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# Efficacy and Safety of Oral Cefixime for the Short-Term Treatment of Typhoid Fever in a Group of Egyptian Children

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# ABSTRACT

This is an interventional prospective pre-post clinical study aimed to evaluate the clinical management of the short course treatment of oral Cefixime in Egyptian hospitalized children with typhoid fever. A final population of 30 children with proven Widal test and blood culture typhoid fever was conducted in the clinical study. All cases received oral Cefixime at admission with a dosage regimen 20 mg/kg/day in divided doses for 7 days. The 30 analyzed cases consumed  $3.9 \pm 1.4$  (Mean  $\pm$  SD) day as a time for fever defervescence. All isolates were sensitive to Cefixime while the highest resistance was observed with Cotrimoxazole (63.33%) followed by Ampicillin (53.33%) and Chloramphenicol (43%). The clinical cure and bacteriological eradication were observed in 90% of the children while one case (3.3%) relapsed within one month so 86.7% cure rate was documented by this study. No severe side effects were detected during treatment; only 2 (6.7%) cases had diarrhea and one (3.3%) case got skin rash without requiring discontinuation of therapy. No mortality reported. Cefixime was well tolerated by most of the children. This study proposed short course treatment of Cefixime as safe and efficient oral option for the management of typhoid fever in children.

Keywords: Cefixime, Typhoid fever, Dosage regimen, Children.

## INTRODUCTION

Typhoid fever is one of the major public health worldwide problems which still cause a very high burden in many low- and middle-income countries. North Africa and the Middle East had categorized as a high incidence area among 17.8 million expected cases with typhoid fever by a new estimate included demographic, environmental, and socioeconomic indicators that serve as candidate predictors of the age-specific incidence of typhoid fever [1].

Typhoid fever is a severe systemic infectious disease caused by the bacterium Salmonella enterica serovar Typhi which is transmitted by the fecal-oral route through contaminated food and water [2]. Typhoid fever incorporates a complicated pathologic process. It presents as an acute febrile disease, but this follows a comparatively long incubation period [3].

Unique opportunities for the development of innovative and sorely required diagnostic, therapeutic, and prevention strategies to hit typhoid fever has been provided by The discovery of typhoid toxin and its role in the pathological process of typhoid fever [4]. Moreover, whole-genome sequence analysis supported defining the emergence of multidrug-resistant (MDR) typhoid by identification of a single dominant MDR lineage, H58 that has emerged and spread all through Asia and Africa over the last 30 years. H58 lineages are relocating antibiotic-sensitive isolates, altering the overall population structure of this pathogen. H58 isolates can harbor a complex MDR element be located in either on transmissible IncHI1 plasmids or within multiple chromosomal integration sites. New mutations that define the H58 lineage to be identified [5-8].

Selection of the appropriate antibiotic for typhoid fever is a winding way which is restricted by many considerations, Salmonella typhi established a multi-drug resistance to the 3 conventional antimicrobials, ampicillin, trimethoprim, and chloramphenicol collectively [9]. Fluoroquinolones were one of the most vital antimicrobials for typhoid management but recently, the decreased susceptibility to fluoroquinolones is on the rise [10]. However, the increasing resistance to fluoroquinolones is not the only obstacle to be considered as the drug of choice in typhoid fever treatment in children but also the safety restrictions of fluoroquinolones in children set the 3rd generation cephalosporin's as the first line of typhoid treatment in children and exaggerate the importance of cephalosporin's full clinical evaluations [11]. So this study intended to assess the efficacy of Cefixime as an important oral third generation cephalosporin member in the treatment of typhoid fever in children.

Cefixime is an oral 3<sup>rd</sup> generation cephalosporin has a broad spectrum of gram-negative and gram-positive aerobic bacteria with high stability to be hydrolyzed by beta-lactamases. Cefixime has a rapid lytic activity comparable to that of the other orally active cephalosporins like cefaclor and cephalexin. It is explained by its high affinity for penicillin-binding proteins 3, la and lb [12]. It is commonly indicated for the treatment of acute upper respiratory tract infections [13], acute bronchitis, acute exacerbation of chronic bronchitis [14], uncomplicated gonorrhea [15], bacterial gastroenteritis [16] and uncomplicated urinary tract infections [17]. Cefixime has a good pharmacokinetics profile which helps cefixime to have easier dosage regimen, more tolerability, and no tough precautions. it has the longest half-life between oral third-generation cephalosporins which allows once-daily dose [18]. Also, Several published studies assessed the clinical and bacteriological efficacy of cefixime in typhoid fever through different dosage regimens reporting different results for efficacy and safety [19-29].

This study aimed to evaluate the efficacy and safety profiles of oral cefixime within the short-term treatment of typhoid fever in a group of Egyptian children.

