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Pattern of antibiotic prescription and physicians' opinion on the resistance of antibiotics used in enteric fever in Bangladesh: a cross sectional survey

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Abstract: *Enteric fever remains to be a major health problem in Bangladesh. Emergence of multidrug-resistant (MDR) Salmonella typhi has further complicated therapy by limiting treatment options and thus has created a major clinical problem worldwide. The study was aimed to determine- i) the trend of antibiotic use and causes of antimicrobial resistance in enteric fever through physicians' opinion and ii) the scenario of antibiotic use in different areas in Bangladesh by prescription survey. This cross sectional survey was conducted by a self-designed standard questionnaire and data were collected manually from November 15, 2013 to January 18, 2014 from three district cities of Bangladesh: Dhaka, Rajshahi and Khulna. Data were collected by directly interviewing the physicians who were treating at least one patient with enteric fever during the study period and from the patient's prescriptions. A total of 200 physicians were interviewed and a total number of 276 prescriptions were analyzed. The highest prescribed antibiotic for typhoid fever was cefixime (32.61%) followed by ceftriaxone (24.28%) and azithromycin (14.13%). Ciprofloxacin was found to be the most resistant antibiotic in typhoid fever according to doctors' opinion. Two or more antibiotics were found to be prescribed in 63.27% of prescriptions. A complete direction for antibiotics use was given in 54.08% of prescriptions and 64.29% patients completed full course of antibiotics. Although 84.69% prescriptions had no clinical test for using antibiotics, the percentages of patients' disease recovery were 65.31%. Most of the physicians believed that irrational use results in bacterial resistance to antibiotics in enteric fever. Our findings are important for developing public awareness and education in antibiotic use.*
Key words: *Antibiotics, Antibiotic resistance, Enteric fever, Prescription patterns.*

I. Introduction

Enteric fever includes typhoid fever– mostly caused by *Salmonella enterica* serotype Typhi; and paratyphoid fever- which is caused by *S. enterica* serotype Paratyphi A (SPA), B, and C [1]. Enteric fever continues to be a major health problem in Bangladesh due to poor hygiene and sanitary conditions prevalent in low-income and middle-income populations. There are approximately 21.6 million cases of typhoid fever worldwide with at least 250,000 deaths occurring every year [2]. The disease is highly epidemic in Asian countries, especially in Bangladesh, Nepal, India, Vietnam and Indonesia [1- 4]. Different types of antibiotics are used for the treatment and prevention of enteric fever. Until 1987, two to three weeks of chloramphenicol or amoxicillin or trimethoprim-sulphamethoxazole was the treatment of choice for enteric fever [1, 4, 5] Later, treatment became difficult due to emergence of MDR *S. typhi* which was resistant to amoxicillin, chloramphenicol and trimethoprim-sulphamethoxazole. In 1990 in Bangladesh was found to have as an expansion of MDR *S. typhi* strains from China, Pakistan, India and Nepal [4- 6]. Fluoroquinolones became the treatment of choice for typhoid fever with 98% cure rate and <2% faecal carriage, and were simultaneously sold widely over the counter to treat fever of various aetiologies in developing countries including Bangladesh [5, 6, 8]. With increased use of fluoroquinolones such as ciprofloxacin, nalidixic acid-resistant *S. typhi* (NART) isolates with decreased susceptibility to ciprofloxacin were in high levels in Central, South, and South East Asia [6- 8]. Therefore, the World Health Organisation recommends that fluoroquinolones or cefixime should be used for the treatment of MDR typhoid fever and azithromycin and/or the third-generation cephalosporins, or a 10–14 day course of high-dose older generation fluoroquinolones (e.g. ofloxacin or ciprofloxacin) for the treatment of nalidixic acid resistant typhoid fever [8]. Recently, nearly ~4% of *S. typhi* isolates showed ciprofolaxin or ofloxacin resistance in Bangladesh due to mutations in *gyrA* and *parC* genes. As a result, these drugs became less optimum for empirical therapy in typhoid fever in spite of recommendation by WHO since similar results have also been reported from India, Nepal and Kuwait [8].

