Journal of Infection (2006) **52**, 56–60

ELSEVIER

BRITISH INFECTION SOCIETY

www.elsevierhealth.com/journals/jinf

# Scrub typhus among hospitalised patients with febrile illness in South India: magnitude and clinical predictors

**G.M. Varghese*, O.C. Abraham, D. Mathai, K. Thomas, R. Aaron, M.L. Kavitha, E. Mathai**

*Christian Medical College, Vellore 632004, India*

Accepted 1 February 2005
Available online 17 March 2005

**KEYWORDS**
Scrub typhus;
India;
Magnitude;
Predictors of mortality

**Summary** *Objectives*: To derive a clinical algorithm for diagnosis of scrub typhus among patients hospitalized with febrile illness and to determine predictors of bad prognosis.
*Methods*: Patients hospitalized with febrile illness of 5–30 days duration were evaluated for common aetiologies. Sera were tested for antibodies (IgM and IgG) to *Orientia tsutsugamushi* using ELISA kit.
*Results*: Among 207 patients, 50 had elevated levels of IgM antibodies. The data of these patients were compared with that of 16 controls having febrile illnesses in whom rickettsial infection was ruled out. Transaminase elevation (>twice normal) was present in 90% and was significantly ($P=0.004$) more common in those with scrub typhus. If a combination of elevated transaminases, thrombocytopenia and leukocytosis is used, the specificity and positive predictive value are about 80%. Case fatality rate was 14%. Univariate analysis showed that hyperbilirubinemia (> 1.5 mg%) has a RR of 9 (95% CI=1.48–58.5) and elevated creatinine level (>1.4 mg%) had a RR of 43.99 (95% CI=3.65–530.5) for death. Elevated creatinine level was found to be an independent predictor of mortality ($P=0.02$).
*Conclusion*: In developing countries with limited diagnostic facilities, it is prudent to recommend empiric therapy in patients with undifferentiated febrile illness having evidence of multiple system involvement especially if there is transaminase elevation. Elevated creatinine may predict bad outcome.


## Introduction

Scrub typhus, a zoonotic disease prevalent in Asia manifests with fever and multiorgan involvement. Worldwide, more than one billion people are at risk of acquiring this disease, and reports of this

* Tel.: +91 416 2282342; fax: +91 416 2232103.
*E-mail address:* georgemvarghese@hotmail.com.

0163-4453/$30.00 © 2005 The British Infection Society. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.jinf.2005.02.001

infection are becoming increasingly common in travellers visiting Asia.[1] This infection has been re-emerging in the Indian subcontinent.[2-4] After a period of rarity for decades, continued presence of this infection in Southern India has been confirmed.[2,5] However, there is a paucity of data on the extent of this problem. The available reports represent only a fraction of the actual cases of this endemic disease. Delays in diagnosis and treatment are major factors contributing to the high mortality. Hence, early diagnosis and treatment of scrub typhus can reduce mortality.

The infected larval stage of the trombiculoid mites (chiggers) transmits the causal agent, *Orientia tsutsugamushi*.[6] The patients usually present 6–12 days after the larval bite with fever. They may have associated headache, myalgia, lymphadenopathy, eschar at the site of bite and skin rash.[7] A necrotic eschar at the site inoculating mite bite is highly suggestive of the diagnosis. Vasculitis, the main pathological feature in scrub typhus affect most organs with varied clinical manifestations. The disease can be at times asymptomatic. However, in untreated cases, mortality could be as high as 40%.[8,9]

Though this infection can be easily treated, clinical diagnosis is often difficult because the characteristic eschar is present only in less than 10% of patients reported from Indian subcontinent.[2,4] Since, re-emergence of this infection has been documented from Southern India and the diagnosis is difficult owing to limited diagnostic facilities especially in rural areas, clinical predictors of diagnosis and prognosis would be extremely useful. Therefore, we designed a prospective study to derive a clinical algorithm for diagnosing scrub typhus and to determine predictors of bad prognosis among hospitalized patients with febrile illness.

## Patients and methods

Patients above the age of 12 years hospitalized with febrile illness of 5–30 days duration in a 1900-bed teaching hospital in Southern India, and one of its rural health centres, were recruited between October 2002 and February 2003. These patients were evaluated for common febrile illnesses like malaria, typhoid fever, dengue fever, leptospirosis, urinary tract infection, pneumonia and sepsis syndrome by conducting appropriate laboratory investigations. Demographic, clinical and laboratory data were recorded using a questionnaire. Clinical course in the hospital, complications and outcome were also recorded.

About 5 ml of blood was collected from patients in whom no cause could be identified for the febrile illness after initial tests and 44 others with a known cause for fever after obtaining informed consent. Serum was separated and stored at −20 °C.

