TRENDS OF ANTIBIOTIC SUSCEPTIBILITY OF *SALMONELLA ENTERICA* SEROVAR TYPHI AND PARATYPHI IN AN URBAN HOSPITAL OF DHAKA CITY OVER 6 YEARS PERIOD

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Abstract

The antibiotic resistance pattern of salmonella is ever changing over time. The present study is a retrospective analysis of *rate of isolation of Salmonella* Typhi and Paratyphi and their antibiotic resistance pattern over 6 years period in an urban hospital of Dhaka city. Blood culture submitted in BIRDEM hospital from 2004-2009 were analyzed. Isolated *Salmonella* sp were identified and antimicrobial susceptibility testing was carried out by a standard disc diffusion method.

Among 385 isolated *Salmonella* sp 304 (79%) were *Salmonella enterica* serovar Typhi and 81 (21%) were *Salmonella enterica* serover Paratyphi A. The rate of isolation of *S.* Paratyphi A has increased over 6 the year period from 14% to 24%. Resistance to individual first line anti-salmonella drugs has increased from 2004 to 2006 (42 to 63%) but has decreased thereafter. Similar pattern was found when simultaneous resistance to three first line antibiotics namely ampicillin, chloramphenicol and co-trimoxazole were considered. Out of total 304 *S.* Typhi, 117 (38%) were simultaneously resistant to all three first line drugs compared to only 1.8% *S.* Paratyphi A. Analysis showed that 80 to 90% of isolated *S.* Typhi was nalidixic acid resistant (NARST) with reduced susceptibility to ciprofloxacin while the rate for *S.* Paratyphi A was 71-94%. All *S.* Typhi and Paratyphi A were sensitive to ceftriaxone. The study showed that there was a gradual decline of resistance of *S.* Typhi to first line antibiotics but very high prevalence of nalidixic acid resistant *S.* Typhi and *S.* Paratyphi in Bangladesh.

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Introduction

Typhoid fever is an important public-health problem in Bangladesh. *Salmonella enterica* serovar Typhi and Paratyphi are common etiological agents of typhoid. With the emergence of resistance to ampicillin, chloramphenicol and cotrimoxazole, first choice of empiric treatment of typhoid fever has changed to ciprofloxacin and ceftriaxone.[1-3] But there are reports of appearance of ciprofloxacin resistant salmonella from Bangladesh and other countries.[4,5] Resistance to ceftriaxone has also been reported from Bangladesh in 1999.[6] Recently, there is emergence of salmonella strains that are ciprofloxacin sensitive but nalidixic acid resistant. Treatment of these strains with the usual dose of ciprofloxacin resulted in poor clinical outcome as well as treatment failure.[7-10] All these reports suggest that fluoroquinolones should no longer be used as the first-line therapy in populations where nalidixic acid resistance is common among isolates of *S.* Typhi. Moreover, recent studies indicate that the proportion of *S.* Paratyphi is increasing over the years in the subcontinent.[11,12] Therefore, it is important to know the species of *Salmonella* that are prevalent in a country and the antibiotic susceptibility pattern of that prevalent *Salmonella* sp.

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The present study investigated the trend of isolation of *Salmonella* species responsible for typhoid fever and their antibiotic resistance pattern over the last six years (2004-2009) in urban area of Dhaka city.

Materials and Methods

A retrospective analysis of *Salmonella* Typhi and Paratyphi isolated from patients attending BIRDEM hospital during 2004 to 2009 was carried out. BIRDEM hospital is a 600 bed tertiary care referral hospital in Dhaka city. All the isolates were identified by colony morphology, standard biochemical reactions and by agglutination with specific antiserum.[13] The isolates were tested for susceptibility to ciprofloxacin 5μg, nalidixic acid 30 μg, chloramphenicol 30 μg, co-trimoxazole 25 μg, ampicillin 10 μg, cefepime30 μg and ceftriaxone 30 μg by a disk diffusion technique as recommended by the NCCLS guideline.[14] All disks were obtained from Oxoid Ltd, Basingstoke, Hampshire, UK. Potency of the disks and antibiotics were standardized using the reference strain *E. coli* ATCC 25922.
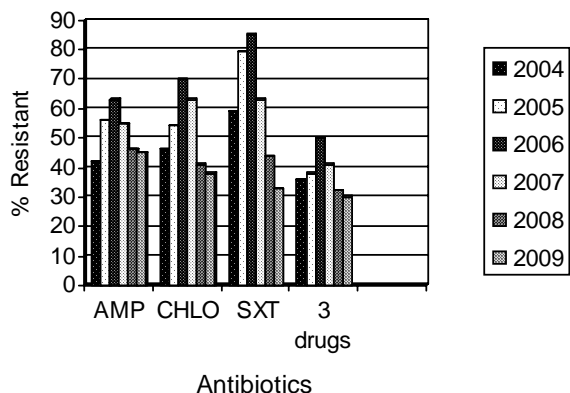
Results