Bangladesh is a developing country with more than 75% of the total population living in rural areas [9]. Though majority of the population live in rural areas, the government healthcare system plays minor roles for the health and sanitation of the village dwellers in Bangladesh [9, 10]. Treatments in the rural areas are mainly provided by unqualified health personnel including medical assistants, mid-wives, village doctors, community health workers in comparison to that of qualified medical graduates (only 10-20%) in urban areas [6, 7, 9]. So,

over-prescribing and inappropriate prescribing of medicines are very common in the country. Moreover, irrational use of antibiotics occurs more frequently in Bangladesh, particularly at rural areas [6, 7. 11]. Awareness and education are necessary for a judicial and constructive approach to prevent irrational usage of antibiotics. In this study, pattern of antibiotic use represents monitoring, evaluation, and suggestions for modifications in the physicians' prescription habits to make patient health care cost reasonable.

The current survey based research was aimed to determine- i) the trend of antibiotic use and causes of antimicrobial resistance in enteric fever through physicians' opinion and ii) the scenario of antibiotic use in different areas in Bangladesh by prescription survey. Our study also unraveled the prevalence of enteric fever in Bangladesh along with some socioeconomic risk factors such as food and hygiene. To the best of our knowledge, this is the first survey among the doctors in adjacent areas of three district cities of Bangladesh to seek their opinion regarding antibiotic use in enteric fever.

II. Materials And Methods

2.1 Study design, setting and study population

The present survey based research was a cross-sectional prospective study carried out in the three district cities of Bangladesh: Dhaka, Rajshahi, and Khulna. Data were collected for over two months period from November 15, 2013 to January 18, 2014.

A self-designed questionnaire was developed and randomly selected general physicians were interviewed with the questionnaire. Total two hundred (200) physicians were surveyed and two hundred and seventy six (276) prescriptions were collected to assess the prescriptions pattern of antibiotics in enteric fever in Bangladesh.

In this health survey any patient aged '0' years to over 60 years whom prescribed one or more antibiotics at any stage during this study period is defined as an 'antibiotic patient'. The term 'antibiotic' is used for 'anti-infective for systemic use' (antibacterials-J01 and anti-mycobacterials-J04), as classified by World Health Organization Collaborating Center (WHOCC) for Drug Statistics Methodology [12]. WHO Anatomical Therapeutic Chemical (ATC) classifications for antibiotics [13, 14] is used in this study

2.2 Data collection

This cross-sectional health survey was carried out with a self-designed standard questionnaire by directly interviewing the 200 doctors, approximately 65 from each city. Two students of the Department of Pharmacy, Jahangirnagar University were assigned and given instruction by the principle investigator for conducting this health survey. Prescription data were collected from the patients by random selecting the patients who came to buy the drugs from the pharmacies [19]. The data collectors were waiting in front of the pharmacy shop and convince them to produce their prescription.

2.3 Ethical Considerations

The research was conducted following the general principles (section 12) of WMA declaration of Helsinki. This survey based research was logistically supported by the Department of Pharmacy, Jahangirnagar University and Novelta Bestway Pharmaceuticals Ltd. As the human subjects involved in our study only participated in the interview, this survey based research did not take any further approval from institutional ethics committee.

2.4 Statistical Analysis

All data were analyzed using **SPSS** (Statistical Package for the Social Sciences 2013) software. Data were presented in numbers, percentages and proportions. Outputs were presented in both graphs and tables. The data were subjected to simple descriptive statistical analyses including frequency distribution, mean, standard deviation and percentage.

III. Results

From the collected prescriptions, the enteric fever patients were categorized according to the age groups and sex. The study results demonstrated that the incidence of enteric fever were highest (54.08%) among the school age populations of 5-15 years old for both sexes (Table 1). Results of this study showed that majority of the patients (62.8%) in the three city areas visited MBBS doctors and 21.5% of patients had access to specialists (Figure 1). A significant portion of patients (15.7%) visited nonqualified health care professionals (Figure 1). The results obtained from Dhaka city were different from the results collected from Rajshahi and Khulna. In Dhaka city, majority of patients visited MBBS doctors and specialists (Figure 1). Whereas, data obtained from Khulna and Rajshahi showed an increasing trend of non-qualified doctors (quack doctors) visit (Figure 1). The average highest prescribed antibiotics for the treatment of enteric fever in three cities were cefixime (32.61%) followed by ceftriaxone (24.28%) and azithromycin (14.13%) (Table 2). Ciprofloxacin was

