

# GASTROINTESTINAL MANIFESTATIONS OF SEPTIC PATIENTS WITH SCRUB TYPHUS IN MAHARAT NAKHON RATCHASIMA HOSPITAL

Aung-Thu<sup>1</sup>, Wichai Supanaranond<sup>2</sup>, Weerapong Phumiratanaprapin<sup>2</sup>, Benjaluck Phonrat<sup>2</sup>,  
Soonthorn Chinprasatsak<sup>3</sup> and Nachapa Ratanajaratroj<sup>3</sup>

<sup>1</sup>Department of Medical Research, Lower Myanmar, Ministry of Health, Myanmar; <sup>2</sup>Department of Clinical Tropical Medicine and Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok; <sup>3</sup>Maharat Hospital, Nakhon Ratchasima, Thailand

**Abstract.** Scrub typhus is an acute febrile illness caused by *Orientia* induced vasculitis, which is common in Asia and the Pacific Islands and is sometimes also encountered in Western countries. Even though it can cause multi-organ dysfunctions, there is limited information regarding the relationship between scrub typhus infection and gastrointestinal dysfunction. Therefore, a cross-sectional study was conducted to discover the gastrointestinal manifestations of septic patients with scrub typhus infection. During the study period, 80 septic cases were recruited, and according to the results of immunofluorescent antibody testing (IFA), 20 (25%) were found to have scrub typhus infection. The most common gastrointestinal symptoms of scrub typhus patients were vomiting 13 (65%), nausea 12 (60%), diarrhea 9 (45%), and hametamesis or melena 5 (25%). Gastrointestinal signs included hepatomegaly 8 (40%), jaundice 7 (35%), and abdominal pain 4 (20%). Elevation of SGOT, SGPT, and alkaline phosphatase were 16 (80%), 14 (70%), and 16 (80%), respectively. Direct bilirubin was elevated in 19 (95%) of the cases and half of the cases had a low serum protein level. Of scrub typhus cases, 8 (40%) had eschars. The sites of eschars were mostly in hidden areas, such as on the back, genitalia and abdomen. Three of the five patients with eschar had hepatomegaly on ultrasound examination. The significant findings of the scrub typhus septic patients with eschar on endoscopic examination were gastritis in two cases, gastritis with gastric erosion in two cases, and one case showed a duodenal ulcer and erosion. The differentiating point for endoscopic findings in scrub typhus compared to the other causes was that the stomach lesions were more frequent and severe than the duodenal lesions. According to our endoscopic findings, physicians should be aware of gastric and duodenal lesions in febrile patients with gastrointestinal symptoms, such as abdominal pain or discomfort and indigestion. Scrub typhus can cause gastrointestinal and liver dysfunction.

## INTRODUCTION

Scrub typhus is an acute febrile zoonosis of rural Asia. The causative organism, *Orientia* (formerly *Rickettsia tsutsugamushi*) is transmitted to humans by the bite of a larval mite (chigger). Scrub typhus gained prominence in World War II, when tens of thousands of soldiers in the Asia-Pacific Theater contracted the disease. The case fatality rate was as high as 35%. Thousands of cases of

scrub typhus still occur each year, and it is an important cause of febrile illness in endemic areas. The disease is transmitted in an extremely large geographic area ranging from the Indian subcontinent to Japan, the Philippines, Indonesia, New Guinea, Sri Lanka, and the Islands of the Chagos Archipelago (Watt and Olson, 2000).

