



## Scrub typhus in Uttarakhand & adjoining Uttar Pradesh: Seasonality, clinical presentations & predictors of mortality

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**Background & objectives:** Scrub typhus is a re-emerging mite-borne rickettsiosis, which continues to be underdiagnosed, with lethal consequences. The present study was conducted to determine the seasonality, clinical presentation and predictors of mortality in patients with scrub typhus at a tertiary care teaching hospital in northern India.

**Methods:** Scrub typhus was suspected in patients attending the hospital as per the standard case definition and serological evidence was obtained by performing an IgM ELISA.

**Results:** A total of 284 patients with scrub typhus from urban and rural areas were seen, predominantly from July to November. The most common clinical presentation was a bilateral community-acquired pneumonia (CAP), which resembled pneumonia due to atypical pathogens and often progressed to acute respiratory distress syndrome (ARDS). An acute undifferentiated febrile illness (AUI) or a febrile illness associated with altered sensorium, aseptic meningitis, shock, abdominal pain, gastrointestinal bleeding or jaundice was also seen. Eschars were seen in 17 per cent of patients, and thrombocytopenia, transaminitis and azotaemia were frequent. There were 24 deaths (8.5%) caused predominantly by ARDS and multi-organ dysfunction. The mortality in patients with ARDS was high (37%). ARDS [odds ratio (OR)=38.29, 95% confidence interval (CI): 9.93, 147.71] and acute kidney injury (OR=8.30, 95% CI: 2.21, 31.21) were the major predictors of death.

**Interpretation & conclusions:** The present findings indicate that scrub typhus may be considered a cause of CAP, ARDS, AUI or a febrile illness with multisystem involvement, in Uttarakhand and Uttar Pradesh, especially from July to November. Empiric therapy of CAP may include doxycycline or azithromycin to ensure coverage of underlying unsuspected scrub typhus.

**Key words** India - mortality - outcomes - pneumonia - scrub typhus - seasonality

Scrub typhus is an acute febrile illness with frequent multisystem involvement caused by *Orientia tsutsugamushi* and transmitted by bites of infected

larvae (chiggers) of trombiculid mites. The target cells of *O. tsutsugamushi* are endothelial cells, monocytes and other cell types and the disease is associated with

vasculitis and endothelial dysfunction<sup>1</sup>. Scrub typhus has been termed as the 'single most prevalent, under-recognized, neglected and severe, but easily treatable disease in the world'<sup>2</sup>. With delays in diagnosis and treatment, the mortality can exceed 30 per cent<sup>1</sup>. In India, initial reports of scrub typhus appeared in the 1930s<sup>3</sup>, and a large number of cases were identified in the Second World War<sup>4</sup>. In later years, scrub typhus has been reported with increasing frequency from diverse ecologies – initially from southern India<sup>5</sup> and later from the Himalayan regions<sup>6</sup>, the plains of northern India<sup>7</sup>, coastal areas<sup>8</sup>, desert regions<sup>9</sup> and even residential localities in metropolitan cities<sup>10</sup>.

Scrub typhus was first reported in the Kumaon hills (now Uttarakhand) in 1938<sup>11</sup>, while serologically confirmed cases were reported from Uttar Pradesh in 1945<sup>12</sup>. In Uttarakhand, a few cases of scrub typhus were reported in 1992<sup>13</sup> and 2009<sup>14</sup>, while reports from Uttar Pradesh have been uncommon. Since 2012, when the National Centre for Disease Control (NCDC) confirmed a multi-State outbreak of scrub typhus<sup>15</sup>, an increased number of patients have been seen in rural as well as urban areas of Uttarakhand and adjoining Uttar Pradesh with diverse clinical manifestations and with severe morbidity and significant mortality.

The present study was conducted to determine the seasonality, clinical features, outcomes and predictors of mortality in patients with scrub typhus admitted in a tertiary care hospital in Uttarakhand.

### Material & Methods

This study was conducted at the Himalayan Hospital, a 750-bed tertiary care teaching hospital located at Jolly Grant, 25 km from Dehradun, Uttarakhand, India, from August 2012 to December 2013. This hospital caters to patients from the seven districts of the Garhwal division, some districts of the Kumaon division and the adjoining districts of Uttar Pradesh and Himachal Pradesh.

