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Clinical Profile and Antibiotic Sensitivity Pattern of Enteric Fever among Children Admitted in a Tertiary Care Hospital in Dhaka

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Abstract **Original Research Article**

Background: Enteric fever is a common public health problem in Bangladesh. Antibiotic therapy is the choice of treatment but development of resistant to common antimicrobial drugs complicates the problem now a days. ***Methodology:*** This prospective observational study conducted in a tertiary care hospital at Dhaka from March to December 2016 among suspected case of Enteric fever as per case definition. ***Results:*** Among 212 suspected enteric fever 117 children were diagnosed as enteric fever by blood culture and/or widal test. Male: female were 1.3: 1. Maximum (70%) children were in age group 5 years or more. Most of the children were from urban slum area (53.6%) of Dhaka city. Cases were admitted throughout the year. Common presentation were fever (100%), anorexia (100%), pain abdomen (74.4%) and loose motions (46.1%). The common signs were hepatomegaly (41.9%), hepatosplenomegaly (5.1%) coated tongue (64.9%), pallor (74.4%). The complications rate was 35.9% and commonest being UTI and pneumonia. The overall positivity of widal test was 89.7% and the culture positivity was 32.5%. Among isolates, 94.7%were Salmonella typhiand 5.3% Salmonella paratyphi A. Among them18.1% isolates were multi drug resistant. Amoxyclav, Amoxycilline and Nalidaxic acid were 100% resistant whereas Cefixime, ceftriaxone. Meropenam and Ofloxacine were 100% sensitive. Ciprofloxacin was 72.2% sensitive among isolates. The most important macrolides, Azithromycin was only 22.2% sensitive among S.Typhi in this study. ***Conclusion:*** Enteric fever is most prevalent during summer & rainy session. WASA supplied water may play a role. Hepatomegaly is common. UTI and pneumonia are the commonest complication. Multidrug resistant cases are not so as high as other countries. Cefixime, Ceftriaxone. Meropenam and Ofloxacine are the drugs of choice. Ciprofloxacin is still could be chosen for the treatment of enteric fever. Higher rate of resistant to Azithromycin is alarming.

Keywords: Antibiotic Sensitivity Pattern, Enteric fever, UTI and pneumonia.

INTRODUCTION

Enteric fever is an endemic disease in many developing countries like Bangladesh. Despite the use of newly developed antibacterial drugs, enteric fevers such as typhoid and paratyphoid are one of major health problems in Bangladesh, especially for the children [1]. Population-based studies from South Asia indicate that young children under 5 years of age bear a large burden of S. Typhi infection [2, 3]. In the developing world, incidence of typhoid fever ranging from 100-1,000 cases per 100,000 population. Almost 80% of the cases are in Asia; the rest occur mainly in Africa and Latin America [4]. Enteric fever is caused by Salmonella entericavarTyphi (S.typhi) and Salmonella entericaVar Paratyphi A (S.Paratyphi A) being the major causative microorganisms are transmitted by the faeco oral route. The disease is mainly associated with low socioeconomic status and poor hygienic practices, with human beings the only natural host and reservoir of infection [5]. Varied presentations of typhoid fever are known in the paediatric age group, such as septicemia in neonates, as diarrhoea in infants, and as lower respiratory tract infections in older children[6] Atypical presentations in older children include splenic abscess, liver abscess, cerebellar ataxia, meningitis, cholecystitis, chorea, palatal palsy, osteomyelitis, peritonitis, aphasia and even psychosis[4,7]. Due to these varied and atypical presentations, it is common for typhoid fever in children to be diagnosed late or even remain unrecognized. Also, no vaccine against typhoid fever is available commercially for children under two years of age [7]. Antibiotic therapy is the mainstay of managing enteric fever. In untreated cases a

