

# Clinical Efficacy of Azithromycin Versus Ciprofloxacin in Treatment of Typhoid Fever in Children

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## ABSTRACT

**Objective:** To compare the clinical efficacy of Azithromycin with ciprofloxacin in treatment of typhoid fever in children.

**Methodology:** After permission from hospital ethical committee (letter attached) and informed written consent taken from attendants of patients of inclusion criteria, data was collected on data collection Performa. Patients fulfilling the criteria were admitted in Paediatric Department, Dar-ul-sehat hospital, Faisalabad. Patients were divided by lottery method into two groups A and B. Group A was given ciprofloxacin 15mg/kg/dose BD orally for 7 days. Group B was given azithromycin 10mg/kg/dose OD orally for 7 days. Both groups were kept under close observation for 7 days. Monitoring of patient during stay was done by researcher. The cost of medicine was beard by hospital.

**Results:** In our study, 65%(n=65) in Cipro group and 52%(n=52) in Azithro group were between 3-8 years of age while 35%(n=35) in Cipro group and 48%(n=48) in Azithro group were between 9-14 years of age, mean+sd was calculated as 7.07+3.25 and 8.27+3.03 years respectively, 48%(n=48) in Cipro group and 55%(n=55) in Azithro group were male while 52%(n=52) in Cipro group and 45%(n=45) in Azithro group were females. Comparison of efficacy of oral azithromycin versus Ciprofloxacin in children with enteric fever shows that 72%(n=72) in Cipro group and 85%(n=85) in Azithro group were treated effectively, p value was calculated as 0.02 showing a significant difference.

**Conclusion:** We concluded that the clinical efficacy of Azithromycin is significantly higher when compared with ciprofloxacin in treatment of typhoid fever in children.

**Keywords:** Children, Typhoid fever, treatment, Azithromycin, ciprofloxacin.

## INTRODUCTION

Salmonella Typhi, one of the most common bacteria that can cause infection in humans and the causative agent of typhoid fever, is one of the most common bacteria that can be found anywhere in the globe.<sup>1</sup> Mean age of occurrence is 5-19 year all over the world, however in certain areas it is common below five years age group.<sup>2</sup> It is mainly transmitted by faeco-oral route. Important initial symptoms are nausea, fever, malaise anorexia, pain in abdomen, headache. Among all 5-15% get complications.<sup>2</sup>

Typhoid fever affects more than 20 million people each year, killing more than 2 lakh people annually.<sup>3</sup> In 2006, WHO estimated case fatality rate between 1.5-3.8%. South Asia has 80% of the global cases and since 1996-2005, incidence of typhoid fever in south Asia is 110 cases/100,000 population. So South Asia is considered to be on the top of acquisition of typhoid fever. Typhoid fever affects around 21 million people each year, killing over 210,000 patients.<sup>4</sup>

Salmonella enterica serovar is the causative agent of multidrug-resistant typhoid fever, which is resistant to first-line therapeutic drugs.<sup>5</sup> Infected children under the age of five are particularly vulnerable to the transmission of this strain, which leads to an increase in both morbidity and mortality.<sup>5</sup> From this time fluoroquinolones (ciprofloxacin, ofloxacin) and nalidixic acid became the treatment of choice for typhoid fever.<sup>6</sup> This extensive antibiotic usage resulted in selection of single point mutation in DNA Gyrase A of S.Typhi, causing resistance to nalidixic acid and decreased susceptibility to fluoroquinolones.<sup>7</sup> This resistance resulted in poor clinical response with ofloxacin and ciprofloxacin (fluoroquinolones) also proved by accumulated data.<sup>8,9</sup> According to current WHO recommendation third generation cephalosporins (cefotaxime, ceftriaxone), macrolides (azithromycin) and fluoroquinolones (ciprofloxacin, ofloxacin) can be used in treatment of typhoid fever.<sup>10</sup>

Azithromycin, an azalid antibiotic has excellent clinical response in treatment of multidrug resistant typhoid fever.<sup>9</sup> Due to controversy in literature and non-conductance of study in last 5 years in Lahore (as resistance against antibiotics changes day by day), my aim of study is to compare the clinical efficacy of azithromycin and ciprofloxacin in local population, because there is

some debate about which antibiotic is more effective and there hasn't been a study done in the past five years (despite the fact that antibiotic resistance is constantly evolving).