## PATIENTS AND METHODS

This is an interventional prospective pre-post clinical study was conducted at Fayoum fever hospital. At the period "between March 2013 to August 2016", Total populations of 74 children of both sexes between 6 months to 12 years were clinically examined by the outpatient clinic of the hospital. All cases had clinical features suspected to be typhoid fever. They were kept and referred to the Inpatient department. Widal test and blood culture were done for confirmation. The final population for the study was 30 cases that undergo follow-up and analysis. Non-confirmed cases or lost cases during follow-up were excluded from the study. Study flow chart is provided in Figure 1.



Figure 1: The flow chart of the study.

#### Inclusion criteria

- Children of either gender male or female with age ranges between six months to 12 years ago.
- Inpatient cases.
- Patients that are clinically suspected to have uncomplicated typhoid fever which confirmed by Widal positive and positive blood culture (golden test for typhoid fever diagnosis).

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• All cases must have the ability to take oral suspensions.

#### Exclusion criteria

- Patients who had received intravenous antibiotics before gathering blood culture samples.
- Cases whose blood culture had other species of Salmonella such as S. paratyphi.
- Outpatients.
- Patients who had recently received 3rd generation cephalosporins within 72 hrs. Prior to admission.
- Cases that had the previous history of enteric fever vaccination.
- Presence of any concomitant disease or infection such as liver disease, tuberculosis .... etc.
- Previous history of hypersensitivity to cephalosporins.
- Clinically diagnosed complicated typhoid fever such as cases suffers from hepatic encephalopathy or gastrointestinal bleeding.
- Cases with hepatic or renal insufficiency.

#### Assessments of outcomes

All clinically suspected typhoid cases referred from the outpatient clinic to the inpatient department for observation, collecting samples and then starting the treatment with Cefixime. Samples collected used for diagnosis confirmation and obtaining the baseline data about the laboratory investigations. Blood cultures were repeated at the 6<sup>th</sup> day and the 28<sup>th</sup> day. After collecting samples for the first time, all cases received oral Cefixime with a dosage regimen 20 mg/kg/day divided into two doses as a dose every 12 hrs. Other treatment factors like antipyretic, cough suppressants, antispasmodics and intravenous fluids for dehydrated cases are prescribed by the inpatient department team. Informed consent was obtained from the parents according to the permission obtained from the ethical committee of the faculty of medicine in Beni-Suef University, Egypt.

According to the general conditions of patients, clinical signs symptoms and laboratory investigations, Primary and secondary outcomes were evaluated during this study.

#### Primary outcomes

• The day of defervescence (fever clearance time FCT) which is calculated as the time interval by day required to reach the regular body temperature (≤ 37.5°C) and remaining for 48 h without elevation.

#### Secondary outcomes

- Acute cure rate which is defined as the clinical and bacteriological cure rate at the end of the treatment with Cefixime. The clinical cure depends on the fever clearance and the disappearance of typhoid's symptoms and signs while the bacteriological cure based on the blood culture result after treatment.
- Relapse which is measured as all recurrent cases within one month starting from the beginning of the treatment. Relapse evaluated clinically based on the reappearance of fever or symptoms again within 3 weeks after treatment and bacteriologically based on the reappearance of the pathogen in the blood culture within 3 weeks after treatment.
- Failure rate which is defined clinically as the cases didn't have complete relief of symptoms until the end of the 5<sup>th</sup> day and bacteriologically depending on the persistence of the pathogen in the blood culture. Clinically failed cases were shifted to ceftriaxone 75mg/kg/day intravenous or intramuscular once daily at the 6<sup>th</sup> day.
- Total cure rate which measured by excluding failure or relapse cases from the total analyzed cases (the total cured cases after treatment).
- Global efficacy estimated by a global assessment by the investigator based on 4 levels scale (poor, fair, good and excellent) marked according to the general conditions of the patient.
- Safety also measured by monitoring patients for any adverse effects or complications during treatment.3 levels scale (weak, moderate and severe) were used by the investigator in safety global assessment.
- Tolerability which is calculated by a global assessment by the investigator through patients and their parents' valuations using 3 levels scale (Poor, good and excellent).

#### Statistical analysis

- Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 in windows 7.
- The simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as a measure of dispersion for quantitative parametric data, and inferential statistics test.

#### Quantitative parametric data handling

- In-depended student t-Test was used to compare measures of two independent groups of quantitative data
- Paired t-test was used in comparing two dependent quantitative data.

## Qualitative data handling

- Chi-square test was used to compare two or more than two qualitative groups.
- Bivariate Pearson correlation test was used to test association between variables.

The level  $P \le 0.05$  was considered the cut-off value for significance.

