57 (25) |
| Pedal edema | 34 (15) |
| Eschar | 32 (14) |
| Lymphadenopathy | 24 (11) |
| Ascites | 23 (10) |
| Facial puffiness | 20 (9) |
| Neck stiffness | 12 (5) |

Coinfection with other tropical infections was noted in nine patients. Three patients were smear positive for malarial parasite (two had *Plasmodium vivax* and one had a dual infection of *Plasmodium falciparum* and *P. vivax*) and six patients were positive for IgM antibody against *Leptospira*. Doxycycline was given to 131 (57%), azithromycin to 97 (42%), and ceftriaxone to 139 (61%) patients. A combination of doxycycline and azithromycin was administered to 46 (20%), and doxycycline with ceftriaxone to 88 (39%). Antimalarial drug (artesunate) was given to 46 (20%) of which eight received a combined doxycycline with artesunate therapy. Thirty-seven cases developed nosocomial infection prompting the use of carbapenems. Ten patients had a mild illness, and were treated with either doxycycline (five cases) or azithromycin (five cases).

Of the 228 cases, 25% developed ARDS requiring endotracheal intubation and mechanical ventilation, 22% developed hypotension requiring inotropic support, 6% developed

TABLE 2
Laboratory parameters of 228 scrub typhus patients

| Laboratory parameters | No. of patients (%) |
|---|---|
| SGOT/SGPT (≥ 2 times normal) | 139 (61) |
| Thrombocytopenia (< $1.0 \times 10^9$/μL) | 205 (90) |
| Hyperbilirubinemia (> 2.5 mg/dL) | 63 (42) |
| Hypoalbuminemia (< 3 g/dL) | 46 (20) |
| Hyponatremia (< 135 milliEq/L) | 37 (16) |
| Anemia (< 11 g/dL) | 125 (55) |
| Hypokalemia (< 3.2 mEq/L) | 20 (9) |
| Hyperkalemia (> 5.2 mEq/L) | 20 (9) |
| Leukopenia (< 4,000/μL) | 15 (6) |
| Metabolic acidosis (pH < 7.3) | 18 (8) |
| Hypernatremia (> 150 mEq/L) | 12 (5) |

SGOT/SGPT = serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase.

TABLE 3
Complications of scrub typhus: comparison of recent studies from India

| Study | Varghese and others (Vellore)[23] | Kumar and others (Chandigarh)[24] | Sharma and others (Chandigarh) present study | Sinha and others (Rajasthan)[25] | Griffith and others (Vellore)[26] |
|---|---|---|---|---|---|
| Year | 2005–2010 | 2011–2012 | 2013–2014 | 2014 | 2014 |
| No. of patients | ($N$ = 623) | ($N$ = 49) | ($N$ = 228) | ($N$ = 42) | ($N$ = 116) |
| Study duration | 60 months | 12 months | 18 months | 3 months | 21 months |
| Design | Retrospective | Retrospective | Prospective | Prospective | Retrospective |
| ARDS | 33.7% | 57% | 25% | 11.9% | 73.3% |
| MODS | 34% | – | 20% | 16.6% | 85.2% |
| Shock | 65.6% | 16% | 27% | 14.2% | 61.7% |
| AKI | 18% | 53% | 32% | 26.1% | 63.8% |
| Presence of eschar | 43% | 18% | 14% | – | 41.6% |
| Thrombocytopenia | 79% | – | 90% | 85% | 86% |
| Acute hepatic dysfunction | 87% | 43% | 61% | 94.6% | 63.8% |
| Mortality | 9% | 16% | 13.6% | 16.6% | 24% |

AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; MODS = multiple organ dysfunction syndrome.

severe thrombocytopenia requiring platelet transfusion, and 8% patients developed acute renal failure requiring dialysis. Thirty-one patients succumbed to the illness giving an overall case fatality rate of 13.6%.

Of all the disease complications that were observed in the present study, the case fatality rate in patients with MODS was 43% and in those without MODS was 11% ($P < 0.001$). In univariate analysis, ARDS requiring mechanical ventilation (relative risk [RR] = 3.917, 95% confidence interval [CI] = 2.61–5.88, $P < 0.001$), acute kidney injury requiring hemodialysis (RR = 6.714, 95% CI = 2.72–16.57, $P < 0.001$), hypotension requiring inotropic support (RR = 3.525, 95% CI = 2.245–5.535, $P < 0.001$), central nervous system dysfunction at presentation (RR = 2.28, 95% CI = 1.46–3.57, $P < 0.001$), and MODS (RR = 3.615, 95% CI = 2.25–5.80, $P < 0.001$) were inversely associated with survival. Survival was significantly higher in patients that presented with a duration of fever < 10 days compared with those that presented ≥ 12 days ($P < 0.05$) after onset.

