

# Randomized Controlled Trial of Azithromycin versus Doxycycline or Chloramphenicol for Treatment of Uncomplicated Pediatric Scrub Typhus

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**Objective:** To evaluate the efficacy and safety of azithromycin for treatment of uncomplicated pediatric scrub typhus.

**Material and Method:** A randomized controlled trial was performed. We compared azithromycin with doxycycline or chloramphenicol in uncomplicated pediatric scrub typhus from inpatient pediatric department of Chiangrai Prachanukroh Hospital. The primary outcome was cure rate at day 3. The secondary outcomes were timing to defervescence within 72 hours, side effects, and relapsed rate. We compared data between both groups with Fisher's exact test or Mann-Whitney U test, and failure rate was demonstrated by Kaplan-Meier survival curve and Log-rank test.

**Results:** We included 57 patients, of whom, 28 were assigned to doxycycline or chloramphenicol (control group) and 29 to azithromycin (study group). The baseline characteristics of both groups were similar. The cure rate was 85.7% in the doxycycline or chloramphenicol group, as compared to 79.3% in the azithromycin group ( $p = 0.73$ ), and a median time to defervescence was 30 hours (IQR 21, 48) vs. 36 hours (IQR 20, 68) respectively ( $p = 0.166$ ). There was a little minor side effect in azithromycin group. No relapsed was found in either groups.

**Conclusion:** Azithromycin was as effective as doxycycline or chloramphenicol in treatment of uncomplicated pediatric scrub typhus.

**Keywords:** Scrub typhus, Doxycycline, Chloramphenicol, Azithromycin

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Scrub typhus is a major cause of subacute fever in pediatric population in the endemic area, especially in the northern part of Thailand. It is an infectious disease caused by *Orientia tsutsugamushi* from the bite of the larva of the trombiculid mite or chigger. The human is the accidental host. The current standard treatment for scrub typhus is administration of doxycycline or chloramphenicol. However, they are not recommended in children younger than eight years of age because doxycycline can cause discoloration of teeth and chloramphenicol can cause bone marrow suppression<sup>(1)</sup>. Although some studies showed that doxycycline use is not associated with increased incidence of teeth discoloration in young children<sup>(2,3)</sup>, many pediatricians do not administer doxycycline to young children with rickettsial infection<sup>(4)</sup>. Previous studies in adult scrub typhus patient found that azithromycin was as effective as doxycycline<sup>(5-7)</sup>. In pediatric scrub typhus, the use of roxithromycin which

is the macrolide antibiotic of azithromycin, was as effective as doxycycline and chloramphenicol<sup>(8)</sup>. However, a previous study in children with scrub typhus at Chiangrai Prachanukroh hospital found that roxithromycin was not effective<sup>(9)</sup>.

Microbiologic studies showed that azithromycin was effective against *Orientia tsutsugamushi*<sup>(10,11)</sup>. Azithromycin is safe in pediatric use and can be given conveniently, using a dosing schedule, due to its long half-life. The objective of this study was to evaluate the efficacy of azithromycin compared to doxycycline or chloramphenicol in the treatment of uncomplicated pediatric scrub typhus.

## Material and Method

A prospective, randomized-open label-controlled study was conducted at the Department of Pediatrics, Chiangrai Prachanukroh Hospital, between June 2010 and May 2013. All hospitalized children age less than or equal to 15 years who presented with fever more than or equal to 38°C for more than five days were screened and enrolled. The study was approved by the Ethic Committee of Chiangrai Prachanukroh Hospital and written informed consent was obtained

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from each subject or parent. Inclusion criteria were 1) clinical history and physical examination compatible with scrub typhus such as high fever, headache, lymphadenopathy, myalgia, and eschar, and 2) laboratory finding showed positive result by dipstick test for scrub typhus (SD Bioline® tsutsugamushi test). Exclusion criteria were 1) patients with history of drug allergy e.g., doxycycline chloramphenicol or azithromycin, 2) scrub typhus with complication e.g., hypotension, stupor, coma, respiratory failure requiring mechanical ventilation, or acute renal failure with renal replacement therapy, and 3) patients who received antimicrobial agent within seven days prior to admission e.g., rifampicin, chloramphenicol, macrolide, fluoroquinolone, or tetracycline. A computer-generated randomization was used to allocate each subject into one of the two treatment arms.

