Acute respiratory failure in scrub typhus patients

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Abstract

Respiratory failure is a serious complication of scrub typhus. In this prospective study, all patients with a diagnosis of scrub typhus were included from a single center Intensive Care Unit (ICU). Demographic, clinical characteristics, laboratory, and imaging parameters of these patients at the time of ICU admission were compared. Of the 55 scrub typhus patients, 27 (49%) had an acute respiratory failure. Seventeen patients had acute respiratory distress syndrome, and ten had cardiogenic pulmonary edema. Respiratory supported patients were older had significant chronic lungs disease and high severity illness scores (Acute Physiology and Chronic Health Evaluation-II and Sequential Organ Failure Assessment score). At ICU admission, these patients presented with more deranged laboratory markers, including high bilirubin, high creatine kinase, high lactate, metabolic acidosis, low serum albumin, and presence of ascites. The average ICU and hospital stay were 4.27 ± 2.74 and 6.53 ± 3.52 days, respectively, in the respiratory supported group. Three patients died in respiratory failure group, while only one patient died in nonrespiratory failure group.

Keywords: Acute respiratory distress syndrome, respiratory failure, scrub typhus

Introduction

Scrub typhus is a life-threatening zoonotic infectious disease and represents one of the most underdiagnosed and underreported acute undifferentiated febrile illnesses. The organism causing scrub typhus, Orientia tsutsugamushi, is an obligate intracytosolic Gram-negative bacterium that is transmitted by feeding larval trombiculid mites, which is both the vector and reservoir of the disease.[1]

In the rural area of Asia, where scrub typhus is endemic, it is among major cause (up to 20%) of acute febrile illness requiring hospital admissions.[2] Scrub typhus clinical manifestation is diverse ranging from a nonspecific febrile illness to severe multiorgan dysfunction, with an overall mortality of 6–24%.[3,4] Acute respiratory failure (ARF) is a serious manifestation of untreated scrub typhus.[5] The purpose of the present study was to investigate the risk factor, clinical course, and outcome of scrub typhus patients complicated with ARF.

Materials and Methods

This was a prospective observational study conducted in a medical Intensive Care Unit (ICU) of a Tertiary Care Hospital in Southern India between June 2013 and December 2014. All consecutive adult patients with a diagnosis of scrub typhus, which was based on the detection of antibodies by a solid phase immunochromatographic assay, were studied. Demographic and clinical characteristics of these patients, including comorbidities, sign and symptoms, biochemical and microbiological investigations, severity scores Sequential Organ Failure Assessment (SOFA) scores, and Acute Physiology and Chronic Health Evaluation...
Diabetes mellitus was common comorbid present in seven patients, followed by chronic lungs disease (six patients) and hypertension (five patients). The mean severity of illness at ICU admission, SOFA score and APACHE-II score were 6.64 ± 3.72 and 13.03 ± 6.46, respectively. The most common symptoms were fever (100%), headache (63.3%), myalgia (52.5%), vomiting (41.8%), diarrhea (16.4%), abdominal pain (38.2%), and altered sensorium (56.4%). Respiratory symptom such as dyspnea (52.2%) and flu-like illness (38.2%) was present in more than half of the patients. Five patients (9%) had seizure (three generalized and two focal) and with 2 having Glasgow Coma Scale (GCS) <8. Other common presentation were skin rashes (32.7%), 13 (23.6%) jaundice, 8 (14.5%) eschar, 29 (52.7%) lymphadenopathy, and 5 (9.1%) presented with minor bleeding.

Common laboratory abnormality [Table 2] seen in these patients were thrombocytopenia (92.7%), anemia (69.1%), leukocytosis (32.7%), leukopenia (9.1), hyperbilirubinemia (50.9%), hypoalbuminemia (90.1%), hyponatremia (40%), high anion gap metabolic acidosis (58.7%), and high blood lactate, i.e., >2 mmol/L (58.7%). High serum LDH and CK were present in 100% and 62.5% of patients, respectively. Ten patients had co-infection (seven dengue, one leptospirosis, and two malaria). Ultrasonography revealed splenomegaly in 38 (69.1%), hepatomegaly 28 (50.9%), ascites 29 (52.7%), pleural effusion 37 (67.3%), and global ventricular dysfunction in 10 (18.2%) patients.

