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Original Article

Is Antimicrobial Resistance Pattern of Enteric Fever Changing in Kathmandu Valley?

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Abstract

Introduction: Enteric fever is a public health problem in developing countries including Nepal. Antimicrobial sensitivity pattern of *Salmonella sp* causing enteric fever is changing over time and also differs according to geographical location. Periodic surveillance of antimicrobial resistance of *Salmonella sp* is mandatory for management of enteric fever rationally. The objective of this study was to analyze the resistance pattern of *Salmonella sp* to commonly used antimicrobials. **Materials and Methods**: This was a retrospective study undertaken reviewing the records of blood isolates of *Salmonella sp* over one year period at Kanti Children's Hospital, Nepal. Antimicrobial sensitivity testing was done following Kirby Bauer's disk diffusion technique using Muller Hinton agar. **Results**: *Salmonella typhi* was found to be 100% resistance to ampicillin and resistance to nalidixic acid and ciprofloxacin was also high. The resistance to chloramphenicol and ofloxacin was low. No resistance was found to amoxicillin, ceftriaxone, cefotaxime and amikacin. However, among the sensitive isolates of *Salmonella typhi* intermediate sensitivity to ceftriaxone and ceftazidime was reported to be high. Among the isolates of *S paratyphi A,* the resistance to nalidixic acid was 100% followed by 75% to ciprofloxacin. No resistance was found to chloramphenicol, ceftriaxone, cefixime, amikacin and low resistance to amoxicillin and ofloxacin. Among the sensitive isolates of *S paratyphi A,* majority of them were only moderately sensitive to cefotaxime and ceftazidime and about 1/3 of the organisms had only intermediate sensitivity to ceftriaxone. **Conclusiion**: Commonly used parenteral third generation cephalosporins, first line drugs like chloramphenicol and amoxicillin and ofloxacin among fluoroquinolones were found to be effective in vitro in treating enteric fever. However, *Salmonella typhi* was found to be highly resistant to the most frequently used drugs like ciprofloxacin and cefixime and *Salmonella paratyphi A* to ciprofloxacin. A comparative chart of antimicrobial sensitivity of enteric fever in children over 10 year period from different hospitals of Kathmandu valley is also presented in the study.

Key words: Antimicrobial sensitivity, Antimicrobial resistance, Enteric fever, *Salmonella sp*

Introduction

Enteric fever is one of the public health problems in developing countries[1,2]. It continues to be endemic in poor countries[3]. Annual global incidence of enteric fever is estimated to be 0.3%[4] reaching 1.0% in disease endemic areas[5]. Worldwide, about 21 millions cases occur annually and among them 1-4% ends fatally predominantly in children, 90% of which happen in Asia[6]. Enteric fever is a public health problem in Nepal as well[7,8]. It occurs in almost every part of our country from mountain areas to Terai plains[9,10].

Enteric fever occurs commonly in monsoon seasons. Outbreaks of enteric fever also usually occur in summer[11,12]. Children are the mostly affected age group[3,10]. Infected persons and healthy carriers are the source of infection. "Five Fs" viz. food, fingers, flies, fomites and faeces are considered to be the main media for spread of this disease. The main factors responsible for such spread are poor sanitation and inadequate facilities for safe drinking water[13].

The main causative agent of enteric fever is *Salmonella typhi* (*S typhi*) followed by *paratyphi A* (*S paratyphi A*). Early diagnosis and treatment reduces the morbidity and mortality from this infection. However, emergence of multi drug resistant (MDR) strains to first line antibiotics viz. chloramphenicol, ampicillin and cotrimoxazole in the late eighties and early nineties posed a great challenge to manage this disease[14,15]. Fluoroquinolones became the drug of choice for managing these cases after the emergence of MDR strains[16]. Unfortunately, these organisms developed resistance to fluoroquionolones also within a decade of their use[7,15]. Third generation cephalosporins were then recommended to treat these resistant cases.[15] But, again there has been a great concern due to report of emerging resistance of these organisms to third generation cephalosporin[17,18].

