

Original Article

## Re-Emergence of Susceptibility to Conventional First Line Drugs in *Salmonella* Typhi and Paratyphi A Isolated from Enteric Fever Patients in a Tertiary Care Hospital of Northern Bangladesh.

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### Summary

Enteric fever is endemic in Bangladesh and involves significant health care cost. The first-line drugs chloramphenicol and co-trimoxazole have not been the part of empirical therapy for decades due to development of multidrug resistant *Salmonella* strains. The objective of this study was to determine the antibiogram pattern of *Salmonella* strains isolated from the blood of clinically suspected enteric fever patients. A cross sectional study was conducted in Rajshahi Medical College Hospital & Dhaka Medical College from August 2014 to July 2015. Total 323 blood samples were collected from suspected enteric fever patients and isolation rate of *Salmonella* was 9.29% [*S.typhi* (3.41%), and *S.paratyphi* A (5.88%)]. Among isolated *S.typhi*, 9.09% were resistant to chloramphenicol, co-trimoxazole and cefixime and there were no *S.typhi* resistant to azithromycin and cefotaxime. Among the isolated *S.paratyphi* A, 5.26% were resistant to chloramphenicol, co-trimoxazole, azithromycin, cefotaxime, and cefixime. There were no ceftriaxone resistant *Salmonella*. Low proportion of resistance to first line antibiotics (chloramphenicol, co-trimoxazole) suggests that these drugs can be used once again.

**Key word:** Antibiotic resistance, Bangladesh, Rajshahi, *Salmonella typhi*, *Salmonella paratyphi* A.

### Introduction:

Enteric fever caused by *Salmonella typhi* and *Salmonella paratyphi* A is endemic in developing countries like Bangladesh<sup>1,2</sup>. In 2010, there were an estimated 13.9-26.9 million cases of typhoid fever and 5 million cases of paratyphoid fever with 0.19 million deaths<sup>3,4</sup>. Mortality rate was 30% in pre-antibiotic era<sup>2</sup> but chloramphenicol introduction in 1948 dramatically reduced the rate. In 1972, an outbreak of chloramphenicol resistant strains occurred in

Mexico and ampicillin and co-trimoxazole became the alternative choice. In 1989, epidemic outbreak of ampicillin, chloramphenicol and co-trimoxazole resistant *S. typhi*<sup>5</sup> shifted the choice to ciprofloxacin and ofloxacin<sup>6</sup>. However, rampant use of these fluoroquinolones made *Salmonella typhi* and *paratyphi* A resistant to nalidixic acid and less responsive to ciprofloxacin<sup>2</sup>. So physicians turn to cephalosporins for treatment of enteric fever and now cephalosporins begin to fail against *Salmonella*<sup>7</sup>.

In recent years, reemergence of susceptibility to conventional first line antibiotics (chloramphenicol and co-trimoxazole) has been reported in India and Nepal<sup>8,9</sup>. In this region where the therapeutic options for treating enteric fever have been reduced, reemergence of susceptibility to chloramphenicol and co-trimoxazole needs to be evaluated to determine the therapeutic importance of these drugs. The knowledge of

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prevalence of *Salmonella* species and determination of their antimicrobial resistance pattern are very important for the guidance of clinical management of enteric fever<sup>10</sup>. This study was undertaken to determine antibiotic susceptibility patterns of the *Salmonella* strains isolated from blood so that appropriate strategies could be achieved in the management of enteric fever.

### Materials and Methods

The study was conducted from August 2014 to July 2015 in the department of microbiology of Rajshahi Medical College Hospital & Dhaka Medical College. The blood samples were collected from suspected enteric fever patients of both outpatient and inpatient department of Medicine and Pediatric units of Rajshahi Medical College Hospital and inoculated in brain heart infusion broth. *S. typhi* and *S. paratyphi A* were identified by standard microbiological procedure and agglutination with Salmonella polyvalent O and specific H antisera. Antimicrobial susceptibility test was done by modified Kirby-Bauer disc diffusion method against chloramphenicol (30µg), co-trimoxazole (25µg), ciprofloxacin (5µg), ofloxacin (5µg), nalidixic acid (30µg), ceftriaxone (30µg), cefixime (5µg), cefotaxime (30µg), azithromycin (30µg) and result was interpreted according to Clinical and Laboratory Standards Institute (2013)<sup>11</sup> and European Committee on Antimicrobial Susceptibility Testing, 2015, guidelines. *Escherichia coli* ATCC 25922 were used to test the validity of antibiotic discs.

