RESEARCH PAPER

Clinico-Bacteriological Profile of Typhoid Fever in a Private Sector Hospital in New Delhi

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Objective: To describe the demographic, clinical, laboratory and bacteriological profile of children with diagnosis of typhoid fever over a six-year period. **Methods:** Case record analysis of hospitalized children (≤5 y) with culture positive typhoid fever. **Results:** Blood culture was positive in 100 (61%) of 166 suspected cases, with 78 isolates of *Salmonella* Typhi and 22 *Salmonella* Paratyphi A. Only 12 children were aged below two years. Hepatomegaly (32), splenomegaly (44), eosinopenia (42), positive widal (15, 21.1%) and positive Typhidot IgM (18, 28.1%) were not consistently observed. High susceptibility to Ampicillin, Chloramphenicol, Cotrimoxazole (87, 89, and 94, isolates, respectively), 100% susceptibility to third generation cephalosporins and Azithromycin, and high resistance to Nalidixic Acid [(*S.* Typhi 48 (61.5%)], *S.* Paratyphi A 16 (72.7%)) were observed. **Conclusion:** We observed a high isolation rate of *salmonella* in blood culture, despite prior use of antibiotics. Most *salmonella* isolates were susceptible *in vitro* to standard drugs, except nalidixic acid.

Keywords: *Antimicrobial resistance, Blood culture, Enteric fever, Eosinopenia, Salmonella.*

Enteric fever, a systemic infection by *Salmonella enterica* serotype Typhi (*S.* Typhi) or *Salmonella enterica* serotype Paratyphi A (*S.* Paratyphi A), affects around 11-21 million individuals globally with a high mortality [1-4]. India has a very high disease burden (214.2 per 1,00,000 individuals/ year) [4], primarily affecting children 5 to 15 years. Recently, there have been concerns of increasing proportion of infections in very young children, rising paratyphoid infections, and emerging drug resistance [4,5]. Also, there are challenges in diagnosis and management of enteric fever due to lack of laboratory-based investigations [6-8]. While blood culture remains the gold standard of diagnosis, the mainstay in developing countries are serological tests, which are suboptimal due to lack of standardization and uniformity [7]. The evolving antimicrobial resistance since 1980's due to their indiscriminate use [2,9-12], warrants continuous surveillance of *Salmonella* across different populations in order to develop effective treatment protocols, prevent drug resistance, and formulate vaccination policies. We studied all cases of suspected enteric fever hospitalized over a 6-year period to describe the clinical and laboratory parameters in children with culture positive typhoid fever, and the trends of antibiotic susceptibility of culture isolates.

METHODS

This was a case record analysis conducted in a private sector hospital in North-West Delhi for a six-year period (April 2010 to March 2016). All patients in the age group of 3 months to 15 years with a discharge diagnosis of enteric fever were included in the study. Information on the socio-demographic profile, duration of symptoms and antibiotic history prior to hospitalization, presenting symptoms, duration of illness, length of hospital stay, clinical data, laboratory parameters and treatment details were extracted from hospital records (discharge files), and collated on a Microsoft excel sheet. The Institutional Review Board and Healthcare Ethics Committee of hospital approved the study.

All patients had complete blood counts (CBC) and blood culture done as per the standard operating procedures (SOP), while hepatic enzymes and serological tests were at the discretion of treating pediatricians. Cases were diagnosed as culture positive enteric fever if the blood culture was positive for *S.* Typhi or *S.* Paratyphi A. Blood cultures were done on BacT/Alert® 3D. Identification and antibiotic susceptibility testing was done by Vitek 2 compact automated system. The antimicrobial susceptibility was compared across two time blocks (2010-2012 and 2013-2016). These time blocks were

selected as there was a relocation and restructuring of the pediatrics department in May 2012 to a different premise but within the same community and zip code. Clinical findings noted were hepatomegaly (liver palpable >2 cm below costal margin) and splenomegaly (clinically palpable). The laboratory parameters extracted were: eosinopenia (absence of eosinophils in peripheral smear), elevated serum transaminases (SGOT and/or SGPT >40 IU/L), Widal test positivity (titers >1:160), and Typhidot IgM test positivity.