chance of developing a carrier state increases**.** To complicate matters further, since 1990s, Salmonella typhi has developed resistance simultaneously to all the drugs used in first line treatment (chloramphenicol, cotrimoxazole and ampicillin). Fluoroquinolones were widely regarded as the most effective drug for the treatment of typhoid fever [8]. But unfortunately, some strains of S. Typhi have shown reduced susceptibility to fluoroquinolones [9]. Also there is high rate of clinical failure seen with fluoroquinolones. At present third generation cephalosporins are used in treatment but there are sporadic reports of resistance to these antibiotics [10]. Recently, Azithromycin is being used as an alternative agent in uncomplicated enteric fever. It has been found that it reduces the clinical failure rate and duration of hospital stay in comparison to fluoroquinolones and relapse rate in comparison to ceftriaxone, when used in the treatment of multidrug resistant typhoid fever [11]. Aztreonam and imipenem are also potential third line drugs which are being used recently.Resistance pattern of Salmonella has been found to be different in different countries and regions of same country [12]. Hence, this study aims to know the clinical profile of pediatric enteric fever and the sensitivity pattern of the disease to drugs in this region.

MATERIALS AND METHODS

This prospective observational study was carried out in the Pediatric inpatient department of Dhaka Medical College hospital during the period of March 2016 to December 2016. Data were obtained from admitted children upto 14 yrs of age with signs and symptoms suggestive of enteric fever as defined by the case definition (any fever ≥100.4°F for ≥3 days plus disturbance of abdominal function like abdominal pain, vomiting, constipation or diarrhea is suggestive in epidemiological area like Bangladesh). Then investigations were sent from these suspected cases. Those who fulfilled any of the following criteria were included in the study. (1) Positive culture for Salmonella enterica (typhi or paratyphi) (2) Widaltitre; TO ≥1:160. Others who were clinically suggestive as enteric fever but had less than significant titre or negative Widal test and negative blood culture were excluded from the study. Thorough and detailed history, clinical examination and laboratory investigations were done in all cases and analyzed. The following investigations were done:

Routine investigations

Haemoglobin estimation, Total and differential count for white blood cells, Erythrocyte sedimentation ratio, Platelate count, Other investigations such as a chest X ray, liver function test (SGPT), abdominal sonography were done where ever required.

Widal test

The Widal tube agglutination test was performed. A titre of ≥1/160 to either O or H antigen in a single serum specimen (in addition to the seroconversion) was taken to be indicative of typhoid fever. The results were correlated with blood culture results and interpreted in conjunction with the patient's history and recent clinical presentation on admission.

Bacterial cultures

Blood cultures were carried out by collecting aseptically 5ml of blood and sent in a same private hospital. Estimations were carried out by BACTEC 9050 Automated Blood Culture Analyzer (FAN method) for at least 48 hours. Positive growths were subjected to standard biochemical tests.

Antimicrobial susceptibility testing

Susceptibility to antimicrobial agents was performed using the Kirby Bauers disc diffusion method as described by the Clinical and Laboratory Standards Institute. Sixteen Antimicrobial agents (discs) tested and reported were obtained from Hi media and included: Amoxyclav, Amoxycilline, Ampicilline, Chloramphenicol, Cotrimoxazole, Azithromycin, Cefixime, Ceftriaxone, Ceftazidime, Cefepime, Merop[enam, Ciprofloxacin, Levofloxacin, Ofloxacine, Nalidaxic acid, Gentamycine. MDRisolates of S. typhi were those resistant to all three first line antityphoid drugs (ampicillin, chloramphenicol and trimethoprim–sulfamethoxazole).

RESULTS

A total of 212 children with suspected enteric fever were admitted during this study period. Among them 117 children were diagnosed as enteric fever by blood culture and/or widal test as per case definition. Among 117 cases 56.4% were male and 43.6% were female with male: female were 1.3: 1. Maximum (70%) children were in age group 5 years or more. Only 6.8% children from < 2 years age group, the youngest patient were only 11 months old in this study. Two patients were 14 years of age. Most of the children were from urban (31.8%) and its slum area (53.6%) of Dhaka city likes Kamrangir Char, Mugda, Badda, Jatrabari, ShaneerAkhara and Matuail. Most of them had poor socioeconomic background. Almost all of them drink Dhaka WASA supplied water and a significant number of them (66.7%) took it without boiling.

