

# Clinical profile and drug resistance patterns of typhoid fever in children: A prospective hospital-based study

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## ABSTRACT

**Background:** *Salmonella typhi* and *Salmonella paratyphi* are important causes of bacteremia in children, especially those from the developing world. The present study is undertaken to study the pattern of antimicrobial resistance of *S. typhi* in culture positive cases of enteric fever.

**Materials and Methods:** This prospective non-randomized study was conducted in the Department of Pharmacology, J. N. Medical College, AMU, Aligarh, in association with the Department of Paediatrics and Department of Microbiology, J. N. Medical College, on pediatric patients attending the Outpatient/Inpatient Department of Paediatrics, over a period of 1 year and 11 months from September 2005 to August 2006. For all patients with suspected enteric fever, the following investigations were sent for complete hemogram, blood culture, and sensitivity test and Widal test.

**Results:** About 114 randomly selected children having clinical features strongly suggestive of uncomplicated enteric fever with either culture positive or serology positive or both were entered in the study. Fever was the most common clinical presentation and was present in 94.7%. Only 25% of patients attended the hospital within the 1<sup>st</sup> week of illness, while maximum (54.6%) patients came to the hospital in the 2<sup>nd</sup> week of illness. Hepatomegaly was more common (43.8%) as compared to splenomegaly (27.1%). The characteristic rose spots of enteric fever were a rare finding in children.

**Conclusion:** Burden of typhoid fever in endemic areas of India underscores the importance of evidence on disease burden in making policy decisions about interventions to control this disease. Our antimicrobial susceptibility data suggest that quinolones and third-generation cephalosporins should be used as first-line antimicrobials in enteric fever. A careful consideration should be given before deciding the antibiotic for treatment to prevent the emergence of antibiotic resistance.

**Key words:** Antibiotic resistance, burden, children, typhoid fever

## INTRODUCTION

Typhoid fever is a systemic infection caused by *Salmonella typhi*, usually through ingestion of contaminated food or water. The acute illness is characterized by prolonged fever, headache, nausea, loss of appetite, and constipation or sometimes diarrhea. Symptoms are often non-specific and clinically non-distinguishable from other febrile illnesses. However, clinical severity varies and severe cases may lead to serious complications or even death. It occurs predominantly in association with poor sanitation and lack of clean drinking water. According to the most recent estimates (published in 2014), approximately 21 million cases and 222,000 typhoid-related deaths occur annually worldwide. A similar but often less severe disease, paratyphoid fever, is caused by *Salmonella paratyphi* A, B, or C.<sup>[1]</sup>

The disease remains an important public health problem in the developing countries. In 2000, it was estimated that over 2.16 million episodes of typhoid occurred worldwide, resulting in 216,000 deaths, and that more than 90% of this morbidity and mortality

occurred in Asia.<sup>[2]</sup> The WHO study revealed that a total of 21,874 episodes of fever were detected. *S. typhi* was isolated from 475 (2%) blood cultures, 57% (273/475) of which were from 5 to 15 years olds. The annual typhoid incidence (per 100,000 person-years) among this age group varied from 24.2 to 29.3 in sites in Vietnam and China, respectively, to 180.3 in the site in Indonesia; and to 412.9 and 493.5 in sites in Pakistan and India, respectively. Altogether, 23% (96/413) of isolates were multidrug resistant (chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole).<sup>[3]</sup>

We analyzed the epidemiological, clinical, and antimicrobiological sensitivity patterns of disease in patients diagnosed with blood culture-positive typhoid fever over a 12-month period in a tertiary care pediatric OPD and IPD in the Northern India.

## MATERIALS AND METHODS

This prospective non-randomized study was conducted in the Department of Pharmacology, J. N. Medical College, AMU, Aligarh,

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in association with the Department of Paediatrics and Department of Microbiology, J. N. Medical College on pediatric patients attending the Outpatient/Inpatient Department of Paediatrics, over a period of 1 year and 11 months from September 2005 to August 2006.

### Inclusion Criteria

Following cases were considered eligible for inclusion in the study.

