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Prospective study to assess the treatment modalities and fever defervescence in patients with scrub typhus from a tertiary care centre in South India

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ABSTRACT

Background and objectives: Fever defervescence in scrub typhus, a zoonotic bacterial infection is used as a surrogate marker of disease resolution. Failure of fever defervescence prompts clinicians to suspect alternate diagnoses and treatment. In this observational study, various treatment regimens were correlated with clinical outcomes.

Methods: All adult patients with a diagnosed scrub typhus were included; various antibiotic regimens used and clinical outcomes were studied. Data was analyzed using SPSS software for windows 16, with a 2-sided *P*-value of 0.05 or less was considered statistically significant.

Results: In 177 hospitalized patients with scrub typhus, combination therapy (doxycycline and azithromycin) was used in 74 subjects with doxycycline and azithromycin used in 46 and 57 subjects, respectively. Incidence of delayed defervescence was seen in 31.6%, Combination therapy being preferred in sicker patients (SOFA score 8.82). Presence of respiratory dysfunction was associated with a delay in fever defervescence [risk ratio 2.50(1.18-5.3)]. Patients receiving doxycycline did better in terms of oxygen requirement and the presence of hypotension. The overall case fatality rate was 5.6%. The severity of illness rather than the choice of antibiotics predicted the outcome in scrub typhus.

Interpretation & conclusion: Combination therapy with doxycycline and azithromycin is the most common regimen used. Incidence of delayed defervescence (31.6%) is increasing despite therapy and the involvement of respiratory dysfunction is an independent predictor of delayed fever defervescence.

Key words Scrub typhus; doxycycline; azithromycin; combination therapy; delayed defervesce

INTRODUCTION

Scrub typhus, a zoonotic bacterial infection is an important cause of acute febrile illness in South East Asia and South Western Pacific regions. It is seen in the tsutsugamushi triangle, the causative organism being *Orientia tsutsugamushi*. The bite of a larval stage (chigger) of the trombiculid mite transmits the infection[1–2]. Clinical features include fever, myalgia, headache, and an eschar at the site of inoculation, and multiple organ dysfunction[1–3]. The illness can range in severity from a mild self-remitting disease to a fatal illness. Mortality is seen in significant proportion of patients (4.6–9%) from South India even with therapy[1, 4–5]. The natural course of the disease lasts for about 14 to 21 days without therapy, and death is seen in the second week of the illness due to multiorgan failure[6]. Tetracycline (doxycycline), macrolides (azithromycin) and chloramphenicol are the most effective antimicrobials. Fever defervescence is seen within 48 hours after the initiation of the therapy, this response being characteristic for diagnosis of scrub typhus. Failure of defervescence within 48 hours is usually suggestive of an alternative diagnosis for acute febrile illness. In the recent times there has been a delay in the time to fever defervescence[7]. The reasons for this phenomenon are not clear, although resistance to drugs is one of the proposed mechanisms[8].

Monotherapy forms the cornerstone in treating patients with scrub typhus; however, combination therapy is increasingly being used in patients with delayed fever defervescence. Treatment outcomes with combination therapy and its effects on patients with severe illness has not been studied in detail. This study was undertaken to examine the different treatment regimens in the treatment of scrub typhus (monotherapy (doxycycline or azithromycin) and combination therapy (doxycycline and azithromycin) with regards to the incidence of delayed defervescence, outcomes and the factors affecting the outcomes.

MATERIAL & METHODS

Design

This was a prospective observational cohort study from November 2013 to April 2015.

Setting

This study was done in Christian Medical College (CMC), Vellore, India, in the departments of General Medicine and Emergency. CMC Vellore is a 2700 bed tertiary care medical college hospital in southern India.

Participants

All patients (aged ≥15 years) who presented with acute febrile illness with a diagnosis scrub typhus were included in the study. A diagnosis of scrub typhus was made with a positive IgM ELISA (Immunoglobulin M, Enzyme linked immune sorbent assay) for scrub typhus and/or a characteristic eschar. Patients with alternative diagnoses were excluded.