The incidence figures for scrub typhus are generally unavailable because adequate surveillance systems are lacking. According to a report by Silpapojakul (1997), the sero-prevalence rates in Korea, India, Nepal, Indonesia, the Philippines and Malaysia were 20, 2, 12, 1-16, 3-11 and 6-69%, respectively. In Thailand, it occurs in 10% of cases of fever of unknown origin (MOPH, Thailand, 1993-2001). Scrub typhus infection is a serious public health problem in the Southeast Pacific

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Correspondence: Dr Aung Thu, Research Officer, Epidemiology Research Division, Department of Medical Research (Lower Myanmar), No. 5, Ziwaka Road, Dagon PO, Yongon 11191, Myanmar.  
Tel: +095-01-251508, 251509 ext 127; Fax: +095-01-251514  
E-mail: athudmr@mail4u.com.mm

and Southeast Asia. (Ralph and Jeronae, 1987; Berman *et al*, 1973; Berman and Kundin, 1973; Joseph and Daniel, 1992; Singharaj and Watt, 1997).

Scrub typhus can be severe with complications, which have been reported in Taiwan to include pneumonitis 36% (3/33), adult respiratory distress syndrome (ARDS) 15% (5/33), acute renal failure 9% (3/33), myocarditis 3% (1/33), and septic shock 3% (1/33) (Tsay and Chang, 1998). Sepsis may be complicated by infections with bacteria, viruses, rickettsiae, mycobacteria, fungi, and parasites (McGowen *et al*, 1975).

Sepsis is also associated with upper gastrointestinal tract bleeding and hepatocellular dysfunction and causes an elevation in liver transaminases (Altemeier and Fullen, 1972). Studies have shown that complications usually develop after the first week of illness; these included pneumonitis, meningoencephalitis, renal failure, and jaundice. (Silpapojakul, 1997). One study in a Taipei hospital revealed that hepatic dysfunction occur in 77% (36/47) of patients. In liver function testing, the percentage of abnormalities were 74.5% for aspartate aminotransferase, 74.5% for alanine aminotransferase, 57.4% for alkaline phosphatase, and 44.7% for serum bilirubin. Six patients presented with a picture of true hepatitis, similar to acute viral hepatitis, indicating that hepatocellular damage does occur in scrub typhus infection.

Endoscopic findings in scrub typhus patients in Korea revealed superficial gastritis (70%), petechiae (37%), purpura (34.5%), hemorrhage (29.3%), erosion (32.7%), and ulcers with bleeding (10.3%) (Kim *et al*, 2000).

Scrub typhus can present with multiorgan involvement, pulmonary complications are common, so most studies have focused on this. The relationship between gastrointestinal dysfunction and scrub typhus has had little attention. The current study was conducted in order to discover the gastrointestinal manifestations of septic patients with scrub typhus and to compare these manifestations with those in non-scrub typhus patients. The results of present study can provide a baseline of information regarding gastrointestinal dysfunction in scrub typhus, to help physicians with their proper management.

## MATERIAL AND METHODS

### Study area and population

The study was conducted from 12 November 2002 to 4 January 2003 in Maharat Hospital Nakhon Ratchasima Province. It is a tertiary hospital, located in the northeastern part of the country. This area is endemic for scrub typhus (MOPH, Thailand, 1993-2001). We conducted the study, in this hospital's medical wards and ICU for 7 weeks, among 80 septic patients. The inclusion criteria for study subjects were: all patients, both male and female, who were admitted to the medical wards or ICU unit at Maharat Hospital during the study period, age  $\geq 14$  years, and septic, by clinical evidence and who met two or more of the following conditions:  $T > 38^{\circ}\text{C}$  or  $T < 36^{\circ}\text{C}$ , tachypnea (RR  $> 20$  breaths/minute), tachycardia (HR  $> 90$  beats/minute),  $\text{PaCO}_2 < 32$  mmHg ( $< 4.3$  Kpa), white blood cell count  $> 12,000$  cells/mm<sup>3</sup> or  $< 4,000$  cells/mm<sup>3</sup> or 10% immature forms. Pregnant women and patients who stayed in hospital  $< 24$  hours were not included in this study.

### Procedure

The Institutional Research Board of Mahidol University gave ethical approval for the study. A complete medical record form (CRF) was filled out, on the day of admission. Before filling out the CRF, we obtained informed consent from the patients.

