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ORIGINAL RESEARCH

Scrub Typhus in Children at Tribhuvan University Teaching Hospital in Nepal

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Introduction: Scrub typhus is an acute undifferentiated febrile illness with varied non-specific manifestations. It dramatically responds to appropriate antibiotic if started earlier in the course of disease leading to significant reduction in morbidities and mortalities.

Objective: To describe the clinical profile, treatment and prognosis of scrub typhus in children.

Patients and Methods: Serologically confirmed children with scrub typhus admitted to Tribhuvan University Teaching Hospital (TUTH) over a period of 3 years (April 15, 2015, to April 14, 2018) were retrospectively analyzed for clinical manifestations, investigations, complications and treatment outcomes.

Findings: A total of 84 children (39 boys, 45 girls) were found to have serologically confirmed scrub typhus. Apart from fever which was invariably present in all children, the most common symptoms were that of respiratory system such as shortness of breath, gastrointestinal system which were vomiting and abdomen pain followed by headache. On physical examination, the most frequent clinical signs were hepatosplenomegaly, edema, eschar and lymphadenopathy. Hepatitis, myocarditis and meningitis were the most common complications. Most patients had the shortest defervescence of less than 48 hours with oral doxycycline (64.7%) followed by intravenous chloramphenicol (56.7%). The overall mortality rate was 4.8%, all due to multiorgan dysfunction.

Conclusion: In a country like Nepal, scrub typhus should be suspected in any child who presents with fever associated with shortness of breath, abdomen pain, vomiting, headache and clinical findings suggestive of multisystem involvement such as hepatitis, myocarditis or meningitis. Early empirical medical management based on high clinical suspicion while waiting for definitive serological report with oral doxycycline or intravenous chloramphenicol may prevent complications of scrub typhus thereby reducing mortality.

Keywords: children, chloramphenicol, doxycycline, fever, Nepal, scrub typhus

Introduction

Scrub typhus is an acute, febrile illness caused by *Orientia tsutsugamushi*, an obligate intracellular gram-negative cocco-bacilli belonging to the Rickettsiae family.[1,2] The term "scrub" is used due to the type of vegetation which is terrain between woods and clearings that harbors the vector.[1] The term "*tsutsugamushi*" has a Japanese origin with "tsutsuga" meaning 'illness' and "mushi" meaning "insect or mite".[3] The endemic zone for scrub typhus is depicted by the triangle formed by Japan, Northern Australia and the Arabian Peninsula.[4]

Scrub typhus is a zoonotic disease that is transmitted to humans through the bite of an infected chigger, the larval stage of trombiculid mites.[5] Humans are accidental hosts

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in this zoonotic disease. The bacteria multiply at the inoculation site with the formation of a papule that ulcerates and becomes necrotic, evolving into an eschar. When bacteria invades endothelial cells, it produces disseminated vasculitic and perivascular inflammatory lesions. Vasculitis leads to significant micro vascular leakage, edema, tissue hypoperfusion and ensuing end-organ ischemic injury.[6,7]

Incubation period of scrub typhus is usually 9–11 days (range, 1–30 days).[7] Fever, headache, abdomen pain, vomiting, hepatosplenomegaly, lymphadenopathy, generalized swelling, rash, shortness of breath are the common clinical features of disease in children.[7,8]

Multiorgan dysfunctions (MODS) such as acute kidney injury (AKI), hepatitis, acute respiratory distress syndrome (ARDS), meningitis or circulatory collapse, myocarditis are the complications that occur in scrub typhus.[3,6,8,9] These serious complications usually occur in the second week of illness.[3,10,11] Eschar, which is pathognomic for this disease is found in 11–43% of cases in various studies.[8,10-13] It is a disease which is very difficult to diagnose early because of nonspecific signs and symptoms. If not diagnosed in time and treated, it can lead to grave complications with MODS and even death.[2]

Scrub typhus is an emerging rickettsial disease in Nepal. Recent outbreaks of scrub typhus from various parts of Nepal following the devastating earthquake in April 2015 reflect the favorable environment for the transmission cycle of this mite-borne disease, particularly in the monsoon season.[5,9] Previously, it was grossly underdiagnosed in Nepal due to its nonspecific clinical presentation, limited awareness and low index of suspicion among clinicians and lack of diagnostic facilities.[9] In a study done in Nepal, almost 26% of the patients were in the pediatric age group.[12] The clinical features of scrub typhus are similar to a variety of other infectious disease such as typhoid, bacterial meningitis, leptospirosis and dengue.[14] Still, there is paucity of data on this disease in children in Nepal. This retrospective study was undertaken with an aim to evaluate the clinico-laboratory profile, morbidities, various treatment modalities and the subsequent outcomes associated in serologically confirmed children with scrub typhus admitted in an urban referral centre.

