



# Antibiotic Use in Scrub Typhus: Systematic Review and Meta-analysis of Clinical Trials

Rajiv Mahajan, Navyug Raj Singh, V. Kapoor

## Introduction

Scrub typhus is a zoonotic disease, caused by *Orientia tsutsugamushi*, an obligate intracellular bacterium transmitted to humans by the bite of a larval lepto-trombidium mite. (1) Scrub typhus is an important cause of acute fever in the Western Pacific region. (2) Recently, scrub typhus has been recognized as common causes of acute undifferentiated febrile illness in rural Southeast Asia. (3, 4) Reports of scrub typhus have emerged from different parts of India also; (5, 6) and more recently reports of outbreaks of scrub typhus fever have emerged in Jammu region too. (7)

Although clinical presentation of patients with scrub typhus has been well documented; most patients with scrub typhus present to hospitals with nonspecific signs and symptoms. Acute undifferentiated fever, i.e., acute fever without an obvious focus of infection, is the most common clinical presentation. (8) Antibiotic treatment is thought to shorten the illness and reduce mortality. It is usually presumptive, being given to cases that are febrile in an area where the disease is endemic. Although chloramphenicol was the first of the agents used for the treatment of scrub typhus (9) currently, tetracyclines and doxycycline are potentially an excellent choice of initial antimicrobial treatment for scrub typhus. (10) Due to emergence of reports of doxycycline-resistance, (11) azithromycin is being used in resistant endemic areas.

Despite the use of antibiotics in scrub typhus for ages, the appropriate length of antibiotic treatment to minimize recrudescence has not been established. The potential advantage of alternative drugs (azithromycin, clarithromycin, rifampicin and ciprofloxacin) has not been directly established. Moreover, only one systematic review about the use of antibiotics in scrub typhus, updated last in 2002 is available. (12) Since then, new drugs have been commissioned for scrub typhus. Above-all, no protocol for use of antibiotics in pregnant women exist. Keeping all these facts in mind, present study was designed to review the information about the effects of antibiotics on scrub typhus, to analyze various clinical trials involving antibiotic-

use in scrub typhus and to design a regimen for the use of antibiotics in patients with scrub typhus.

## Materials and Methods

A meta-analysis was performed by including all completed, randomized controlled clinical trials enrolling patients with scrub typhus, as defined by trial authors and in which all arms of the trials have at least one active comparator, thus excluding placebo control trials. Flow diagram was used to present abstract, introduction, methods, results and discussion sections. A Medline search, using the keywords, 'scrub typhus or 'Rickettsia tsutsugamushi' or 'Orientia tsutsugamushi' was performed on November 14<sup>th</sup>, 2009. Limits activated were Randomized clinical trials and humans. The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed by both authors (R M, N R). Disagreements were resolved by consulting a third person. The quality of trials was assessed using some items of the scale proposed by Jadad *et al.* (13). A further search was performed on EMBASE for randomized clinical trials on humans, up to November 1<sup>st</sup>, 2009, and on Cochrane database, on November 12<sup>th</sup>, 2009, with the same keywords and limits.

Completed but still unpublished trials were identified through a search of website like ([www.clinicaltrials.gov](http://www.clinicaltrials.gov), [clinicaltrials.ucla.edu](http://clinicaltrials.ucla.edu) & [clinicaltrials.ploshubs.org](http://clinicaltrials.ploshubs.org))

Outcomes measured were number of febrile patients after 48hrs of treatment, duration of fever and relapse within three months (return of fever or other symptoms during follow up).

## Statistical Analysis

Data was analyzed using comprehensive meta-analysis version 2, Biostat, and SPSS 16.0. Mantel-Haenszel odds ratio (MH-OR) with 95% confidence interval (CI) was calculated using a fixed-effect model for binary data and mean difference with 95% CI was calculated for continuous data. Heterogeneity was calculated using the I<sup>2</sup> statistics. Publication/disclosure bias was estimated by using the Begg and Mazumdar rank correlation test;

From the Assistant Professor, Department of Pharmacology, Adesh Institute of Medical Sciences & Research, Bathinda-(India)

Correspondence to : Dr Rajiv Mahajan, Assistant Professor, Deptt. of Pharmacology, Adesh Institute of Medical Sciences & Research, Bathinda-Pb. (India)