Statistical analysis: Data were analyzed using IBM SPSS Statistics software (v.20.0; IBM SPSS, Armonk, NY) and cross tabulation was done for determining the frequencies of clinical and laboratory parameters in culture positive cases. Significance of the laboratory values, antibiotic susceptibility for *S.* Typhi and *S.* Paratyphi A was obtained by chi-square test at 5% level of significance or by Fischer's exact test when applicable. For significance between medians (age, duration of fever and hospital stay), Wilcoxon test was used.

RESULTS

During the study period, a total of 166 children with suspected enteric fever were admitted; 100 were culture positive (*S.* Typhi 78, *S.* Paratyphi A 22) accounting for 2.2% of the 4468 Pediatric hospital admissions. Majority of the patients were in the age range of 5 to 15 years while only 12 (12%) were ≤2 years. The median (IQR) age of culture positive patients for *S.* Typhi and *S.* Paratyphi A was 9 (4.7, 14) years and 7.5 (5, 9) years, respectively. The median (IQR) duration of fever prior to admission was 7 (5, 15) days, and the median (IQR) duration of hospital stay was 4 (3, 6) days for both *S.* Typhi and *S.* Paratyphi. A total of 64 (64%) patients with positive blood cultures had a prior history of antibiotic usage. Hepatomegaly and splenomegaly were seen in 32 and 44 patients respectively (***Table* I**). Complications were few, with encephalopathy and shock in 1.8% (*n*=3); one patient relapsed and there was no mortality. Eosinopenia was observed in 42 (42%) of culture positive cases, with no difference between *S.* Typhi and Paratyphi. Liver transaminases (SGOT and SGPT) were estimated in 62 culture positive enteric and were elevated in 48 (77.4%) and 46 (74.2%) patients, respectively. Typhidot and Widal test were available for 64 and 71 of culture positive cases, and were positive in 18 (28.1%) and 15 (21.1 %), respectively. All patients were treated with ceftriaxone and 17 received azithromycin in addition. Majority of the patients who received combined treatment had prolonged fever (>7 days).

The antibiotic susceptibility of *Salmonella* Typhi and Paratyphi for Nalidixic acid, Fluoroquinolone, Ceftriaxone, Cefixime, Azithromycin, Amoxycillin, Cotrimoxazole, and Chloramphenicol is presented in ***Table* II**. Majority of *Salmonella* Typhi and Paratyphi showed resistance to nalidixic acid (61.5% and 72.7%, respectively). High susceptibility to Amoxycillin, Cotrimoxazole, and Chloramphenicol (first line drugs) was observed. All isolates were susceptible to third generation cephalosporins – Cefixime and Ceftriaxone. One isolate of *S.* Paratyphi A was resistant to azithromycin. A significant decrease in resistance from 80.8% to 51.9% was observed for Nalidixic acid from 2010-2012 and 2013-2016 for *S.* Typhi. Similarly, for *S.* Paratyphi, a reduction in resistance from 100% to 57.1% was seen for Nalidixic Acid during these time periods. No evidence of change in resistance was observed for Ceftriaxone, Cefixime, Azithromycin, Amoxycillin, Cotrimoxazole, and Chloramphenicol during these two time periods, and all showed high susceptibility over the six-year period (***Table* II**).

TABLE I CLINICAL AND LABORATORY PARAMETERS OF CHILDREN WITH CULTURE POSITIVE ENTERIC FEVER (*N*=100)

Parameter	*S. Typhi (n=78)*	*S. Paratyphi A (n=22)*	*P value*
Male sex	50 (64.1)	13 (59.1)	0.667
Age (y)*	9 (4.8, 14)	7.5 (5, 9)	0.053
Duration of fever (d)*	7 (5, 10)	7 (6, 15.5)	0.477
Duration of hospital stay(d)*	4 (3-6)	4 (3.8, 5)	0.876
Prior intake of antibiotics	53 (67.9)	11 (50)	0.121
Hepatomegaly	26 (33.3)	6 (27.3)	0.590
Splenomegaly	32 (36.4)	12 (54.5)	0.259
Eosinopenia[#]	33 (42.3)	9 (40.9)	0.907
SGOT >40 (IU/L)[$]	38 (77.6)	10 (76.9)	0.787
SGPT >40 (IU/L)[$]	37 (75.5)	9 (69.2)	0.587
Positive Typhidot test[@]	12 (25.5)	6 (35.3)	0.243
Positive Widal test**	13 (21.7)	2 (18.2)	0.048

