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# Antibiotic Sensitivity Pattern of *Salmonella typhi* in Children of Typhoid Fever Aged between 6 Months to 18 Years in a Tertiary Care Hospital, Chittagong, Bangladesh

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**Abstract:** This cross sectional study was carried out in the Pediatric & Medicine wards of Chittagong Medical College Hospital (CMCH), Chittagong during the period between July 2012 and June 2013, the study was aimed to identify antibiotic sensitivity pattern of Salmonella typhi among children of typhoid fever in a tertiary care hospital. We selected 150 suspected cases of typhoid fever (age >6 months to18years) admitted in the above mentioned hospital and enrolled in this study. Majority (56.7%) of the patients belonged to 1-5 years of age and male to female ratio was 1.2:1. More than a half (56.0%) of the patients came from rural area. Blood C/S for salmonella typhi was found positive in 16(10.7%) cases and out of which only 1(6.25%) received typhoid vaccination. In the investigation, mean Hb was found 10.78±.55 g/dl with range from 5 to 145 g/dl. Mean TC was 13018.44±6510.33/cu mm with range from 1060 to 42000 /cu mm. Mean N was found 67.78±15.61% with range from 25 to 92%. Mean L was 27.59±15.24% with range from 6 to 72 %. Mean M was 2.57±0.93 % with range from 1 to 6 %. Mean E was 1.68±0.87 % with range from 0 to 6 %. Mean B was 0.31±0.54 % with range from 0 to 2 %. Antibiotic sensitivity among culture positive patients showed that Azithromycin, Ceftriaxone and Imipenam were 100% sensitive followed by Cefixime 68.8%%, Nalidixic acid (Intermediate sensitive) 56.3%, Chloramphenicol 38.35%, Ciprofloxacin (Intermediate sensitive) 25% and Ampicillin (Intermediate sensitive) 18.8%. Almost half (47.3%) of the patients received antibiotic during pre admission period whereas 7 (43.8%) of the culture positive patients received pre admission antibiotics. At the end, we can conclude that knowledge of antibiotic sensitivity may have beneficial effect in successful treatment of typhoid fever in children.Unnecessary uses of antibiotic can hinder such sensitivity pattern,
**Keywords:** Antibiotic Sensitivity pattern, Salmonella typhi, Typhoid fever.

## INTRODUCTION

Typhoid fever is an acute systemic infection caused by Salmonella enterica serotype Typhi or Paratyphi. The worldwide incidence of typhoid fever is estimated to be approximately 16 million cases annually, of which 7 million cases occur in Southeast Asia. More than 600,000 people die due to this disease each year [1]. Typhoid fever is generally considered a disease of school children and young adults, although there is evidence of a substantial disease burden in preschool children in some countries where disease is endemic [2]. *S. Typhi* is the dominant cause of typhoid fever in most areas, although the proportion of infections attributed to *S. Paratyphi* A has been increasing in the north of the Indian subcontinent and China [3]. ICDDR, B in 2001 conducted a study at Kamalapur in Dhaka and concluded approximate incidence of typhoid fever in our population documented by positive blood culture is 3.9 episodes per year per 1000 populations. The isolation of *S. Typhi* or *S. Paratyphi* A from blood, bone marrow, rose spots or other sterile sites provides the most conclusive confirmation of typhoid fever. Therefore, culture should be considered as the gold standard and used for evaluating all diagnostic tests, irrespective of their level of sophistication [8]. Bacterial isolation confirms the clinical diagnosis and allows antimicrobial-susceptibility testing which can direct appropriate therapy yet it is only positive in approximately 40–60% of presumptive cases [4]. In order to effective treatment

