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

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Introduction

Scrub typhus is a zoonotic disease, caused by Orientia tsutsugamushi, an obligate intracellular bacterium transmitted to humans by the bite of a larval leptotrombidium mite. (1) Scrub typhus is an important cause of acute fever in the Western Pacific region. (2) Recently, scrub typhus has been recognized as a common cause 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 14th, 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 1st, 2009, and on Cochrane database, on November 12th, 2009, with the same keywords and limits. Completed but still unpublished trials were identified through a search of websites like (www.clinicaltrials.gov, clinicaltrials.ucla.edu & clinicaltrials.plosclubs.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 I2 statistics. Publication/disclosure bias was estimated by using the Begg and Mazumdar rank correlation test;
Table 1. Characteristics of the Studies for Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Active treatment (dose)</th>
<th>Comparator (dose)</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Any other comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelby (9)</td>
<td>Tetracycline [2gm/dx7d]</td>
<td>Chloramphenicol [3gm/dx7d]</td>
<td>NA</td>
<td>NR</td>
<td>Continuation of treatment beyond 3 days decided by physicians</td>
</tr>
<tr>
<td>Brown (14)</td>
<td>Doxycycline [200mg single dose]</td>
<td>Tetracycline [2gm/dx7d]</td>
<td>NA</td>
<td>NR</td>
<td>If no improvement at 48hs, free to give additional drug</td>
</tr>
<tr>
<td>Song (15)</td>
<td>Doxycycline [200mg dx3d]</td>
<td>Tetracycline [2gm dx7d]</td>
<td>NA</td>
<td>NR</td>
<td>-----</td>
</tr>
<tr>
<td>Watt (16)</td>
<td>Rifampicin [600mg dx5d]</td>
<td>Doxycycline [200mg dx7d]</td>
<td>A</td>
<td>NA</td>
<td>At the beginning, third group was combination of doxycycline and rifampicin, but after one year of trial changed to rifampicin 40mg/day</td>
</tr>
<tr>
<td>Kim (17)</td>
<td>Azithromycin [500mg single dose]</td>
<td>Doxycycline [200mg dx7d]</td>
<td>A</td>
<td>OL</td>
<td>-----</td>
</tr>
<tr>
<td>Kim (18)</td>
<td>Telithromycin [800mg dx5d]</td>
<td>Doxycycline [200mg dx7d]</td>
<td>A</td>
<td>OL</td>
<td>-----</td>
</tr>
</tbody>
</table>

NA: Not adequate NR: Not reported A: Adequate OL: Open label

Tetracycline;Doxycycline;Rifampicin ;Azithromycin;Telithromycin

Table 2. Outcome Measures in Various Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug (dose)</th>
<th>Patients febrile after 48 hours (n)</th>
<th>Median duration of fever (RR 95% CI)</th>
<th>No of Patients relapsed (n)</th>
<th>[RR 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelby (9)</td>
<td>Tetracycline [2gm dx7d]</td>
<td>1 [1.07 (1.03, 1.12)]</td>
<td>No figures</td>
<td>2 [0.0 (0.0, 0.0)]</td>
<td></td>
</tr>
<tr>
<td>Brown (14)</td>
<td>Doxycycline [200mg single dose]</td>
<td>3 [0.46 (0.12, 1.75)]</td>
<td>No figures</td>
<td>0 [Not estimable]</td>
<td></td>
</tr>
<tr>
<td>Song (15)</td>
<td>Tetracycline [2gm dx7d]</td>
<td>11 [0.41 (0.22, 0.77)]</td>
<td>34 hrs [3.0 (1.27, 6.76)]*</td>
<td>3 [0]</td>
<td></td>
</tr>
<tr>
<td>Watt (16)</td>
<td>Rifampicin [600mg dx5d]</td>
<td>10 [0.47 (0.19, 0.96)]</td>
<td>22.5-27.5 hrs</td>
<td>0 [8.79 (0.44, 176.96)]</td>
<td></td>
</tr>
<tr>
<td>Kim (17)</td>
<td>Azithromycin [470mg single dose]</td>
<td>1 [1.33 (0.19, 0.80)]</td>
<td>21 hrs [8.0 (1.46, 1.46)]*</td>
<td>0 [Not estimable]</td>
<td></td>
</tr>
<tr>
<td>Kim (18)</td>
<td>Telithromycin [800mg dx5d]</td>
<td>1 [0.47 (0.24, 0.80)]</td>
<td>20.45 hrs [-2.16 (-8.34, 3.76)]*</td>
<td>0 [Not estimable]</td>
<td></td>
</tr>
</tbody>
</table>

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 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**