## RESULTS

This study consisted of 30 cases as the final populations were admitted to an Egyptian hospital (Fayoum fever hospital) with typhoid fever confirmed by positive Widal test and positive blood culture. Their ages ranged between 6 months and 12 years with mean age  $6.5 \pm 4.2$  years. The demographic characteristics and some baseline data for the study populations are illustrated in Table 1. Figure 2 demonstrates the age distribution among the study group.

Age in years	6.5 ± 4.2			
Male	17 (56.7%)*			
Female	13 (43.3%)			
Urban	8 (26.7%)			
Rural	22 (73.3%)			
Initial temp at admission	39.03 ± 0.82			
Pretreatment fever in days	11.1 ± 3.6			
Note: *Number (%)				

**Table 1:** The demographic characteristics of the final study population.



Figure 2: Age distribution among the study group.

All strains were sensitive to Cefixime, Ceftriaxone, and Levofloxacin. (96.67%) of cases were sensitive to Cefotaxime while (73.3%) of cases were sensitive to Ciprofloxacin. (63.3%) of cases were sensitive to Ofloxacin. The highest *in vitro* antibiotic resistances were encountered with Cotrimoxazole (63.33%) followed by Ampicillin (53.33%) and Chloramphenicol (43%). (70%) of strains were resistant to more than one antimicrobial agent while (10%) of cases were resistant to Chloramphenicol, Cotrimoxazole, and Ampicillin collectively (MDR).

The time of temperature defervescence in this study was the primary outcome which achieved within  $3.9 \pm 1.4$  days. Fever cleared in 10% of cases on the second day. 40% of patients had no fever after 3 days of treatment, 76.7% of cases cured after four days. Fever cleared collectively in 90% of the patient after the 5<sup>th</sup> day. Fever cleared in The 3 failure cases at the days 6<sup>th</sup>, 7<sup>th</sup> and 8<sup>th</sup> by one case each day. The daily improvement in the total mean body temperature during treatment with Cefixime is demonstrated in Figure 3.

Note: \* Number (%)



Figure 3: The improvement in the body temperature during treatment with cefixime.

Based on the blood cultures, the pathogen was persistent in 3 cases while pathogen reappeared in one case 3 weeks after the treatment recording one bacteriologically relapse case. In this study, bacteriologically assessed outcomes were consistent with clinically assessed outcomes. The treatment outcomes are described in Table 2.

Defervescence of Temperature in days	3.9 ± 1.4		
Bacteriological cure	27 (90%)*		
Acute clinical cure	27 (90%)		
Bacteriological failure	3 (10%)		
Acute clinical failure	3 (10%)		
Bacteriological relapse	1 (3.3%)		
Clinical relapse	1 (3.3)		
Total cure	26 (86.7%)		
Total failure	4 (13.3%)		
	•		

Table 2: Treatment outcomes.

Baseline data about clinical symptoms, clinical signs and laboratory findings were documented at admission time. Improvements in the clinical signs and symptoms were evaluated daily. The baseline data about clinical signs, symptoms and the duration to be relieved during treatment by Cefixime is shown in Table 3.

Variables	Parameters (days)					
	No. (%)	Mean ± SD				
Clinical signs and symptoms						
Fever	30 (100%)	$3.9 \pm 1.4$				
Abdominal tenderness	4 (13.3%)	3.3 ± 1.3				
Coated tongue	7 (23.3%)	$2.9\pm0.90$				
Rose spots on skin	1 (3.3%)	3 ± 0				
Dehydration	5 (16.7%)	$2.8\pm0.84$				
Toxic look	16 (53.3%)	$1.5 \pm 0.63$				
Chills	21 (70%)	$2.7 \pm 1.2$				
Vomiting	7 (23.3%)	$2.1 \pm 1.2$				
Appetite loss	25 (83.3%)	2.5 ± 1.4				
Cough	11 (36.7%)	3 ± 1.4				
Diarrhea	8 (16.7%)	3 ± 1.5				
Abdominal pain	14 (46.7%)	$1.9 \pm 1.1$				
Constipation	2 (6.7%)	2.5 ± 0.71				

**Table 3:** Clinical signs and symptoms at admission time and the duration required to be relieved.

General laboratory investigations were performed for the all children at admission time and re-evaluated after treatment.

There is statistically significance difference with p-value <0.05 in hemoglobin level, platelet count, number of eosinophil before and after treatment with high mean after treatment which indicates improve in cases while There is statistically significant difference with p-value <0.05 in liver function tests (ALT, AST, and total bilirubin), and kidney function tests (creatinine level) before and after treatment with low mean after treatment which indicates improve in cases. Table 4 refers to the baseline data about laboratory finding and the effect of Cefixime on the laboratory findings.