of typhoid fever, culture and antibiotic sensitivity tests must first be determined. Once culture & sensitivity results confirm the type of bacterial infection and sensitivity pattern, treatment may be modified [5].The case fatality rate of Salmonella infections are increasing globally, especially in many South Asian countries [3]. Today due to its changing modes of presentation, as well as the development of multidrug resistance, typhoid fever is becoming increasingly difficult to diagnose and treat. There are reports of changing clinical features in typhoid fever caused by drug resistant S. Typhi leading to difficulty in clinical diagnosis **[**6, 7]. In many developing countries, people have access to antibiotics without any prescription, which may lead to improper use [8]. Drug resistance in typhoid fever is considered as one of the important factors in the morbidity and mortality of the disease. Since the introduction of chloramphenicol in 1948, it has been the drug of choice in the treatment of typhoid fever in most parts of the world. But indiscriminate use of the drug and acquisition of plasmid mediated R factor has led to the development of resistance to S. Typhi against this drug [9**]**. The emergence of strains of Salmonella typhi resistant to multiple antibiotics poses a serious problem. The first major epidemic of multidrug resistant S. Typhi was reported in 1972 in Mexico [10]. Since then, an increasing frequency of antibiotic resistance has been reported from all parts of the world, but more so from the developing countries [11]. The uses of chloramphenicol, ampicillin and cotrimoxazole have become infrequent and quinolones have become the first line of treatment of typhoid fever. However, over the last few years there has been increase in the defervescence period in patients treated with quinolones [12]. Initially, reduced use of amoxicillin, cotrimoxazole, or chloramphenicol was associated with a decreased prevalence of MDR strains, but more recently, continued dependence on ciprofloxacin for the empirical treatment of typhoid fever in Bangladesh and elsewhere has led to the emergence of resistance of S. Typhi to this drug **[**13, 14].Typhoid fever is endemic in Bangladesh, where there is a high incidence in children [18]. The emergence of MDR S. Typhi isolates in the early 1990s, particularly from the Indian subcontinent, prompted the suggestion that ceftriaxone, ceftazidim and ciprofloxacin should be the drug of choice for empirical treatment of typhoid fever [15-17]. The fluroquinolone group of drugs emerged as useful drugs for the treatment of multidrug resistant S. typhi. But unfortunately, same factors of indiscriminate antibiotic use and cross resistance within the antibiotic group which lead to the emergence of chloramphenicol resistant organism are still operative [18]. In this context of changing the dynamics of resistance to antibiotics, it is imperative for optimal patient care that accurate and early isolation of S. Typhi and its antibiotic susceptibility pattern be available to the clinician. This study is believed to identify the antibiotic sensitivity pattern in blood culture positive patients of typhoid fever. The study result is expected to aware healthcare providers to avoid unnecessary antibiotic usage.

## OBJECTIVES

### General objective

- To determine antibiotic sensitivity pattern of Salmonella typhi.

### Specific objectives

- To identify the cases of typhoid fever by blood culture.
- To observe the laboratory profile of typhoid fever children.

## METHODS AND MATERIALS

We conducted a laboratory based descriptive cross sectional study during the period of July 2012 and June 2013 in the Departments of Pediatrics & Medicine, Chittagong Medical College Hospital. We selected suspected cases of typhoid fever (age >6 months to18yrs) admitted in Pediatric & Medicine wards of CMCH as study participants maintaining some inclusion criteria based on the protocol. Clinically suspected patients of typhoid fever who were > 06 months old and who presented with ≥ 3 days of fever during the study period were eligible for enrollment. Patients were allocated a study ID number at the time of enrollment. Parents of enrolled patients were asked to give informed consent and answer a brief questionnaire about clinical signs and symptoms, antimicrobial treatment, and history of typhoid fever and vaccination. On admission, a blood culture sample was taken before receiving antibiotics.

### Used Sample size equation

To determine the sample size the following formula was followed

$$n = \frac{z^2 pq}{d^2}$$

n= The desired sample size
z= Standard normal deviate usually set at 1.96
p= Proportion in the population (30.8% i.e. 0.308)
q= 1-p =0.692

Examination of the microbiology laboratory records showed that 30.8% (95% CI 26.8 - 35.1%) consecutive patients admitted to the hospital and investigated with a blood culture and a Widal test had a blood culture positive for S. typhi [35].

d= Degree of accuracy which is considered as 0.05
According to this formula the targeted sample was 327.5 = 328

The duration of data collection in current study is only 6 months. The targeted sample size could not be collected during this period, Therefore 150 patients with

suspected typhoid fever were taken in this study. Study conducted according to the rule of ethical committee of CMCH.