Sera were tested in batches for IgM and IgG antibodies to *O. tsutsugamushi* using a commercial ELISA kit (Panbio, Brisbane, Australia). The kit uses a specific 56 kDa recombinant antigen of *O. tsutsugamushi* and has sensitivity and specificity of above 90%.[10] Manufacturer's instructions were followed for performance quantitation and interpretation of the test. Equivocal results were considered negative. Weil Felix (WF) test was also performed on the sera using OX-19, OX-2, and OX-K antigens by standard methods, to initiate treatment.

Anti-microbials were initiated by the attending physicians, based on the clinical features and results of initial investigations. Specific therapy for scrub typhus, doxycycline 100 mg twice daily, was started either empirically or on the basis of WF test.

Statistical analysis was done using SPSS software. The association of clinical and laboratory parameters with positive serum IgM antibody to *O. tsutsugamushi* were determined using chi-square test. Univariate and multivariate logistic regression analysis were done to determine the predictors of mortality. The statistical significance was determined at 5% level.

## Results

Among 207 patients included in the study, 113 had a specific cause identified on initial evaluation (Fig. 1). Fifty of the remaining 94 patients (53.2%), had

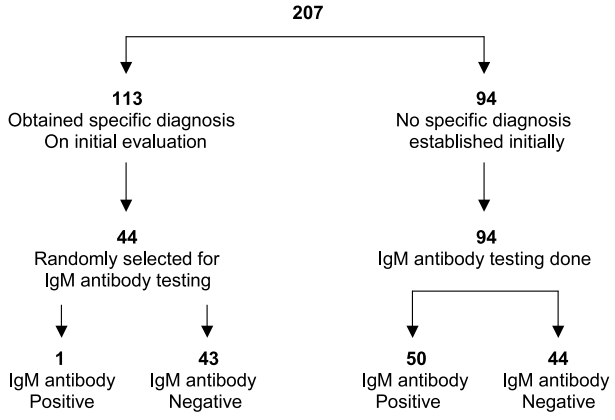


**Figure 1** Evaluation of 207 patients with fever of 5–30 days duration.

elevated levels of IgM antibodies to *O. tsutsugamushi* suggesting acute scrub typhus. IgG levels were also elevated in 33 of these patients. One patient had only IgG antibody elevated. Clinical and laboratory data of the 50 patients with IgM antibody to *O. tsutsugamushi* are presented in Table 1. Of the 44 patients still without a specific diagnosis, 16 were fully investigated as they continued to have fever after admission. The data of these 16 patients were used for comparison.

Median age of patients with IgM antibody elevation was 36.5 years (range: 12–75 years) and 40 (80%) were subsistent farmers with low income. Severe headache was a frequent (66%) feature. Only 8% of the patients had an eschar and 2% had maculo-papular rash. None of the patients had prior antibiotic therapy with doxycycline, azithromycin or chloramphenicol for the febrile illness. Laboratory evidence of abnormal liver function was present in 90% of patients. Transaminase elevation was significantly ($P=0.004$) more common in those with scrub typhus (Table 1). Levels of more than twice the normal had a positive predictive value of 84% in identifying the patients with scrub typhus. Platelet counts of $<100\,000$/cumm was seen in 62.5% of patients. Nineteen patients (38%) had involvement of more than two systems, the most common being hepatic and hematological.

Case fatality rate was 14%. Of the seven patients who died, six presented later in the course of disease with hepatic and renal failure. Death occurred within 48 h of hospitalization, although four patients were initiated on treatment with doxycycline. The remaining three received penicillin or cefotaxime since a diagnosis of scrub typhus was not considered.

Among those who survived, twenty patients who received doxycycline (100 mg twice daily) only, and two patients each who received either chloramphenicol or azithromycin had fever defervesence in 3 days. Seven patients received only ciprofloxacin. Fever subsided after 5 days in five of them, but the remaining two were given doxycycline as well since the fever persisted. Fever resolved without any treatment in five patients. Seven others who received antibiotics other than doxycycline, chloramphenicol, azithromycin or ciprofloxacin also recovered.

Univariate analysis for predictors of mortality (Table 2) showed that hyperbilirubinemia ($>$ 1.5 mg%) at admission has a relative risk (RR) of 9 (95% CI = 1.5–58.5) and elevated creatinine levels ($>1.4$ mg%) has a RR of 43.99 (95% CI = 3.7–530.5). On multivariate analysis, elevated creatinine levels ($>1.4$ mg%) at admission was found to be an independent predictor of fatal outcome ($P=0.02$). Only one of the 44 patients with fever due to causes other than scrub typhus had elevated IgM level. This patient had proven falciparum malaria.