- Age up to 15 years.
- All cases of suspected enteric fever on clinical grounds (Butler *et al.*, 2001).

Laboratory investigations were sent to support the clinical diagnosis.

### Exclusion Criteria

- Patients in whom diagnosis other than enteric fever was made and laboratory criteria for the diagnosis of enteric fever were not fulfilled.
- All cases with a history of treatment with macrolides/fluoroquinolone within 1 week.
- Complicated cases of enteric fever.

A written consent was obtained from the parent/attendant of the patient for inclusion in the study. A detailed clinical evaluation and clinical profile were obtained and recorded on a format used in the study.

### Laboratory Investigations

For all patients with suspected enteric fever, the following investigations were sent.

- A complete hemogram.
- Blood culture and sensitivity test.
- Widal test.

Other tests (if indicated) such as malaria parasite smear, urine analysis, stool analysis, liver function tests, renal function tests, chest X-ray, ultrasonography abdomen, and electrocardiogram were done.

### Collection of Samples

Blood for culture was collected from peripheral vein after taking all aseptic precautions. About 2 ml of blood was inoculated immediately into a culture bottle containing brain heart infusion broth with 0.025% sodium sulfonate as the culture medium, and the bottle was sent to the Department of Microbiology. For blood for serology, approximately 3 ml of blood was collected in plain vial and serum separated for Widal test. Blood for routine investigations was collected in oxalate vials.

### Laboratory Procedure

#### Blood culture

The inoculated blood culture bottle was incubated at 37°C for 14 days. Repeated examinations of blood culture bottles were performed at different times during the incubation, first at 24 h, next at 48 h, then daily up to 7 days, and finally, at the end of 2 weeks. As soon as turbidity was observed, the blood culture was examined by a Gram-stained film and by subculture on MacConckey culture media and blood culture plates, which were kept overnight at 37°C. Next day, subculture plates were observed for any lactose non-fermenting colonies. Gram stain

film was studied. The required biochemical tests were done to identify *S. enterica* serotype *typhi* and *paratyphi* A and B. Antibiotic sensitivity was done by disc diffusion method of Bauer *et al.* (1966).<sup>[4]</sup>

### Antimicrobial Susceptibility Testing Kirby-Bauer or disk diffusion method<sup>[4]</sup>

The bacterium is swabbed on the agar and the disks antibiotic discs are placed on the top. The antibiotic diffuses from the disc into the agar. The quantity of the antibiotic decreases as it gets away from the disc.

### Antibiotic disk for sensitivity testing

If the organism is killed or inhibited by the concentration of the antibiotic, there will be no growth in the immediate area around the disc: This is called the zone of inhibition.

### Antimicrobial Discs

Commercially prepared discs, procured from HiMedia Laboratories, India, were used as per the NCCLS recommendations. The discs were stored in sealed cartridges along with a desiccant at 20°C in a freezer. The strains were tested for their antimicrobial disk susceptibility to ampicillin, chloramphenicol, cotrimoxazole, nalidixic acid, azithromycin, ofloxacin, ceftriaxone, cefotaxime, cefixime, amikacin, ciprofloxacin, gentamicin, and amoxicillin [Figure 1 and Table 1].