*Case definitions and data sources:* Cases of scrub typhus were suspected on the basis of presence of one or more of the following features - (i) acute-onset fever with or without headache, cough with or without shortness of breath, abdominal pain, conjunctival infection, lymphadenopathy or rash; (ii) presence of a primary punched out ulcer or eschar; (iii) acute febrile illness, in which other causes had been excluded and in which defervescence occurred within 48 h of administration of tetracyclines<sup>16</sup>.

Data on cases of scrub typhus were collected prospectively among consecutive patients presenting to Himalayan Hospital during the study period. Serological evidence of scrub typhus was obtained by demonstration of IgM antibodies to 56 kDa antigen of *O. tsutsugamushi*, using a commercial IgM ELISA (Scrub Detect™, InBios International Inc., Seattle, Washington, USA). The cut-off used for the IgM ELISA was an optical density of >0.5 as used in other studies<sup>17</sup>.

Information on putative risk factors for exposure to mite larvae was elicited, and any relevant investigations and therapy before admission were noted. Each patient was examined in detail for the presence of rash, eschar and lymphadenopathy. Patients underwent a complete haemogram, urinalysis, assessment of renal and hepatic function, chest X-ray and evaluation for other causes of fever (malaria, dengue and typhoid), as considered appropriate. Patients presenting with neurological symptoms underwent cerebrospinal fluid (CSF) examination and imaging.

Systemic involvement in scrub typhus was defined as follows: (i) pneumonia: radiologic evidence of opacities; (ii) acute respiratory distress syndrome (ARDS): presence of bilateral infiltrates with severe hypoxaemia with normal cardiac function; (iii) acute hepatitis: total bilirubin >2.5 mg/dl and/or elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 2.5 times above the upper limit for normal readings (*i.e.*, >100 IU/l); (iv) acute renal failure: serum creatinine >2.0 mg/dl; (v) shock: systolic BP <90 mm Hg; (vi) acute confusional state: altered sensorium in a patient with scrub typhus with/without CSF changes; (vii) multi-organ dysfunction: progressive abnormalities in two or more systems.

The study protocol was approved by the Institutional Review Committee of the Himalayan Institute of Medical Sciences.

*Statistical analysis:* Association between categorical variables was assessed using Chi-squared test. Student's *t* test (unpaired) and Mann-Whitney U-test were used to compare means and medians, respectively. The multivariate logistic regression analyses of outcomes of death due to scrub typhus were performed, and variables were included in the final model if the univariate analysis showed  $P < 0.25$  or if the variable was of known clinical importance. Statistical analysis was done using STATA 11 (Stata Corp, College Station, Texas, USA).

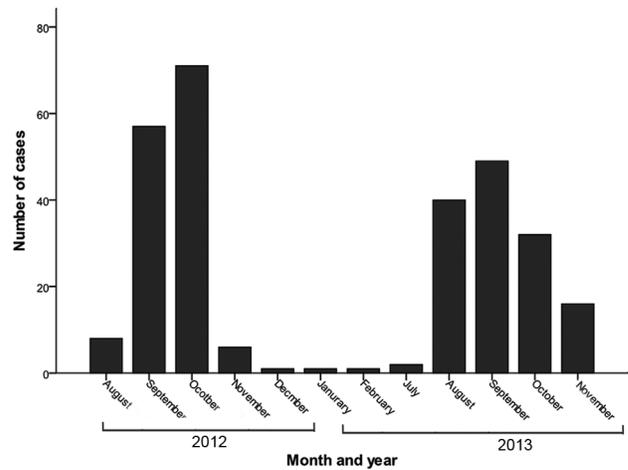
**Results**

A total of 284 adults were diagnosed with scrub typhus during the study period (143 cases in 2012 and 141 cases in 2013). During this period, a total of 2524 cases of acute febrile illnesses were seen. The predominant causes were dengue (1278 cases, 50.6%), typhoid fever (575 cases, 22.8%), malaria (380 cases, 15.1%), scrub typhus (284 cases, 11.2%) and leptospirosis (7 cases, 0.3%). The distribution with regard to States, districts and rural-urban residence of the patients with scrub typhus is shown in Table I. There were cases from both urban and rural areas, and in Haridwar district, the cases from urban areas outnumbered those from the rural area. The presentation according to the month of the year is shown in Fig. 1. Scrub typhus in the region had a consistent seasonal pattern with a few cases in the months between January and June and a predilection for occurrence in the months from July to November. Scrub typhus occurred in both men and women with no predilection for gender (Table II).

