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Original Research Article

Clinical characteristics and outcome of patients hospitalised with Scrub typus -A tertiary care hospital study in Northern India

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Abstract

Background: Scrub typhus is a re-emerging but under-reported infectious diseases that leads to significant morbidity and mortality, if failed to diagnose at appropriate time. The objective of the present study was to, know the Clinical Characteristics and Outcome of adult patients hospitalised with Scrub typhus in a tertiary care hospital in a hilly state of Uttarakhand.

Materials and Methods: A total of 68 patients of Scrub Typhus from June 2020 to December 2020 were enrolled in the study. All hospitalised patients included in study were evaluated by detailed history, laboratory tests and outcome in response to treatment with Scrub typhus active antibiotics.

Results: Majority of the cases (54 of 68{79.4 %}) were reported during monsoon and post monsoon season from July to October month. It affects patients of all age group but majority (47 of 68{70.0%}) of patients in our study were young between the age of 18‑40 years. Females were more in number (41of 68, {60.3%}) in comparison to males (27of 68, {39.7%}). Fever in (68 of 68{100%}) was universal complaint associated with severe headache in (18 of 68{26.5%}) patients. Other common symptoms reported were cough & breathlessness in (25 of 68{40.0%}), Nausea and vomiting in (15 of 68 {20%}), abdominal pain in (13 of 68{19.2%}), and altered sensorium in (05 of 68 {8.3%}). GI system involvement in the form of Acute hepatitis with rise in SGOT/SGPT was the most common complication seen in (52 of 68{76.5%}) followed by Respiratory involvement in form of interstitial Pneumonia, interstitial Pneumonia with Pleural effusion, and ARDS was seen in (26 of 68{38.3%}). Renal involvement in the form of AKI with rise in urea and creatinine was seen in (17 of 68{25.0%}) patients. Only 6 (8.8%) of 68 patients received appropriate antibiotics for scrub typhus before admission. Treatment failure, defined by failure to defervescence within 72 hours of scrub typus active antibiotics treatment initiation was noted in 09 (13.2%) patients, out of which 06 (8.8%) patients died in the hospital. No evidence of relapse or reinfection was noted in any patient.

Conclusion: The diagnosis of scrub typhus is challenging due to nonspecific sign and symptoms. A misdiagnosis leading to delayed targeted medical intervention with Scrub typhus active antibiotics (Chloramphenicol, Doxycycline, Azithromycin and Clarithromycin) is the likely contributory factors for high mortality (6 of 68, {8.8%}) in our study.

Keywords: Adult respiratory distress syndrome, Orientia tsutsugamushi, Chigger mites, Scrub typhus active antibiotics (Chloramphenicol, Doxycycline, Azithromycin and Clarithromycin), IV- Intravenous.

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1. Introduction

Scrub typhus, is an important and neglected vector borne zoonotic disease caused by Orientia tsutsugamushi and is transmitted to humans through the bite of chigger larvae (trombiculid mites).[1-3] It can affect individuals of all ages, including children and has the potential of causing life threatening febrile infection in humans. An increase in the incidence of scrub typhus has been documented in various Asian countries, including India, likely linked to both the extensive use of β-lactam antibiotics and the urbanization of rural areas.[4] It is considered as a re-emerging infectious disease in India,[5] with outbreaks reported in sub-Himalayan regions stretching from Jammu to Nagaland.[6-8] The seasonal occurrence of the disease varies according to the climate in different regions.

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Diagnosing scrub typhus can be challenging due to its non-specific symptoms. While fever is the most common manifestation, patients may also experience headache, muscle pain, abdominal pain, cough, lymphadenopathy, and hepatosplenomegaly.[9] Severe cases can lead to complications such as interstitial pneumonia, acute respiratory distress syndrome (ARDS), acute liver failure, acute renal failure, disseminated intravascular coagulation (DIC), meningitis, and myocarditis.[10] Timely diagnosis and treatment with Scrub typhus active antibiotics, are critical in reducing the risk of complications and death. Effective treatment includes antibiotics such as Chloramphenicol, Doxycycline, Azithromycin, and Clarithromycin.[11] The rapid reduction in fever following treatment with Scrub typhus active antibiotics is a hallmark of scrub typhus, often used as a diagnostic indicator for O. tsutsugamushi infection.[12]

This study aims to examine the clinical characteristics of scrub typhus and assess the factors influencing treatment outcomes with antibiotics known to be effective against the disease in hospitalized patients

2. Material and Methods

2.1. Study design

Prospective cross-sectional observational study.