The most common organ failures were respiratory (49.1%), followed by coagulation (16.4%), cardiovascular (12.7%), central nervous system (9.1%), liver (9.1%), and kidney (7.4%). Twenty-nine (52.7%) patients required respiratory support for the neurological cause (GCS <8), while 27 (49.1%) needed ventilation for ARF. Fourteen (25.5%) patients presented with shock (ten cardiogenic and four septic shock) required vasoactive drugs, and 7.3% patients required renal replacement therapy for acute kidney injury (AKI). The average ICU and hospital stay is 4.27 ± 2.74 and 6.53 ± 3.52, respectively, which was significantly higher in respiratory failure patients (P = 0.000). In follow-up, overall four (7.3%) patients died (three in respiratory failure group).

ARDS was cause of MV support in 17 patients and rest 10 patients required respiratory support for cardiogenic pulmonary edema [Table 3]. Respiratory supported patients were older (45.15 ± 12.55, P = 0.054), had significant chronic lungs disease (P = 0.008), high severity illness score APACHE-II (P = 0.001), and SOFA (P = 0.000) score [Table 1]. Signs and symptoms
such as flu-like illness ($P = 0.041$), dyspnea ($P = 0.000$), myalgia ($P = 0.009$), lymphadenopathy ($P = 0.001$), and hypotension ($P = 0.000$) were more commonly seen in respiratory supported group. Laboratory and imaging parameter that were significantly associated with respiratory support cohort are hyperbilirubinemia ($P = 0.021$), low serum albumin ($P = 0.021$), elevated serum CK ($P = 0.007$), blood lactate ($P = 0.047$), high anion gap metabolic acidosis ($P = 0.038$), pleural effusion ($P = 0.001$), ascites ($P = 0.043$), and global hypokinesia of left ventricle ($P = 0.000$) [Table 2]. Clinical feature that were negatively associated with respiratory failure group were seizure ($P = 0.021$) and altered sensorium ($P = 0.022$). Although anemia (69.1%), thrombocytopenia (92.7%), leukocytosis (32.7%), leukopenia (9.1%), liver injury (58.1%), AKI (29.1%), and hyponatremia (40%) are commonly found in scrub typhus patients, none were significantly associated with respiratory support group.

Among the respiratory failure patients, ARDS group were found to have significant low PaO$_2$/FiO$_2$ ($P = 0.000$) and high Murray lung injury score ($P = 0.000$), with no difference in mortality [Table 3]. The mean MV and NIV support days were nonsignificant ($4.60 \pm 2.79$ vs. $3.17 \pm 0.98 P = 0.932, 2.69 \pm 1.44$ vs. $1.83 \pm 0.753 P = 0.190$, respectively) between ARDS and cardiogenic pulmonary edema groups.

### Discussion

In the present cohort of patients with scrub typhus, half (49.1%) of the patients require MV support for respiratory failure. Eleven (40.7%) patients required IMV, 16 (59.26%) required NIV. Respiratory manifestations of scrub typhus are usually seen during the 2nd week of untreated illness,$^{[4,5]}$ and the presentation ranged from flu-like symptoms, bronchitis, interstitial pneumonitis to

