

# Study on Clinico -Laboratory Profile of Children with Scrub Typhus

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## Abstract

Scrub typhus is an acute, febrile, infectious illness caused by *Orientia* (formerly *Rickettsia*) *tsutsugamushi*, an obligate intracellular gram-negative bacterium. Humans are accidental hosts in this zoonotic disease. The present retrospective study describes clinical profile of the children hospitalized in hospital with Scrub Typhus infection during period 2010-2011. 19 hospitalized children with clinical features suggestive of Rickettsial disease (fever, generalized rash) who tested ELISA positive for IgM against Scrub Typhus were included in the present study between the age of 1 years and 15 years. All children presented with fever (100%). 42.10% had lymphadenopathy, 47.36% had eschar and 57.89% patients had cough. 26.31, 21.05%, 10.52%, had hepatomegaly, pain abdomen, and respiratory distress and gastrointestinal bleed respectively. All of the children were investigated and treated with as per protocol. None of them died. We think that Rickettsial infection is not quite common in this region but study showed that it is not an uncommon entity and thus, high degree of suspicion, knowledge of geographical distribution and clinical features of Rickettsial disease helps in its early diagnosis and treatment.

**Key words:** Rickettsial, Scrub Typhus, *Orientia Tsutsugamushi*.

## Introduction

Scrub typhus is an acute, febrile, infectious illness is caused by *Orientia tsutsugamushi*, an obligate intracellular gram-negative bacterium, which was first isolated in Japan in 1930. The term scrub is used because of the type of vegetation (ie, terrain between woods and clearings) that harbours the vector. However, the name is not entirely correct because certain endemic areas can also be sandy and semiarid. Cases diagnosed in the United States have been imported from regions of the "tsutsugamushi triangle," which extends from northern Japan and far-eastern Russia in the north, to northern Australia in the south, and to Pakistan and Afghanistan in the west, where the disease is endemic. The range includes tropical and temperate regions, extending to altitudes of more than 3200 meters in the Himalayas. Although it was originally recognized as one of the tropical rickettsial diseases, *O tsutsugamushi* has

a different cell wall structure and genetic composition than that of the rickettsiae.

Western medicine became more interested in this infection during military campaigns fought in East Asia. During World War II, 18,000 cases were observed in Allied troops<sup>1</sup>. It was the second or third most common infection reported in US troops stationed in Vietnam<sup>2</sup> and continues to infect troops in the region<sup>3,4</sup>. Scrub typhus is often acquired during occupational/agricultural exposures<sup>5</sup> because active rice fields are an important reservoir for transmission. Because of reports of *O tsutsugamushi* strains with reduced susceptibility to antibiotics<sup>6</sup>, as well as reports of interesting interactions between this bacterium and HIV, a renewed interest in this illness has emerged<sup>7,8</sup>.

## Epidemiology

Mortality rates in untreated patients range from 0-30% and tend to vary with the patient's age and region of infection. In the preantibiotic era, mortality rates in Japan averaged 30%. The mortality was 15% in patients aged 11-20 years, 20% in those aged 21-30

Manuscript received: 11<sup>th</sup> January 2012.

Reviewed: 21<sup>st</sup> March 2012

Author Corrected: 4<sup>th</sup> April 2012

Accepted for Publication: 22<sup>nd</sup> August 2012

years, and 59% in those older than 60 years. In Taiwan, the overall mortality was estimated at 11% but was only 5% in children and 45% in the elderly. With appropriate treatment, mortality is quite rare<sup>9</sup>. However, mortality is still approximately 15% in some areas due to missed or delayed diagnosis. If severe complications such as adult respiratory distress syndrome (ARDS) arise, mortality may still be high.

Scrub typhus is endemic in regions of eastern Asia and the southwestern Pacific (Korea to Australia) and from Japan to India and Pakistan<sup>10-15</sup>.

