Clinical Study of 20 Children with Scrub Typhus at Chiang Rai Regional Hospital

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20 children, diagnosed with scrub typhus who attended Chiang Rai Regional Hospital during a period of 6 months from June 2003 to December 2003, were studied prospectively. All cases were serologically proved to be scrub typhus by using Dipstick or indirect immunofluorescent antibody (IFA) technique. The most common clinical feature was eschar (75%). Others included hepatomegaly (65%), cough (60%), lymphadenopathy (40%), tachypnea (35%), constipation (25%), abdominal pain (20%), edema (20%), splenomegaly (15%), vomiting (15%), rash (15%) and petichia (5%) respectively. Chest radiography showed abnormalities in 85% with mostly bilateral interstitial infiltrations. Elevated of SGOT, SGPT were detected in 18 (90%) and 15 (75%) cases. Hypoalbuminemia was detected in 12 (60%) cases. Complete blood count showed PMN leukocytosis (> 60%) in 12 (60%) cases, lymphocytosis (> 40%) and atypical lymphocytosis (> 5%) in 1 (5%) case each and thrombocytopenia in 16 (80%) cases. The Weil-Felix test was positive in 1 (5%) case. Complications were pneumonia with or without pulmonary edema, meningitis and shock. Chloramphenicol and doxycycline were successfully treated and roxithromycin was not effective.

Keywords: *Scrub typhus, Clinical feature, Complication*

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Scrub typhus is an infectious disease caused by *Orientia tsutsugamushi* and is transmitted to humans by the bite of a chigger, an infected thromboculid mite. It is usually a disease of rural areas and is prevalent in Southeast Asia including Thailand. A previous study has indicated that scrub typhus accounted for at least 6% of these acute FUOs among children in Southern Thailand[1]. A serological survey in rural villages in Chiang Rai Province, the Northernmost part of Thailand showed nearly 60% prevalence of antibody against *O tsutsugamushi*[2]. However, there are few studies of pediatric scrub typhus from Northern Thailand[3-5]. The purpose of this study is to present clinical manifestation, laboratory findings and therapeutic outcomes in pediatric scrub typhus.

Material and Method

Pediatric patients admitted to Chiang Rai Hospital between June and December 2003, with the diagnosis of scrub typhus, were included in the present study. Serum samples from children who presented with fever for more than 5 days and without obvious causes were tested for antibody against *O tsutsugamushi*. The diagnosis of scrub typhus in the present study was based on the presence of a single indirect immunofluorescent antibody (IFA) titer against *O tsutsugamushi* of $\geq$ 1:400[6] or positive result by the INDX Dip-s-ticks scrub typhus test[7] (INDX® Dip-s-ticks®. *O tsutsugamushi*. PANBIO INDX, Inc Baltimore, MD 21227 USA). Children with the diagnosis of scrub typhus were enrolled and followed prospectively by the same physician. Complete blood count (CBC) and peripheral blood smear for malarial parasite, liver function test (LFT), Widal test, Weil Felix test and chest x-ray (CXR) were done on the first day of admission in all patients and repeated periodically if nessessary. Urinalysis and renal function test, hemoculture, cold agglutinin, leptospira antibody, echocardiogram, computed tomography (CT) scan and lumbar puncture were performed when clinically indicated. CXR was interpreted by

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radiologists. Patients were treated with one of the following regimens: 1) a 7-day course of doxycycline 4 mg/kg/day orally 2) a 7-14 day course of chloramphenicol 100 mg/kg/day intravenously 3) a 7-day course of roxithromycin 10 mg/kg/day orally. Patients who failed to respond to roxithromycin were treated with the first regimen. Failure to respond was defined as no defervescense within 72 hrs and clinically did not improve after treatment.