| Table 1: Demographic, clinical characteristics of scrub typhus patients at intensive care unit admission and their outcome |
| --- |
| All patients ($n = 55$) | Respiratory failure ($n = 27$) | Nonrespiratory failure ($n = 28$) | $P$ |
| Age in years | 41.36±14.38 | 45.15±12.55 | 37.71±15.29 | 0.054 |
| Sex (male/female) | 26/29 | 12/15 | 14/14 | 0.687 |
| Co-morbid illness | 26 | 16 | 10 | 0.730 |
| Diabetic mellitus | 3 | 4 | 0.730 |
| Hypertension | 2 | 3 | 0.677 |
| Hypothyroidism | 3 | 1 | 0.290 |
| Chronic lungs disease | 6 | 0 | 0.008* |
| Chronic liver disease | 2 | 1 | 0.540 |
| Chronic kidney disease | 0 | 1 | 0.331 |
| Immune compromised | 0 | 0 | 0.730 |
| APACHE-II score | 13.03±6.46 | 15.78±6.179 | 10.36±5.625 | 0.001* |
| SOFA score | 6.64±3.72 | 8.70±3.303 | 4.64±2.972 | 0.000* |
| Day of illness on admission in ICU | 10.02±4.75 | 10.11±4.94 | 9.93±4.66 | 0.888 |
| Fever | 55 (100) | 27 (100) | 28 (100) | 0.888 |
| Headache (%) | 34 (63.6) | 18 (66.7) | 16 (57.1) | 0.477 |
| Flu-like symptom (%) | 21 (38.2) | 14 (51.8) | 7 (25) | 0.041* |
| Dyspnea (%) | 29 (52.7) | 24 (88.9) | 5 (17.8) | 0.000* |
| NM pain (%) | 29 (52.7) | 19 (70.4) | 10 (35.7) | 0.009* |
| Joints pain (%) | 17 (30.9) | 10 (37.0) | 7 (25) | 0.343 |
| Vomiting (%) | 23 (41.8) | 11 (39.3) | 12 (42.8) | 0.876 |
| Diarrhea (%) | 9 (16.4) | 2 (7.4) | 7 (25) | 0.081 |
| Abdominal pain (%) | 21 (38.2) | 13 (48.1) | 8 (28.6) | 0.140 |
| Jaundice (%) | 13 (23.6) | 9 (33.3) | 4 (14.3) | 0.100 |
| Concomitants (%) | 15 (27.3) | 10 (37) | 5 (17.8) | 0.114 |
| Lymphadenopathy (%) | 29 (52.7) | 20 (74.1) | 9 (32.1) | 0.001* |
| Escher (%) | 8 (14.5) | 5 (18.5) | 3 (10.7) | 0.421 |
| Bleeding (%) | 5 (9.1) | 4 (14.8) | 1 (3.6) | 0.153 |
| Seizure (%) | 5 (9.1) | 4 (14.8) | 1 (3.6) | 0.021 |
| Altered sensorium (%) | 31 (56.4) | 11 (39.3) | 20 (71.4) | 0.022 |
| AKI (%) | 16 (29.1) | 9 (33.3) | 7 (25) | 0.505 |
| Need for RRT (%) | 4 (7.3) | 3 (11.1) | 1 (3.6) | 0.290 |
| Shock (%) | 14 (25.5) | 13 (48.1) | 1 (3.6) | 0.000 |
| Need of mechanical ventilation (%) | 29 (52.7) | 27 (100) | 2 (7.1) | 0.003* |
| Mechanical ventilation day(s) | 3.82±2.04 | 2.5±0.77 | 0.400 |
| Invasive | 2.42±1.305 | 0.00 | 0.000* |
| Noninvasive | 2.67±2.59 | 2.93±2.18 | 0.000* |
| ICU stay days | 4.27±2.74 | 5.67±2.59 | 2.93±2.18 | 0.000* |
| Hospital stay days | 6.53±3.52 | 8.11±3.45 | 5.00±2.89 | 0.001* |
| Mortality (overall) | 5 (9.1) | 4 (14.8) | 1 (3.6) | 0.290 |

*Significant difference between the compared groups. APACHE: Acute physiology age chronic health evaluation, SOFA: Sequential organ failure assessment, ICU: Intensive care unit, RRT: Renal replacement therapy, AKI: Acute kidney injury
Table 2: Laboratory and imaging parameters of scrub typhus patients at intensive care unit admission

