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Clinical profile and improving mortality trend of scrub typhus in South India

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SUMMARY

Background: Scrub typhus, a bacterial zoonosis caused by *Orientia tsutsugamushi*, may cause multiorgan dysfunction syndrome (MODS) and is associated with significant mortality. This study was undertaken to document the clinical and laboratory manifestations and complications and to study time trends and factors associated with mortality in patients with scrub typhus infection.

Methods: This retrospective study, done at a university teaching hospital, included 623 patients admitted between 2005 and 2010 with scrub typhus. The diagnosis was established by a positive IgM ELISA and/or pathognomonic eschar with PCR confirmation where feasible. The clinical and laboratory profile, course in hospital, and outcome were documented. Factors associated with mortality were analyzed using multivariate logistic regression analysis.

Results: The most common presenting symptoms were fever (100%), nausea/vomiting (54%), shortness of breath (49%), headache (46%), cough (38%), and altered sensorium (26%). An eschar was present in 43.5% of patients. Common laboratory findings included elevated transaminases (87%), thrombocytopenia (79%), and leukocytosis (46%). MODS was seen in 34% of patients. The overall case-fatality rate was 9.0%. Features of acute lung injury were observed in 33.7%, and 29.5% required ventilatory support. On multivariate analysis, shock requiring vasoactive agents (relative risk (RR) 10.5, 95% confidence interval (CI) 4.2–25.7, $p < 0.001$), central nervous system (CNS) dysfunction (RR 5.1, 95% CI 2.4–10.7, $p < 0.001$), and renal failure (RR 3.6, 95% CI 1.7–7.5, $p = 0.001$) were independent predictors of mortality. Over 4 years, a decreasing trend was observed in the mortality rate.

Conclusions: Scrub typhus can manifest with potentially life-threatening complications such as lung injury, shock, and meningoencephalitis. MODS occurred in a third of our patients. The overall case-fatality rate was 9%, with shock, renal failure, and CNS associated with a higher mortality.

1. Introduction

Scrub typhus is an acute febrile illness endemic to the 'tsutsugamushi triangle', which encompasses broad areas of south and southeastern Asia, the Asian Pacific Rim, and northern Australia, with a population of over one billion people.[1] This infection is caused by the obligate intracellular Gram-negative bacterium *Orientia tsutsugamushi*, which was previously categorized in the *Rickettsia* genus.[2] During the Second World War, scrub typhus caused major epidemics resulting in significant morbidity and mortality in the border regions of India and Burma.[3] Although reports of the disease were rare for several decades, a clear re-emergence has been documented from several states in India, including Himachal Pradesh, Tamil Nadu, Kerala, Maharashtra, Bihar, Karnataka, Jammu and Kashmir, Uttaranchal, Rajasthan, West Bengal, and Meghalaya.[4–7] In some regions, scrub typhus accounts for up to 50% of undifferentiated fever presenting to the hospital, and more than one million people are affected worldwide annually.[8,9]

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The disease is transmitted to humans by the bite of the larval stage of the trombiculid mite (chigger) of the *Leptotrombidium* genus, which typically feeds on wild rats.[10] *O. tsutsugamushi* is injected into the human host from the chigger's digestive system. It subsequently adheres to and invades the host's phagocytes and endothelial cells, possibly by means of the 56-kDa type-specific antigen (TSA) protein, the transmembrane protein unique to this organism. Once inside these cells, as with other rickettsial illnesses, an acute vasculopathy ensues, which can affect a broad range of organs, leading to various potentially life-threatening complications.