Results

From "a number of screening patients", a diagnosis of scrub typhus was made in 20 patients. 13 patients had positive with dipstick scrub typhus test and the other 7 with IFA test. 13 were male and 7 were female. Their mean age was 6.45 years (range 1.25-14). 3 cases (15%) were diagnosed as dengue virus infection before admission. The duration of illness before hospitalization ranged from 5-14 days with an average

Table 1. Demographic data, clinical manifestations and therapeutic outcome of 20 patients with scrub typhus

Case No	Sex	age (yr)	Duration of fever before admission (day)	Initial diagnosis	Antibiotic	Complication	Response to treatment (Defervescense)
1	Female	12	10	pneumonia	Roxithromycin	-	No feverlysis within 3 days and defervescense within 24 hrs after doxycycline
2	Male	2.75	8	prolonged fever	Chloramphenicol	-	Within 48 hrs
3	Male	10	10	R/O scrub typhus	Chloramphenicol	-	Within 72 hrs
4	Male	4	7	AFI	Chloramphenicol	-	Within 48 hrs
5	Male	3.75	7	pneumonia	Chloramphenicol	-	Within 72 hrs
6	Male	7	7	AFI	Doxycycline	-	Within 48 hrs
7	Male	7	8	AFI	Chloramphenicol	-	Within 16 hrs
8	Female	6	7	prolonged fever	Chloramphenicol	Pneumonitis	Within 48 hrs
9	Female	2	10	pneumonia	Chloramphenicol	Pneumonitis	Within 38 hrs
10	Male	2.55	14	Abdominal pain	Roxithromycin	-	Within 24 hrs
11	Male	13	5	R/O DHF	Roxithromycin	-	No feverlysis within 3 days and defervescense within 24 hrs after doxycycline
12	Male	14	7	pneumonia	Chloramphenicol	-	Within 24 hrs
13	Female	5	5	R/O DHF	Chloramphenicol	Pneumonitis with pulmonary edema (day3)	Within 48 hrs
14	Female	2	10	prolonged fever	Roxithromycin	Pneumonitis	> 72 hrs but clinical stable
15	Female	7	14	prolonged fever	Chloramphenicol	-	Within 12 hrs
16	Male	7	7	peritonitis	Doxycycline	Pneumonitis with pulmonary edema (day3)	Within 72 hrs
17	Female	14	8	septic shock	Chloramphenicol	Pneumonitis with shock	Subtemperature on admission
18	Male	2.6	6	convulsion	Chloramphenicol	Encephalitis, Left hemiparesis and aphasia	Within 36 hrs
19	Male	3.25	7	AFI	Chloramphenicol	-	Within 48 hrs
20	Male	1.25	7	R/O DHF	Chloramphenicol	Pneumonitis	Within 24 hrs

AFI = Acute febrile illness, DHF = Dengue hemorrhagic fever

of 8.2 days. The average temperature on admission was 38.1 C (range 35-40 C). The most common clinical finding was eschar, which was present in 15 cases (75%). Fourteen patients had one eschar each, and one patient had 2 eschars. They were found at the following sites: axilla (8), genitalia (5), inguinal area (1), occipital area (1) and ear (1), and the size ranged from 3 mm to 10 mm in diameter. Other physical findings were hepatomegaly (65%), cough (60%), tachypnea (35%), constipation (25%), edema (20%), abdominal pain (20%), splenomegaly (15%), vomiting (15%), rash (15%) and petichia (5%). Clinical status and therapeutic outcome are demonstrated in Table 1.

Pulmonary edema developed in patients No 13 and 16. Both of them had interstitial and alveolar infiltrations and received intravenous (IV) fluid for maintenance requirement. Patient No 13 received chloramphenicol and patient No 16 received doxycycline, and defervescense occurred within 2 and 3 days respectively. Day 3 of admission, they developed respiratory distress and CXR revealed increased cardiomegaly with pulmonary edema (Fig. 1). Echocardiogram showed normal findings in both patients. IV fluid was stopped and furosemide was given intravenously, with other supportive therapy. The conditions of patients were rapidly improved within 24 to 48 hours and repeated CXR showed nearly complete clearing of pulmonary infiltrations.

Case No 17, a 14 year old girl developed shock and subtemperature on admission. She had an 8-day history of fever and 2 days of cough and dyspnea. CXR revealed bilateral interstitial and alveolar infiltrations, with cardiomegaly and pleural effusion. Blood for cold agglutinin was negative and hemoculture showed no growth. On admission, chloramphenicol was given, with dopamine and other supportive therapy. Her condition gradually improved within 3 days, and repeated CXR showed decreased pulmonary infiltrations.