### Result

Among 323 samples, 30 (9.29%) yielded growth. The frequency of *S.typhi* and *S.paratyphi A* were 11(3.41%) and 19(5.88%) respectively (Table-I). 9.09% *S.typhi* were resistant to chloramphenicol, co-trimoxazole and cefixime and all *S.typhi* were sensitive to azithromycin and cefotaxime. Similarly, 5.26% *S.paratyphi A* were resistant to chloramphenicol, co-trimoxazole, azithromycin, cefotaxime, and cefixime. All *Salmonella* isolates were sensitive to ceftriaxone (Table-II).

**Table-I Result of blood culture among 323 suspected enteric fever patients.**

Organisms	Positive n(%)
<i>S.typhi</i>	11(3.41)
<i>S.paratyphiA</i>	19(5.88)
Other than <i>Salmonella</i>	38(11.76)

**Table-II Antimicrobial resistance pattern of *S.typhi* (n=11) and *S.paratyphi A* (n=19).**

Antimicrobial agents	Resistant	
	<i>S.typhi</i> n(%)	<i>S.paratyphi A</i> n(%)
Azithromycin	-	1(5.26)
Cefixime	1(9.09)	1(5.26)
Cefotaxime	-	1(5.26)
Ceftriaxone	-	-
Ciprofloxacin	2(18.18)	3(15.79)
Chloramphenicol	1(9.09)	1(5.26)
Co-trimoxazole	1(9.09)	1(5.26)
Nalidixic acid	8(72.73)	19(100)
Ofloxacin	1(9.09)	4(21.05)

### Discussion

Chloramphenicol, co-trimoxazole and ampicillin were used to treat patients suffering from enteric fever until nineties. Then multidrug resistant (MDR- resistant to ampicillin, chloramphenicol and co-trimoxazole) *Salmonella* emerged that made fluoroquinolones the treatment of choice. However, fluoroquinolones were being rampantly used for treatment of enteric fever as well as for other infectious diseases in Bangladesh, for that reason strains with reduced susceptibility to ciprofloxacin and other fluoroquinolones due to mutation in quinolone resistance determining region (QRDR) emerged. At present third generation cephalosporins are used to treat enteric fever in Bangladesh.

In 2002, proportion of chloramphenicol resistant *Salmonella typhi* was 42% with similar resistance pattern for co-trimoxazole as well in Dhaka<sup>6</sup>. Whereas, we showed 9.09% resistance rate of *S.typhi* to both chloramphenicol and co-trimoxazole. *S.paratyphi A* also showed lower resistance rate (5.26%) to both of these antibiotics. Decreased resistance to these antibiotics for *Salmonella* was similar to studies from India<sup>8</sup> and Nepal<sup>12,9</sup>. Conventional first-line drugs have been restricted for therapeutic use for almost two decades due to the development of resistant strains, for that reason *S.typhi* and *S.paratyphi A* isolates sensitive to these drugs are reviving. In contrast, more than 60% *S.typhi* in Pakistan<sup>7</sup> and more than 20% *S.paratyphi A* in India<sup>13</sup> were resistant to these drugs. Although, many *Salmonella* strains seem to be sensitive to fuoroquinolones in vitro (Table-2), they don't work as good *in vivo* because most of them are nalidixic acid resistant due to mutation in QRDR region of *gyrA* gene<sup>14</sup>.

Higher susceptibility of *Salmonella* to ceftriaxone and cefixime in our study agreed with a study in Pakistan<sup>7</sup>. Resistance rate to azithromycin in this study was also lower in *Salmonella* which is similar to the reports from India<sup>15</sup>.

It is clear from our study that, current trend of antibiotic susceptibility of *Salmonella* isolates is high frequency of nalidixic acid resistance with reemergence of susceptibility conventional drugs. These findings would be helpful to concerned health authorities to rationalize the policy of empirical therapy of enteric fever. Although the third generation cephalosporin ceftriaxone is effective, the cost and route of administration makes ceftriaxone less appropriate for therapeutic use in developing countries such as Bangladesh, especially in rural areas. Cefixime and azithromycin can be taken orally but they are relatively costly. Moreover, drugs are sold over the counter in Bangladesh and anybody can buy drugs without physician's prescription and resistance to these drugs is increasing. Thus, the use of chloramphenicol and cotrimoxazole which are economically affordable would be useful in empirical therapy against *Salmonella* in developing countries like Bangladesh. However, treatment should be given after testing antibiotics susceptibility if possible.

### Conclusion

Both *Salmonella* species in our study were less frequently resistant to first line antibiotics (chloramphenicol and cotrimoxazole). This finding might be useful to revise current empirical therapy policies for enteric fever to include these drugs in the treatment regimens as an alternative to third generation cephalosporins. Where facilities are available, treatment should be given after testing antibiotics susceptibility.

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