

# Clinico-Laboratory Profile, Complications and Therapeutic Outcome of Scrub Typhus in Children

Ram Hari Chapagain,<sup>1</sup> Sumit Agrawal,<sup>2</sup> Sunita pokharel,<sup>3</sup> Madhusudhan Kayastha,<sup>2</sup> Susan Bhattarai,<sup>2</sup> Anshu Jha,<sup>2</sup> Prerana Gauchan,<sup>2</sup> Santosh Adhikari,<sup>2</sup> Bishnu Rath Giri,<sup>2</sup> Ravindra kumar Sah<sup>4</sup>

<sup>1</sup>National Academy of Medical Sciences and Kanti Children's Hospital Kathmandu Nepal, <sup>2</sup>Department of pediatrics, Kanti Children's Hospital, <sup>3</sup>Department of Medical record, Kanti Children's Hospital, <sup>4</sup>Ministry of Health and population, Kathmandu, Nepal.

## ABSTRACT

**Background:** Scrub typhus, an important cause of undifferentiated fever, is grossly neglected and often misdiagnosed in low and middle income countries like Nepal. The main aim of this study was to describe the clinico-laboratory profile, drug used in treatment, predictor of PICU admission and therapeutic outcome of serologically confirmed scrub typhus among Nepalese children.

**Methods:** A prospective observational study was carried out in children aged up to 14 years with serologically (IgM ELISA) diagnosed Scrub typhus, admitted in a tertiary care hospital of central Nepal between Jan 2019 to Dec 2019.

**Results:** All 100 children with scrub typhus presented with fever. Other symptoms and sign were cough (29%), abdominal distension (22%) hepatomegaly (45%), splenomegaly (28%), crepitation (10%) and eschar (6%). Similarly, thrombocytopenia (72%), and increased liver enzymes SGPT (51%) and SGOT (62%) were found. Co-infection with dengue (5%) brucella (5%) and UTI (5%) were seen. Thirty six percent has some form of complication. Fifty eight percent of children were treated with azithromycin and 25% treated with doxycycline. The mean length of hospital stay was  $6.68 \pm 2.97$  days with a mean duration of defervescence being  $30.07 \pm 26.65$  hours. The increased risk of PICU admission was found in those children with crepitation in chest (OR: 15.17, 95% CI: 3.4-66.8) during presentation and those children not getting azithromycin as treatment (OR: 3.8, 95% CI: 1.2-11.7)

**Conclusions:** Scrub typhus should be considered as a differential diagnosis in any community acquired acute undifferentiated febrile illness regardless of the presence of an eschar. Sepsis, meningitis and pneumonia are important complications. Child having crepitation on presentation has an increased chance admission in critical care unit. The child receiving azithromycin has less chance to land in PICU.

**Keywords:** Clinico-laboratory profile; complications; fever; scrub typhus.

## INTRODUCTION

Scrub typhus, is endemic to a part of the world known as the "tsutsugamushi triangle" which includes Nepal.<sup>1,2</sup> The official outbreak confirmation of scrub typhus in Nepal was in 2015<sup>2</sup>. The WHO identifies scrub typhus as a re-emerging disease in South-East Asia with a case fatality rate up to 30% if left untreated.<sup>3</sup> Scrub typhus can manifest with nonspecific symptoms and should be considered as an important cause of acute undifferentiated fever in tropical and subtropical regions.<sup>4,5,6</sup> The recommendation of duration of treatment is not uniform.<sup>7,8</sup>

There are limited studies regarding the incidence and clinical profile of scrub typhus in children, despite the

epidemiological mention of children constituting up to half of scrub typhus cases in some regions along with Nepal.<sup>9</sup> Therefore, we studied the clinico-laboratory profile, drug used in treatment and therapeutic response, predictor of PICU admission and outcome of serologically confirmed scrub typhus in children in tertiary care referral children hospital .

## METHODS

A prospective observational study was conducted at Kanti Children's Hospital, tertiary care referral government pediatric hospital situated in the capital of Nepal, over a period of 12 months (1<sup>st</sup> Jan 2019- 31<sup>st</sup> Dec 2019) after obtaining ethical clearance from the institutional ethical committee of Kanti Children's

**Correspondence:** Dr Ram Hari Chapagain, National Academy of Medical Sciences, Kanti Childrens Hospital Kathmandu Nepal. Email: [chapagainrh2007@gmail.com](mailto:chapagainrh2007@gmail.com), Phone: + 9779841409080.