Acute fever is the most common presenting symptom, often associated with breathlessness, cough, nausea, vomiting, myalgia, and headache.[11,12] An eschar at the site of inoculation can be found, if searched for thoroughly, in a highly variable percentage of people (10–92%).[13] The infection can range from a self-limiting disease to a fatal illness in 35–50% of cases, with multiorgan dysfunction, if not promptly diagnosed and appropriately treated.[14] Severe complications, including acute respiratory distress syndrome (ARDS), hepatitis, renal failure, meningoencephalitis, and myocarditis with shock, may occur in varying proportions of patients. The vast variability and non-specific presentation of this infection have often made it difficult to diagnose clinically. Basic laboratory tests, such as complete blood counts, which are relied on to give diagnostic clues, are often normal, although thrombocytopenia is very common.[5,15] One of the most consistent laboratory findings in scrub typhus is a mild transaminitis, which has been reported in the majority of patients in several studies (66.7% to >90%).[4,5,11] Renal dysfunction, as evidenced by an elevation in creatinine, has also shown a high degree of variability in previous research, although most studies have reported it to be present in 10–20%.[4,5] Diagnostic tests such as the Weil–Felix test are very insensitive and non-specific.[16] The current choice for the serologic diagnosis is IgM ELISA testing or immunofluorescence assay (IFA), which is considered the gold standard, although it is less frequently available.

The goal of this retrospective study was to provide a detailed panel of clinical aspects of this disease based on a large patient population, thus helping to create a better clinical and laboratory profile of this reemerging disease for clinicians to work with. We also set out to study the trend in mortality over time. Compared to our previous prospective analysis,[17] we have included substantially more patients and are thus able to present a more precise clinical picture and mortality trend, which is the focus of this work. Patients from the previous analysis were included in this current data.[17]

2. Methods

Patients over the age of 16 years admitted with scrub typhus to the Christian Medical College, Vellore, a 2700-bed medical college hospital, between 2005 and 2010, were included in this retrospective study. The diagnosis was confirmed through serum IgM ELISA scrub typhus and/or presence of an eschar with PCR confirmation. Data were collected regarding patient demographics, clinical features, vital parameters, laboratory data (complete blood counts, serum creatinine, and liver function tests), chest radiography findings, duration of hospital stay, duration of ventilation, need for dialysis, complications, and outcome on a predesigned data abstraction form. The nature and extent of organ dysfunction was also noted. Multiorgan dysfunction syndrome (MODS) was diagnosed as per established criteria (Table 1). MODS was defined as the simultaneous or sequential development of potentially reversible physiological derangement involving two or more organ systems (respiratory, cardiovascular, renal, hepatic, and neurological systems). IgM ELISA was performed on serum samples using the Scrub Typhus Detect test (InBios International, Inc., Seattle, WA, USA) as per the manufacturer's instructions. An optical density (OD) >0.5 was considered positive.

Table 1
Diagnostic criteria for organ dysfunction syndrome[a]

Organ system	Diagnostic criteria
Pulmonary	• Moderate or severe hypoxia (PaO_2 <60 mmHg/SaO_2 <90%) • PaO_2/FiO_2 <300 mmHg (40 kPa) • Need for ventilatory assistance
Renal	• Creatinine ≥2.5 mg/dl
Cardiovascular	• Blood pressure <80/60 mmHg despite fluid resuscitation • Need for vasopressor support in spite of fluid resuscitation
Hepatic	• Total bilirubin ≥2.5 mg/dl
CNS	• GCS ≤8/15 or 5T/10

CNS, central nervous system; Glasgow Coma scale score.
[a] Multiorgan dysfunction syndrome (MODS) is defined as dysfunction of two or more organ systems.

2.1. PCR analysis

Eschar samples were used for PCR. Bacterial DNA, extracted using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) in accordance with the manufacturer's instructions, was used as the template for the PCR. A standard PCR targeting the 56-kDa protein was carried out as reported previously,[4] using the oligonucleotide primers OtsuF 5′-AATTGCTAGTGCAATGTCTG-3′, and OtsuR 5′-GGCATTATAGTAGGCTGAG-3′. The expected amplicon size was 410 bp.