A total of 385 *Salmonella* were isolated from blood cultures over the period of 6 years. *S.* Typhi was the predominant serotype followed by *Salmonella P*aratyphi A (Table-1). The isolation rate of *S.* Typhi has gradually decreased where as that of *S.* Paratyphi A has increased over last six years.

Single and multi drug resistance to 3 first line antibiotics namely ampicillin, chloramphenicol and cotrimoxazole of isolated *S.* Typhi during 2004 to 2009

Fig-1: *Single and multi drug resistance rate to 3 first line antibiotics namely ampicillin (AMP), chloramphenicol (CHLO) and cotrimoxazole (SXT) of isolated S.* Typhi *during 2004-2009. Note:* 3 drugs indicate concurrent resistance to AMP, CHLO and SXT

is shown in Fig-1. There was a gradual decline of resistance to ampicillin, chloramphenicol and cotrimoxazole since 2007 onwards. The overall simultaneous resistance to three first line anti-salmonella antibiotics namely ampicillin, chloramphenicol and co-trimoxazole of isolated *S.* Typhi during 2004-2009 was 38% (117 out of 304) and the range was between 30-50%. Simultaneous resistance to first line drugs in *S.* Typhi showed an upward trend up to 2006 and then went downwards.

The resistant pattern of *S.* Paratyphi A from 2007 to 2009 is shown in Fig 2. But its resistance pattern from 2004 to 2006 has not been shown as there were few isolates. The resistance of *S.* Paratyphi A to ampicillin, chloramphenicol and cotrimoxazole were low (5-20%) compared to *S.* Typhi. The rate of multi drug resistance

Table-1: *Species distribution of Salmonella sp. isolated between 2004- 2009*

Year	Total number of *Salmonella*	*Salmonella* Typhi		*Salmonella* Paratyphi A	
		Number	%	Number	(%)
2004	51	44	86	7	14
2005	31	26	84	5	16
2006	83	70	84	13	16
2007	87	68	78	19	22
2008	65	44	68	21	32
2009	68	52	76	16	24
Total	**385**	**304**	**79**	**81**	**21**
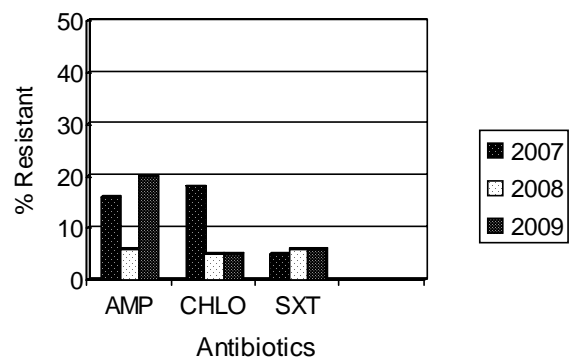
Fig-2: *The resistance pattern of isolated S.* Paratyphi A *to three first line anti- antibiotics during 2007-2009.*

Table-2: *Rate of isolation of nalidixic acid resistant S. Typhi and S. Paratyphi A from 2004-2009.*

Year	Total Number of *Salmonella*	*S.* Typhi N	NARST N	NARST %	*S.*Paratyphi A N	NARSPT N	NARSPT %
2004	48	41	33	80.5	7	6	86
2005	27	23	23	100	4	3	75
2006	64	54	49	91	10	9	90
2007	70	53	47	89	17	12	71
2008	65	44	39	89	21	19	90
2009	68	52	46	88	16	15	94
Total	342	267	237	88.8	79	64	81.0