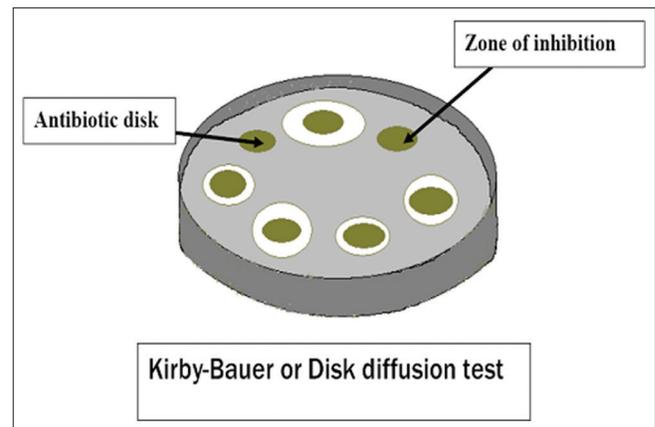


Figure 1: Recommended disk potency for different antibiotics

Table 1: Disc potency of different antibiotics<sup>[5]</sup>

Antibiotics	Disk potency
Nalidixic acid	30 µg
Ampicillin	10 µg
Chloramphenicol	30 µg
Cotrimoxazole	25 µg (23.75 µg TMP/1.25 µg SMX)
Azithromycin	15 µg
Ofloxacin	5 µg
Ceftriaxone	30 µg
Cefotaxime	30 µg
Cefixime	5 µg
Amikacin	10 µg
Ciprofloxacin	5 µg
Gentamicin	10 µg
Amoxicillin	10 µg

NCCLS performance standard for antimicrobial disk susceptibility tests. 7<sup>th</sup> Ed. Approved standard M2-A7 Vol. 20 No.1 2000 NCCLS. Villanova.

On removal from refrigerator for usage, the containers were left at room temperature for about an hour. This allowed the disc to equilibrate at room temperature, thus minimizing the amount of condensation that occurs when warm air comes in contact with cold discs.

### Media Preparation

Mueller-Hinton agar was autoclaved and 25–30 ml was poured into sterile disposable 10 cm Petri dishes on a level surface to give a uniform depth of 4 mm. The prepared plates were stored in inverted position at 4°C.

### Procedure

Five colonies from overnight growth of test strain were picked up and suspended in a test tube containing sterile normal saline. The density was adjusted by comparing the test suspension with 0.5 McFarland turbidity standards.

### McFarland Turbidity Standard<sup>[6]</sup>

0.5 McFarland turbidity standard was used for antimicrobial susceptibility testing, which represents  $1.5 \times 10^8$  bacteria/ml. Within 15 min of the preparation of inoculum, a sterile swab was dipped into the test inoculum and the excess was removed by the rotation of swab against the side of tube above the fluid level. The swab was streaked over the surface of medium 3 times by rotating the plate through an angle of 60° after each application. Then, the swab was passed around the edge of agar surface. The inoculated plates were dried at room temperature with the lids closed.

Antibiotic discs were applied on the surface of dried inoculated plate using sterile forceps and were gently pressed down to ensure even contact with the medium. Plates were incubated at 37°C for 18 h.

### Interpretation

Diameter of each zone including the diameter of the disc was measured and recorded in mm with the help of sliding calipers. The plate was held at 3 inches above black background, and the plate was illuminated with reflected light directly from above at 45° angle. End point of inhibition was judged by the naked eye at the point of abrupt diminution of growth or to the point of 80% inhibition. The results were interpreted according to the recent NCCLS criterion as sensitive, intermediate sensitive, or resistant.

### Widal Test<sup>[7-9]</sup>

This is a serological test done for the diagnosis of enteric fever. It detects antibodies produced by the host in response to infection with *S. typhi* and *S. paratyphi* A and B. This is a tube agglutination test where antigen is in the particle form. The bacterial suspension is used as an antigen. Since antibodies are detected only after 7–10 days of illness, Widal test is usually done during the 2<sup>nd</sup> week of illness. Patient's serum is tested for antibodies against O antigen of *S. typhi* and H antigen of *S. typhi*, *S. paratyphi* A, and *S. paratyphi* B. Positive result is indicated by the presence of agglutination. Absence of agglutination indicates a negative result. The paratyphoid *O* antigens are not employed as they cross react with the typhoid *O* antigen. Patient's serum

is diluted by doubling dilution, and in each row, there are five tubes of serum dilutions and the last tube in each row is the corresponding antigen control tube which does not contain the patient's serum. To these different dilutions, 0.3 ml of patient's serum and equal volume of antigen are added and the rack is incubated in a water bath at 37°C overnight. Two types of tubes are generally used in the test.

First row TH (d) - for H antigen of *S. typhi*.

Second row TO (9, 12) - for antigen of *S. typhi*.