CRF included the following: history and physical examination done on admission. Baseline parameters, included CBC, BUN, creatinine, random blood sugar, electrolytes, SGPT, SGOT, alkaline phosphatase, total and direct bilirubin, total protein and albumin, urine examination, hemoculture of at least three specimens and a chest x-ray were done on the day of admission. Blood for malaria parasites, stool examination, Widal test, leptospiral antibody titer, sputum examination for AFB, Gram stain and culture, x-ray and ultrasound of the abdomen were optional investigations.

Endoscopy was done in the patients with an eschar or in clinically suspected scrub typhus cases, who complained of gastrointestinal symptoms (*eg* abdominal pain, indigestion, etc). And it was not performed in cases of severe shock, recent myocardial infarction, unstable angina, car-

diac arrhythmia, atlanto-axial subluxation, possible visceral perforation, peptic ulcer, history of taking non-steroidal anti-inflammatory drugs. Before endoscopy, the investigator thoroughly explained the risks and benefits of this procedure and obtained informed consent verbally.

IFA serology for scrub typhus was performed by a trained laboratory technician at the hospital. IgM  $\geq$  400 or IgG  $\geq$  1,600 was defined as scrub typhus infection.

### Data analysis

Data entry and statistical analysis were done using Epi Info version 6.04. The results were reported in proportions/percentages for categorical data and medians and ranges for continuous data. Comparison between the groups was tested by the  $\chi^2$  method and the significant p-value was set at  $\leq$  0.05.

## RESULTS

### Demographic characteristics of study subjects

In Table 1, the median and range of ages of both scrub typhus infected and non-typhus infected patients were 57.5 (30-77) years and 47.5 (15-80) years, respectively.

Fifty-five percent (11 of 20) of septic patients with scrub typhus infection were aged greater or equal to 55 years but the proportion of septic patients due to non scrub typhus infection in this particular age group was 38.4% (23 of 60). The proportions of females to males were scrub typhus 60% vs 40%, and non-scrub infection 53.3% vs 46.7%. Regarding occupation, the ma-

majority of cases were farmers (*ie* 55%) in scrub and 31.7% in non-scrub typhus infection. Second most common groups were dependents, 20% in scrub typhus and 31.7% in non-scrub typhus infection.

Of the septic cases, 25% (20 of 80) were found to have scrub typhus infection by IFA test, while 75% (60 of 80) were due to other causes.

### Gastrointestinal manifestations of study subjects

Table 2 reveals that nausea, vomiting and diarrhea were common features in both groups; nausea (60% vs 48.3%), vomiting, (65% vs

Table 1  
Demographic profiles of scrub typhus and non-scrub typhus septic patients.

Demographic profiles	Septic patients with scrub typhus infection N=20 (%)	Septic patients with non-scrub typhus infection N=60 (%)
Age groups (years)		
≤ 34	1 (5.0)	15 (25.0)
35-44	4 (20.0)	11 (18.3)
45-54	4 (20.0)	11 (18.3)
≥ 55	11 (55.0)	23 (38.4)
Sex		
Male	8 (40.0)	28 (46.7)
Female	12 (60.0)	32 (53.3)
Occupation		
Farmer	11 (55.0)	19 (31.7)
Gardener	2 (10.0)	1 (1.7)
Seller	0 (0.0)	5 (8.3)
General worker	3 (15.0)	16 (26.6)
Dependent	4 (20.0)	19 (31.7)

Table 2  
Gastrointestinal symptoms and signs in scrub typhus and non-scrub typhus septic patients on admission.

