# To Study the Effectiveness of Oral Azithromycin as Compared to Parenteral Ceftriaxone in the Treatment of Uncomplicated Enteric Fever

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## Abstract

**Aim** This study aims to compare the effectiveness of oral azithromycin and intravenous ceftriaxone in the treatment of uncomplicated enteric fever in children aged between 2 and 12 years.

**Methods** This prospective randomized open-labeled study was conducted in the Department of Pediatrics in a medical college of South India. A total of 126 children with proven enteric fever were randomized into two treatment groups. One group received oral azithromycin (20 mg/kg/d) and the other group received parenteral ceftriaxone (75 mg/kg/d), both of which were given for a duration of 7 days. The study population was observed for fever defervescence, duration of hospital stay, and relapse.

**Results** The mean time for fever defervescence was 3.68 ± 2.109 and 4.08 ± 1.903 days in the azithromycin group and the ceftriaxone group, respectively. The mean duration of hospital stay was 7.35 ± 2.604 days in the azithromycin group and 9.44 ± 0.249 days in the ceftriaxone group. In the azithromycin group three children had treatment failure and had to crossover to ceftriaxone group. Among the four treatment failures in the ceftriaxone group, two cases relapsed within 4-week follow-up period. There was no relapse in the azithromycin group.

**Conclusion** Oral azithromycin is as effective as intravenous ceftriaxone in treating uncomplicated typhoid fever in children with respect to fever defervescence, duration of hospital stay, and relapse.

**Keywords**
- randomized
- enteric fever
- azithromycin
- ceftriaxone

## Introduction

Typhoid fever accounts for significant morbidity among children in our country. Financial constraints are encountered, not only by the expenses of hospital admission for intravenous (IV) antibiotics but also by the loss of wages of working parents. The recent upsurge in multidrug-resistant *Salmonella typhi* (MDRST) and nalidixic acid-resistant *S. typhi* (NARST) is a rising concern to the managing physician and has prompted further clinical trials to search for newer drugs.

With the increasing development of nalidixic acid (quinolone) resistance among *S. typhi*, third generation cephalosporins are being used in the management of MDRST. Intravenous ceftriaxone administration is associated with high cost, prolonged hospitalization, and morbidity due to IV drug use.[1–3]

Recently, several isolated reports of resistance to ceftriaxone have been reported from different parts of the world and India. In view of emergence of MDRST and NARST, several studies are being performed worldwide to study the clinical,

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epidemiological, and treatment aspects of MDRST and NARST, thereby beginning the quest for newer drugs.[2–4]

An exclusive pediatric study from India, comparing the outcomes of ceftriaxone and azithromycin are very few. Our institution caters to the care of children from industrial sectors and the standard of care for enteric fever at the time of the study was IV ceftriaxone, requiring on an average 10 days of hospitalization. This was translating to huge wage loss for working parents. So this study was undertaken in an attempt to find effective oral drugs to treat enteric fever to overcome the financial loss for parents.

This study aims to compare the effectiveness of oral azithromycin and IV ceftriaxone in the treatment of uncomplicated enteric fever in children aged between 2 and 12 years.

## Methods

This prospective, randomized open-labeled study was conducted in the Department of Pediatrics in a Government Medical College of south India between July 2013 and August 2014, after obtaining institutional ethical committee clearance. The study population comprised of 126 pediatric inpatients between 2 and 12 years of age with proven typhoid fever.

Children with fever and blood culture positive for *S. typhi* and paratyphi A and B and or positive Widal test, or rising titers of O and H antigens with clinical course suggestive of enteric fever, were included in the study. Those with complications (jaundice, severe gastrointestinal bleeding, myocarditis, intestinal perforation, renal failure, pneumonia, an altered level of consciousness or shock, etc.), or hypersensitivity to either of the drugs, or mixed infections, or lack of parental consent, were excluded from the study.

The children were divided into two groups by block sampling using lots. Children under the ceftriaxone group were administered injection ceftriaxone 75 mg/kg/d twice a day for 7 days. Those under the azithromycin group received azithromycin suspension or tablet 20 mg/kg/d as a single dose for 7 days. Clinical examination of all children was done twice a day and vitals and temperature charting was done every 4 hours. The effectiveness of the treatment was assessed by the time taken for fever clearance in hours starting from the hour the drug was started. Comparison of the effectiveness was also done in terms of duration of hospital stay and occurrence of relapse.

