ORIGINAL ARTICLE

Oral Azithromycin Vs Intravenous Ceftriaxone in the Treatment of Enteric Fever: A Systematic Review and Meta-Analysis

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Background: Typhoid fever, also known as enteric fever, is a severe systemic illness characterized by fever and gastrointestinal manifestations that commonly affects children and young adults. It is most prevalent in South-Central Asia, Southern Africa, and Southeast Asia. Alternative drugs for the treatment of enteric fever have been studied to decrease toxicity and increase compliance. Oral azithromycin has been proposed and is widely studied as a suitable treatment alternative.

Objective: The objective of this study is to compare oral azithromycin with intravenous ceftriaxone in the treatment of uncomplicated typhoid fever in terms of cure, duration of fever, relapse, and adverse events.

Methodology: A systematic review and meta-analysis were done with eligible studies taken from PUBMED, MEDLINE, and Cochrane Clinical Trial Registry. Six studies passed the eligibility criteria and were analyzed using Review Manager 5.3.

Results: Azithromycin showed comparable results with ceftriaxone in terms of cure, duration of fever and adverse events. However, azithromycin proved superior in decreasing relapse.

Conclusion: Azithromycin is comparable to ceftriaxone in the treatment of uncomplicated typhoid fever in terms of cure, duration of fever, and occurrence of adverse events. Azithromycin likewised had a lower incidence of relapse.

Recommendations: We recommend conducting local trials in pediatric patients, to compare azithromycin with standard antibiotic regimen for typhoid fever, to help update local recommendations and expand choices for antibiotic use.

KEYWORDS: *enteric fever, azithromycin, ceftriaxone*

INTRODUCTION

Enteric fever is a severe systemic illness characterized by fever and gastrointestinal manifestations[1,2]. The organism classically responsible for typhoid fever is *Salmonella enterica* serotype Typhi (formerly *S. typhi*), while *Salmonella paratyphi, Salmonella schotmuelleri,* or *Salmonella hirschfeldii* cause paratyphoid fever. The two diseases are sufficiently similar hence are known collectively as enteric fever[3]. Enteric fever is more common in children and young adults than in older patients[4]. Worldwide, enteric fever is most prevalent in impoverished areas that are overcrowded with poor access to sanitation. Incidence estimates suggest that South-central Asia, Southeast Asia, and Southern Africa are the regions with a high incidence of *Salmonella typhi* infection[5].

Enteric fever is usually treated with a single antibacterial drug. Antibiotic selection depends on the severity of illness, local resistance patterns, feasibility of oral medications, clinical setting, and available resources. The optimal drug and duration of therapy are uncertain[6]. Main options are fluoroquinolones, third generation cephalosporins, and azithromycin. For patients with severe systemic disease, initial therapy with a parenteral agent is started. Patients with uncomplicated disease on the other hand, are started on oral antibiotics. However, some antibiotics are contraindicated for use in pediatric patients. For example, fluoroquinolones are not recommended for use in children due to toxicities such as bone marrow depression[7]. Differences in treatment regimens may vary per country due to unique resistance rates. For example, quinolone resistance have been noted in other countries, hence their antibiotic agent of choice is azithromycin[8]. Emergence of multiple drug-resistant strains seen in various countries such as India have shifted their choice of antibiotics to either azithromycin or ceftriaxone[9].

Locally, the Antimicrobial Resistance Surveillance Program (ARSP) of the Department of Health (DOH) reported that the resistance rates for typhoidal *Salmonella* to first-line drugs amoxicillin, ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole are low[10]. The DOH recommends the following first line drugs for uncomplicated typhoid fever: amoxicillin, ampicillin, chloramphenicol, or trimethoprim-sulfamethoxazole. Second line drugs are cefixime, ciprofloxacin, or azithromycin[11]. Most of these drugs are given in two to four doses per day for seven to fourteen days, except for azithromycin which is given once a day.

Azithromycin once a day for 5 days, although a second line agent, has certain advantages. These include ease of administration as it is given orally, once daily dosing, and shorter duration of treatment. This led to studies exploring azithromycin as an alternative drug in the treatment of uncomplicated typhoid fever when limitations with first line agents are encountered.