Third row AH (a) - for H antigen of *S. paratyphi* A.

Fourth row BH (b) - for antigen of *S. paratyphi* B.

Results are read by viewing the tubes with the aid of a magnifying glass. First, observe the antigen control tubes which should show no agglutination and a compact bottom should be seen at the base. H agglutinin is large, loose, cottony, and fluffy clumps which are formed at the bottom of the tube. O agglutinins are small granules which are formed and settle at the bottom like a carpet. The end titer of the serum is the highest dilution of the serum giving visible agglutination.

### Interpretation

- i. A progressive rise in the titer between the first and second samples is highly significant. A positive or a negative result in a single test is not conclusive.
- ii. Repeated subclinical or past clinical infections in areas endemic for typhoid fever result in repeated boosting of immune system, and the serum of these uninfected subjects can cause agglutination at low dilutions, so titers are considered significant when agglutination for O antigen is more than 100 and for H antigen more than 200 against *S. typhi*.
- iii. Demonstration of 4-fold rise in titer in subsequent days is diagnostic.
- iv. H agglutinins tend to persist longer than O agglutinins after infection
- v. Persons immunized with TAB vaccine may show high titers to all the antigens.

### Laboratory Criteria for the Diagnosis of Enteric Fever

- A positive blood culture or
- A significant titer on Widal (the antibody titer was considered suggestive of enteric fever when the test showed "d"  $\geq 200$  and or "9, 12"  $\geq 100$ ) or both of the above.

### RESULTS

This prospective study entitled was undertaken by the Department of Pharmacology, JN Medical College, AMU, Aligarh, over a period of 1 year and 11 months from September 2004 to August 2006 after taking the Institutional Ethics Committee permission. About 142 randomly selected children having clinical features strongly suggestive of uncomplicated enteric fever with either culture positive or serology positive or both were entered in the study. Four patients were found after the entry in the study to have taken fluoroquinolone before coming

to hospital; two patients were removed later when found to have renal impairment, and one patient removed due to severe congestive heart failure. In 11 patients who were only serology positive, an alternative diagnosis was made finally on follow-up and 10 patients did not turn up for regular follow-up as required in the study. Hence, only a total of 114 patients could be taken up for the final evaluation in the study.

Table 2 shows the baseline characteristics of study participants. The youngest patient in this study was an 8-month-old male child. The mean age of all patients was  $7.73 \pm 3.14$  years. There were a total of 71 male and 43 female patients in the study. Males were affected more as compared to females. The mean weight of all patients was  $20.0 \pm 8.43$  kg [Table 2]. Table 2 shows age distribution in which the maximum incidence of disease was found in 5–10 years of age group (30, 26.32%) and minimum incidence in <1 year of age group (0.88, 1.8%). There was only single patient of an 8-month-old male child in <1 year age group who was culture-proven case of enteric fever. The incidence of fever in 1–5 years of age group was similar as in 10–15 years of age group, i.e., 26.3%.

Table 3 shows the duration of fever at presentation. Only 25% patients attended the hospital within the 1<sup>st</sup> week of illness, while maximum (54.6%) patients came to the hospital in the 2<sup>nd</sup> week of illness. Fever more than 3 weeks was seen in 5.5% of cases. About 2.9% of patients were ill for more than 4 weeks before seeking proper medical advice. The mean duration of fever before coming to the hospital was 11.5 days.

Table 4 shows the grade of fever in patients included in the study. Moderate grade was the most common as seen in 65.7% of cases,

whereas 23.2% of patients had mild-grade fever. Only 12.9% of cases reported high-grade fever.

[Continuous: Temperature remains throughout the day and at no time touches the baseline.

Remittent: The same as continuous fever but the diurnal variation is  $> 2^\circ\text{F}$ . Intermittent: Fever presents only for some hours during the day and remits to normal for the rest of the day. Stepladder: Temperature shows an upward rising trend continuously for 4-5 days.]