Encephalitis developed in patient No 18, a 2-year old boy with 6 days history of fever and one day of generalized seizure. Physical examination revealed a stuporous boy, with a body temperature of 38.6 C, hepatomegaly and an eschar at the left inguinal area. Opthalmoscopic examination showed papilledema of both optic discs. CXR showed bilateral interstitial infiltrations. Chloramphenicol was given, with other supportive therapy. Cerebrospinal fluid (CSF) examination revealed 11 WBC/mm^3 (all mononuclear cells), protein of 57 mg/dl and glucose of 87 mg/dl (blood sugar was 131 mg/dl). He developed left hemiparesis with motor aphasia during admission. CT brain showed

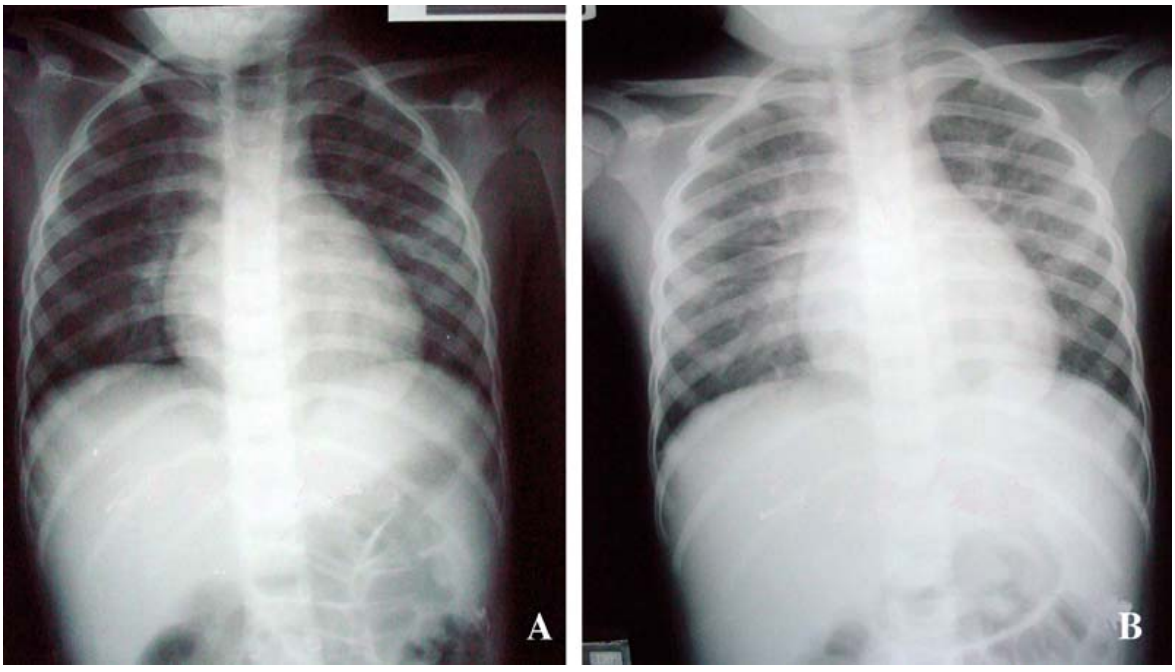

Fig. 1 Chest x-ray of patient No 13
A) On admission, showing bilateral interstitial and alveolar infiltrations with cardiomegaly
B) Day 3 after admission, showing increased cardiomegaly with pulmonary edema

unremarkable study. He was discharged on day 16 of admission and completely recovered within 2 weeks without neurological deficit.

Leukocyte count ranged from 2,700-11,900 cells/mm^3 with an average of 6,743 cells/mm^3. Neutrophilia (PMN > 60%) was found in 60% of patients. Lymphocytosis (lymphocyte >40%) and atypical lymphocytosis (atypical lymphocyte>5%) occurred in one patient each. Sixteen patients (80%) had thrombocytopenia (platelet count < 100,000/mm^3). Pneumonitis was detected on CXR in 17 cases (85%). Ten cases had no respiratory symptoms, whereas the others had symptoms of cough with dyspnea and/or tachynea. In asymtomatic cases, CXR showed bilateral interstitial infiltrations in 9 cases and unilateral in the other. In symptomatic cases, CXR showed bilateral interstitial infiltrations in 3 cases and both bilateral interstitial and alveolar infiltrations in the others. Cardiomegaly was found in 5 cases (25%), and two had associated pleural effusion. Regarding LFT, the mean value of serum albumin was 2.9 gm%(range, 2-4.2 gm%) and hypoalbuminemia (serum albumin <3 gm%) occurred in 60% of cases. Abnormal SGOT and SGPT levels were detected in 90% and 75% of all cases and the mean values were 199.4 and 116 U/L, respectively. Hemoculture, obtained in 6 patients showed no growth. Antibody against Salmonella spp (Widal test) (20 patients), Leptospira spp (8 patients) and Mycoplasma spp (4 patients) were all negative. Pyuria occurred in 3 of 11 patients. BUN and creatinine were normal in 11 patients who were tested. Only one patient (5%) had positive Weil-Felix test with antibody titer $\geq$ 1:320.