When there was a failure to respond to either drug by 7 days as evidenced by persistence of fever, it was considered as treatment failure. Treatment failure in azithromycin arm crossed over to the ceftriaxone group and was treated with ceftriaxone till 24 to 48 hours after defervescence. Children who failed to respond to ceftriaxone were considered as treatment failure and were started on alternate drugs.

All the children in both the groups were reviewed at 30 days and stool culture was done. Children who had a recurrence of fever were again investigated for typhoid fever and if the culture was positive were considered to have a relapse.

Statistical methods were applied to quantitative data and qualitative data. Quantitative data were presented by *N*, mean, standard deviation, and range. For qualitative data, frequency count *N* and percentage were tabulated in tables. To analyze the data, appropriate statistical tests were applied. To compare the difference between two means, independent *t*-test was used.

All the statistical analyses had been done by using statistical software SPSS (version 16.0, IBM Corp., Armonk, New York, United States).

## Result

Among the 126 participants enrolled in the study, the mean age was 6.98 ± 3.25 years. Overall, 56% ($n = 71$) of the total children were boys and 43.6% ($n = 55$) were girls. The mean duration of fever among all children, at the time of admission was 7.66 ± 3.39 days, with 5.6% ($n = 7$) presenting within 3 days of fever onset, 56.3% ($n = 71$) between 3 and 7 days, and 38% of the cases presented with fever lasting for more than 7 days. It was predominantly intermittent type of fever, being associated with chills and rigors in 44.44% ($n = 56$) of the cases.

Out of 126 children enrolled, 101 were blood culture positive with or without Widal positivity. Among the culture-positive cases, 96% cases in both groups grew *S. typhi* and remaining 4% grew *Salmonella paratyphi*. In the azithromycin group, 24 children were only blood culture positive, 25 were both blood culture and Widal positive, while 14 cases were only Widal positive enteric fever. Similarly, in the ceftriaxone group, 21 cases were only blood culture positive, 31 were both blood culture and Widal positive, and 11 of them had only Widal positivity.

Resistance to nalidixic acid was seen in 42.8% ($n = 21$) of cases in the azithromycin group and 11.5% ($n = 6$) cases in the ceftriaxone group. Multidrug-resistant *S. typhi* was grown in 6% ($n = 3$) cases in the azithromycin group and in 5.8% ($n = 3$) cases in the ceftriaxone group. Ceftriaxone resistance was observed in 18.4% ($n = 9$) cases in the azithromycin group and in 7.7% ($n = 4$) cases in the ceftriaxone group (►**Table 1**).

History of treatment with antibiotics was observed in 27% of total cases ($n = 34$), 32% ($n = 20$) of cases in the ceftriaxone group, and 22% ($n = 14$) of cases in the azithromycin group. The antibiotics used were either oral cephalosporins or fluoroquinolones.

The mean fever clearance time in the azithromycin group was 3.68 ± 2.109 days (standard error [SE]: 0.266 and 95% confidence interval [CI]: [3.148,4.212]) and in the ceftriaxone group was 4.08 ± 1.903 days (SE: 0.24 and 95% CI: [3.60,4.56]). The *p* value obtained on comparing the two groups with respect to fever clearance is 0.27.

**Table 1** Drug sensitivity and resistance pattern

| Drug resistance | Azithromycin | | Ceftriaxone | |
|---|---|---|---|---|
| | *N* | % | *N* | % |
| Nalidixic acid-resistant *Salmonella typhi* | 21 | 42.8 | 6 | 11.5 |
| Multidrug-resistant *Salmonella typhi* | 3 | 6 | 3 | 5.8 |
| Ceftriaxone-resistant *Salmonella typhi* | 9 | 18.4 | 4 | 7.7 |

**Table 2** Independent *t*-test for outcome measures

| Equal variances assumed | Levene test for equality of variances | | *t*-Test for equality of means | | | | | 95% Confidence interval of the difference | |
|---|---|---|---|---|---|---|---|---|---|
| | *F*-test value | *p* Value | *t*-Test value | df | *p* Value | Mean difference | Standard error difference | Lower | Upper |
| Defervescence | 0.798 | 0.373 (NS) | −1.109 | 124 | 0.27 (NS) | −0.397 | 0.358 | −1.105 | 0.312 |
| Duration of hospital stay | 1.26 | 0.264 (NS) | −5.09 | 124 | 0.0001[a] | −2.095 | 0.412 | −2.91 | −1.28 |
| Duration at diagnosis | 1.879 | 0.173 (NS) | 0 | 124 | 1 (NS) | 0 | 0.233 | −0.462 | 0.462 |
| Relapse | 1.022 | 0.314 (NS) | −1.075 | 124 | 0.285 (NS) | −0.079 | 0.074 | −0.226 | 0.067 |

Abbreviation: NS, nonsignificant.