It appears that the antimicrobial sensitivity pattern changes over time and differs from institution to institution in the same period of time. This could be due to the phenomenon of antimicrobial cycling[19] that may be taking place spontaneously. For instance, *Salmonella sp* have become sensitive to ampicillin/amoxicillin, cotrimoxazole and chloramphenicol once again[15,20]. Therefore, there is a great need of constant surveillance and antimicrobial sensitivity testing from different geographical areas to keep update with emerging patterns of drug sensitivity in enteric fever[2]. The findings from such studies help apply evidence based rational prescription practices because prudent and potent antimicrobial use not only prevents the emergence and spread of resistant strains of microorganisms but also benefit the patients and a nation as whole[21]. Therefore, this study was conducted to analyze the antimicrobial sensitivity pattern of blood isolates of *Salmonella sp* in children at Kanti Children's Hospital.

Materials and Methods

This was a retrospective study conducted at Kanti Children's Hospital, Kathmandu, Nepal over one year period from April 2011 to March 2012. Records of all blood samples collected for cultures from children aged 1 day to 14 years attending this hospital out-patient department and admitted in the hospital were analyzed for this study. This hospital is a referral centre for children throughout Nepal; however children from outside the Kathmandu valley usually come after antimicrobial treatment for infections.

Three ml of blood was collected by aseptic venipuncture and mixed in 30 ml of broth for culture. If the collected blood volume was not adequate (less than 3 ml) the volume of the broth was made 90% of the amount of blood collected. Blood samples collected were subjected to bacteriological culture and incubated at 37^0C over night followed by sub-culture on MacConkey agar. Incubation was continued for growth negative cultures for 72 hours sub-culturing at 48 and 72 hours. Growth negative cultures even after this period were regarded as negative.

The non lactose fermenting colonies in MacConkey agar resembling *Salmonella sp* were further subjected to serotyping. Blood isolates other than *Salmonella sp* were not included in the study. Blood isolates of *Salmonella sp* were subjected to antibacterial susceptibility testing following Kirby Bauer's disk diffusion technique using Muller Hinton agar. The antimicrobial impregnated discs were placed on the surface of the agar plate and incubated at 37^0C for 18 hours. Diameter of the zone of inhibition was measured for individual antimicrobial and interpreted as sensitive, intermediate and resistant on the basis of zone size as per manufacturer's instruction. Antimicroibioal discs used in this study were amikacin, amoxicillin, ampicillin, cefixime, cefotaxime, ceftazidime, ceftriaxone, chloramphenicol, ciprofloxacin, cotrimoxazole, cloxacillin, nalidixic acid, norfloxacin, ofloxacin and tobramycin. However, only 6-7 antimicrobial discs were tested for each culture positive sample. If the culture positive sample was found resistance to all 6 or 7 antimicrobials it was tested for other antimicrobials. Selection of the antimicrobial discs to be used was based on the availability of the discs in the hospital laboratory.

The variables investigated were age and sex of the child, *Salmonella species* and their antimicrobial sensitivity pattern as data only on these variables were available in the records. Data analysis was done using SPSS software package version 16.

Permission to undertake this study was taken from the institutional review committee of the hospital.

Results

Total number of blood samples collected for culture during one year period was 10883, among them only 60 samples yielded *Salmonella sp*. Growth of *Salmonella sp* was not observed in children less than one year of age. Of the 60 positive samples, samples from male patients outnumbered females (60.0% vs 40.0%). The most affected age group was 6-10 year followed by age group of 1-5 years (Table 2). *S typhi* constituted more than double of the samples (72.0% vs 28.0%). Positive samples were found to be more in spring (March, April, May), summer (June, July, August) and early autumn months (September) with highest peak in June (Fig. 1).

Salmonella typhi was found to be 100.0% resistant to ampicillin and resistance to nalidixic acid and ciprofloxacin was also high (59.4% and 46.4% respectively). No resistant strain was shown to amoxicillin, ceftriaxone, cefotaxime and amikacin. Resistance to chloramphenicol and ofloxacin was low. However, only moderate sensitivity of *Salmonella typhi* to ceftriaxone and ceftazidime was worth noting here. (Table 3).