Fourteen patients (70%) were successfully treated with chloramphenicol and 2 (10%) with doxycycline. Of the 4 patients treated with roxithromycin, 2 failed to respond within 72 hrs of therapy and antibiotics were changed to doxycycline. All patients recovered completely.

Discussion

Scrub typhus is widely endemic in many countries in Asia including Thailand. A two-year nationwide study in Thailand by Leelarasamee A et al[8] showed that 7.5% of patients with acute undifferentiated febrile illness (AUFI) were caused by scrub typhus. Most of the patients in the present study were school-aged and predominantly male children, similar to previous studies[1,3-5]. This may be explained by the chance of exposure to chiggers in male children who like to play outdoors. Although the clinical manifestations of scrub typhus in children often lacks the classical features, are nonspecific and may be easily misdiagnosed. However, eschars, a pathognomonic sign of scrub typhus, were present in 75% of the presented patients and were usually painless and single. The lesion is usually found in moist intertriginous areas such as genitalia, axilla and inguinal regions. Therefore, a careful search for eschars especially in the intertriginous areas is essential for clinical diagnosis.

Serious complications of scrub typhus usually occur in the second week of untreated illness. Pneumonitis is the most common complication and diffuse bilateral interstitial lung involvement is the most frequent CXR finding in scrub typhus[1]. Shock is another complication of scrub typhus and occurred in one (case No 17) of the present study. Interstital pneumonia was seen in 55 to 96% of autopsied findings[9]. In the present study, CXR abnormalities were documented in 17/20 (85%) of patients and consistent with those reported in other studies[4,10]. The clinical course of pneumonitis in the presented patients was mild to moderately severe or asymptomatic, except for 2 cases in whom pulmonary edema developed during treatment due to fluid overload. These findings differ from that reported by Punyagupta S and Pothirat C[11,12] in which complications were those of the adult respiratory distress syndrome from disease process rather than from fluid overload. Therefore, intravenous fluid therapy should be carefully evaluated in patients with scrub typhus pneumonitis especially those who have cardiomegaly since the basic pathological changes in the lung are vasculitis and perivasculitis[9] which lead to increased permeability in the vessels and myocarditis may occur as well. Central nervous system (CNS) involvement is another major complication of scrub typhus and occurs in about 2-5%[1]. The manifestations range from aseptic meningitis to meningoencephalitis, and focal neurological signs are rare. In the present study, the authors found only one case who presented with fever with multiple episodes of seizure and had focal neurological deficit i.e. left hemiparesis. CT brain showed no abnormality and this may reflect the generalized cerebral involvement due to scrub typhus. The pathological changes in the brain are reversible, since the lesions, although widespread, are predominantly vascular and actual tissue destruction is rare, like in a presented case who recovered completely within a few weeks after discharge.

In the present study, most patients had mild to moderate elevation of SGOT and SGPT levels (SGOT had higher levels than SGPT), and hypoalbuminemia. These findings are nonspecific and may occur in other

systemic infections eg. dengue infection[13,14]. Non-specific clinical manifestation, thrombocytopenia and mild to moderate hepatitis occur in patients with scrub typhus to dengue infection. Thus, physicians may sometimes have difficulties to give correct diagnosis. However, prolonged duration of illness, no hematocrit rising and neutrophilia help support scrub typhus[15,16].

The Weil-Felix test, which is widely used in many hospitals, lacks sensitivity. A previous study by Chouriyagune C et al[17] found that the Weil-Felix test was positive with acute sera in only 15% of adult cases. In our study, the sensitivity of this test for acute sera in children was only 5%. This may be due to immune response in pediatric patients does not result in the production of agglutinating antibodies to OX-K. So the Weil-Felix test should not be used as a screening test for diagnosis of scrub typhus.

