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Antibiotic Sensitivity and Resistance Patterns of Salmonella Typhi in Rajshahi Medical College Hospital

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Abstract

Typhoid and paratyphoid fevers, collectively known as enteric fever, is caused by *Salmonella enterica* subspecies serovars Typhi and Paratyphi A, B and C. Despite this declining global trend, enteric fever is still considered to be a major public health hazard in Bangladesh and other developing countries due to poor sanitation, inadequate food safety measures and poor personal hygiene. In Bangladesh, the incidence of typhoid fever was reported to be 200 episodes per 100,000 person-years during 2003–2004. Multidrug-resistant (resistance to the first-line antimicrobials ampicillin, cotrimoxazole, and chloramphenicol) strains of *S.* Typhi and *S.* Paratyphi are on the rise globally and even cases of extensively drug-resistant (XDR) typhoid cases resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, third generation cephalosporins and fluoroquinolones are being reported from many corners of the world. This descriptive, observational study was carried out in Rajshahi Medical College Hospital Hospital, Rajshahi, Bangladesh from July 2017 to June 2019. Antibiotic sensitivity pattern of total 76 cases of enteric fever due to Salmonella Typhi were studied. Blood culture was carried out by BACT ALERT-3D, Automated blood culture analyzer from BioMeriuex SA, France Patented FAN Plus method. Based on the minimum inhibitory concentration (MIC), the organism was categorized as sensitive, intermediate, and resistant against the respective antibiotics as per Clinical and Laboratory Standards Institute (CLSI) criteria. We are reporting antibiotic sensitivity and resistant patterns of S. Typhi documented in Rajshahi Medical College Hospital, a large tertiary care hospital in Northern Bangladesh.

Key Words: Antibiotic sensitivity, antibiotic resistance, salmonella typhi

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Introduction

Typhoid and paratyphoid fevers, collectively known as enteric fever, is caused by *Salmonella enterica* subspecies serovars Typhi and Paratyphi A, B and C.[1] Typhoid fever is endemic in Asia, Africa, Latin America, the Caribbean, and Oceania, but 80% of cases occur in Bangladesh, China, India, Indonesia, Laos, Nepal, Pakistan and Vietnam.[2] In 2017, 14·3 million (95% uncertainty interval [UI] 12·5–16·3) cases of enteric fever occurred globally, a 44·6% (42·2–47·0) decline from 25·9 million (22·0–29·9) in 1990. Mortality from typhoid and parathyphoid fever was estimated to be 135·9 thousand (76·9–218·9) in

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2017, a 41·0% (33·6–48·3) decline from 230·5 thousand (131·2–372·6) in 1990.[3]

Despite this declining global trend, enteric fever is still considered to be a major public health hazard in Bangladesh and other developing countries due to poor sanitation, inadequate food safety measures and poor personal hygiene. In Bangladesh, the incidence of typhoid fever was reported to be 200 episodes per 100,000 person-years during 2003–2004.[4]

Meanwhile, multidrug-resistant (resistance to the first-line antimicrobials ampicillin, cotrimoxazole, and chloramphenicol) strains of *S.* Typhi and *S.* Paratyphi are on the rise globally[5] and even cases of extensively drug-resistant (XDR) typhoid cases resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, third generation cephalosporins and fluoroquinolones are being reported from many corners of the world.[6] Over 300 XDR typhoid cases have been reported in Sindh, Pakistan, since November 2016. Additionally, a single case of travel-associated XDR typhoid has recently been identified in the United Kingdom. This XDR *S.* Typhi clone harbored a promiscuous antibiotic resistance plasmid previously identified in other enteric bacteria.[6] Chiou et al studied **a**ntimicrobial **r**esistance in *Salmonella enterica* Serovar Typhi Isolates from Bangladesh, Indonesia, Taiwan, and Vietnam in 2014. He noted that, the isolates from Bangladesh and Vietnam were genetically closely related but were distant from those from Indonesia and Taiwan. All but a few isolates from Indonesia and Taiwan were susceptible to all antimicrobials tested. The majority of isolates from Bangladesh and Vietnam were multidrug resistant (MDR) and belonged to the widespread haplotype H58 clone.[7]

The increasing antibiotic resistance in *S.* Typhi observed in many developing countries adds urgency to the need to know local antibiotic sensitivity and resistance pattern which will help to formulate regional hospital antibiotic policy. Antibiotic sensitivity and resistance patterns of salmonella typhi have not been adequately studied in Northern Bangladesh. This study is likely to help physicians on their antibiotic choices in the management of typhoid fever.

Materials and Methods

This descriptive, observational study was carried out in Rajshahi Medical College Hospital, Rajshahi, Bangladesh from July 2017 to June 2019. Antibiotic sensitivity pattern of total 76 cases of enteric fever due to Salmonella Typhi were studied. Blood culture was carried out by BACT ALERT-3D, Automated Blood Culture Analyzer from BioMeriuex SA, France Patented FAN Plus method. For antibiogram of isolated Salmonella typhi, antibiotics were selected as per schedule of Clinical and Laboratory Standards Institute (CLSI) 2017 guideline. Based on the minimum inhibitory concentration (MIC), the organism was categorized as sensitive, intermediate, and resistant against the respective antibiotics as per CLSI criteria. The antibiotic discs used were azithromycin, ceftriaxone, ceftazidime, cefepime, cefixime, cefuroxime, ampicillin, amikacin, gentamycin, ciprofloxacin, levofloxacin, meropenem, imipenem, tetracycline, cotrimoxazole, chloramphenicol and amoxiclav.

SPSS 20 software was used for data analysis.