Table-1: Distribution of the Children by age& Sex

Age group	Sex of the	Children	Total
	Male	Female	
< 2 years	3	5	8
2 - <5 years	16	11	27
5 - < 10 years	33	25	58
10 yrs or more	14	10	24
Total	**66**	**51**	**117**

In this study, almost all patients were presented with high grade continued fever along with loss of appetite. No case in this study had stepped ladder type of fever. Abdominal pain experienced in 74.4% children. Diarrhea was more common than constipation. More than one-third (37.6%) of the children presented with cough. During clinical examination, coated tongue was found in 64.9% cases. More than half (52.9%) of the patient had no organomegaly but 41.9% had hepatomegaly only, none of them had splenomegaly. Three-fourth (74.4%) of them was pale. Most (94%) of the patients had tachycardia but relative bradycardia was not found. Caecal gurgling was found only in 5.9% cases. About one-fourth (23.9%) of the patients were toxic during their presentation.

Table-2: Symptoms & Sign at presentation

Symptoms	**N**	**%**
High Fever	117	100.0
Abdominal Pain	87	74.4
Vomiting	23	19.7
Loss of appetite	117	100
Constipation	18	15.4
Diarrhea	54	46.1
Constipation followed by diarrhea	11	9.4
Altered Sensorium	4	3.4
Headache	14	12.0
Cough	44	37.6
Sign	**N**	**%**
Coated tongue	76	64.9
Hepatomegaly	49	41.9
Splenomegaly	0	0.0
Hepatospenomegaly	6	5.1
None	62	52.9
Pallor	87	74.4
Tachycardia	110	94.0
Relative Bradycardia	0	0.0
Caecal gurgling	7	5.9
Toxicity	28	23.9
Obtundation	20	17.1

About three-fourth of the children (71%) in this study were presented to us during their 8-14 days of illness. During their admission blood was sent for widal test and blood culture irrespective of the duration of illness. Among them 79 cases had only Significant Widal test, 12 were only Blood culture positive and remaining 26 cases had both blood culture and Widal test positive. So total widal test positive cases were 105 (89.7%) and blood culture positive cases were 38 (32.5%).Table 3 showed that younger age group had more blood culture positive cases than Widal test. During first week of illness blood culture was significantly positive (among 25 cases 15 were blood culture positive during 3-7 days illness).

Table-3: Association between the Investigations with Age group of children & Duration of Fever at Presentation

		Investigations		
Age Group	**Only Widal +ve**	**Only Blood Culture +ve**	**Both + ve**	**Total**
< 2 years	2	4	2	8
2 - <5 years	18	5	4	27
5 - < 10 years	42	3	13	58
10 yrs or more	17	0	7	24
Chi-Square=21.6	df=6	P<0.001		
Duration of Fever				
3 - 7 days	10	12	3	25
8 - 14 days	65	0	18	83
>14 days	4	0	5	9
Chi-Square=54.8	df=4	P<0.001		
Total	**79**	**12**	**26**	**117**

Among 38 Salmonella isolates, 36 were S.Typhi (94.7%) and 2 were S. Paratyphi (5.3%) were found in this study. Among the isolates, 16 antibiotics were tested to see the sensitivity pattern. It was found that Cefixime, Ceftriaxon, Meropenam and quinolone derivatives like Ofloxacine were 100% sensitive among the isolates. The other quinolones Ciprofloxacin was 72.2% sensitive among S Typhi isolates and 50% among S. Paratyphi isolates but the levofloxacin was less sensitive (52.8%) among the isolates. The most important macrolides, Azithromycin was only 22.2% sensitive among S. Typhi but 100% sensitive among S. Paratyphi isolates in this study. A significant number of isolates were found sensitive in Chloramphenicol (27.8%) and Cotrimoxazole (38.9%) but Amoxyclav, Amoxycilline and Nalidaxic acid were 100% resistant among the isolates. MDR was found among 18.1% isolates in this study.