Patients and Methods

Medical records of all children up to 16 years of age admitted in Pediatric Ward, Tribhuvan University Teaching Hospital (TUTH) from April 15, 2015, to April 14, 2018, with a diagnosis of scrub typhus using appropriate clinical features and a single positive serological test were retrospectively reviewed. The serological test performed was scrub typhus immunoglobulin M (IgM) ELISA kit by In Bios International Inc, USA. This study was approved by the Institutional Review Board (IRB) of TUTH. Patient's parental consent to review their medical records is not required by the Institutional Review Board of TUTH in a retrospective study. All institutional rules and regulations needed for a retrospective study including maintenance of privacy and confidentiality of patient data were fully complied with throughout the whole processin compliance with the Declaration of Helsinki.

A proforma was used as a data collecting form to collect information on demographic profile, clinical and laboratory features. Treatments provided at the time of presentation and during disease course for each patient were also recorded. Time to fever defervescence to a particular antibiotic was noted from the patient record file. Complications of disease such as heart failure, respiratory or renal failure, disseminated intravascular coagulation (DIC) and others along with the need of Pediatric Intensive Care Unit (PICU), inotropic support, and mechanical ventilator support, duration of PICU stay, hospital stay and mortality were noted in the proforma. Investigations such as blood and urine culture, rapid antigen test for malaria, HIV-
ELISA, Mantoux test, gastric aspirate to find acid-fast bacilli, Widal test, dengue IgM antibody test, serology for leptospira and brucella, chest X-ray, etc were also performed to rule out differential diagnosis wherever necessary based on history and clinical examination for selected cases.

The medical terms and conditions for enrolled children were defined in Table 1.

Treatment guidelines for the cases were based on the standard textbook of pediatrics[7] and Epidemiology and Disease Control Division (EDCD) interim guidelines on prevention and control of scrub typhus of Nepal, 2015[9,24] as mentioned inTable 2.

Intravenous doxycycline was not available at that time in Kathmandu. Doxycycline is available as a capsule of 100 mg in Nepal so smaller children requiring doxycycline less than 100 mg were prescribed syrup chloramphenicol in this study as described as alternative therapy in Table 2. The patients with features of meningitis or multiorgan involvement at presentation or who developed

Table 1 Definitions of Various Medical Conditions/Complications

Myocarditis[11]	(1) Congestive cardiac failure (CCF) or cardiomegaly or (2) Hemodynamic compromise that required a vasopressor (≥5 µg/kg/min of dobutamine or dopamine), use of noradrenaline/adrenaline or (3) Elevated CPK-MB (creatine phosphokinase MB) levels (>25 U/L) in the blood
Hypotension[11]	A systolic blood pressure below the fifth percentile for the corresponding age, sex and height
Acute Kidney Injury[15]	According to Kidney Disease: Improving Global Outcomes (KDIGO) definition and classification
Acute Respiratory Distress Syndrome[16]	According to consensus recommendations from the Pediatric Acute Lung Injury Consensus
Meningitis[17]	Presence of altered sensorium and signs of meningeal irritation or elevated cells and protein on cerebrospinal fluid (CSF) analysis.
Multiorgan Dysfunction (MODS)[8,18]	Any alteration of organ function that requires medical support for maintenance involving two or more organ systems (respiratory, cardiovascular, renal, hepatic, and neurological systems)
Generalized lymphadenopathy[19]	When there is enlargement of more than two noncontiguous node regions
Disseminated Intravascular Coagulation (DIC)[17,20]	Clinical manifestations of bleeding along with thrombocytopenia and elevated coagulation profile (prolong prothrombin (PT), International Normalized Ratio (INR) and activated prothrombin time (aPTT) Prolong PT as >12 seconds, prolong INR as >1.2, prolong aPTT>37 seconds
Anemia[20]	When hemoglobin (Hb) is less than value of that for age and gender (for 1–23 months <10.5 g/dL, 2–9 years <11.5 g/dL, 10–17 years male <12.5 g/dL, female <12 g/dL)
Hepatitis[17,20]	When liver transaminase and or serum bilirubin are found to be elevated. Transaminitis is considered for raised serum glutamic oxaloacetic transaminase (SGOT) for 1–9 years >55 IU/L and 10–16 years >45 IU/L, raised serum glutamic pyruvic transaminase (SGPT) > 45IU/L
Hyperbilirubinemia[20]	Raised bilirubin is >1 mg/dL (17umol/L)
Raised serum creatinine[20]	Serum creatinine is raised if serum creatinine as for <1 year is >35 µmol/L, 1–9 years >62 µmol/L, 10–16 year s>88 µmol/L
Proteinuria[21]	Routine urine examination showing albumin ≥2+
Relapse[22]	The reappearance of fever and clinical manifestations of scrub typhus, in the absence of any other identifiable cause, within 30 days after completing therapy
Nonresponse to initiated drug[7]	When child does not achieve resolution of fever within five days of initiating drugs as mentioned in Table 2
Hemophagocytic Lymphohistiocytosis (HLH)[23]	Based on diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis (HLH 2004) as (1) persistent fever, (2) splenomegaly, (3) cytopenias, at least two lineages of hematopoiesis (hemoglobin <9 g/dL, neutrophils<1.0 × 10^9/L, platelets <100 × 10^9/L), (4) hypofibrinogenemia (<150 mg/dL) and/or hypertriglyceridemia (>265 mg/dL), (5) hyperferritinemia (>500 ng/mL), (6) hemophagocytosi, (7) low natural killer cell activity, and (8) high concentration of soluble receptor for interleukin 2 (sCD25). Five of the above eight criteria were sufficient for the diagnosis of HLH.

these complications during hospital stay were started on intravenous chloramphenicol which has a bactericidal effect.[25]

The collected data were entered into Microsoft Excel spreadsheet and analyzed using SPSS version 20 for Windows (IBM Corporation, Armonk, NY, USA).

