Defervescence of enteric fever in children treated with ceftriaxone: A hospital-based study in Nepal

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Research Article

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Abstract

Background: Enteric fever (EF) continuous to be a serious health threat in Nepal and children are mostly affected from this systemic illness with gruesome complications if left untreated. Accurate diagnosis and appropriate antimicrobial therapy still remain a challenge here. Though ceftriaxone is used as the drug of choice in hospitalized patients, there are concerns on emerging cephalosporin resistance in adults, though not reported in children yet. The objectives of this study were to assess the defervescence time and outcomes of children hospitalized with EF treated with ceftriaxone.

Methods: This prospective observational study was conducted at Kathmandu tertiary hospital, Nepal for 12 consecutive months. Children (5-16 years) diagnosed with enteric fever using WHO or validated clinical diagnostic criteria were eligible for recruitment. After taking written informed consent, enrolled children were treated as per the institutional treatment protocol with a same brand of ceftriaxone of standard daily dose and duration of 7 days for uncomplicated and 10 days for complicated. Data on defervescence time, treatment outcomes and their clinical and laboratory profile were collected in the predesigned proforma and analyzed.

Results: Of 106 enrolled children, the predominant manifestations were headache (95.3%), loss of appetite (94.3%) and abdominal pain (90.6%). The main laboratory findings were positive Widal test (74%) and thrombocytopenia (50%). Nine children (8.5%) showed blood culture positivity. *Salmonella* typhi with nalidixic acid resistant strains and *Salmonella* paratyphi A were isolated (2:1) and were sensitive to ceftriaxone (100%). The defervescence mean time was 3.94 days (± 0.96 SD). Children with positive blood culture had significantly longer defervescence time than those with negative culture (4.56 versus 3.89 days; p=0.04). One child developed complication (pneumonia). No children died or encountered treatment failure. Thrombophlebitis (38.7%) was the only adverse effect of ceftriaxone.

Conclusion: Ceftriaxone of once daily dosing regimen exhibited safe and satisfactory treatment outcomes with approximate four days to defervescence. Ceftriaxone can still be drug of choice for the treatment of EF in hospitalized children. Further studies with a greater number of isolates for the classical clinical profile of EF and cephalosporin susceptibility in children may confirm or refute these findings.

Background

Enteric fever (EF) is an acute, systemic and life-threatening infectious disease caused by *Salmonella enterica* serovars Typhi and Paratyphi A, B, C. It is transmitted through fecal-oral route. These bacteria thrive in environments of poor sanitation and inadequate clean water supply.

Globally, there are an estimated 11–21 million cases of EF and approximately 128000–161000 deaths annually [1]. This disease is responsible for significant burden of morbidity and mortality worldwide especially in developing countries [1–3]. In Nepal, EF is endemic in all populated areas including Kathmandu valley. The growing population density with increased urbanization and lack of safe clean

water supply has led to high prevalence of EF in the country recently [(4)]. *Salmonella* is by far the most common single pathogen isolated in blood cultures in Nepal [5, 6].

The diverse clinical manifestations of EF in children often mimic other endemic infectious illness causing diagnostic challenges later developing severe complications and deaths. The complications have been reported more in children than in adults [7] and those who have been ill for more than two weeks of duration [8]. Though blood culture is gold standard for diagnosis the isolation rate is only 40–60%, primarily due to widespread use of antimicrobials before patients present to health center [1.9]. In day-to-day practice, most cases are diagnosed clinically without sufficient microbiological evidence. Widal test is still widely used for the diagnosis despite cross reactivity limitations [9, 10].

The emergence of antimicrobial resistance is a significant challenge with several outbreaks caused by multidrug resistant strains (MDRS) of *S.typhi* in developing countries. In recent years, decreased susceptibility has been reported to fluoroquinolones in many countries including India [11, 12] and Nepal [13, 14] thereby ciprofloxacin is no longer the empirical choice for EF. The resistant strains have been found to be susceptible to third generation cephalosporins, which became the drugs of choice for the treatment of EF [15]. However, there are reports on increased minimum inhibitory concentration and resistance development to ceftriaxone in adults [16, 17] mediated by acquisition of β-lactamases causing delayed defervescence and treatment failure. Late defervescence leads to uncertainty of diagnosis, multiple investigations and different therapeutic trials thereby excessive hospital resources utilization as well as financial burden to the patients.