*Risk factors for exposure to mites and previous diagnosis/treatment for scrub typhus:* A majority of patients reported the presence of bushes around the houses (71%) and rodents at home (61%). Nearly half of the patients resorted to open air defecation (49%) or travelled to the forest for the collection of fodder (48%).

None of the patients recalled a bite in the period before onset of illness. Details of earlier investigations were available in 172 patients, of whom only one patient (in 2013) had been subjected to any diagnostic test for scrub typhus. Patients presenting with pneumonia had received earlier treatment, usually only with a beta-lactam antibiotic or a respiratory fluoroquinolone (like levofloxacin).

*Clinical and laboratory features:* The clinical and laboratory features of the patients are given in Table II.



**Fig. 1.** Scrub cases by month and year from August 2012 to November 2013.

**Table I.** Distribution of cases of scrub typhus: according to State, district and urban-rural residence

State	District	Urban (n=111) (%)	Rural (n=173) (%)	Total (n=284)
Uttarakhand	Haridwar	40 (78)	11 (22)	51
	Dehradun	13 (27)	35 (73)	48
	Tehri Garhwal	7 (27)	16 (73)	23
	Pauri Garhwal	6 (29)	15 (71)	21
	Rudraprayag	2 (25)	7 (75)	8
	Chamoli	3 (43)	4 (57)	7
	Udham Singh Nagar	-	2 (100)	2
	Nainital	2 (50)	2 (50)	4
	Uttarkashi	1 (33)	3 (67)	3
	Bageshwar	-	1 (100)	1
	Total	74 (44)	96 (56)	170
Uttar Pradesh	Saharanpur	29 (38)	50 (62)	79
	Bijnor	5 (24)	18 (76)	22
	Muzaffarnagar	3 (44)	4 (56)	7
	Moradabad	-	3 (100)	3
	Rampur	-	2 (100)	2
	Total	37 (32)	77 (68)	114

A non-productive cough appearing a few days after the onset of fever and shortness of breath, which was often rapidly progressive, was the most common systemic symptom. Abdominal pain arousing the suspicion of an acute abdomen, symptoms of altered sensorium and convulsions were also noted in some patients. A few patients presented with jaundice and symptoms of upper gastrointestinal (GI) bleeding. The clinical course of patients was sometimes unexpected, with the onset or rapid progression of hypoxaemia despite early therapy and the appearance of cardiac arrhythmias.

On clinical examination, the most frequent abnormality was found to be hepatomegaly, followed by cervical and/or axillary adenopathy (Table II), conjunctival icterus and hypoxaemia on pulse oximetry. A striking and consistent finding in patients with pneumonia was the relative paucity of physical signs despite the often extensive involvement of both lungs. Eschar was seen in 49 (17%) patients in the neck, axilla, abdomen, inguinal and pubic regions (Fig. 2). When the presence of eschars was compared across clinical presentations of scrub typhus, eschars were particularly associated with the presence of ARDS ( $P=0.008$ ), wherein these were documented in nearly one-third of cases.

On laboratory evaluation, the leucocyte count was normal in more than half of cases and elevated in one-third of patients (Table II). The most common laboratory abnormalities were elevation of transaminases, thrombocytopenia, hypoalbuminaemia, while elevated total bilirubin level and serum creatinine were seen in nearly half of patients (Table II). Due to lack of a productive cough, sputum examinations could not be done in patients. The X-rays revealed bilateral interstitial patterns (with reticulonodular and ground-glass opacities) initially, extensive air-space consolidation in patients with ARDS (Fig. 3)