This study aimed to investigate the efficacy of oral azithromycin against parenteral ceftriaxone in the treatment of uncomplicated typhoid fever, and whether intravenous drugs may be replaced with oral azithromycin for the convenience and for better compliance among pediatric patients[12-21].

MATERIALS AND METHODS

Research Design

A systematic review and meta-analysis of studies that compared oral azithromycin with intravenous ceftriaxone for treatment of enteric fever was done. The authors followed the PRISMA statement guidelines during the preparation of this systematic review and meta-analysis and performed all steps in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[12].

Data Source

A systematic search of peer-reviewed studies was conducted in three databases – MEDLINE, EMBASE and CENTRAL – from their initiation date to October 2018. Three groups of search terms were used: (1) azithromycin, (2) ceftriaxone, and (3) typhoid fever (or enteric fever). The search was conducted with no restriction by language or study design. The bibliographies of the studies were also searched for additional relevant records.

Eligibility Criteria

All studies which satisfied the following criteria were included: (1) Population: uncomplicated typhoid fever, enteric fever, paratyphoid fever; subjects aged 2 to 18 years (2) Intervention: oral azithromycin (3) Comparator: intravenous ceftriaxone (4) Outcomes: cure rate, relapse, duration of fever, and adverse effects and

(5) Study design: randomized controlled trials (RCTs) and observational studies.

The following were excluded: (1) in vitro and animal studies and (2) studies whose outcomes were not described in numerical form. Duplicates were removed prior to eligibility assessment. References were screened in two steps: the first step involved screening of titles/abstracts for matching with the inclusion criteria and the second step was screening the retrieved full-text articles for eligibility for meta-analysis.

Study Selection

Articles identified from the systematic search were exported to EndNote X9 (Thomas Reuters, 2018). Two review authors screened the title and abstract of the articles independently, and potentially relevant articles were obtained in full text and further assessed for eligibility based on the inclusion and exclusion criteria.

Data Extraction

Two independent authors extracted the relevant data from included studies. Disagreements were discussed and consensus among the reviewers was achieved. The extracted data included the following domains: (1) characters of study design 2) baseline characteristics of enrolled patients (3) risk of bias (ROB) and (4) outcomes in terms of cure, time to defervescence, relapse, and adverse events.

Risk of Bias Assessment

To assess the ROB in retrieved clinical trials, the Cochrane ROB assessment tool of the Cochrane Handbook for Systematic Reviews of Interventions was used. The bias domains were then plotted.

Statistical Analysis

The overall effect estimate was calculated as the odds ratio (with 95% CI) for dichotomous outcomes (clinical cure and relapse) and as the mean difference (95% CI) between the azithromycin and ceftriaxone groups for continuous outcomes (duration of fever). Random-effects meta-analysis was carried to pool the data, using the Mantel-Haenszel method for dichotomous outcomes, and the DerSimonian and Laird inverse-variance method for continuous outcome in Review Manager 5.3 (2011).

Ethical Considerations

The study is a research synthesis which focuses on empirical studies. It attempted to summarize and draw conclusions from statistical integration of data from separate similar published and unpublished studies that relate to the same or related research problem. No humans or animals participated in the present study. The study was presented to the Philippine Children's Medical Center Institutional Review Board and Ethics Committee and was approved.

RESULTS AND DISCUSSION

A total of 336 studies were screened from the title and abstract and 42 duplicates were removed. The remaining 294 studies were further screened. Six studies met the criteria for inclusion and subsequent data extraction. The six studies ([13,14,15,16,17,18]) included 520 patients. The risk of bias assessment of all six trials was generally low risk (Figure 1). All trials used adequate methods to randomly generate the allocation sequence and all included trials reported well-defined inclusion and exclusion criteria. However, due to the nature of administration of the drugs being studied and the subjective method of reporting symptoms as part of outcome assessment, there was no blinding, and this decreased the strength of the studies. Care must be taken when interpreting the data produced in this study.

