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ORIGINAL ARTICLE

Prevalence of Multidrug Resistant Typhoid Fever

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ABSTRACT

Background: Typhoid fever is a systemic infection caused by several *Salmonella enterica* serotypes including *S. Typhi and S. Paratyphi* A. The Indian subcontinent has the highest incidence of the disease worldwide. It is also an epicenter of enteric fever caused by multidrug-resistant (resistant to three conventional antibiotics namely chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole) and nalidixic acid resistant (NAR) strains.

Patients and Methods: A total of 92 paediatric patients, diagnosed on the basis of positive blood culture for Salmonella typhi or Salmonella paratyphi were included in the study to determine their bacteriological sensitivity pattern. Laboratory tests performed were complete blood count, Widal test (if duration of fever was beyond one week), and bacteriological sensitivity to antibiotics. Blood specimens were cultured to evaluate the yield of Salmonella typhi or paratyphi. Comparison of clinical features between antibiotic sensitive and resistant cases was made to see whether clinical presentation varies with respect to antimicrobial sensitivity.

Results: Of the 92 patients, half (51%) was male and half (49%) female with mean age of the patients being 5.89 ± 3.04 years. The average duration of illness was 12.6 ± 2.8 days and 53% had step ladder pattern of fever and 47% intermittent fever. Majority of the patients complained loss of appetite (96.7%) and nausea/vomiting (90.2%). Of the positive blood culture patients 80% had isolates of *S. typhi* and 20% *S. paratyphi* strains. Over half (52.2%) was sensitive to amoxicillin, 63% to chloramphenicol, 78.3% to cotrimoxazole, 62% to ciprofloxacin, 98.9% to ceftriaxone and 100% to cefixime. Thirteen percent of patients exhibited concomitant resistance to amoxycillin, chloramphenicol and cotrimoxazole (multidrug-resistance). Widal test demonstrated that about 44% of the cases had a 4-fold increase in 'O' agglutinin titres, 27.2% 8-fold and 15.2% 16-fold. A similar rise in 'H' agglutinin titres to *S. typhi* antigen was also observed (46.7% 4-fold, 19.6% 8-fold and 15.2% 16-fold). In contrast, very few patients had 4-, 8- and 16-fold rise of 'O' antibody titres to *S. paratyphi* antigen (4.3%, 3.3% and 2.2% respectively). Rise of 4-fold 'H' antibody titres to *S. paratyphi* antigen was rare.

Conclusion: It was concluded that, antibiotic should be initiated only after availability of culture and sensitivity report or at least after a positive Widal test report.

Key words: multidrug-resistant (MDR) *S. typhi* and *S. paratyphi*, bacteriological sensistivity pattern.

INTRODUCTION

Typhoid fever is a distinctive acute multisystemic febrile disease caused primarily by *Salmonella typhi*. It is recognized as a major cause of morbidity globally with over 21.6 million cases annually worldwide and an estimated 216000 deaths. Almost 80% of these deaths occur in Asia alone.[1] Enteric fever, being transmissible by faeco-oral route, is primarily a disease of region where overcrowding, poor sanitation and untreated water are the norm.[2] The attack rate

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as high as 1100 per 100000 populations have been documented in developing countries.[3] The recent explosive emergence and spread of multi-drug resistance to the conventionally used antibiotics for the treatment of typhoid fever, namely chlormphenicopl, ampicillin and cotrimoxazole caused significant therapeutic and public health problem.[4] MDR typhoid fever in childhood is frequently associated with a more sever clinical illness and higher rates of toxicity, hepatomegaly, hypotensive shock and death.[5] There is an urgent need to keep the possible emergence of unbeatable strains to a minimum by prudent use of existing drugs and by resting the temptation to use yet more antibiotics.[6] Resistance of *S. typhi* and *S. paratyphi* against commonly used antibiotics is frequently reported. Therefore, susceptibility pattern of the causative agents of enteric fever and thereby finding the prevalence of MDR require constant reappraisal to update our physicians with current knowledge which could help them taking rational decision in treating enteric fever with antibiotics. That purpose the present study is intended to assess the current pattern of bacteriological sensitivity of *S. typhi* and *S. paratyphi* to the antibiotics generally used by the physicians.