**Blood Culture**

One hundred & fifty patients of clinical Typhoid Fever cases were evaluated for the study. After admission in ward, study cases were selected according to the inclusion criteria. A written informed consent was filled up by the attendant for permission. Data was collected by a questionnaire. After a detailed history, general and relevant systemic examinations were done properly & were documented. Then under all aseptic precaution on the day of admission blood culture samples were collected (1ml. for children aged > 6months to <5years, 5ml for children aged 5 - < 15years and 8ml. for patients aged 15 – 18years) using pediatric bottle as appropriate. Bottles were incubated in the ßacT / Alert automated system for 5-7 days at a renowned well-equipped, quality-controlled clinical Laboratory of Chittagong. Positive bottles were processed by preparing a smear for Gram stain and sub culturing onto sheep blood, chocolate and MacConkey agars. The sheep blood & chocolate agar was incubated in CO2 (candle jar) at 35 – 37c for 48hrs; the MacConkey agar in air for at 35-37c for 48hrs. Suspected colonies were identified by serological test. Antimicrobial sensitivity was assessed by the disc diffusion methods or E-test on a Muller-Hilton agar plate according to CLSI guidelines. Patients data was evaluated meticulously using SPSS (Statistical package for social science) for windows. The measure of mean and Standard deviation was performed. Analysis of the significance of categorical variables was performed with the chi-square test. P value was obtained. A probable value of less than 0.05 was considered as significant. Data was presented by appropriate method by frequency table, bar chart & pie chart in a simplified manner.

**RESULTS**

**Table-1: Age distribution of the study patients (n=150)**

| Age (years) | Number of patients | Percentage |
|---|---|---|
| 1-5 | 85 | 56.7 |
| 6-10 | 52 | 34.7 |
| 11-15 | 13 | 8.7 |
| Mean±SD | 5.41±3.53 | |
| Range (min-max) | 1-15 | |

**Table-2: Distribution of the study patients according to Sex, Residence, Pre Admission Antibiotic, Blood C/S (n=150)**

| Characteristics of the study participants | Number of patients | Percentage |
|---|---|---|
| Sex | | |
| Male | 83 | 55.3 |
| Female | 67 | 44.7 |
| Habitat | | |
| Rural | 84 | 56.0 |
| Urban | 66 | 44.0 |
| Pre Admission Antibiotic | | |
| Received | 71 | 47.3 |
| Not received | 79 | 52.7 |
| Blood C/S | | |
| Positive blood C/S for Salmonella typhi | 16 | 10.7 |
| Negative | 134 | 89.3 |

**Table-3: Pre Admission Antibiotic and Typhoid vaccination among culture positive patients (n=16)**

| Antibiotic | Number of patients | Percentage |
|---|---|---|
| Received | 07 | 43.8 |
| Not received | 09 | 56.2 |
| Typhoid vaccination | | |
| Received | 1 | 6.25 |
| Not received | 15 | 93.75 |

**Table-4: Distribution of the study patients according to investigations (n=150)**

| Investigations | Mean | ±SD | Min | -max |
|---|---|---|---|---|
| Hb (g/dl) | 10.78 | ±1.55 | (5 | -14.5) |
| TC (/cu mm) | 13018.44 | ±6510.33 | (1060 | -42000) |
| N (%) | 67.78 | ±15.61 | (25 | -92) |
| L (%) | 27.59 | ±15.24 | (6 | -72) |
| M (%) | 2.57 | ±0.93 | (1 | -6) |
| E (%) | 1.68 | ±0.87 | (0 | -6) |
| B (%) | 0.31 | ±0.54 | (0 | -2) |

**Table-5: Antibiotic Sensitivity among culture positive patients (n=16)**

| Sensitivity | Number of patients | Percentage |
|---|---|---|
| Ciprofloxacine (Intermediate) | 04 | 25.0 |
| Azithromycin | 16 | 100.0 |
| Cefixime | 11 | 68.8 |
| Nalidixic acid (Intermediate) | 09 | 56.3 |
| Cotrimoxazole | 00 | 0.0 |
| Ampicillin (Intermediate) | 03 | 18.8 |
| Chloramphenicol | 06 | 37.5 |
| Ceftriaxone | 16 | 100.0 |
| Imipenam | 16 | 100.0 |