The objectives of this study were to determine the defervescence and treatment outcomes of ceftriaxone in hospitalized children with EF presenting to a tertiary care hospital in Kathmandu, Nepal, and to describe clinical and laboratory characteristics of those children.

Materials And Methods

Ethical approval

Approval for this study was granted by the Institutional Review Board of the Institution, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal [reference number 33(6-11-E) 2/071/92) dated 15th August 2014].

Study design, setting and participants

This was a prospective observational study conducted over a year (17thAugust 2014 to 17thAugust 2015) at Tribhuvan University Teaching Hospital, Kathmandu, in Nepal.

The study population was children aged 5 to 16 years admitted with fever of three days or more and fulfilling either the WHO definition for EF [18] or the clinical validated diagnostic criteria of EF [19] (Table 1).

Table 1. Inclusion criteria

Children between 5 and 16 years of age were eligible if they were admitted with at least three days of fever, and either A or B	
A. WHO case definition of EF (confirmed or probable)	**B. Validated clinical diagnostic criteria (3 major plus 3 minor or more)**
Confirmed case: Patient with fever (≥37.5°C or ≥ 99.6°F) that has lasted for at least three days, with a laboratory-confirmed positive culture (blood, bone marrow, bowel fluid) of *S. typhi*.	***Major criteria:*** - Fever - Headache - Relative bradycardia
Probable case: Patient with fever (≥37.5The°C or ≥99.6 °F) that has lasted for at least three days, with a positive sero diagnosis or antigen detection test (Widal test; TO/TH or AO/AH titer ≥ 160) but without *S. typhi* isolation.	***Minor criteria:*** - Pain abdomen - Splenomegaly, hepatomegaly, or both - Chills - Diarrhoea - Vomiting

We excluded children under 5 years of age, immunocompromised (HIV, immunosuppressive drugs), referred from other hospitals with prior treatment with ceftriaxone, with known allergy to ceftriaxone or penicillin, and children whose parents or care taker did not give consent. We took prior approval from institutional review board. After taking written informed consent from the parents of all children and filling up each predesigned proforma, children were treated as per the institutional treatment protocol with same brand of ceftriaxone 75mg/kg once daily for 7 days for uncomplicated EF and 10 days for complicated EF. Axillary body temperature was recorded at the time of admission, the time of medication and four-hourly by using digital thermometer with daily monitoring for clinical response. The intravenous cannulas were changed every 72 hours (or earlier, if signs of thrombophlebitis).

Data collection

The data on demography, details on clinical features for each enrolled child were collected from the filled predesigned proforma. Data on laboratory parameters, antibiotic sensitivity pattern, treatment outcomes from ceftriaxone (fever defeverscence, recovery, complications and drug adverse effects) and length of hospital stay were collected as the following definitions.

The defervescence (also known as fever clearance time) was defined as the time between administration of the first dose of ceftriaxone and the first day the patient's axillary temperature dropped to and remained at less than 99.6°F for at least 48 hours.

The patients were classified as clinically recovered if they remained afebrile (axillary temperature less than 99.6^0F for 48 hours) after completion of seven days of ceftriaxone without developing complications. Fever persistence despite 10 days of ceftriaxone therapy or the need of additional antibiotics was considered as treatment failure. The outcome was recorded as death of any enrolled child who did not survive due to EF during the study period.

Statistical Analysis

Data were captured using Microsoft Excel and analysed by using SPSS software (SPSS- Statistics 2014 version 21.0). Categorical data were grouped and expressed as frequency and percentage, whereas numerical data were expressed as mean and standard deviation (SD). We compared defervescence between subgroups, by using *T*-test taking P value < 0.05 as statistically significant.

Results

A total 521 children were screened for fever of 3 days and more during the study period. Out of them 118 were diagnosed to have enteric fever. Twelve patients presented exclusion criteria, leaving a total of 106 children for enrollment and analysis (Fig. 1).

The distribution of boys and girls were equal. The age range of the study population was 5 years or more to 16 years and age groups were divided into two categories (Table 2). The mean age group was 10.79(±2.93) years. Sixty children (57%) were aged 11 to 16 years.

