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Current antibiotic use in the treatment of enteric fever in children

Sushila Dahiya[1], Rooma Malik[1], Priyanka Sharma[1], Archana Sashi[2], Rakesh Lodha[3], Sushil Kumar Kabra[3], Seema Sood[1], Bimal Kumar Das[1], Kamini Walia[4], V.C. Ohri[4] & Arti Kapil[1]

Departments of [1]Microbiology, [2]Medicine & [3]Paediatrics, All India Institute of Medical Sciences & [4]Division of Epidemiology & Communicable Diseases, Indian Council of Medical Research, New Delhi, India

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***Background & objectives*: Antimicrobial resistance is a major challenge in the treatment of typhoid fever with limited choices left to empirically treat these patients. The present study was undertaken to determine the current practices of antibiotic use in children attending a tertiary care hospital in north India.**

***Methods*: This was a descriptive observational study in children suffering from enteric fever as per the case definition including clinical and laboratory parameters. The antibiotic audit in hospitalized children was measured as days of therapy per 1000 patient days and in outpatient department (OPD) as antibiotic prescription on the treatment card.**

***Results*: A total of 128 children with enteric fever were included in the study, of whom, 30 were hospitalized and 98 were treated from OPD. The mean duration of fever was 9.5 days at the time of presentation. Of these, 45 per cent were culture positive with *Salmonella* Typhi being aetiological agent in 68 per cent followed by *S.* Paratyphi A in 32 per cent. During hospitalization, the average length of stay was 10 days with mean duration of defervescence 6.4 days. Based on antimicrobial susceptibility ceftriaxone was given to 28 patients with mean duration of treatment being six days. An additional antibiotic was needed in six patients due to clinical non-response. In OPD, 79 patients were prescribed cefixime and additional antibiotic was needed in five during follow up visit.**

***Interpretation & conclusions*: Based on our findings, ceftriaxone and cefixime seemed to be the first line of antibiotic treatment for typhoid fever. Despite susceptibility, clinical non-response was seen in around 10 per cent of the patients who needed combinations of antibiotics.**

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

Typhoid fever is a community-acquired systemic infection which continues to be a public health problem in developing countries. It is more common in resource-limited overcrowded communities with poor access to sanitation. Although the infection can occur at any age, the higher incidence in children reflects the active transmission in a community[1]. A meta-analysis on the burden of typhoid and paratyphoid fever in India has shown an estimated prevalence of laboratory-confirmed enteric fever among individuals to be seven per cent for *Salmonella* Typhi and 0.9 per cent for *Salmonella* Paratyphi A

with the highest incidence in children[2,3]. The problem in the management of enteric fever is compounded by the increasing antimicrobial resistance to the first-line antibiotics used for the enteric fever[4,5]. Multidrug-resistant strains were prevalent worldwide and had previously caused outbreaks in India[6,7]. In recent years, there has been an increase in fluoroquinolones resistance[8-10] because of which ciprofloxacin is no longer the empirical choice of treatment in our country[11-13].

Ceftriaxone and cefixime are presently the drug of choice to treat these infections but there are also reports on increased minimum inhibitory concentration (MIC) to ceftriaxone[14] causing delayed defervescence and even reports on the full resistance[15]. Azithromycin, the current alternative treatment option requires more clinical and laboratory data to support its use in the treatment of complicated enteric fever[16,17]. Possibilities of using the current drugs in combinations are an alternative solution which is being evaluated[18,19].

The present study was undertaken with the objectives to determine the current antibiotic use or prescriptions for the treatment of typhoid fever in children presenting to a tertiary care hospital in north India.

Material & Methods

This descriptive study was conducted in the departments of Paediatrics and Microbiology, All India Institute of Medical Sciences (AIIMS), New Delhi, India. All patients who met the case definition as described below were included in the study. Those who did not give consent were excluded. From September 2013 to December 2016, all the children presenting to paediatrics services with a diagnosis of enteric fever as per the case definition were included in the study after informed written consent. Based on the pre-defined proforma, patient's demographic and clinical details were recorded.

Case definitions: This was based on Paediatric department, AIIMS, New Delhi, protocols adapted from the WHO and Indian Academy of Pediatrics (IAP)[20,21] guidelines.

Confirmed case: A patient with fever (38˚C and above) that has lasted for at least three days, with a laboratory-confirmed positive culture (blood, bone marrow and bowel fluid) of *Salmonella* Typhi or *S.* Paratyphi A.