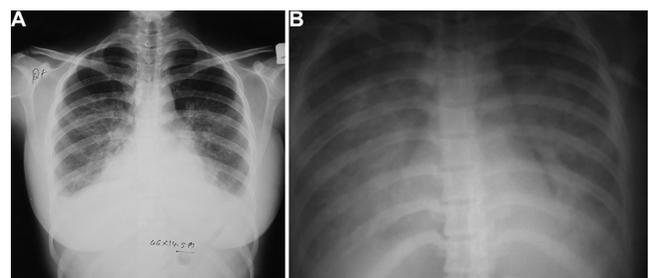
**Fig. 2.** Eschars in patients with scrub typhus. (A) An eschar on the neck of a patient with scrub typhus. (B) A close up of the eschar shows the typical cigarette burn appearance of an eschar.

and occasional pleural effusion. CSF examination was done in 14 patients. The pattern was similar to aseptic meningitis, with a predominant mononuclear pleocytosis (median count of 85 cells/ $\mu$ l) and raised CSF protein (median - 125 mg/dl), with normal CSF glucose [median (interquartile range [IQR]) of 76 mg/dl (64, 91)] (Table II).

Table III shows the clinical presentations of scrub typhus patients. It was most often presented as community-acquired pneumonia (CAP) (in 115 cases), which was bilateral and frequently complicated by ARDS. ARDS was seen in 46 cases (16.2%) overall and in 40 per cent of the cases of pneumonia. Patients with scrub typhus and pneumonia also had significant thrombocytopenia, with a median (IQR) platelet count of 60,000/ $\mu$ l (35000-105000).

The other clinical presentations of scrub typhus were an acute undifferentiated febrile illness (AUF), acute febrile encephalopathy or fever followed by shock, jaundice and GI bleeding (Table III). The median (IQR) durations of fever in the different presentations were similar.

*Treatment, outcomes and predictors of mortality:* Patients received oral doxycycline and/or intravenous (iv) azithromycin<sup>18</sup>, along with beta-lactam antibiotics (in the case of pneumonia), along with supportive care which included oxygen, mechanical ventilation, haemodialysis and blood products. Steroids were given to patients with shock, requiring vasopressors, and also often to those with early ARDS. Treatment was successful in 242 (85.2%) patients. Forty two patients (14.8%) had unfavourable outcomes after admission and despite receiving therapy for scrub typhus. This included deaths in 24 patients (8.5%), while 18 patients (6.3%) who were also seriously ill left against medical



**Fig. 3.** (A) A patient with scrub typhus presenting with fever and shortness of breath. X-ray shows an interstitial pattern with ground glass opacities in bilateral lower lobes. (B) An X-ray of a patient with scrub typhus who progressed rapidly to acute respiratory distress syndrome. X-ray showing extensive air space consolidation.

**Table II.** Demographic characteristics, symptoms, signs and laboratory features in patients with scrub typhus (n=284)

Patients' parameters	Values
Age in yr, median (IQR)	35.5 (27-45)
Men (%)	135 (47.5)
Women (%)	149 (52.5)
Fever, n (%)	284 (100)
Duration of fever in days, median (IQR)	8 (7, 12)
Vomiting, n (%)	113 (40)
Headache, n (%)	104 (37)
Shortness of breath, n (%)	101 (35)
Cough, n (%)	89 (29)
Abdominal pain, n (%)	66 (23)
Diarrhoea, n (%)	29 (10)
Altered sensorium, n (%)	28 (9.9)
Jaundice, n (%)	14 (5)
Convulsion, n (%)	12 (4)
Melena, n (%)	8 (3)
Temperature (°F), mean±SD	99.8±1.65
Systolic BP in mm Hg, mean±SD	102±18.8
Systolic BP <90 mm Hg, n (%)	31 (10.9)
SpO <sub>2</sub> , mean±SD	94.09±6.76
SpO <sub>2</sub> <90, n (%)	52 (18)
Jaundice on examination, n (%)	59 (20.8)
Eschar, n (%)	49 (17.3)
Lymphadenopathy (cervical and/or axillary), n (%)	71 (25)
Hepatomegaly, n (%)	94 (33)
Splenomegaly, n (%)	44 (15)
Haemoglobin in g/dl, median (IQR)	11.2 (9.8-12.4)
TLC in cells/μl, median (IQR)	8900 (6180-13,000)
Normal TLC, TLC 4000-11,000 cells/μl, median (IQR)	156 (55)
Leucocytosis, TLC >11,000 cells/μl, median (IQR)	102 (36)
Platelet count <150,000/μl, n (%)	231 (80.9)
Platelet count in cells/μl, median (IQR)	80,000 (40,000-127,000)
AST in IU/l, median (IQR)	116 (69-191)
ALT in IU/l, median (IQR)	75 (46-119)
Serum albumin in g/dl, median (IQR)	2.3 (1.9-2.8)
Serum albumin <3.5 g/dl, n (%)	201 (71)
Total bilirubin in mg/dl, median (IQR)	1.25 (0.7-2.4)
Bilirubin >1.3 mg/dl, n (%)	136 (48)
Serum creatinine in mg/dl, median (IQR)	1.1 (0.8-1.6)
Elevated serum creatinine (>1.2 mg/dl in men, >0.9 mg/dl), n (%)	137 (48)
Bilateral opacities (interstitial opacities or air space consolidation) (n=115) n (%)	108 (94)