**Table 1** Clinical and laboratory data of 50 patients with IgM antibody to *O. tsutsugamushi* as compared to 16 controls having undifferentiated febrile illness with absent IgM antibody

| | IgM antibody positive patients ($n=50$) | IgM antibody negative controls ($n=16$) | *P* value |
|---|---|---|---|
| Fever duration $<7$ days | 4 (8%) | 6 (37.5%) | |
| Fever duration 7–14 days | 36 (72%) | 10 (62.5%) | |
| Fever duration 15–21 days | 10 (20%) | - | |
| Myalgias | 19 (38%) | 3 (18.7%) | 0.15 |
| Headache | 33 (66%) | 9 (56.3%) | 0.48 |
| Nausea or vomiting | 28 (56%) | 9 (56.3%) | 0.98 |
| Altered sensorium | 9 (18%) | 7 (43.8%) | 0.05 |
| Cough | 12 (24%) | 1 (6.3%) | 0.16 |
| Jaundice | 6 (12%) | 6 (37.5%) | 0.06 |
| Rash | 1 (2%) | 1 (6.3%) | 0.43 |
| Eschar | 4 (8%) | - | - |
| Leukocyte count $>11\,000$/mm$^3$ | 16 (32%) | 8 (50%) | 0.19 |
| Platelet count $<100\,000$/mm$^3$ | 25 (62.5%) ($n=40$) | 9 (75%) ($n=12$) | 0.51 |
| Transaminase level $>$ twice normal | 36 (90%) ($n=40$) | 7 (50%) ($n=14$) | 0.004 |
| Bilirubin level $>1.5$ mg% | 12 (30%) ($n=40$) | 9 (64.3%) ($n=14$) | 0.02 |
| Creatinine $>1.4$ mg% | 5 (12.2%) ($n=41$) | 3 (20%) ($n=15$) | 0.66 |
| Abnormal chest X-ray | 18 (46.2%) ($n=39$) | 5 (38.5%) ($n=13$) | 0.62 |

**Table 2** Predictors of mortality in patients with scrub typhus

| | Expired ($n=7$) | Alive ($n=43$) | RR (CI) | *P* |
|---|---|---|---|---|
| Headache | 4 (57.1%) | 29 (67.4%) | 0.64 (0.13–3.28) | 0.59 |
| Leukocyte count $>11\,000/mm^3$ | 4 (57.1%) | 12 (27.9%) | 3.44 (0.67–17.7) | 0.14 |
| Platelet count $<100\,000/mm^3$ | 6 (85.7%) | 19 (57.6%) ($n=33$) | 4.42 (0.48–40.9) | 0.19 |
| Transaminase level > twice normal | 7 (100%) | 29 (87.9%) ($n=33$) | 2395 (0–6.08) | 0.88 |
| Bilirubin level > 1.5 mg% | 5 (71.4%) | 7 (21.2%) ($n=33$) | 9.28 (1.48–58.5) | 0.02 |
| Creatinine > 1.4 mg% | 4 (57.1%) | 1 (2.9%) ($n=34$) | 43.9 (3.65–530.5) | 0.003 |
| Abnormal chest X-ray | 5 (71.4%) | 13 (40.6%) ($n=32$) | 3.65 (0.61–21.8) | 0.15 |

## Discussion

This first prospective study from India following re-emergence of scrub typhus shows that up to a quarter of acute febrile illnesses requiring hospitalization could be due to scrub typhus during the cooler months. This infection remains under diagnosed, as the current algorithm for evaluation of acute febrile illnesses in most parts in India does not include this entity.

For surveillance purposes, the clinical case definition used in Japan is the presence of eschar, rash, lymphadenopathy, high fever and response to tetracycline derivatives. This is based on a high prevalence (>85%) of the pathognomonic eschar and rash.[7] This definition is not suitable for the Indian subcontinent since eschar and rash were seen in less than 10% of cases. Reports from Thailand also show that eschar is present in only <15% of their cases[1] and none in a series from Sri Lanka.[4] Scarcity of primary lesion has been noted in earlier reports from India.[11] This probably is related to variation in strain types in this area.

As reported by Tsay et al.[12] and observed by us earlier,[2] most patients had elevated transaminases and thrombocytopenia. Elevated transaminase levels had the best predictive values in identifying scrub typhus in patients with undifferentiated febrile illness. Since, predictive values are dependent on prevalence, this inference may be limited to outbreak situations. If a combination of tests i.e. elevated transaminases, thrombocytopenia and leukocytosis is used, the specificity and positive predictive value are about 80%. However, there were only 16 patients with undifferentiated febrile illness as controls for comparison. No single parameter was found to be sensitive enough in predicting scrub typhus.