Table 5 shows the pattern of fever in patients who were included in the study. The most common pattern of fever observed was continuous 45.3%. Remittent fever was observed in 31.5% of patients, next common to continuous fever, while intermittent fever was observed only in 18.6% of cases. It is important to note that stepladder pattern as described characteristic pattern of enteric fever was rarely observed in children and present only in 4.6% of cases.

Table 6 shows symptoms at the time of presentation. Fever was the most common clinical presentation and was present in 94.7%. Chills along with the fever were uncommon finding and only presented in 7% of cases. Gastrointestinal symptoms in the form of pain abdomen, vomiting, diarrhea, and constipation were other common presenting symptoms observed in 38.5%, 34.2%, 25.4%, and 41.2% of cases, respectively. Constipation was more common as compared to diarrhea. Jaundice and myalgia were rare findings presented in 3.5% and 2.6% of cases. It is important to note that headache was also among the common feature and was present in 35% of cases. Respiratory symptoms which are usually uncommon findings were observed in 10.5% of cases in our study.

Table 7 shows physical findings in patients who were included in the study. Hepatosplenomegaly was a common finding during

**Table 2: Baseline characteristics of the cases (n=114) (% , mean±SD, range)**

Characteristics	Results
Age (years)	7.73±3.14 (0.8–12)
Age group (years)	
<1	0.88 (1.8%)
1–5	30 (26.32%)
5–10	53 (46.49%)
10–15	30 (26.32%)
Sex (male/female)	71/43 (1.65:1)
Weight (kg)	20.0±8.43 (6–42)

**Table 3: Fever at presentation in cases (n=114)**

Duration of fever (days)	Total (%)
1–7	27 (25)
8–14	59 (54.6)
15–21	13 (12)
22–28	6 (5.5)
>28	3 (2.9)

**Table 4: Grades of fever in cases (n=114)**

Grade of fever	Total (%)
Mild (up to 100°F)	25 (23.2)
Moderate (up to 100–103°F)	71 (65.7)
High (104≥F)	12 (11.1)

**Table 5: Pattern of fever (n=114)**

Type of fever	Total (%)
Continuous	49 (45.3)
Remittent	34 (31.5)
Intermittent	20 (18.6)
Stepladder	5 (4.6)

**Table 6: Symptoms at the time of presentation among study participants**

Presenting symptoms	Total (%)
Fever	108 (94.7)
Chills	8 (7.0)
Pain abdomen	44 (38.5)
Headache	40 (35.0)
Vomiting	39 (34.2)
Diarrhea	29 (25.4)
Constipation	47 (41.2)
Anorexia	48 (42.1)
Altered sensorium	16 (14.0)
Convulsions	3 (2.6)
Jaundice	4 (3.5)
Myalgia	3 (2.6)
Cough/respiratory distress	12 (10.5)

the examination. Hepatomegaly was more common (43.8%) as compared to splenomegaly (27.1%). The characteristic rose spots of enteric fever were a rare finding in children and were present in only one patient among all 114 cases examined. Relative bradycardia which was described as characteristic feature of enteric fever was an uncommon finding in children.

Table 8 shows the results of culture and serology (Widal test) results. The *S. typhi* was isolated from 33.3% of cases, while in rest 66.6% of patients, the diagnosis of enteric fever was made by significant titer on Widal test. Table 8 further shows the results of blood culture and Widal test separately. It is important to observe that there were 4.3% of cases in the study showed widal test inconclusive inspite culture of blood showed a positive result.

Table 9 shows culture and sensitivity result in the present study. Azithromycin, ceftriaxone, and cefotaxime were showing maximum sensitivity against *S. typhi*.

Table 10 shows the results of overall culture and sensitivity pattern of *S. typhi*. The results of Table 10 reveal that quite high percentage of *S. typhi* was resistant to first-line drugs, i.e., chloramphenicol, ampicillin, and cotrimoxazole. Maximum number of *S. typhi* (60%) was resistant to ampicillin. None of the *S. typhi* was found resistant to azithromycin, and the same was true for cefotaxime and amikacin [Table 11 and Figure 2].

