

# Clinico-epidemiological and Outcome of Scrub Typhus in Paediatric Patients: An Observational Study from Odisha, India

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## ABSTRACT

**Introduction:** Scrub typhus is re-emerging as a common prolonged febrile illness in children with serious complication involving major organ systems. It is easily treatable yet treatment is challenging with respect to early identification of predictors of serious disease that greatly affects the outcome in this vulnerable population.

**Aim:** To study the clinical profile, analyse the complication and outcome of these patients.

**Materials and Methods:** This was a hospital-based, prospective observational study. It was conducted in the Department of Paediatrics, SCB Medical College and Hospital, Cuttack from October 2017 to September 2019. All children with clinical features of scrub typhus were subjected to Immunoglobulin M (IgM) scrub typhus test. All observational data were analysed by IBM Statistical Package for the Social Science (SPSS) software, version 25.0 and Chi-square test was used with  $p < 0.05$  as statistically significant.

**Results:** Out of total 196 subjects, majority 87 (44.4%) were found to be in the age group of 1-5 years of age and majority were males (55.1%). Fever was universally present (100%). Eschar, the pathognomonic lesion of scrub typhus was found only in 47.4% of the patients. Acute hepatitis was the most frequent complication encountered (33.2%). Majority (87.2%) of the patients improved and were successfully discharged. A total of 61 (31%) patients, out of the 196 included in the study, required admission to ICU. Mortality was more marked in patients suffering from shock, acute hepatitis, Acute kidney Injury, meningoencephalitis and myocarditis and Multiple Organ Dysfunction Syndrome (MODS) ( $p < 0.05$ ).

**Conclusion:** Paediatric scrub typhus is quite common in the state of Odisha. Young age of presentation, presence of multi system involvement and delayed initiation of anti-rickettsial drugs due to delay in referral was also observed to be one of the poor prognostic factors.

**Keywords:** Doxycycline, Eschar, Febrile children, Hepatitis

## INTRODUCTION

Scrub typhus is more prevalent in the rural areas of Tsutsugamushi triangle, yet most cases remain undiagnosed and underreported [1]. The absence of definitive signs and symptoms combined with a general dependence upon serological tests makes the differentiation of scrub typhus from other common febrile diseases (murine typhus, typhoid fever and leptospirosis) quite difficult [2]. It is known that *O. tsutsugamushi* is responsible for approximately one million cases of scrub typhus each year within endemic areas, and that an estimated one billion people per year are at risk of becoming infected [3].

In the Indian subcontinent, first cases were from Assam during the period of World Wars [4]. It was not late until whole of the subcontinent became an endemic zone for the disease. The impact was higher in the states of Haryana, Jammu and Kashmir, Himachal Pradesh, Uttaranchal, West Bengal, Assam, Maharashtra, Goa, Kerala and Tamil Nadu [5]. The cases are seen from rural and urban backward areas which are the natural habitats of the vector. However, there is increasing serological evidence from metropolitan cities [5-7]. In an Indian multicentre survey, out of all cases admitted in Intensive Care Unit (ICU) with suspected diagnosis of tropical fevers, scrub typhus formed >15% of cases [7].

Among children the literature available is sparse, however studies in Thailand and Sri Lanka showed that scrub typhus is the cause of 1-8% of acute fevers of unknown origin among children [8]. Nevertheless, the incidence among children is considered to be half of those of that in adults [9,10]. Children often present in post monsoon season with undifferentiated fever and various degrees of organ involvement that can have severe manifestations in children leading to intensive care admission and may progress to fatal multiorgan failure, if untreated [11]. A late presentation, delay in diagnosis and treatment causes overall 11.1% deaths in children below 10 years because of the low index of suspicion, and nonspecificity of signs and symptoms [12].

Odisha is situated in the Eastern Ghats and has been reporting seasonal Acute Encephalitis Syndrome (AES) outbreaks since 2009 at the specific interval [13]; but the aetiology has not been established. On the basis of the Gorakhpur report, when serological analysis of 30 AES archived samples collected from hospitalised children during the 2016 epidemic, it was found that 23.3% (7/30) of the Juvenile Encephalitis (JE) suspected cases were positive for scrub typhus [14]. However, longitudinal, comprehensive and exclusive data on paediatric scrub typhus that include varied clinical presentations and therapeutic outcome are lacking from this part of the country. So, there is a need to study the occurrence of similar trends in eastern part of India [15]. Therefore, this study was undertaken to analyse varied clinical presentations, complication and outcome of scrub typhus.

## MATERIALS AND METHODS

This was a hospital-based, prospective observational study. It was conducted in the Department of Paediatrics, SCB Medical College and Hospital, Cuttack from October 2017 to September 2019. Institutional Ethical Committee clearance (724/15.1.2019) was availed for the study and informed consent was obtained from the parents of the patients.