Gastrointestinal symptoms and signs	Septic patients with scrub typhus infection N=20 (%)	Septic patients with non-scrub typhus infection N=60 (%)	p-value <sup>a</sup>
Nausea	12 (15.0)	29 (36.2)	0.37
Vomiting	13 (16.3)	25 (31.3)	0.07
Diarrhea	9 (11.3)	28 (35.0)	0.89
Hematemesis or melena	5 (6.25)	12 (15.0)	0.64
Abdominal pain	4 (5.0)	19 (23.8)	0.32
Jaundice	7 (8.8)	14 (17.5)	0.31
Hepatomegaly	8 (10.0)	14 (17.5)	0.15

<sup>a</sup>Chi-square test

Table 3  
Laboratory findings in scrub typhus and non-scrub typhus septic patients on admission.

Parameters	Septic patients with scrub typhus infection N=20 Median (ranges)	Septic patients with non-scrub typhus infection N=60 Median (ranges)
Hemoglobin (g/dl)	10.6 (4.4-16.7)	10.6 (6.5-14.6)
Total WBC ( $\times 10^3$ cell/mm <sup>3</sup> )	12.8 (5.5-61.7)	10.3 (1.4-41.1)
Neutrophil (%)	80.3 (30.8-95.7)	77 (43-97.2)
Lymphocyte (%)	12.4 (2-56.9)	14.9 (1.8-46)
Platelet ( $\times 10^3$ cell/mm <sup>3</sup> )	119 (21-506)	189 (19-689) (n=59)
Blood sugar (mg/dl)	100.4 (60.3-284) (n=14)	107.3 (49.7-258.8) (n=49)
Total serum protein (g/dl)	6.1 (4.8-8.3)	6.8 (3.9-9.1) (n=54)
Serum albumin (g/dl)	2.8 (2.2-4.2)	3.2 (2.2-4.5) (n=55)
Serum globulin (g/dl)	3.3 (2-5)	3.4 (1-6) (n=54)
SGPT (U/l)	86.9 (8-299)	38.2 (11.4- 1,145) (n=58)
SGOT (U/l)	148.5 (22-486)	61.8 (16-1,200) (n=58)
Alkaline phosphatase (U/l)	178 (46-557) (n=12)	95.7 (33.6-314) (n=38)
Total bilirubin (mg/dl)	1.5 (0.3-18.4)	1.3 (0.2-27.2) (n=58)
Direct bilirubin (mg/dl)	0.95 (0.1-10.3)	0.75 (0.1-20) (n=58)

41.7%), and diarrhea (45% vs 46.7%) in scrub typhus and non-scrub typhus cases respectively. Jaundice (35%) and hepatomegaly (40%) were found to be a common clinical sign in scrub typhus patients. In non-scrub cases, the percentages of jaundice and hepatomegaly were 23.3% each. Splenomegaly was detected in 5% of scrub typhus cases. There were no significance difference in gastrointestinal symptoms and signs between scrub and non-scrub typhus patients ( $p > 0.05$ ).

#### Laboratory findings of study subjects

Platelet counts were low in the scrub typhus group compared to the non-scrub group [119 (21-506) cell/mm<sup>3</sup> vs 189 (19- 689) cell/mm<sup>3</sup>].

Blood sugar levels were normal in both groups, but the median level was lower in scrub typhus cases (100.4 mg/dl vs 107.3 mg/dl) compared to non-scrub typhus cases. The total serum protein in scrub typhus and the serum albumin in

both groups was found to be low. Serum globulins were high in both scrub typhus and non-scrub typhus.

The median levels for SGPT and SGOT in both groups, and alkaline phosphatase in the scrub typhus group were higher than normal. The liver enzymes were two times higher in the scrub typhus group (Table 3).