**Table 1. Characteristics of the Studies for Meta-Analysis**

Study	Active treatment (dose)	Comparator (dose)	Randomization	Blinding	Any other comment
Sheehy (9)	Tetracycline (2gm/dx3d) [n=30]	Chloramphenicol (3gm/dx3d) [n=30]	NA	NR	Continuation of treatment beyond 3 days decided by physicians
Brown (14)	Doxycycline (200mg single dose) [n=31]	Tetracycline (2gm/dx7d) [n=24]	NA	NR	If no improvement at 48hrs, free to give additional drug
Song (15)	Doxycycline (200mg/dx3d) [n=66]	Tetracycline (2gm/dx7d) [n=50]	NA	NR	-----
Watt (16)	Rifampicin (600mg/dx7d) [n=26] Rifampicin (900mg/dx7d) [n=24]	Doxycycline (200mg/dx7d) [n=28]	A	NA	At the beginning, third group was combination of doxycycline and rifampicin, but after one year of trial changed to rifampicin 900mg/day
Kim (17)	Azithromycin (500mg single dose) [n=47]	Doxycycline (200mg/dx7d) [n=46]	A	OL	-----
Kim (18)	Telithromycin (800mg/dx5d) [n=47]	Doxycycline (200mg/dx5d) [n=45]	A	OL	-----

NA: Not adequate NR: Not reported A: Adequate OL: Open label  
Tetracycline;Doxycycline;Rifampicin ;Azithromycin;Telithromycin

**Table 2. Outcome Measures in Various Studies**

Study reference)	Drugs	Patients febrile after 48 hours (n) [RR (95% CI)]	Median duration of fever [RR (95% CI)]	No of Patients relapsed (n) [RR (95% CI)]
Sheehy (9)	Tetracycline [n=30] Chloramphenicol [n=30]	1 [1 (0.07, 15.26)] 1	No figures	2 [0.4 (0.08, 1.90)] 5
Brown (14)	Doxycycline [n=31] Tetracycline [n=24]	3 [0.46 (0.12, 1.75)] 5	No figures	0 [Not estimable] 0
Song (15)	Doxycycline [n=66] Tetracycline [n=50]	No figures	34 hrs [-3.0 (-12.76, 6.76)]* 37 hrs	0 [Not estimable] 0
Watt (16)	Rifampicin [n=50] Doxycycline [n=28]	11 [0.41 (0.22, 0.77)] 15	22.5-27.5 hrs 52 hrs [-19.5 to -14.5]#	0 [8.79 (0.44, 176.96)] 2
Kim (17)	Azithromycin [n=47] Doxycycline [n=46]	1 [0.31 (0.19, 0.68)] 3	21 hrs [-8.0 (-14.65, 1.46)]* 29 hrs	0 [Not estimable] 0
Kim (18)	Telithromycin [n=47] Doxycycline [n=45]	1 [0.47 (0.24, 0.80)] 2	20.45 hrs [-2.16 (-8.34, 5.6)]* 22.60 hrs	No figures

RR: Risk ratio, CI: Confidence interval, \*: Mean difference with 95% CI, #: Only mean difference, no CI Tetracycline;Doxycycline;Rifampicin ;Azithromycin;Telithromycin

Kendall's tau without continuity correction was calculated. As no clinical trial enrolled pregnant women, so to arrive at a conclusion for pregnant women, we relied heavily on case reports and case series.