Table 2. Age and gender distribution of study population (N=106)

	n	%
Age group in years		
5 to 10	46	43
11 to 16	60	57
Gender		
Male	53	50
Female	53	50

The mean duration of fever at hospitalization was 8.16 (±3.23) days and 96 children (90.6%) had prior history of oral antibiotic consumption on enrollment. Headache (95.3%), loss of appetite (94.3%), abdominal pain (90.6%) and vomiting (89.6%) were predominant symptoms. The most predominant signs were coated tongue (81.1%), isolated hepatomegaly (78.3%) and isolated splenomegaly (67.9%). The mean pulse rate on admission was 91 bpm (±12SD). The other clinical features are shown in Fig. 2.

Most children (85.8%) had normal total leucocyte count, 10.4% children had leucopenia and only 3.8% had leucocytosis. Only 8.5% of the children were found to be anemic. Half of the children (50%) had thrombocytopenia. All the cases had normal liver function test except for one child who had mild elevation of liver enzymes. Approximately 74% of the cases had a positive Widal test (Table 3). Nine cases (8.5%) yielded isolates of *S. typhi (n=6)* and *S. paratyphi A (n=3)* in blood culture.

Table 3. Baseline laboratory profile of the cases in the study

Investigations	n	%
Total Leukocyte Count:		
Normal (4-10.5x10^3cells/mm^3)	91	85.8
High (>10.5x10^3 cells/mm^3)	4	3.8
Low (<4 x10^3 cells/mm^3)	11	10.4
Hemoglobin:		
Normal	97	91.5
Anemia (<11gm/dl)	9	8.5
Platelet count:		
Normal	53	50
Thrombocytopenia (< 1.5 lac/mm^3)	53	50
Thrombocytosis (>4.0 lac/mm^3)	0	0
Liver Function Test:		
Normal	105	99.1
Deranged (Transaminitis/hyperbilirubinemia)	1	0.9
Blood culture:		
Negative	97	91.5
Positive (*S. typhi and S. paratyphi)*	9	8.5
Widal test (TO>1:160)		
Positive	78	73.6
Negative	28	26.4

Antibiotic sensitivity pattern showed 100% sensitive to cephalosporin group of antibiotics (cefixime, ceftriaxone and cefotaxime) and two thirds of the cases showed resistance to quinolones including nalidixic acid (6/9; 66.6%). Primary antimicrobials like ampicillin, chloramphenicol and cotrimoxazole showed 33% sensitivity (Fig.3).

The overall mean time of defervescence was 3.9 days±0.96. The mean time of defervescence was longer in culture positive and those who weren't on prior oral antibiotics than in culture negative (4.6 versus 3.9 days; p=0.04) and those already on oral antibiotics (4.4 versus 3.9 days; p 0.11) respectively (Table 4).

Table 4. Defervescence time of EF

Defervescence time		n	Mean (SD)	p-value
All children		106	3.94 (0.96)	
Blood culture	Positive	9	4.56 (1.13)	0.04
	Negative	97	3.89(0.93)	
Prior oral antibiotic intake at admission	Present	96	3.90 (0.93)	0.11
	Absent	10	4.40(0.93)	

All children recovered well with ceftriaxone except for one developed pneumonia as a complication. There was neither treatment failure nor mortality (Table 5). The mean duration of hospital stay was 7.56±1.18 days. Most of the children (83%) stayed total duration of 7 days for the treatment and eighteen children for 10 days duration. Among 18 children who stayed for 10 days, 14 children had thrombophlebitis, 3 had blood culture positive and one who developed pneumonia as complication of EF. There were no cases that stayed beyond 2 weeks or less than a week.

Table 5. Summary of treatment outcomes of EF cases with ceftriaxone

Outcomes	n (N = 106)	%
Recovered without complications	105	99.0
Developed complications	1	0.9
Treatment failure	0	0
Death	0	0
Thrombophlebitis due to Ceftriaxone	41	38.7

Discussion

Most children (60%) in the present study were school age (11-16 years) which was similar in the findings of other studies [20-22]. This could be due to outdoor eating habits of school going children in poor hygienic conditions from the street vendors. There was no difference in gender distribution, consistent with the results from Pakistan by Khan MN et al [22] but Singh DS et al [21] observed males predominance than females.

The overall mean time taken for defervescence with ceftriaxone monotherapy was 3.94 days (± 0.96 SD) is consistent with similar findings from the studies in Nepal [23] Egypt [24,25] and India [26]. The mean defervescence time between blood culture positive and negative, it was observed that it took longer in culture positive than in the culture negative cases (4.6 versus 3.9 days) with statistically significance (p=0.04). Similar results were reported by Rathore MH et al [27], Tatli MM et al [28] and Khatri R et al [29]. This most probably is explained by the bacteriologically confirmed Salmonella cases having high bacterial loads, requiring longer treatment for fever clearance.