NARST= nalidixic acid resistant S. Typhi; NARSPT= nalidixic acid resistant *S.* Paratyphi

of S. Paratyphi A has not been shown in Fig-2 also as there were small number of isolates per year. However, multi drug resistance in *S.* Paratyphi A was almost absent and static during the period. Only 1(1.3%) out of 81 isolates in *S.* Paratyphi A was resistant to three first line antibiotics simultaneously during the same period. No ceftriaxone resistant *S.* Typhi or Paratyphi was detected during the six year period. However, the resistance to cefixime, a third generation cephalosporin, of *S.* Typhi and *S.* Paratyphi A ranged from 12-28% and 7-29% during 2004-2009 and 2007-2009 respectively.

Table-2 shows that 80-100% of the isolated *S.* Typhi and 75-94% of *S.* Paratyphi A were nalidixic acid resistant. There were no remarkable changes in the resistance pattern of *S.* Typhi and *S.* Paratyphi A to nalidixic acid in last 6 years. Only few isolates of *S.* Typhi were found fully resistant to ciprofloxacin during the period.

Discussion

Typhoid fever is endemic in Bangladesh.[16] The present study was conducted as a part of the continuous surveillance about the prevalence of *Salmonella* sp and their antimicrobial susceptibility pattern which was very important to institute appropriate antimicrobial therapy. The study revealed that there was gradual emergence of *S.* Paratyphi A during the period as a cause of typhoid fever. Among the total isolated salmonella, *S.* Typhi was about 79% where as *S.* Paratyphi A was 21%. The proportion of *S.* Paratyphi A had increased over 6 years from 14% in 2004 to

24% in 2009. Similar emergence of *S.* Paratyphi A in subcontinent has been reported.[11,12]

The number of *S.* Typhi simultaneously resistant to all three first line drugs namely ampicillin, chloramphenicol and cotrimoxazole declined towards 2007 and continued through 2009. It might be due to the loss of unstable resistant gene resulting from removal of selection pressure of these antibiotics.[15] Re-emergence of the sensitivity to these drugs were also reflected from the individual upward trend of sensitivity pattern through recent years. *S.* paratyphi A showed moderate to high sensitivity to those drugs through out the last six years and there was only one multi drug resistant isolate out of total 81 isolates.

With the emergence of salmonella strains resistant to the first line drugs, quinolones and third generation cephalosporin (ceftriaxone and cefixime) are extensively being used in the treatment of typhoid fever during last decade. But, no ceftriaxone resistant isolate was found during the six years study period. However, 7-28% *S.* Typhi and *S.* Paratyphi A were resistant to cefixime.

Ciprofloxacin is being used as the first choice of empiric treatment of typhoid in Bangladesh for last several years. But the current study revealed that about 80-100% of *S.* typhi and *S.* Paratyphi A were resistant to nalidixic acid. The treatment of typhoid due to nalidixic acid resistant *Salmonella* sp with ciprofloxacin is less effective as there were reports of treatment failures from Bangladesh and other countries.[7-10] It was due to higher minimum inhibitory concentration of ciprofloxacin of these isolates. Nalidixic acid resistant *S.* Typhi had been reported to have higher minimum inhibitory concentration of ciprofloxacin compared to susceptible strains.[10] So, it has been recommended that quinolones should not be used as the first-line therapy in populations like Bangladesh where nalidixic acid resistance is common among isolates of salmonella. However, gatifloxacin may be used as alternative as because it has different mechanism to develop resistance than that of ciprofloxacin.[17]

Thus, our study indicates that the isolation of *S.* Paratyphi A is increasing over the years and the resistance to antibiotics among *S.* Typhi and *S.* Paratyphi is rising in our country. On the other hand, there has been a re-emergence of sensitivity to first line anti-salmonella drugs like ampicillin,

chloramphenicol and cotrimoxazole. Nalidixic acid resistant organisms should be screened routinely to detect organisms with reduced susceptibility to ciprofloxacin to avoid treatment failure with quinolone therapy.

