ORIGINAL ARTICLE

Epidemiological Profile and Outcome Predictors of Pediatric Scrub Typhus at a Tertiary Care Health Institution in the Sub-Himalayan Region

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Received on: 21 June 2022; *Accepted on:* 26 September 2022; *Published on:* 15 April 2023

Abstract

Background: Scrub typhus is an important differential cause of acute undifferentiated febrile illness in the pediatric age-group. Diagnosis of scrub typhus is made by evaluating a child's history of exposure, clinical spectrum, and results of serologic testing. A high degree of clinical suspicion leading to early diagnosis and timely intervention has greatly reduced mortality due to various associated complications. This study aimed to study the epidemiological profile and outcome predictors for scrub typhus in admitted children in a tertiary care academic hospital in the Indian sub-Himalayan region.

Methods: It was a cross-sectional study enrolling children aged 1 month to 18 years, diagnosed with scrub typhus based on IgM ELISA between January 2019 and December 2021. Detailed history, clinical examination findings, laboratory profile, complications, and outcomes were recorded and analyzed accordingly.

Results: A total of 82 children were enrolled with 63.4% belonging to the 11–18 years age-group. High admission rates were observed in the months of May to August and September to December. Common presenting symptoms were fever (100%), nausea/vomiting (35.4%), headache (25.6%), shortness of breath (25.6%), pain abdomen (18.3%), and altered sensorium (9.8%); while classical eschar was seen in only 3.7% children. On examination, children had generalized lymphadenopathy, hepatosplenomegaly, hypotension, ascites, periorbital edema, maculopapular rash, and meningeal signs. The most common associated complications were septic shock, acute respiratory distress syndrome (ARDS), myocarditis, meningoencephalitis, and multiple organ dysfunction syndrome (MODS). The median duration of defervescence after starting antimicrobial therapy was 4 days. Children presenting with shock, ARDS, MODS, and meningoencephalitis had a statistically significant unfavorable outcome.

Conclusion: Pediatric scrub typhus is a common infection in sub-Himalayan terrain. Physicians should be sensitized regarding symptoms, signs, and risk factors of scrub typhus. All cases of febrile illness should be evaluated for scrub typhus. As early detection and timely management lead to a higher recovery rate and prevention of complications; the present study would help clinicians identify severe cases and manage them accordingly.

Keywords: Children, Himalayas, Outcome predictors, Scrub typhus.

Pediatric Infectious Disease (2023): 10.5005/jp-journals-10081-1376

Introduction

Scrub typhus is one of the oldest recognized vector-transmitted zoonoses.[1] World Health Organization has reported scrub typhus as one of the world's most underdiagnosed and underreported diseases that often requires hospitalization.[2] In India, scrub typhus has been documented from the states of Jammu and Kashmir, Himachal Pradesh, Uttarakhand, Rajasthan, Assam, West Bengal, Maharashtra, Kerala, and Tamil Naidu.[3]

Scrub typhus is an important cause of acute undifferentiated fever in children.[4] It is the most common tropical rickettsial infection caused by *Orientia tsutsugamushi*, transmitted by the bite of chigger (larval) stage of *Leptotrombidium* mite.[5] Classically at the site of mite feeding, an eschar is formed which starts as a vesicular lesion and later on progresses as an ulcer with a black necrotic center and an erythematous border along with regional lymphadenopathy.[6] The organism then spreads by hematogenous as well as lymphatogenous routes. The pathogenic mechanism is perivasculitis and disseminated vasculitis.[7] The pulmonary involvement can be in the form of interstitial pneumonitis, interstitial edema, and hemorrhage caused by vasculitis.[8] Abdominal involvement occurs in the form of hepatomegaly, splenomegaly, periportal edema, gall bladder wall thickening, and lymphadenopathy while the involvement of the central nervous system is usually in the form of meningoencephalitis.[9] Untreated cases can have mortality rates as high as 30–35%.[10]

The greatest challenge to a pediatrician is difficulty in its diagnosis as it has various nonspecific clinical presentations resembling other common tropical diseases like dengue, malaria, enteric

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How to cite this article: Chaudhary N, Bajaj M, Sharma M, *et al.* Epidemiological Profile and Outcome Predictors of Pediatric Scrub Typhus at a Tertiary Care Health Institution in the Sub-Himalayan Region. Pediatr Inf Dis 2023;5(1):1–5.