The predominant symptoms after fever were headache and gastrointestinal symptoms. Constipation was observed more common (28%) in this study than diarrhea (13%) in contrast to findings in the separate studies in India [20,30,31] and Nepal [21,32] where diarrhea was a more frequent presentation than constipation. This could be because the age group in the current study was > 5 years and diarrhea is known to be more common in the younger age, < 5 years with enteric fever. The main clinical signs observed were coated tongue (81%), isolated hepatomegaly (78%) and splenomegaly (68%), similar to that reported by Malini et al [20] and Laishram et al [31]. Relative bradycardia considered to be salient feature of enteric fever in adults was infrequently observed in our study, consistent with other studies [31,33].

The predominant laboratory findings were normal total leukocyte count (85%) and only 10% had leucopenia. Normal leucocyte has been observed by other studies done in Nepal by Singh DS et al [21] and in India [20,26,34]. Thus, leucopenia, relative bradycardia and diarrhea may not be common features of enteric fever in children. Thrombocytopenia was present in half of the children (50%) but none had

severe thrombocytopenia nor thrombocytosis. Similar findings were reported by Malini et al [22] Laishram et al [31] and Al Reesi M et al [35]. Thrombocytopenia was reported as a marker for severity and complications in enteric fever in the study done by Laishram et al [31]. However, Malini et al [20] reported no statistical significance between thrombocytopenia and the occurrence of complications. In the present study, only one child with moderate thrombocytopenia developed pneumonia.

A significant proportion of children (73.6%) were Widal positive but only 5 of the 78 Widal positive isolated *S. typhi* in the blood culture. This high percentage of Widal positivity is in accord with the findings by Kumar et al [33], Chowta et al [36] and Malla et al [37]. Despite the drawbacks on Widal test, it is commonly used for diagnosis as it is cost effective and easily available as compared to other serodiagnostic tests [38]. Widal titre of TO/TH > 1:160/1:160 may be considered the laboratory supporting test for diagnosis of EF considering that the rate of culture positive is only 10% in Nepal [39]. Likewise, the culture positivity in our study was only 8.5% which is comparable to the study reported by Shah G et al [32]. This poor yield may be related to multiple factors like inadequate volume of blood collected, inadequate laboratory media and the delay in incubating the media after the blood withdrawal. The important factor in this study could be the significant proportion of children (90.6%) already on oral antibiotic therapy before blood culture collection.

Out of 9 culture positive cases, 6 isolated typhi strains and only 3 isolated paratyphi serovars in the present study. A 2/3rd cases (66.6%) of Salmonella growth had fluoroquinolone resistant strains with 33.3% yielding nalidixic acid resistant *S.typhi* (NARST) strains though it was from the small number of total isolates. In the last two decades, there has been a change in the pattern of EF with the emergence of MDRS. The multiple studies [13,40,41] in Kathmandu, Nepal reported paratyphi as more prevalent serovars and some studies [14,15,32] observed high prevalence of NARST. This could be due to the wide use of quinolones for the treatment of EF, along with the easy availability of oral quinolones from pharmacies without a prescription. The higher frequency of NARST isolates indicates the possibility of fluoroquinolone resistance occurring in near future as a consequence of the rampant use of fluoroquinolones. NARST strain is a marker for predicting low level resistance to ciprofloxacin among *S. typhi* and also an indicator of treatment failure to ciprofloxacin [43]. Asian countries were reported to have increased rate of NARST strains as described by Ochial LR et al [44].

In this study, salmonella isolates showed 100% susceptible to third generation cephalosporins viz Cefixime, Ceftriaxone and Cefotaxime consistent with similar findings described by other authors in Nepal [13,21,45] and in India [20,26,46]. The response to ceftriaxone monotherapy was significant (100%) with no treatment failure nor mortality, with similar results observed by other authors [12,30].

A complication was seen in only one child in the present study which is comparable to the observation by Succinder M et al [26] where as other authors observed more complications including gastrointestinal and neurological [20,32]. Low incidence of complications in our study could be because of less than 2 weeks duration of illness (mean duration of fever on presentation 8.13 ±3.23 days), low yield of salmonella in

the blood culture hence less bacterium inoculum, prompt adequate and appropriate antibiotic therapy and duration as per institutional standard protocol.