About 4.8% ($n = 3$) cases in the azithromycin group failed to respond to the drug by 7 days and hence crossed over to the ceftriaxone group. In the ceftriaxone group 6.3% ($n = 4$) cases had treatment failure. The mean duration of hospital stay in the azithromycin group was 7.35 ± 2.604 days (SE: 0.328) and in the ceftriaxone group was 9.44 ± 0.249 days (SE: 0.249). The *p* value obtained on comparing the two groups with respect to the duration of hospital stay was 0.0001 which is highly significant (►**Table 2**).

During 30-day follow-up, 3.2% ($n = 2$) cases in the ceftriaxone group had relapsed but there was no relapse in the azithromycin group. The *p* value obtained on comparing both the groups with respect to relapse is 0.285 which is statistically insignificant (►**Fig. 1**).

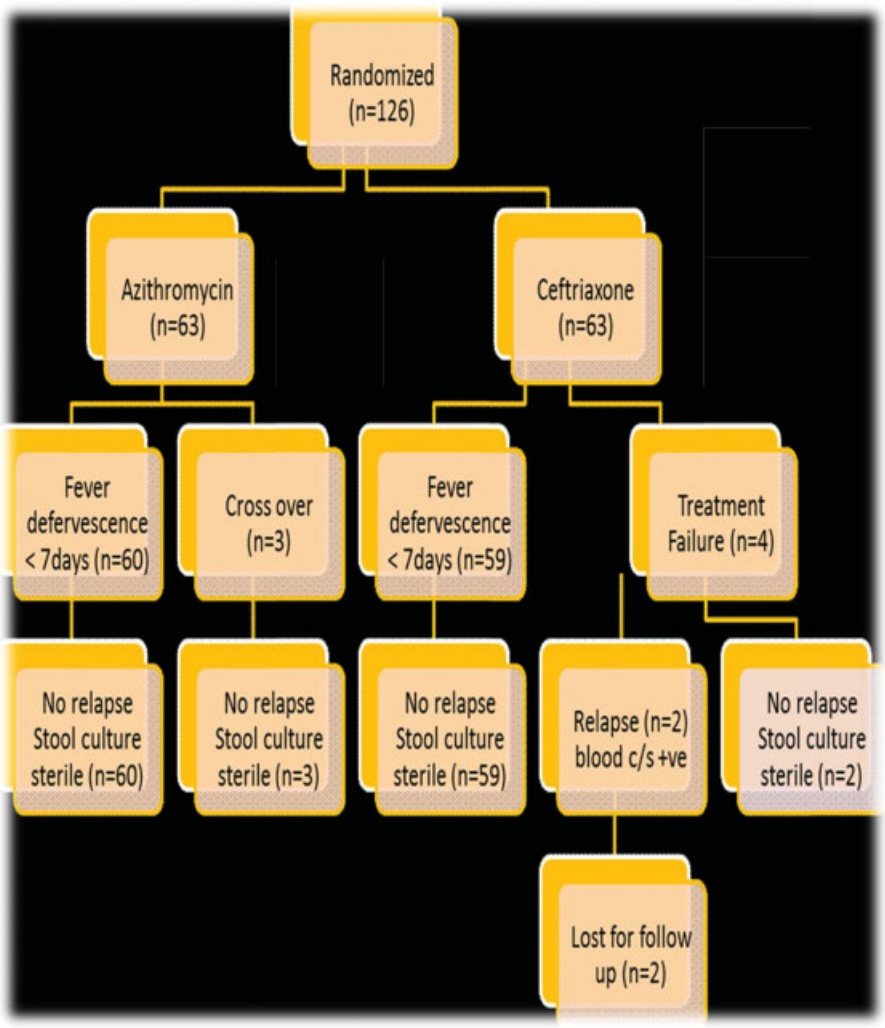


**Fig. 1** Flowchart of treatment and its outcome.

## Discussion

In our study, a comparison of the relative efficacy of azithromycin and ceftriaxone was done in terms of fever defervescence, duration of hospital stay, and relapse.