METHODS

Paediatric patients up to the age of 12 years, diagnosed primarily as typhoid fever in the Paediatric Department of Bangabandhu Sheikh Mujib Medical University, Dhaka were studied in a cross sectional design over a period of 1 year from March 2009 to February 2010. A total of 92 subjects consecutively included in the study. The variables studied were age, sex and mode of clinical presentations, laboratory findings, type of bacteria and their sensitivity pattern. The diagnostic criteria were positive blood culture for *Salmonella typhi* and *paratyphi*. Laboratory tests performed were complete blood count, Widal test, blood culture and bacteriological sensitivity to antibiotics. Widal test was performed on admission if fever was beyond one week. Blood specimens were cultured to evaluate the yield of *Salmonella typhi or paratyphi*. Ten ml of blood was collected aseptically in a heparinized test-tube containing lytic solution and was centrifuged at 3000 rpm for 30 minutes. The supernatant was discarded and 1 ml of the deposit containing the pathogen was vigorously vortexed and entire sediment was directly inoculated onto blood agar or MacConkey agar media. The inoculated culture plates were immediately placed in an incubator at 37°C for 24-48 hours. All the isolated *S. typhi* were put into antibiotic susceptibility test by Kirby-Bauer disk diffusion technique. Panel of antibiotics, namely chloramphenicol, cotrimoxazole, amoxycillin, ciprofloxacin, cephradine, gentamicin, ceftriaxone, azithromycin and nalidixic acid were tested on Muller-Hinton agar media.[7] Comparison of clinical features between antibiotic sensitive and resistant cases was made to see whether clinical presentation varies with respect to antimicrobial sensitivity. The descriptive statistics used to analyze the data were frequency, mean and standard deviation, while the inferential statistics used to analyse the data was Chi-square (χ^2) Test. The level of significance was set at 0.05.

RESULTS

The mean age at presentation was 5.89 ± 3.04 years and more than half (51%) of the patients was male and male to female ratio was roughly 1:1 respectively. More than three–quarters (76.1%) of the patients at presentation had been suffering from the disease for 10-15 days and the average duration of illness was 12.6 ± 2.8 days. Fifty three percent had step ladder pattern of fever, while rest 43(47%) had intermittent fever. More than half (56.5%) of the patients exhibited a pulse rate ranging from 100-120 per minute, 31.5% from 80-100/minute and 12% >120/minute. Almost two-third (66.3%) of the patients exhibited a temperature ranging from 101-102^0 F (23.9% exhibited >102^0 F and 9.8% less than 101^0 F. About 15% of patients had raised ESR (> 50 mm at 1st hour) while rest (84.8%) had ESR 50 or < 50 mm at 1st hour. Majority (80%) of patients had isolates of S. typhi and 18(20%) had *S. paratyphi* strains. Thirteen percent of patients exhibited resistance to amoxycillin, chloramphenicol and cotrimoxazole (multidrug-resistance) (Table I).

TABLE I : Distribution of patients by baseline variables (n = 92).

Baseline variables	Frequency	Percentage
Duration of illness (days)		
<10	05	5.4
10-15	70	76.1
>15	17	18.5
Pattern of fever		
Step ladder	49	53.0
Intermittent fever	43	47.0
Pulse rate (per minute)		
80-100	29	31.5
100-120	52	56.5
>120	11	12.0
Temperature		
<101	09	9.8
101-102	61	66.3
> 102	22	23.9
ESR* (at the 1st hour)		
≤ 50	78	84.8
>50	14	15.2
Type of organism		
S. typhi	74	80.0
S. paratyphi strains	18	20.0
Multi-drug resistant	12	13.0

Majority of the patients complained loss of appetite (96.7%) and nausea/vomiting (90.2%). Nearly half (46.7%) of the patients had diarrhoea, 23.6% cough, 20.7% chills, 5.4% sweating, 19.6% headache, 19.6% constipation, 2.2% jaundice, 4.3% pain in the right hypochondrium. Most (83.7%) of the patients exhibited hepatomegaly, 79.3% coated tongue, 67.4% splenomegaly, 45.7% abdominal discomfort, 41.3% relative bradycardia, 29.3% abdominal distension, 7.6% toxima, 5.4% dehydration and 3.3% muscle cramp (Table II). Sensitivity pattern of microorganisms demonstrate that out of 92 culture positive cases of enteric fever, 52.2% were sensitive to amoxicillin, 63% to chloramphenicol, 78.3% to cotrimoxazole, 62% to ciprofloxacin, 98.9% to ceftriaxone and 100% to cefixime (Table III).