Hospital (Ref: 450-30 Dec 2018). Children aged 1 month -14 years were included in the study. All suspected cases were followed and serologically confirmed admitted cases who gave written consent were included in the study. Scrub typhus was diagnosed based on test result of IgM ELISA (In Bios International Inc., Seattle, WA). All admitted cases suspected of scrub typhus who had undergone scrub typhus serology were approached and serologically confirmed cases were observed till the hospital stay. Data on age at admission, gender, initial presenting symptoms, examination findings on admission and investigations (renal function test (RFT), liver function test (LFT), total leucocyte count, total platelets count, blood culture, widal test and tests for other co-infections) were collected. Common infectious conditions that could clinically mimic scrub typhus were also collected by performing peripheral smear, rapid antigen test for malaria, dengue (NS1 antigen and IgM antibody) test, K39, widal test, Brucella and leptospira serology. Data on drug used for treatment, time taken for defervescence, co-infections, short term outcome (improved and discharged, transferred to PICU, death) and duration of hospital stay were recorded. Suspected cases were acute undifferentiated febrile illness of ≥5 days with/ without eschar. Leukocytosis and leucopenia were defined as total leukocyte count more than 11,000/mm<sup>3</sup> and less than 4,000/mm<sup>3</sup> respectively. Thrombocytopenia and severe thrombocytopenia were defined as platelet count less than 1,50,000/mm<sup>3</sup> and 50,000/mm<sup>3</sup> respectively. Hyponatremia was defined as serum sodium less than 135 mEq/L. Creatinine more than > 1.5 mg/dl , SGPT and SGOT > 45 IU/L each were considered as increased level and abnormal .Widal test positive was defined as titre more than 1:80. Acute kidney injury (AKI) is considered when there is rise of serum creatinine of at least 0.3 mg/dl or 50% higher than baseline within a 24-48 hour period or a reduction in urine output to 0.5 mL/kg per hour for longer than 6 hours. Acute hepatitis is defined as elevation of serum transaminases more than 2 times the normal upper limit, and myocarditis is considered when child developed tachypnea, tachycardia and/or (S3- gallop, shock) along with echocardiographic finding suggestive of reduced ejection fraction and elevated cardiac enzymes (CPK-MB) Data was entered and analyzed using SPSS software version 19.0. The descriptive statistics of the study variables were expressed in frequency and percentage and they were summarized with the help of mean ± standard deviation and Odds Ratio. The predictor variables were analyzed with multiple logistics regression.

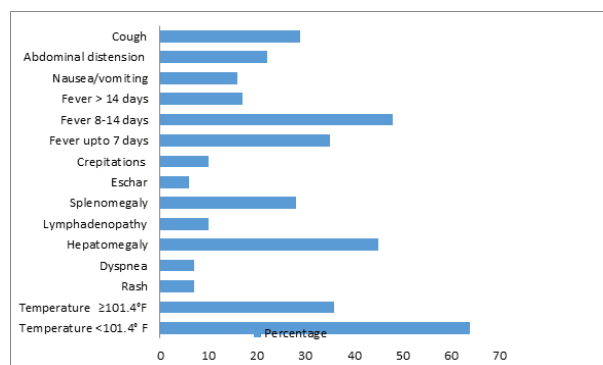
**RESULTS**

During the study period of January 1, 2019 to December

31, 2019, a total of 216,200 children visited the Kanti Children’s Hospital and among them 9,725 were admitted. Among the admitted children, 3164 were related to fever. Among the febrile children, as many as 1,155 children were clinically suspected to have scrub typhus and were tested serologically, of which, a total of 100 (11.5%) children tested positive for scrub typhus and were hence diagnosed to have scrub typhus and all of them were included in the study. Out of 100 cases, 51 (51.0%) were female. Their mean age (S.D) was 7.2 ± 4.0 years. Thirty eight out of 100 (38.0%) cases belonged to the age group 1-5 years. Patients from all 7 province were admitted with majority were from Bagmati Province (38%). and out of these 38 cases, 11 were from Dhading district.