Results

Mean age of the study participants were 21.6 years; 62.8% of the study participants were male and 31.2% were female. Sixty five (85.5%) patients were in the 15-25 year age range, and eleven (14.5%) patients were above the 25 year age. Twenty three patients (30.3%) patients were found to have MDR typhoid (resistant to ampicillin, cotrimoxazole and chloramphenicol), 2 patients (2.6%) had XDR typhoid (resistant to third generation cephalosporins, ciprofloxacin, ampicillin, cotromoxazole and chloramphenicol). Out of seventeen antibiotics tested, only imipenem and meropenem showed 100% sensitivity. Ceftriaxone resistance was noted in 6.6% of cases (Table 1).

Table 1: Antibiotic sensitivity and resistance pattern of Salmonella Typhi

Name of the antibiotic	Sensitive n (%)	Intermediate n (%)	Resistant n (%)
Azithromycin	4 (5.3%)	5 (6.6%)	67 (88.1%)
Ceftriaxone	64 (84.2%)	7 (9.2%)	5 (6.6%)
Ceftazidime	66 (86.8%)	6 (7.9%)	4 (5.2%)
Cefepime	59 (77.6%)	8 (10.6%)	9 (11.8%)
Cefixime	31 (40.8%)	34 (44.7%)	11 (14.5%)
Cefuroxime	10 (13.1%)	51 (67.2%)	15 (19.7%)
Ampicillin	23 (30.3%)	12 (15.8%)	41 (53.9)
Amikacin	71(93.4%)	4 (5.3%)	1 (1.3%)
Gentamycin,	18 (23.7%)	54 (71.0%)	4 (5.3%)
Ciprofloxacin	15 (19.8%)	52 (68.4%)	9 (11.8%)
Levofloxacin	71 (93.4%)	5 (6.6%)	0 (0%)
Imipenem	76 (100%)	0 (0%)	0 (0%)
Meropenem	76 (100%)	(0%)	0 (0%)
Tetracycline	22 (28.9%)	29 (38.2%)	25 (32.9%)
Cotrimoxazole	45 (59.2%)	13 (17.1%)	18 (23.7%)
Amoxiclav	16 (21.0%)	18 (23.7%)	42 (55.3%)
Chloramphenicol	24 (31.6%)	9 (11.8%)	43(56.6%)

Discussion

Widespread abuse of antibiotics is rampant in Bangladesh. Peoples' ability to purchase antibiotics from drug-stores without prescription, extensive use of antibiotics in the poultry and cattle industry, and inappropriate antibiotics prescription by the healthcare professionals are the three most important cause of increasing antibiotic resistance. Globally, since 1948, chloramphenicol remained the drug of choice for treatment of enteric fever until early 70's, when emergence of chloramphenicol resistance forced to reduce its use. After that, ampicillin and cotrimoxazole were successfully used for some years until the emergence of strains resistant to both of them.

Drug resistant Salmonella Typhi is becoming a cause for concern in Northern Bangladesh. Khatun H et al reported 100% sensitivity of S. typhi to cefixime and ceftriaxone n 2018.[8] In contrast, we have found 14.5% resistance to cefixime and 6.6% resistance to ceftriaxone. Interestingly, 45 (59.2%) of our isolates of S. Typhi were sensitive to cotrimoxazole; this reemergence of susceptibility is probably due to the emergence of de novo susceptible strains or the loss of high molecular weight self-transmissible plasmids.[9] But, despite the low cost, cotrimoxazole

is unlikely to be prescribed to treat enteric fever in Bangladesh because of the risk of cotrimoxazole-induced Stevens-Johnson syndrome.

Lucky H et al reported that, in Jakarta, Indonesia, susceptibility of Salmonella Typhi isolates to the 1st line antibiotics i.e., amoxicillin, ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, ceftriaxone, nalidixic acid, ciprofloxacin and Levofloxacin was good (more than 80% sensitivity) and the trend remain unchanged from 2008 to 2017. But, we are observing increasing antibiotic resistance in Bangladesh.[10]

In Bangladesh, azithromycin was widely used to treat enteric fever for many years. Khatun H et al reported that, between 2010 to 2014, only 5 isolates of S. Typhi out of 431 in ICDDRB hospital, Dhaka, were resistant to azithromycin.[8] But, in recent years, clinicians do not consider azithromycin as a first line agent because of increasing resistance to azithromycin. Patel SR et al from Varanasi, India, reported azithromycin resistance in 21.3% cases in 2017.[11] In our study, we have noted 88.1% isolates of S. Typhi were resistant to azithromycin.

Ciprofloxacin resistance is noted in 11.8% of our S. Typhi isolates; in contrast, Patel SR reported resistance to ciprofloxacin in 25.5% of cases.[11] Levofloxacin sensitivity was noted in 93.4% of our isolates; intermediate sensitivity was shown to levofloxacin in 6.6% cases but no case of levofloxacin resistant isolate was noted in our study. There are two drugs in our study which shown 100% sensitivity i.e. imipenem and meropenem.

Since 2016, an ongoing outbreak of XDR typhoid fever has sickened more than 5,000 people in Pakistan.[12] In our study, 2.6% of the isolates were XDR S. Typhi. Unless government of Bangladesh implement stricter regulations on antibiotic use, the number of cases with XDR enteric fever is likely to increase in the coming years.

Conclusion

Alarming increase of antibiotic resistance in patients with enteric fever is being noted in Northern Bangladesh. Regular monitoring, reporting of antibiotic sensitivity and resistance pattern is needed from all corners of the country. Individual hospitals should develop and implement their own antibiotic stewardship program to counter increasing antibiotic resistance.

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