References

1. Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant Salmonella typhi: a worldwide epidemic. *Clin Infect Dis* 1997; **24**(Suppl 1): S106-9.

2. Saha SK, Saha SK. Antibiotic resistance of *Salmonella typhi* in Bangladesh. *J Antimicrob Chemother* 1994; **33**: 190-1.

3. Islam A, Buttler T, Kabir I, Alam NH. Treatment of typhoid fever with ceftriaxone for 5 days or chloramphenicol for 14 days: a randomized clinical trial. *Antimicrob Agents Chemother* 1993; **37**: 1572-5.

4. Murdoch DA, Banatvala NA, Bone A, Shoismatulloev BI, Ward LR, Threlfall EJ. Epidemic of ciprofloxacin-resistant *Salmonella typhi* in Tajikistan. *Lancet* 1998; **351**: 339.

5. Asna SM, Haq JA, Rahman MM. Nalidixic acid resistant *Salmonella enterica* serovar Typhi with decreased susceptibility to ciprofloxacin caused treatment failure: a report from Bangladesh. *Japanese J Infect Dis* 2003; **56**: 32-3.

6. Saha SK, *et al*. A highly ceftriaxone-resistant *Salmonella typhi* in Bangladesh. *Pediatric Infectious Disease Journal* 1999; **18**: 387.

7. Slinger R, Desjardins M, McCarthy AE, Ramotar K, Jessamine P, Guibord C and Toy B. Suboptimal clinical response to ciprofloxacin in patients with enteric fever due to *Salmonella* spp. with reduced fluoroquinolone susceptibility: a case series. *BMC Infectious Diseases* 2004; **4**: 36.

8. Kadhiravan T, Wig N, Kapil A, Kabra SK, Renuka K and Misra A. Clinical outcomes in typhoid fever: adverse impact of infection with nalidixic acid-resistant *Salmonella typhi*. *BMC Infectious Diseases* 2005; **5**: 37.

9. Threlfall EJ,Ward LR. Decreased susceptibility to ciprofloxacin in *Salmonella enterica* serotype Typhi, United Kingdom. *Emerg Infect Dis* 2001; **7**: 448-50.

10. Rahman MM, Haq JA, Morshed MAHG, Rahman MA. *Salmonella enterica* serovar Typhi with decreased susceptibility to ciprofloxacin—an emerging problem in Bangladesh. *International Journal of Antimicrobial Agents* 2005; **25**: 345–353.

11. Padmapriya V, Kenneth J, Amarnath SK. Re-emergence of *Salmonella* Paratyphi A: a shift in immunity? *National Medical Journal of India* 2003; **16**: 47-48.

12. Mohanty S, Renuka K, Sood S, Das BK, and Kapil A. Antibiogram pattern and seasonality of *Salmonella* serotypes in a North Indian tertiary care hospital. Epidemiol. *Infect* 2006; **134**: 961–966.

13. Baron EJ, Peterson LR, Finegold SM, editors. *Enterobacteriaceae*. Bailey and Scott's diagnostic microbiology. 9th ed. St. Louis, MO: Mosby; 1994; 362–85.

14. National Committee for Clinical Laboratory Standards (NCCLS). Performance standards for antimicrobial disk susceptibility testing. 14th Informational Supplement (M100-S14). 2004; Villanova, PA.

15. Towner KJ.Bacterial genetics. In: Greenwood D. Slack RCB. Peutherer JF. Medical Microbiology.14th ed. New York: Churchill Livingstone. 1992; 85-94.

16. Alam, MN, Haq, SA, Majid, MN, Hasan, Z, Ahsan, SA, Ahmed, N and Rahman, KM: Multidrug resistant enteric fever in Bangladesh. *Bangladesh J. Med* 1992; **3**: 38-41.

17. Pandit A, Arjya A, Day JN, Paudyal B, Dangol S, Zimmerman MD, Yadav B, Stepniewska K *et al*. An open randomized comparison of gatifloxacin versus cefixime for the treatment of uncomplicated enteric fever. Plos One 2007; **6**: e542: 1-9.