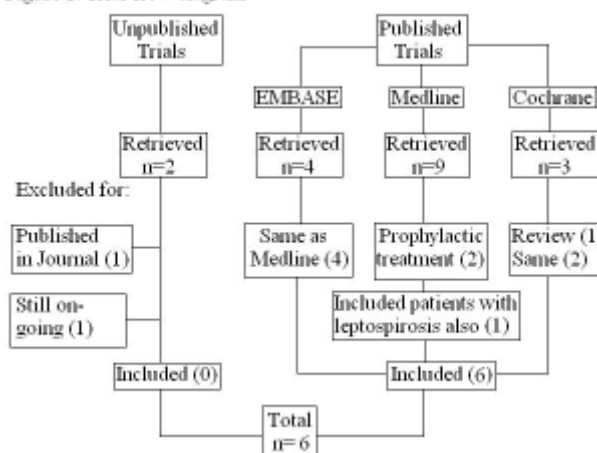
### Results

The Medline and EMBASE search provided nine and four randomized clinical trials respectively; all the articles retrieved on EMBASE had already been identified through Medline. A further Cochrane search yielded three results, out of which one was systematic review and the remaining two trials had already been identified through Medline. Out of nine trials retrieved on Medline, two were for use of antibiotics in prophylactic treatment while in one clinical trial, efficacy of antibiotics was tested on both scrub typhus and leptospirosis patients, and it was not easy to differentiate the number of scrub typhus patients receiving antibiotics. Thus ultimately, only six randomized controlled trials were included for further studies. (9, 14-18) Five out of six trials have doxycycline as one of the comparator arm; while one trial compared efficacy of tetracyclines vs

**Table 3. Drugs Used During Pregnancy and Outcomes**

Drugs used	Number of patients	Outcome
Chloramphenicol	1	Preterm delivery and baby died due to respiratory distress syndrome
Ciprofloxacin	5	Stillbirth-3, Abortion-1, Low birth weight baby-1
Minocycline	1	Favorable
Azithromycin (Single 500mg dose)	13	Favourable-12, death-1

**Figure 1: Trial-flow diagram**



chloramphenicol. In all, 494 patients of scrub typhus were enrolled in these randomized controlled trials. Out of these, 216 patients received doxycycline, 104 patients received tetracycline, 50 patients were treated with rifampicin, 47 with telithromycin, 47 with azithromycin and 30 with chloramphenicol. The trial flow is summarized in Fig 1, and the characteristics of the trials included in the meta-analysis are summarized in (Table 1).

Considering number of patients febrile after 48hrs of treatment as the primary outcome measure, Begg and Mazumdar rank correlation test was applied to verify publication/disclosure bias. Kendall's tau was -0.32 (P=0.23). No heterogeneity was detected. Effect of different drugs on different outcome measures i.e. number of patients febrile after 48hrs, duration of fever and number of patients relapsed; in different studies included in the meta-analysis are shown in (Table 2). As is evident from table 2, risk ratio for number of patients febrile after 48 hrs of treatment and number of patients relapsed with doxycycline was less as compared to chloramphenicol and tetracycline but it was more when compared to rifampicin, azithromycin and telithromycin. Similar results were found for duration of fever as an outcome. Literature search yielded five case-reports/case series regarding drug use in scrub typhus complicating pregnancy; in all reporting 20 cases. (19-23) Various drugs used in pregnant women with scrub typhus and pregnancy outcomes are shown in (Table 3). Table 3 clearly shows that single dose of 500mg azithromycin was



far more efficacious and safer than other drugs, for the treatment of women with scrub typhus during pregnancy.

### Discussion

A very common problem with the trials included was regarding diagnostic criteria and tests used to define scrub typhus. Thus all randomized trials with scrub typhus patients as defined by authors were included in meta-analysis. Unfortunately the studies included in this review did not use intention-to-treat analysis, which may influence effect estimates. In addition, in most of the clinical trials concealment of allocation was poorly reported, and studies were small. Moreover, none of the trials reported the effect of earlier exposures on outcomes. Thus, it could not be ascertained that what should be treatment options in endemic areas. Also all trials included patients with mild to moderate scrub typhus; thus drug use in serious/advance cases and cases with complications can not be ascertained.

As no randomized trial included pregnant women, so to ascertain a treatment protocol for pregnant women, we have to rely on case reports. Although case reports can not replace, randomized controlled trials, but they can certainly give an insight to the problem and can be direction-indicators. Doxycycline and tetracycline are not recommended for use in pregnant women, even otherwise. In the reported studies, azithromycin was by far better than any other drug in pregnant women with scrub typhus. With ciprofloxacin, outcomes were not favorable. Only death reported with azithromycin was due to late start of therapy (19).

### Conclusion

In few comparative studies doxycycline, tetracycline and chloramphenicol have been used with varied success, in different doses. Similarly, in recent studies doxycycline has been used as one of the comparator arm. A fair protocol for antibiotic use in scrub typhus, recommended by authors is use of doxycycline 200mg/day for 5-7 days. Doxycycline is also the best option for empirical therapy of scrub typhus. When cost is not a criterion, azithromycin 500mg single dose (max three doses) should be used. In areas reporting resistance to doxycycline; azithromycin 500mg single dose, rifampicin 600mg/day for 7 days or telithromycin 800mg/day for 5 days should be tried. In pregnant women with scrub typhus, use of single dose of 500mg azithromycin is the treatment of choice. The key to treatment in pregnant women is early initiation of therapy.