The main adverse effect of ceftriaxone observed was thrombophlebitis (38.7%) but no major adverse events that led to interruption or discontinuation of the ceftriaxone were seen. Thrombophlebitis could be due to mechanical or chemical irritation of veins. Ceftriaxone is known to cause chemical phlebitis. Urbanetto J S et al [47] observed significant association of ceftriaxone with incidence of post-infusion phlebitis, however ceftriaxone has proven safe without causing any significant adverse effects in either once daily or twice daily dosing regimens [48,49].

The results of this study might not be generalizable to the patients in all health facility since the study was done among hospitalized children only at single tertiary hospital. Majority children had taken oral antibiotic prior admission, possibility of low yielding of growth in the culture and hence the diagnoses in culture negative were based on validated clinical diagnostic features and Widal test. Though new noninvasive assays like polymerase chain reaction-based tests and proteomics for rapid diagnosis of EF are available but their utility for detection is still debated and more over it will be unaffordable for developing countries who are endemic, thus in practice Widal test still plays major role for diagnosis in spite of poor sensitivity and specificity.

Conclusion

Children with EF were commonly affected with one-week duration of illness with diverse clinical presentations. Ceftriaxone of once daily dosing regimen exhibited safe and satisfactory treatment outcomes though defervescence after 3 days. Ceftriaxone can still be drug of choice for the treatment of EF in hospitalized children however we believe that studies with a greater number of isolates should be conducted on cephalosporin susceptibility and MIC in children with enteric fever which will confirm or refute these findings as there are no reports in pediatric population.

Declarations

Ethical approval and consent to participate

Approval for this study was granted by the Institutional Review Board of the Institution, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal [reference number 33(6-11-E) 2/071/92) dated 15th August 2014]. After taking written informed consent from the parents of all children and filling up each predesigned proforma, children were treated with same brand of ceftriaxone 75mg/kg once daily for 7 days for uncomplicated EF and 10 days for complicated EF. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article

Competing interests

None

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None

Author's contribution

TL and FCG conceived and designed the study. TL implemented recruitment process and collected and entered data. TL and SB analyzed and interpreted data. TL wrote the first draft of the manuscript. SB appraised the manuscript and contributed to it by revising the different versions. All authors read and approved the final manuscript.