The earlier fever defervescence seen with azithromycin marks its potential as a promising oral alternative. This inference though statistically not significant (►**Table 2**), because of the small number, paves the way for larger studies in future. The difference in defervescence pattern with the use of both the drugs in our study is, however, contrary to that observed by Frenck et al[5] wherein they had observed early defervescence with ceftriaxone rather than with azithromycin (►**Table 3**). The emerging resistance over the past 10 years has probably caused the change in fever defervescence pattern with the usage of both the drugs. Gupta et al[6] had noted a fever clearance time of 4.3 days with ceftriaxone. In other noncomparative studies where only azithromycin was used, such as those done by Aggarwal et al[7] and Hussain et al,[8] the mean duration of defervescence was 3.45 ± 1.97 and 4 days, respectively. These observations concurred with our findings.

The *p* value obtained on comparing the two groups with respect to the duration of hospital stay was 0.0001 which was highly significant (►**Table 2**). Thus with the use of azithromycin, there is a convenience of early discharge soon after fever and toxemia clears as the course can be completed even at home. In nontoxic cases, azithromycin can be used on outpatient basis thus making it a better alternative.

In enteric fever, there always remains a potential risk of relapse following even effective treatment. About 3.2% ($n = 2$) cases treated with ceftriaxone relapsed within 4 weeks of treatment, which was lesser when compared with that observed by Bhutta,[9] Parry et al,[10] and Dutta et al[11] (5–10%) and Frenck et al[5] (19%) in their studies. Azithromycin group did not have any relapse, which was similar to that seen in studies by Frenck et al,[5] Aggarwal et al,[7] and Hussain et al.[8] Use of azithromycin seems to confer some protection against relapses which can be considered as a definite advantage. Out of the four cases of treatment failure in the ceftriaxone group, two cases had relapsed. The dreaded complication of asymptomatic carrier state following enteric fever is more of adult concern and children are sort of protected from this state. This is also seen in our study wherein none of the children in both the groups had a positive fecal culture during the 4-week follow-up, which was similar to the observation made by Frenck et al,[5] Girgis et al,[12] and Chandey et al,[13] but contrary to that observed by Hussain et al[8] wherein a relapse rate of 5.33% was reported.

On analyzing the drug resistance pattern, it was interesting to know that though MDRST formed a small proportion (►**Table 1**), ceftriaxone resistance is seen in quite a few. The majority of ceftriaxone resistance was seen in the azithromycin group but two out of the four in the ceftriaxone group had relapsed. The emerging ceftriaxone resistance is worrying and needs to be tackled fast. After the study in our Institution, we have changed the antibiotic policy which precludes the use of ceftriaxone in any patients other than complicated enteric fever without getting the approval of our microbiologist.

**Table 3** Fever clearance time (d)

| Study group | Ceftriaxone | Azithromycin |
|---|---|---|
| Frenck et al (2004)[5] | 3.6 ± 1.6 | 4.5 ± 1.9 |
| Gupta et al[6] | 4.3 | |
| Aggarwal et al (2010)[7] | | 3.45 ± 1.97 |
| Hussain et al (2011)[8] | | 4 |
| Parry et al (2007)[10] | | 5.8 ± 0.7 |
| Chandey et al (2012)[13] | | 3.65 |
| Girgis et al (1999)[12] | | 3.8 ± 1.1 |
| Our study | 4.08 ± 1.903 | 3.68 ± 2.109 |

## Conclusion

Oral azithromycin is as effective as IV ceftriaxone in treating typhoid fever. Though the time taken for fever clearance was not statistically significant between the two treatment groups, azithromycin has a slightly earlier fever clearance than ceftriaxone with no relapse.

Being an oral drug, it does significantly reduce the duration of hospitalization, thereby reducing the loss of working days for the child's parents and finally reducing the socioeconomic burden to some extent.

In view of emerging ceftriaxone resistance, rational antibiotic policy should restrict the irrational use of ceftriaxone.

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