## DISCUSSION

Typhoid fever accounts for a significant cause of morbidity in children in the developing countries. A population-based study from Delhi has reported an incidence rate of typhoid per 1000 years be 27.3 at age under 5 years, 11.7 at 5–19 years, and 1.1 between 19 and 40 years.<sup>[10]</sup> Typhoid fever presents with a

wide range of symptoms. Due to the use of antibiotics before diagnosis, children may not present with typical symptoms. However, in a study by Devaranavadi *et al.*,<sup>[11]</sup> the most common symptom was fever (100%), followed by anorexia (61%), vomiting (44%), pain abdomen (18%), diarrhea (16%), headache (12%), and cough (10%). The most common symptoms apart from fever were anorexia, vomiting, pain abdomen, and diarrhea, followed by headache and cough. A study done by Sinha *et al.*<sup>[10]</sup> and Kapoor *et al.* also reported similar results.<sup>[12]</sup> Other studies also showed similar clinical picture.<sup>[13,14]</sup> Contradictory to this, a study done by Joshi *et al.* reported headache as the most common symptom next to fever.<sup>[15]</sup> Fever was the common clinical presentation seen in 108 (94.7%) cases similar to studies done by other authors.<sup>[16-19]</sup> The clinical features of typhoid fever seen in our series are in comparison with other published studies.<sup>[19,20]</sup>

Hepatomegaly was more common (43.8%) as compared to splenomegaly (27.1%) in the present study. The characteristic rose spots of enteric fever were a rare finding in children and were present in only one patient among all 114 cases examined. Relative bradycardia which was described as characteristic feature of enteric fever was an uncommon finding in children. Hepatomegaly (43.8%) and splenomegaly (27.1%) were observed less frequently in our study compared to a study by Patankar and Shah<sup>[21]</sup> who found very high incidence of hepatomegaly (81.8%) and splenomegaly (48.5%) in their study. However, splenomegaly (36%) and hepatomegaly (17%) were seen in a study done by Mathura *et al.*<sup>[22]</sup> Briedis and Robso reported that 30% of patients with typhoid fever had splenomegaly.<sup>[23]</sup>

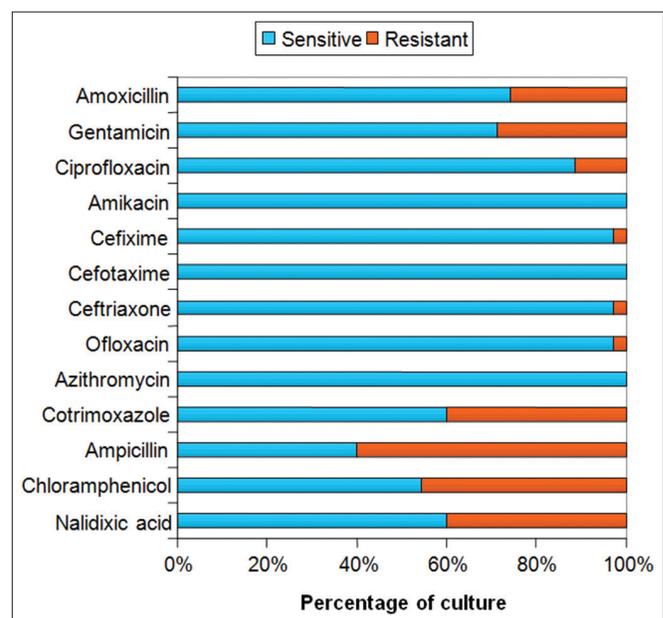
Relative bradycardia and constipation considered to be salient features of enteric fever in adults were very infrequently seen in our study with children. Few other studies have also found these to be inconsistent features of enteric fever.<sup>[14]</sup> A study by Devaranavadi *et al.*<sup>[11]</sup> depicted antibiotic sensitivity patterns among culture-positive cases. Ceftriaxone and cefixime sensitivity was seen in all the cases (100%), followed by ofloxacin (96%),