No resistance of *S paratyphi A* was shown to chloramphenicol, ceftriaxone, cefixime and amikacin. The resistance to amoxicillin and ofloxacin was low. The resistant rate of nalidixic acid was 100.0% and that of ciprofloxacin was also high (75.0%). One fifth of the *S paratyphi A* was resistant to ceftazidime and 1/3 of it to cotrimoxazole. However, it is worth noting that majority of isolated *S paratyphi A* were only moderately sensitive to cefotaxime and ceftazidime and about 1/3 of the organisms also had only intermediate sensitivity to ceftriaxone. (Table 4).

Table 1: Distribution of blood samples for culture by age and sex (n=10883)

Age-group	Male		Female		Total	%
	No	%	No	%		
< 1 month	1679	62.2	1020	37.8	2699	24.8
1-11months	1493	64.1	836	35.9	2329	21.4
1-5 yrs	2157	61.6	1347	38.4	3504	32.2
6-10 yrs	1025	63.6	586	36.4	1611	14.8
11-14 yrs	441	59.6	299	40.4	740	6.8
Total	6795	62.4	4088	37.6	10883	100.0

Table 2: Culture positive samples of *Salmonella sp* by age and sex (n=60)

Age-group	Male		Female		Total	%
	No	%	No	%		
1-5 yrs	13	52.0	12	48.0	25	41.7
6-10 yrs	18	66.7	9	33.3	27	45.0
11-14 yrs	5	62.5	3	37.5	8	13.3
Total	36	60.0	24	40.0	60	100.0

Table 3: Antibiotic sensitivity pattern of *Salmonella typhi* (n=43)

Antibiotics	Sensitivity pattern						
	Total	Sensitive	%	Intermediate	%	Resistance	%
Chloramphenicol	41	40	97.6	0	0.0	1	2.4
Ciprofloxacin	41	21	51.2	1	2.4	19	46.4
Ceftazidime	40	17	42.5	13	32.5	10	25.0
Ofloxacin	39	33	84.6	5	12.8	1	2.6
Nalidixic acid	32	12	37.5	1	3.1	19	59.4
Ceftriaxone	31	17	54.8	14	45.2	0	0.0
Amoxycillin	30	29	96.7	1	3.3	0	0.0
Cefixime	15	9	60.0	2	13.3	4	26.7
Amikacin	9	9	100.0	0	0.0	0	0.0
Cefotaxime	7	7	100.0	0	0.0	0	0.0
Ampicillin	5	0	0.0	0	0.0	5	100.0
Cotrimoxazole	2	2	100.0	0	0.0	0	0.0
Tobramycin	4	3	75.0	0	0.0	1	25.0

Table 4: Antibiotic sensitivity pattern of *Salmonella paratyphi A* (n=17)

Antibiotics	Sensitivity pattern						
	Total	Sensitive	%	Intermediate	%	Resistance	%
Chloramphenicol	17	17	100.0	0	0.0	0	0.0
Ciprofloxacin	16	4	25.0	0	0.0	12	75.0
Ceftazidime	16	4	25.0	9	56.2	3	18.8
Ofloxacin	16	10	62.5	4	25.0	2	12.5
Nalidixic acid	13	0	0.0	0	0.0	13	100.0
Ceftriaxone	9	6	66.7	3	33.3	0	0.0
Amoxycillin	15	10	66.7	3	20.0	2	13.3
Cefixime	6	4	66.7	2	33.3	0	0.0
Amikacin	4	4	100	0	0.0	0	0.0
Cefotaxime	4	1	25.0	3	75.0	0	0.0
Ampicillin	1	0	0.0	0	0.0	1	100.0
Cotrimoxazole	3	2	66.7	0	0.0	1	33.3
Cloxacillin	1	0	0.0	0	0.0	1	100.0

Table 5: Comparative chart of antibiotic resistance pattern of *Salmonella sp* in children by different studies conducted in Kathmandu valley (%).*

