Re-Emargence 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 Bangladesh1-2. 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 deaths3-4. Mortality rate was 30% in pre-antibiotic era2 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. typhi5 shifted the choice to ciprofloxacin and ofloxacin6. However, rampant use of these fluoroquinolones made Salmonella typhi and paratyphi A resistant to nalidixic acid and less responsive to ciprofloxacin2. So physicians turn to cephalosporins for treatment of enteric fever and now cephalosporins begin to fail against Salmonella7.

In recent years, reemergence of susceptibility to conventional first line antibiotics (chloramphenicol and co-trimoxazole) has been reported in India and Nepal8-9. 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
prevalence of Salmonella species and determination of their antimicrobial resistance pattern are very important for the guidance of clinical management of enteric fever. 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) and European Committee on Antimicrobial Susceptibility Testing, 2015, guidelines. Escherechia 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.

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Positive n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.typhi</td>
<td>11(3.41)</td>
</tr>
<tr>
<td>S.paratyphi A</td>
<td>19(5.88)</td>
</tr>
<tr>
<td>Other than Salmonella</td>
<td>38(11.76)</td>
</tr>
</tbody>
</table>

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

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

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. 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 and Nepal. 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 are resistant to these drugs are reviving. In contrast, more than 60% S.typhi in Pakistan and more than 20% S.paratyphi A in India were resistant to these drugs. Although, many Salmonella strains seem to be sensitive to fluoroquinolones 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.

Higher susceptibility of Salmonella to ceftriaxone and cefixime in our study agreed with a study in Pakistan. Resistance rate to azithromycin in this study was also lower in Salmonella which is similar to the reports from India.
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 cephalosporinceftriaxone 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 co-trimoxazole 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 co-trimoxazole). 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.

**REFERENCES:**