Source of support: Nil

Conflict of interest: None

fever, leptospirosis, malignancy, etc.[11] When diagnosed timely, it has very specific and effective antibiotic therapy.[12] If delayed, children develop complications like interstitial pneumonia, ARDS, renal failure, septic shock, myocarditis, gastrointestinal bleeding, meningoencephalitis, and at times MODS. Mortality from such complications is about 7–30%[13] and is attributable to multiple organ failure, respiratory failure, and disseminated intravascular coagulation.[13] Despite the high prevalence, very few pediatric studies have been carried out in the sub-Himalayan belt for understanding the disease. Thus, this study was conducted to study the epidemiological and laboratory profile of scrub typhus, its complications, and associated outcomes.

Methods

It was a cross-sectional study including children of age-group 1 month to 18 years with diagnosed scrub typhus admitted to children's ward or pediatric intensive care unit (PICU). The study was conducted for a period of 3 years (January 2019 to December 2021). Children were enrolled as cases only after testing positive for IgM ELISA. Children with undifferentiated fever who were positive for IgM ELISA for scrub typhus with other coinfections and confirmed by appropriate laboratory tests were excluded. The criteria of organ system dysfunction, shock, ARDS, MODS, and acute kidney injury (AKI) were defined according to standard guidelines.[14–16] After enrolment; clinical, laboratory, and management profiles were documented and information was recorded on a Microsoft Excel sheet. The data were then transferred to Epi Info version 7.2 and relevant statistical tests were applied for significance testing; with a two-tailed *p*-value of less than 0.05 taken as statistically significant. Prior ethical clearance was taken from Institute Ethics Committee and informed consent was taken from the participant and guardian. Personal identifiers were omitted for ensuring the confidentiality and anonymity of the participants.

Results

A total of 82 children were diagnosed to have scrub typhus with ages ranging from 11 months to 18 years with a mean age of 11.9 (±4.1) years with maximum admissions, that is, 52 (63.4%) in the 11–18 years age-group. Female gender preponderance (65.9%) was observed. A high admission rate was seen in the months of May to August (35.4%) and September to December (36.6%) of each year. The demographic profile of the participants is summarized in Table 1. Table 2 highlights the clinical profile of the participants in terms of signs and symptoms. All admitted children had fever at admission with 48.8% having a duration of less than 7 days. Nausea/vomiting, headache, shortness of breath, pain abdomen, altered sensorium, and seizures were commonly presenting complaints. In clinical signs, generalized lymphadenopathy, hepatosplenomegaly, hypotension, ascites, basal crept, and rash were observed frequently. Meningeal signs were elicited in 8.5% of enrolled children. Table 3 depicts various laboratory parameters of enrolled children with scrub typhus showing derangements. Derangements were observed in liver and kidney function tests along with dyselectrolytemia.

Commonly observed complications were septic shock, AKI, ARDS, myocarditis, meningoencephalitis, and MODS. Myocarditis was evidenced by electrocardiograph findings and raised cardiac enzyme levels. A total of 42 (51.2%) children needed PICU care and after stabilization shifted to a high dependency unit. The rest of the children were managed in the general ward. About 15 (18.3%) children received ventilatory support and 9 (10.9%) succumbed during management (Table 4). All children were treated with doxycycline (4.4 mg/kg/day in two divided doses) and/or azithromycin (15–20 mg/kg/day OD) for 5–7 days. Doxycycline was a universally used drug followed by a combination with azithromycin (51.2%). Duration of treatment

Table 1: Demographic profile of enrolled children

Parameter	*Subparameter*	*Number (%)*
Age	1 month–1 year	1 (1.2)
	1 year–5 years	5 (6.1)
	5 years–10 years	24 (29.3)
	11 years–18 years	52 (63.4)
Gender	Male	28 (34.1)
	Female	54 (65.9)
Month-wise distribution	January–April	13 (15.9)
	May–August	29 (35.4)
	September–December	30 (36.6)