Results

A total of 84 children were found to have scrub typhus with positive IgM ELISA from April 15, 2015 to April 14, 2018. Seventy-four children were admitted through the pediatric emergency ward and rest from the pediatric outpatient department (OPD). The female to male ratio is 1.15:1 (45:39). The

Table 2 Treatment Modality Based on EDCD Guideline on Prevention and Control of Scrub Typus of Nepal

S. No.	Treatment Modality
1	Azithromycin (10 mg/kg) single dose for children less than eight years
2	Doxycycline (2.2 mg/kg) orally twice daily was suggested for three days after resolution of fever (usually 5–10 days course) for children more than eight years old.
3	Alternative therapy advised was quinolones (oral 10 mg/kg/dose or intravenous 5 mg/kg/dose ciprofloxacin or levofloxacin) twice daily for 5–10 days and oral or intravenous chloramphenicol 25 mg/kg/dose six-hourly for 5–10 days[23]
4	All patients suspected to have meningitis or multiorgan involvement due to scrub typhus are started on intravenous chloramphenicol before serological report is available.

age of the patients ranged from nine months to 16 years with a mean age of ten and half years. Children between 10 and 14 years of age accounted for the most cases 37 (44%). The demographic data is shown in Table 3. The highest number (83%) of cases was observed between the months of August and October in three consecutive years as shown in Figure 1.

The clinical features of children at the time of presentation in hospital are shown in Table 4. All 84 patients presented with fever and the majority (70%) had a fever for 7–14 days prior to presentation. Other common symptoms were shortness of breath 42 (50%), abdominal pain 36 (43%), vomiting 35 (42%) and headache 32 (38%) followed by cough in 22 (26%), altered sensorium in 17 (20%), chest pain in 13 (15%), seizure and myalgia in 11 (13%) each. An eschar was observed in 22 (26%) of the patients. Most were found in the groin (7) followed by axillary region (6). Similarly, among clinical signs,

Table 3 Demographic Data of Children with Scrub Thypus

	Number (%)
Gender	
Female	45 (53.6)
Male	39 (46.4)
Age	
<3years	4 (4.8)
3–5years	10 (12)
6–9years	16 (19.1)
10–14years	37 (44)
>15 years	16 (19.1)

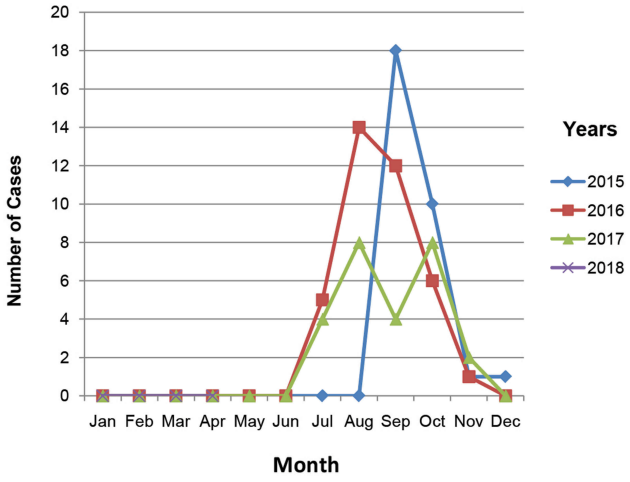

Figure 1 Incidence of scrub typhus according to seasonal variation.

hepatomegaly was encountered in 55 (65%), splenomegaly in 39 (46.5%), edema in 32 (38%), lymphadenopathy in 20 (23.8%), icterus in 14 (17%), maculopapular rash in 10 (12%) of the 84 patients.

The most common provisional diagnoses made were enteric fever (19%) followed by meningitis (14%) and sepsis (10.7%). The diagnosis was correctly assumed in 16 (20%) children pending serological report during hospital admission.

Tables 5 and 6 show laboratory parameters and the complications observed among children diagnosed with scrub typhus respectively. Four children died, all due to MODS. These children were admitted to PICU directly from the pediatric emergency ward on arrival to hospital with provisional diagnosis of septic shock. In total 27 (32.1%) children were admitted to the PICU and among them, 12 children needed mechanical ventilation during their treatment.

The number of children on various initial drugs at presentation or instituted after admission in this study are illustrated in Table 7. Figure 2 with flow chart shows different treatment regimens, fever defervescence timings and disease outcome. Drugs were started according to the standard text of pediatrics and EDCD interim guideline on prevention and control of scrub typhus of Nepal September 2015 (Table 2). However, children who were already on antibiotics effective against *O. tsutsugamushi* on presentation were continued with the same drugs. Alterations were made in drug regimens as recommended on EDCD interim guideline whenever necessary such as presence of complications or development of complications like meningitis during the course of hospital stay.

