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Research Article

**COMPARISON OF EFFICACY OF AZITHROMYCIN AND
CEFTRIAXONE IN MANAGEMENT OF ENTERIC FEVER IN
CHILDREN**¹Dr. Abdul rehman, ²Dr. Sarmad Nasir, ³Dr. Ayesha Zahoor¹Nishtar Medical College Multan, Pakistan, ²Independent Medical College Faisalabad, Pakistan,³Yusra Medical and Dental College (SZABU), Pakistan.**Article Received:** March 2019**Accepted:** April 2019**Published:** May 2019**Abstract:**

Study was conducted on 108 children who were suffering from uncomplicated enteric fever. The drug efficacy of azithromycin and ceftriaxone was compared. These drugs were advised in following doses, azithromycin at the dose of 10mg/kg/day with maximum dose of 500mg/day and ceftriaxone was given at the dose of 75mg/kg/day and maximum dose of 2.5g/day. 64 patients from the collected sample were detected pre-treatment culture positive for *Salmonella typhi*. out of 64, 31 were prescribed azithromycin while 29 were prescribed ceftriaxone. The response to both these drugs was significant. No life threatening or clinically significant side effect was observed in any case. Patients who were prescribed ceftriaxone, four of them presented again with relapse. Azithromycin had effective response against *salmonella typhi* and it can be used for the cue of enteric fever in developing countries.

Keywords: *Salmonella typhi*, enteric fever, azithromycin, ceftriaxone, response, relapse.**Corresponding author:****Dr. Abdul rehman,**

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INTRODUCTION:

Enteric fever is caused by a gram negative bacteria *salmonella typhi* and *salmonella paratyphi*. Disease symptoms include fever high grade continuous or step ladder pattern associated with rigors and chills, headache, abdominal pain, loss of appetite, change in normal bowel habits, on examination there is toxic look, coated tongue, hepatomegaly, splenomegaly, dehydration, signs of shock, jaundice. The complications associated with the enteric fever include intestinal perforation, intestinal obstruction, abdominal distension, absent bowel sounds, jaundice, CNS manifestation. The organism was initially detected by certain factors related to it. Widal,

typhidot, blood culture, urine culture and stool culture was used initially for laboratory detection of enteric fever. Blood culture nowadays is considered gold standard for diagnosis of enteric fever.

The most common problem faced by developing countries is multidrug resistant enteric fever. This is a great challenge for the treatment of enteric fever. The laboratory techniques used initially are obsolete now as their false positivity or false negativity rate is much higher and leads to misdiagnosis.

The treatment protocols for enteric fever are symptomatic management of patient and then use of antibiotics.

*Complicated Typhoid Fever						
Fully sensitive	Fluoroquinolone e.g ofloxacin	15	10-14	Ceftriaxone	60-75	10-14
	Or Chloramphenicol	100	10-14	Or Cefotaxime	80	10-14
	Or Ampicillin	200	10-14			
Multidrug resistant strains (Isolates fully resistant to amoxicillin, trimethoprim-sulfamethoxazole and chloramphenicol)	Fluoroquinolone	15	10-14	Ceftriaxone Or Cefotaxime	60-75 80	10-14 10-14
Quinolone -resistant	Ceftriaxone Or Cefotaxime	60-75 80	10-14 10-14	Azithromycin	10-20	7
Extensively drug resistant (XDR) (isolates fully resistant to amoxicillin, trimethoprim-sulfamethoxazole, chloramphenicol, fluoroquinolones and cephalosporin)	Meropenem	60	10-14	Azithromycin or Meropenem	20 60	7-10 10-14
	Additional treatment with Dexamethasone (3 mg/kg for the initial dose, followed by 1 mg/kg every 6 hours for 48 hours) for patients with shock, obtundation, stupor or coma and with abdominal complications e.g. intestinal perforation					

Figure: 1 Complications of enteric fever.

Table : Antibiotic choices for treatment of typhoid in children results of culture and sensitivity

Optimal Therapy				Alternate Effective therapy		
Susceptibility	Antibiotic	Daily dose (mg/kg/day)	Duration	Antibiotic	Daily dose (mg/kg/day)	Duration
Uncomplicated Typhoid Fever						
Fully sensitive	Chloramphenicol Or Amoxicillin	50-75 75-100	14-21 14	Fluoroquinolone e.g. ofloxacin or ciprofloxacin	15	5-7
Multidrug resistant strains (Isolates fully resistant to amoxicillin, trimethoprim-sulfamethoxazole and chloramphenicol)	Fluoroquinolone or Cefixime	15 15-20	5-7 7-14	Azithromycin	8-10	7
Quinolone-resistant	Ceftriaxone	60-75	10-14	Cefixime Or Azithromycin	15-20 20	7-14 7
Extensively drug resistant (XDR) (isolates fully resistant to amoxicillin, trimethoprim-sulfamethoxazole, chloramphenicol, fluoroquinolones and cephalosporin)	Azithromycin	20	7-10	Meropenem	60	10-14

Figure:2 Antibiotics for treatment of typhoid.

METHODS:

Study was conducted at Holy Family Hospital, Rawalpindi, Pakistan during April to December 2018. All referred patients were initially evaluated for clinical diagnosis of enteric fever. Later the patients on the basis of initial clinical diagnosis were admitted in the separate ward and blood culture was sent for all these cases before starting any antibiotic. Patients with fever more than 38.5°C lasting for more than 4 days with minimum 2 of following criteria abdominal pain, loss of appetite, hepatomegaly, splenomegaly and or rose spots were enrolled. Patients with other immunocompromised conditions, already taken antibiotics, sensitive to cephalosporins, inability to take oral medications, enteric complications were excluded from study.

