IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 8 Ser.13 (August. 2020), PP 45-50
www.iosrjournals.org

Clinical Management of Enteric Fever in Children: A Study in a Tertiary Care Hospital, Dhaka, Bangladesh.

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Abstract
Introduction: *Enteric (Typhoid) fever is generally caused by a bacterium called Salmonella entericaserovarTyphi which is associated with the bacteria that cause salmonella food poisoning. It is a major public health issue in developing and developed countries. Around, 21.6million people suffer from this disease, and it occurs almost 216,500 deaths annually.Almost 80% of the suffering and death cases were testified from Asia, while the rest (20%) of them were from Africa and Latin America. In South Asia, it is evaluated that in the region of 400 million people (23% of the population) subsists in high-risk situations for aquatic diseases.****Aim of the study:****To analyze the management of Enteric fever in children admitted in a tertiary care hospital.****Material & Methods:*** *This was an observational study which was conducted at the Department of Paediatric Infectious Diseases and Community Paediatrics, Bangladesh Institute of Child Health (BICH), Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh during the period from January 2018 to December 2018. Total 133 cases were selected using random sampling technique. Informed written consent was obtained from each patient before the procedure. A pre-designed questioner had been used to collect all the necessary data from the participants. Program MS-Excel was used in collecting data, SPSS version 21 was used in analyzing data. On the other hand, several tables were used to disseminate data. Following was the inclusion and exclusion criteria of the present study.****Results:*** *Culture positive demonstrates that, 50(37.6%) cases are positive where 44(88%) cases were S. typhi and 6(12%) cases were paratyphi; 83(62.4%) cases were negative. Widal test results by the duration of illness in presenting with clinical presentation suspicious of typhoid fever shows that, of the total 121(91%) positive cases duration of illness of ≤ 7 days was 50(86.2%), duration of illness of >7 days was 71(94.7%); of the total 12(9%) negative cases duration of illness of ≤ 7 days was 8(13.8%), duration of illness of >7 days was 4(5.3%). Widal + CS positive shows, 44(33.1%) cases were widalpositive+CS positive, 83(62.4%) cases were widalpositive+CS negative, 6(4.5%) cases were widalpositive+CS negative. Diagnostic test evaluation describes that out of the total 121 widal test positive, 44 were blood culture positive and 77 were blood culture negative; while out of 12 widal test negative, 6 were blood culture positive and 6 were blood culture negative. Of the total 121 widal test positive, 44 were blood culture positive and 77 were blood culture negative; while out of 12 widal test negative, 6 were blood culture positive and 6 were blood culture negative. Antibiotic sensitivity and resistance pattern shows that, 45(90.0%) were ceftriaxone sensitive, 21(42.0%) were ciprofloxacin sensitive, 27(54%) were amoxicillin sensitive, 19(38.0%) were azithromicin sensitive, 40(80.0%) were cefixim sensitive and 24(48.0%) were chloramphenical sensitive. The number of S. typhi isolates resistant to antibiotics shows there were no ceftriaxone isolates but 5(10%) ciprofloxacin, 11(22%) amoxicillin, 10(20%) azithromicin, 3(6%) cefixim, 8(16%) chloramphenical and 11(22%) MDR isolates were present.* ***Conclusion:*** *Public health authorities need to be warned of cases of S. typhi and S. paratyphi infection and regulate suitable supervision of cases and contacts as instructed in that region. Children and staff in child care centres are left out until 3 consecutive stool cultures, serene at least 48 hours after accomplishment of antibiotic treatment, are negative.*

Key Words: *Enteric Fever, Typhoid, Management,Paediatric,Antibiotic Sensitivity,Resistance Pattern.*