Table 4 Clinical Profile of Children with Scrub Typus at Presentation

Symptoms	Number (%)
Fever	
<7 days	6 (7.1)
7–13 days	59 (70.2)
14–29 days	16 (19.1)
≥30 days	3 (3.6)
Respiratory manifestations	
Shortness of breath	42 (50)
Cough	22 (26)
Chest pain	13 (15.5)
Gastrointestinal manifestations	
Abdominal pain	36 (43)
Vomiting	35 (42)
Loss of appetite	7 (8)
Loss stool	4 (5)
Central nervous system manifestations	
Headache	32 (38)
Altered sensorium	17 (20.2)
Seizure	11 (13.1)
Musculoskeletal manifestations	
Myalgia	11 (13)
Joint pain	2 (2.4)
Rash	1 (1.2)
Ophthalmological manifestations 13 (15.5)	
Red eye (unilateral/bilateral) with/without eye pain	7
Decreased vision	4
Diplopia	2
Clinical signs	
Hepatomegaly	55 (65.5)
Splenomegaly	39 (46.4)
Edema (pedal/periorbital/generalized)	32 (38)
Eschar	22 (26)
Hypotension	21 (25)
Lymphadenopathy	20 (24)
Generalized	10
Cervical	13
Axillary	11
Inguinal	7
Pallor	17 (20)
Icterus	14 (17)
Ascitis	12 (14)
Raised intracranial pressure	12 (14.3)
Maculopapular rash	11 (13)
Ophthalmological manifestations	11 (13)
Conjunctivitis	9
Anterior ulcerative blepharitis (both eyes)	1
Bilateral anterior uveitis	1

Table 5 Laboratory Abnormalities in Children with Scrub Typus

Laboratory Parameters	Number n/N[a] (%)
Raised SGOT	50/60 (83.3)
Raised SGPT	47/60 (78.3)
Raised bilirubin	20/36 (55.55)
Raised INR	4/16 (25)
Anemia	68/84 (81)
Leucocytosis	33/84 (39.2)
Leucopenia	3/84 (3.6)
Thrombocytopenia	44/84 (52.4)
Raised serum creatine phosphokinase MB	27/42 (64.28)
Hyponatremia	30/79 (38)
Hypoalbuminemia	14/23 (60.8)
Albuminuria	17/84 (20.2)
Raised serum creatinine	25/84 (29.76)

Notes: [a]N, total number of children investigated; n, number of children with abnormal report among total number of children investigated.

Table 6 Complications of Scrub Typus Seen in Children

Complications	Number (%)
Hepatitis	50 (59.5)
Myocarditis	34 (40.5)
CCF	23 (27.4)
Meningitis	29 (34.5)
Pneumonia	21 (25)
MODS	16 (19)
ARDS	13 (15.5)
AKI	12 (14.3)
Pleural effusion	9 (10.7)
DIC	5 (5.9)
Cranial nerve palsy (bilateral sixth cranial nerve)	2 (2.4)

Table 7 Number of Children on Different Drugs at Presentation or Initiated at the Time of Admission

S. No.	Name of Antibiotics	Number of Children
1	Oral doxycycline	34
2	Intravenous chloramphenicol	41
3	Oral chloramphenicol	2
4	Oral azithromycin	3
5	Intravenous azithromycin	1
6	Intravenous cefepime	1
7	Intravenous levofloxacin	2
	Total	84

Twenty-two out of 34 children (64.7%) had the shortest defervescence of less than 48 hours when treated with oral doxycycline followed by 23 out of 41 patients (56.7%) in the intravenous chloramphenicol group.