Initial work up after admission, history taking, and physical examination were performed by the physician. Laboratory tests such as complete blood count, blood urea nitrogen, creatinine, aspartate aminotransferase, and alanine aminotransferase were done as baseline. In the study group, the patients received three days course of azithromycin (Pfizer International) as oral sachet form (20 mg/kg/dose initially, maximum 1,000 mg followed by 10 mg/kg/dose, maximum 500 mg for 2 days). In case of treatment failure in the study group, patients were changed to standard treatment.

In the control group, the patients aged less than eight years old were treated with intravenously chloramphenicol 100 mg/kg/day divided every six hours, and those aged eight years old or more were given doxycycline (GPO®) as oral form 2.2 mg/kg/dose (maximum 100 mg/dose) every 12 hours in the first day followed by the same dose once daily for at least five days or until defervescence (body temperature <37.3°C for at least three days)<sup>(12)</sup>. Body temperature was recorded from axilla every four hours. History taking and physical examination were performed by physician at least once daily and monitored for complications from disease and drug side effect. The patients were discharged from the hospital after defervescence for at least 24 hours and followed-up by telephone at two weeks and one month. Baseline data, treatment outcomes, drug side effect, and relapse were recorded.

The primary outcome was cure or failure. Cure was defined as defervescence (body temperature <37.3°C) within 72 hours after initiating antibiotic treatment and persist for more than 48 hours. Failure

was defined as persistent of fever over 72 hours or developed complication from scrub typhus during antibiotic treatment.

The secondary outcome was evaluated according to the following definitions. Time to defervescence was defined as the interval between the time at which the first dose of antibiotic was administered and the time at which the body temperature was less than 37.3°C and persisted for more than 48 hours. Relapse was defined as relapse of fever within 30 days after end of treatment and clinical findings compatible with scrub typhus in the absence of other identifiable cause of fever. Adverse events were defined as symptoms or signs appeared during treatment and related to the administration of antibiotic.

### **Statistical analysis**

Fischer's exact test was used for the comparison of rates and proportions. Independent-sample t-test was used to compare normally distributed variables and Mann-Whitney U test for continuous variables that were not normally distributed. Kaplan-Meier survival curve and log rank test were used to compare the fever clearance time and the cure rate between two groups, respectively.

### **Results**

Fifty-seven patients with confirmed scrub typhus were randomized, 29 cases in the study group (azithromycin) and 28 in the control group (nine cases with doxycycline and 19 with chloramphenicol). There was no difference in baseline characteristics between the two groups of patients as shown in Table 1. The cure rates were 79.3% in the azithromycin group and 85.7% in the doxycycline/chloramphenicol group ( $p = 0.73$ ) based on intention to treat analysis (Table 2). The median time to defervescence was 36 hours (IQR = 20, 68) in the azithromycin group and 30 hours (IQR = 21, 48) in the doxycycline/chloramphenicol group ( $p = 0.166$ ). Log rank test did not detect significant difference time to defervescence between two groups (Fig. 1). Failures of treatment in both groups resulted from no fever lysis within 72 hours except for one case in azithromycin group who had complication (hypotension); a 5-year-old boy with seven days history of fever, headache, and fatigue with an initial physical examination that revealed a body temperature of 38.1°C, blood pressure = 90/60 mmHg, respiratory rate = 44/minute, generalized lymphadenopathy and an eschar at the perianal area. On admission, azithromycin was given as study group. On day 2 after admission,