Although there has been a reported by Watt G et al[18] that adult patients with scrub typhus responded poorly to antibiotics. Doxycycline and chloramphenicol were successfully used to treat pediatric scrub typhus in our cases and other studies[3,4]. Roxi-thromycin was successfully treated in only one of four cases in our study. This is different from a previous study recently reported by Lee K Y et al[19]. They found that roxithromycin was as effective as doxycycline and chloramphenicol in children with scrub typhus. This may be due to the fact that patients were infected with different strains of *O tsutsugamushi*. This original study is a case series of pediatric scrub typhus. The major disadvantage of this study is limitation of the number of patients in a short duration of study. Thus, the data cannot be generalized, and a larger study should be performed to evaluate clinical features and therapeutic outcome.

In conclusion, the present study showed that pediatric scrub typhus was a febrile illness with non-specific clinical features. Eschar was the most common clinical findings and usually occurred in the intertriginous areas. It should be thoroughly examined in all febrile patients without localizing signs of infection where specific serodiagnostic test is not commercially available in endemic area. The Weil-Felix test had low sensitivity for early detection. The most common complication was pneumonia and diffuse interstitial lung infiltration was the most frequent CXR findings. Doxycycline and chloramphenicol were successfully treated, whereas roxithromycin was not effective.

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References

1. Silpapojakul K, Chupuppakarn S, Yuthasompob S, Varachit B, Chaipak D, Borkerd T, et al. Scrub and murine typhus in children with obscure fever in the tropics. Pediatr Infect Dis J 1991; 10: 200-3.
2. Takada N, Khamboonruang C, Yanaguchi T, Thitasut P, Vijrasthira S. Scrub typhus and chiggers in northern Thailand. Southeast Asian J Trop Med Public Health 1984; 15: 402-6.
3. Sirisanthana V, Puthanakit T, Sirisanthana T. Epidemiologic, clinical and laboratory features of scrub typhus in thirty Thai children. Pediatr Infect Dis J 2003; 22: 341-5.
4. Sornchai P, Kanjanavanit S. Pediatric scrub typhus in Nakornping Hospital. Thai J Pediatr 2000; 39: 20-9.
5. Sirisanthana V, Poneprasert B. Scrub typhus in children at Chiang Mai University Hospital. J Infect Antimicrob Agents 1989; 6: 22-7.
6. Brown GW, Shirai A, Rogers C, Groves MG. Diagnostic criteria for scrub typhus: probability values for immunofluorescent antibody and Proteus OX-K agglutinin titers. Am J Trop Med Hyg 1983; 32: 1101-7.
7. Weddle JR, Chan TC, Thompson K, Paxton H, Kelly DJ, Dasch G, et al. Effectiveness of a dot-blot immnunoassay of anti-Rickettsia tsutsugamushi antibodies for serologic analysis of scrub typhus. Am J Trop Med Hyg 1995; 53: 43-6.
8. Leelarasamee A, Chuprapawan C, Chenchittikul M, Udompanthurat S. Etiologies of acute undifferentiated febrile illness in Thailand. J Med Assoc Thai 2004; 87: 464-72.
9. Chayakul P, Panich V, Silpapojakul K. Scrub typhus pneumonitis: an entity which is frequently missed. Q J Med 1988; 68: 595-602.
10. Choi YH, Kim SJ, Lee JY, Pai KY, Lee YS. Scrub typhus: radiological and clinical findings. Clin Radiol 2000; 55: 140-4.
11. Punyagupta S. Cardiopulmonary complication in an acute febrile patient. J Infect Dis Antimicrob Agents 1985; 2: 194-7.
12. Pothiratana C. Scrub typhus pneumonia with adult respiratory distress syndrome. J Infect Dis Antimicrob Agents 1987; 4: 68-72.
13. Ukarapol N, Wongsawasdi L. Hepatic involvement of dengue hemorrhagic fever in pediatric patients. Thai J Pediatr 2000; 39: 1-7.