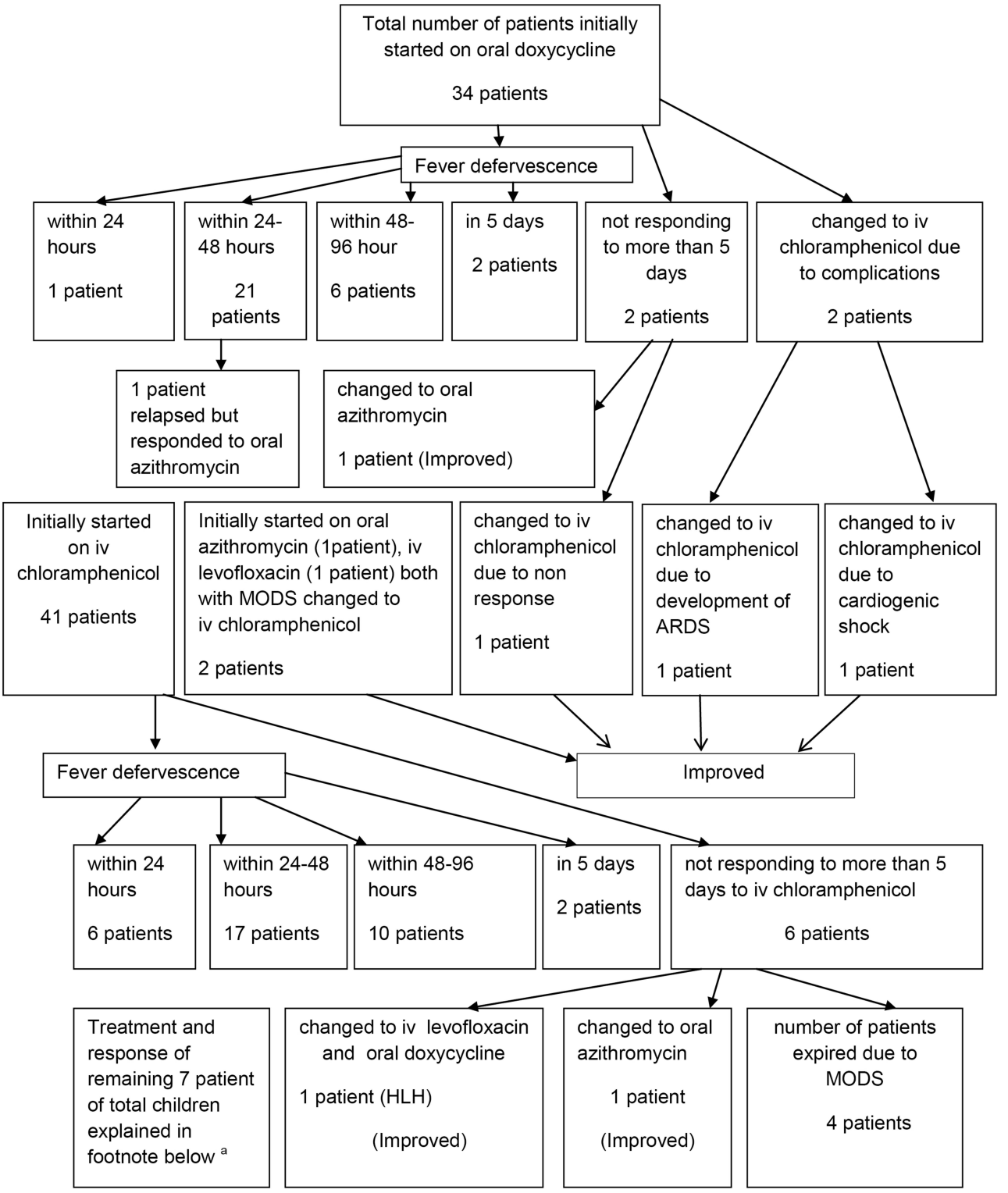

Figure 2 Flowchart showing treatment, fever defervescence and other outcomes. In the remaining seven patients of total children, two children initially on oral chloramphenicol and oral azithromycin each, one each on intravenous (iv) azithromycin, iv levofloxacin, iv cefepime improved on same regimens.

Fever defervescence was seen fastest within 24 hours in intravenous chloramphenicol group with 6 out of 41 patients (14.63%) as compared to the oral doxycycline group with 1 out of 34 patients (2.9%).

Few interesting case scenarios of scrub typhus were found in this study. There was a relapse of scrub typhus with reappearance of fever after 16 days of treatment with even seven days of initial oral doxycycline in a 15 year old

boy. He was readmitted and reinvestigated further to rule out other causes of fever which turned out to be negative. He became afebrile with oral azithromycin for three days.

A nine month old infant who is the youngest patient in this study presented with fever for 10 days, had left sided tonic-clonic movement of limbs, left sided hemiparesis, hepatosplenomegaly, and congestive cardiac failure. Lumbar puncture report revealed total leucocyte count of 18 cells per cubic mm (polymorphs 20%, lymphocyte 80%), protein 131 mg/dL, and glucose 62 mg/dL in cerebrospinal fluid. The magnetic resonance imaging (MRI) of his head revealed diffuse heterogeneous mild high signal intensity in subcortical and deep white matter of bilateral cerebral hemisphere more pronounced in right side probably due to demyelination. He was initially started on intravenous ceftriaxone which was continued for two days only. As the serology report showed positive for scrub typhus and negative for other differential diagnosis, intravenous ceftriaxone was stopped and intravenous chloramphenicol was given for 10 days. He was diagnosed as acute demyelinating disease (ADEM) due to scrub typhus. Other medications provided were intravenous methylprednisolone for treatment of demyelination, intravenous furosemide for congestive cardiac failure and intravenous phenytoin for left-sided seizure. He improved and was later referred to a rehabilitation center for stimulation and physiotherapy.

Similarly, an eight year old boy had persistent fever with hepatosplenomegaly, MODS with septic shock and myocarditis at presentation. He was intubated, kept in PICU and initially treated with intravenous chloramphenicol. On the seventh day of his stay in PICU, he developed DIC, AKI, pulmonary hemorrhage so oral doxycycline and intravenous levofloxacin were started. On further evaluation, he had deranged liver function test (increased AST, ALT, hypoalbuminemia), pancytopenia, hypofibrinogenemia (125 mg/dL), increased fibrinogen degradation product (1.2 mg/L), hyperferritinemia (767 ng/mL), hypertriglyceridemia (2.4 mmol/L), increased lactate dehydrogenase (1752 U/L). The diagnosis of hemophagocytic lymphohistiocytosis (HLH) due to scrub typhus was thus made. He improved and was discharged after 14 days of oral doxycycline and intravenous levofloxacin.