Variables

Data was collected for the baseline demographic characteristics, clinical features, laboratory parameters, organ dysfunction and antibiotic therapy received. Sequential organ failure assessment (SOFA) score was calculated to assess the severity of the illness[9]. The variables included age, sex, and duration of fever, comorbidities, presence of an eschar, laboratory investigations and organ dysfunction. All patients were followed up until fever defervescence or death. The antibiotic therapy was determined by the treating physician with principal investigator having no role in the initiation or modification of treatment regimen. The patients either received oral doxycycline or azithromycin or a combination of the two. The duration of the antimicrobial therapy for both monotherapy and combination therapy was 7 days. Organ dysfunction was defined as

Respiratory dysfunction: PaO_2 (partial pressure of oxygen in arterial blood)/FiO_2 (fraction of inspired oxygen) ratio of < 300 or the need for ventilator assistance.

Renal dysfunction: Increase in serum creatinine by ≥ 0.3mg/dl within 48 hr or increase in serum creatinine to 1.5 times baseline which is known to have occurred within the prior 7 days or urine volume < 0.5ml/kg/hr for 6 hr. (The kidney disease: Improving global outcomes, KDIGO definition).

Cardiovascular dysfunction: Hypotension or need for inotropes or vasopressor support.

Hepatic dysfunction: Serum Bilirubin ≥2 mg/dl or threefold elevation of liver enzymes.

Neurologic dysfunction: Alteration in the level of consciousness or neurological deficits.

Outcome variable

Primary outcome was defined as incidence of delayed defervescence (fever persisting after 48 hr of initiation of appropriate antibiotic therapy), the time of defervescence was defined as the first day of the highest axillary body temperature using digital thermometer lower than 37.7°C (100°F) for more than 3 consecutive days without the use of antipyretics. Secondary outcomes studied were the time duration for fever defervescence, mortality or leaving against medical advice (LAMA), duration of hypotension and oxygen requirement.

Laboratory test

All patients underwent hematological tests which included complete blood count, liver function tests, renal function tests, serum electrolytes, chest radiograph, appropriate cultures and serological tests. Scrub Typhus detect IgM ELISA (InBios International Inc., Seattle, USA) was used for serological diagnosis. An optical density of ≥0.5 was diagnostic of scrub typhus.

Statistical analysis

Statistical analysis was performed using Statistical package for social sciences (IBM Corp, released 2015, IBM SPSS, Version 23.0, Armonk). Descriptive data are given as mean and SD (standard deviation) or as median and range as appropriate. Chi-square test or Fisher exact test were used to compare dichotomous variables and t-test or Mann-Whitney test were used for continuous variables as appropriate. The association of delayed defervescence to the various variables was analyzed by univariate analysis and their 95% confidence intervals were calculated. For all tests, a 2-sided P-value of 0.05 or less was considered statistically significant.

Ethical statement

This study was approved by the Institutional Review Board of Christian Medical College, Vellore (IRB Min. No.8488, dated 09/08/2013) and patient confidentiality was maintained using unique identifiers and by password protected data entry software with restricted users. The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was determined to require Institutional Review Board / Ethics Committee review, and the corresponding protocol / approval number is IRB Min. No. No.8488, dated 09/08/2013.

RESULTS

The present study included 177 patients with a diagnosis of scrub typhus during the study period. The Strobe

Table 1. Baseline characteristics including demography and clinical features in patients with scrub typhus at admission