Author & date of study	No of isolates	Antibiotics tested and antibiotic resistance (%)									
		Amoxycillin	Ampicillin	Chloramphenicol	Cefixime	Cefotaxime	Ceftriaxone	Ciprofloxacin	Cotrimoxazole	Nalidixic acid	Ofloxacin
Ansari, 2002	37	40.0	NA	56.0	NA	0.0	NA	0.0	52.0	NA	NA
Bhattarai, 2002	14	35.7	NA	28.6	NA	0.0	NA	0.0	35.7	NA	NA
Sharma, 2005	317	4.5	NA	6.1	NA	0.0	1.6	14.0	5.8	NA	14.0
Prajapati, 2008	235	18.3	NA	6.0	NA	0.0	1.4	4.7	5.9	NA	6.9
Singh, 2010	21	19.1	NA	19.1	9.6	NA	9.6	28.6	33.3	28.6	4.8
Joshi, 2011	40	NA	25.0	0.0	0.0	0.0	0.0	12.5	0.0	57.5	5.0
Present study	60	4.4	100.0	1.7	19.0	0.0	0.0	54.4	20.0	71.0	5.5

*Sensitivity to azithromycin in children was done only in the study by Joshi et al[23], who observed the resistance to be 8.0%. Likewise, sensitivity to norfloxacin and gentamycin was done only in the studies by Bhattarai et al[10] (14.3%) and Ansari et al[25] (0.0) respectively; sensitivity to amikacin and ceftazidime was done only in the present study.

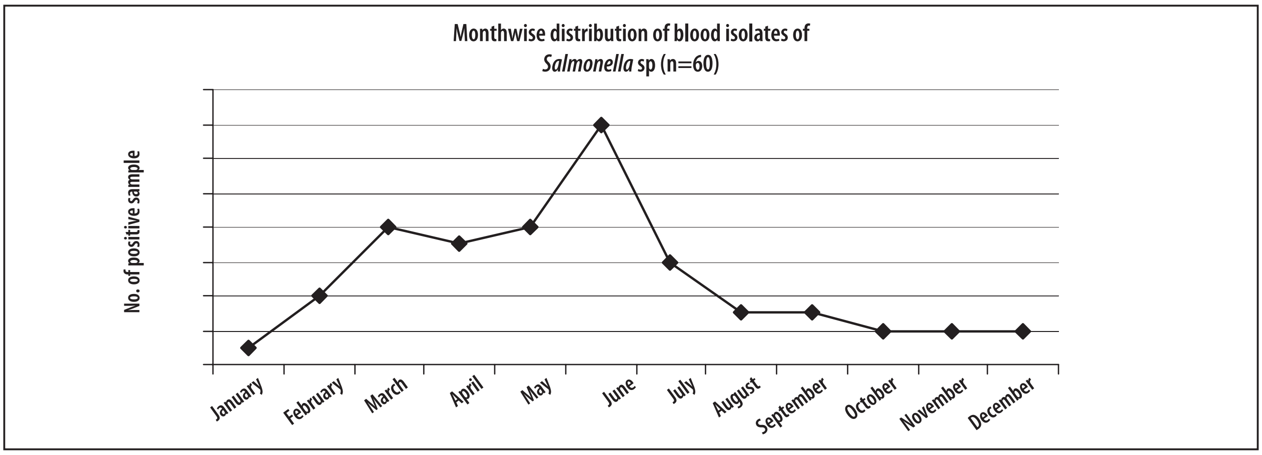

Fig 1: Showing seasonal variation of Typhoid fever.

Discussion

This study highlights the sensitivity pattern of *Salmonella sp* to different antimicrobials in children. It study shows that the occurrence of enteric fever is perennial with more number in spring, summer and early autumn and a peak in the month of June. This type of seasonal distribution of enteric fever is the typical description of occurrence of enteric fever as mentioned in the textbooks. Similar observations were seen in other series as well[22, 23, 24, 25]. The seasonal variation of occurrence of enteric fever is considered due to more chances of contamination of foods and water by faeces of infected persons and healthy carriers in the rainy season.[26] Moreover, flies are also more abundant in this season. The "five Fs" (food, fingers, flies, fomites and faeces) are considered to be the main media for spread of disease and they play more vital roles in transmission of disease in the monsoon season.

The male predominance observed in this study is in agreement with findings by other authors[22, 23, 24, 27]. This observation might be due to behavior of male children being out-door for different plays.