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Patients' parameters	Values
Unilateral opacities (n=115), n (%)	7 (6)
Pleural effusion (n=115), n (%)	7 (6)
Evidence of global hypokinesia on echocardiography, n (%)	5 (1.8)
CSF cell count in cells/ $\mu$ l (n=14), median (IQR)	18 (5-85)
CSF protein in mg/dl (n=14), median (IQR)	125 (62-203)
CSF glucose in mg/dl (n=14), median (IQR)	76 (64-91)

SD, standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; SpO<sub>2</sub>, arterial oxygen saturation determined by pulse oximetry; CSF, cerebrospinal fluid

**Table III.** Clinical presentation and causes of death seen in patients with scrub typhus (n=284)

Clinical presentations	n (%)
CAP	115 (40.1)
CAP without ARDS	69/115 (60)
CAP with ARDS	46/115 (40)
Undifferentiated fever	78 (27.5)
Acute confusional state/acute febrile encephalopathy	28 (9.6)
Fever and shock	31 (10.9)
Fever with GI/hepatic presentations	15 (5.3)
Jaundice in the presence of acute undifferentiated fever	12 (4.2)
GI bleeding	3 (1.1)
Others	17 (6)
Causes of death (Total deaths=24)	
ARDS	17 (70.8)
Multi-organ dysfunction in patients with ARDS	14/17 (82.3)
Multi-organ dysfunction without ARDS	4 (16.7)
Myocarditis without ARDS or multi-organ dysfunction	2 (8.3)
DVT with suspected pulmonary embolism	1 (4.2)

ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; DVT, deep vein thrombosis; GI, gastrointestinal

advice (LAMA). The major causes of death were ARDS and multi-organ dysfunction (Table III). Of the 46 patients with ARDS, 19 (41%) recovered successfully while the unfavourable outcomes of death and LAMA were seen in 17 (37%) and 10 (22%), respectively. Two patients died of myocarditis without ARDS or multi-organ dysfunction (Table III).

Deaths usually occurred in the second week of illness, and the duration of fever on admission in those who died was not significantly different than in those who survived (Table IV). In-hospital mortality

was predominantly early: the median duration of stay in those who died was two days, compared to a median of six days in those who survived ( $P<0.001$ ) (Table IV). While age, gender and residence were not associated with the risk of death, an increase in total leucocyte count and serum creatinine and a decrease in platelet count, serum albumin and oxygen saturation were significantly associated with death (Table IV). On univariate analysis, the indicators of severe sepsis (thrombocytopenia, azotaemia, hyperbilirubinaemia, ARDS, shock) as well as hypoalbuminaemia were all associated with increased odds of death (Table V). However, on multivariate logistic regression analysis, ARDS [odds ratio (OR)=38.29, 95% confidence interval (CI): 9.93, 147.71] and acute kidney injury (OR=8.30, 95% CI: 2.21, 31.21) remained strong risk factors for mortality, while the associations of thrombocytopenia, hyperbilirubinaemia, low albumin and shock were no longer significant (Table V).