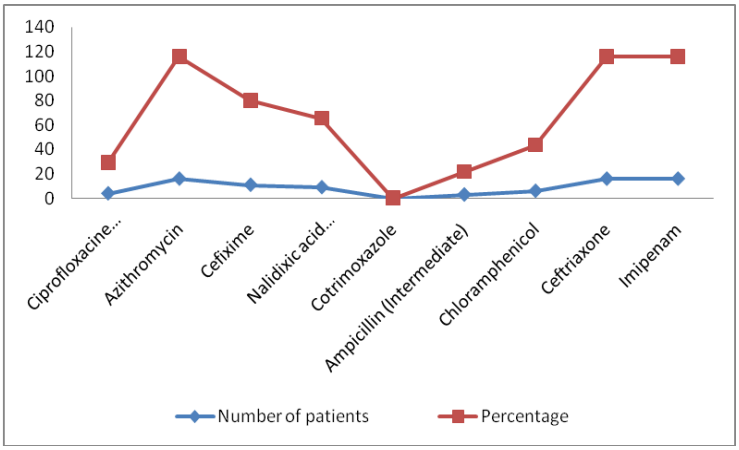


**Fig-1: Antibiotic Sensitivity among culture positive patients (n=16)**

## DISCUSSION

Typhoid fever is one of the most common infectious diseases in developing countries including Bangladesh. The disease is present especially in areas where healthcare facilities are limited and peoples are illiterate, living in unhygienic surroundings, drink raw-water from tube-wells and not habitual of hand-washing. Symptoms and signs of the disease are non-specific, measuring antibiotic sensitivity patterns are essential for the treatment of typhoid fever.

This cross sectional study was carried out with an aim to assess the pattern of drug sensitivity of salmonella typhi in children admitted in a tertiary care hospital. In this current study it was observed that the mean age was 5.41±3.53 years varied from 1 to 15 years and more than a half (56.7%) of the patients belonged to 1-5 years. Naheed *et al*. [27] showed 57.0% of their studied patients by 5 years old, which is comparable with the current study. Similarly, House *et al.* [29] found the median age was 7 years of the typhoid patients with IQR was 5 to 14 years. Choo *et al*. [20] included one patient with typhoid fever in the birth to l-year age group, three patients in the 1- to 2-year age group and 38 patients in the >2-year age group. In another study, Kawano *et al*. [36] showed the mean age was 2.5 years, which is lower than the current study. On the other hand, House *et al.* [29] has observed the median age 18 years with interquartile range [IQR] 11 to 26 years. Similarly, Tam *et al.* [24] showed the typhoid patients aged from 11 to 43 years with median age 24.5 years, which are higher than the current study. In this present study it was observed that typhoid fever was more common in male subjects, male was found 55.3% and female 44.7% and male to female ratio was 1.2:1, which is consistent with Mathura *et al.* [31] study, where they found male to female ratio of almost 3.1, Similar observation were also found by House *et al.*

[28]; Kawano *et al*. [35] and Nagshetty *et al*. [32] where all the above authors found typhoid fever to be predominant in male subjects. In this current series it was observed that more than a half (56.0%) of the patients came from rural area and 44.0% from urban area. In this present series it was observed that only 6.25% patient received vaccination and rest 93.75% patients didn't receiv vaccination. In this current study it was observed that the mean Hb was 10.78±1.55 g/dl varied from 5 to 145 g/dl, TC was 13018.44±6510.33/cu mm with range from 1060 to 42000 /cu mm, N was 67.78±15.61% with range from 25 to 92%, L was 27.59±15.24% with range from 6 to 72 %, M was 2.57±0.93 % with range from 1 to 6 %, E was 1.68±0.87 % with range from 0 to 6 %, B was 0.31±0.54 % with range from 0 to 2 %. It was observed that blood C/S for salmonella typhoid was positive in 10.7% cases. In a super speciality children hospital at New Delhi done by Manchanda *et al*. [30], a total of 56 S. typhi and five S. paratyphi a isolates were obtained among the 673 blood cultures performed, that was 8.3% in their study, which is comparable with the current study. Krishnan *et al*. [33] found in their study that 70% and 30% of the isolates were Salmonella enterica serovar typhi and Paratyphi A, respectively. The diagnosis was confirmed in 47.0% of 97 by the isolation of S. typhi on blood and/or bone marrow cultures observed by Bhutta and Mansurali [6]. In another study, Abdoel *et al*. [22] found 42.5% culture-positive patients. The final diagnosis was based on a positive blood culture in 118 (65.9%) patients and on clinical symptoms and signs consistent with typhoid or paratyphoid fever in 61 (34.1%) patients found by Hatta *et al*. [22]. Salmonella typhi was isolated from the cultures of 112 patients and S. paratyphi from six of them by the authors.