Variable	Doxycycline (n=46)	Azithromycin (n=57)	Combination therapy (n=74)	Total (n=177)
Sex male, Number (%)	27 (58.7%)	24 (42.1%)	33 (44.6%)	84 (47.45%)
Age, years (Mean (SD))	44 (15.8)	47.5 (15.9)	47.3 (15.1)	46.26 (15.5)
Duration of fever, Days (Mean (SD))	8.65 (3.7)	8.96 (4.5)	8.37 (3.4)	8.66 (3.9)
Diabetes mellitus	4 (8.7%)	5 (8.7%)	8 (10.8%)	17 (9.6%)
Pulse, per min (Mean (SD))	105.8 (15.7)	107.8 (19.4)	115.1 (21.6)	109.6 (19.9)
Blood pressure systolic, mmHg (Mean (SD))	106.6 (12.3)	108.6 (18.5)	101.8 (20.09)	105.6 (18)
Eschar, Number (%)	30 (65.2%)	35 (61.4%)	50 (67.5%)	115 (64.9%)
SOFA, (Mean (SD))	3.78 (2.5)	6.49 (4.89)	8.82 (5.2)	6.36 (4.96)
Laboratory Characteristics				
Haemoglobin, g%(Mean (SD))	12.4 (1.9)	11.1 (2.5)	11.85 (2.4)	11.78 (2.3)
Total leukocyte counts, per mm^3 (Mean (SD))	11622 (6430)	11393 (4425)	12825 (5767)	11946 (5566)
Platelet count, per mm^3 (Mean (SD))	95445 (69536)	83894 (67411)	80243 (68612)	86527 (68359)
Creatinine, mg/dl (Mean (SD))	1.2 (0.89)	1.46 (1.15)	1.78 (1.32)	1.53 (1.18)
Total bilirubin, mg/dl (Mean (SD))	1.39 (1.84)	2.23 (2.72)	2.19 (1.96)	1.93 (2.22)
Albumin, mg/dl ((Mean (SD))	2.95 (0.50)	2.62 (0.5)	2.59 (0.68)	2.72 (0.6))
SGOT, IU/L (Mean (SD))	114.5 (74.5)	136.1 (92.9)	173.1 (227.7)	141.06 (162)
SGPT, IU/L (Mean (SD))	78 (73.5)	74.1 (62.7)	70 (63.8)	74 (65.8)
Alkaline phosphatase, IU/L (Mean (SD))	145 (92.4)	219 (171.4)	204.6 (116.5)	189.5 (134)
Organ dysfunction				
Respiratory dysfunction, Number (%)	28 (60.8%)	33 (57.9%)	59 (79.7%)	120 (67.8%)
Hepatic dysfunction, Number (%)	25 (54.3%)	33 (57.9%)	53 (71.6%)	111 (62.7%)
Renal dysfunction, Number (%)	4 (8.6%)	8 (14%)	16 (21.6%)	28 (15.8%)
CNS dysfunction, Number (%)	3 (6.5%)	16 (28%)	34 (49.9%)	34 (29.9%)
Cardiovascular dysfunction, Number (%)	0	13 (22.8%)	28 (37.8%)	41 (23.1%)

SOFA= sequential organ failure assessment, SGOT=serum glutamic-oxaloacetic transaminase, SGPT serum glutamic-pyruvic transaminase, SD=standard deviation, CNS=Central nervous system, Combination therapy=Azithromycin and doxycycline

statement is shown in Figure 1. The mean age of presentation was 46.2 (SD:15.5) years with females being more predominant (53%). The mean duration of fever at presentation was 8.66 (SD:3.9) days with an eschar being seen in 64.9% of the patients. SOFA score was used to assess the severity of the illness. The severity of the disease was higher in the combination therapy group as evidenced by elevated SOFA scores (8.82). Monotherapy (azithromycin or doxycycline) was preferred therapy in patients with less severity. Thrombocytopenia and leukocytosis, a characteristic feature of this disease, was seen in most of the subjects with scrub typhus. Hepatic involvement manifested as elevations in transaminases and alkaline phosphatase. The respiratory system was the most common organ system involved, with doxycycline group having marginally increased respiratory involvement compared to other groups. The combination therapy group had more evidence of multiorgan system involvement compared to the other groups (Table 1).