### Discussion

Our study included 284 patients with scrub typhus from northern India, predominantly from Uttarakhand and from a few adjoining districts of Uttar Pradesh. Scrub typhus has been described as an occupational disease of rural residents<sup>19</sup>, but a substantial proportion of our patients were from urban areas of both States. A seasonal pattern with occurrence in July-November was evident, and the maximum cases were seen in September and October. This seasonal pattern was consistent with reports from north India<sup>6</sup>, western India<sup>8</sup> and north-eastern India<sup>20</sup> but was different from the pattern observed in south India, where the disease has been reported during the cooler months, from October to February<sup>5</sup>.

The most common clinical presentation was CAP, with a non-productive cough, bilateral infiltrates, and the paucity of physical signs, resembling pneumonia caused by atypical organisms such as *Legionella*

**Table IV.** Comparison of demographic, clinical and laboratory characteristics of those who died versus those with a successful outcome

Patient characteristics	Patients who died (n=24)	Patients who survived (n=242)
Age, (yr) mean $\pm$ SD	38.31 $\pm$ 15.71	40.75 $\pm$ 15.68
Gender (%) <sup>†</sup>		
Men (n=135)	11 (8.2)	118 (87.4)
Women (n=149)	13 (8.7)	124 (83.2)
Residence (%) <sup>††</sup>		
Urban (n=111)	8 (5.9)	100 (90.0)
Rural (n=173)	16 (9.2)	142 (82.1)
Duration of fever at admission in days, median (IQR)	8 (7-13)	8 (7-12)
Eschar, n (%)	3 (12)	39 (16.18)
Arterial oxygen saturation per cent, (mean $\pm$ SD)	90.42 $\pm$ 10.48**	94.52 $\pm$ 6.16
Total leucocyte count in cells/ $\mu$ l, (mean $\pm$ SD)	14,824 $\pm$ 8519*	10,602 $\pm$ 8806
Serum albumin in g/dl, (mean $\pm$ SD)	1.81 $\pm$ 0.57**	2.58 $\pm$ 0.84
Serum creatinine in mg/dl, (mean $\pm$ SD)	2.57 $\pm$ 1.59**	1.39 $\pm$ 1.26
Platelet count in cells/ $\mu$ l, (mean $\pm$ SD)	64,484 $\pm$ 39,398*	101,457 $\pm$ 78,937
Acute respiratory distress syndrome, n (%)	17 (68)***	19 (7.92)
Shock, n (%)	7 (28.0)**	21 (8.75)
Duration of hospitalization (before death or discharge), median (IQR)	2 (1.5-5.5)***	6 (4-9)
Total duration of illness before event (death or recovery), median (IQR)	12.5 (9-18.5)	15 (11-22)

*P*\* $<$ 0.05 \*\* $<$ 0.01 \*\*\* $<$ 0.001 compared to patients who survived. <sup>†</sup>6 men and 12 women left against medical advice and are not included in this Table; <sup>††</sup>3 persons living in the urban area and 15 persons from rural area left against medical advice and are not included in this Table. IQR, interquartile range; SD, standard deviation; SpO<sub>2</sub>, arterial oxygen saturation determined by pulse oximetry; ARDS, acute respiratory distress syndrome

**Table V.** Univariate and multivariate odds ratios of selected patient characteristics for the outcome of death

Patient characteristic	n (% of total)	Univariate OR (95% CI)	Multivariate OR (95% CI) <sup>§</sup>
Thrombocytopenia (platelet count $<$ 100,000/ $\mu$ l)	164 (57.8)	3.17 (1.15-8.76)	0.84 (0.22-3.15)
Hyperbilirubinemia (bilirubin $\geq$ 4 mg/dl)	61 (21.5)	2.74 (1.15-6.54)	2.68 (0.74-9.72)
Low albumin (serum albumin $<$ 3.0 g/dl)	178 (62.7)	3.58 (1.19-10.80)	1.94 (0.45-8.34)
Acute kidney injury (creatinine $\geq$ 2 mg/dl)	56 (19.7)	7.76 (3.21-18.77)	8.30 (2.21-31.21)
Shock (systolic BP $<$ 90 mmHg)	31 (10.9)	4.31 (1.61-11.58)	1.26 (0.33-4.77)
Acute respiratory distress syndrome	46 (16.2)	28.38 (10.47-76.91)	38.29 (9.93-147.71)