### Indian Scenario

Scrub typhus is prevalent in many parts of India but specific data are not available. There have been outbreaks in areas located in the sub-Himalayan belt, from Jammu to Nagaland. There were reports of scrub typhus outbreaks in Himachal Pradesh, Sikkim and Darjeeling (West Bengal) during 2003-2004 and 2007. Scrub typhus is considered a reemerging infectious disease in India<sup>16</sup>. A recent report based on serology suggests that, at least in southern India and Himalaya human rickettsioses and scrub typhus continue to occur and that the magnitude of the problem is not recognized<sup>17</sup>. It affects people of all ages; out of these paediatric scrub typhus is quite common and reported in past<sup>18,19</sup>.

Scrub typhus is transmitted to humans and rodents by some species of trombiculid mites. The mite is very small (0.2 - 0.4mm) and can only be seen through a microscope or magnifying glass. Humans acquire the disease from the bite of an infected chigger<sup>20,21</sup>. The bite of the mite leaves a characteristic black eschar that is useful to the physicians for making the diagnosis. The adult mites have a four-stage lifecycle: egg, larva, nymph and adult. The larva (chigger) is the only stage that can transmit the disease to humans and other vertebrates, since the other life stages (nymph and adult) do not feed on vertebrate animals. Both the nymph and the adult are free living in the soil. The disease is transmitted from mites to 'rats and mice' and the mites in their larval stage contract the disease organism by biting these rodents. Man is an accidental host. The disease is not directly transmitted from person to person.

Clinical suspicion may be delayed or absent in areas where the disease has not been documented or in regions lacking diagnostic facilities. Suspecting the diagnosis and initiating prompt antimicrobial drug therapy are important to prevent mortality. However, few studies have characterized pediatric scrub typhus in Rishikesh. We describe paediatric scrub typhus cases at a teaching hospital.

### Materials and Methods

The study was conducted at the Rishikesh Branch of Himalayan hospital, a secondary-care teaching hospital and one of the major hospitals in Rishikesh. We reviewed 19 paediatric cases with confirmed scrub typhus admitted, (Cases in whom all common causes were excluded (malaria/typhoid/UTI/Dengue) to our hospital in 2010-2011. The cases were confirmed by positive serology with an immunofluorescence antibody test (an IgM titer for scrub typhus) or a positive result with polymerase chain reaction (PCR). Epidemiological variables included in the analysis were gender, age, and city of residence. Clinical manifestations were fever, cough, rash, poor appetite, headache, vomiting, drowsiness, neck stiffness, lymphadenopathy, jaundice, eschar, abdominal pain, ascites, hepatomegaly, splenomegaly, and cholecystitis. Laboratory data were CRP, AST, ALT, and albumin levels, and white blood cell count in the blood and cerebrospinal fluid. The presence or absence of proteinuria was also documented.

### Results

**Table 1:** Showing general characteristics.

Data	Number of cases	Percentage
<b>Gender</b>		
Male	10	52.63
Female	9	47.36
<b>Age in years</b>		
Below 5 years	11	57.89
5-10 years	4	21.05
11-15 years	4	21.05
<b>Residence</b>		
Garhwali	15	78.94
Rishikesh	4	21.05

**Table 2:** Showing Symptoms/Signs found in this study.

	No of cases	Percentage (%)
<b>Fever duration</b>		
1-3 Days	2	10.52
3-7 Days	13	68.42
More than 7 Days	4	21.05
<b>Symptom/Signs</b>		
Eschar	9	47.36
Cough	11	57.89
Poor appetite	10	52.63
Lymphadenopathy	8	42.10
Headache	7	36.64
Rash	6	31.57
Hepatomegaly	5	26.31
Vomiting	4	21.05

Drowsiness	3	15.78
Abdominal pain	4	21.05
Splenomegaly	5	26.31
Neck stiffness	2	10.52
Jaundice	3	15.78
Ascites	1	5.26
Respiratory distress	2	10.52
Shock	2	10.52