Table 2: Clinical profile of enrolled children at the time of admission

Clinical symptoms	*Number (%)*	*Clinical signs*	*Number (%)*
Fever	82 (100)	Lymphadenopathy	77 (93.9)
<7 days	40 (48.8)		
>7 days	42 (51.2)		
Headache	33 (40.2)	Hepatosplenomegaly	72 (87.8)
Shortness of breath	30 (36.6)	Hypotension	46 (56.1)
Nausea/vomiting	29 (35.4)	Pallor	45 (54.9)
Cough	28 (34.1)	Ascites	35 (42.7)
Pain abdomen	21 (25.6)	Periorbital edema	31 (37.8)
Loose stools	15 (18.3)	Basal crept	21 (25.6)
Myalgia	14 (9.8)	Rash	13 (15.9)
Altered sensorium	13 (15.9)	Conjunctival congestion	10 (12.2)
Seizure	4 (4.9)	Meningeal signs	7 (8.5)
		Petechial spots	6 (7.3)
		Icterus	3 (3.7)
		Eschar	3 (3.7)

Table 3: Laboratory values of admitted children

Parameter	*Value (mean ± SD)*	*Deranged parameter subcategorization*	*Number (%)*
Hemoglobin (gm/dL)	10.7 ± 1.3	Hb <10 (gm/dL)	19 (23.2)
Leucocyte count (cells/mm^3)	8,410.3 ± 3,795.7	<4,000	8 (9.8)
		>11,000	21 (25.6)
Platelet count (cells/mm^3)	128,187.5 ± 115,731.5	10,000–50,000	6 (7.3)
		50,001–100,000	47 (57.3)
		100,001–250,000	29 (35.4)
SGOT (U/L)	160.2 ± 160.1	SGOT >45 U/L	65 (79.3)
SGPT (U/L)	78.7 ± 65.5	SGPT >45 U/L	56 (68.3)
Serum albumin (gm/dL)	3.1 ± 0.6	Serum albumin <2.5 gm/dL	15 (18.3)
Serum bilirubin (mg/dL)	1.8 ± 2.2	Direct bilirubin >2 mg/dL	21 (25.6)
		Indirect bilirubin >1.2 mg/dL	12 (14.6)
Blood urea nitrogen (mg/dL)	22.9 ± 19.8	Blood urea nitrogen >30 mg/dL	12 (14.6)
Serum creatinine (mg/dL)	0.8 ± 0.7	Serum creatinine >1.5 mg/dL	8 (9.8)
Serum sodium (mg/dL)	135.9 ± 5.1	Serum sodium <135 mg/dL	29 (35.4)
		Serum sodium >145 mg/dL	3 (3.7)
Serum potassium (mg/dL)	4.1 ± 0.5	<3.5 mg/dL	3 (3.7)
		>4.5 mg/dL	0
Serum chloride (mg/dL)	102.6 ± 6.9	<96 mg/dL	9 (10.9)
		>110 mg/dL	1 (1.2)
Blood glucose (mg/dL)	108 ± 40.3	<45 mg/dL	0

ranged between 7 and 10 days of doxycycline/azithromycin along with empirically added antibiotic which was omitted after confirmation of scrub typhus. The median (interquartile range) duration of defervescence after starting antimicrobial therapy was 4 (2–6) days. Table 5 shows the comparison between survivors and nonsurvivors regarding various complications. Children having shock, ARDS, MODS, and meningoencephalitis had statistically significant unfavorable outcomes.