2.2. Study setting

The study was conducted in the Department of Internal Medicine, SMIH- a tertiary care teaching hospital of Shri Guru Ram Rai Institute of Health and Medical Sciences, Dehradun in the state of Uttarakhand.

2.3. Study period

June 2020 to December 2020 for a period of 7 months after getting approval from IEC.
The study group consist of Patients admitted in medicine wards and Intensive Care Units (ICU) as per criteria mentioned.

2.3. Inclusion criteria

Patients admitted in Medicine ward and Intensive Care Units (ICU) with history of fever who were tested positive for IgM antibodies against *O. tsutsugamushi* by solid phase immune chroma to graphic test assay.

2.4. Exclusion criteria

1. Patients admitted with other causes of fever like Malaria, Dengue fever, Leptospirosis, Typhoid fever, Urinary Tract Infections, H1N1 viral infection.
2. Patients < 18 years of age.
3. Pregnant females
4. Chronic renal disease.
5. Chronic liver disease.
6. Underlying malignancy.

Patients positive for IgM scrub typhus antibodies and admitted in hospital were enrolled for the study. Test for serum IgM for scrub typhus was done using Bioline Rapid Diagnostic Test kit by Abbott Diagnostic Korea Inc. an immunochromatographic based test (ICT) in the Microbiology Department of our hospital. Complete Demographic, Clinical and Laboratory data was collected individually on study Proforma. Complete history including antibiotic taken before hospital admission, were noted in all the patients. Special investigations like lumbar puncture and NCCT- head were done in few selected patients only.

2.5. Data analysis

Microsoft Excel spread sheet was used to collect and analyse the data. The results were reported in percentage for both numerical and categorical data.

3. Results

Table 1: Month wise distribution of cases of Scrub typhus included in study (n=68)

Month	No. of cases	Percentage (%)
June	05	7.4
July	15	22.0
August	17	25.0
September	12	17.7
October	10	14.7
November	07	10.3
December	02	2.9

Table 2: Demographic data and clinical profile of 68 patients of Scrub typhus included in the study.

Demographic data and Clinical Characteristics of Patients of Scrub typhus (n=68)		
Age (years)	**No. of cases**	**Percentage**
18-40	47	69.2%
41-50	14	20.6%
> 50	07	10.2%
Gender		
Male	27	39.7%
Female	41	60.3%
Duration of fever (Days)		
1-7 days	18	26.5%
7-14 days	44	64.7%
> 14 days	06	8.8%
Clinical Features		
Symptoms		
Fever	68	100.0%
Breathlessness	25	40.0%
Headache	18	26.5%
Nausea /Vomiting	15	22.0%
Abdominal pain	13	19.2%
Jaundice	12	17.7%
Oliguria	11	16.2%
Altered sensorium	05	7.4%

Signs		
Lymphadenopathy	22	32.3%
Pallor	15	22.0%
Icterus	11	16.2%
Hepatomegaly	12	17.6%
Splenomegaly	13	19.2%
Meningeal signs	05	7.4%
Eschar	05	7.4%

Table 3: Showing laboratory parameters in patients of Scrub typhus

Laboratory Investigations	**No of cases**	**Percentage (%)**
Haemoglobin (Hb) < 11 g/dl	26	38.3
Total Leucocyte Count (TLC)		
Leucocytosis > (11000/cu. mm.)	24	35.3
Leucopenia < (4000/cu. mm.)	07	10.2
Platelet Count (PLT)		
< 1.5 lakh/cu. mm.	25	36.8
<50,000/cu. mm.	08	11.8
Sr. Bilirubin > 1.3 mg/dl	22	32.2
SGOT(AST) > 59 U/L	52	76.4
SGPT(ALT) >50 U/L	50	73.6
Sr. Creatinine > 1.3 mg/dl	17	25.0

3.1. Month wise, Age and Sex distribution of the patients

This study was conducted over a period of 7 months from June -December 2020. More than 2/3rd patients (79.4%) reported in month of July to October, coinciding with monsoon and post monsoon period in Uttarakhand. Majority of the patients admitted were young, with almost (70.0%) were less than 40 years of age. More females patients 41(60.0%) were affected compared to 27(40%) males.