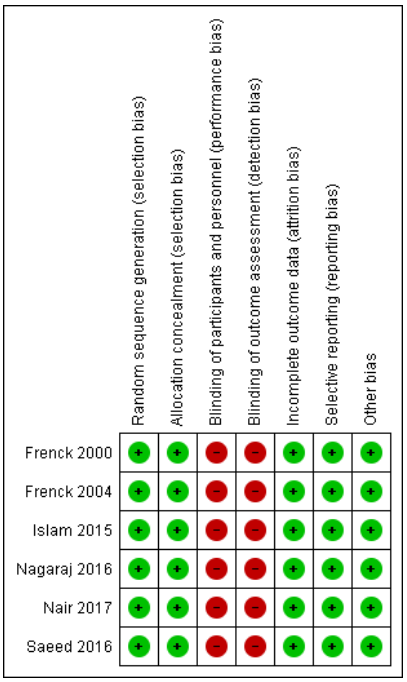

Figure 1. Risk of bias assessment

Criteria for enrolment in the included studies were patients presenting with signs and symptoms of uncomplicated typhoid fever with positive blood or stool culture for *S. typhi* or *S. paratyphi.* Dosage of azithromycin used in the studies ranged from 500 mg to 1 g per day (10-20 mg/kg/day) for five to seven days. Ceftriaxone was given at 75-100 mg/kg/day for the same duration as azithromycin.

Characteristics of Subjects

All studies included subjects who were children and adolescents with age range of 2 to 18 years. Mean age of patients was 7.01 years in the azithromycin-treated group and 6.73 years in ceftriaxone-treated group. The study population was comprised of 54% males and 46% females. A total of 259 patients were treated with azithromycin while 261 were treated with ceftriaxone (Table 1).

Table 1. Characteristics of the subjects included in the meta-analysis

Study ID	N		Mean age of patients (years)		Male/Female	
	Azithromycin	Ceftriaxone	Azithromycin	Ceftriaxone	Azithromycin	Ceftriaxone
Frenck, 2000	34	30	9.7	10.1	20/14	17/13
Frenck, 2004	32	36	3.6	3.35	19/13	20/16
Islam, 2015	50	48	6.64	6.65	Not reported	Not reported
Nagaraj, 2016	63	63	3.25	3.25	35/28	36/27
Saeed, 2016	50	50	7.47	6.68	27/23	27/23
Nair, 2017	30	34	11.4	10.4	14/16	14/20
Total	259	261	7.01	6.73	115/94	114/99

Outcome Measures

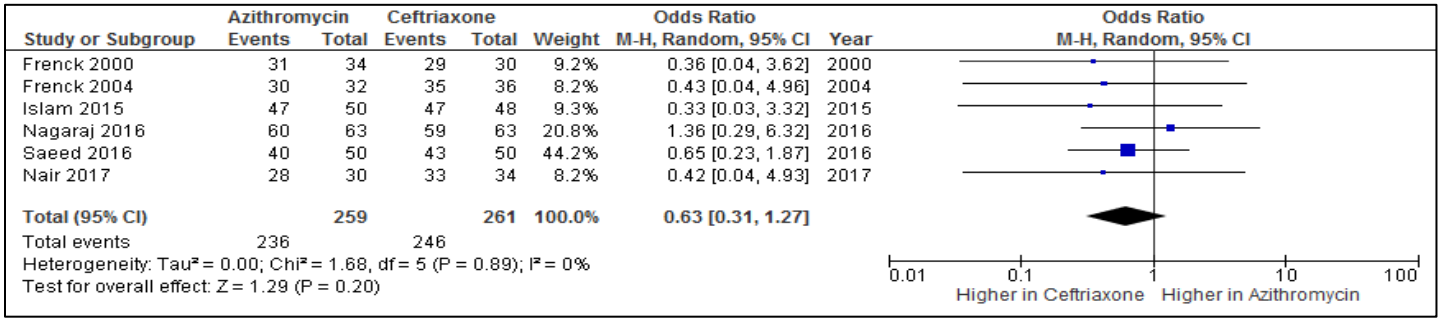

Figure 2. Forest plot for clinical cure after treatment of azithromycin versus ceftriaxone: (OR 0.63, 95% CI 0.31 to 1.27; p=0.20)

Clinical cure after treatment with azithromycin did not differ significantly from ceftriaxone (Figure 2). The pooled estimate shows that the odds of clinical cure is similar between the azithromycin and ceftriaxone group (OR 0.63, 95% CI 0.31 to 1.27; p=0.20). The level of heterogeneity is 0% (no heterogeneity).