Discussion

Due to nonspecific clinical presentations and the advent of good detection tests, scrub typhus has become all season and pan-Indian disease in the last decade. Early diagnosis of scrub typhus is challenging given seasonal predilection and overlapping clinical features with many other tropical infections. The present study showed that children of any age can be infected with scrub typhus. The mean age of infected children was 11.9 ± 4.1 years with age-group of 11–18 years affected most commonly; which is similar to studies conducted earlier.[5] Growth of secondary vegetation (scrubs) during the rainy season, the prevalence of vectors, and increased outdoor activities by older children during this season increase the risk of infection. The present study reported female gender preponderance in enrolled children during this period; which is contrary to other studies done earlier.[5,17] This may be explained as it is a tertiary care referral institute leading to variable gender-wise admission rates. Maximum cases were observed in the months of May to August and September to December; observation is similar to other previous studies reporting clustering of cases around monsoon and early winter months.[5,17]

Fever was present in all admitted children which was intermittent and high grade. Various studies have also reported fever in all patients.[5,13] Headache, shortness of breath, vomiting, abdominal pain, cough, and loose stools were among other symptoms observed which were similar to previously conducted studies.[5,13,17] Central nervous system-associated symptoms like altered sensorium and seizures were also observed similar to previous studies.[18,19] Nonspecific symptoms indicating multiorgan involvement were observed. The study noticed lymphadenopathy, tender hepatosplenomegaly, hypotension, ascites, periorbital edema, and maculopapular rash as the most common signs at presentation; these findings were similar to other studies.[17,19,20] Lymphadenopathy was mostly generalized with frequent involvement of tender cervical, axillary, and inguinal nodes. Hepatomegaly was found more common than splenomegaly. Hypotension was observed in 42 children and was responsive to fluid therapy in half of the children. The rest of the children required the use of noradrenaline with or without

Table 4: Complications of admitted children

Complication	*Number (%)*
Septic Shock	46 (56.1)
ARDS	21 (25.6)
AKI	20 (24.4)
Myocarditis	15 (18.3)
Meningoencephalitis	13 (15.9)
MODS	12 (14.6)
Death	9 (10.9)

Table 5: Complications of scrub typhus and predictors of outcome

Predictor	*Survivors*	*Nonsurvivors*	*p-value*
Shock	37	9	0.024
ARDS	13	8	0.001
MODS	3	9	0.001
Meningoencephalitis	8	5	0.001

Table 6: Complication profile of various pediatric scrub typhus studies

Parameter	*Nallasamy et al.*[24]	*Pathak et al.*[20]	*Sandesh et al.*[19]	*Kiruthika et al.*	*Present study*
Setting	North India	Nepal	North India	South India	North India
Year	2013–2015	2016–2017	2012–2019	2012–2019	2019–2021
Patient no.	160	76	84	84	82
Age range	3 months–12 years	1 month–16 years	1 month–18 years	1 month–18 years	1 month–18 years
Design	Retrospective	Prospective	Retrospective	Retrospective	Cross-sectional
Hepatitis	62%	34.2%	61.8%	61.9%	79.26%
Shock	17%	–	30%	19%	51.21%
ARDS	11%	–	16%	16%	25.60%
AKI	16%	65.8%	11.3%	11.3%	24.39%
Myocarditis	3%	72.4%	–	30%	18.29%
Meningoencephalitis	29%	14.5%	11.3%	11.3%	15.85%
MODS	13%	–	6.4%	6.4%	14.63%
Mortality	8.8%	3.9%	4.87%	3.2%	10.97%

dopamine along with ventilatory support. Ascites and periorbital edema had been reported in 37–60% of children in prior Indian studies.[17,19] Eschar was observed in only 3.7% of children in the axilla and scalp. Indian studies have reported eschar in 10–90% of children.[19,20] The low incidence of eschar in the present study may be due to dark skin and missing eschar along the hairline as such eschars are likely to remain undetected. Meningeal signs were elicited in 8.5% of recruited children; which is less than the studies done earlier (30–35%) which may be explained by early treatment, diagnosis, and referral done by referring physicians these days.[19,20]

Among laboratory parameters, elevated liver enzymes, thrombocytopenia, hyponatremia, deranged kidney functions, and hypoalbuminemia were commonly observed; which is in corroboration with previous similar Indian studies.[19–21] Recent studies have concluded that 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 doxycycline and azithromycin as treatment options; the review also found that there were few treatment failures with the abovementioned drugs.[22,23] Majority of children in the present study were treated with only doxycycline and showed a favorable clinical response compared to other studies.[19,21,24] Azithromycin was used only in PICU admitted sick children in combination with doxycycline. Thus, we can conclude that doxycycline is currently the best drug for managing scrub typhus.

