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Research Article

Antimicrobial Resistance in Typhoidal *Salmonella* in a Tertiary Care Teaching Centre in North India

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A B S T R A C T

Introduction: Enteric fever continues to carry a high burden of morbidity and mortality in India. There have been reports of emergence of ceftriaxone resistant typhoidal Salmonella from Asia. Monitoring of antimicrobial resistance trends in typhoidal Salmonella is crucial to support in clinical decision making.

Aim: To study the current susceptibility pattern of typhoidal salmonella isolates in our setup.

Methods: This retrospective study was conducted on 144 non-repeat blood-culture isolates of S. Typhi, and S. Paratyphi A obtained from 3926 blood cultures received at 510-bedded tertiary-care hospital of North-India from 2017-2019. Identification and antibiograms were obtained by Vitek-2 compact and Kirby-Bauer's disc diffusion with sensitivity to azithromycin, and chloramphenicol.

Result: S. Typhi and *S. Paratyphi A* in a ratio of 5.2:1 were seen between months of June and July predominantly distributed between 1-10 years age group. *S. Typhi* resistance to co-trimoxazole, chloramphenicol, ceftriaxone and azithromycin was 21.4%, 25.6%, 12.3% and 28% respectively. S. Paratyphi A resistance to co-trimoxazole, chloramphenicol, ceftriaxone and azithromycin was 4.3%, 17.3%, 34.7% and 21.7% respectively.

Conclusion: Enteric-fever is a major public-health problem in India. Emergence of ceftriaxone-resistant Salmonella mandates appropriate investigation of all febrile illnesses with blood culture whenever possible. Provision of safe drinking water, good sanitation, hygiene and vaccination strategies are needed to sustain herd-immunity.

Keywords: Salmonella Typhi Paratyphi A Ceftriaxone Resistant

Introduction

Typhoid fever and paratyphoid fever is faeco-orally transmitted disease characterized by high fever and other systemic signs of bacteremia caused by *Sal. enterica* subspecies enterica *Se. Typhi* and *Se. Paratyphi* respectively. Enteric fever if left untreated, the course can be severe and lethal. WHO has recommended risk-based use of typhoid polysaccharide vaccine against *S. Typhi*. The estimated number of typhoid fever cases in low and middle income countries in 2010 after adjusting for water-related risk was 11.9 million cases with 129,000 deaths.[1] Currently, third-generation cephalosporins such as ceftriaxone are recommended as first-line therapy.[2] Enteric fever continues to carry a high burden of morbidity and mortality in India.

The emergence and rapid spread of ceftriaxone-resistant *S. Typhi* and *S. Paratyphi A* is alarming. To date, only sporadic reports of ceftriaxone-resistant *S. Typhi* have been published, mainly from Asia (including Japan) but also from West and southern Africa.[3] As the antimicrobial resistance in typhoid fever has been increasing, this study was designed to study the current susceptibility pattern of typhoidal Salmonella strains in our setup.

Materials and Methods

We conducted a retrospective analysis of Salmonella isolates from blood cultures received in Microbiology Laboratory at ESIC College & Hospital Faridabad from Jan 2017-Dec 2019. The study was reviewed and approved by institutional ethics committee. All the blood culture samples of patients (indoor and outdoor) with febrile illness were processed in BacT/ Alert blood culture system (Biomerieux, France). The study isolates were identified and tested for Antimicrobial Resistance (AMR) profiles by VITEK 2 (Biomerieux, France) employing the Clinical and Laboratory Standards Institute (CLSI) guidelines relevant to the year.[4] In addition, antimicrobial susceptibility was done for azithromycin (15 µg) and chloramphenicol (30 µg) (OXOID) using Kirby-Bauer's disc diffusion method as these antimicrobials are not covered in susceptibility panel for gram negative bacilli in VITEK 2. The laboratory participates in external quality assurance scheme. Serotyping of the strains was done with Denka Seiken (Tokyo, Japan) antisera. *E. coli* ATCC 25922 was used for quality control.

Result

A total of 3926 blood cultures were received from January 2017 to December 2019. Out of these, (10%) 395 blood cultures were positive. A total of (36.4%) 144 isolates were identified as *Sal. enterica* during the study period. Out of these, 121 (84 %) *S. Typhi*, and 23 (15.9 %) were *S. Paratyphi A*. Serotyping showed complete concordance with identification by VITEK 2. Most of the salmonellae were isolated in the months of June and July, with the majority being in the 1-10 years followed by 21-30 years age groups with a male preponderance. Table 1, shows that the percentage antimicrobial resistance for ciprofloxacin in *S. Typhi* was 87.6%. Similarly in S. Paratyphi A, ciprofloxacin resistance was 82.6% (Table 2). Ceftriaxone, cotrimoxazole, azithromycin, chloramphenicol resistance was detected in *S. Typhi* as 12.3%, 21.4%, 28% & 25.6% respectively (Table 1). Whereas resistance to ceftriaxone, cotrimoxazole, azithromycin, chloremphenicol in *S. Paratyphi A* was 34.7%, 4.3%, 21.7%, 17.3% respectively (Table 2). All the isolates were sensitive to meropenem. No multidrug-resistant *Salmonella* strains were isolated.