**Table 1. Key socio-demographic parameters of scrub typhus patients.**

Study Variable	n	%
<b>Age Group</b>		
< 1 year	4	4.0
1-5 years	38	38.0
5-10 years	30	30.0
10-14 years	28	28.0
<b>Gender</b>		
Male	49	49.0
Female	51	51.0
<b>Geographic location</b>		
Province 1	6	6.0
Province 2	26	26.0
Bagmati Province	38	38.0
Gandaki Province	10	10.0
Province 5	13	13.0
Karnali Province	3	3.0
Sudurpaschim Province	4	4.0



**Figure1. Clinical symptoms and signs among hospitalized patient with Scrub typhus**

The predominant symptoms during presentation were

fever of 8-14 days (n=48, 48.0%), vomiting (n=16, 16.0%), abdominal distention (n=22, 22.0%) and cough (n=29, 29.0%). Hepatomegaly (n=45, 45.0%), splenomegaly (n=28, 28.0%) and lymphadenopathy (n=10, 10.0%) were the predominant clinical signs. Eschar and rashes were found in only (n=6, 6.0%) and (n=8, 8.0%) of the children respectively.

Among the enrolled children, thrombocytopenia was seen in (n=72, 72.0%) and One eighth (n=12) had severe thrombocytopenia. Though (n=66, 66.0%) had normal leucocyte count, (n=26, 26.0%) had leukocytosis. Liver enzymes SGPT and SGOT were found to be abnormal in (n=51, 51.0%) and (n=62, 62.0%) children respectively.

**Table 2. Laboratory Values among hospitalized patients with Scrub typhus**

Variables	Frequency (n=100)	Percent (%)
<b>Platelets count</b>		
≤50,000/mm <sup>3</sup>	12	12
50,001 - 1,50,000/mm <sup>3</sup>	60	60
1,50,001 - 4,50,000/mm <sup>3</sup>	28	28
<b>Serum creatinine</b>		
≤1.5 mg/dl	94	94
> 1.5 mg/dl	6	6
<b>Serum Sodium</b>		
135-145 mEq/L	82	82
< 135 mEq/L	14	14
> 145 mEq/L	4	4
<b>Serum Potassium</b>		
3.5-5.5 mEq/L	86	86
<3.5 mEq/L	8	8
> 5.5 mEq/L	6	6
<b>Serum Albumin</b>		
< 2.5 g/dl	7	7
≥2.5 g/dl	93	93
<b>SGOT</b>		
≤45 IU/L	38	38
> 45 IU/L	62	62
<b>SGPT</b>		
≤45 IU/L	49	49
> 45 IU/L	51	51
<b>Blood Culture</b>		
Positive	4	4
Negative	96	96

Co-infections were seen in 21% (n=21) patients. Five of them were infected with dengue, 5 had brucellosis, 5 had UTI and 6 had other infectious disease.

At least one systemic complication was found in 36.0% (n=36,) of children. Sepsis (n=14, 14.0%), meningitis (n=10, 10.0%) and pneumonia (n=8, 8.0%) were the common complication. Number of children got admitted to PICU was 19 (n=19, 19.0%) and 5 died due to scrub typhus and associated complications (n=5, 5.0%).

**Table 3. Co morbidities, outcome, complications, length of stay and drug used for treatment and its duration among hospitalized patients with scrub typhus.**

Variables	Frequency (n=100)	Percent (%)
<b>Final Outcome</b>		
Improved and discharged	95	95
Mortality	5	5
<b>Type of complications</b>		
Pneumonia	8	8
Meningitis	10	10
Sepsis	14	14
AKI	1	1
Hepatitis	2	2
Myocarditis	1	1
<b>Co-infection</b>		
Brucellosis	5	5
Dengue	5	5
UTI	5	5
Others	6	6
<b>Length of Hospital Stay</b>		
≤ 3 days	5	5
4-7 days	68	68
> 7 days	27	27
<b>Drug used for treatment</b>		
Azithromycin	58	58
Doxycycline	25	25
Both Doxycycline and Azithromycin	5	5
Others	12	12

Others: Ceftriaxone, ceftazidime, Vancomycin, meropenam and ofloxacin

Azithromycin and doxycycline were the common drugs used in the treatment of scrub typhus. Mean length of stay was 6.68 ±2.97 days with mean duration for being afebrile: 30.07 ± 26.65 hours.

The scrub typhus has the season trends. Most of cases

were seen in August to November.