It was assumed that 80% of individuals will respond to treatment and response was defined as recovery from fever within 5 days of starting treatment. Type 1 error 0.05 and type 2 error 0.2, 30 subject would be allotted in each treatment group. Age stratification into 3 groups was done, 4 to 7, 8 to 12 and 13 to 17 years. Informed consent was taken from all participants. Open label prescription was done. Either azithromycin or ceftriaxone was given after random allocation of individuals into two groups. A unique study number was given to the bottles. All medicines were given to patients by nursing staff of hospital.

Patients under study remained admitted in hospital during their treatment course and 3 days after completion of course. Blood culture was performed on day 1, 4 and 10 and then at 1 month after treatment. Blood and stool cultures were performed. Other baseline investigations were performed on presentation day and repeated on day 10.

During in hospital stay, vitals (including body temperature) were monitored 8 hourly, and clinical examination was performed daily. During clinical examination, coated tongue, abdominal tenderness, splenomegaly, hepatomegaly, or rash were specifically noted, besides general examination. A questionnaire was circulated daily during hospitalization to record symptomatology (including fever, headache, rash, abdominal pain, constipation, diarrhea, and/or anorexia) and possible adverse events. Patients were regularly checked at 2 and 4 weeks post-treatment and were asked to return immediately if they became sick before advised follow up time.

Responses to treatment were classified as clinical cure or failure and as microbiological cure or failure. "Clinical cure" was defined as resolution of all typhoid-related symptoms or signs after 7 days of treatment. Therapy response, "fever" was defined as ≥ 1 rectal temperature $>38.4^{\circ}\text{C}$ during 24 hours. "Clinical failure" was defined either as persistence of

≥ 1 typhoid-related symptoms/signs at the time of enrollment, or appearance of complication (including pneumonia, intestinal hemorrhage or perforation, shock, or coma) 4 days later. "Microbiological cure" was defined as a sterile blood culture on days 4 and 10 of therapy. "Relapse" reappearance of signs and symptoms within 4 days after treatment of *S. typhi* or *S. paratyphi* from the blood. The χ^2 test was used to determine significant differences in cure rates

between groups. For groups with < 5 events in a cell, Fisher's exact test was used.

RESULTS:

Table 1 shows demographic and pretreatment data, no difference in treatment response was noticed in both groups [table 1]. Antimicrobial susceptibility testing showed that all 64 blood culture isolates of *S. typhi* were susceptible to azithromycin, ceftriaxone, and ciprofloxacin.

Table 1 Admission characteristics of azithromycin and ceftriaxone recipients who had typhoid fever and for whom blood ...

Characteristic	Azithromycin recipients (n = 30)	Ceftriaxone recipients (n = 30)
Age, mean \pm (range)	8.7 (5-17)	10.1 (5-14)
Sex, male	26	17
Duration of fever before admission, mean \pm (range)	8.7 (5-30)	8.2 (3-15)
Blood culture result		
<i>Salmonella typhi</i>	34	30
<i>Salmonella paratyphi</i>	8	8
Blood culture that yielded MDR <i>S. typhi</i>	5	6
Stool culture result		
<i>S. typhi</i>	7	3
<i>S. paratyphi</i>	0	0
Laboratory test result, mean \pm SD (normal range)		
Hemoglobin level, g/dL (11-18)	10.4 \pm 1.2	10.8 \pm 1.3
WBC count, cells/mm ³ (4.5-10.5 \times 10 ⁹)	6.2 \pm 2.3	6.5 \pm 1.6
Platelet count, cells/mm ³ (150,000-350,000)	202,000 \pm 75,000	201,000 \pm 90,000
Total bilirubin level, mg/dL (0.2-1.0)	0.4 \pm 0.3	0.5 \pm 0.1
AST level, U/L (0-33)	87 \pm 48	85 \pm 70
Blood urea nitrogen level, mg/dL (7-18)	10.3 \pm 3.3	11.8 \pm 6
Serum creatinine level, mg/dL (0.5-1.3)	0.7 \pm 0.3	0.6 \pm 0.2

NOTE: Data are no. of patients, unless otherwise indicated. AST, aspartate aminotransferase; MDR, multidrug resistant.

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Both drugs had excellent treatment response [table 2]. There was quick treatment response; the mean time to defervescence \pm SD was 4.1 ± 1.1 days and 3.9 ± 1.0 days for azithromycin recipients and ceftriaxone recipients, respectively ($P = NS$). 91% individuals showed positive treatment response to azithromycin, while (97%) of patients treated with ceftriaxone ($P = NS$) 3 out of azithromycin group could not fulfill responder's definition. All 3 subjects received ceftriaxone for an additional 5-7 days after they had received azithromycin for 7 days; all 3 had complete cures without any significant consequences.

DISCUSSION:

Enteric fever occurs in 3 to 10 patients in every one lac travelers to developing countries. Enteric fever is much more common in developing countries [1]. The antibiotic malpractice has led to development of resistance in *salmonella typhi*. Bhutta AZ in his article studied the effect of various antibiotics to the culture positive enteric fever patients [2].

No specific clinical manifestations are there for multidrug resistant typhoid fever. The gold standard test for diagnosis of enteric fever is blood culture. Ceftriaxone and ciprofloxacin is used for the

treatment of multidrug resistant enteric fever, concluded in a drug trial conducted in 2011 by Zaki SA, et al. [4]. Multiple drug trials are underway to know the effective response against salmonella typhi. Thompson CN, et al. concluded in his study that WHO guidelines about use of fluoroquinolones for the treatment of enteric fever now needs to be changed due to prevalence of multidrug resistant strains[5]. Chloramphenicol and ceftriaxone and ciprofloxacin has been tested by multiple researchers so far [7,8]. Azithromycin is the new under trial drug for patients with multiple drug resistant strains of enteric fever causative organism.

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