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Figures

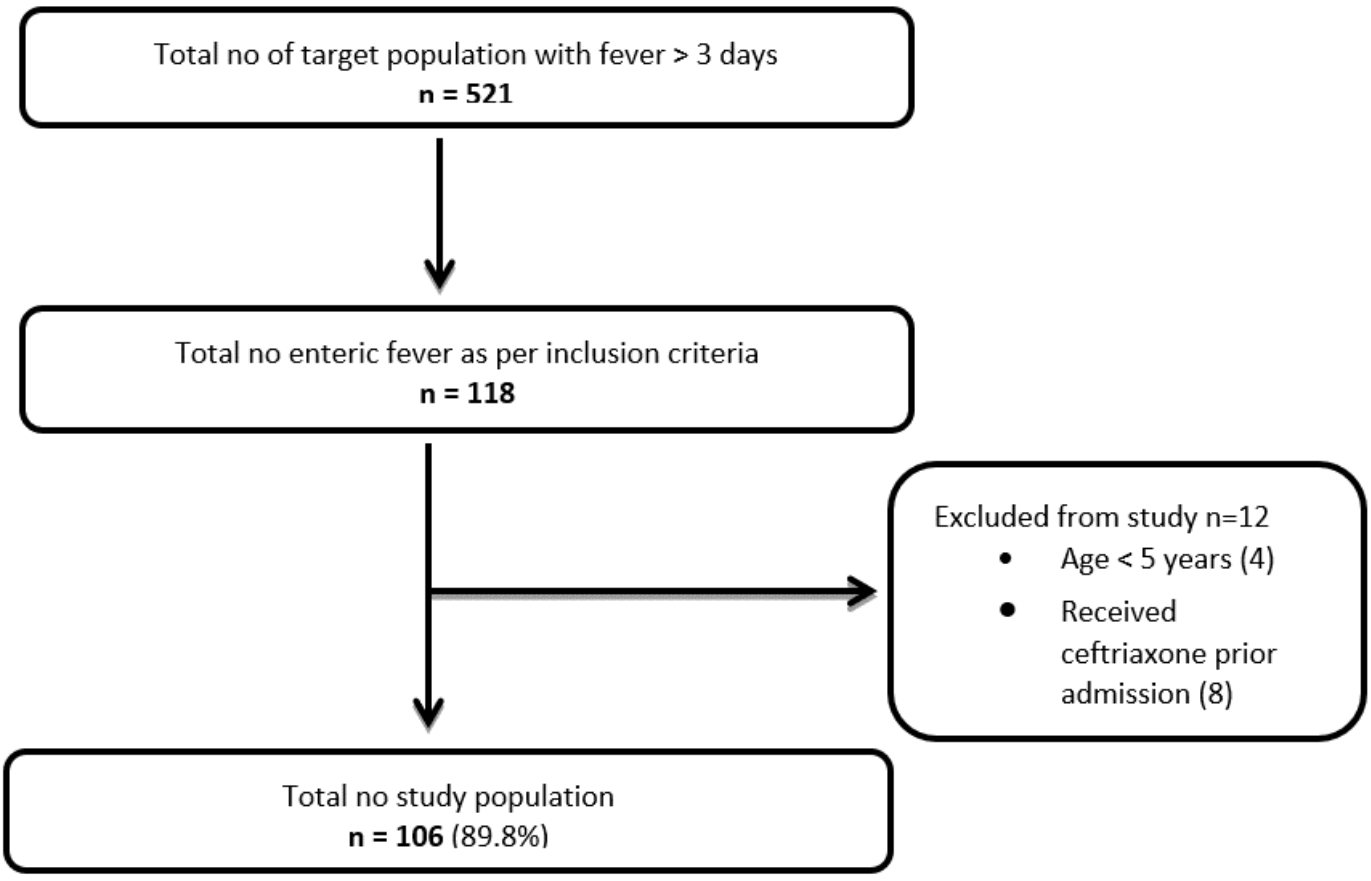

Figure 1

Study profile

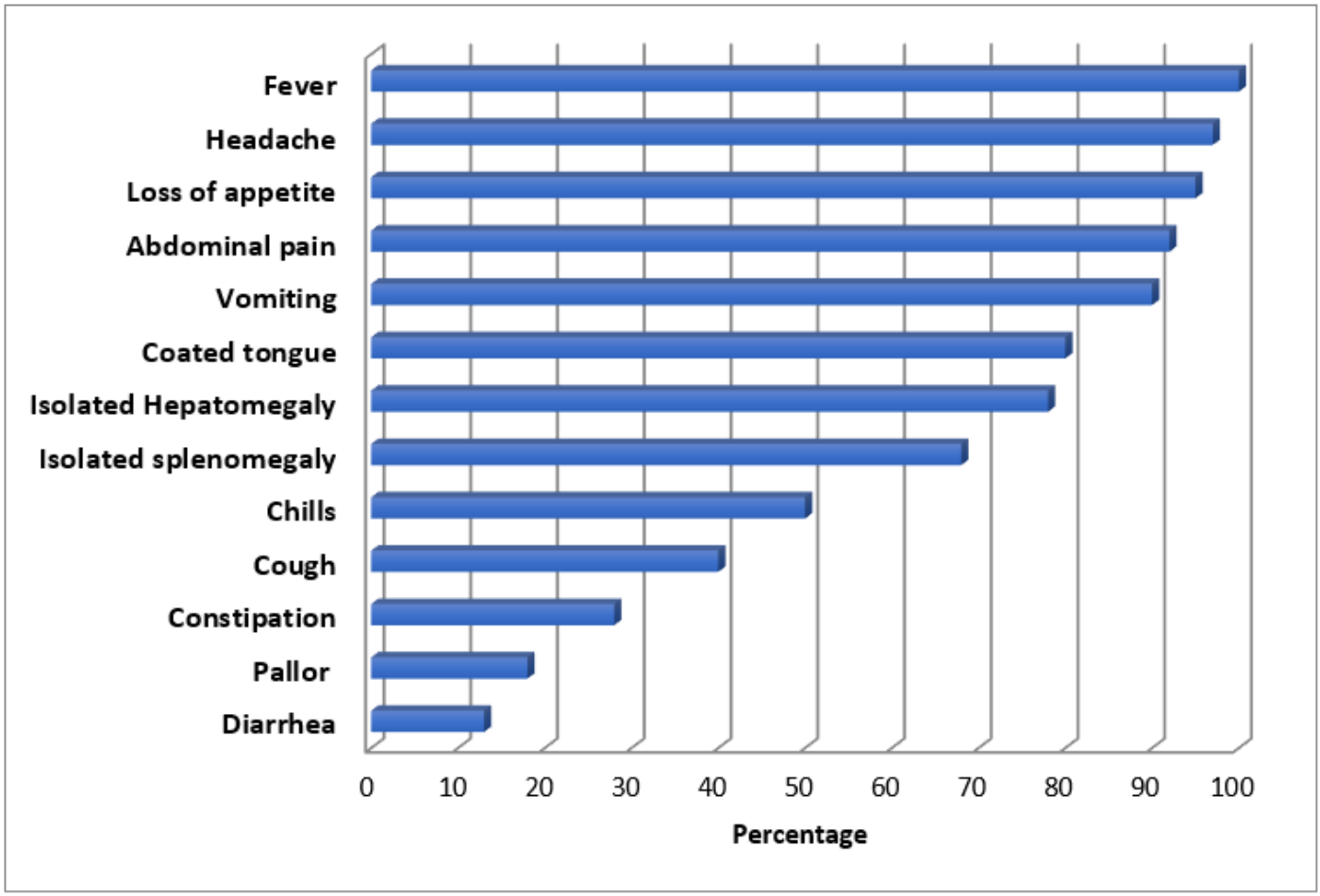