14. Kalyanarooj S, Vaugh DW, Nimmannitya S, Green S, Suntayakorn S, Kunentrasai N, et al. Early clinical and laboratory indicators of acute dengue illness. J Infect Dis 1997; 176: 313-21.
15. Watt G, Jongsakul K, Chouriyagune C, Paris R. Differentiating dengue virus infection from scrub typhus in Thai adults with fever. Am J Trop Med Hyg 2003; 68: 536-8.
16. Chanta C, Mahaprom W, Triratanapa K, Predisripipat K, Suwansingh S. Comparative clinical and laboratory findings between DHF and scrub typhus in children admitted at Chiangrai Hospital. Thai J Pediatr 2004; 43: 160-5.
17. Chouriyagune C, Watt G, Strickman D, Jinasen R. The Weil-Felix test for the diagnosis of scrub typhus in Thailand. Intern Med 1992; 8: 29-33.
18. Watt G, Chouriyagune C, Ruangweerayud R. Scrub typhus infections poorly responsive to antibiotics in northern Thailand. Lancet 1996; 348: 86-9.
19. Lee KY, Lee HS, Hong JH, Hur JK, Whang KT. Roxithromycin treatment of scrub typhus (tsutsugamushi disease) in children. Pediatr Infect Dis J 2003; 22: 130-3.

การศึกษาทางคลินิกในผู้ป่วยเด็กที่เป็นโรคสครับทัยฟัสที่โรงพยาบาลศูนย์เชียงราย

จุลพงศ์ จันทร์ต๊ะ, สุวลี จันทร์ต๊ะ

การศึกษาแบบไปข้างหน้าในผู้ป่วยเด็ก 20 รายที่ได้รับการวินิจฉัยเป็นสครับ ทัยฟัส และรับการรักษาที่โรงพยาบาลศูนย์เชียงราย เป็นระยะเวลา 6 เดือน ตั้งแต่เดือนมิถุนายน 2546 พ.ศ. ถึงธันวาคม พ.ศ. 2546 ผู้ป่วยทุกรายได้รับการตรวจยืนยันการวินิจฉัยโดยอาศัยการทดสอบ Dipstick หรือ Indirect immunofluorescent antibody (IFA) ลักษณะอาการทางคลินิกที่พบบ่อยที่สุดคือ eschar พบถึงร้อยละ 75 รองลงมาได้แก่ ตับโต (ร้อยละ 65) ไอ (ร้อยละ 60) หายใจเร็ว (ร้อยละ 35) ท้องผูก (ร้อยละ 25) ปวดท้อง (ร้อยละ 25) บวม (ร้อยละ 20) ม้ามโต (ร้อยละ 15) อาเจียน (ร้อยละ 15) ผื่น (ร้อยละ 15) และจุดเลือดออก (ร้อยละ 5) ตามลำดับ การตรวจภาพรังสีปอด พบความผิดปกติถึงร้อยละ 85 โดยส่วนใหญ่จะเป็นลักษณะ interstitial infiltrations ในปอดทั้งสองข้าง พบค่า SGOT, SGPT เพิ่มขึ้น 18 ราย (ร้อยละ 90) และ 15 ราย (ร้อยละ 75) พบภาวะอัลบูมินในเลือดต่ำ 12 ราย (ร้อยละ 60) การตรวจนับเม็ดเลือดพบการเพิ่มสูงขึ้นของ PMN (> 60%) 12 ราย (ร้อยละ 60) การเพิ่มสูงขึ้นของ lymphocyte (> 40%) และ atypical lymphocyte (> 5%) อย่างละ 1 ราย พบเกล็ดเลือดต่ำ 16 ราย (ร้อยละ 80) การทดสอบ Weil Felix พบผลบวก 1 ราย (ร้อยละ 5) ภาวะแทรกซ้อนได้แก่ ปอดอักเสบซึ่งอาจพบภาวะน้ำท่วมปอดร่วมด้วย เยื่อหุ้มสมองอักเสบ และช็อก การรักษาได้ผลดีด้วยยา chloramphenicol และ doxycycline ส่วนยา roxithromycin ไม่มีประสิทธิภาพเพียงพอในการรักษา

คำชี้แจง

1. การให้ยา doxycycline หลังจากที่ให้ยา roxithromycin ไม่ได้ผลเนื่องจากสามารถให้รับประทานได้ และให้เพียงวันละ 2 ครั้ง ในขณะที่การรักษาด้วยยา chloramphenicol ที่โรงพยาบาล จะเริ่มการรักษาด้วยยาฉีด

2. กรณีหาก failure ต่อ doxycycline และ chloramphenicol สามารถใช้ยา เป็นทางเลือกในการรักษา อย่างไรก็ตามจากประสบการณ์การรักษา scrub typhus ในเด็กที่ผ่านมา ยังไม่พบเชื้อดื้อต่อยาทั้งสองนี้