Discussion

After the devastating earthquake in Nepal in August 2015, more than 500 confirmed cases and 14 deaths due to scrub typhus were reported from the various districts of the country over the period of one year.[8] The outbreaks could have been triggered by close contact between human beings and rats that might have come out of their usual underground habitat after the collapse of many houses.[9] Before that there was no evidence of outbreak of scrub typhus, which may be due to lack of systematic investigation and surveillance. According to a recent study published by Karki et al, 146 (36.4%) were children among 401 cases detected during April to December 2016.[9] In the current study, 84 children up to 16 years with scrub typhus were admitted in Pediatric Ward, Tribhuvan University Teaching Hospital (TUTH) from April 15, 2015 to April 14, 2018. Heightened awareness regarding scrub typhus in 2015 helped in higher detection of affected children on 2016 and 2017. Among 84 children, majority 37 (44%) of children were 10–14 years which is similar to a previous study indicating higher exposure to infected chigger.[17] However, there was no difference in incidence of scrub typhus among different gender.

In our study, children in the age group less than 5 years were 16.7%, 6–9 years were 19.1%, whereas more than 10 years were 53%. In some studies, most patients were in the age group 5–10 years but in other studies, the patient number was highest in the age group of less than or around five years.[11,25,26]

This study depicts the incidence of scrub typhus between the months of June and December with disease peaking in the months of July and August which coincides with rainy season as suitable for the growth of vegetation and trombiculid mite and its transmission among children. This finding is similar to an earlier study.[28] This observation is slightly different from another study in which the disease detection was more in the months of May to August.[26]

All children presented with fever which has also been observed in other studies.[10,27,28] Most of them (70%) had fever for 7–13 days. The next most common symptoms were that of respiratory symptoms such as shortness of breath (50%), cough (26%) and chest pain (15.5%) which is similar to studies done in Eastern Nepal[29] and India.[30] Gastrointestinal symptoms such as abdominal pain (43%) and vomiting (42%) were also common in the present study which is in congruence with previous studies.[11,17,30] Headache, abnormal body movement and altered sensorium were found in 38%, 22.6%, and 13%, respectively.

On physical examination, the most common signs were hepatomegaly (65%), splenomegaly (46%) then edema (38%). The range of hepatomegaly being detected has a wide variation from 29% to 95% according to various studies. The presence of splenomegaly is an important clinical finding of scrub typhus that distinguishes it from dengue as splenomegaly is uncommon in dengue.[10] Other studies also showed wide range in detection of splenomegaly which is from 26% to almost 60%.[10,11,17,25-27,31]

Presence of an eschar provides a valuable clinical clue in the early diagnosis of scrub typhus.[13] It may develop before the onset of systemic signs. It usually occurs in areas where the skin is thin, moist or wrinkled such as axilla, genitalia and inguinal areas where the clothing is usually tight.[10] Eschar was found in 22 children (26%) in this study which is in contrast to a few other studies which showed a higher detection rate.[13,30]

Finding of lymphadenopathy in our study was 24% only which is low in comparison to other studies.[10,17,30] Presence of lymphadenopathy can be a differentiating feature from other causes of fever such as malaria and dengue.[17]

Analysis of laboratory parameters revealed a major proportion of children (81%) had anemia which may be contributed by underlying nutritional deficiency. Thrombocytopenia was detected between 20 and 88% in various studies but in our study it was 52%.[17,25,27,30] Leukopenia was uncommon in our study being around 3.6% whereas it was seen in 23% of the patients in another study.[17] Leukocytosis was seen in 39.2% which is almost the same as that seen in other studies ranging from 21–47%.[17,25,26]

Out of 36 children, 17 children (20.2%) were clinically icteric and had hyperbilirubinemia on investigation as well. Among 60 children, increased SGOT and SGPT were found in 50 (83.3%) and 47 (78.3%) patients respectively. Dyselectrolytemia such as hyponatremia was found in 30 children out of 79 children investigated (38%) which helps in diagnosing rickettsial infection. Prevalence of hyponatremia ranged from 15–32% in other studies.[11,26]

While evaluating the complication of scrub typhus, the present study shows hepatitis in 59.5%, myocarditis in 40.5%, CCF in 27.4% and meningitis in 34.5%. Complications pertaining to liver, heart and brain were also revealed in similar studies.[6,8,12] Presence of hypotension was 25% which is lower to the rate seen in other studies.[10,11,28] Meningitis and meningoencephalitis was high in our study (30.4%) which was similar to the study done by Bhat et al.[10] Myocarditis as a complication was low in some studies with range of 2–10% whereas in our study and that done by Kumar et al, it was more than 30%.[11] AKI as a complication is observed in various studies with a range between 2% and 20% and in our study it was 14%.[11,17,26,27]

