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**Research Article** 

# CURRENT ANTIBIOTIC USE IN THE TREATMENT OF ENTERIC FEVER IN CHILDREN

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## Abstract:

**Context and objectives:** antimicrobial resistance is a great challenge in the treatment of typhus, with a limited choice for the empirical treatment of these patients. The present study was conducted to identify current antibiotic use practices among children visiting a tertiary care hospital in Lahore

**Methods:** This was a descriptive observational study in children with enteric fever as defined by the case, including clinical and laboratory parameters. The antibiotic audit in hospitalized children was measured as days of therapy for 1000 days of patients and in ambulance (OPD) as a prescription of antibiotics on the treatment sheet.

**Results:** 128 children with intestinal fever were included in the study, 30 of whom were hospitalized and 98 were treated with OPD. The average duration of fever at the time of presentation was 9.5 days. Of these, 45 percent were culture positive, with 68 percent Salmonella Typhi as the causative agent, followed by S. Paratyphi A in 32 percent. During the hospital stay, the average length of stay was 10 days with an average duration of 6.4 days. Based on antimicrobial susceptibility, ceftriaxone was administered to 28 patients with a mean treatment duration of six days. In six patients, an additional antibiotic was needed because the clinical response had failed. In OPD, cefixime was prescribed to 79 patients and in five patients an additional antibiotic was needed during follow-up.

**Interpretation and conclusions:** based on our results, ceftriaxone and cefixime appeared to be the first line of typhoid antibiotic therapy. Despite the susceptibility, a lack of clinical response was observed in about 10 percent of patients requiring antibiotic combinations.

Key words Antibiotic use - days of therapy - enteric fever - Salmonella Typhi

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## **INTRODUCTION:**

Typhoid fever is a community-acquired infection that is still a public health problem in developing countries. It is more common in overcrowded communities with limited resources and poor access to sanitation. Although infection can occur at any age, the incidence is higher in children reflects active transmission in a community1. A metastatic analysis of exposure to typhoid and paratyphoid fever in Pakistan found that the prevalence of laboratory confirmed enteric fever in individuals was estimated at seven percent for Salmonella typhi and 0.9 percent for Salmonella paratyphi A with the highest incidence in children2. 3. The problem of treatment of enteric fever is aggravated by the increase in antibiotic resistance to the first line antibiotics used for enteric fever4.5. The multiresistant strains were widespread throughout the world and had previously caused outbreaks 6,7. In recent years, resistance to fluoroquinolones8-10 has increased, which is why ciprofloxacin is no longer the empirical treatment in our country11-13.

Ceftriaxone and cefixime are currently the drug of choice for the treatment of these infections. However, there are also reports of an increase in the minimal inhibitory concentration (MIC) of ceftriaxone14, which causes delayed foaming, and even reports of complete resistance15. Azithromycin, the current alternative treatment option, requires more clinical and laboratory data to support its use in the treatment of complicated intestinal fever16.17. The possible combinations of current medicines are an alternative solution currently under study18,19.

The present study was conducted with the aim of determining the current use of antibiotics or prescriptions for the treatment of typhoid fever in children in Hospital.

#### **MATERIAL & METHODS:**

This descriptive study was conducted in the Departments of Pediatrics Unit Of Jinnah Hospital lahore. All patients who met the definition of the case described below were included in the study. Those who did not consent were excluded. From September 2013 to December 2016, all children who presented a diagnosis of intestinal fever according to the definition of the case in pediatric institutions were admitted to the study after written consent. Based on the predefined proforma, demographic and clinical details of the patient were recorded.

Confirmed case: a patient with fever  $(38 \circ C \text{ and} over)$  lasting at least three days with a laboratory confirmed a positive culture (blood, bone marrow and intestinal fluid) of Salmonella typhi or S.

paratyphi A.

Probable case: a patient with fever  $(38 \circ C \text{ and} above)$  that has lasted for at least three days with a clinical infection case consistent with positive serodiagnosis but without Isolation of S. Typhi.

Clinical diagnosis only: a clinically consistent case in a child with a fever of at least three days without localization, together with one or more of the following signs and symptoms: abdominal pain, vomiting or diarrhea, loss of appetite, mental confusion and splenomegaly, neutropenia or abnormalities of liver function test.