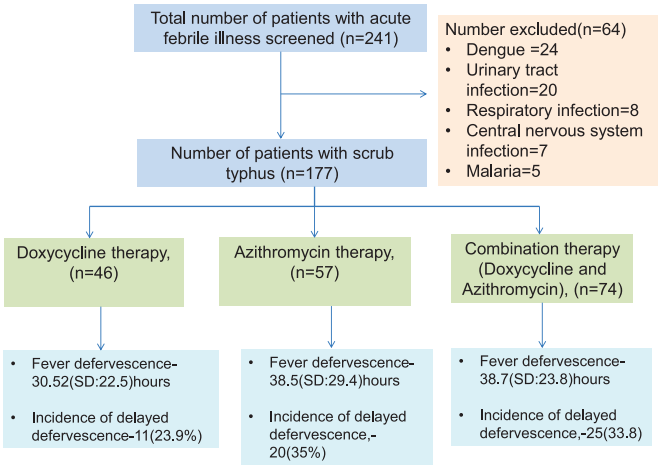

Fig. 1: Strobe statement

Patients receiving doxycycline (23.9%) did better compared to the other two groups with respect to the incidence of delayed defervescence (primary outcome). Doxycycline group also had early fever defervescence (30.52 hr). The overall mortality was seen in 5.6% patients, with increased mortality seen in the combination therapy group, with no statistical difference between the groups (p value 0.346). Doxycycline therapy group did better in

Table 2. Outcomes of patients receiving monotherapy and combination therapy in patients with scrub typhus

Variable	Doxycycline (n=46)	Azithromycin (n=57)	Combination therapy (n=74)	Total (n=177)
Incidence of delayed defervescence (>48 hours), Number (%)	11(23.9%)	20(35%)	25(33.8%)	56(31.6%)
Fever Defervescence, hours (Mean (SD))	30.52(22.5)	38.5(29.4)	38.7(23.8)	
Mortality + LAMA, Number (%)	1(2.1%)	6(10.5%)	7(9.5%)	14(7.9%)
Total duration of hypotension, days (Mean (SD))	0.043(0.2)	0.47(1.0)	0.95(1.7)	
Total duration of oxygen requirement, days (Mean (SD))	0.5(1.26)	1.73(2.49)	3.55(3.16)	

LAMA=Leave against medical advice

Table 3. Univariate analysis for monotherapy versus combination therapy for incidence of delayed defervescence

Variable	Monotherapy with doxycycline, n (%)	Combination therapy, n (%)		
Incidence of delayed defervescence >48 hours	11 (30.6%)	25 (69.4%)	Risk ratio 1.62 (0.70-3.72)	P Value 0.251
	Monotherapy with Azithromycin, n (%)	Combination therapy, n (%)		
Incidence of delayed defervescence >48 hours	20 (44.4%)	25 (55.6%)	Risk ratio 0.94 (0.45-1.95)	P Value 0.876
	Monotherapy awith either Azithromycin or doxycycline, n (%)	Combination therapy, n (%)		
Incidence of delayed defervescence >48 hours	31 (55.4%)	25 (44.6%)	Risk ratio 1.18 (0.62-2.24)	P Value 0.603

Combination therapy-Azithromycin and doxycycline

Table 4. Univariate analysis for the factors affecting the incidence of delayed defervescence in patients with scrub typhus

Variable	Without delayed defervescence, n (%)	With delayed defervescence, n (%)	Risk Ratio	P value
Respiratory dysfunction	75 (62.5%)	45 (37.5%)	2.50(1.18-5.33)	0.016
Hepatic dysfunction	75 (67.6%)	36 (32.4%)	1.10(0.57-2.13)	0.768
Renal dysfunction	20 (71.4%)	8(28.6%)	0.74(0.34-1.16)	0.450
CNS dysfunction	37 (69.8%)	16 (30.2%)	0.90(0.45-1.82)	0.786
Eschar presence	81 (70.4%)	34 (29.6%)	0.76(0.39-1.47)	0.419
>2 organ system involvement	35 (66%)	18 (34%)	1.16(0.58-2.30)	0.664
SOFA score of >6	48 (71.6%)	19 (28.4%)	0.78(0.40-1.51)	0.464