During the course of this study, a total of 245 children were selected, 35 patients were lost because of early discharge from the hospital before the drug regimen completion and presence of other co-morbidities identified during the investigations. Another 14 children were lost during follow-up, so 196 were considered to be a part of this study.

**Sample size calculation:** The sample size was calculated based on another study (23.3% prevalence) and with the margin of error of 6% and 95% confidence interval [14]. So, the total sample size taken for the study was 196 (considering 5% attrition).

Children were selected with history of fever and clinical features of rickettsial fever; diagnosis was confirmed for scrub typhus using Inbios Scrub typhus Detect™ IgM Enzyme-Linked Immunoassay

(ELISA) kit for detection of IgM antibodies in human serum to *Orientia tsutsugamushi* antigens.

#### Inclusion criteria:

- All children (six months to 14 years of age) that presented with the complaints of undifferentiated fever for more than 5 days with compatible clinical features (rash, eschar, hepatosplenomegaly, lymphadenopathy, aseptic meningitis) and suggestive epidemiological features (infected larval mite bite) of scrub typhus were evaluated.
- Inbios Scrub typhus Detect™ IgM ELISA kit was used for detection of IgM antibodies in human serum to *Orientia tsutsugamushi* antigens. Patients with positive IgM antibodies against *O. tsutsugamushi* were diagnosed as having scrub typhus.
- Parents/guardians consenting to the enrolment.

#### Exclusion criteria:

- Other causes of fever such as malaria, dengue fever, viral pharyngitis, enteric fever, urinary tract infection
- Those associated with congenital anomaly and any co-morbidity were excluded.

At the time of admission after detailed history, documenting vitals and complete clinical examination, cases were confirmed with IgM ELISA for scrub typhus. Investigations were undertaken to evaluate the organ involved and exclude co-infection in paediatric scrub typhus which is not uncommon in this situation [16]. We have also taken this step to avoid multiple sampling issues in these sick children. Investigations performed were: complete blood count with peripheral smear, liver function test, renal function test, serum electrolytes. Other causes for fever like Urinary Tract Infection (UTI), pneumonia, malaria, typhoid and dengue were ruled out using urine Routine and Microscopy (RM) and Culture sensitivity, Chest x-ray, CBC for Malarial parasites as well as Malarial Parasite-Immunochromatography Technique (MP-ICT), blood cultures and Non-Structural 1 (NS-1) antigen IgM dengue antibody, Widal Test. However, the analysis of these reports is beyond the scope of present study.

In the study, doxycycline was used as the first drug of choice in the management of all cases of Scrub typhus. A 2.2 mg/kg/dose Intravenous twice daily for uncomplicated cases until 48 hr of afebrile then orally same dose was continued for a total duration of 5-7 days. In complicated cases, Intravenous dosage was continued for 7-10 days. The 2<sup>nd</sup> line drug was azithromycin 10 mg/kg/day which was used in cases where doxycycline could not be afforded by the patient family.

## STATISTICAL ANALYSIS

The collected data were analysed with Statistical Package for the Social Science (SPSS) version 25.0. Descriptive statistics, frequency analysis, percentage analysis were used for categorical variables and for continuous variables the mean and SD were used. To find the significant difference between the bivariate samples in independent groups, the independent t-test was used. To find the significance in categorical data, Pearson Chi-square test was used. In all the above statistical tools, the probability value of <0.05 was considered as significant level.

## RESULTS

Out of 196 patients, the majority (87, 44.4%) were in the age group of 1-5 years, and most (108, 55.1%) of the patients were males [Table/Fig-1]. Eschar was found in 47.4% of the patients. Total 53.6% of the patients, even though did not have eschar, were IgM positive for scrub typhus [Table/Fig-2].

As depicted in [Table/Fig-3], acute hepatitis was the most common complication encountered by patients. The incidence of complication, except pneumonia, was significant with respect to morbidity. These complications were managed with enteral antibiotics either doxycycline or azithromycin and further complications were managed based on standard established Paediatric Intensive Care Protocols.

Age (in years)	Frequency n (%)
<1	36 (18.4%)
1-5	87 (44.4%)
6-10	53 (27%)
11-14	20 (10.2%)
Gender	
Male	108 (55.1)
Female	88 (44.9)

**[Table/Fig-1]:** Distribution of cases according to age and sex; (N=196).

Symptoms	Frequency	Percentage (%)
Fever	196	100
<7 days of fever	38	19.4
>7 days of fever	158	80.6
Headache	102	52
Myalgia	108	55.1
Cough/breathlessness	105	53.6
Vomiting	100	51
Pain abdomen	84	42.9
Diarrhea	35	17.9
Decreased urination	28	14.3
Facial puffiness	65	33.2
Bleeding	15	7.7
Altered sensorium	41	21
Convulsion	33	16.8
Signs		Percentage (%)
Pallor	81	41.3
Icterus	15	7.7
Lymphadenopathy	57	29.1
Oedema	54	27.6
Rash	49	25.0
Eschar	93	47.4