Table 1.Antimicrobial resistance patterns obtained for S. Typhi isolates recovered from blood cultures of patients between 2017 and 2019 (n=121)

Antimicrobial agents	Sensitive No. (%)	Intermediate No. (%)	Resistant No. (%)
Ampicillin	93 (76.8)	-	28 (23.1)
Ciprofloxacin	15 (12.4)	23	83 (68.5)
Nalidixic acid	0	-	121 (100)
Sulfamethoxazole/Trimethoprim	95 (78.5)	-	26 (21.4)
Ceftriaxone	95 (78.5)	11 (9)	15 (12.3)
Azithromycin	87 (71.9)	-	34 (28)
Chloramphenicol	90 (74.3)	-	31 (25.6)
Meropenem	121 (100)	0	0

Table 2.Antimicrobial resistance patterns obtained for S. Paratyphi A isolates recovered from blood cultures of patients between 2017 and 2019 (n=23)

Antimicrobial agents	Sensitive No. (%)	Intermediate No. (%)	Resistant No. (%)
Ampicillin	-	5 (21.7)	18 (78.2)
Ciprofloxacin	4 (17.3)	-	19 (82.6)
Nalidixic acid	0	-	23 (100)
Sulfamethoxazole/ Trimethoprim	22 (95.6)	-	1 (4.3)
Ceftriaxone	10 (43.4)	4 (17.3)	8 (34.7)
Azithromycin	18 (78.2)	-	5 (21.7)
Chloramphenicol	19 (82.6)	-	4 (17.3)
Meropenem	23 (100)	0	0

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Discussion

Enteric fever continues to be a major public health burden in India. There have been emerging reports of the recent change of AMR pattern of typhoidal Salmonella from India. A high percentage of blood cultures (10%) grew typhoidal *Salmonella*. In this study, *S.* Typhi was the most common serotype (84%) similar to the results of other Indian studies.[5,7,8]

The preferred test for assessing fluoroquinolone susceptibility or resistance in *Salmonella spp.* is a ciprofloxacin MIC test.[4] All the 144 isolates tested were 86.8% resistant to fluoroqinolones. High-level fluoroquinolone resistance has been reported in Salmonella isolates in various studies ranging from 84.5% to 95.5%.[6,8] In view of development of high level of Fluoroquinolone resistance, third generation cephalosporins and azithromycin are currently the preferred drugs for treatment of enteric fever leading to their widespread use.

As per recent National treatment guidelines for antimicrobial use in infectious diseases, Azithromycin or Cefixime is recommended as a monotherapy for uncomplicated enteric fever in outpatient settings while Ceftriaxone is the drug of choice where parenteral therapy required for inpatients.[2] Concurrent with their use, reports of resistance to resistance to third generation cephalosporins have emerged leading to treatment failures. Bhattacharya et al, in 2011 study from Orissa reported resistance of 3.0 to 6.25 per cent against third generation cephalosporins among the salmonella isolates.[7] Makkar A et al. in a study from Delhi reported 3.86%, 17.2% resistance to third generation cephalosporins in *S. Typhi* & *S. Paratyphi A* respectively.[8] On similar lines, we found 12.3% S. Typhi and a higher percentage of *S. Paratyphi A* (34.7%) strains ceftriaxone resistant in this study. However, other studies from north India did not report any resistance to ceftriaxone.[9,10]

Member of the macrolide class, Azithromycin is a very effective and convenient oral option for treatment of typhoid fever in adults and children. In several Indian studies, susceptibility of *Salmonella* serotypes to azithromycin has been documented varying from 91-92%.[11] Dutta et al in a study from Kolkata reported sensitivity of 72% in *Sal. Paratyphi A* isolates.[12] We report similar pattern in our study, as 71.9% *S*. Typhi and 78.2% *S. Paratyphi* were sensitive to azithromycin.

76.8% of the *S. Typhi* isolates were sensitive to ampicillin, 78.5% of them to co-trimoxazole and 74.3 % to chloramphenicol. Similarly, 21.7 % of the *S. Paratyphi A* isolates were intermediate to ampicillin, 95.6 % of them sensitive to co-trimoxazole and 82.6 % sensitive to chloramphenicol. None of the isolate was MDR. Non-susceptibility of Typhoidal *Salmonella* to first-line antimicrobials (chloramphenicol, co-trimoxazole and ampicillin) has decreased over time as also reported by other studies.[5, 6, 13,14] Hence routine surveillance of resistance determinants is essential to understand the comeback of first generation of antibiotics for the treatment of typhoid fever.

Ceftriaxone is commonly used as monotherapeutic agent for treatment of typhoid fever. Resistance to ceftriaxone and azithromycin has complicated treatment of typhoid infection. The treatment options available for resistance isolates are fourth generation cephalosporins, carbapenems, and tigecycline or combination antibiotic therapy. The study shows a worrying increase of ceftriaxone resistant isolates. There is a need to ramp up typhoid vaccination in pediatric population and adhere to safe food and water practices. Management of acute febrile illness should be guided by appropriate investigation including blood culture whenever possible.

Conflict of Interest: None

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