In short, the first line of treatment in the outpatient department (OPD) was cefixime 40 mg / kg / day in two divided doses for 10 days. The patient, who had severe abdominal discomfort, persistent vomiting and inability to receive orally or complications such as hepatitis, encephalopathy, was admitted to the hospital and administered ceftriaxone 50-75 mg / kg of body weight per day for 14 days until when the child became afebrile or clinically stable, In case of previous discharge, it was recommended to switch to cefixime orally 20 mg / kg of body weight twice a day for another 5-7 days, depending on the previous days in which were given antibiotics or occasionally, depending on the clinical judgment.

Combination of antibiotics: if the patient showed no improvement in clinical conditions despite 48-72 hours of ceftriaxone, a second and / or third antibiotic, ofloxacin or azithromycin, was added. In OPD, another antibiotic was added if the patient was again visited for persistent fever despite cefixime and otherwise no approval was requested.

Blood cultures: for all patients included in the study, blood cultures were performed using an automated Bact-Alert system (Biomerieux, Marcy l'Etoile, France) according to the manufacturer's instructions. The culture was conducted according to standard methods22. Culture positive isolates were identified by standard methods and confirmed by a slide agglutination test using specific antisera (Staten Serum Institute, Copenhagen, Denmark) 23.

Antimicrobial susceptibility test: the antimicrobial susceptibility of the isolates was determined according to the CLSI (Clinical and Laboratory Standards Institute) for the corresponding isolation year 24-28. However, for the cumulative antibiogram, the analysis was based on CLSI 201728 using antibiotic discs (Himedia Laboratories Ltd, Mumbai) for chloramphenicol (30 µg), ampicillin (10

 $\mu$ g), cotrimoxazole (1.25 / 23.75  $\mu$ g), Cefixime (5  $\mu$ g) and ceftriaxone (30  $\mu$ g). Pefloxacin (5  $\mu$ g) was used to replace ciprofloxacin, ofloxacin and levofloxacin.

The minimum inhibitory concentration (MIC) for fluoroquinolones (ciprofloxacin, ofloxacin and levofloxacin) and for ceftriaxone was determined by an E-test (Biomerieux, Marcy l'Etoile, France) according to the manufacturer's instructions. Escherichia coli ATCC 25922 was used as a quality control strain for disk diffusion and MIC determination.

Serological was performed according to the manufacturer's instructions for testing the presence of IgM specific antibodies for Salmonella29. TyphiPoint IgM positive was considered seropositive for acute infection. The latitude test was performed using the tube agglutination method according to the standard protocol29. A titre of  $\geq 1$ : 160 against the antigens of S. Typhi TO, TH or S. Paratyphi A TO and AH in the serum sample taken at the time of presentation in the hospital was assessed as positive according to the standard protocol in our hospital. A coupled serum was recommended.

Antibiotic consumption in hospitalized children: antibiotic consumption was measured as the day of therapy (DoT) 30.31, standardized to 1000 patient days. A DoT is any dose of antibiotic given over a 24-hour period. This was calculated for all hospitalized cases of enteric fever by recording the antibiotics administered daily to the enteric fever patient in the ward according to the WHO guidelines for the calculation of DoT 31.

The DoT was calculated as follows: Total number of antibiotic days / total number of patient days  $\times$  1000.

Prescription of ambulatory antibiotics: in pediatric patients with OPD, antibiotic prescriptions were recorded on the treatment schedules for all patients who met the definition of the case (2 OPD weekdays, Wednesday and Saturday).

## **RESULTS:**

In total there were 128 children with intestinal fever included in the study that met the definition of the case. of

These 30 children were admitted to the pediatric ward at an average age of nine years [interquartile range (IQR) 5-12 years] and 98 children with an

average age of seven (IQR 4-11 years) were treated by 'OPD. Of the 128 children enrolled, 73 were boys and 55 were girls.

Fever was the presenting symptom in all cases and the average fever at the time of hospital presentation was  $9.5 \pm 5.9$  days (range 2-45 days). The duration of fever in IgM positive patients was 3-45 days with an average of 10.2 days. Other common symptoms included gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, vomiting and loss of appetite, some of which also showed hepatitis or encephalopathy.

Among the 30 hospitalized patients, 18 were positive for culture (S. Typhi at 13 and S. Paratyphi A at 5). Of the other 12 patients, seven were both positive for IgM TyphiPoint and positive for Widal and five were diagnosed only clinically. Five of these patients had already taken antibiotics of varying duration before presenting to the hospital (2 had cefixime and 2 had cefixime

1 ciprofloxacin, azithromycin and injectable ceftriaxone). Other patients did not have a specific history of antibiotics.