3.2. Clinical characteristics of patients with Scrub typhus

Fever was universal complaint at the time of presentation (68 of 68{100%}). The fever was high grade, continuous associated with severe headache in (18 of 68{26.5%}) patients. Majority of patients 44 of 68{64.7%}) presented with 7-14 days duration of fever and around (18 of 68{26.5%}) presented with < 7 days duration of fever. Headache noted in (26.5%) was very severe and an important clinical finding. Cough was another common presenting complaint associated with breathlessness in (26 of 68{38.3%}) patients. Nausea with loss of appetite was another common complaint and in around (15 of 68{22%}) patients was associated with episodes of vomiting. Other common clinical findings noted were jaundice in 12 (17.6%), abdominal pain in 13 (19.2%) and altered sensorium in 05 (7.4%) patients. On examination, lymphadenopathy noted in 22 (32.3%) was the most common finding, which can be easily missed if patient is not examined properly and is an important diagnostic clue for Scrub typhus. pallor was noted in 15 (22.0%) patients followed by icterus in 11(16.2%). Hepatomegaly in 12 (17.6%) and splenomegaly in 13 (19.2%) were other important findings noted in patients of Scrub typhus. Around 5 (7.4%) patients presented with altered sensorium were critically sick and were treated on the lines of meningoencephalitis. Eschar Pathognomonic of Scrub typhus was noted in only 5 (7.4%) patients.

3.3. Complications observed in patients with Scrub typhus

The complications seen in patients of Scrub typhus in our study are depicted in **Table 4**. Liver involvement in the form of raised transaminases was the most common complication noted in (52;76.5%) patients followed by Respiratory dysfunction in (26; 38.3%) and Acute kidney injury in (17; 25.0%) with oliguria in 11 (16.2%) respectively. Among the 26 patients with respiratory dysfunction, Interstitial Pneumonia (16, 23.6%), Interstitial Pneumonia with pleural effusion (04, 5.9%) were the commonest findings, followed by ARDS in (06; 8.8%) respectively.

Table 4: Distribution of complications and outcome seen in patients of Scrub typhus included in study.

Complications and outcome		
Complication	**No of cases**	**Percentage**
Hepatic dysfunction	52	76.5%
Acute kidney injury (AKI)	17	25.0%
Interstitial Pneumonia	16	23.6%
Interstitial Pneumonia with Pleural effusion	04	5.9%
ARDS	06	8.8%
Meningoencephalitis	05	7.4%
Myocarditis	01	1.5%
Mortality	06	8.8%

3.4. The treatment given to patients hospitalised with Scrub typhus

The treatment given are outlined in **Table 5**. Preadmission antibiotics were received by all the 68 (100%) patients {likely due to poor Government policy of Over The Counter (OTC) availability of antibiotics in India} but only, 6 (8.8%) of the patients received appropriate antibiotics active against Scrub typhus, that too not in recommended doses. After hospital admission and diagnosis, all the patients were given antibiotic active against scrub typus, (Chloramphenicol, Doxycycline, Azithromycin and Clarithromycin) plus either 3rd generation Cephalosporin or Piperacillin-Tazobactum, as per culture sensitivity report and clinical presentation of the patients. During the study period Intravenous (IV) Chloramphenicol was extensively used and resulted in highest recovery rate followed by (IV) Doxycycline and then (IV) Azithromycin. Chloramphenicol IV was given in dose of 1 gm 6 hourly as infusion form, Doxycycline IV in dose of 100 mg 12 hourly and Azithromycin IV in dose of 500 mg twice daily as infusion form. Not even a single Adverse Drug Reaction (ADR) reported with use of IV Chloramphenicol in

any patients in our study. Mortality 6 (8.8%) was mostly seen in patients transferred from other hospital with multiorgan dysfunction especially in patients with ARDS requiring mechanical ventilation.

Table 5: Showing in detail the treatment of scrub typhus patients

Treatment of Scrub Typhus patients	Scrub Typhus Patients (STP) n=68 (%)
Pre-admission antibiotics n(%)	68 (100%)
Antibiotics (n=68)	
Amoxycillin plus clavulanic acid n (%)	25 (36.7%)
3rd Generation Oral Cephalosporin	32 (47.0%)
Cefixime n (%)	16 (23.5%)
Cefpodoxime n (%)	14 (20.6%)
Cefixime plus Ofloxacin n (%)	5 (7.4%)
3rd generation Cephalosporin IV with scrub typhus active antibiotics n (%)	06 (8.8%)
Post-admission antibiotics n (%)	68 (100%)
IV Doxycycline alone	10 (14.7%)
3rd generation I.V. Cephalosporin* and Chloramphenicol	12 (17.6%)
Piperacillin-Tazobactum and Chloramphenicol	28 (41.2%)
Piperacillin-Tazobactum plus Chloramphenicol and Azithromycin	18 (26.5%)

*IV third generation cephalosporin include Ceftriaxone, Cefoperazone, ceftazidime.