Date of Submission: 11-08-2020 Date of Acceptance: 27-08-2020

I. Introduction

Enteric (Typhoid) fever is generally caused by a bacterium called *Salmonella entericaserovar*Typhi which is associatedwith the bacteria that cause salmonella food poisoning. It is a major public health issue in developing and developed countries. Around, 21.6million people suffer from this disease, and it occurs almost 216,500 deaths annually.[1,2] Almost 80% of the suffering and death cases were testified from Asia, while the rest (20%) of them were from Africa and Latin America.[2] In South Asia, it is evaluated that in the region of 400 million people (23% of the population) subsists in high-risk situations for aquatic diseases [3].The preeminent technique to diagnose enteric fever is by accumulating a number of blood cultures initially in the disease. A single blood culture is positive in only half of cases. No less than one stool sample ought to be sent for bacterial culture and sensitivity (yield is 30% to 50%). Urine culture has the lowermost yield.[4]Widal test is a serologic assay for identifying immunoglobulins M and G (IgM and IgG) to the O and H antigens of Salmonella. Fresher serologic assesses are not voluntarily accessible. Hospitalized patients diagnosed with enteric fever call for contact precautions up until culture results are negative for 3 consecutive stool specimens.[5]Conflicting opinions about the rate of disease in young children, especially infants do exist[6-11], despite the fact that a significant load of disease is grieved by young children in endemic regions.[6,7] It's been a decade since immunization exertions in endemic regions have been focused on school vaccination movements.[8] There are two licensed typhoid fever vaccines available, 1)the oral Ty21a vaccine; 2) the parenteral Vi polysaccharide (ViPS) vaccine, both of which have inadequate practice in preschool children down to the mode of administration as capsules via the per oral route (Ty21a), or an lower immune reaction in children lees than 2 years of age (ViPS).[9] Auspicious conjugate vaccines are on the skyline, but the immunization policy and the target population for these vaccines are yet to be defined, for instance existing epidemiological data is not sufficiently enlightening concerning sources of infection.[10]The present study was undertaken with the objectives toanalyze the management of Enteric fever in children admitted in a tertiary care hospitalin Bangladesh.

II. Methodology And Materials

This was an observational study which was conducted at the Department of Paediatric Infectious Diseases and Community Paediatrics, Bangladesh Institute of Child Health (BICH), Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh during the period from January 2018 to December 2018. The aim of the study was to analyze the management of Enteric fever in children admitted in a tertiary care hospital. Total 133 cases were selected using random sampling technique. Informed written consent was obtained from each patient before the procedure. A pre-designed questioner had been used to collect all the necessary data from the participants. Program MS-Excel was used in collecting data, SPSS version 21 was used in analyzing data. On the other hand, several tables were used to disseminate data. Following was the inclusion and exclusion criteria of the present study.

- **Inclusion Criteria**
  - Patients admitted at the Department of Paediatric Infectious Diseases and Community Paediatrics, Bangladesh Institute of Child Health (BICH), Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh
  - Patient aged below 16 years
- **Exclusion Criteria**
  - Patients aged above 16 years

III. Results

Of the total 133 study subjects, 60.2% were aged <60 months, and the rest 39.8% were aged ≥60 months; Mean±SD age (in months) were 55.26±36.20; age range were between 7-172 months. Male subjects were 71 (53.4%) and female subjects were 62 (46.6%); male to female ratio was 1.1: 1. Of the total study subjects, 116(87.2%) were from urban area, 4 (3%) were from urban slum area and the rest 13 (9.8%) were from rural area. Table II reflects the distribution of the study subjects by H/O typhoid vaccination. Of the total study subjects, only 11.3% had H/O typhoid vaccine and the rest 88.7% had never taken the vaccination. Distribution of the study subjects by clinical parameters (Table III) shows, 129 had fever and Mean±SD duration of the fever was 10.23±5.71. Analyzing types of fever, it was observed 92(69.2%) had continuous fever and 41(30.8%) had intermittent. Symptoms were, 53(39.8%) abdominal pain, 48(36.1%) diarrhea, 25(18.8%) constipation, 52(39.1%) vomiting and 14(10.5%) others. Signs were, toxic 85(63.9%), median temperature in (25^{th}, 75^{th}centile) 102.0 (101.0, 103.0), median pulse in (25^{th}, 75^{th} centile) 100 (96.0, 110.0), coated tongue 99(74.4%),