Widal test findings are illustrated in table IV. About 44% of the cases had a 4-fold increase in 'O' agglutinin titres, 27.2% 8-fold and 15.2% 16-fold. A similar rise in 'H' agglutinin titres to S. typhi antigen was also observed (46.7% 4-fold, 19.6% 8-fold and 15.2% 16-fold). In contrast, very few patients had 4-fold, 8-fold and 16-fold rise of 'O' antibody titres to S. paratyphi antigen (4.3%, 3.3% and 2.2% respectively). Rise of 4-fold 'H' antibody titres to S. paratyphi antigen was rare (Table IV). The median count of WBC was 8000/mm3 of blood. The differential count of WBC shows that neutrophil was 59%, lymphocyte 36%, esinophil 2% and monocyte 3% (Table V). Comparison of relevant clinical characteristics between typhoid fever cases with and without multi-drug resistance did not reveal any association with WBC count (in terms of leucopenia), type of fever (in terms of step ladder pattern of fever) and pulse rate (in terms brtadycardia) ($p > 0.05$ in each case) (Table VI).

TABLE II : Distribution of patients by mode of clinical presentation.

Clinical presentation	Frequency	Percentage
Loss of appetite	89	96.7
Nausea/vomiting	83	90.2
Hepatomegaly	77	83.7
Splenomegaly	62	67.4
Coated tongue	73	79.3
Diarrhoea	43	46.7
Abdominal discomfort	42	45.7
Relative bradycardia	38	41.3
Chills	19	20.7
Sweating	05	5.4
Headache	18	19.6
Constipation	18	19.6
Jaundice	02	2.2
Cough	22	23.9
Pain in the right hypochondrium	04	4.3
Bleeding per rectum	01	1.1
Burning micturation	01	1.1
Inability to rise from squatting	01	1.1
Abdominal distension	27	29.3
Toxemia	07	7.6
Muscle cramp	03	3.3
Dehydration	05	5.4

TABLE III : Sensitivity of isolated Salmonella strains to different antibiotics .

Antibiotics	Sensitive	
	Frequency	Percentage
Amoxicillin	48	52.2
Chloramphenicol	58	63.0
Cotrimoxazole	72	78.3
Ciprofloxacin	57	62.0
Ceftriaxone	91	98.9
Cefexime	92	100.0

TABLE IV : Distribution of the patients by different antibody titer (n = 92).

Widal test	Frequency	Percentage
TO		
Normal	02	2.2
2 - fold	11	12.0
4 - fold	40	43.5
8 - fold	25	27.2
16 - fold	14	15.2
TH		
Normal	04	4.3
2 - fold	13	14.1
4 - fold	43	46.7
8 - fold	18	19.6
16 - fold	14	15.2
AO		
Normal	31	33.7
2 - fold	52	56.5
4 - fold	04	4.3
8 - fold	03	3.3
16 - fold	02	2.2
AH		
Normal	30	32.6
2 - fold	58	63.0
4 - fold	04	4.3

TABLE V : Total and differential counts of WBC (n= 92).

WBC count	Findings	
	Median	Range
Total count (per cubic ml of blood)	8000	4000-14500
Differential count (%)		
Neutrophil	59	27 - 80
Lymphocyte	36	16 - 63
Esinophil	02	0 - 63
Basophil	00	0 - 1
Monocyte	03	0 - 10

TABLE VI : Association between clinical characteristics and MDR.

Clinical characteristics	MDR		p-value
	Yes (n=12)	No (n=80)	
Total count of WBC (per mm^3)			
< 6000 (absolute leucopenia)	2(16.7)	20(25.0)	
6000-11000 (relative leucopenia)	9(75.0)	51(63.8)	0.746
> 11000 (leucocytosis)	1(8.3)	9(11.3)	
Fever			
Step ladder	8(66.7)	41(51.3)	0.318
Intermittent	4(33.3)	39(48.8)	
Relative bradycardia			
Present	7(58.3)	31(38.8)	0.332
Absent	5(41.7)	49(61.3)	

Data were analysed using Chi-square (χ^2)

DISCUSSION

The present study showed that over half of the patients (52.2%) was more than 5 years and male to female ratio of was roughly 1:1. However, Verma9 reported 65% of typhoid fever cases to be in the age group 0-2 years, 27% in 2-5 years and 13% in 5-9 years which are not consistent with the present study. Another study conducted by Kumar[6] demonstrated a male to female ratio of 2:1 which is also different from our study.

The mean duration of illness at presentation (12.6 ± 2.8) was also observed to be somewhat higher than that reported by Ndububa and colleagues (9.67 days).[10]

Though step ladder pattern of fever is one of the characteristics of classical typhoid fever, a little more than half (53%) had step ladder pattern of fever and 47% had intermittent fever. The most predominant symptoms and signs with which the patients presented were loss of appetite (96.7%), nausea/vomiting (90.2%), hepatomegaly (83.7%), coated tongue (79.3%), and splenomegaly (67.4%). Nearly half of the patients had diarrhoea, abodominal discomfort and relative bradycardia.