As regards to safety profile for treatment, the majority of cases were normal without any sign of side effects except 6.7% show moderate diarrhea, and 3.3% show skin rash which didn't require discontinuation of therapy. No severe side effects were observed among the study group.

Cefixime was well tolerated in the most of the cases. More than 90% had between good and excellent tolerability with 50% excellent, and 43.3% for good, only 6.7% had poor tolerability.

Variables	Before treatment	After treatment	p-value	Significance
	$Mean \pm SD$	Mean ± SD		
HB%	$10.6\pm1.2$	$10.9\pm0.91$	<0.001*	HS
PLT	$194.03 \pm 41.1$	$243.6 \pm 42.1$	< 0.001*	HS
WBCs	$5.9\pm2.7$	6.6 ± 1.1	0.11	NS
Lymphocytes	$35.1 \pm 14.1$	33.7 ± 4.7	0.5	NS
Neutrophils	$60.3 \pm 13.3$	$60.9\pm0.80$	0.8	NS
Eosinophils	$1.23 \pm 1.3$	2.23 ± 1	0.001*	HS
Basophil	$0\pm 0$	0 ± 0		
Monocyte	$3.4 \pm 1.4$	3.2 ± 1.4	0.6	NS
ALT	$47.2\pm18.8$	29.5 ± 10.5	< 0.001*	HS
AST	$52.2\pm20.9$	36.1 ± 15.5	<0.001*	HS
Total bilirubin	$0.73\pm0.20$	0.64 ± 0.11	< 0.001*	HS
Creatinine	$0.76\pm0.12$	$0.69\pm0.08$	<0.001*	HS

**Table 4:** The laboratory findings before and after treatment.

## DISCUSSION

Antimicrobial drugs are the backbone of the management of invasive salmonellosis. In the most recent two decades, multidrug-resistant (MDR) *Salmonella enterica* serovars have emerged worldwide, thereby reducing the available treatment choices [30].

The successive variations in susceptibility pattern of *S. enterica* serovars which led to significant decrease in susceptibility to fluoroquinolones, high sensitivity to ceftriaxone and a re-emergence of chloramphenicol, co-trimoxazole sensitivity require continuous surveillance of antibiogram of *Salmonella* strains to justify the management protocols for invasive salmonellosis and avoid the emergence of resistant strains [31]. That will cause a delay in diagnosis and treatment. An empiric antibiotic has to be indicated, third-generation cephalosporins should be used until culture and Antibiotic Sensitivity Test results are available [32,33]. This explains the clinical researchers' interest in Cefixime for typhoid fever. Consistency with previous experiences [22,34], all the isolated salmonella strains in this study was sensitive to cefixime like several pathogens. These bacteriologic data provided cefixime as a suitable empiric cephalosporin to be indicated for typhoid fever and supposed that the enhancement of cefixime bioavailability by any pharmaceutical technique will increase its antimicrobial *invivo* activity [35].

Two main dosage regimens managed by the previous studies of typhoid fever, Cefixime could be administered as 10-12 mg/kg/day in a long course treatment [19,25,26] or administered as 20 mg/kg/day in short course treatment [23,24]. This study aimed to assess the efficacy and safety profiles of cefixime in typhoid treatment in children through short-course treatment. Fever

clearance time, acute treatment cure, acute treatment failure, relapse, total treatment cure, safety and tolerability profiles were checked as treatment indicators regarding these parameters to a 7-day course treatment.

Relative short fever clearance time was observed by this study which is similar to that described by a published clinical study [21] and lower than that reported by other studies [19,22-24,27,28] while was higher than that documented by a previous experience [29].

Despite the total failure rate increased in Egypt from 6.7% [21] to 14% in this study, 86% of cases were successfully treated in this study introducing cefixime as a good oral option for typhoid treatment. The clinical cure documented in this study is lower than that was described by many studies [22,24,26,27] while higher than that reported by others [23,25,28]. One (3.3%) case relapsed after 3 weeks while the experienced relapse rate ranging from 0% to 8.57% by the previously published studies [28,29].

Significant improvements in signs, symptoms and several laboratory abnormalities were documented in this study that supported restoring the body homeostasis based on the treatment by Cefixime [30-35].

No significant side effects were observed during treatment. few mild to moderate side effects were documented which didn't require discontinuation of therapy. These data are consistent with that reported by the most of the previously mentioned studies. Cefixime 20mg/kg/day is well tolerated among the children of this study.

There was no available comparative group in the study which is considered as the main limitation of the study.

## CONCLUSION

Cefixime is an effective and safe oral third generation cephalosporin in the treatment of uncomplicated typhoid fever in children. Rapid relief of fever could be obtained by a well-tolerated short course of treatment (cefixime 20 mg/kg/day).

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