Probable case: A patient with fever (38ºC and above) that has lasted for at least three days, with a clinically consistent case with positive serodiagnosis but without *S.* Typhi isolation.

Clinical diagnosis only: Clinically consistent case in a child presenting with fever of at least three days with no localization along with one or more of the following signs and symptoms: abdominal pain, vomiting or diarrhoea, loss of appetite, mental confusion and on examination had either splenomegaly, neutropenia or abnormal liver function tests.

The study was approved by the Institutional Ethics Committee of AIIMS (Ref. No. IEC/NP-463/2012 and RP-18/2013).

Antibiotic management protocol: This was based on the protocols of the Paediatrics Department at AIIMS, New Delhi, adapted from IAP[21] guidelines. Briefly, 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 presented with severe abdominal symptoms, persistent vomiting and inability to accept orally or with complications such as hepatitis, encephalopathy were hospitalized and ceftriaxone 50-75 mg/kg body weight per day for 14 days was given till the child became afebrile or clinically stable. If discharged earlier switch to oral cefixime 20 mg/kg body weight twice a day was advised for another 5-7 days depending on the previous days for which antibiotic was given or occasionally ofloxacin was given depending on the clinical judgement.

Combination of antibiotics: If despite 48-72 h of ceftriaxone the patient showed no improvement in clinical condition, a second and/or third antibiotic ofloxacin or azithromycin was added. In OPD, if the patient visited again due to persisting fever despite cefixime and otherwise not requiring admission, another antibiotic was added.

Blood cultures: Blood cultures were done for all the patients included in the study using Bact Alert automated system (Biomerieux, Marcy l'Etoile, France) as per manufacturer's instructions. Culture was done according to the standard methods[22]. The culture positive isolates were identified by standard methods and confirmed by slides agglutination test using specific antisera (Staten Serum Institute, Copenhagen, Denmark)[23].

Antimicrobial susceptibility testing: Antimicrobial susceptibility of the isolates was determined as per Clinical and Laboratory Standards Institute (CLSI)

for the corresponding year of isolation[24-28] but for the cumulative antibiogram the analysis was based on CLSI 2017[28] using antibiotic disks (Himedia Laboratories Ltd, Mumbai) for chloramphenicol (30 µg), ampicillin (10 µg), co-trimoxazole (1.25/23.75 µg), cefixime (5 µg) and ceftriaxone (30 µg). Pefloxacin (5 µg) was used as a surrogate for ciprofloxacin, ofloxacin and levofloxacin.

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

Serological tests: TyphiPoint (AB Diagnopath Manufacturing Private Limited, Rajasthan, India) was done according to the manufacturer instructions to look for the presence of *Salmonella*-specific IgM antibodies[29]. TyphiPoint IgM positive was considered as seropositive for acute infection. Widal test was done using tube agglutination method according to the standard protocol[29]. A titre of ≥1:160 against *S.* Typhi antigens TO, TH or *S.* Paratyphi A TO and AH in serum sample collected at the time of presenting to the hospital was taken as positive as per standard protocol in our hospital. A paired serum was advised.

Antibiotic use in hospitalized children: Antibiotic use was measured as days of therapy (DoT)[30,31] standardized to 1000 patient days. One DoT is any dose of antibiotic received during a 24 h period. This was calculated for all the hospitalized cases of enteric fever by recording the antibiotics given to the enteric fever patients daily in the ward as per the WHO guidelines to calculate DoT [31].

DoT was calculated as follows:

Total number of days of antibiotic/Total number of patient days ×1000.

Antibiotic prescription in outpatients: In case of paediatrics OPD patients, the antibiotic prescriptions on the treatment cards were recorded for all patients meeting the case definition (on 2 OPD days of a week Wednesdays and Saturdays).

Results

A total of 128 children with enteric fever were included in the study who met the case definition. Of these, 30 were admitted to the paediatric ward with median age being nine years [interquartile range-(IQR) 5-12 yr] and 98 children with mean age being seven years (IQR 4-11 yr) received treatment from the OPD. Of the 128 enrolled children, 73 were boys and 55 were girls.

Fever was the presenting symptom in all the cases and the mean duration of fever at the time of presenting to the hospital was 9.5±5.9 days (range 2-45 days). The duration of fever for IgM positive patients was 3-45 days with mean 10.2 days. The other common presenting symptoms included gastrointestinal symptoms such as abdominal pain, diarrhoea, nausea, vomiting and loss of appetite with some also presenting as hepatitis or encephalopathy.