#### Biochemical findings of scrub typhus patients

Fifty percent (10 of 20) of scrub typhus cases presented with abnormal blood sugar levels. Total bilirubin was abnormal in 35% (7 of 20) and direct bilirubin was abnormal in 95% (19 of 20) of scrub typhus cases. SGPT was abnormal in 70% (14 of 20), SGOT in 80% (16 of 20), and alkaline phosphatase was abnormal in 80% (16 of 20) cases of scrub typhus. In 50% of scrub typhus cases, the total serum protein was lower than 6.6 g/dl. Serum albumin was found to be low in

**Table 4**  
Blood biochemical test results for scrub typhus patients on admission.

Parameters	N=20	%
Blood sugar		
Abnormal (<70 - >110 mg/dl)	10	50
Total bilirubin		
High (>1.0 mg/dl)	7	35
Direct bilirubin		
High (>0.2 mg/dl)	19	95
SGPT		
High (>50 U/l)	14	70
SGOT		
High (>50 U/l)	16	80
Alkaline phosphatase		
High (>110 U/l)	16	80
Total serum protein		
Low (<6.6 g/dl)	10	50
Serum albumin		
Low (<3.8 g/dl)	4	20
Serum globulin		
High (>3.2 g/dl)	4	20

20%, and high serum globulin levels were detected in 20% of scrub typhus cases (Table 4).

**Findings of eschar with scrub typhus**

From 20 scrub typhus patients, who were diagnosed by IFA, 8 (40%) had an eschar. The majority of eschars (75%) were in hidden areas, such as the back, abdomen, and genitalia.

The laboratory results in the scrub typhus eschar patients had elevations of SGOT, SGPT, and alkaline phosphatase in all the patients except in patient No. 3 who had a normal alkaline phosphatase level (Table 5).

Among the 8 eschar positive patients, only 5 had endoscopy. One patient refused, another had a contraindication (alter consciousness), and the final was transferred to the surgical ward for upper GI bleeding. According to the post-operative note, this patient had arterial bleeding from the lesser curvature of the stomach and a cirrhotic liver. This patient also had a history of a peptic ulcer and alcohol drinking. The endoscopic findings of our patients were as follows: two had gastritis, another two had gastritis with gastric erosion in the antrum and the last one had a duodenal ulcer with erosion and hemorrhage (Table 5).

**Table 5**  
Laboratory, ultrasound, and endoscopic findings of scrub typhus patients with eschar.

Patients	Age/sex	Coexisting disease	Bilirubin (mg/dl)		SGOT (U/l)	SGPT (U/l)	Alkaline phosphatase (U/l)	US abdomen	Endoscopy (U/l)
			Total	Direct					
1	66/F	Alcohol drinking	4.1	3.7	216	82	NA	Normal	Gastritis
2	39/M	None	1.5	0.9	78.3	62.9	NA	ND	Gastritis with erosion
3	30/M	Alcohol drinking	1.1	0.6	289.1	114.4	46	hepatomegaly	Gastritis
4	69/F	None	8.4	6.9	168.8	92.9	407.7	hepatomegaly	DU with erosion
5	43/M	Alcohol drinking	1.2	0.4	394	299	289	ND	Gastritis with erosion
6	51/F	None	0.6	0.4	486	181	176	Hydronephrosis (L)	Refused
7	63/F	None	2.0	1.0	189	80	557	hepatomegaly	ND
8	50/M	Peptic ulcer Alcohol drinking	1.1	0.7	134	77	155	ND <sup>b</sup>	(Altered consciousness) ND <sup>b</sup>

NA=not available; ND=not done; cirrhosis<sup>a</sup> (operative finding); bleeding lesser curve<sup>b</sup> (operative finding); L=left; DU=duodenal ulcer.

On ultrasound, only 5 out of 8 patients were investigated and only one had normal findings (Table 5).

## DISCUSSION

Our study showed that more than half of the scrub typhus patients were in the older aged group and the majority were farmers. The proportion of females who were infected was higher than males. This is consistent with the study done by Strickman *et al* (1994) and Ogawa *et al* (2001b). Their study also showed that the proportion of people with antibodies to rickettsiae was related to gender, age, and occupation (Strickman *et al*, 1994). Our findings also agree with a 1999 MOPH report, which stated that the at risk age is higher than 35 years. Due to the nature of their work, farmers, gardeners, and general workers are exposed to the rice fields, vegetation, and grasslands where the rodent-vector lifecycle is taking place.