The study revealed that hepatitis, shock, ARDS, AKI, myocarditis, meningoencephalitis, and MODS were the main complications; which were compared with other studies (Table 6). The study revealed that hepatitis, shock, and mortality rate was comparatively more than in previous studies. Our study also revealed that children presenting with shock, ARDS, MODS, and meningoencephalitis were more likely to have an adverse outcome; which is similar to earlier studies.[20,24] Hence it can be concluded that low blood pressure, shock, deranged liver enzymes, AKI, ARDS, and meningoencephalitis need to be managed early with antibiotics and good supportive care so that multiorgan dysfunction can be avoided to reduce mortality.

Conclusion

The study presents an account of scrub typhus in a North Indian tertiary care health institution. The clinical spectrum ranged from fever and associated minor features to much dreaded systemic involvement. The battery of hematological and biochemical investigations can aid in predicting scrub-related outcomes. The possibility of scrub typhus should be explored in the pediatric age-group if the clinical picture hints about it, particularly in the rainy season and early winters. Preventive measures (covering exposed body parts and utilization of bed nettings) are recommended to protect children during conducive seasons. The study further strengthens the role of a much cheaper drug like doxycycline in the management of ailment. In addition, scrub typhus should be suspected early in a child to prevent life-threatening complications and poor outcomes. The vision of sustained development can be realized in the true sense only if pediatric morbidity and mortality are addressed equally for infectious diseases, lifestyle ailments, and nutritional disorders.

Limitations of Study

As the study was carried out through the COVID-19 pandemic, due to restricted outdoor activities infection rate might have been affected. This might have led to decreased admission and ultimately decreased sample size of the study; affecting the external validity of the study findings.

What is Already Known?

Scrub typhus is a pan-Indian febrile illness with significant morbidity and mortality.

What This Study Adds?

It affects all age-groups and should be kept as a differential diagnosis of various tropical pediatric infections.

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References

1. Luce-Fedrow A, Lehman ML, Kelly DJ, et al. A review of scrub typhus (*Orientia tsutsugamushi* and related organisms): then, now, and tomorrow. Trop Med Infect Dis 2018;3(1):8. DOI: 10.3390/tropicalmed3010008