## METHODOLOGY

In this study, 120 children (60 in each group) of both genders between 3-14 years of age having typhoid fever presenting within first four weeks of fever were selected for study whereas those having fever other than typhoid fever or having current history of oral or intravenous antibiotics were excluded from this trial. Any patient with isolation of the bacteria through culture of the bone marrow aspirate or from any one of the following: blood, stool, or urine was taken as a case of typhoid fever. After permission from hospital ethical committee and informed written consent taken from attendants of patients of inclusion criteria, data was collected on data collection Performa. Patients fulfilling the criteria were admitted in Paediatric department, Dar-ul-sehat hospital, Faisalabad. Patients were divided by lottery method into two groups A and B. Cipro group was given ciprofloxacin 15mg/kg/dose BD orally for 7 days. Group B was given azithromycin 10mg/kg/dose OD orally for 7 days. Both groups were kept under close observation for 7 days. Monitoring of patient during stay was done by researcher. The cost of medicine was beard by hospital. Efficacy was labeled as "Improvement in symptoms of typhoid fever and three consecutive readings of temperature below 99F taken 8 hourly within 7 days of treatment". CBC, CRP, and ESR was done for all patients. Both groups were compared for efficacy and P value less than 0.05 was considered significant. Chi square test was used to compare the frequency of efficacy in both groups.

## RESULTS

Age distribution showed that 65%(n=65) in Cipro group and 52%(n=52) in Azithro group were of 3-8 years and 35% (n=35) in Cipro group and 48% (n=48) in Azithro group of 9-14 years. Mean Age was 7.07+3.25 and 8.27+3.03 years respectively.

Patients were distributed equally according to gender in each group.

Comparison of efficacy of oral azithromycin versus Ciprofloxacin in children with enteric fever shows that 72%(n=72) in Cipro group and 85%(n=85) in Azithro group were treated effectively while 28%(n=28) in Cipro group and 15%(n=15) in Azithro group were not treated effectively, p value was calculated as 0.02 showing a significant difference. (Table No. 1)

Table 1: Comparison Of Efficacy Of Oral Azithromycin Versus Ciprofloxacin In Children With Enteric Fever (n=120)

Efficacy	Cipro group (n=60)		Azithro group (n=60)	
	No. of patients	%	No. of patients	%
Yes	72	72	85	85
No	28	28	15	15
Total	100	100	100	100

P value:0.02

## DISCUSSION

Typhoid fever is prevalent and sometimes fatal in children characterized by bacteremia and inflammatory damage of the gut. Since 70s, chloramphenicol was preferred in the typhoid treatment but MDR Salmonella typhi has required the quest for alternate therapeutic options. The cumulative prevalence of Multiple Drug-Resistant Salmonella typhi was shown to be 67.2%. Only 32.8% of Salmonella typhi isolates were sensitive to chloramphenicol and amoxicillin.<sup>69</sup> The fact that the minimum inhibitory concentration (MIC) of azithromycin against S. typhi ranges from 4 to 16 g/ml in vitro suggests that the antibiotic is of limited use in the treatment of typhoid fever.

According to a study in clinical research unit of Oxford University Chi Minn City Vietnam, the clinical cure rate in terms of resolution of fever was 82% with only azithromycin and 64% with ofloxacin. The resistance strains are better treated with 7 days course of azithromycin.<sup>11</sup> A study conducted in Shoukat Khanum Hospital in May 2011 to determine the mean inhibitory concentration of salmonella typhi and paratyphi with azithromycin also suggests that azithromycin can be effectively used for treatment of typhoid fever. Salmonella Typhi and Paratyphi A and C isolates had a mean inhibitory concentration (MIC) of azithromycin that indicates it could be utilised for therapeutic purposes.<sup>12</sup> A study conducted in 2009 suggests that fluoroquinolones (ciprofloxacin, ofloxacin) and azithromycin are almost equal in clinical efficacy in treatment of typhoid fever.<sup>6</sup> However a study conducted in 2011 suggests that fluoroquinolones are found to be superior than other recent antibiotics (azithromycin, cephalosporins).<sup>13</sup>