SOFA= sequential organ failure assessment, CNS=central nervous system

terms of resolution of hypotension (1.03 hr) and requirement of oxygen (0.5 days) compared to the other groups (p value <0.001) (Table 2). Univariate analysis showed that respiratory dysfunction was an independent factor associated with delayed fever defervescence (risk ratio, RR 2.50) and failed to show any statistical difference between the antibiotic groups with regards to the primary outcome. This shows that involvement of respiratory system rather than the choice of antibiotic regimen could predict the delay in fever defervescence (Tables 3 & 4).

DISCUSSION

Scrub typhus is an emerging public health threat in southern India and Southeast Asian countries. Scrub typhus causes multiorgan dysfunction leading to mortality if left untreated. Chloramphenicol was one of the earliest antibiotics used which caused reduction of mortality and morbidity[10]. The other groups of antimicrobials used for the treatment include doxycycline, tetracycline, macrolides (azithromycin), and rifampicin. The current treatment of choice is with either doxycycline or azithromycin[11].

Fever defervescence with therapy has been used as a surrogate marker for the diagnosis of scrub typhus. Poor response to therapy warrants the need for evaluation of other etiologies. Fever defervescence with single dose of doxycycline (88%) was seen in most patients of earlier studies[12]. In our study, the doxycycline group had the lowest fever defervescence time (30.52 $\pm$ 22.5 hr) which was similar to previous studies. The duration of fever defervescence in azithromycin and combination therapy group were also comparable to the previous studies[11]. Of late, there has been an increase in the incidence of delayed

fever defervescence[7]. The reasons for this phenomenon are not clear, however resistance to drugs is one of the proposed mechanisms for the delay[8]. The incidence of delayed defervescence in our cohort was 31.6% with patients receiving doxycycline having the lowest (23.9%). In comparison to the previous studies, our cohort had an increase in the incidence of delayed defervescence. There was no difference in the fever defervescence between the antibiotic groups, which was similar to the previous studies[13–14]. Earlier studies have looked at combination therapy with rifampicin and doxycycline in which combination therapy did better than monotherapy[15]. There were no studies on combination therapy with azithromycin and doxycycline for scrub typhus. In our cohort, monotherapy with doxycycline did marginally better than combination therapy (azithromycin and doxycycline). In terms of organ system resolution, doxycycline group did better with respect to recovery of hypotension and requirement of oxygen. Combination therapy did not seem to have any added benefit compared to the monotherapy group. Respiratory system dysfunction was the most common involvement; this finding was similar to studies done earlier from this institution by Griffith *et al*[16]. Our study showed that involvement of the respiratory system was an independent factor predicting the delay in fever defervescence (Risk ratio of 2.50). The case fatality rate (5.6%) was significantly lower compared to the previous studies from south India; however there was no statistical difference between the antibiotic groups[4].

The strengths of the study are large sample size with comparable number of patients in the three groups and this being the first study to evaluate the effect of combination therapy (doxycycline and azithromycin) in scrub typhus. The limitations of study are the observational study design and the possibility of a selection bias with more critically ill patients receiving combination therapy. The reasons for doxycycline doing better than other regimens have not been adequately explored; multifactorial role needs to considered. The study was not powered to analyse all the effects of one therapeutic arm over the other.

CONCLUSION

Combination therapy with doxycycline and azithromycin is the most common regimen used and have been used mostly in sicker patients depending upon the treating physician's discretion. The incidence of delayed defervescence (31.6%) is increasing despite prompt and appropriate therapy, and the reasons have not been elucidated so far, although respiratory dysfunction appears to be an independent predictor of delayed fever defervescence. We need large scale randomised prospective trials in this area to determine the effects of antibiotics and also the appropriate regimen. Studies are needed to look at drug resistance (doxycycline/azithromycin) in scrub typhus and whether other antibiotics (chloramphenicol) have a role in combating resistance.

Conflict of Interest: None

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