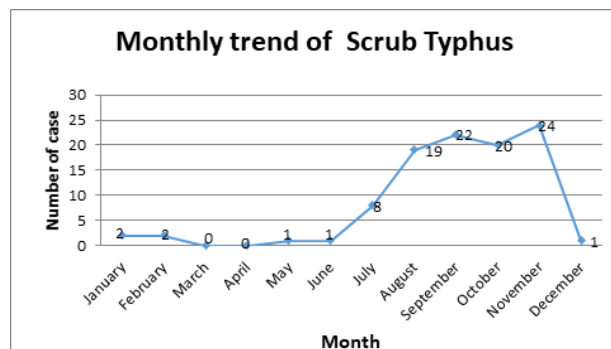


Figure 2. Monthly trend of hospitalized patient with Scrub typhus.

## DISCUSSION

Scrub typhus is an acute febrile illness characterized by widespread infection of vascular endothelial cells resulting in significant vascular compromise and ensuing end-organ damage, most often manifested in brain and lungs<sup>10</sup>. In this prospective study, we describe the clinico-laboratory profile, co-infection, risk factor for PICU admission, drugs used for treatment and outcome of pediatric scrub typhus at the only tertiary pediatric hospital of Nepal.

During the study period, fever (31.2%) was one of the most common causes of admission in the hospital. Among children admitted with a provisional diagnosis of undifferentiated fever 100 (11.5%) patients were due to scrub typhus. Scrub typhus is one of the leading causes of undifferentiated fever in this “tsutsugamushi triangle”. Similar finding was observed by Sivarajan et al. in India.<sup>11</sup> The presenting mean age (S.D) was 7.2(±4.0) years with 58.0% above 5 years. Similar finding was observed in other studies.<sup>6,12</sup> There was a youngest child of 6 month in our study however the minimum age reported by Palanivel et al. was 60 days.<sup>13,14</sup> The male female ratio was almost as equal as per other study.<sup>3</sup>

Kanti Children’s Hospital, the only governmental tertiary level pediatric referral hospital in Nepal, receives patients from different parts of Nepal. Among the 100 children, 38 were from Bagmati province, followed by 26 from province 2 which is nearer to the hospital. Though most cases among the study population were admitted between August to November, similar to those reported by Shah et al<sup>12</sup> in the same hospital in 2018, Karki et al<sup>1</sup> and Sharma et al.,<sup>13</sup> further studies are required to explain the temporal variation of scrub typhus cases.

The clinical manifestations of scrub typhus in children are mostly non-specific and likely to be misdiagnosed. Fever was reported in all children in the present study

similar to the observations in other studies.<sup>9,12,14,15</sup> Corroborating with other studies<sup>6,7,15</sup> the present one also reaffirms that scrub typhus commonly presents with non-specific symptoms like acute onset of fever with myalgia, breathlessness, cough, nausea, vomiting, headache etc. It is difficult to differentiate scrub typhus from other co-endemic diseases like malaria, dengue, enteric fever and leptospirosis. Typical eschar was documented only in 6% of the study population. The presence of eschar is a valuable clinical clue in the diagnosis and can be seen in 7% to 68% of cases,<sup>7</sup> however, absence doesn’t rule out the disease.<sup>14</sup> Therefore, a high index of clinical suspicion, exploring the history of environmental exposure and vigilant search for the eschar are crucial for diagnosis.

Thrombocytopenia was a major finding observed in 72.0% of children in this study similar to the results reported by Palanivel et al.<sup>4</sup> This result is in contrary to the results found by Bhat et al<sup>7</sup> (27.2%) and Narayanasamy et al. (3%).<sup>15</sup> Leukocytosis and leukopenia were observed in 26.0% and 8.0% respectively. Hyponatremia was seen 14.0% of children in the present study whereas Narayanasamy et al<sup>10</sup> has reported it to be 40%. Likewise raised liver enzymes (SGPT 51.0%, SGOT 62.0%) were also observed. Higher rise of liver enzymes in serum (AST in 81.8%, ALT in 73.3% and ALP in 56.1% of cases) was also observed in another study done in India.<sup>16</sup> We observed that 49.0% of presenting children had hemoglobin level less than 10 gm% but this might be because of childhood anemia, which is common in our country so we can’t correlate scrub typhus with hemoglobin concentration.