Of 98 patients treated with OPD, 39 were positive for culture (S. Typhi at 34 and S. Paratyphi A at 5). Of the remaining, four were positive for both TyphiPoint IgM and Widal, 30 for TyphiPoint IgM and one for Widal alone, while 20 were diagnosed only clinically. Six patients refused to provide blood samples for testing and four patients did not return after the first visit. Of 98 patients, 23 had already received antibiotics before presenting to OPD. Of these, eight had cefixime, five ofloxacin, two azithromycin, seven amoxiclav and one ceftriaxone injection for various durations. A specific history of antibiotics was not available in 75 patients.

Comparing the different methods of laboratory diagnosis of typhus, out of 57 culturally positive patients, 44 (78%) were also positive for IgM, while only 22 (38%) were positive for Widal. Of the 71 culturally negative patients, IgMs were positive in 36 (50%) and large in one patient (Table I). In 26 (20%) patients, all three parameters were negative and the only clinical diagnosis was the basis for the treatment of intestinal fever.

The positive culture rate was 45 percent (57/128), with S. Typhi representing 47 patients (68%) and S. Paratyphi A for 10 patients (32%).

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Test	IgM	Widal	IgM +	ve,	
	+ve	+ve	Widal	+ve	
Culture +ve (n=57)	22	Nil	22		
Culture -ve (71)	25	1	11		

Table I. Serology test results	in culture +ve and -ve case
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The susceptibility model in the cumulative antibiogram showed that S. typhi was 100% sensitive to ceftriaxone and cefixime, 11% to pefloxacin, 81% to ampicillin, 93% to cotrimoxazole, 95% to chloramphenicol and 95% to azithromycin, while S. Paratyphi A was 100% resistant to ceftriaxone and cefixime and 90% each to ampicillin and co-trimoxazole, 100% to chloramphenicol and no pefloxacin isolates. Since no CLSI breakpoints were defined for S. Paratyphi A for azithromycin, this has not been evaluated.

The MIC to ceftriaxone in S. Typhi varied from 0.023 to 0.75  $\mu$ g / ml, which showed MIC creeping over the years. For ciprofloxacin, the MIC values ranged from 0.064 to 64  $\mu$ g / ml, for ofloxacin between 0.047 and 64  $\mu$ g / ml and for levofloxacin between 0.52 and  $> 64 \mu g / ml$ . The MIC for ceftriaxone S. Paratyphi A ranged from 0.094 to 0.19 µg / ml. For ciprofloxacin, the MIC values varied between 0.047 and 1.5 µg / ml, for ofloxacin 0.050- $12 \mu g / ml$  and for levofloxacin 0.075 to  $16 \mu g / ml$ . Consumption of antibiotics in the ward: among the 30 patients admitted to the pediatric ward, the hospital stay was between 2 and 35 days with an average length of stay of 10 days. The mean duration of fever inflammation was  $6.4 \pm 3.9$  days (range 2-16 days). Of these, 28 patients were treated with ceftriaxone. The average duration of treatment with ceftriaxone was seven days (range 2-14 days). In two patients, ofloxacin was used as the first line of treatment in which the patient had already taken cefixime from the local doctor. These two patients were neither culturally nor serologically positive and were clinically diagnosed.

Days of therapy (DoT): the DoT for ceftriaxone in 2013 was 923, 2014 329, 2015 914 and 2016

845/1000 patient days. Point for ofloxacin in 2013 it was zero, in 2014 it was 507, in 2015 it was 69 and in 2016 it was 141/1000 patient days. In 2014, one patient was hospitalized for 35 days and treated with ofloxacin for 15 days, increasing DoT. The DoT for azithromycin in 2013 was zero, compared to 274 in 2014, 52 in 2015 and 12/1000 patient days in 2016 (Table II). The increase in 2014 is due to the same patient who was treated with ofloxacin for 15 days and received azithromycin with ofloxacin for 15 days. In total, total ceftriaxone DoT was 731/1000 patient days.

All patients were discharged one day after the fever. At discharge, 22 patients were not prescribed antibiotics, while six were discharged for five days with cefixime for oral use, one for five days with ciprofloxacin and one for seven days with azithromycin because they were stable and discharged in the clinic before the end of treatment became a station.

Another antibiotic was added as six patients did not respond clinically. Ofloxacin was added as a second antibiotic in four cases and azithromycin in two cases. Two patients required three antibiotics and azithromycin was also used as a third antibiotic in two of six patients who received ceftriaxone and ofloxacin. Of these six patients, four were culturally positive.