prescribed frequently for typhoid fever in Rajshahi and Khulna than that of Dhaka city (Table 2). The results of physicians' survey indicated that average highest number of physicians (52.13%) preferred to prescribe cefixime – a third generation cephalosporin antibiotic followed by ceftriaxone which was favoured by 33.23% physicians in treating typhoid fever (Fig 2). Other doctors preferred to prescribe azithromycin, fluoroquinolones and cefuroxime axetil (Fig 2). The physicins' opinion for choice of antibiotic in typhoid fever corroborated with the findings of our prescription survey (Table 2). From the collected prescriptions, cefixime was found to be the most prescribed antibiotic (36.73%) for typhoid fever followed by ceftriaxone (18.37%) and azithromycin (17.35%) respectively (Table 2).

The survey showed that 50.89% of physicians considered ciprofloxacin as the most resistant antibiotic to treat typhoid fever (Fig 3). Whereas 19.88% of physicians thought other fluoroquinolones (levofloxacin) were resistant against *Salmonella typhi* (Fig 3). In case of relapse, ceftriaxone and azithromycin were preferred by 49.83% and 32.33% of doctors respectively to treat typhoid fever (Fig 4).

In this study, 24.28% of physicians said that self-medication was a major contributing factor to drug resistance and whereas 21.97% of physicians considered incomplete dose as the reasons for drug-resistance (Fig 5). A total 13.83% of physicians answered overdose of medicine and 10.98% of physicians answered inadequate dose and duration are responsible for the development of antibiotic resistance in Bangladesh (Fig 5).

In this study, two or more antibiotics were found to be prescribed in 63.27% of prescriptions (Table 3). A complete direction for antibiotics use was given in 54.08% of prescriptions and 64.29% patients completed full course of antibiotics (Table 3). Although 84.69% prescriptions had no clinical test for using antibiotics, the percentages of patients' disease recovery was 65.31% (Table 3). However, a significant percentage of patients (34.69%) showed noncompliance to antibiotics (Table 3).

IV. Discussion

Results of this study showed that the prevalence of enteric fever was particularly high among the school going populations which corroborates with the findings of other studies [2, 6, 9]. This result may be due to the fact that these populations are more likely to have unsafe drinking water and street foods at schools [9]. Different studies showed a positive correlation between education of parents on health care and the incidence of typhoid fever [9-12]. So, it is expected that the prevalence of typhoid fever could be reduced by doing health awareness campaign among the school going children in Bangladesh. In our study, highest number of patients visited MBBS doctors followed by specialist doctors. This results reflected presence of hospitals and medical colleges in the city areas. Previous study showed that in rural areas, majority of the patients did not have access to MBBS doctors or specialists. In rural areas most of patients visit quack doctors [13-19].

This survey demonstrated that the first line choice of antibiotics of suspected cases of enteric fever is cefixime and ceftriaxone as they were preferred by the maximum number of physicians. This is perhaps because of third generation cephalosporins have been recommended as an alternative to quinolone treatment in enteric fever [13, 14]. Several physicians have claimed good results with them, particularly with cefixime. A recent study demonstrated that azithromycin, in comparison with fluoroquinolones, performed better, with fewer clinical failures and shorter mean stay time in hospital [15]. However, the study showed no differences in microbiological failure, relapse, or fever clearance time [15].

Doctors prefer cefixime because of its convenient oral administration and better efficacy. This antibiotic breaks the cell wall of *Salmonella typhi* and acetylcysteine neutralizes the endotoxin which is release by the bacteria as a waste product of metabolism. It was also found that doctors prescribe azithromycin (23.34%) in various specialized cases. Ceftriaxone (6%) is prescribed by doctors in the rare cases of typhoid fever such as, in severe condition and particularly in children <5 years old [14- 16] .