Scrub typhus leads to many complications. Sepsis (n=14, 14.0%), meningitis (n=10, 10.0%) and pneumonia (n=8, 8.0%) were the three major complications seen in children with scrub typhus in the present study. At least one systemic complication was found in (n=36, 36.0%) children; hepatitis, AKI and myocarditis were also observed in very few numbers whereas Patahak et al reported myocarditis (72.4%), hypoalbuminemia (71.1%) and AKI (65.8%) as major complications<sup>17</sup>. Kumar et al. observed myocarditis (34.0%), hypoalbuminemia (54.0%) and AKI (20.0%) as the three leading complications in general population. Another recent longitudinal study (2016) in Meghalaya India in 90 scrub typhus cases with mean age (SD) 36.3 (13.4) years showed that acute hepatitis (n = 15, 16.7%), pneumonitis (n = 14, 15.6%) and AKI (n = 11, 12.2%) were common complications<sup>6</sup>. This suggests that the complication in children is different than adults with scrub typhus.

A Cochrane review (2018) concluded that tetracycline, doxycycline, azithromycin, and rifampicin are effective drugs available for the treatment of scrub typhus and suggested that there may be little or no difference

between tetracycline, doxycycline and azithromycin as treatment options though some treatment failures were noted for all drugs.<sup>18</sup> But our study found that the child who got azithromycin has less chance to land in PICU than those who received other than azithromycin ( $P < .010$ ). Azithromycin was used in more than half of the cases (58.0%) irrespective of age in the study population. This could be due to the availability of azithromycin in tablet as well as in suspension formulation. Doxycycline was used in 25.0% cases in contrast to the study by Bhat et al<sup>9</sup> and Palanivel et al<sup>14</sup> where doxycycline was a commonly used drug for scrub typhus. Few scrub typhus cases received both doxycycline and azithromycin and 12.0% cases received other treatment which might be due to consideration of managing co-infections and complications.

The length of treatment to prevent recrudescence is not clear. Azithromycin was used for 5 to 7 days in the majority of cases in the present study. Though single dose of azithromycin for scrub typhus has been recommended in the present context without reliable and rapid diagnostics; it is thought to be hazardous to use a single dose of azithromycin for undifferentiated febrile illness as scrub typhus in Nepal, as there can be co-infection with other diseases like leptospirosis, requiring longer treatment.<sup>19</sup> Mean duration for being afebrile was observed  $30.07 \pm 26.65$  hours in the present study which also shows that single dose of azithromycin is not sufficient. There has been other recommendation for continuation of treatment for a minimum of 5 days or 3 days until the child has been afebrile.<sup>7</sup> Based on this we can recommend to administer azithromycin for at least 5 days for treatment of scrub typhus though clinical trial is the best one to recommend in this regard. Ojha and Rayamajhi have suggested rifampicin as a potential treatment option for scrub typhus.<sup>19</sup> However, in a country like Nepal, where tuberculosis is also widespread, it might be more prudent to reserve rifampicin for the treatment of tuberculosis.<sup>18</sup> Rifampicin was not used for scrub typhus at Kanti Children's Hospital.

Admission to PICU was required for ( $n=19$ , 19.0%) of children in the present study which is higher than 11.3% reported by Shah et al in same setting on 2017,<sup>12</sup> while 39.0% of cases required PICU admission in the study by Rajendran et al.<sup>20</sup> The increased risk of PICU admission was found in those children with crepitation during auscultation in chest (OR: 15.17, 95% CI: 3.4-66.8) during presentation and those children not getting azithromycin as treatment (OR: 3.8, 95% CI: 1.2-11.7). Age, duration of fever, intensity of fever, presence of hepatomegaly, splenomegaly, laboratory findings of leukocytosis, hypernatremia, increased GPT or GOT level had not increased the risk of PICU admission in this

present study.

The mortality was observed to be ( $n=5$ , 5.0%) in this study. Tayler et al reported the median mortality of all patient series to be 6.0% with a wide range (min-max) of 0-70% after analyzing 19,644 patients from 76 studies containing 89 patient series.<sup>21</sup> All mortality in our study was from PICU. Mean length of hospital stay was found to be  $6.68 \pm 2.97$  days which was similar to the results shown by other studies.<sup>12,19</sup>

## CONCLUSIONS

Scrub typhus is an important cause of febrile illness in children with multisystem involvement in Nepalese context. Co-infections with sepsis, UTI, dengue and leptospira should be considered. Scrub typhus may lead to complications in almost one third of children with possible need for PICU admission with some mortality. Crepitation on chest auscultation at the time of presentation and treatment other than azithromycin are the risk factors for PICU admission.

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