2. World Health Organization. WHO Recommended Surveillance Standards. 2nd ed. World Health Organization; 1999. [last accessed on 2022 May 12] Available from: https://apps.who.int/iris/handle/10665/65517
3. Mahajan SK, Rolain JM, Sankhyan N, et al. Pediatric scrub typhus in Indian Himalayas. Indian J Pediatr 2008;75(9):947–949. DOI: 10.1007/s12098-008-0198-z
4. Batra HV. Spotted features and typhus fever in Tamil Nadu commentary. Indian J Med Res 2007;126(2):101–103. Available from: https://journals.lww.com/ijmr/Citation/2007/26020/Spotted_fevers___typhus_fever_in_Tamil_Nadu.5.aspx (accessed on 2022 May 12).
5. Kumar M, Krishnamurthy S, Delhikumar CG, et al. Scrub typhus in children at a tertiary hospital in Southern India: clinical profile and complications. J Infect Public Health 2012;5(1):82–88. DOI: 10.1016/j.jiph.2011.11.001
6. Ramyasree A, Kalawat U, Rani ND, et al. Seroprevalence of scrub typhus at a tertiary care hospital in Andhra Pradesh. Indian J Med Microbiol 2015;33(1):68–72. DOI: 10.4103/0255-0857.148381
7. Wang CC, Liu SF, Liu JW, et al. Acute respiratory distress syndrome in scrub typhus. Am J Trop Med Hyg 2007;76(6):1148–1152. DOI: 10.4269/ajtmh.2007.76.1148
8. Park JS, Jee YK, Lee KY, et al. Acute respiratory distress syndrome in scrub typhus: diffuse alveolar damage without pulmonary vasculitis. J Korean Med Sci 2000;15(3):343–345. DOI: 10.3346/jkms.2000.15.3.343
9. Viswanathan S, Muthu V, Iqbal N, et al. Scrub typhus meningitis in South India—a retrospective study. PLoS One 2013;8(6):e66595. DOI: 10.1371/journal.pone.0066595
10. Luhr OR, Antonsen K, Karlsson M, et al. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. Am J Respir Crit Care Med 1999;159(6):1849–1861. DOI: 10.1164/ajrccm.159.6.9808136
11. Manu JR, Gupte AB, Varghese GM, et al. DHR-ICMR, guidelines for diagnosis and management of rickettsial diseases in India. Indian J Med Res 2015;141:417–422. DOI: 10.4103/0971-5916.159279
12. Varghese GM, Janardhanan J, Trowbridge P, et al. Scrub typhus in South India: clinical and laboratory manifestations, genetic variability, and outcome. Int J Infect Dis 2013;17(11):e981–e987. DOI: 10.1016/j.ijid.2013.05.017
13. Sankhyan N, Saptharishi LG, Sasidaran K, et al. Clinical profile of scrub typhus in children and its association with hemophagocytic lymphohistiocytosis. Indian Pediatr 2014;51(8):651–653. DOI: 10.1007/s13312-014-0470-4
14. Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6(1):2–8. DOI: 10.1097/01.PCC.0000149131.72248.E6
15. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16(5):428–439. DOI: 10.1097/PCC.0000000000000350
16. KDIGO Clinical Practice Guideline for Acute Kidney Injury. J Int Soc Nephrol 2012;2(1). [last accessed on 2022 May 18]. Available from: https://kdigo.org/guidelines/acute-kidney-injury
17. Huang CT, Chi H, Lee HC, et al. Scrub typhus in children in a teaching hospital in eastern Taiwan, 2000–2005. Southeast Asian J Trop Med Public Health 2009;40(4):789–794. Available from: https://www.tm.mahidol.ac.th/seameo/2009-40-4/19-4518.pdf (accessed on 2022 May 12)
18. Sharma SR, Masaraf H, Lynrah KG, et al. Tsutsugamushi disease (scrub typhus) meningoencephalitis in North Eastern India: a prospective study. Ann Med Health Sci Res 2015;5(3):163–167. DOI: 10.4103/2141-9248.157486
19. Sandesh G, Jyoti S, Sanjeev C, et al. Clinico-laboratory profile of scrub typhus from mid and lower Himalayan region in North India. Pediatr Infect Dis 2015;7(3):67–70. DOI: 10.1016/j.pid.2015.11.003
20. Pathak S, Chaudhary N, Dhakal P, et al. Clinical profile, complications and outcome of scrub typhus in children: a hospital based observational study in central Nepal. PLoS One 2019;14(8):e0220905. DOI: 10.1371/journal.pone.0220905
21. Palanivel S, Nedunchelian K, Poovazhagi V, et al. Clinical profile of scrub typhus in children. Indian J Pediatr 2012;79(11):1459–1462. DOI: 10.1007/s12098-012-0721-0
22. Sayed EI, Liu Q, Wee I, et al. Antibiotics for treating scrub typhus. Cochrane Database Syst Rev 2018;24(9):CD002150. DOI: 10.1002/14651858.cd002150
23. Veerappan I, Ramar R, Palanisamy S. Antibiotic response to pediatric scrub typhus in South India: is clinical failure to azithromycin to be worried? J Trop Pediatr 2021;67(1):fmab013. DOI: 10.1093/tropej/fmab013
24. Nallasamy K, Gupta S, Bansal A, et al. Clinical profile and predictors of intensive care unit admission in pediatric scrub typhus: a retrospective observational study from North India. Indian J Crit Care Med 2020;24(6):445–450. DOI: 10.5005/jp-journals-10071-23445