2.2. Statistical analysis

Statistical analysis was performed using SPSS software for Windows version 16.0 (SPSS Inc., Chicago, IL,USA). Descriptive data are given as the mean ± standard deviation (SD), or as the median and interquartile range (IQR). The Chi-square test or Fisher's exact test was used to compare dichotomous variables and the *t*-test or Mann–Whitney test was used for continuous variables, as appropriate. The associations of clinical and laboratory features with the outcome were analyzed by univariate and multivariate logistic regression, and 95% confidence intervals were calculated. For all tests, a two-sided *p*-value of 0.05 or less was considered statistically significant.

3. Results

Six hundred twenty-three patients admitted with scrub typhus during the 5-year study period were included. The proportions of males and females were almost equal (48% vs. 52%). The mean age of patients was 45 ± 15 years and the mean duration of illness before presentation to the hospital was 9.6 ± 4.8 days. Agricultural laborers comprised 41% of the total patient population. The most common presenting symptoms were fever (100%), nausea/vomiting (54%), shortness of breath (49%), headache (46%), cough (38%), and altered sensorium (26%). An eschar was noted in 43.5% of patients. Common laboratory findings included elevated transaminases (87%), thrombocytopenia (79%), and leukocytosis (46%). The transaminitis tended to be mild (2–3 times the normal values). Creatine phosphokinase (CPK) levels were found to be high in the group with MODS as compared to the group with no MODS (mean value 1336 vs. 135 IU/l, respectively; $p < 0.001$). The overall case-fatality rate was 9.0%. The patient characteristics are provided in Table 2.

About a third of patients (34%) had evidence of MODS. The case-fatality rate for those who developed MODS was significantly higher than that for those who did not (25% vs. 0.7%, $p < 0.001$). Among those with MODS, respiratory system dysfunction occurred

Table 2
Patient characteristics

Patient characteristics	Multiorgan dysfunction present $n = 212$ (34%)	Multiorgan dysfunction absent $n = 411$ (66%)
Age, years, mean ± SD	45.6 ± 14.8	44 ± 15.8
Sex male/female, *n*/*n*	96/116	204/207
Occupation, *n* (%)		
Agricultural worker	87 (41.0)	176 (42.8)
Other	125 (58.9)	235 (57.1)
Duration of illness before admission, days, median (IQR)	8 (1–45)	10 (1–45)
Pre-morbid conditions, *n* (%)		
Diabetes mellitus	24 (11.3)	47 (11.4)
Hypertension	29 (13.7)	46 (11.2)
COPD/asthma	5 (2.4)	10 (2.4)
Chronic renal failure	2 (0.9)	2 (0.5)
Pregnancy	10 (4.7)	14 (3.4)
Clinical symptoms and signs, *n* (%)		
Headache	69 (32.5)	216 (52.6)
Altered sensorium	62 (29.2)	99 (24.1)
Seizures	27 (12.7)	31 (7.5)
Nausea/vomiting	109 (51.4)	226 (55.0)
Myalgia	34 (16.0)	86 (20.9)
Diarrhea	35 (16.5)	57 (13.9)
Cough	88 (41.5)	149 (36.3)
Shortness of breath	156 (73.6)	147 (35.8)
Rash	7 (3.3)	10 (2.4)
Eschar	98 (46.2)	173 (42.1)
Heart rate/min, mean ± SD	105 ± 19	96 ± 14
Systolic blood pressure, mmHg, mean ± SD	106 ± 17	114 ± 15
Laboratory values		
Hemoglobin, g/dl, mean ± SD	11.8 ± 2.5	11.8 ± 2.2
WBC count, $\times 10^9$/l, median (IQR)	11.65 (1.20–50.00)	9.80 (1.90–36.60)
Platelet count, $\times 10^9$/l, median (IQR)	51 (5–343)	95 (3–529)
Bilirubin, mg/dl, median (IQR)	2.6 (0.3–30.9)	0.8 (0.2–14.4)
Total protein, g/dl, mean ± SD	5.8 ± 0.7	6.5 ± 0.8
Albumin, g/dl, mean ± SD	2.3 ± 0.5	2.8 ± 0.6
AST, IU/l, median (IQR)	156 (14–2698)	116 (12–1839)
ALT, IU/l, median (IQR)	83 (12–1775)	80 (10–753)
ALP, IU/l, median (IQR)	187 (58–975)	122 (24–715)
Serum creatinine, mg/dl, median (IQR)	1.8 (0.6–12.5)	1 (0.4–5.7)
CPK, IU/l, median (IQR)	184 (21–22 234)	87 (20–140 500)
Case-fatality, *n* (%)	53 (25)	3 (0.7)