Table-4: Sensitivity patterns of Salmonella enterica isolates

Name of Antibiotics	**S.Typhi N=36 (%)**	**S. Paratyphi N=2 (%)**
Amoxyclav	0 (00)	0 (00)
Amoxycilline	0 (00)	0 (00)
Ampicilline	6 (16.7%)	0 (00)
Chloramphenicol	10 (27.8%)	0 (00)
Cotrimoxazole	14 (38.9%)	0 (00)
Azithromycin	8 (22.2%)	2 (100%)
Cefixime	36 (100%)	2 (100%)
Ceftriaxone	36 (100%)	2 (100%)
Ceftazidime	18 (50%)	1 (50%)
Cefepime	31 (86.1%)	2 (100%)
Meropenam	36 (100%)	2 (100%)
Ciprofloxacin	26 (72.2%)	1 (50%)
Levofloxacin	19 (52.8%)	0 (00)
Ofloxacine	36 (100%)	2 (100%)
Nalidaxic acid	0 (00)	0 (00)
Gentamycine	14 (38.9%)	0 (00)

MDR = 18.1 %

Among 117 cases of enteric fever, 42 (35.9%) cases complicated with different illness. Most common complication was UTI which were presented during 2nd or 3rd week of illness. Cough was the presentation of enteric fever of many children in this study but cough with radiological evidence of Pneumonia was the second most common complication in this study (Table 4).

Table-5: Complications of Enteric Fever

Complications	**Total**	**%**
Pneumonia	17	40.4
UTI	20	47.6
Encephalopathy	1	2.4
Hepatitis	2	4.8
Cholecystitis	1	2.4
peritonitis	1	2.4
Total	**42**	**100**

All patients recovered, and 35.9% cases developed complications such as UTI (47.6%) and pneumonia (40.4%) but severe complication like Hepatitis (4.8%), cholycystitis (2.4%), peritonitis (2.4%) and encephalopathy (2.4%) were less. Enteric fever present almost all the year in this study. But most patients (59%) were prevalent during May to August months.

Table-6: Monthly admission of Enteric Fever

Months	**N**	**%**
March	8	6.8
April	11	9.4
May	15	12.8
June	19	16.3
July	17	14.5
August	18	15.4
September	10	8.6
October	11	9.4
November	6	5.1
December	2	1.7
Total	**117**	**100.0**

DISCUSSION

In this prospective observational study, a total of 117 children with enteric fever were analyzed. The maximum (70%) children were in age group 5 years or more which is comparable to that inSubindra (73%) [13] Study. The male to female ratio in this study was 1.3: 1. Pandey KK. Reported 1.2:1[14].

In this study, cases were admitted throughout the year showing the endemicity of the disease. Maximum cases were admitted during May to August months (59%). This period coincides with the onset of monsoon and increase in housefly population, which facilitates faeco-oral transmission. Moreovermost of the children in this study were from urban slum area (53.6%) of Dhaka city. Almost all of them drink Dhaka WASA supplied water and maximum of them (66.7%) drink water without boiling. Pandey K.K[14] reportedmaximum incidence between May – July, Sudharshan Raj C [15] reported45.6% betweenJune-September and Arora *et al.* [16] reported 40.6% cases in the period of September-October.

The most common symptoms in this study were fever (100%), anorexia (100%), pain abdomen (74.4%), loose motions (46.1%), constipation (15.4%), vomiting (19.7%), cough (37.6%) and altered sensorium (3.4%). These symptoms were also seen in studies conducted by TanejaSood *et al*. [17] and Sudharshan Raj C study [15]. In the present study maximum cases (71%) had fever for 8-14 days prior to admission which was comparable to that of Arora *et al*. (51.6%) [16] Study. Almost all cases showed continued high fever. No case in this study had stepped ladder type of fever and this finding is same as reported byKapoor JP *et al*.[18]

