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ORIGINAL ARTICLE

Antibiotic Resistance among Enteric Fever Pathogens in a Tertiary Care Children Hospital of Bangladesh

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Abstract

Background: *Enteric fever, a public health problem endemic in Bangladesh involves multiple systems. Fluoroquinolones and third generation cephalosporins are first line drugs used in treatment, which has led to increased minimal inhibitory concentration (MIC) of ciprofloxacin causing therapeutic failure. In recent years using these drug some treatment failure found.*

Objectives: *To study the antibiotic resistance among enteric fever pathogens in young children and to study the isolation rate of S. typhi and S. paratyphi among different age groups of children.*

Methods: *A prospective study was done in Pediatric Infectious & Community Pediatrics Department of Dhaka shishu (Children) Hospital among admitted children age 1 to 15 years from January 2018 to January 2019. During this period 62 blood culture samples with growth of S.typhi & S.paratyphi were processed. The antibiotic susceptibility was done by modified Kirby disk diffusion.*

Results: *During this 1 year from 72 admission days, 216 suspected enteric fever children admitted in Pediatric Infectious & Community Pediatric Department. Out of these 216 patients, isolation rate of enteric fever pathogens by blood cultures was 62 (28.7%). Majority of the isolates were S. typhi (75.8%) and S. paratyphi A were 24.2%. Among them 40(64.5%) isolates were from 5 to 15 years of age. Antibiotic resistance pattern was Ampicillin 37.1%, Chloramphenicol 30.64%, Co-trimoxazole 35.48%, Ceftriaxone (0%), Azithromycin (19.35%), resistance or reduced susceptibility to Ciprofloxacin was found in 77.41%, Nalidixic acid 100%, ten isolates (16.12%) were MDR. The most susceptible antibiotic was ceftriaxone while most resistant was nalidixic acid.*

Conclusion: *The increasing numbers of enteric fever pathogens with decreasing susceptibility to ciprofloxacin and azithromycin is a concern. Increasing dependency to ceftriaxone and cefixime may cause resistance to these drugs near future. So, we can choose older drugs again in some cases.*

Key words: *S. typhi, S. paratyphi, resistance.*

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Introduction

Enteric fever is caused by Salmonella enterica, subspecies enterica serovar typhi and serovars paratyphi A, B and C.[1] It continues to be a global public health problem with over 21 million case and at least 216,510 death occurring annually.[2,3] Several studies in areas of endemicity and outbreaks have shown that about one - quarter to one-third of pediatric enteric fever cases are under five years of age, and that between 6% and 21% are under two years of age.[4-7]

Enteric fever causes prolonged illness characterized by bacteremia, diseases is basically presented as fever with chills and rigor, anorexia, cough, weakness, sore throat, dizziness, muscle pain, abdominal discomfort with either diarrhea or constipation.[8] Due to these varied presentations, it is common for enteric fever in children to be diagnosed late or even remain unrecognized.

In the late 1980s, some S. typhi strains developed resistance to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole.[9] The quinolones group of drugs then emerged as the treatment of choice for typhoid fever but resistance developed eventually which led to a shift in the third generation cephalosporins.[10] In the last two decades, multidrug-resistant (MDR) S. typhi strains have emerged and spread worldwide, resulting in high rates of morbidity and mortality.[11]

The present prospective study was designed to explore the antibiotic sensitivity trends in blood culture positive enteric fever cases and extent of drug resistance before treatment is administered.

Materials and Methods

A prospective study was carried out at Department of Pediatric Infectious Diseases and Community Pediatrics of Dhaka Shishu (Children) Hospital, for a duration of 1 year (January 2018 to January 2019). Out of the total 216 suspected Enteric fever children admitted during this time 62 were blood culture positive, children aged 1 to 15 years having fever for 4-7 days. With the growth of S. typhi and S. paratyphi were included in this study. Blood was collected from patients at the day of enrolment (T1), then at early convalescence 7-10 days later (T2) and at late convalescence 21-28 days (T3) after the S. typhi bacteremia. Both males and females were included in the study. Blood culture was done by the BacT ALERT microbial detection system (Biomeriux, Inc. Durham, North California and USA). Positive samples were sub cultured on blood agar, chocolate agar, and MacConkey agar and incubated over night at 37^0C. Growth of gram negative bacteria was identified by conventional methods /automated Vitek 2 Compact system. The identification of the isolates of S. typhi and S.paratyphi was confirmed by agglutination with polyvalent and group specific antisera [8, 9]. The antibiotic susceptibility of the isolates of S. typhi and S.paratyphi was done by modified Kirby Bauer disk diffusion method according to CLSI guidelines on Muller-Hinton agar plates. The results were interpreted using CLSI guidelines 2012.[10,11] The antibiogram was noted. For all the isolates, MIC of ciprofloxacin was tested using the Automated Vitek 2 system (Bio-Mérieux, Co., Ltd.) to detect the DCS phenotype. The susceptibility to azithromycin was determined following the zone size used for Enterobacteriaceae. The antibiotic treatment given was recorded from the case records.We categorized our patients into two groups based on their age: Group I (young children; 1-5 years of age; N=22), Group II (older children; 6-15 years of age; N=40). Analysis of data and preparation of figures used statistical software SPSS version 23. Statistical evaluation of differences among groups was performed using the unpaired t test. Results were considered statistically significant if $p<0.05$. The study has been approved by the Institutional Ethics Committee.