**[Table/Fig-2]:** Distribution of presenting symptoms and signs; (N=196).

Complications	Frequency n (%)	Outcome		p-value
		Death (%) n=25	Discharge (%) (n=171)	
Pneumonia	49 (25)	4 (16)	45 (26.3)	0.07
Acute respiratory distress syndrome	13 (6.6)	10 (40)	3 (1.7)	0.02
Shock	25 (12.8)	19 (76)	6 (3.5)	0.03
Acute hepatitis	65 (33.2)	21 (84)	44 (25.7)	0.01
Acute kidney injury	18 (9.2)	9 (36)	9 (5.2)	0.003
Meningoencephalitis	45 (23)	14 (56)	31 (18.1)	0.02
Myocarditis	4 (2)	3 (12)	0	0.01
Multiple organ dysfunction syndrome	49 (25)	24 (96)	25 (14.6)	0.03

**[Table/Fig-3]:** Complicated presentations and the relation with outcome. Chi square Test; p-value

As is evident from the [Table/Fig-4], Doxycycline (94.4%) was used in majority of the patients. Total 87.2% of the patients were discharged and 12.8% died. Patient were discharged after full course of therapy and complete recovery and followed-up for two weeks.

## DISCUSSION

Scrub typhus caused by *O. tsutsugamushi* from a bite of larval stage mite, can present as mild to severe disease in children. It can affect almost every organ system. In this study, the clinical profile, the complication and outcome of these patients have been outlined.

According to [Table/Fig-5], authors have documented 1 to 5 years as the most vulnerable age group which is similar to the observation done

Antibiotic	Frequency n (%)
Doxycycline	185 (94.4)
Azithromycin	11 (5.6)
Outcome	
Discharge	171 (87.2)
Death	25 (12.8)
Mean duration of hospitalisation (in days)	6.5±1.6 (discharged)
	5.3±0.8 (died)
Mean duration of resolution of symptoms (in days)	3.3±1.5 (discharged)

**[Table/Fig-4]:** Antibiotics used and the outcome.

by Palanivel S et al., toddlers and old children are likely victims due to their outdoor exposure during play and other activities [14,15,17-19]. Fever was the most common presenting symptom in this study (n=196) and most of the patients presented with fever of duration longer than seven days (n=158) as evident in [Table/Fig-6] [20-27]. Bajracharya L, Kumar M et al., also observed fever in all cases in their study [21,22]. Thus, all of the cases presenting with prolonged fever should be suspected, investigated routinely for scrub typhus,

so as to not miss any cases. The next most common presenting symptoms were myalgia, cough/breathlessness, headache and vomiting, pain abdomen and loose stools as seen in [Table/Fig-6].

As seen in [Table/Fig-6] pallor was a significant observation in this study, which can be attributed to the associated nutritional deficiency. Further studies are necessary to correlate the findings between the disease and undernutrition. Eschar, the pathognomonic lesion of scrub typhus was found in only 93 (47.4%) patients in this study. Among the clinical signs apart from eschar; pallor, lymphadenopathy, oedema were common among the patients studied. Somashekar HR et al., and Rathaur V and Pathania MA, also found high incidence of pedal oedema and facial puffiness in their studies [25,26]. Gurunathan PS et al., reported a low incidence of rash (18%) in their studies contrary to the present study where rash was found in 25% of the patients [27].

As seen in [Table/Fig-7], acute hepatitis was the most frequent complication; seen in 65 (33.2%) patients [15,17,18,21,22]. The present study centre is a tertiary referral centre where most patients are referred from peripheral primary care or district level with complications. This referral bias may have led to high complication rates in this study.

Variables	Present study	Palanivel S et al., [17]	Narayanasamy DK et al., [18]	Rathi NB et al., [19]	Basu S et al., [15]	Bal M et al., [14]
Male: female	1.22:1	1:1.3	1:1	2:1	1.1:1	1.62:1
Age group with maximum incidence	1 m-5 y	2 m-11 y	5 m-12 y	8 m-20 y	-	6-10 y