### References

1. Watt G, Parola P. Scrub typhus and tropical rickettsioses. *Curr Opin Infect Dis* 2003;16:429-36.
2. Silpapojakul K. Scrub typhus in the Western Pacific region. *Ann Acad Med Singapore* 1997;26:794-800.
3. Brown GW, Shirai A, Jegathesan M *et al.* Febrile illness in Malaysia-an analysis of 1,629 hospitalized patients. *Am J Trop Med Hyg* 1984;33:311-15.

4. Leelarasamee A, Chupaprawan C, Chenchittikul M, Udompanthurat S. Etiologies of acute undifferentiated febrile illness in Thailand. *J Med Assoc Thai* 2004;87:464-72.
5. Paddidri VS, Gupta NP. Rickettsiosis in India: A review. *J Indian Med Assoc* 1978;71:104-07.
6. Pavithran S, Mathai E, Moses PD. Scrub Typhus. *Indian Pediatrics* 2004;41:1254-57.
7. Vaz LS, Gupta NK. Outbreak of Scrub Typhus in Jammu-A Report. *MJAFI* 2006;62:342-43.
8. Suttinont C, Losuwanaluk K, Niwatayakul K *et al.* Causes of acute undifferentiated febrile illness in rural Thailand: A prospective observational study. *Ann Trop Med Hyg* 2006;100:363-70.
9. Sheehy TW, Hazlett D, Turk RE. Scrub typhus: A comparison of chloramphenicol and tetracyclines in its treatment. *Arch Intern Med* 1973;132:77-80.
10. Panpanich R, Gamer P. Antibiotics for treating scrub typhus. *Cochrane Database Syst Rev* 2000;2:CD002150.
11. Watt G, Chouriyagune C, Ruangweerayud R, *et al.* Scrub typhus infections poorly responsive to antibiotics in northern Thailand. *Lancet* 1996;348:86-89.
12. Panpanich R, Gamer P. Antibiotics for treating scrub typhus. *Cochrane Database Syst Rev* 2002;3:CD002150.
13. Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996;17:1-12.
14. Brown GW, Saunders JP, Singh S, Huxsoll DL, Shirai A. Single dose doxycycline therapy for scrub typhus. *Trans R Soc Trop Med Hyg* 1978;72:412-16.
15. Song JH, Lee C, Chang WH, *et al.* Short-course doxycycline treatment versus conventional tetracycline therapy for scrub typhus: a multicenter randomized trial. *Clin Infect Dis* 1995;21:506-10.
16. 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.
17. Kim YS, Yun HJ, Shim SK, Koo SH, Kim SY, Kim S. A comparative trial of a single dose of azithromycin versus doxycycline for the treatment of mild scrub typhus. *Clin Infect Dis* 2004;39:1329-35.
18. Kim DM, Yu KD, Lee JH, Kim HK, Lee SH. Controlled trial of a 5-day course of telithromycin versus doxycycline for treatment of mild to moderate scrub typhus. *Antimicrob Agents Chemother* 2007;51:2011-15.
19. Mahajan SK, Rolain J, Kashyap R, *et al.* Scrub Typhus Complicating Pregnancy. *JAPI* 2009;57:720-21.
20. Kim YS, Lee HJ, Chang M, Son SK, Rhee YE, Shim SK. Scrub typhus during pregnancy and its treatment: A case series and review of the literature. *Am J Trop Med Hyg* 2006;75:955-9.
21. Phupong V, Srettakraikul K. Scrub typhus during pregnancy: a case report and review of the literature. *Southeast Asian J Trop Med Public Health* 2004;35(2):358-60.
22. Mathai E, Rolain JM, Verghese L, *et al.* Case reports: scrub typhus during pregnancy in India. *Trans R Soc Trop Med Hyg* 2003;97:570-72.
23. Tsui MS, Fang RC, Su YM, *et al.* Scrub typhus and pregnancy: a case report and literature review. *Zhonghua Yi Xue Za Zhi (Taipei)* 1992;49:61-63.