Doxycycline is the antibiotic of choice for scrub typhus.[13] In this series also doxycycline produced quick fever defervescence in most patients. There are, however, reports of clinical failure with doxycycline from neighboring countries.[14] Although four patients who were initiated on doxycycline therapy died in our series, it is unlikely to be due to resistance since all of them had developed organ failure before initiating therapy. However, more prospective observations are required on this issue. Chloramphenicol, another inexpensive antibiotic, was also found effective. Therefore, it appears that in India, at present either of these drugs may be used for treating patients with scrub typhus. Clinical response to ciprofloxacin was less satisfactory.

Fatality due to scrub typhus can be as high as 30%.[15] The case fatality rate observed in this series is similar to the fatality of 15% reported from Thailand.[1] Renal and hepatic dysfunction at admission predicts a bad outcome. Creatinine elevation was the only independent predictor.

This study documents a high incidence of scrub typhus in Southern India where scrub typhus and other rickettsial diseases have been neglected for decades. Concurrent reports of high incidence from Sri Lanka and the Maldives might indicate the general re-emergence of scrub typhus that would be of importance for travel medicine physicians caring for patients visiting Asian countries. This is the first prospective study from India addressing the magnitude of scrub typhus in patients hospitalized with febrile illness. Since, morbidity and mortality associated with scrub typhus can be reduced significantly if treated early, it may be prudent to recommend empiric therapy with doxycycline in patients with fever of more than 5 days duration and evidence of multiple system involvement especially if there is transaminase elevation.

## References

1. Watt G, Kantipong P, Jongsakul K, Watcharapichat P, Phulsuksombati D, Strickman D. Doxycycline and rifampicin for mild scrub-typhus infections in Northern Thailand: a randomised trial. *Lancet* 2000;**356**:1057–61.
2. Mathai E, Rolain JM, Varghese GM, Abraham OC, Mathai D, Raoult D, et al. Outbreak of scrub typhus in Southern India during cooler months. *Ann N Y Acad Sci* 2003;**990**:359–64.

3. Lewis MD, Yousuf AA, Lerdthusnee K, Razee A, Chandranoi K, Jones JW. Scrub typhus reemergence in the Maldives. *Emerg Infect Dis* 2003;**12**:1638–41.
4. Kularatne SA, Edirisingha JS, Gawarammana IB, Urakami H, Chenchittikul M, Kaiho I. Emerging rickettsial infections in Sri Lanka: the pattern in the hilly Central Province. *Trop Med Int Health* 2003;**8**:803–11.
5. Mathai E, Lloyd G, Cherian T, Abraham OC, Cherian AM. Serological evidence for the continued presence of human rickettsioses in Southern India. *Ann Trop Med Parasitol* 2001; **95**:395–8.
6. Tamura A, Ohashi N, Urakami H, Miyamura S. Classification of *Rickettsia tsutsugamushi* in a new genus, *Orientia* gen. nov., as *Orientia tsutsugamushi* comb. nov. *Int J Syst Bacteriol* 1995;**45**:589–91.
7. Ogawa M, Hagiwara T, Kishimoto T, Shiga S, Yoshida Y, Furuya Y, et al. Scrub typhus in Japan: epidemiology and clinical features of cases reported in 1998. *Am J Trop Med Hyg* 2002;**67**:162–5.
8. Watt G. Scrub typhus. In: Ledingham JGG, Warrell DA, editors. *Concise Oxford textbook of medicine*. New York: Oxford University Press; 2000. p. 1698–700.
9. Singharaj P, Watt G. Scrub typhus. *J Trop Med Parasitol* 1997;**20**:23–7.
10. Coleman RE, Sangkasuwan V, Suwanabun N, Eamsila C, Mungviriya S, Devine P, et al. Comparitive evaluation of selective diagnostic assays for the detection of IgG and IgM antibody to *Orientia tsutsugamushi* in Thailand. *Am J Trop Med Hyg* 2002;**67**:497–503.
11. Padbidri VS, Gupta NP. Rickettsiosis in India: a review. *J Indian Med Assoc* 1978;**71**:104–7.
12. Tsay RW, Chang FY. Serious complications in scrub typhus. *J Microbiol Immunol Infect* 1998;**31**:240–4.
13. Strickman D, Sheer T, Salata K, Hershey J, Dasch G, Kelly D, et al. In vitro effectiveness of azithromycin against doxycycline-resistant and -susceptible strains of *Rickettsia tsutsugamushi*, etiologic agent of scrub typhus. *Antimicrob Agents Chemother* 1995;**39**:2406–10.
14. Watt G, Chouriyagune C, Ruangweerayud R, Watcharapichat P, Phulsuksombati D, Jongsakul K, et al. Scrub typhus infections poorly responsive to antibiotics in Northern Thailand. *Lancet* 1996;**348**:86–9.
15. Parola P, Miller RS, McDaniel P, Telford 3rd SR, Rolain JM, Wongsrichanalai C, et al. Emerging rickettsioses of the Thai-Myanmar border. *Emerg Infect Dis* 2003;**9**:592–5.