Results

Of the total 216 patient, 62 blood cultures were positive. Isolation rate of enteric fever pathogens was 28.7% . Among these, S. typhi were isolated in 47 (75.8%) cases compared to S. paratyphi A which were 15 (24.2%) in number. Maximum isolation rate was reported in the month of june (10 isolates). Among the isolates 40(64.5%) were from 5 to 15 years of age (Table I and Table II).

Table I
Salmonella isolates among enteric fever patients from January 2018 to January 2019

Time period	Total no of Salmonella isolates	S. typhi	S. paratyphi
January 2018	3	3	0
February 2018	2	2	0
March 2018	4	3	1
April 2018	6	4	2
May 2018	7	4	3
June 2018	10	6	4
July 2018	9	6	3
August 2018	6	5	1
September 2018	5	4	1
October 2018	3	3	0
November 2018	2	2	0
December 2018	3	3	0
January 2019	2	2	0

Table II
Age wise distribution of salmonella isolets

Age group	Age range	Total Enteric fever pathogens
Group I Young children	1-5 years	22
Group II Older children	6-15 years	40

In young children among 22 S. typhi & S. paratyphi, the number of isolates with resistance to ampicillin, chloramphenicol and co-trimoxazole was 10(45.5%), 7(31.8%) and 8(36.4%), respectively; and 3(13.6%) isolated strains were MDR. Out of 40 S. typhi & S.paratyphi strains isolated from older children, 13(32.5%), 12 (30%) and 14(46.6%) were resistant to ampicillin, chloramphenicol and co-trimoxazole, respectively; and 7 (17.5%) were MDR. All 62(100%) strains isolated from the two age groups were sensitive to ceftriaxone but in older group 1 (2.5%) showed reduce to susceptibility. In young group 2(9.1%) and older group 5(12.5%) shown reduced susceptibility to cefixime. Azithromycin were resistant 3(13.6%) and 9(22.5%) in young and older group respectively. 48(77.4%) children had reduced susceptibility or resistance to ciprofloxacin and 62 (100%) resistance to nalidixic acid (Table-III).

Table III
Antibiotic susceptibility pattern of isolated strains from the patients of two groups

Antibiotics	Young children n(%)	Older children n(%)	Total n(%)
Resistance to ampicillin	10(45.45)	13(32.5)	23(37.1)
Resistance to chloramphenicol	7(31.81)	12(30)	19(30.64)
Resistance to co-trimoxazole	8(36.36)	14(46.67)	22(35.48)
MDR*	3(13.63)	7(17.5)	10(16.12)
Resistance to nalidoxic Acid	22(100)	40(100)	62(100)
Resistance or reduce susceptibility to ciprofloxacin	15(68.1)	33(82.5)	48(77.41)
Resistance to ceftriaxone	0(0)	0(0)	0(0)
Reduced susceptibility to cefixime	2(9.1)	5(12.5)	7(11.3)
Resistance to azithromycin	3(13.63)	9(22.5)	12(19.35)

*Multi drug resistance

Discussion

Typhoid and paratyphoid fever is endemic in this region. In our study we found The rate of isolation of enteric fever pathogens was 62(28.8%) where as Porwal et al[12] found 7.1% in their admitted patients presenting with 4-5 days of fever. In this study we found S. typhi were isolated more in number (75.8%) compared to S. paratyphi A (24.2%), a finding consistent with other previous studie.[13] Out of 62 cases, 40 S.typhi & S.paratyphi strains isolated from older children, age 5 years to 15 years.

The most susceptible antibiotic was ceftriaxone and the resistance was more to Ampicillin and reduced susceptibility to Ciprofloxacillin among the enteric fever pathogens.

We found in our study In young children among 22 S. typhi & S. paratyphi, the number of isolates with resistance to ampicillin, chloramphenicol and co-trimoxazole was 10(45.5%), 7(31.8%) and 8(36.4%), respectively; and 3(13.6%) isolated strains were MDR. Similar finding shown by Khanam et al[14] in their study that was as, in young children s. typhi resistance to ampicillin, chloramphenicol, co-trimoxazole 13(39%),10(30%),10(30%) and 5(15%) isolated strain were MDR.

In particular, our observation that approximately 15%of S. typhi isolates were multi drug resistant and resistance to nalidixic acid and decreased susceptibility to ciprofloxacin are now common in Dhaka. Our observation shown that over all reduced susceptibility to cefixim 7(11.1%) and resistance to azithromycin 12(19.35%). But Rajesh et al[15] in 2018 found azithromycin resistance in 0.8%. Our study found resistance to nalidixic acid 62(100%) which is inconsistent with Khanam et al[14].

Conclusion

There is re-emergence of sensitivity to the traditional drugs like ampicillin, chloramphenicol, cotrimoxazole. With the widespread injunctions use of quinolones there is emergence of strains of S. typhi & S. parathyphi resistant to quinolone. To combat that, cephalosporin are being used. Time has come to reconsider bringing back the traditional drugs or use other alternatives like azithromycin.

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