<sup>§</sup>Multivariate OR adjusted for age, and presence/absence of acute respiratory distress syndrome and thrombocytopenia, hypoalbuminaemia, hyperbilirubinaemia, acute kidney as defined in the Table. OR, odds ratio; CI, confidence interval; BP, blood pressure

spp., *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*<sup>21</sup>, which often progressed to ARDS. A similar predominance of pneumonia as the most common presentation and ARDS as the major complication has been noted in other studies<sup>9,17</sup>.

The epidemiologic and clinical features that suggest a diagnosis of scrub typhus in a patient with febrile illness are a history of environmental

exposure, the presence of eschar, maculopapular rash and adenopathy<sup>22</sup>. In our study, none of these features occurred consistently in majority of patients. Eschar was seen only in 17 per cent of patients. The low frequency of eschar (10-19%) has been reported earlier<sup>6,8,20</sup>, with some reports failing to find eschars in any patients<sup>10,23</sup>. The laboratory abnormalities comprised normal or elevated leucocyte counts,

thrombocytopenia, an AST-predominant transaminitis, hyperbilirubinaemia, hypoalbuminaemia and azotaemia. The CSF abnormalities were suggestive of aseptic meningitis. Elevated transaminases (especially AST) and thrombocytopenia have been consistently reported in other studies from India<sup>8,9,17</sup>, but these are also common in other acute febrile illnesses such as dengue fever<sup>24,25</sup>. The finding of thrombocytopenia in patients with scrub typhus and pneumonia may be diagnostically helpful as only a few causes of CAP are associated with a low platelet count<sup>26</sup>.

The deaths in patients resulted largely from ARDS, associated in most cases with multi-organ dysfunction. ARDS has been documented as occurring in 9.5-60 per cent cases from different parts of India<sup>6,8,17</sup>. However, in a study from Sikkim, ARDS was not reported at all<sup>27</sup>. ARDS was associated with a high mortality rate (37%) in our study, similar to the 33 per cent reported in another recent study from Rajasthan<sup>9</sup>. This may be related to delayed presentation of patients, low awareness of scrub typhus among healthcare providers in the region, and previous ineffective empiric therapy for CAP, which consisted of only beta-lactams such as ceftriaxone or a respiratory fluoroquinolone, which do not provide coverage for scrub typhus. The treatment of patients presenting with CAP with a combination of a beta-lactam agent and macrolide (azithromycin) or doxycycline as suggested in the therapeutic recommendations for CAP to ensure coverage of atypical pathogens<sup>28</sup>, would have ensured coverage for underlying scrub typhus. This could have prevented the progression to ARDS and a fatal outcome.

The strengths of our study was large number of patients drawn from urban and rural areas. The study had certain limitations. It was conducted at a tertiary care centre, and the clinical spectrum and profile might not be representative of scrub typhus at other levels of care. Further, ELISA targeting specific IgM antibodies against a 56 kDa recombinant antigen of *O. tsutsugamushi* was used to obtain serological evidence of scrub typhus since isolation facilities, indirect immunofluorescence and polymerase chain reaction (PCR)-based assays were not available.

In conclusion, our results showed cases of scrub typhus as an important cause of acute febrile illness presenting as an undifferentiated fever, bilateral pneumonia resembling atypical pneumonia or fever with diverse sepsis syndromes in areas of Uttarakhand and Uttar Pradesh, particularly from July to November. In resource-limited settings and pending laboratory

confirmation, clinicians may implement a 'suspect and treat' strategy and initiate prompt treatment with doxycycline or azithromycin, to prevent serious morbidity and fatality in this potentially treatable and curable illness. CAP was the most common presentation of this re-emerging, under-recognized and widely prevalent disease. Empiric therapy of patients with CAP may, therefore, include macrolides (azithromycin) or doxycycline in addition to a beta-lactam agent, to ensure coverage against atypical pathogens, including *O. tsutsugamushi*, since scrub typhus may be an underlying and unsuspected cause.

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**Conflicts of Interest:** None.

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