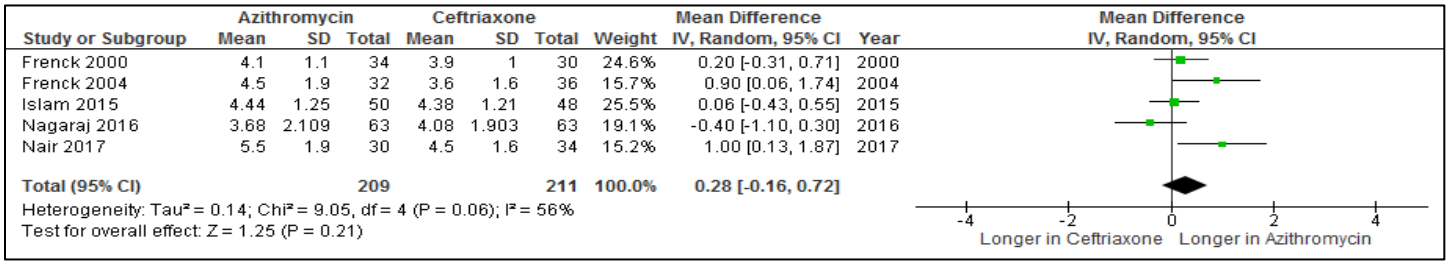

Figure 3. Forest plot for duration of fever after treatment of azithromycin versus ceftriaxone: (95% CI -0.16 to 0.72, p=0.21)

Duration of fever is the same between the azithromycin and ceftriaxone group (Figure 3). The pooled mean difference is 0.28 days (95% CI -0.16 to 0.72, p=0.21). The level of heterogeneity is 56% (moderate to substantial).

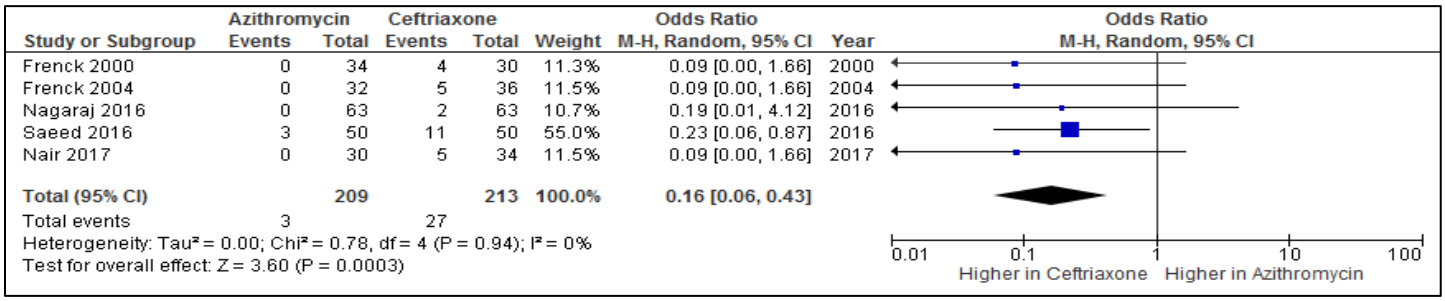

Figure 4. Forest plot for relapse after treatment of azithromycin versus ceftriaxone: (OR 0.16, 95% CI 0.06 to 0.43; p=0.0003)

There is a significantly lower incidence of relapse after treatment with azithromycin compared with ceftriaxone (Figure 4). The pooled estimate shows that the odds of relapse is 6.25 times more likely in the ceftriaxone group compared to the azithromycin group (OR 6.25, 95% CI 2.33 to 16.67, p=0.0003). The level of heterogeneity is 0% (no heterogeneity).

There were no serious adverse events reported in any of the trials. The most common adverse events reported in both treatment groups were diarrhea and vomiting (Table 2). However, these were not severe to warrant change in management. One study also concluded that it is likely that many of the gastrointestinal events were associated with typhoid fever and not with treatment[14]. Subjects with laboratory evidence of adverse events were asymptomatic and intervention was not needed[13,14]. All adverse events were self-limiting.