Figure 2

Pattern of clinical profile on presentation

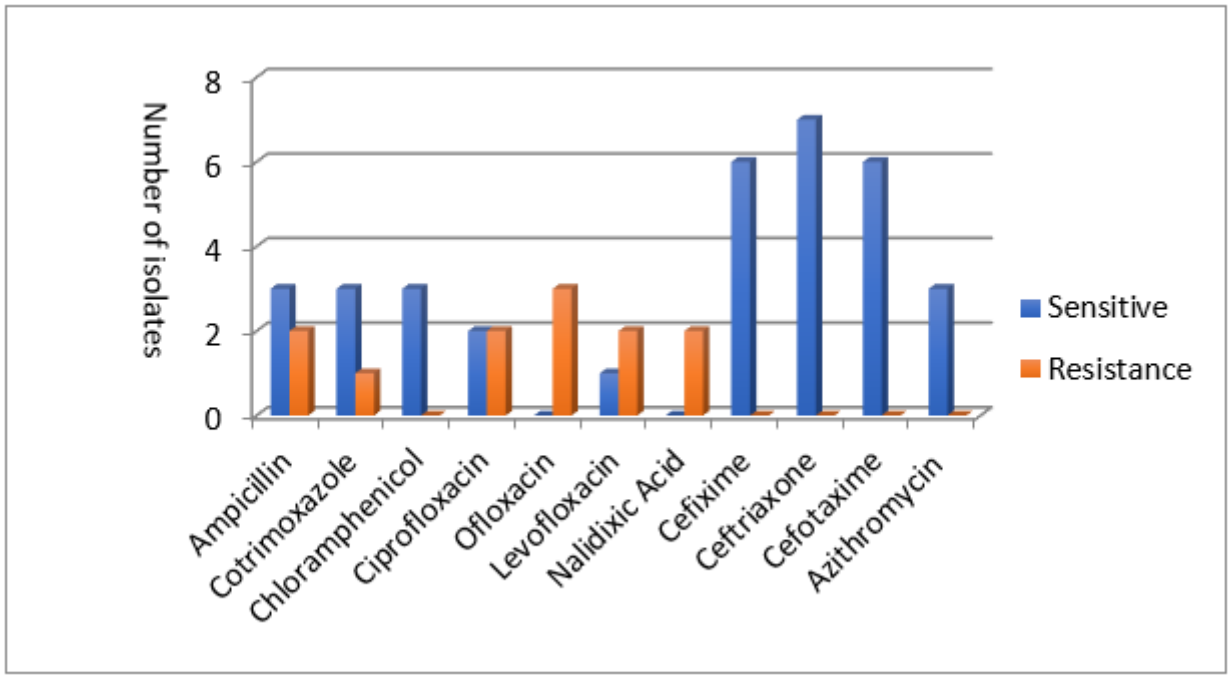

Figure 3

Antibiotic sensitivity pattern of Salmonella typhi and paratyphi.