| Parameter                          | All patients (n=55) | Respiratory failure (n=27) | Nonrespiratory failure (n=28) | P  |
|-----------------------------------|---------------------|---------------------------|------------------------------|----|
| Anemia (Hb<12 g %)                | 38(55) (69.1)       | 74.1 (20)                 | 64.3 (18)                    | 0.442 |
| Leukocyte count                   |                     |                           |                              |    |
| Abnormal                          | 23 (41.8)           | 13 (48.1)                 | 10 (35.7)                    | 0.919 |
| Leukocytosis (> 11,000/mm³)       | 18 (32.7)           | 12 (44.4)                 | 6 (21.4)                     |    |
| Leukopenia (< 4000/mm³)           | 5 (9.1)             | 1 (3.7)                   | 4 (14.3)                     |    |
| Thrombocytopenia (/mm³)            |                     |                           |                              |    |
| < 1.5 Lakh                        | 51 (92.7)           | 27 (100)                  | 24 (85.7)                    | 0.037* |
| 100,000-150,000                   | 15 (27.3)           | 5 (18.5)                  | 10 (35.7)                    |    |
| 50,000-100,000                    | 27 (49.1)           | 18 (66.6)                 | 9 (32.1)                     |    |
| < 50,000                          | 9 (16.4)            | 4 (14.8)                  | 5 (17.8)                     |    |
| Bilirubin (> 1.2 mg/dl)           | 28 (50.9)           | 18 (66.6)                 | 10 (37.7)                    | 0.021* |
| AST (> 40 U/L)                    | 44 (80)             | 24 (88.9)                 | 20 (71.4)                    | 0.109 |
| ALT (> 60 U/L)                    | 32 (58.2)           | 20 (74.7)                 | 12 (42.8)                    | 0.053 |
| Prothrombin time (INR > 1.2)      | 22 (40)             | 11 (40.7)                 | 11 (39.3)                    | 0.914 |
| APTT (> 1.5 times than normal)    | 8 (14.5)            | 5 (18.5)                  | 3 (10.7)                     | 0.421 |
| AKI (serum creatinine > 1.5 mg/dl)| 16 (29.1)           | 9 (33.3)                  | 7 (25)                       | 0.505 |
| Serum albumin (< 3.5 g/dl)        | 50 (90.1)           | 27 (100)                  | 23 (82.4)                    | 0.021* |
| Very low albumin (< 2.5 g/dl)     | 33 (60)             | 20 (74.1)                 | 13 (46.4)                    | 0.037* |
| Hyponatremia (< 130 mEq/L)        | 22 (40)             | 11 (40.7)                 | 11 (39.3)                    | 0.914 |
| LDH (280 U/L)                     | 27/27 (100)         | 17 (100)                  | 10 (100)                     | 0.354 |
| CK (350 U/L)                      | 25/40 (62.5)        | 19 (76)                   | 6 (40)                       | 0.007* |
| Blood lactate (> 2 mmol/L)        | 27/46 (58.7)        | 18 (66.7)                 | 9 (32.1)                     | 0.047* |
| High AG metabolic acidosis (%)    | 32 (58.2)           | 20 (74.1)                 | 12 (42.8)                    | 0.038* |
| Hepatomegaly                      | 28 (50.9)           | 17 (62.9)                 | 11 (39.3)                    | 0.082 |
| Ascites                           | 29 (52.7)           | 18 (66.7)                 | 11 (39.2)                    | 0.043* |
| Pleural effusion                  | 37 (67.3)           | 24 (88.9)                 | 13 (46.4)                    | 0.001* |
| Abnormal chest X-ray             | 30 (54.5)           | 24 (88.9)                 | 6 (21.4)                     | 0.000* |
| Two-dimensional - echocardiography (global dysfunction) | 10 (18.2) | 10 (37.0) | 0 (0) | 0.000* |

*Significant difference between the compared groups. AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. LDH: Lactic dehydrogenase. CK: Creatine kinase. APTT: Activated partial thromboplastin time. AKI: Acute kidney injury. INR: International normalized ratio.

Table 3: Severity of hypoxemia and ventilator support in patients with respiratory failure

| Parameter                          | ARDS (n=17) | Cardiogenic pulmonary edema (n=10) | P  |
|-----------------------------------|-------------|------------------------------------|----|
| PaO₂/FIO₂ ratio                   |             |                                    |    |
| ≤ 100                             | 1           | 1                                  | 0.000* |
| 101–200                           | 14          | 9                                  |    |
| 201–300                           | 2           | 0                                  |    |
| LIS* (> 2.5)                      | 3           | 0                                  | 0.000* |
| Need of ventilation               |             |                                    |    |
| Invasive MV                       | 5**         | 6***                               |    |
| Noninvasive MV                    | 12          | 4                                  |    |
| Ventilator support (s)            |             |                                    |    |
| Invasive MV day (s)               | 4.60±2.79   | 3.17±0.98                          | 0.932 |
| Noninvasive MV day (s)            | 2.69±1.44   | 1.83±0.753                         | 0.190 |
| ICU stay days                     | 5.88±2.71   | 5.30±2.45                          |    |
| Hospital stay days               | 8.59±3.79   | 7.30±2.75                          |    |
| Mortality                         | 2           | 1                                  |    |