**Table 1.** Baseline characteristics of the study patients

Characteristics	Azithromycin (n = 29)	Doxycycline or chloramphenicol (n = 28)	p-value
Female, n (%)	11 (37.9)	8 (28.6)	0.576
Age (year)	6.6±3.4	6.2±4.0	0.651
Fever time (day)	7.7±2.9	7.5±2.1	0.782
Peak temperature (degree celcius)	39.6±0.8	39.6±0.7	0.888
Eschar, n (%)			
Yes	12 (41.4)	11 (39.3)	0.543
Hb (gm/dl)	11.6±1.1	11.2±2.0	0.329
WBC (cell/cu.mm)	8,805.9±4,010.7	8,772.8±6,240.4	0.981
Neutrophil (%)	61.9±13.9	58.4±14.3	0.349
Lymphocyte (%)	29.1±14.1	31.4±10.8	0.489
Platelet (cell/cu.mm)	165,931.0±104,461.9	153,046.4±119,314.6	0.666
AST (IU/L)	108.3±111.1	112.9±78.7	0.313
ALT (IU/L)	66.7±60.9	69.9±54.9	0.354
BUN (mg/dl)	9.4±2.3	10.3±3.5	0.270
Cr (mg/dl)	0.5±0.1	0.5±0.2	0.825

Hb = hemoglobin; WBC = white blood cell; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; Cr = creatinine

Data presented as mean ± SD and number (percentage)

**Table 2.** Result and time to defervescence

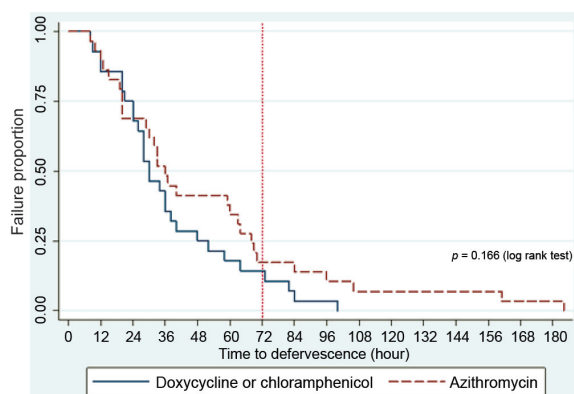
Characteristics	Azithromycin (n = 29)	Doxycycline or chloramphenicol (n = 28)	p-value
Cure rate, n (%)	23 (79.3)	24 (85.7)	0.730
Median time to defervescence (hour) (IQR)	36 (20, 68)	30 (21, 48)	0.166

he developed hypotension (blood pressure = 74/40) and antibiotic was changed to chloramphenicol with supportive therapy. Defervescence occurred on day 3 after admission and his clinical condition improved. There was one adverse event (nausea) in the azithromycin group. Forty-three of 57 patients were

followed-up and no relapse was observed in both groups.

### Discussion

Scrub typhus is a common infectious disease in Southeast Asia including Thailand, especially in the northern part<sup>(9,13,14)</sup>. Early diagnosis and prompt treatment with conventional antibiotics like doxycycline and chloramphenicol can reduce morbidity, mortality, and complication. However, the antibiotic treatment of pediatric scrub typhus is problematic due to side effects. Previous study showed that roxithromycin is as effective as doxycycline and chloramphenicol, but a study in Chiangrai Prachanukroh Hospital showed that it was not effective in pediatric scrub typhus<sup>(9,10)</sup>. Studies about macrolide antibiotic, such as azithromycin, in treatment of scrub typhus in adult showed that it is as effective as doxycycline<sup>(5,6)</sup>. The authors did not identify significant difference in efficacy of azithromycin versus doxycycline or chloramphenicol in uncomplicated pediatric scrub typhus.

**Fig. 1** Kaplan-Meier survival estimates according to study group.

However, failure rate from doxycycline or chloramphenicol in the present study were slightly higher than previous study in pediatric scrub typhus<sup>(8)</sup>. This may be due to the infection from resistant strains of *Orientia tsutsugamushi*, which was reported from Chiang Rai, Thailand<sup>(15)</sup>. Although the median time to defervescence of azithromycin was longer than doxycycline or chloramphenicol groups but the difference was not statistically significant. There was no significant difference in side effects between two groups. In the present study, we found no relapse in both groups.

Azithromycin is the macrolide antibiotic that exhibit good intracellular penetration and long half-life (more than 50 hours in children), which can be used once-daily and on short course regimen. Azithromycin has also been shown to achieve high concentration in neutrophil and macrophage that phagocytose the pathogens.