In present study, according to doctors' opinion, ciprofloxacin was named as the most resistant antibiotic in typhoid fever. The emergence of fully ciprofloxacin-resistant *S. typhi* strains is an alarming development that further limits treatment options. The present investigation revealed that the most prescribed antibiotic generic in our country is cefixime. Similar study demonstrated that ceftriaxone, cefotaxime and cefixime were effective for the treatment of MDR, NART and ciprofloxacin-resistant *S. typhi* strains [16]. Another study showed that cefixime had gained popularity in prescription since the quinolones showed therapeutic failure [17].

In a developing country like Bangladesh, majority of the health professionals are not qualified and they do not prescribe antibiotics by following the prescription guidelines of antibiotics. Evidence showed that antibiotics are the most frequently prescribed and misused drugs by patients and prescribers [18, 19]. Although a considerable cases of antibiotics were prescribed for patients without clinical tests and without having complete direction for antibiotic use, the percentage of patients' disease recovery was encouraging. This result might be because of physicians' long clinical experience and as well as of broad spectrum nature of the prescribed antibiotics. In Bangladesh, most of the people do not have the minimal awareness regarding resistance, antibiotics and infections. In this study, the majority of doctors expressed their opinion that self-medication of

antibiotic is the main reason for development of drug resistance. According to doctors' opinion, other contributing factors to drug resistance were overuse, incomplete dose and duration of antibiotics. Moreover, hospitals are also responsible for inappropriate or misuse of antibiotic because of non-evidence based practice globally [19-22]. If Patients do take antibiotic for a short time or in an inadequate manner, this contribute to drug resistance development and increase in health care cost. For the poor population of Bangladesh, health care cost is the major factor to be considered for treatment of diseases [19, 23]. This survey based study provides a clue for the prescribing patterns of antibiotic and other medicines in treating enteric fever by physicians in Bangladesh. The present study showed that two or three drug combinations were more prescribed than monotherapy in the management of typhoid fever which indicated a tendency of physicians to overprescribe antibiotics. Moreover, the high incidence of polypharmacy prescriptions that found in this study also contributed to increase antibiotic resistance.

V. Conclusion:

In short, the incidence of enteric fever was found higher among the school-age children who might have exposure to food and water from unsafe sources. This study also suggests that self-medication, incomplete dose and discontinuation of antibiotics were the main factors that contribute to the development of antibiotic resistance. It is important to have guidelines for antibiotic prescription and use of appropriate drugs for the treatment of typhoid fever to avoid unnecessary prescribing of multiple drugs. Over the counter sale of antibiotics should be more regulated so that self-medication and misuse can be controlled. The findings of this study are important for public health, education and awareness development. Our results also have significant implication for execution of antibiotic-prescription regulations guidelines in enteric fever in Bangladesh.

Conflict of interest

The authors declare that the article content has no conflict of interest.

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Figures and Tables

Table 1: Age and sex distribution of collected prescriptions for cases of typhoid fever in three cities in Bangladesh

Age Group (in Year)	Frequency of Prescription (TNP=276)		Individual Percentage (%)		Total Frequency	AVP (%)
	Male	Female	Male	Female		
5-15	101	51	56.25	52.94	152	55.07
15-30	46	17	25.00	17.65	63	22.83
31-45	11	16	6.25	17.65	27	9.78
46-60	17	9	9.38	8.82	26	9.42
>60	6	2	3.13	2.94	8	2.90

TNP=Total Number of Prescriptions, AVP=Average Percentage

Table 2: Frequency and pattern of prescribed antibiotics in enteric fever of the collected prescriptions

	TNP (N=276)			**IP (%)**			**AVP (%)**	**SD**	**95% CI**
Name of the antibiotics	**DHK (n=100)**	**KHUL (n=96)**	**RAJ (n= 80)**	**DHK**	**KHUL**	**RAJ**			
Cefixime	34	27	26	34.0	28.13	32.50	32.61	1.34	32.12 to 25.21
Ceftriaxone	26	22	18	26.0	22.92	22.50	24.28	1.34	16.99 to 5.01
Azithromycin	11	19	8	11.0	19.79	10.0	14.13	1.1	9.13 to 6.87
Ciprofloxacin	10	14	14	10.0	14.58	17.50	13.77	1.1	17.06 to 13.60
Cefuroxime Axetil	6	7	6	9.0	7.29	7.50	6.88	0.54	8.96 to 5.04
Cotrimoxazole	5	6	6	8.0	6.25	7.50	6.16	0.27	13.99 to 8.01
Other antibiotics	2	1	2	2.0	1.04	2.50	2.17	0.24	1.29 to 1.34

Here, DHK= Dhaka, KHUL= Khulna, RAJ = Rajshahi,
TNP=Total Number of Prescriptions, IP=Individual Percentage, AVP=Average Percentage, SD=Standard Deviation calculated by MS Office Excel-2007, 95% CI= Confidence Interval calculated by modified Wald method at 95% Confidence level.