The most commonly affected age group (6-10 year) reported in this series is similar to the findings observed by Sharma AK[22] and Singh et al[25]. This age group is more vulnerable to exposure to contaminated foods and water and has not still developed the immunity against the disease. Ten to fourteen years was the most frequently affected age group in studies by Bhattarai et al[11] and Joshi et al[24] and under seven years was in studies by Prajapati et al[23] and Ansari et al[27]. A large scale study in five Asian countries showed the incidence of typhoid fever to be equal in both pre-school (2-5 year old) and school aged children (5-15 year old)[28]. This discrepancy in the age group could be due to relatively small sample size and most of the studies being hospital based.

The antimicrobial resistance pattern of *Salmonella sp* observed by different studies in children in Nepal is shown in table 5 for comparison.

Chloramphenicol, ampicillin and cotrimoxazole were regarded as first line drugs in the treatment of enteric fever. The development of resistance to all these 3 drugs is called as multi drug resistant (MDR) strains. The emergence of resistance to these first line antimicrobials, especially chloramphenicol in the late eighties and early nineties posed a great challenge to manage this disease[14,15]. However, *Salmonella sp* has been found sensitive to these first line drugs once again[8,15,22,23,29]. For instance, one study reported that the resistance of *S typhi* to ampicillin, cotrimoxazole and chloramphenicol decreased from 80.0%, 80.0% and 50.0% in 1995 to 37.5%, 37.5% and 12.5% in 2003 respectively. On the other hand, the resistance to ciprofloxacin and nalidixic acid rose from 0.0% and 87.2% in 1999 to 12.5% and 93.8% respectively in 2003. However, resistance to ceftriaxone remained 0.0% during that period[15].

The present study also found chloramphenicol very effective against *Salmonella sp* in vitro. But, ampicillin resistance was 100.0%. In the contrary, another series reported ampicillin to be 100.0% sensitive to *Salmonella sp*[29]. These observations could be due to antimicrobial cycling that is taking place in the prescription practices spontaneously. Furthermore, physicians might have become more cautious to use chloramphenicol because of its reported side effect of bone marrow suppression. In the contrary, some of the studies have reported resistance of *S typhi* to chloramphenicol to be still high ranging from 27.0 to 57.10%[13, 17, 30.]

Fluoroquinolones, especially ciprofloxacin and ofloxacin, became the drug of choice for managing MDR cases after the emergence of MDR strains[16]. Unfortunately, these organisms also developed resistance to fluoroquionolones within a short period of their use.[7,15] For instance, the resistance of *S typhi* to ciprofloxacin increased from 0.0% in 1998 to 12.5% in 2003. Manchanda et al[29] in 2004 reported the resistance rate of ciprofloxacin as high as 21.6%. The trend of resistance developed by *Salmonella sp* over time as reported by different studies in children in Nepal is shown in table 5 for comparison. It is seen from the table that the resistance to ciprofloxacin increased from 0.0% in 2002 to 28.6% in 2010. The present study found resistance to ciprofloxacin even higher (54.4%). However, this difference in resistance pattern should be interpreted with much caution as the methods used in these studies were different (the studies conducted in 2002 and 2010 were prospective and present study being retrospective).

The Nepalese studies mentioned in Table 5 were conducted in different hospitals by different persons where as the Indian study[15] was conducted by the same person in the same place over time. The discrepancies observed in these different studies might be due to the fact that the resistance pattern of enteric fever varies with geographical locations[28, 29]. However, it is evident that the resistance pattern to ciprofloxacin is in the increasing trend. As shown in table 5, only optimistic fluoroquinolone seems ofloxacin which has had constantly low level of resistance pattern over time. In the contrary, Manchanda et al[29] reported the resistance to ofloxacin to be as high as 19.6%. Nalidixic acid resistance against *Salmonella sp* is considered as a marker of increased minimum inhibitory concentration (MIC) of fluoroquonolones[17]. Therefore, Jamil et al[17] recommends treating nalidixic acid resistant strains of *Salmonella sp* for prolonged period (14 days) with higher doses of fluoroquonolones to avoid treatment failure.