**Table 3:** Showing Laboratory findings in paediatric scrub typhus patients.

Lab parameters	No of cases	Percentage (%)
Leukocytosis(WBC > 10,000 cells/mm <sup>3</sup> )	9	47.36
CRP elevation(CRP > 0.5 mg/dl)	17	89.47
AST elevation(AST > 40U/l)	16	54.21
ALT elevation(ALT > 40U/l)	14	73.68
Hypoalbuminemia(Albumin < 3.5 d/dl)	9	47.36
CSF leukocytosis(CSF WBC > 5 cells/mm <sup>3</sup> )	2/2	10.52
Proteinuria(Urine protein ≥ 1+)	8	42.10
Thrombocytopenia	13	68.42

A total of 19 scrub typhus cases were diagnosed from 2010 to 2011, with the greatest number of infections ( $n=12$ ) seen in 2011. All cases were serologically confirmed. The demographic results are seen in Table 1. Both males ( $n=10$ ) and females ( $n=9$ ) were among identified cases.

Children age 0 to 5 years old constituted for 57.89% of cases, children age 6 to 10 years old constituted 21.05% of cases, and children age 11 to 13 years old constituted 21.05% of cases. The majority of infections occurred between May and August. The largest number of cases were ( $n=15$ ) from Garwal region. Cases were also seen in Rishikesh ( $n=4$ ).

The clinical symptoms are shown in Table 2. All patients presented with fever, ranging from 1 to 14 days prior to hospital admission. Other symptoms included the presence of eschar ( $n=9$ ), lymphadenopathy ( $n=8$ ), poor appetite ( $n=10$ ), headache ( $n=7$ ), skin rash ( $n=6$ ), and hepatomegaly ( $n=5$ ). Other symptoms and signs were Vomiting ( $n=4$ ), Drowsiness ( $n=3$ ), Abdominal pain ( $n=4$ ), Splenomegaly ( $n=5$ ), Neck stiffness ( $n=2$ ), Jaundice ( $n=3$ ), Ascites( $n=1$ ), Respiratory distress( $n=2$ ) and shock ( $n=2$ ).

Several laboratory values were consistently elevated among cases, including white blood cell count ( $>10,000$  cells/mm<sup>3</sup>, 47.36% of cases), CRP level ( $>0.5$  mg/dl, 89.47%), ALT level

( $>40U/l$ , 73.68%), and AST level ( $>40U/l$ , 54.21%). Thrombocytopenia ( $<150,000/mm^3$ ) was seen in 68.42% of cases and hypoalbuminemia ( $<3.5$  g/l) was seen in 47.36% of cases. proteinuria ( $\geq 1+$ ) was identified in 42.10% of cases. Lumbar punctures were performed in 2 cases, both had cerebrospinal fluid leukocytosis ( $>5$  cells/mm<sup>3</sup>). No mortalities occurred in the subjects.

## Discussion

Scrub typhus, also known as tsutsugamushi disease, is an acute febrile illness caused by infection with *Orientia tsutsugamushi* and characterized by focal or disseminated vasculitis and perivasculitis, which may involve the lungs, heart, liver, spleen, and central nervous system<sup>22,23,24</sup>. The symptoms are usually mild and the clinical course selflimited, with spontaneous recovery after a few days. The diagnosis of scrub typhus is based on the patient's history of exposure, the clinical features, and the results of serologic testing<sup>(25,26)</sup>. The article provides a review of the clinical features and the complications of scrub typhus.