4. Discussion

Scrub typhus is an under acknowledged neglected disease of serious public health concern in India. A total of 68 patients admitted in Medicine wards and Medical ICU were enrolled in this study. Scrub typus cases are reported each year during monsoon season, so this study was planned accordingly from June 20- December 2020 for a period of 7 months coinciding with monsoon and post mansoon season in hilly state of Uttarakhand.

A total of 6 patients admitted in Medical ICU died during the study period, (4 patients with ARDS on ventilatory support and 2 patients with meningoencephalitis). Majority of cases around (79.8%) reported in month of July-October

Majority of the patients were young with almost (70%) patients were less than 40 years of age. (36 of 68{60%}) patients were females. This is because in hilly areas females are actively involved in harvesting and other field activities, where they accidently come in contact with larval mites. Kumar R *et al*,[13] also reported similar results with 62 % patients were < 50 year of age.

High grade continuous fever was most common presenting symptom. Majority of patients (44 of 68{64.7%}) reported in our study, had history of fever duration between 7-14 days. The study was conducted in a tertiary care centre and get referrals from almost every corner of Uttarakhand, so most patients had a history of fever lasting > 7 days. Gopal D S *et al*,[14] reported similar results with 42.1% (118/280) patients presented with > 10 days duration of fever, and 32.1% (90/280) had prolonged pyrexia beyond 2 weeks. Leucocytosis noted in 35.3% (24/68) patients was an important finding with but few patients around 10.3% (7/60) had Leucopenia. Thrombocytopenia was another important finding observed in many patients. 36.8% (25/68) patients had platelet count < 1.5 lakh/cu.mm, out of which 11.8% (8/68) had severe thrombocytopenia <50,000/cu.mm.

GI symptoms like nausea/vomiting, upper abdomen tenderness with loss of appetite were predominantly due to Liver involvement in the form of Acute Hepatitis with five to even > 10 fold rise in AST/SGOT (52; 76.5%) and ALT/SGPT (50; 73.6%) respectively. In a similar study done by Varghese GM *et al*,[15] abnormal liver function tests with elevated transaminases (SGOT/SGPT) was noticed in (87%) cases and thrombocytopenia in (79%), and leucocytosis in (46%) cases respectively.

Respiratory dysfunction (26 of 68{38.3%}) was reported in the form of Interstitial Pneumonia (16, 23.6%), Interstitial Pneumonia with pleural effusion (04, 5.9%) followed by ARDS in (06; 8.8%) cases respectively. In a similar study done by Philomena J *et al*,[16] reported pneumonia in 4% patients only but ARDS in 11% patients almost comparable to 8.8% reported in our study. Renal involvement in the form of AKI with rise in creatinine was seen in (17 of 68{25.0%}) patients. Study done by Attur R.P. *et al*,[17] shows AKI in 23.2% patients almost similar as reported in our study.

Appropriate antibiotics were administered once the patient with history of fever tested positive for IgM scrub typhus antibodies. Among Scrub typhus active antibiotics used, early defervescence rate were seen with use of IV Chloramphenicol followed by Doxycycline and Azithromycin respectively. Lee M *et al.*[18] reported similar results {defervescence after therapy mean duration (1.26 ± 0.03) days} in 19 patients treated with Chloramphenicol. However, antibiotics used in the community and other health care facilities frequently excluded coverage for scrub typhus.[19] As a consequence, effective treatment was delayed in most of the patients, which might have contributed to high complication (76.5%) and treatment failure (13.3%) rates in our study. High mortality (8.8%) was seen mostly in patients transferred from other hospitals with multiorgan dysfunction and in patients who developed ARDS and required mechanical ventilation.

5. Limitations of the Study

As only hospitalised patients which were sick and mostly transferred from peripheral hospitals were included in the study, could be one factor for high mortality (10%) seen in our study.

6. Conclusion

Scrub typhus is a re-emerging disease in India and has to be considered in the differential diagnosis of fever of unknown origin with multiorgan dysfunction. This study highlights the clustering of cases in monsoon and post monsoon season from July-October in hilly state of Uttarakhand. Among Scrub typhus active antibiotics given, I.V. Chloramphenicol has shown highest efficacy and early defervescence in patients > 18 years of age. Early diagnosis and prompt treatment with Scrub typhus active antibiotics can significantly reduce complications and mortality.

7. Source of Funding

None.

8. Conflicts of Interest

The authors declare no conflicts of interest.

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