SD, standard deviation; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; CPK, creatine phosphokinase.

most commonly (in 76.9%) and ventilator support was required in 68.9%. Hepatic dysfunction with bilirubin >2 mg/dl was found in 63.7%. Shock requiring vasoactive agents was present in 65.6% of cases, meningitis or meningoencephalitis in 15.6%, central nervous system (CNS) dysfunction (Glasgow coma scale (GCS) score ≤8/15) in 31%, and renal failure with creatinine >2 mg/dl in 44.3% of the patients with MODS (Table 3).

Univariate analysis showed that CNS dysfunction, elevated bilirubin and alkaline phosphatase, shock requiring vasoactive agents, requirement for ventilator support, and renal failure were associated with a poor outcome (Table 4). Among these, shock requiring vasoactive agents (relative risk (RR) 10.5, 95% confidence interval (CI) 4.2–25.7, $p < 0.001$), CNS dysfunction (RR 5.1, 95% CI 2.4–10.7, $p < 0.001$), and renal dysfunction (RR 3.6, 95% CI 1.7–7.5, $p = 0.001$) were found to be independent predictors of mortality on multivariate analysis using the forward method (Table 5). The mortality rate over 4 years showed a downward trend from 14.6% to 7.6% (Figure 1).

Table 3
Organ system dysfunction in patients with scrub typhus

Complication	No. (%)	MODS present	MODS absent
ARDS	210 (33.7)	163 (76.9)	47 (11.4)
Shock requiring inotropic support	144 (23.1)	139 (65.6)	5 (1.2)
Hepatitis[a]	212 (34)	135 (63.7)	77 (18.7)
Meningoencephalitis	145 (23.3)	33 (15.6)	112 (27.3)
Renal failure[b]	112 (18)	94 (44.3)	18 (44)
Invasive ventilation	184 (29.5)	146 (68.9)	38 (9.2)
CNS dysfunction	71 (11.4)	66 (31.3)	5 (1.2)

MODS, multiorgan dysfunction syndrome; ARDS, acute respiratory distress syndrome; CNS, central nervous system.
[a] Bilirubin ≥2 mg/dl.
[b] Serum creatinine ≥2 mg/dl.

4. Discussion

Scrub typhus is a potentially fatal infection that affects about one million people every year.[9] Our patients presented to the hospital with a mean duration of illness of 9 days, with symptoms of fever, nausea/vomiting, shortness of breath, cough, headache, and altered mental status. About a third of our patients had evidence of MODS and the overall mortality was 9%, with shock requiring vasoactive agents, CNS dysfunction, and renal failure being independent predictors of mortality.

This overall case-fatality in our study of 9.0% is lower than the 14% previously reported from our own institution in 2002–2003.[18] In the present study, analysis of the mortality trend over the 4-year period showed the mortality rate to have halved from 14.6% in 2007 to 7.3% and 7.6% in 2009 and 2010, respectively. Reports from northern India have also shown a trend towards decreasing mortality, with a rate of 17.2% reported in 2004 and 14% reported in 2006.[4,19] This trend may primarily be due to increased awareness and early recognition and treatment of the cases by physicians.