Third generation cephalosporins were recommended to treat fluoroquinolone resistant cases of enteric fever[15]. But, reports of emerging resistance of *Salmonella sp* to third generation cephalosporins challenged the concerned personnel once again[17,18,30]. The commonly used third generation cephalosporins viz. cefixime, cefotaxime and ceftriaxone for the treatment of enteric fever have been found resistant by some studies in Nepal as well, although the resistance reported is low[23,25]. The present study also observed cefotaxime and ceftriaxone effective in vitro treatment of *Salmonella sp*. However, the concern is with reported high percentages of intermediate sensitivity to ceftriaxone (45.2% for *S typhi* and 56.2% for *paratyphi A*). The high resistance rate of cefixime (19.0%) found in this series contradicts the observations made by other studies (1.0% by Jamil et al[17] and 9.6% by Singh et al[25]). This high reported resistance of *Salmonella sp* to cefixime in the present study could be due to rampant irrational use of cefixime in the communities.

Aminoglycosides are not recommended drugs for the treatment of enteric fever. Hundred percent sensitivity of *Salmonella sp* to amikacin observed in the present study is in agreement with the finding of study by Neopane et al.[8] However, the sensitivity reported by Bhatia et al[2] is only 84%.

The increasing resistance of *Salmonella sp* to different antimicrobials has major implications on the management of enteric fever. It results in increase of cost of treatment as inexpensive drugs need to be replaced by the expensive newer drugs[28]. The oral antimicrobials have to be replaced by parenteral ones needing hospital admission of the patients that will further increase the cost of treatment and also increase the disease burden. Moreover, such expensive antibiotics may not be available and affordable to many poor people living in the communities. Thus, the emergence of drug resistance especially to common, first line antibiotics and fluoroquionolones has made very difficult and expensive for health services to manage the disease[31]. Furthermore, this increasing resistant pattern may lead to inadequate treatment of enteric fever resulting in more complications including persistent carriage of the organisms in the gall bladder known as post-treatment complication[26]. These chronic carriers will become the source of further dissemination of organisms causing enteric fever in the community.

The number of culture positive cases over one year period found in this study was only 60, which is considered very low. It is said that *S. Typhi* and *S. Paratyphi A* are not always culturable even in good microbiological laboratories. Furthermore, *S. Typhi* is ordinarily cultured from 5-10 ml of blood in 30-50 ml of broth[32]. It is difficult to draw such amount of blood in children, compromising diagnosis in them. However, the number of culture positive cases in 2005 and 2008 was 317 and 235 respectively in the same place and in the same period although the total number of blood samples collected for culture was almost the same in those three years. One possible reason for such decline in the number of culture positive cases could be due to effectiveness of the recently initiated pilot vaccination program in schools of neighbouring Lalitpur and Bhaktapur districts against *Salmonella typhi*[33] as the children from these districts also seek health services to the study place and students from Kathmandu district attend the schools in these districts as well. Another reason could be due to improvement in sanitary practices over the years. There is a need for further exploration to identify the exact cause of observed decline. It has been argued that mass vaccination program against typhoid along with provision of safe water supplies and effective sanitation in the endemic countries may be effective in controlling enteric fever.[13,28] It has been recommended enrolling pre-school children too in vaccination programs because of their increased susceptibility to substantial clinical illness [30] as pre-school children (2-5 year old) are found equally affected by *Salmonella sp* as school aged children (5-15 year old) [28] Further studies on the estimation on the impact of disease with larger sample size and for identifying age groups at highest risk are helpful to optimize vaccination strategies in our setting[34].

This study is considered a part of local microbiological surveillance and monitoring. It is hoped that it has added recent information about changing trends of antibiotic sensitivity pattern of *Salmonella sp*. It is also assumed that this study will help us choose empirical antibiotics more rationally and develop local antimicrobial policies for the treatment of enteric fever. However, limited numbers of antimicrobial discs (6-7 discs per blood isolate) used for sensitivity test are the major limitation of this study.

In conclusion, the number of *salmonella sp* isolates was very low. Commonly used parenteral third generation cephalosporins, first line drugs chloramphenicol and amoxicillin and ofloxacin among fluoroquinolones seem effective in vitro in treating enteric fever. However, most frequently used drugs like ciprofloxacin and cefixime appear highly resistant. It is recommended to undertake further study to identify the causes for low yield.

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