rose spots 19(14.3%), pallor 69(51.9%), jaundice 6(4.5%), abdominal distension 20(15%), abdominal tenderness 18(13.5%), hepatomegaly 22(16.5%), splenomegaly 5(3.8%) and others 4(3%). Laboratory investigations is shown in Table IV. In Table VCulture positive is shown which demonstrates that, 50(37.6%) cases are positive where 44(88%) cases were S. typhi and 6(12%) cases were paratyphi; 83(62.4%) cases were negative. Widal test results by the duration of illness in presenting with clinical presentation suspicious of typhoid fever (Table VII) shows that, of the total 121(91%) positive cases duration of illness of ≤ 7 days was 50(86.2%), duration of illness of >7 days was 71(94.7%); of the total 12(9%) negative cases duration of illness of ≤ 7 days was8(13.8%), duration of illness of >7 days was 4(5.3%). widal + CS positive (Table VIII) shows, 44(33.1%) cases were widalpositive+CS positive, 83(62.4%) cases were widalpositive+CS negative, 6(4.5%) cases were widalpositive+CS negative. Diagnostic test evaluation is shown in Table IX. Of the total 121 widal test positive, 44 were blood culture positive and 77 were blood culture negative; while out of 12 widal test negative, 6 were blood culture positive and 6 were blood culture negative. Of the total 121 widal test positive, 44 were blood culture positive and 77 were blood culture negative; while out of 12 widal test negative, 6 were blood culture positive and 6 were blood culture negative. Antibiotic sensitivity and resistance pattern (Table X) shows that, 45(90.0%) were ceftriaxone sensitive, 21(42.0%) were ciprofloxacin sensitive, 27(54%) were amoxicillin sensitive, 19(38.0%) were azithromicin sensitive, 40(80.0%) were cefixim sensitive and 24(48.0%) were chloramphenical sensitive. Table XI shows the number of S. typhi isolates resistant to antibiotics. There were no ceftriaxone isolates but 5(10%) ciprofloxacin, 11(22%) amoxicillin, 10(20%) azithromicin, 3(6%) cefixim, 8(16%) chloramphenical and 11(22%) MDR isolates were present.

Table I: Demographic characteristics of the study subjects (n=133)

Demographic characteristics	Frequency	Percentage (%)
Age (in months)		
< 60	80	60.2
≥ 60	53	39.8
Total	133	100.0
Mean±SD	55.26±36.20	
Range	(7 – 172) months	
Sex		
Male	71	53.4
Female	62	46.6
Male : Female ratio	1.1 : 1	
Residence		
Urban	116	87.2
Urban slum	4	3.0
Rural	13	9.8

Table II: Distribution of the study subjects by H/O typhoid vaccination (n=133)

H/O of vaccination	Frequency	Percentage (%)
Yes	15	11.3
No	118	88.7
Total	133	100.0

Table III: Distribution of the study subjects by clinical parameters (n=133)

Clinical parameters	Frequency	Percentage (%)
Fever	129	97.0
Duration of fever (mean±SD) days	10.23±5.71	
Type of fever		
Continuous	92	69.2
Intermittent	41	30.8
Symptoms		
Abdominal pain	53	39.8
Diarrhoea	48	36.1
Constipation	25	18.8
Vomiting	52	39.1
Others	14	10.5
Signs		
Toxic	85	63.9
Median temperature in (25^{th}, 75^{th} centile)	102.0 (101.0, 103.0)	
Median pulse in (25^{th}, 75^{th} centile)	100 (96.0, 110.0)	
Coated tongue	99	74.4
Rose spots	19	14.3
Pallor	69	51.9
Jaundice	6	4.5
Abdominal distension	20	15.0

Abdominal tenderness	18	13.5
Hepatomegaly	22	16.5
Splenomegaly	5	3.8
Others	**4**	**3.0**