Table 4
Predictors of mortality (univariate analysis)

	Dead $n=56$ (8.9%)	Alive $n=567$ (91%)	RR (CI)	p-Value
Duration of illness, days, mean ± SD	7.86 ± 3.8	9.76 ± 4.9	0.9 (0.82–0.96)	0.004
Altered sensorium, n (%)	27 (48.2)	134 (23.6)	3 (1.7–5.2)	<0.001
Seizures, n (%)	12 (21.4)	46 (8.1)	3.1 (1.5–6.3)	0.002
Shortness of breath, n (%)	42 (75)	261 (46)	3.5 (1.8–6.5)	<0.001
Heart rate/min, mean ± SD	112.6 ± 20.1	97.9 ± 15.8	1.04 (1.03–1.06)	0.001
Systolic BP ≤90 mmHg at admission, n (%)	16 (28.5)	70 (12.3)	2.8 (1.5–5.3)	0.001
WBC count, $\times 10^9$/l, median (IQR)	15.5178 (2.200–42.100)	10.785 (1.200–50.000)	1.00 (1.00–1.00)	<0.001
Platelet count, $\times 10^9$/l, median (IQR)	65.268 (6.000–331.000)	100.051 (3.000–529.000)	1.00 (1.00–1.00)	0.002
Bilirubin ≥2.5 mg/dl, n (%)	33 (58.9)	179 (31.6)	3.1 (1.7–5.4)	<0.001
AST, IU/l, median (IQR)	241.9 (31–2698)	171.1 (12–1850)	1.001 (1–1.002)	0.02
ALT, IU/l, median (IQR)	104.6 (20–823)	105.8 (10–1775)	1 (0.99–1.003)	0.93
ALP, IU/l, median (IQR)	226.3 (66–594)	178.8 (24–975)	1.002 (1.001–1.004)	0.01
ARDS, n (%)	38 (67.9)	172 (30.3)	4.8 (2.7–8.7)	<0.001
Hypotension requiring inotropic support, n (%)	47 (83.9)	97 (17.1)	25.3 (12–53.3)	<0.001
Serum creatinine ≥2.5 mg/dl, n (%)	32 (57.1)	80 (14.1)	8.1 (4.5–14.5)	<0.001
CNS dysfunction, n (%)	32 (57.1)	39 (6.9)	18.1 (9.6–33.6)	<0.001
Requiring ventilatory support, n (%)	48 (85.7)	136 (24)	19.01 (8.7–41.2)	<0.001

RR, relative risk; CI, confidence interval; SD, standard deviation; BP, blood pressure; WBC, white blood cell; IQR, interquartile range; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; ARDS, acute respiratory distress syndrome; CNS, central nervous system.

Table 5
Independent predictors of mortality

Independent predictors	95% CI	p-Value
Hypotension requiring inotropes	10.1 (4.5–22.9)	<0.001
Creatinine >2 mg/dl	3.5 (1.7–7.1)	0.001
CNS dysfunction	6 (2.8–12.8)	<0.001
Bilirubin >2 mg/dl	1.4 (0.7–2.8)	0.36
Ventilation	2.2 (0.76–6.7)	0.14

CI, confidence interval; CNS, central nervous system.

Multiorgan failure was seen in a very high proportion (34%) of our patients. Pulmonary dysfunction was the most common complication (33.7%), and the majority of these patients (69%) required invasive ventilator support. Previous studies from India have shown an incidence of ARDS of 8–10%.[4,12] The case-fatality rate in those with ARDS was 18% in our study as compared to a higher rate (25%) seen in prior work.[20] Acute renal failure was seen in 18% of our patients. This incidence of renal impairment is lower than the 23.2% incidence reported by Attur et al.[21] and much lower than the 66.4% incidence reported by Mahajan et al.[4] Our incidence of meningoencephalitis (23.3%) was found to be higher than the 9.5% and 14% reported in other studies from India.[4,12] Cases with meningitis had a lower rate of mortality, at 6.2%, than the higher rates among cases with renal impairment (57%), pulmonary