In our study, one case of hemophagocytic lymphohistiocytosis (HLH) was found similar to a study done by Khandelwal et al.[17] In the study done by Sankhyan et al three cases (20%) of HLH were diagnosed out of which one child died.[28]

In our study, the mainstay of antibiotics was oral doxycycline and intravenous chloramphenicol. This is similar to the treatment regimen employed by Bhat et al.[10] A remarkable response to doxycycline or chloramphenicol has also been observed in their study as well. In the study by Kumar et al, all three drugs (azithromycin, chloramphenicol and doxycycline) were used.[27] In a Sri Lankan study, rapid response to treatment with intravenous chloramphenicol was observed in comparison to oral chloramphenicol.[31] In the study done by Kumar et al, a dramatic response was seen with doxycycline.[11] Most of our patients on oral doxycycline also responded to the antibiotic and those not responding were changed to intravenous chloramphenicol or azithromycin. Rapid response in form of early defervescence to doxycycline may be taken as diagnostic intervention to support etiological diagnosis as scrub typhus. When analyzed retrospectively, the present study shows that more children had early defervescence (within 24 hours) to intravenous chloramphenicol compared to oral doxycycline. Development of EDCD interim guideline on prevention and control of scrub typhus in September 2015 which was updated in August 2016 helped in early treatment and fewer referrals from other parts of the country to referral center such as present research hospital in 2017.

No mortality was seen in one study, whereas mortality ranged from 7.3–12 0.7% in other studies.[10,17,18,25,27,30] Mortality rate in our study was 4.8%.

A limitation of this study is that various serotypes have not been separately identified hence the impact and virulence of a particular serotype cannot be estimated and used for prognosis of morbidity and mortality. The study cases were designated as having scrub typhus on the basis of single serological test with appropriate clinical and laboratory features. For the diagnosis of scrub typhus, the gold standard method of micro-immunofluorescence assay has not been used. It would have been better to have other tests for confirmation but this has been limited due to financial and socioeconomic conditions. However,

other relevant tests have been done where necessary to rule out other diseases in the differential diagnosis. It is not possible for children less than five years of age to accurately verbalize some of the complaints such as headache and chest pain which were also not documented in their individual medical record file as clinical symptoms. As the number of such children is small, the overall impact on the frequency of such complaints is likely to be minimal. This is a common problem seen in all studies involving small children. The study is a tertiary care hospital-based study where mostly only referral cases reach the hospital thus the study cannot reflect community settings. The true community incidence of the disease may be higher.