Table IV: Laboratory investigations (n=133)

Variables	Median	Mean±SD	Range
Hb (gm%)	10.30	10.12±1.59	5.40 – 14.10
TC (mm^2)	8000.0	8409.5±3366.3	2000-19000
Poly (%)	56.0	56.6±11.47	34 – 80
Lympho (%)	37.0	38.21±11.61	10.0 – 61.0
Platelet count	200000	225376±119245	14600-663000

Table V: Culture positive (n=50)

Culture test	Frequency	Percentage (%)
Positive	50	37.6
• S. typhi	44	88.0
• Paratyphi	6	12.0
Negative	83	62.4

Table VII: Widal test results by the duration of illness in presenting with clinical presentation suspicious of typhoid fever

Widal test result	Duration of illness		Total	p-value
	≤ 7 days (n=58) No. (%)	> 7 days (n=75) No. (%)		
Positive	50(86.2%)	71(94.7%)	121(91.0%)	0.091
Negative	8(13.8%)	4(5.3%)	12(9.0%)	
Total	58(100.0%)	75(100.0%)	133(100.0%)	

Table VIII: Widal + CS positive

Variables	Frequency	Percentage (%)
WidalPositive+CS Positive	44	33.1
Widalpositive+CS negative	83	62.4
Widal negative + CS positive	6	4.5
Total	133	100.0

Table IX: Diagnostic test evaluation

Variables		Blood culture		Total
		Positive	Negative	
Widal Test	Positive	44	77	121
	Negative	6	6	12
Total		50	83	133

Table X: Antibiotic sensitivity and resistance pattern

Antibiotic	Sensitive	Intermediate	Resistant
Ceftriaxone	45(90.0%)	2(4.0%)	0(0.0%)
Ciprofloxacin	21(42.0%)	19(38.0%)	5(10.0%)
Amoxicillin	27(54%)	0(0.0%)	11(22.0%)
Azithromicin	19(38.0%)	14(28.0%)	10(20.0%)
Cefixim	40(80.0%)	0(0.0%)	3(6.0%)
Chloramphenical	24(48.0%)	1(2.0%)	8(16.0%)

Table XI: Number of S. typhi isolates resistant to antibiotics

Antibiotic	No of isolates	Percentage
Ceftriaxone	0	0.0
Ciprofloxacin	5	10.0
Amoxicillin	11	22.0
Azithromicin	10	20.0
Cefixim	3	6.0
Chloramphenical	8	16.0
MDR	11	22.0