Fever was the commonest clinical presentation in the present case series (100% cases) in contrast to other reports from India where headache and myalgia (93.8%) were the most common manifestations of scrub typhus followed by fever<sup>27</sup>. Unlike reports from other studies, the clinical presentations in the present cases were peculiar in the sense that only 36.64% of cases presented with headache, myalgia and generalized body ache. Previous studies from various authors reveal that in India the rash is generally not seen so commonly<sup>28, 29</sup> and it was the same in the present case series. The painless chigger bite can occur on any part of the body but it is often located in areas that are hard to examine, such as the genital region or under the axilla. An eschar forms at the bite site in about half of the primary infections. It begins as a small papule, enlarges, undergoes central necrosis, and acquires a blackened crust to form a lesion resembling a cigarette burn<sup>30</sup>. The reported percentages of eschar formation showed substantial variations across different studies ranging from 15–100%<sup>31–34</sup>. Eschars can be detected relatively frequently in white skinned individuals. However, it is relatively difficult to detect on dark-skinned individuals as in India<sup>30</sup>. We noticed eschars in only 9 cases (47.36%). However, eschars have been described as the single most important diagnostic clue and therefore needs to be looked for in all febrile patients without localizing signs of the disease<sup>35</sup>.

Though rash is considered as a hallmark of rickettsial disease, it is neither seen at presentation nor in all the patients<sup>36,37</sup>. We found skin rashes only in 6 (31.57%) case. Lymphadenopathy, rash, leucocytosis and organomegaly, which are features of the disease in South East Asian countries, were not prominent in the present study, a finding similar to earlier studies from India<sup>38</sup>. Gastrointestinal symptoms mainly in the form of pain abdomen, vomiting and loose stool were found in 21.05% and 21.05% cases, respectively. This finding was consistent with the series by Liu YX et al who reported an overall 56% cases with gastrointestinal symptoms<sup>39</sup>. The reports from Jammu suggested that the percentages of cases with increased WBC counts were 28.57% , which were lower than those reported in the current study. Thrombocytopenia which was reported in 38.09% % cases in Jammu<sup>40</sup> is also lower than that obtained in the current study.

We found elevated aspartate aminotransferase (AST) in 54.21%, elevated alanine aminotransferase (ALT) level in 73.68%, hypoalbuminemia in 47.36% cases which is unlike the findings of Huang CT et al.<sup>41</sup> Non-specific lung infiltrates with predilection to the lower zone is described in scrub typhus<sup>42</sup> and was seen in 2 cases (10.52%) in the present series with both clinical and radiological findings.

Neurological complications in the form of meningoencephalitis were seen in 2 cases (10.52%). Mahajan SK, Rolain JM et al has reported 4 cases with meningoencephalitis among 27 confirmed cases of scrub typhus which correlates with the present findings<sup>43</sup>. Acute renal failure (ARF) has been described as a potential complication of scrub typhus cases<sup>44</sup> and one case of ARF was observed in the present case series that responded to conservative management. We also found 2 cases of shock in present study.

All patients responded to the initial antibiotic therapy and no case of clinical drug resistance was found.

Treatment schedule for scrub typhus followed in our department. Failure to respond was defined as no defervescence within 72 h and no clinical improvement after treatment.

1. A 7-day course of doxycycline 4 mg/kg/day orally in patients with no complications and above 8 years of age.
2. A 7–14 day course of chloramphenicol 100 mg/kg/day intravenously in those patients with complications such as meningoencephalitis, septic shock or myocarditis.

3. A 7-day course of azithromycin 10 mg/kg/day orally in those patients with no complications but below 8 years of age (As per unit policy, tetracyclines were avoided below 8 years of age).

Rickettsial diseases are rarely diagnosed in India because of nonspecific clinical presentation, low incidence of accompanying eschar, low index of suspicion and lack of adequate diagnostic facilities. Various studies showed that rickettsial diseases may not be a rare entity in our region and should be actively investigated as a potential cause of fever of unknown origin.

**Acknowledgement:** Nil

**Funding:** None

**Conflict of Interest:** None

**Permission from IRB:** Yes

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**How to cite this article ?**

Jain N, Jain V. Study on Clinico -Laboratory Profile of Children with Scrub Typhus. *J Nepal Paediatr Soc* 2012;32(2):187-192.

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