Table 3: Pattern of antibiotic prescription and usages in enteric fever in three cities in Bangladesh

Parameters	Prescription Pattern	Frequency (TNP=98)	Percentage
Pattern of antibiotics Prescription	Single antibiotic	36	36.73
	Multiple antibiotics	62	63.27
Information on direction for antibiotic use	Complete	53	54.08
	Not mentioned	35	35.75
Clinical test for prescribing antibiotics	With test	15	15.31
	Without test	83	84.69
Completion of full antibiotic course	Yes	63	64.29
	No	35	35.71
Patient's compliance	Disease recovery	64	65.31
	Noncompliance	34	34.69

TNP=Total Number of Prescriptions

Figure 1: Prescriptions collected from different health care professionals

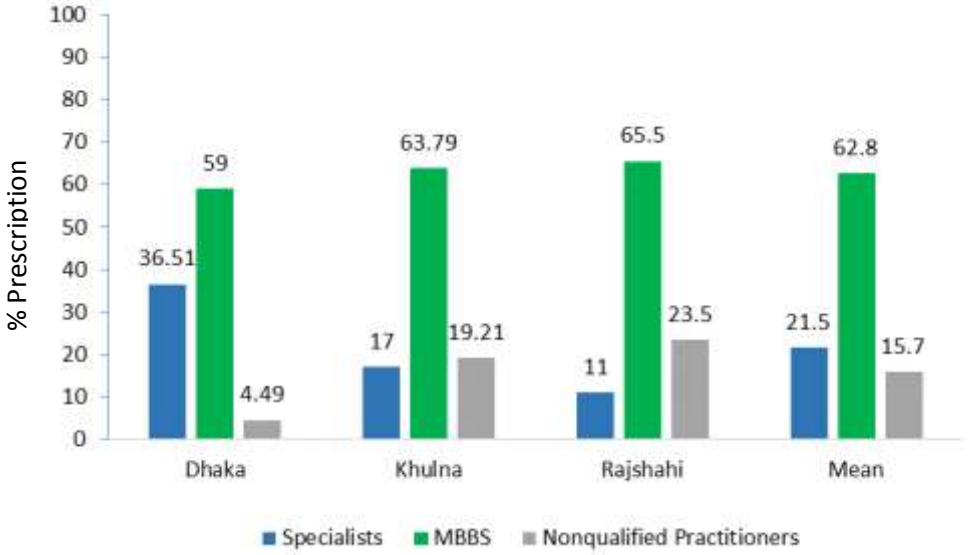

Figure 2: Trend of antibiotic prescriptions in typhoid fever

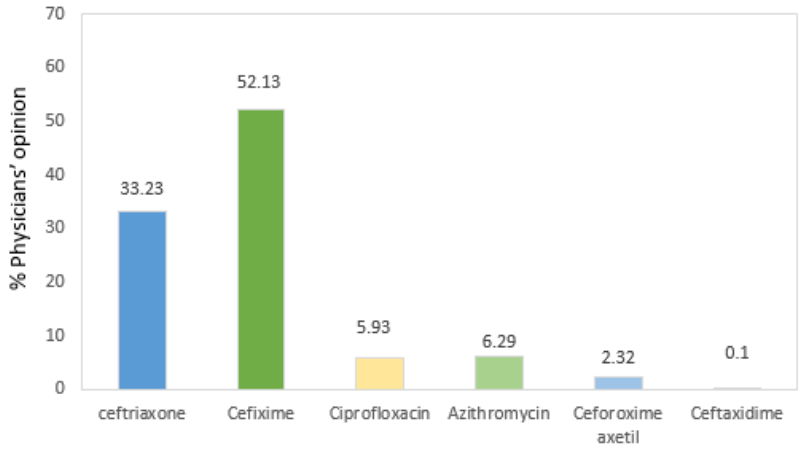

Figure 3: Most Resistant antibiotics according to doctors' opinion

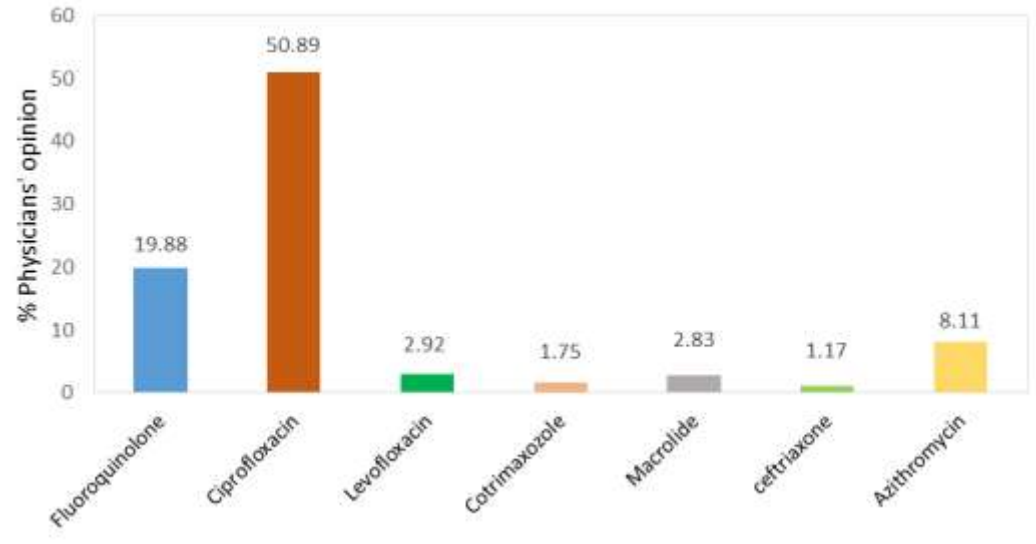

Figure 4: Trend of antibiotic prescription in case of relapse of typhoid fever

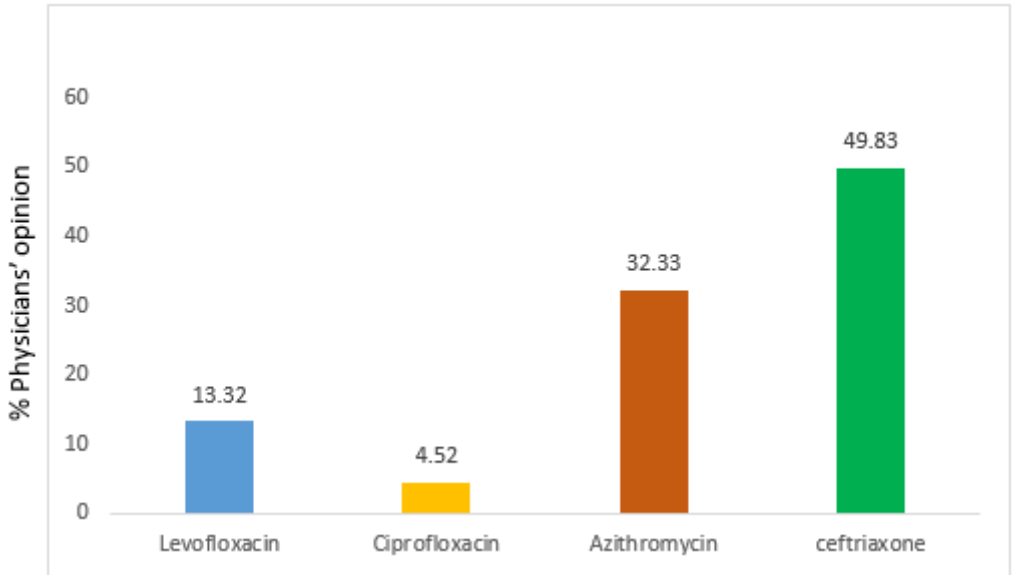

Figure 5: Causes of antimicrobial resistance in typhoid fever according to doctors' opinion