## DISCUSSION

Scrub typhus, an infective vasculitic-perivasculitic disease, is caused by *O. tsutsugamushi*. The disease is a zoonosis and is transmitted to humans sojourning though scrub vegetation by the bite of trombiculid chigger mites.[1–3] This infection is also known to occur in diverse geographical places like deserts, rice fields, and seashores. In India, the disease was documented for the first time during the World War II among field troops in Assam and West Bengal. Since then, a pan-India presence of scrub typhus has been well documented particularly from south India and the Himalayan region of north India.[5–7] It was only recently that outbreaks of the disease were reported from many other areas of sub-Himalayan north India and central India.[9,10] The present outbreak occurred in 228 patients from all over north India with Haryana, Punjab, Himachal Pradesh, and Chandigarh contributing to 88% of all cases. Classically known as a postmonsoon disease, this seasonal occurrence of scrub typhus was a prolonged one, extending well into the month of December of both 2013 and 2014. The continuation of the rainy season till late November of 2013 could have a bearing on the prolonged outbreak of this disease. In the present study, a definite exposure to scrub vegetation was seen in only 15% cases, a changing epidemiological trend that needs to be studied further for the effect of the environment on the dispersion of both the scrub vegetation and vector biology related to trombiculid mites in north India. In a study from South Korea, behavioral factors that may have a bearing on scrub typhus were squatting for defecating or urinating, directly resting on grass, and working with bare hands and short sleeves.[16] Behavioral trends such as these are also widely prevalent in India.

Two diagnostic modalities were used to diagnose scrub typhus in our patients, IgM ELISA and PCR. Despite the fact that immunofluorescence test is classically taken as the gold standard for diagnosing rickettsial infections, IgM ELISA is used by many laboratories for its cost, simplicity, and convenience. The IgM ELISA used in our study has a sensitivity of 90–95%, and has been shown to be comparable to the microimmunofluorescence test in a previous study.[17,18] The nested PCR protocol has a specificity of 100%.[18] In this study, all PCR products were sequenced and verified to be *O. tsutsugamushi*. The majority of our PCR isolates closely clustered with *Boryong* prototypes that have been isolated from patients of scrub typhus from Korea.[19]

In this study, patients presented with diverse clinical symptoms and signs. The commonest presenting symptoms of high-grade fever with chills, shortness of breath, and jaundice are nonspecific for tropical fevers. Nearly one-fourth of our patients presented with altered sensorium, similar to other studies.[12–22] The pathognomonic eschar was present in 14% patients (Table 3), a figure considerably higher than a previous study from the Himalayan region (9.5% patients), but lesser than that reported from south India (43.5%) and Jeju Island in South Korea (75.8%).[26,28,29] This variation in the presence of eschar may be explained by the geographic distribution of different strains of the organism. Lymphadenopathy, present in a nearly 11% third of our patients, was also lesser than in the studies from Vietnam and Thailand.[30,31] A maculopapular rash, as a presenting feature, was seen in 9% of our patients, as compared with 22% patients from Vellore, 20% patients from the Himalayan region of north India, 30% patients in Thailand, and 55.7% patients from Jeju Islands, South Korea.[23–32] In the present study, splenomegaly was present in 45% of patients. Another study from north India has reported a higher splenomegaly rate of 59%.[33]

Gastrointestinal manifestations like abdominal pain (28%), vomiting (23%), and diarrhea occurred in 10% of patients in this series. Vomiting and diarrhea occurred in 60% and 10%

cases in a previous study from our institute, and in 54% and 30% cases in a study from south India.[9,23] This highlights the fact that febrile patients of scrub typhus can also present with prominent gastrointestinal symptoms.

Among the laboratory findings, thrombocytopenia was noted in 89.9% of cases in our study. Most studies in India have reported almost similar rates of thrombocytopenia (Table 3).[34,35] The common disease complications noted in most studies of scrub typhus are MODS, ARDS, and acute renal failure (Table 3). MODS was seen in 20% of our cases with a case fatality of 43%. A study from south India has reported MODS in 34% of their cases.[23] ARDS occurred in 25% in our study, whereas earlier studies have reported ARDS in 8–34%.[23,27,28] An intensive care unit (ICU) study from south India has shown ARDS (96%) as the most common indication among scrub typhus patients requiring admission to their ICU.[26] Acute kidney injury was noted in 32% of our scrub typhus patients, which is lower than the previous study from our center reporting 53% of cases with renal failure.[24]

In our study, the case fatality rate was 13.6%. Data from other Indian studies have shown that the case fatality rate in scrub typhus has ranged from 1.2% to as high as 46.3% depending on the complications.[30–33] From south India, other studies have reported nearly similar fatality rates that the authors attributed to a lack of awareness of this disease.[35] From the same region of south India, an observational study has shown a reduction in mortality with an increasing awareness of this infectious disease.[23]

The strength of this study is that it is the largest prospective study that has been carried out in India. This is also the first study to establish the genetic similarity of *O. tsutsugamushi* with the *Boryong* prototype, the organism widely prevalent in Korea.[19]

## CONCLUSIONS

With the changing epidemiology of scrub typhus, it is now among the commonest causes of AFI in India. A high index of suspicion should be maintained, and an early diagnosis and management is warranted to prevent disease complications. Early presentation of disease with duration of fever < 10 days has better prognosis when compared with a fever duration of > 12 days. Despite apparent similarities in the clinical presentation of this disease in the subcontinent, in northern India, the presence of eschar was much lower and shock was seen in a lesser number of cases when compared with southern India. Multiorgan failure, respiratory dysfunction, and shock are the important life-threatening complications that lead to higher case fatality rates. Thus, in north India, an increasing awareness about the disease presentation, clinical features, and laboratory findings will help in reducing the mortality from this infectious disease.

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