Cough, chills, headache, constipation and abdominal distension were less commonly complained, while toxemia, dehydration and muscle cramp were seldom encountered. In Durrani and Rab's[11] study the common symptoms were nausea/vomiting (70%) and headache (71%). Loss of appetite (40%) and diarrhoea (40%) were less common. Constipation (23%), bleeding per rectum (20%) and burning micturation (14%) were even less. Chills, jaundice, cough, pain in the right hypochondrium and inability to rise from squatting position were the rare presentations.

The clinical signs they observed were hepatomegaly (28%), coated tongue (34%), splenomegaly (50%) and relative bradycardia (35%) and anaemia (33.7%). These findings are more or less consistent with findings of our study.

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Antibiotic sensitivity revealed that over half (52.2%) of the patients was sensitive to amoxicillin, 63% to chloramphenicol, 78.3% to cotrimoxazole, 62% to ciprofloxacin, 98.9% to ceftriaxone and 100% to cefixime. Verma and associates9 in a study conducted in 2007 demonstrated a similar sensitivity to cotrimoxazole (76%) but a higher sensitivity to chloramphenicol (86%) and ciprofloxacin (95%). Like our study they also found nearly 100% sensitivity to ceftriaxone and cefixime. In our study sensitivities to amoxicillin and chloramphenicol were observed to be much lower than those observed in Verma's study. Thus the findings of the study clearly indicate that salmonella strains are rapidly getting resistance to amoxicillin, chloramphenicaol and ciprofloxacin probably for their indiscriminate use, while the drug cotrimoxazole is showing revival of sensitivity to the bacteria because of its long absence of use in enteric fever cases.

Thirteen percent of patients exhibited resistance to amoxicillin, chloramphenicol and cotrimoxazole (multidrug-resistant). Kumar and associates6 reported 66.7% enteric fever cases to be multidrug-resistant sharply contrasting with findings of our study. The findings also points that though MDR strains are still lower, there is a concern that the trend is increasing and if the indiscriminate use of antibiotics cannot be controlled the MDR strains will keep increasing.

MDR *S. typhi* is endemic and causes large epidemics in many parts of Southeast Asia, including India, Pakistan, Bangladesh, Vietnam, Malaysia, Indonesia, China and Tajikistan.[11,12] There is also a pseudoepidemic region that consists of the Middle East and Egypt, where infection with MDR *S. typhi* is generally related to migrant workers from the endemic zone but epidemics can result. Sporadic infections occur in Europe and North America, most often in immigrants who have returned to their original home country for a holiday.[11] Until recently, apart from one small outbreak in south Africa, MDR *S. typhi* was not a problem in sub-Saharan Africa. However, since 1997 increasing numbers of MDR *S. typhi* have been isolated from patents in Nirobi, Kenya, with explosive outbreaks related to damaged water supply systems. Very recently, MDR *S. typhi* was also detected in Ghana.[12] Thus far, MDR *S. typhi* does not appear to have arrived in South or Central America.

The prevalence of MDR S. typhi can be very high. For example, in Vietnam and Pakistan, 60-80% of the positive blood cultures were MDR *S. typhi*.[14] In the endemic zones of India, there has been an encouraging decline in MDR *S. typhi*, with a re-emergence of sensitive strains.[15] Similar phenomenon also happened in Bangladesh. In 1994 3.4% of blood culture isolates were MDR *S. typhi* but this declined to 1% in 1996.[16] The isolation rate of antibiotic susceptible *S. typhi* (approximately 3.3%) remained the same throughout this period.

Studies in Vietnam elegantly demonstrated that fluoroquinolones such as ofloxacin or ciprofloxacin were highly effective drugs for the treatment of MDR *S. typhi*. These could be given to produce rapid defervescence with a low incidence of subsequent carrier state. Unfortunately, this led to a vast and unregulated overuse of fluoroquinolones. The clinical diagnosis of typhoid is difficult; it can be confused with a number of other febrile illnesses and, because the fluoroquinolones are so easy to administer orally with few side effects, they were used as blind empirical therapy for any febrile illness that might or might not be typhoid fever. As might be expected, MDR and fluoroquinolone-resistant strains of *S. typhi* emerged, causing both sporadic and epidemic disease.[17]

CONCLUSION

The prevalence of MDR strains of S. typhi is still low in Bangladesh. But there is concern that prevalence may increase rapidly, as the treatment seeking behaviour is favourable for the development of MDR strains. To avoid emergence of resistant strains further, indiscriminate use of antibiotics is to be avoided, and if possible, antibiotic should be initiated only after availability of culture and sensitivity report or at least after a positive Widal test report.

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