The common signs were hepatomegaly (41.9%), hepatosplenomegaly (5.1%) coated tongue (64.9%), pallor (74.4%) and caecal gurgling (5.9%) cases, which was also reported by Kapoor JP *et al*. [18] and Sudharshan Raj C[15] but they reported isolated splenomegaly > 65% cases. Whereas in this study no cases was found with isolated splenomegaly and more than half (52.9%) of the cases have no organomegaly which was consistant with FarhanaKhanam *et al.* study [19]. The other signs tachycardias (94%) and toxic look (23.9%) in this study were also reported by Sudharshan Raj C[15]. No cases had found relative bradycardia as other study[14,15,19]. All patients recovered but 35.9% cases developed complications and commonest being UTI and pneumonia. Severe complication likeHepatitis(4.8%), cholycystitis (2.4%), peritonitis(2.4%) and encephalopathy (2.4%) were less. W. Abdullah Brooks *et al*. [20]. Reported similar results but Helal N[21] reported only 11.2% complications in their study.

The overall positivity of widal test in this study was 89.7% as comparable toSudharshan Raj C study [15], they reported 89.8% positivity and 90% reported by Mishra *et al*.[22] The culture positivity in this study was 32.5%. Which is in concordance with that of Manchanda *et al*. (33.5%)[23] study. Use of antibiotics prior to admission was probably responsible for low culture positivity rates. Among the 38 culture positive cases, Widal test was positive in 26 cases (68.4%). In 12 cases, Widal test remained negative on repeating after one week. From the total isolates, 5.3% were *Salmonella paratyphi A* whereas the remaining was *Salmonella typhi*(94.7%) in this study. Helal N[21] also showed similar result but the reported rate of isolation of*paratyphiA*in literature is 20%[24].

The present study found 18.1% isolates to be multi drug resistant which was comparable with FarhanaKhanam *et al*. [19] (15%) study conducted in Dhaka slum area. But Garg *et al*. [25] and Arora *et al*. [16] reported 67% and 82.5% respectively. In this study, 72.2%, 83.3%, 61.1% of the isolates were resistant to chloramphenicol, ampicillin and co-trimoxazole which were comparable withSudharshan Raj C study [15]. Lower percentage of chloramphenicol (72.2%) and co-trimoxazole (61.1%) resistance may be due to re-emerging sensitivity as reported by Urmila jhamb[26]. Amoxyclav, Amoxycilline and Nalidaxic acid were 100% resistant to isolates found in this study. Widespread use of might be responsible for resistance to these drugs. Adnan *et al*. [27] also reported, almost all isolates were resistant to nalidixic acid. Resistance to nalidixic acid has also been reported in India and China [28, 29]. No resistance was found to Cefixime, ceftriaxone. Meropenam and Ofloxacine in this study.These results suggest that these drugs resistance are still not high in this part of Banladesh. Sudharshan Raj C [15] and FarhanaKhanam *et al.* [19] showed the same results. Although previous studies showed the growing resistance of ciprofloxacin [30, 31] but we found Ciprofloxacin was 72.2% and levofloxacin was 52.8% sensitive among isolates. On the other hand the most important macrolides, Azithromycin was only 22.2% sensitive among S. Typhi in this study. Adnan *et al*. [27] reported the same result but farhanakhanam *et al*. [19] reported 100% sensitive to Azithromycin.

Contributory factors may be drug overuse, misuse and inappropriate prescribing practices by physicians along with intrinsic microbiological plasmid-mediated factors. Moreover, increased population can lead to increased dissemination of antibiotic resistant bacteria and resistant genes [27]. As Bangladesh is a developing country, increase in population density and urbanization may facilitate the spread of resistant bacteria and gene, which was also seen in other countries [31].

CONCLUSION

Enteric fever is endemic in Bangladesh but most prevalent during summer & rainy session. WASA supplied water may play a role to develop enteric fever.

Fever, anorexia and pain abdomen are the main complaints. Hepatomegaly is common. UTI and pneumonia are the commonest complication. Widal test is still a reliable test for the diagnosis of enteric fever. Multidrug resistant cases are not so as high as other countries. Amoxycilline & Nalidaxic acid are almost resistant to all salmonella strain. Higher rate of resistant to Azithromycin is seen in this study. Cefixime, Ceftriaxone. Meropenam and Ofloxacine are the drugs of choice. Ciprofloxacin is still could be chosen for the treatment of enteric fever.

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