Among the 30 hospitalized patients, 18 were found to be culture positive (*S.* Typhi in 13 and *S.* Paratyphi A in 5). Of the other 12 patients, seven were both TyphiPoint IgM positive and Widal positive and five were diagnosed clinically only. Five of these patients had already taken antibiotics of various durations before presenting to the hospital (2 had cefixime and 1 each ciprofloxacin, azithromycin and injectable ceftriaxone). In case of other patients, no specific prior antibiotic history was available.

Of the 98 patients treated from OPD, 39 were culture positive (*S.* Typhi in 34 and *S.* Paratyphi A in 5). Of the rest, four were positive for both TyphiPoint IgM and Widal, 30 for TyphiPoint IgM and one alone for Widal while 20 were diagnosed only clinically. Six patients refused to give blood samples for the tests and four patients did not come back after the first visit for follow up. Of the 98 patients, 23 patients had already received antibiotics before presenting to OPD. Of these, eight had cefixime, five ofloxacin, two azithromycin, seven amoxyclav and one had injection ceftriaxone for various durations. In 75 patients, no specific antibiotic history was available.

Comparing different modalities of laboratory diagnosis of typhoid fever, it was found that of the 57 culture positive patients, 44 (78%) were also IgM positive while widal was positive in only 22 (38%). Amongst the culture negative 71 patients, IgM was positive in 36 (50%) and widal alone in one (Table I). In 26 (20%) patients, all three parameters were negative and clinical diagnosis alone was the basis of treatment of enteric fever.

The culture positive rate was 45 per cent (57/128) with *S.* Typhi being responsible in 47 patients (68%)

Table I. Serology test results in culture +ve and -ve cases

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

while *S.* Paratyphi A for 10 (32%). Antimicrobial susceptibility pattern on cumulative antibiogram showed that among *S.* Typhi, 100 per cent were susceptible to ceftriaxone and cefixime, 11 per cent to pefloxacin, 81 per cent to ampicillin, 93 per cent to co-trimoxazole, 95 per cent to chloramphenicol and 95 per cent to azithromycin while for *S.* Paratyphi A 100 per cent were susceptible to ceftriaxone and cefixime, and 90 per cent each to ampicillin and co-trimoxazole, 100 per cent to chloramphenicol while no isolate was susceptible to pefloxacin. As there are no CLSI breakpoints defined as yet for *S.* Paratyphi A for azithromycin, it was not evaluated.

The MIC to ceftriaxone in *S.* Typhi ranged from 0.023 to 0.75 µg/ml which showed creeping MICs over the years. For ciprofloxacin the values of MIC ranged from 0.064 to 64 µg/ml, for ofloxacin, it was 0.047-64 µg/ml, and for levofloxacin, it ranged from 0.52 to >64 µg/ml. The MIC to ceftriaxone for *S.* Paratyphi A ranged from 0.094 to 0.19 µg/ml. For ciprofloxacin the values of MIC ranged from 0.047 to 1.5 µg/ml, for ofloxacin it was 0.050-12 µg/ml, and for levofloxacin, it ranged from 0.075 to 16 µg/ml.

Antibiotic use in the ward: Among the 30 patients admitted to the paediatric ward, the duration of hospital stay ranged from 2 to 35 days with average length of stay of 10 days. The mean duration of defervescence of fever was 6.4±3.9 days (range 2-16 days). Of these, 28 patients were treated with ceftriaxone. The mean duration of treatment with ceftriaxone was seven days (range 2-14 days). In two patients, ofloxacin was used as the first line of treatment where the patient gave a history of already having consumed cefixime from local practioner. These two patients were also neither culture nor serology positive and were diagnosed clinically.

Days of therapy (DoT): The DoT for ceftriaxone in 2013 was 923, in 2014 it was 329, in 2015, it was 914, and in 2016, it was 845/1000 patient days. DoT for ofloxacin in 2013 was nil, 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 given ofloxacin for 15 days which increased its DoT. DoT for azithromycin in 2013 was nil, in 2014 it was 274, in 2015, it was 52 and in 2016, it was 12/1000 patient days (Table II). The increase in 2014 was due to the same patient as mentioned above with ofloxacin DoT, who stayed for 35 days and was given azithromycin along with ofloxacin for 15 days. Overall, the total DoT of ceftriaxone was 731/1000 patient days as compared to ofloxacin and azithromycin for which the values were 198 and 90/1000 patient days.

All the patients were discharged one day after becoming afebrile. On discharge, no antibiotics were prescribed in 22 patients, while six were discharged on oral cefixime for five days, one on ciprofloxacin for five days and one on azithromycin for seven days as they were stable and discharged before completion of the duration of treatment in the ward.