*Values in n (%) or *median (IQR); [#] n=78 and 22 for S. Typhi and S. Paratyphi, respectively; [$]n=49 and 13 for S. Typhi and S. Paratyphi, respectively; [@] n=47 and 17 for S. Typhi and S. Paratyphi, respectively; ** n=60 and 11 for S. Typhi and S. Paratyphi, respectively.*

DISCUSSION

In this hospital-based series of children with blood culture positive enteric fever, we observed that despite a prior history of antibiotic usage, blood culture had high yield. Widal test and Typhidot had poor sensitivity, being positive in about one-fourth of culture positive patients. High resistance to fluroquinolones, as indicated by the surrogate nalidixic acid resistance, decreased significantly

WHAT THIS STUDY ADDS?

- Hepatosplenomegaly, eosinopenia, raised transaminases, Widal and Typhidot tests do not seen to be the valid markers for diagnosis of enteric fever.
- Blood culture should be the standard operating procedure for diagnosis of typhoid fever despite prior antibiotic usage.

TABLE II ANTIBIOGRAM FOR *SALMONELLA* TYPHI AND PARATYPHI ACROSS 2010-12 AND 2013-16

Antibiotic resistance	*2010-2012*		*2013-2016*	
	S. Typhi (n=26)N (%)	*S. Paratyphi (n=8)N (%)*	*S. Typhi (n=52)N (%)*	*S. Paratyphi (n=14)N (%)*
Nalidixic acid	21 (80.8)	8 (100)	27 (51.9) *	8 (57.1) #
Ciprofloxacin /Fluoroquinolone	3 (11.5)	0 (0)	10 (19.2) $	0 (0)
Azithromycin	0 (0)	1 (12.5)	0 (0)	0 (0)
Amoxycillin	2 (7.7)	1 (12.5)	6 (11.5)	4 (28.6)
Cotrimoxazole	1 (3.8)	1 (12.5)	4 (7.7)	0 (0)
Chloramphenicol	1 (3.8)	1 (12.5)	5 (9.6)	4 (28.6)

*No isolate was resistant to Cefixime or Ceftriaxone during either time period; *P=0.014; #P=0.051; $P=0.053 for comparison between 2010-2012 and 2013-2016.*

from 2010 to 2016, probably because of a restricted use of fluoroquinolones in pediatric practice. High susceptibility to first line drugs Amoxycillin, Chloramphenicol and cotrimoxazole offers an opportunity to include these drugs in the treatment regimen. Both *S.* Typhi and *S.* Paratyphi had uniform susceptibility to third generation cephalosporins and azithromycin.

The main limitation of this study is hospital-based nature of data, which may not reflect the actual situation in the community. The clinical history and examination conducted by different team members at different time periods might have lacked uniformity. The use of antibiotics prior to hospitalization was based on a solicited history, and lacked documentation of specific drug in few cases. Discretionary use of hepatic enzymes and serological tests limited the number available for analysis. Minimum inhibitory concentration (MICs) and genomic sequencing of the isolates could have provided more insights into the emerging antimicrobial resistance, but were not available in this study. The retrospective nature of data and small sample size for trend comparison were other potential limitations.

The proportion of children below two years in our series is much lower than that reported in some earlier reports (16-30%) [2,9]. Increasing paratyphoid infections as observed in few earlier studies [9-11] was not observed by us. Varying vaccine coverage and or time trends of circulation of the enteric organisms is the likely reason. A very high yield of blood culture was observed in our study (61%) in contrast to other Indian studies (8%-30%) [9-11]. There have been recent reports of MDR and XDR *Salmonella* Typhi lineage of clade H58 deriving resistance determinants from ESBL *E. coli* [12-15], indicating a potential global threat. High antimicrobrial resistance was not observed in our study.

We conclude that blood culture, irrespective of prior antibiotic usage, should be the only test to be relied upon for diagnosis of enteric fever. Though resistance to nalidixic acid is high, the organism remains susceptible to most first-line and standard drugs used in current treatment protocols. There is a need for continuous microbiological surveillance from different geographical areas in order to detect any early pattern of antimicrobial resistance.

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