*Significant difference between the compared groups. **One patient was converted from noninvasive MV to invasive MV. ***Two patients were converted from noninvasive MV to invasive MV. PaO₂/FIO₂ ratio: PaO₂ is partial pressure of arterial oxygen and FIO₂ is fraction of inspired oxygen. LIS*: Lung injury score. ICU: Intensive care unit. MV: Mechanical ventilation. ARDS: Acute respiratory distress syndrome.

In the current study, scrub typhus patients with respiratory failure were older (45.15 ± 12.55 years) and had high SOFA and APACHE-II score compare to the nonsupported patient. The incidence of respiratory failure was higher in patients with chronic lung disease (22.2%, P = 0.008), which is contrary to previous studies.

Clinical manifestation of scrub typhus ranges from a mild to a fatal illness. The typical scrub typhus begins insidiously as an acute febrile illness with fever, headache, malaise, rashes, myalgia, sore throat, cough, vomiting, diarrhea, lymphadenopathy, eschar, and abdominal pain. In the respiratory failure group, dyspnea, cough, myalgia, and lymphadenopathy were significantly present, and this finding is consistent with the findings of the previous study. If treated with appropriate antibiotic, symptom resolve rapidly. Untreated patients entering the 2nd week of illness develop a serious complication such as severe respiratory distress syndrome, encephalitis, interstitial pneumonia, myocarditis, AKI, acute hepatic failure, pancreatitis, and septic shock. These severe clinical manifestations are due to generalized vasculitis due to the invasion of the endothelial cell by the organism and perivascular infiltrate of leukocyte. The common organ failures seen in our cohort were respiratory (49.1%), coagulation...
Although the previous study showed a significant high incidence of leukocytosis and low hematocrit in ARDS group, our study did not find. Abnormal liver biochemical test (bilirubin, alanine aminotransferase, and aspartate aminotransferase) was increased in both group, but only bilirubin level was significantly higher in the respiratory supported group in accordance with other studies. Other laboratory abnormalities significantly seen in our patients with respiratory support were hypoalbuminemia, hyperlactemia, high serum creatinine kinase, and high anion gap metabolic acidosis, which was not observed in other studies except hypoalbuminemia. The mechanism of hypoalbuminemia in scrub typhus is due to poor oral intake, decrease synthesis of protein from the injured liver, increase catabolism of protein, and vascular leakage of protein due to vasculitis or perivasculitis. This widespread vascular permeability leads to anasarca and polyserositis such as pleural effusion and ascites. The reported incidence of abnormal chest radiographic in scrub typhus infection varies from 59% to 72%, which was slightly higher from our cohort (54.5%). The common findings are the bilateral diffuse area of reticulonodular opacity predominantly in middle and lower lobe of lungs. Pleural effusion is a common finding with a reported incident varies from 12% to 43%, but our cohort had a higher incidence of pleural effusion (overall, 54.4%) and 88.9% in respiratory supported patients.

Mortality rates of severe complicated scrub typhus are estimated to be approximately 35% to 40% and scrub typhus complicating ARDS mortality is about 22–45%. In our cohort of patients, the overall mortality was 7.3% (4/55), while 11.1% in respiratory failure patients, which was insignificant compared to nonrespiratory failure group. This low mortality in our cohort could be due to appropriate early antibiotic (doxycycline) therapy and better ICU care down the years compared to older studies.

**Conclusion**

ARF is a serious and common complication of patients with scrub typhus who require ICU admission. These patients presented with more deranged laboratory markers, including high bilirubin, high CK, high lactate, metabolic acidosis, low serum albumin, and presence of ascites, at the time of ICU admission. Moreover, these patients require more days of ICU and hospital stay in comparison to patients without respiratory failure.

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**Conflicts of interest**

There are no conflicts of interest.

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