**Table 7: Physical findings among study participants**

Presenting sign	Total (%)
Toxic look	13 (11.4)
Pallor	66 (57.8)
Icterus	4 (3.5)
Coated tongue	17 (14.9)
Abdominal tenderness	17 (14.9)
Hepatomegaly	50 (43.8)
Splenomegaly	31 (27.1)
Rose spots	1 (0.87)
Rhonchi/rales	7 (6.1)
Relative bradycardia	3 (2.6)
Meningismus	2 (1.75)
Cervical lymphadenopathy	8 (7.0)
Sudaminous rashes	31 (27.1)

**Table 8: Results of culture and serology**

Investigations	Total (%)
Culture positive	38 (33.3)
Serology positive	76 (66.6)
Widal positive and culture positive	33 (28.9)
Widal negative and culture positive	5 (4.3)
Widal positive and culture negative	76 (66.6)



**Figure 2: Sensitivity pattern of *Salmonella typhi***

**Table 9: Culture sensitivity pattern in among study participants**

Drug	<i>S. typhi</i> (35)		<i>S. paratyphi</i> (3)	
	Sensitive (%)	Resistant (%)	Sensitive (%)	Resistant (%)
Chloramphenicol	19 (54.3)	16 (45.7)	2 (66.6)	1 (33.3)
Ampicillin	14 (40)	21 (60)	1 (33.3)	2 (66.6)
TMP-SMX	21 (60)	14 (40)	3 (100)	0
Azithromycin	33 (94.3)	2 (5.7)	3 (100)	0
Ofloxacin	31 (88.6)	4 (11.4)	2 (66.6)	1 (33.3)
Ceftriaxone	32 (91.4)	3 (8.6)	3 (100)	0
Cefotaxime	32 (91.4)	3 (8.6)	3 (100)	0
Cefixime	31 (88.6)	4 (11.4)	3 (100)	0
Amikacin	28 (80)	7 (20)	2 (66.6)	1 (33.3)
Ciprofloxacin	25 (71.4)	10 (28.6)	1 (33.3)	2 (66.6)
Gentamicin	25 (71.4)	10 (28.6)	1 (33.3)	2 (66.6)
Amoxicillin	26 (74.3)	9 (25.7)	1 (33.3)	2 (66.6)

**Table 10: Sensitivity pattern of *S. typhi* in Aligarh**

Antibiotic	Sensitive (%)	Resistant (%)
Nalidixic acid	21 (60.0)	14 (40.0)
Chloramphenicol	19 (54.3)	16 (45.7)
Ampicillin	14 (40.0)	21 (60.0)
Cotrimoxazole	21 (60.0)	14 (40.0)
Azithromycin	35 (100)	0 (0)
Ofloxacin	34 (97.1)	1 (2.9)
Ceftriaxone	34 (97.1)	1 (2.9)
Cefotaxime	35 (100)	0 (0)
Cefixime	34 (97.1)	1 (2.9)
Amikacin	35 (100)	0 (0)
Ciprofloxacin	31 (88.6)	4 (11.4)
Gentamicin	25 (71.4)	10 (28.6)
Amoxicillin	26 (74.3)	9 (25.7)

**Table 11: Sensitivity pattern of *S. paratyphi* in Aligarh**

Antibiotic	Sensitive (%)	Resistant (%)
Nalidixic acid	1 (33.3)	2 (66.7)
Chloramphenicol	1 (33.3)	2 (66.7)
Ampicillin	1 (33.3)	2 (66.7)
Cotrimoxazole	2 (66.7)	1 (33.3)
Azithromycin	3 (100)	0 (0)
Ofloxacin	3 (100)	0 (0)
Ceftriaxone	3 (100)	0 (0)
Cefotaxime	3 (100)	0 (0)
Cefixime	3 (100)	0 (0)
Amikacin	1 (33.3)	2 (66.7)
Ciprofloxacin	1 (33.3)	2 (66.7)
Gentamicin	0 (0)	3 (100)
Amoxicillin	1 (33.3)	2 (66.7)

ciprofloxacin (87%), chloramphenicol (84%), cefotaxime (82%), amoxicillin (70%), and azithromycin in 20 cases (60%). *S. typhi* was more sensitive to ceftriaxone and cefixime followed by ofloxacin. Least sensitivity was seen with azithromycin. A study by *et al.* showed that 61 isolates of *S. typhi* were sensitive to cefexime (fourth-generation cephalosporin), 96% to third-generation cephalosporins, and 95% to quinolones. There was an intermediate sensitivity to ampicillin (92%) and chloramphenicol