Table 2. List of adverse events in both treatment arms

Study ID	Clinical Adverse Event		Laboratory Adverse Event	
	Azithromycin	Ceftriaxone	Azithromycin	Ceftriaxone
Frenck, 2000	Not described	Pain on injection site (1)	Thrombocytosis (4) AST elevation (2) ALT elevation (1)	Thrombocytosis (3) AST elevation (4) ALT elevation (1)
Frenck, 2004	Vomiting (11) Diarrhea (10) Nausea (5) Abdominal pain (5) Anorexia (3) Cough (3)	Vomiting (7) Diarrhea (15) Nausea (7) Abdominal pain (5) Anorexia (6) Cough (2)	Thrombocytosis (7) AST elevation (2) ALT elevation (2)	Thrombocytosis (7) AST elevation (2) ALT elevation (5)
Islam, 2015	Not described	Not described	Not described	Not described
Nagaraj, 2016	Not described	Not described	Not described	Not described
Saeed, 2016	Not described	Not described	Not described	Not described
Nair, 2017	Vomiting (6) Diarrhea (8)	Vomiting (5) Diarrhea (12)	Not described	Not described

DISCUSSION

In other countries, alternative drugs for the treatment of enteric fever were explored due to emergence of drug-resistant strains of *Salmonella.* An orally administered drug was explored and given to patients without the risk of intravenous injections such as pain or infection. Local guidelines include oral antibiotics that are given over multiple doses with a longer duration as opposed to azithromycin. Azithromycin is a potentially useful drug in the treatment

of typhoid fever because of its high intracellular tissue penetration and long elimination half-life (72 h)[19]. This meta-analysis addresses the available evidence on the efficacy and safety of azithromycin in treating enteric fever in comparison to ceftriaxone.

Clinical cure and duration of fever was comparable for azithromycin and ceftriaxone. However, relapse was significantly lower in the subjects treated with azithromycin compared to those given ceftriaxone. Compared to ceftriaxone, azithromycin has a longer half-life and a high intracellular tissue penetration, leading to eradication of residual organisms even after completion of therapy. Azithromycin is also found to have a higher concentration in the biliary tract, which contributes further to these findings[13]. No serious adverse events were seen in both treatment arms. Most adverse events were gastrointestinal in nature, and these are not severe enough to warrant alteration of treatment. Laboratory abnormalities like elevation in liver enzymes and platelet counts (thrombocytosis) were also clinically insignificant.

In the National Antibiotic Guidelines of the Philippine DOH, in the treatment of typhoid fever, azithromycin is indicated as a second-line therapy[11]. In this meta-analysis, azithromycin has been shown to be a safe and effective drug, further expanding possible treatment choices for enteric fever when limitations with first line agents are encountered.

Aside from antibiotic treatment, efforts of the World Health Organization (WHO), UNICEF, and various national and international agencies have also focused on the prevention of typhoid and other water-borne illnesses[20]. These include boosting vaccination, water, sanitation, and hygiene programs to improve water quality and public health practices. Typhoid fever incidence rates and trends decreased proportionally with the successful implementation of public health measures.

CONCLUSION

Evidence from this meta-analysis shows that oral azithromycin is comparable with intravenous ceftriaxone for treatment of uncomplicated typhoid fever in terms of cure, duration of fever, and adverse events. However, it appears to be better than ceftriaxone in terms of preventing relapse. This latest evidence agrees with the findings of previous meta-analyses comparing azithromycin with other alternative treatments[19.21]. Adverse events are also mild and self-limiting in both treatment regimens and are not clinically significant. Azithromycin can be recommended as an alternative therapeutic option in the local setting when adverse events with first line agents are encountered.

However, because of the small number of trials eligible for this meta-analysis and the wide confidence intervals, further evidence is needed to give a strong recommendation for the preferential use of azithromycin over standard antibiotic regimens. We recommend conducting trials for pediatric patients locally, to compare azithromycin with standard antibiotic regimen for typhoid fever.

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