Oxford University Chi Minn City Vietnam's clinical research unit conducted a similar trial, and the clinical cure rate in terms of fever reduction was 82% with azithromycin, and 64% with ofloxacin. A 7-day regimen of azithromycin is the most effective treatment for resistant bacteria.<sup>11</sup> Also in May 2011, researchers at Shoukat Khanum Hospital found that azithromycin was efficient in treating typhoid fever by determining the mean inhibitory concentrations of salmonella typhi and paratyphi with the antibiotic. It was shown by the minimum inhibitory concentration (MIC) of Salmonella Typhi, Paratyphi A and Paratyphi C when they were exposed to azithromycin that it may have promise for use in therapeutic settings.<sup>12</sup> According to the findings of a study that was carried out in 2009, the clinical efficacy of fluoroquinolones (such as ciprofloxacin and ofloxacin) and azithromycin in the treatment of typhoid fever is practically same.<sup>6</sup>

NA Trivedi and others<sup>14</sup> intended to evaluate the quality of the evidence that supports the preference of azithromycin for the treatment of uncomplicated typhoid fever over the other medicines. They discovered that azithromycin has a relative risk (RR) of 0.46 for lowering the likelihood of cystic fibrosis, while ceftriaxone had an RR of 0.1 for considerably lowering the likelihood of recurrence. They came to the conclusion that azithromycin can be suggested as a second-line therapy in MDR typhoid fever. However, in order to arrive at a definitive result, major trials encompassing paediatric age group patients are needed to be conducted. They reached to

the conclusion that azithromycin can be recommended because there were no reports of major side effects in any of the trials.

Oral azithromycin was found to be as effective as nalidixic acid in treating Shigella gastroenteritis in children by Miron et al.<sup>15</sup> Nalidixic acid (55 mg/kg/day) was initially given to all 61 children in the study, but 25 had their azithromycin (10 mg/kg/day) dose increased due to persistent diarrhoea. Compared to the nalidixic acid-only group, all azithromycin-treated patients had their diarrhoea under control within 48 hours of starting treatment.

The treatment response to ciprofloxacin was very similar to that which was discovered in field testing with bacteria that were entirely responsive. According to studies<sup>16</sup> and<sup>17</sup> fluoroquinolone-resistant S. typhi strains are susceptible to treatment with short-course therapy<sup>16</sup> and<sup>17</sup> respectively.

It is evident that intra- and extracellular ciprofloxacin concentrations are consistently higher than the MIC following therapy with 500mg of ciprofloxacin twice daily. A 500 mg dose of ciprofloxacin given two times daily resulted in intracellular quantities of ciprofloxacin exceeding MIC, as macrophages are known to accumulate the drug 5-fold.<sup>18</sup> Ciprofloxacin, on the other hand, appears to target both intra- and extra cellular populations when taken at typical clinical levels. During an acute case of typhoid fever, it is believed that approximately forty percent of the S. Typhi bacilli reside in the extracellular compartment.<sup>19</sup> In light of these findings, we hypothesize that azithromycin has a lower systemic plasma concentration than ciprofloxacin, which results in little to no clearance of extracellular bacteria, which prolongs the duration of bacteremia and fever clearance time.

According to the findings of some studies, prolonged bacteremia is linked to clinical deterioration as well as treatment failure.<sup>20</sup> These findings lend credence to the contention that rapid bacterial clearance is necessary to shorten the amount of time needed for fever to clear up and to improve clinical recovery. On the other hand, normal responses to azithromycin treatment can include a prolonged reduction in fever and bacteremia. An apparent lack of progress could encourage specialists to increase the dosage or try a different therapy, which would disrupt the treatment course and eventually make it last longer. Patients should receive sufficient counselling regarding the expected length of recovery time in order to reduce the likelihood that they will not comply with therapy.

However, in light of our results and other studies, the hypothesis of our study that "there is difference in clinical efficacy of azithromycin and ciprofloxacin in treatment of typhoid fever in children" is justified.

## CONCLUSION

We concluded that the clinical efficacy of Azithromycin is significantly higher when compared with ciprofloxacin in treatment of typhoid fever in children.

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