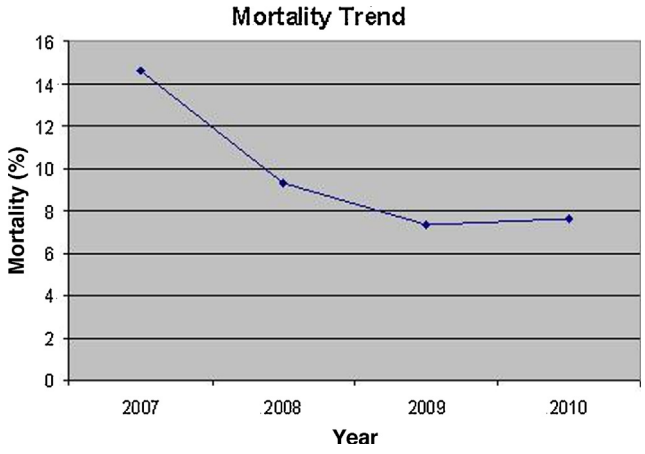

Figure 1. Mortality trend over the 4 years 2007–2010.

complications (68%), hypotension requiring inotropes (84%), and hepatitis (59%). Our study revealed practically relevant complications such as renal failure, hypotension requiring inotropes, and CNS dysfunction to be independent predictors of mortality. This adds to prior works, which have identified the absence of an eschar, intensive care unit admission, and high APACHE II score to be independent predictive variables associated with a fatal outcome.[22,23]

The occupation and scrub vegetations surrounding the house of the patients are known to have a strong association with acquisition of the infection.[24] In this study, 42% of the patients were agricultural laborers and 36% housewives, indicating an increased risk of infection in those who encounter scrub vegetation in their daily life. Our rate of finding an eschar, in 43.5% of patients, is similar to that reported from other studies that have been performed close to this geographic area, with an eschar noted in 46% of patients by Vivekanandan et al. in Pondicherry.[12] However, in North India, Mahajan et al. reported finding an eschar in only 9.5% of patients,[4] while in Korea an eschar has been documented in as many as 90% of patients.[22] The variation in prevalence of an eschar may represent the different geographic distribution of the various strains of the organism, or inadequate search for the eschar; further research is warranted in this area.[25]

The finding of mild hepatitis in 87% of our patients is consistent with previous reports.[4,5,11] Thrombocytopenia was also noted in similar percentages of patients as in previous studies.[5] However, data reported from northern China suggest significantly lower rates of thrombocytopenia, ranging from 4.6% to 48.9%.[15] This may partly be explained by the lower threshold used in their study (100 vs. 150×10^9/l), as studies done in Pondicherry, near our center, also found lower rates (10%) with the same lower threshold. The observed thrombocytopenia does tend to be mild in this disease:[5,12] about 60% of our patients had platelet counts $<100 \times 10^9$/l and only 19.5% had severe thrombocytopenia ($<30 \times 10^9$/l). Leukocytosis ($>11 \times 10^9$/l), a common sign of bacterial etiology, was found in less than 50% (42.6%) of our patients. This finding was present in an even lower percentage of patients in the study by Liu et al. in northern China (10.5%).[15] However, the result of the leukocyte count was very inhomogeneous in our study, with a range from minimum 1.2×10^9/l to maximum 50×10^9/l.

One of the limitations of our study is that strain variation and the virulence of infecting strains, which have earlier been reported to be associated with the severity of the symptoms and clinical

presentation in scrub typhus,[1,25] were not explored. Hence, further investigations focusing on the types of circulating strain are imperative to obtain a complete clinical profile of this infection. The study may also be limited by the inherent disadvantages of a retrospective study design from a single medical center, such as the bias in patient selection or referral and the potentially incomplete data available for some of the patients.

In conclusion, scrub typhus is a serious acute febrile illness associated with significant mortality. Respiratory dysfunction, shock, and acute renal failure are serious life-threatening complications of this disease. Mortality is significantly higher in patients with CNS dysfunction or renal failure, and in those requiring vasoactive agents for shock. Scrub typhus is present in regions that are co-endemic for diseases that may present with similar clinical syndromes, such as malaria, dengue, typhoid, and leptospirosis. The mortality from this infection does appear to have been decreasing over the last several years. However, developing increasing awareness of this infection among clinicians in endemic settings and reliable methods for more rapid diagnosis will be the key to further reducing the mortality caused by this deadly disease.

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