The findings of common gastrointestinal symptoms and signs in the present study, such as nausea, vomiting, abdominal pain, jaundice, and hepatomegaly are consistent with the study done by Chinprasatsak *et al* (1996). The findings of Tsay and Chang (1998), revealed that their jaundice and hepatomegaly detection rates were lower than in our study. Although the predilection of *Orientia tsutsugamushi* is for the liver sinusoidal epithelial cells, the pathogenicity of *Orientia tsutsugamushi* in human is as diverse as the heterogeneity of the strain, ranging from typical disease to inapparent infection. The higher prevalence of jaundice and hepatomegaly in our study may be due to underlying liver disease, such as alcoholic hepatitis, a chronic viral hepatitis carrier state or secondary infection, which are not rare in Southeast Asia (Brown *et al*, 1984). The other possible reason is that jaundice can be found in non hepatobiliary sepsis cases because our study population were septic cases also. Our study found splenomegaly in only 5% (1 of 8). This sign is not common in Asian patients (Silpapojakul, 1997).

Our finding of liver enzyme abnormalities is consistent with other studies conducted by Tsay and Chang (1998), Yang *et al* (1995), Ogawa *et al* (2001a), and Chen *et al* (2001). Liver involvement with jaundice and abnormal liver function test results may be explained by the occurrence

of sinusoidal infiltration with intrahepatocellular cholestasis (Silpapojakul, 1997), pericholangitis (Stickman, 1994), and perivascular lesions in the portal area of the liver, along with nonspecific focal areas of fatty degeneration in hepatocytes (Watt and Olson, 2000). Some variations in liver involvement may be due to the virulence of the infecting strain, and age, immune status and genetic variation of the host (Groove and Osterman, 1978).

The pattern of liver enzyme abnormalities in our study was similar to alcoholic liver disease. Without doing gamma glutamyl transpeptidase testing it is difficult to differentiate whether it is due to the liver involvement of scrub typhus infection or not. Elevation of the AST may not necessarily be from hepatic origin. Alkaline phosphatase elevation alone is not sufficient to prove cholestasis. To do this, we would need to measure 5'-nucleotidase or gamma glutamyl transpeptidase (Daniel *et al*, 2002). Due to limitations, we could not measure these enzymes. Elevation of AST, ALT, and alkaline phosphatase and the presence of jaundice and hepatomegaly were found in a significant portion of our patients. Therefore, we can say some liver dysfunction may occur in scrub typhus infection.

Low levels of serum protein and albumin in our scrub typhus patients may be due to underlying liver disease, suppression of liver function due to a septic process or the loss of albumin in the urine due to scrub typhus infection.

Regarding endoscopy, the limited number of patients enrolled in this study make it impossible to apply the results to scrub typhus patients as a whole. Our findings were similar to the findings of 58 patients studied in Korea. The endoscopic findings of scrub typhus infection may be due to vasculitis of the gastrointestinal tract resulting from scrub typhus infection. The lesions were more frequent and severe in the stomach than the duodenum, which is a distinguishing feature of endoscopic findings in scrub typhus infection (Kim *et al*, 2000).

On ultrasound, we found that three (of five) patients had liver abnormalities. Due to the different reporting system of the hospital, we were unable to get a detailed description of these abnormalities. These are no specific ultrasonic find-

ings in the literature to compare with. We recommend further studies to explore the ultrasound changes in the hepatobiliary system with scrub typhus infection.

According to our findings, scrub typhus infection can present with gastrointestinal dysfunction. Therefore, scrub typhus should be considered in differential diagnosis of systemic diseases involving the liver, such as malaria, leptospirosis, dengue, and typhoid fever.

We would like to recommend further endoscopy and ultrasonic studies with adequate sample sizes to evaluate gastrointestinal dysfunction in scrub typhus.

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