There was an addition of another antibiotic due to clinical non-response in six patients for which ofloxacin was added in four and azithromycin in two as a second antibiotic. Two patients needed three antibiotics where azithromycin was used adjunctively as a third antibiotic in two of six patients already on ceftriaxone and ofloxacin. Of these six patients, four were culture positive.

Antibiotic prescription in the OPD: Among the 98 patients presenting to the OPD, 79 were prescribed

Table II. Days of therapy (DoT) for ceftriaxone, ofloxacin and azithromycin in hospitalized patients from 2013-2016

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

Table III. Antibiotic prescribed in outpatient department patients for typhoid fever from 2013-2016

Duration	Number of patients	Cefixime (%)	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 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

cefixime, 11 ofloxacin and two azithromycin. Ten patients could not be followed for modifications of initial presumptive therapy (amoxiclav in 6 and no antibiotic in 4) because they either did not give a blood sample for laboratory tests or did not return for follow up after culture reports were available. The combination of antibiotics was needed based on the clinical judgement on follow up in five patients who were already on cefixime, of whom ofloxacin was added to cefixime in four while azithromycin and ciprofloxacin was added in one patient each.

It was observed that the number of patients who were prescribed cefixime increased from 81 per cent in 2013 to 100 per cent in 2016 while the use of ofloxacin was 19 per cent in 2013, but in 2016, it was prescribed only in addition to first-line antibiotic based on the clinical judgement (Table III). Azithromycin was used minimally in our settings.

Discussion

The third-generation cephalosporins are presently the drug of choice for the treatment of typhoid fever. The clinical studies on efficacy are available for parenteral ceftriaxone only (not oral cefixime) and increasing MIC to ceftriaxone is a cause of concern[13,14].

The present study was undertaken to determine the antibiotic use in enteric fever in children presenting to a tertiary care centre in north India. All the patients included in our study had fever with a mean duration of 9.5 days at the time of presentation. Moreover, about 20 per cent of the patients had also provided history of taking some antibiotics before the visit either oral cefixime or ciprofloxacin or unknown to them. This could be a reason for more severe cases presenting and low blood culture positivity being only 45 per cent.

S. Typhi was found to be a major etiological agent of enteric fever in our patients followed by *S.* Paratyphi A. Ceftriaxone was prescribed as the first line in hospitalized patients while in OPD it was cefixime. However, if the patient did not show clinical improvement, another drug such as ofloxacin or azithromycin was added. The non-response to the initial antibiotic was responsible for prolonged hospitalization and increased morbidity due to increased defervescence. The delay in clinical response to ceftriaxone might be due to high MIC and required the addition of a second antibiotic in 10 per cent patients and a third antibiotic in two per cent. This combination, however, was sequentially added, mostly on the review of clinical condition.

With many reports of ceftriaxone resistance and absence of any new drug, the studies are ongoing to understand the combination of antibiotic in the treatment of typhoid fever. In an API conclave on enteric fever, it was recommended that combination therapy should be used in case of fever lasting for seven days and no clinical improvement with monotherapy[32,33].

The fixed-dose combinations are in use but without any data to support their advantage. Before the fixed-dose combinations are prescribed, second antibiotic should be added only on clinical judgment in selected cases. Furthermore, there is a need to strengthen preventive measures like safe water supply and by developing new vaccines that are effective against both *S.* Typhi and *S.* Paratyphi A as there is no new drug is in the horizon.

The limitation of the present study was the diagnosis of typhoid fever using serology or clinical parameters having low specificity. There was a possibility of many cases being falsely labelled as typhoid. The use of IgM TyphiPoint test is limited. It was done for all patients irrespective of duration of fever. Widal test alone in the diagnosis of typhoid fever is of limited value especially in a single serum and we could not get any paired serum sample. This was another limitation of the present study.

To conclude, our results indicated a creeping MIC to ceftriaxone. While multidrug therapy in typhoid fever

must be given in selected cases only, role of many fixed drug combinations available needs to be evaluated. Our study highlights the need for clear-cut guidelines in the treatment of typhoid fever using multidrug therapy in the time of emerging antimicrobial resistance in *S.* Typhi and *S.* Paratyphi A.

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***Conflicts of Interest*:** None.

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For correspondence: Dr Arti Kapil, Department of Microbiology, All India Institute of Medical Sciences, New Delhi 110 029, India
e-mail: akapilmicro@gmail.com