In vitro study showed that azithromycin was effective against *Orientia tsutsugamushi*<sup>(11)</sup>. Mechanism of action of azithromycin is by reverse binding to 50s subunit of the bacterial ribosome resulting in inhibition of microbial protein synthesis<sup>(16)</sup>. The common side effects of azithromycin are mild gastric upset and abdominal pain. In the present study, there was no significant difference in gastrointestinal side effect between azithromycin and doxycycline or chloramphenicol group. The limitation of the present study was the small sample size, so, further study should be performed to evaluate efficacy of azithromycin in pediatric scrub typhus.

In conclusion, azithromycin appeared to be safe and equally effective as doxycycline or chloramphenicol in treatment of mild uncomplicated pediatric scrub typhus.

#### **What is already known on this topic?**

The conventional treatment for scrub typhus with antimicrobial agents like doxycycline and chloramphenicol has been shown to be effective in shortening the course of illness and its associated morbidity and mortality. Doxycycline is not recommended in children younger than eight years of age because it can cause discoloration of teeth, while chloramphenicol may cause bone marrow suppression during treatment. Previous studies in adult scrub typhus showed that azithromycin was as effective as doxycycline; however, no data were available regarding the efficacy of azithromycin in pediatric scrub typhus.

#### **What this study adds?**

The result of the present study showed that azithromycin appeared to be as effective as doxycycline or chloramphenicol in treatment of uncomplicated pediatric scrub typhus with minor side effect.

#### **Acknowledgement**

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#### **Potential conflicts of interest**

None.

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## การเปรียบเทียบผลของการใช้ยา *azithromycin* กับ *doxycycline* หรือ *chloramphenicol* ในการรักษาสครับไทฟัส ในเด็กที่ไม่มีภาวะแทรกซ้อน

จุดประสงค์ จันทรดีตะ, ปิติ เพลินชัยวานิช

**วัตถุประสงค์:** เพื่อต้องการศึกษาผลการรักษาและความปลอดภัยของยา *azithromycin* เปรียบเทียบกับยา *doxycycline* หรือ *chloramphenicol* ในผู้ป่วยเด็กโรคสครับไทฟัส ที่ไม่มีภาวะแทรกซ้อน

**วัสดุและวิธีการ:** ผู้ป่วยที่เข้ารับการรักษาในแผนกผู้ป่วยในกลุ่มงานกุมารเวชกรรม โรงพยาบาลเชียงรายประชานุเคราะห์ ได้รับการแบ่งแบบสุ่ม เป็นกลุ่มทดลอง ซึ่งได้รับยา *azithromycin* และกลุ่มควบคุมซึ่งได้รับยา *doxycycline* หรือ *chloramphenicol* ผลการรักษาจะพิจารณาจาก ไข้ลดลงภายใน 72 ชั่วโมง ระยะเวลาที่ไข้ลดลง และอัตราการกลับเป็นซ้ำ เปรียบเทียบกลุ่มศึกษาโดย Fisher's exact test หรือ Mann-Whitney U test และแสดงอัตราล้มเหลวของการรักษาด้วย Kaplan-Meier survival curve และ Log-rank test

**ผลการศึกษา:** ผู้ป่วยเด็กทั้งหมด 57 ราย ได้รับการสุ่ม โดย 28 ราย อยู่ในกลุ่มควบคุม (*doxycycline* หรือ *chloramphenicol*) 29 ราย อยู่ในกลุ่มทดลอง (*azithromycin*) โดยทั้งสองกลุ่มข้อมูลพื้นฐานใกล้เคียงกัน พบว่ามีอัตราการหายขาดใกล้เคียงกัน คือ 85.7% ในกลุ่มควบคุม และ 79.3% ในกลุ่มทดลอง  $p = 0.73$  มัชยฐานระยะเวลาที่ไข้ลดลง คือ 30 ชั่วโมง (IQR 21, 48) กับ 36 ชั่วโมง (IQR 20, 68) ตามลำดับ  $p = 0.166$  โดยกลุ่มทดลองมีผลข้างเคียงจากการได้ยาเล็กน้อยและทั้งสองกลุ่มไม่พบการกลับเป็นซ้ำ

**สรุป:** ยา *azithromycin* มีประสิทธิภาพในการรักษาสครับไทฟัสในเด็กที่ไม่มีภาวะแทรกซ้อน เทียบเท่ากับยา *doxycycline* หรือ *chloramphenicol*

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