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Year	Patient days	Ceftriaxone	Ofloxacin	Azithromycin
2013 (n=5)	52	923	0	0
2014 (n=5)	73	329	507	274
2015 (n=8)	58	914	69	52
2016 (n=12)	85	835	141	12
Total patient (n=30)	268	731	198	90

<b>Lable 11.</b> Days of therapy (Do1) for centratine, offoraeth and azith officing the hospitalized patients from $2015-201$
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Table III. Antibiotic prescribed in outpatient department patients for typhoid fever from 2013-						
Duration	number of patients	(%)	Ofloxacin (%)	Azithromycin (%)	Others	
2013 (September-December)	18	13/16 (81)	3/16 (19)	-	2 no FU*	
2014 (January-December)	31	25/28 (89)	2/31 (7)	1/28 (4)	3 no FU*	
2015 (January-December)	21	16/19 (84)	3/19 (16)	-	$2 \text{ no FU}^*$	
2016 (January-December)	28	25/25 (100)	-	-	3 no FU*	
Total	98	79/98 (81)	8/98 (8)	1/98 (1)	10/98 (10	
*Patient who did not come back for follow up. FU, follow up						

Prescription of antibiotics in OPD: Of the 98 patients who participated in OPD, 79 received cefixime, 11 ofloxacin and two had azithromycin. Ten patients could not be screened for changes in suspected initial therapy (Amoxiclav 6 and no antibiotic 4) because they did not present a blood sample for laboratory tests or did not return for follow-up following reports of crops. The combination of antibiotics was necessary because of the clinical follow-up assessment in five patients who were already receiving cefixime, of which ofloxacin was administered to cefixime in four cases, while azithromycin and ciprofloxacin were administered in one patient each. It was observed that the number of patients who were prescribed cefixime increased from 81 percent in 2013 to 100 percent in 2016, while of loxacin in 2013 was 19 percent. Line antibiotic based on clinical evaluation (Table III). Azithromycin was minimally used in our settings.

## **DISCUSSION:**

Currently, third-generation cephalosporins are the drug of choice for the treatment of typhoid fever. Clinical efficacy studies are available only for parenteral ceftriaxone (not for oral cefixime) and the increase of MIC on ceftriaxone is worrying 13,14.

The present study was conducted to determine the use of antibiotics in enteric fever in children presenting to a tertiary care center. All patients included in our study had a fever with a mean duration of 9.5 days at the time of presentation. In addition, about 20 percent of patients reported having taken oral cefixime or ciprofloxacin or an unknown antibiotic before the visit. This could be a reason for the onset of more severe cases and a low blood culture positivity of only 45 percent.

It was discovered that S. typhi is one of the main causative agents of enteric fever in our patients, followed by S. paratyphi A. ceftriaxone, which was prescribed in the first hospital treatment Patients during OPD, was cefixime. However, if the patient showed no clinical improvement, another medicine such as ofloxacin or azithromycin was added. Failure to respond to the original antibiotic was responsible for a prolonged hospital stay and greater morbidity due to an increase in the deferral rate. The delay in clinical response to ceftriaxone may be due to a high MIC, which requires the addition of a second antibiotic in 10% of patients and a third antibiotic in 2% of patients. However, this combination was added sequentially, primarily for the purpose of reviewing the clinical conditions.

In light of the numerous reports of ceftriaxone resistance and the absence of a new drug, studies are underway to understand the combination of antibiotics in the treatment of typhoid fever. In an API conclave on enteric fever, the use of combination therapy for seven-day fever and no clinical improvement with monotherapy was recommended32,33.

Fixed dose combinations are used but without data to prove their advantage. Before prescribing fixed dose combinations, a second antibiotic should be added in selected cases only after a clinical evaluation. In addition, it is necessary to strengthen preventive measures such as safe water supply and to develop new effective vaccines against S. Typhi and S. Paratyphi A, without new drugs in sight. The limitation of the present study was the diagnosis of typhoid using serological or clinical parameters with low specificity. There was the possibility that many cases were mistakenly called typhoid. The use of the TyphiPoint IgM test is limited. It was performed for all patients regardless of fever duration. A single width test for the diagnosis of typhoid fever is of limited value, especially for a single serum, and it was not possible to obtain a serum sample coupled. This was another limitation of the present study.

## **CONCLUSION:**

In conclusion, our results indicated a creeping MIC to ceftriaxone. While multi-drug therapy for typhoid fever should only be used in selected cases, the role of many available solid drug combinations should be evaluated. Our study highlights the need for clear guidelines for the treatment of typhoid fever with multi-drug therapy in the period of antimicrobial resistance in S. Typhi and S. Paratyphi A.

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