IV. Discussion

Ever since Salmonella typhi has developed in 1990s, resistance instantaneously to all the drugs used in first line management (chloramphenicol, cotrimoxazole and ampicillin) and are known as Multi Drug Resistant typhoid fever (MDRTF). Some evidence of reemergence of entirely vulnerable strain to first line drugs.[12] In recent times, azithromycin is being used as an unconventional agent for the management of basic typhoid fever.[13]Aztreonam and imipenem are also prospective third line drugs which are used in recent times.[14] In the present study, of the total 133 study subjects, 60.2% were aged <60 months, and the rest 39.8% were aged ≥60 months. Chandrasekhar, et al.[15] in their study showed that 60% of typhoid patients were above 5 years of age which is almostsimilar to our study. Another study from a Tertiary care hospital in Chennai, South India showed that 169 (53.48%) out of 316 cases of typhoid fever were > 5 years of age.[16]In our study, we have noticed that, 44(33.1%) cases were widalpositive+CS positive, 83(62.4%) cases were widalpositive+CS negative, 6(4.5%) cases were widalpositive+CS negative. Diagnostic test evaluation also showed out of the total 121 widal test positive, 44 were blood culture positive and 77 were blood culture negative; while out of 12 widal test negative, 6 were blood culture positive and 6 were blood culture negative. Of the total 121 widal test positive, 44 were blood culture positive and 77 were blood culture negative; while out of 12 widal test negative, 6 were blood culture positive and 6 were blood culture negative. Antibiotic sensitivity and resistance pattern showed that, 45(90.0%) were ceftriaxone sensitive, 21(42.0%) were ciprofloxacin sensitive, 27(54%) were amoxicillin sensitive, 19(38.0%) were azithromicin sensitive, 40(80.0%) were cefixim sensitive and 24(48.0%) were chloramphenical sensitive. Table XI shows the number of S. typhi isolates resistant to antibiotics. There were no ceftriaxone isolates but 5(10%) ciprofloxacin, 11(22%) amoxicillin, 10(20%) azithromicin, 3(6%) cefixim, 8(16%) chloramphenical and 11(22%) MDR isolates were present. A previous study conductedin Kenyan between 2004 and 2006 established that 13% of *S.* Typhi isolates had reduced susceptibility to ciprofloxacin and 70% were MDR.[17] These data recommend a tendency of growing commonness of drug-resistant *S.* Typhi in current years. This upsurge in the frequency of *S.* Typhi with abridged vulnerability to ciprofloxacin has been also described from other parts of the African continent, as well as the Democratic Republic of the Congo (15%) and South Africa (5%).[18,19]This study validates as well a high incidence of MDR *S.* Typhi in Tanzania. In Burkina Faso, Guinea-Bissau, Madagascar, and Senegal, only little numbers of *S.* Typhi were isolated, and none were MDR. In a study conducted in Burkina Faso, 12 *S.* Typhi were isolated from 711 febrile patients; not any were MDR or ciprofloxacin resistant.[20] A survey conducted in Guinea-Bissau in 2010 isolated neither MDR nor ciprofloxacin-resistant isolates among 3 *S.* Typhi strains.[21] Surveillance data from Senegal between 1999 and 2009 reported 127 *S.* Typhi; again, none were fluoroquinolone resistant or MDR[22], whereas another Senegalese study of data up to 2002 reported 1 of 232 isolates (0.4%) to be MDR.[23] Studies have recommended that patients in Indian subcontinent or with the history of travel to the Indian subcontinent should have ciprofloxacin as first line therapy. [24,25] Yet, S. typhi isolates resistant to ciprofloxacin and ceftriaxone (MIC, 64 mg/L) have been reported[26,27,28] S. typhi strains with reduced susceptibility to fluoroquinolones have become a main problem in Asia and other parts of the world.[29]Some reports showed that treatment of patients infected with alike isolates is at possible risk of therapeutic disappointment.[30]

LIMITATIONS OF THE STUDY

This was anobservational study conducted in a singlecentered unit. Thesamplesizewas comparatively small. So, it might not reflect the scenario of the whole country.

V. Conclusion and Recommendations

Empirical parenteral ceftriaxone antibiotic therapy possibly will be substituted with ampicillin, cotrimoxazole, azithromycin or ciprofloxacin if bacteria are disposed, but also rest on the site of infection, the host and the clinical response. Benefits of ciprofloxacin are that for vulnerable S. typhi, there is quicker resolution of the fever, less relapses and an inferior rate of stool carriage. Fluoroquinolones are not permitted for use in children younger than 18 years of age. Antibiotic treatment for 10 to 14 days is suggested for enteric fever, even thoughdiminutive courses of 7 to 10 days have been operative in simple enteric fever. Meningitis should be treated for at least 4 weeks, osteomyelitis for 4 to 6 weeks. Public health authorities need to be warned of cases of S. typhi and S.paratyphi infection and regulatesuitablesupervision of cases and contacts as instructed in that region. Children and staff in child care centres are left out until 3 consecutive stool cultures, serene at least 48 hours after accomplishment of antibiotic treatment are negative.

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Dr. Md. Mizanur Rahman, et. al. "Clinical Management of Enteric Fever in Children: A Study in a Tertiary Care Hospital, Dhaka, Bangladesh.*" IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(8), 2020, pp. 45-50.