We observed that Azithromycin, Ceftriaxone and Imipenam were 100% sensitive followed by Cefixime 68.8%%, Nalidixic acid (Intermediate) 56.3%, Chloramphenicol 37.5%, Ciprofloxacine (Intermediate) 25.0%, and Ampicillin (Intermediate) 18.8% sensitive. Cotrimoxazole was 100% resistant to Salmonella typhi, Manchanda *et al*. [22] showed all isolates of S. typhi were sensitive to amoxycillin+clavulanate, gentamicin, cefixime, cefotaxime and ceftazidime. Multidrug resistance (MDR, resistance to three drugs) was seen in 22 cases (39%) and resistance to five drugs was seen in 12 cases (21%). Only two isolates were resistant to chloramphenicol (3%). All S. paratyphi a isolates were sensitive to ampicillin and chloramphenicol and resistant to nalidixic acid. MIC distribution data for chloramphenicol revealed elevated MIC but still in susceptible range. Krishnan *et al*. [33] found that Salmonella enterica serovar typhi and paratyphi A, were highly sensitive to choloramphenicol (86.0%), ampicillin (84%), and cotrimoxazole (88%). Highest sensitivity was seen for cephalosporins, followed by quinolones. Seventeen/21 (81%) and 100% of the Salmonella enterica serovar typhi strains belonged to E1 phage type and biotype 1, respectively. Antibiogram showed 2% of the strains to be sensitive to all the drugs tested and 2% were MDR and showed the presence of plasmids. In another study, Mathura *et al.* [31] showed **s**ensitivity to ceftriaxone was 100%. There have been some reports of the reemergence of the sensitivity of S. typhi to chloramphenicol and other first line drugs. Bhatia and others reported that the highest (96%) sensitivity of Salmonella typhi to chloramphenicol in India [12]. Another study by Yashavanth and Vidyalakshmi found that the re- emergence of chloramphenicol (97.4%) sensitivity among the strain of S. typhi pathogens in Mangalore in 2007 [34]. Ashwini Kumar *et al*. [2] found 96.2% sensitivity to cephalosporins & 70.8% to fluoroquinolones in their study. Bulbul *et al*. found 100% sensitivity of ceftriaxone and ceftazidime, 81, 25% sensitivity of ciprofloxacine and azithromycin, 37.5% sensitivity of ampicillin, chloramphenicol & cotrimoxazole along with 100% resistance of nalidixic acid. Abro AH *et al*. found 100% sensitivity of 3rd generation cephalosporins [30] showed Imipenam to be 100% sensitive, meropenam to be 97.6%, ceftriaxone to be 90, 6% and ciprofloxacin to be 57.5% sensitive in their study result. The above findings are comparable with the current study. In this study it was observed that almost a half (47.3%) of the patients received antibiotic during pre admission period and more than a half (56.2%) of the culture positive patients took antibiotic before admission in the hospital.

**Limitations of the study**

The study population was selected from one selected hospital in Chittagong, so that the results of the study may not be reflect the exact picture of the country. The present study was conducted at a very short period of time. Small sample size was also a limitation of the present study. A bulk of the patients had prior antibiotics intake which might lead to lower detection of culture positive cases which might hinder the drug sensitivity pattern.

## CONCLUSION & RECOMMENDATIONS

A considerable variation has been noted in the antimicrobial susceptibility patterns among isolates of S. Typhi as suggested in various studies conducted in different geographical locations. Knowledge of the prevalence of S. Typhi and their antimicrobial susceptibility patterns is of utmost importance in the institution of appropriate antimicrobial therapy. This study was undertaken to assess antibiotic sensitivity pattern of Salmonella typhi in typhoid fever children admitted in a tertiary care hospital. Typhoid fever remains to be an endemic disease in this locality. Identifying drug sensitivity pattern can guide the physicians to choose appropriate antibiotic which not only reduce patients' suffering but will also limit development of drug resistant Enteric fever. Doctors should ethically prescribe antibiotics to treat febrile

patients to prevent such drug resistance in the community.

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