**[Table/Fig-5]:** Comparison of demography of the present study with other studies in Scrub Typhus. m: months; y: years

Variables		Present study (N=196)	Bhat NK et al., [20]	Bajracharya L [21]	Kumar M et al., [22]	Patnaik S et al., [23]	Sharma SR et al., [24]	Somashekar HR et al., [25]	Rathaur V and Pathania M [26]	Gurunathan PS et al., [27]
Region		Odisha	Uttarakhand	Katmandu	Pondicherry	Odisha	Meghalaya	Tamil Nadu	Uttarkhand	Tamil Nadu
Symptoms	Fever	100%	100%	100%	100%	100%	100%	-	100%	-
	Duration of fever in days (mean±SD)	8.45±3.62	8.85±3.18	-	-	-	-	-	-	-
	Fever more than 7days (%)	80.6%	81%	94%	84%	-	-	-	-	86.2
	Myalgia	55.1%	-	-	26%	-	-	-	-	-
	Cough/resp distress	53.6%	18.7	50%	51%	44%	34%	37%	35%	-
	Headache	52%	26%	38%	-	-	-	44%	57.5%	-
	Nausea/ vomiting	51%	66%	42%	49%	-	73%	44%	52.5%	86.2%
	Altered sensorium	21%	51%	20%	17%	-	60%	18%	-	-
Signs	Pallor	41.3%	-	-	-	-	-	-	-	-
	Lymphadenopathy	29.1%	34%	24%	37	24%	13%	37%	70%	-
	Oedema	27.6%	41%	38%	60%	40%	43%	26%	32.5%	49.23%
	Eschar	47.4%	23%	26%	11%	46%	0	14%	35%	55.5%
	Hepatomegaly	-	78%	91%	91%	93%	-	60%	55%	80.6%
	Splenomegaly	-	63.5%	60%	60%	63%	26%	37%	70%	

**[Table/Fig-6]:** Comparison of clinical profile of the present study with other studies in scrub typhus [20-27].

Complications	Present study (N=196)	Basu S et al., [15]	Palanivel S et al., [17]	Kumar M et al., [22]	Bajracharya L [21]	Narayanasamy DK et al., [18]
Pneumonia (%)	25	-	-	3	-	16
Acute respiratory distress syndrome (%)	6.6	-	4.47	9	13	8
Septic shock (%)	12.8	27.9	44.77	-	-	46
Acute Hepatitis (%)	33.2	3.3	10.44	31	59.5	8
Acute kidney Injury (%)	9.2	3.3	10.44	20	14.3	12
Meningoencephalitis (%)	23	34.4	5.97	20	34.5	8
Myocarditis (%)	2	13.2	23.88	34	40.5	24
Multiple organ dysfunction syndrome (%)	25	-	7.46	-	19	-
Outcome (mortality) (%)	12.8	1.6	11.94	2.85	4.8	0
Therapy doxycycline (%)	94.4	100	69	100	100	-
Azithromycin (%)	5.6	-	31	-	nil	-

**[Table/Fig-7]:** Comparison of complications seen in the present study with other studies in scrub typhus.

Mortality was more marked in patients suffering from Acute Respiratory Distress Syndrome (ARDS), shock, acute hepatitis, Acute Kidney Injury (AKI), meningoencephalitis and myocarditis and MODS ( $p < 0.05$ ) and the relationship was statistically significant. The relationship between pneumonia and ARDS was not found to be statistically significant. A comparison was made based on outcome found in this study with other previous studies [Table/Fig-8] [20-24].

Studies	Region	Total study subjects	Outcome	
			Discharge (%)	Death (%)
Present study	Odisha	196	87.2	12.8
Bhat NK et al., [20]	Uttarakhand	96	92.7	7.3
Bajracharya L [21]	Kathmandu	84	95.2	4.8
Kumar M et al., [22]	Pondicherry	35	97	3
Patnaik S et al., [23]	Odisha	25	96	4
Sharma SR et al., [24]	Meghalaya	23	100	0

**[Table/Fig-8]:** Comparison of outcome in present study with other studies [20-24].

Majority i.e., 171 (88%) of the 196 scrub typhus patients admitted to the study hospital during the study period were discharged and 25 (12.8%) patients died. This higher mortality in the present study could be due to authors' centre is a tertiary care hospital catering to patients from far off places, who arrive in a late stage of the disease.

### Limitation(s)

Patients having any co-existing illness along with scrub typhus had been excluded from this study. A long-term prospective study may be conducted on patients with scrub typhus having other associated infectious illnesses and their outcome. Delayed referral and admission to the hospital as well as delayed initiation of definitive therapy may have led to an increase in the number of deaths and other complications. So, there is a need to study timeline of occurrence of complication after the onset of symptoms.

### CONCLUSION(S)

Paediatric scrub typhus is quite common in the eastern state of Odisha and must be considered as a close differential diagnosis of any acute undifferentiated febrile illness. Prolonged fever with non specific symptoms like myalgia and headache or with specific signs like pedal oedema and facial puffiness should alert the physician for underlying scrub typhus even in the absence of an eschar. Mortality is marked in patients suffering from shock, acute hepatitis, AKI, meningoencephalitis, myocarditis and Multiple Organ Dysfunction Syndrome (MODS).

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