Conclusion

In a country like Nepal, scrub typhus should be suspected in any child who presents with prolonged fever, mainly during monsoon period, and whenever associated with shortness of breath, abdominal pain, vomiting, headache and clinical findings suggestive of multisystem involvement such as shock, hepatitis, myocarditis, or meningitis. Findings of eschar, thrombocytopenia with hyponatremia in children support the diagnosis. Early treatment with antibiotic such as doxycycline or chloramphenicol for those with signs of multiorgan involvement pending serology and definite diagnostic investigations decreases mortality.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Chauhan M, Mahajan S, Manish S, Abrol R. Scrub typhus: an emerging scourge. *Indian J Basic Appl Med Res*. 2015;9(4):394–401.
2. Oberoi A, Varghese SR. Scrub typhus–an emerging entity. A study from a tertiary care hospital in North India. *Indian J Public Health*. 2014;58:281–283. doi:10.4103/0019-557X.146299
3. Viswanathan S, Muthu V, Iqbal N, Remalayam B, George T. Scrub typhus meningitis in South India — a retrospective study. *PLoS One*. 2013;8(6):e66595. doi:10.1371/journal.pone.0066595
4. Koh GC, Maude RJ, Paris DH, Newton PN, Blacksell SD. Diagnosis of scrub typhus. *Am J Trop Med Hyg*. 2010;82:368–370. doi:10.4269/ajtmh.2010.09-0233
5. Nayak N. Scrub typhus in Nepal. *Nepal J Epidemiol*. 2016;6(2):563–564. doi:10.3126/nje.v6i2.15162
6. Rathi N, Rathi A. Rickettsial infections: Indian perspective. *Indian Pediatr*. 2010;47(2):157–164. doi:10.1007/s13312-010-0024-3
7. Reller ME, Dumler JS. Scrub typhus *(Orientiatsu tsugamushi)*. In: Kliegman RM, Staton BF, Geme JW, Schor NF, editors. *Nelson Text Book of Pediatrics*. 19th ed. Philadelphia: Elsevier; 2011:1045–1046.
8. Varghese GM, Trowbridge P, Janardhanan J, et al. Clinical profile and improving mortality trend of scrub typhus in South India. *Int J Infect Dis*. 2014;23:39–43. doi:10.1016/j.ijid.2014.02.009
9. Karki KB, Acharya BP, Dhimal M, et al. *Descriptive Epidemiology of Scrub Typhus in Nepal*. Nepal Health Research Council; 2017.
10. Bhat NK, Dhar M, Mittal G, et al. Scrub typhus in children at a tertiary hospital in North India: clinical profile and complications. *Iran J Pediatr*. 2014;24(4):387–392.
11. Kumar M, Krishnamurthy S, Delhikumar CG, Narayana P, Biswal N, Srinivasan S. Scrub typhus in children at a tertiary hospital in Southern India: clinical profile and complications. *J Inf Public Health*. 2012;5(1):82–88. doi:10.1016/j.jiph.2011.11.001
12. Sedhain A, Bhattarai GR. Clinical presentation of scrub typhus during a major outbreak in Central Nepal. *Asian J Med Sci*. 2017;8(4):27–31. doi:10.3126/ajms.v8i4.17163
13. Rose W, Rajan R, Punnen A, Ghosh U. Distribution of eschar in pediatric scrub typhus. *J Trop Pediatr*. 2016;62(5):415–420. doi:10.1093/tropej/fmw027
14. Rose W. Scrub typhus in children. *Curr Med Issues*. 2017;15:90–94. doi:10.4103/cmi.cmi_26_17
15. KDIGO AKI Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012,2. Available from: http://www.kdigo.org/clinical_practice_guidelines/AKI.php. Accessed March 14, 2020.
16. The Pediatric Acute Lung Injury Consensus Conference Group (2015). 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
17. Khandelwal S, Meena KJ, Sharma SB. Scrub typhus in children: clinical profile and complications. *Ped Oncall*. 2015;12(4). doi:10.7199/ped.oncall.2015.68
18. Turner DA, Cheifetz IM. Shock. In: Kliegman RM, Geme JW, Blum NJ, Tasker RC, Shah SS, Wilson KM, editors. *Nelson Text Book of Pediatrics*. 21st ed. Philadelphia: Elsevier; 2020:572–574.
19. Tower RL, Camitta BM. Lymphadenopathy. In: Kliegman RM, Geme JW, Blum NJ, Tasker RC, Shah SS, Wilson KM, editors. *Nelson Text Book of Pediatrics*. 21st ed. Philadelphia: Elsevier; 2020:2624.
20. Lo SF. Reference interval for laboratory tests and procedures. In: Kliegman RM, Stanton BF, Geme JW, Schor NF, editors. *Nelson Text Book of Pediatrics*. First south Asia ed. Reed Elsevier India Private Limited; 2016:3465–3471.
21. Rathi NB, Rathi AN, Goodman MH, Aghai ZH. Rickettsial diseases in Central India: proposed clinical scoring system for early detection of spotted fever. *Indian Pediatr*. 2011;48:867–872. doi:10.1007/s13312-011-0141-7
22. Pachiappan N, Gane BD. Comparison of doxycycline and azithromycin for the treatment of scrub typhus in children. *J Evolution Med Dent Sci*. 2016;5(20):998–1000. doi:10.14260/jemds/2016/232
23. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124–131. doi:10.1002/pbc.21039
24. EDCD interim guideline on prevention and control of scrub typhus. September 2015 [Updated August, 2016]. Available from: http://www.edcd gov.np/resources/download/scrub-typhus-guideline-on-prevention-and-control. Accessed March 14, 2020.
25. Krishnan MP, Padarthi SC. Clinical, laboratory profile and outcome of scrub typhus in children. *IOSR –JDMS*. 2016;15(2):30–32.
26. Jain N, Jain V. Study on Clinico-laboratory profile of children with scrub typhus. *J Nepal Paediatr Soc*. 2012;32(2):187–192. doi:10.3126/jnps.v32i2.5683
27. Kumar S, Kumar M, Aggarwal B, Kumari R. Scrub typhus in children: clinical profile and complications at a tertiary care teaching hospital in Uttarakhand. *Indian J Child Health*. 2017;4(2):188–192. doi:10.32677/IJCH.2017.v04.i02.018

28. Sankhyan N, Saptarishi LG, Sasidaran K, Kanga A, Singhi SC. Clinical profile of scrub typhus in children and its association with hemophagocytic lymphohistiocytosis. *Indian Pediatr*. 2014;51:651–653. doi:10.1007/s13312-014-0470-4
29. Yadav SP, Dharel D, Shah GS, Bhattarai NR, Khanal B. Scrub typhus an emerging public health threat in eastern Nepal: an analysis from a tertiary center during two years outbreak. *Int J Contemp Pediatr*. 2018;5:1715–1718. doi:10.18203/2349-3291.ijcp20183504
30. Palanivel S, Nedunchelian K, Poovazhagi V, Raghunadan R, Ramachandran P. Clinical profile of scrub typhus in children. *Indian J Pediatr*. 2012;79(11):1459–1462. doi:10.1007/s12098-012-0721-0
31. Silva ND, Wijesundara S, Liyanapathirana V, Thevanesam V, Stenos J. Short report: scrub typhus among pediatric patients in Dambadeniya: a base hospital in Sri Lanka. *Am J Trop Med Hyg*. 2012;87(2):342–344. doi:10.4269/ajtmh.2012.12-0170