(80%). Notably, azithromycin resistance was observed in 63% of isolates. All patients ultimately made full recoveries.<sup>[24]</sup>

A study in Pondicherry by Madhulika *et al.*<sup>[25]</sup> consisting of 157 clinical isolates of *S. typhi* showed no antibiotic resistance against ciprofloxacin and ceftriaxone, whereas 64.9% resistance was reported against cotrimoxazole. In contrast to this, a study by Chandane P *et al.* (2017) demonstrated 27.5% and 9.3% resistance against ciprofloxacin and ceftriaxone, respectively.<sup>[26]</sup> An increasing trend in ciprofloxacin resistance was observed when compared with the data obtained by Mannan *et al.*, 2014, which showed 8% resistance compared to the 27.5% observed in the present study.<sup>[27]</sup> Based on these observations, it is imperative to carry out various longitudinal studies to establish the existence of antibiotic-resistant *S. typhi* in the Indian population. Another study by Rather *et al.*, 2013, conducted in Kashmir, India, focused on antibiotic sensitivity patterns of *Salmonella* isolated from different water sources from Kashmir. They reported 100% sensitivity against gentamicin and 91.67% sensitivity for amikacin and ciprofloxacin.<sup>[28]</sup>

Public health interventions to minimize human carrier contact improved personal hygienic measures including health-care behavior strategies, typhoid vaccination, and rational antibiotic selection based on sensitivity pattern to prevent resistance will help to reduce the morbidity and mortality of this global health problem.<sup>[16]</sup>

## CONCLUSION

*S. typhi* and *S. paratyphi* are important causes of bacteremia in children, especially those from the developing world. Typhoid fever accounts for significant cause of morbidity in children in developing countries. Typhoid fever continues to be a major health problem, resulting in significant number of children requiring hospitalization. There is a lack of standardized treatment protocols for such patients in the literature, and there are also reports of therapeutic failure related to resistance to commonly used antibiotics. Our antimicrobial susceptibility data suggest that quinolones and third-generation cephalosporins should be used as first-line antimicrobials in enteric fever. The high unresponsiveness against fluoroquinolones may be due to the overuse of these antibiotics in the treatment of typhoid and in other unrelated infections. There is an urgent need for large-

scale, community-based clinical trials to evaluate the effectiveness of different antibiotics in enteric fever. Enteric fever is a major public health problem in developing countries including India. Appropriate antimicrobial therapy can reduce morbidity and mortality associated with this illness.

## REFERENCES

1. Typhoid. Available from: <http://WWW.WHO.Int/Immunization/Diseases/Typhoid/En/>. [Last accessed on 2018 May 31].
2. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ* 2004;82:346-53.
3. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing D, Bhattacharya SK, Agtini MD, *et al*. Domic typhoid study group. A study of typhoid fever in five Asian countries: Disease burden and implications for controls. *Bull World Health Organ* 2008;86:260-8.
4. Bauer AW, Kirby WM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol* 1966;45:493-6.
5. Baker CN, Thornsberry C, Hawkinson RW. Inoculum standardization in antimicrobial susceptibility tests: Evaluation of the overnight agar cultures and the rapid inoculum standardization system. *J Clin Micro* 1983;17:450-7.
6. McFarland J. Nephelometer: An instrument for media used for estimating the number of bacteria in suspensions used for calculating the opsonic index and for vaccines. *J Am Med Assoc* 1907;14:1176-8.
7. Widai FM. Serodiagnostic de la fièvre typhoïde a-propos d'une modification par MMC nicolle et al. Halipie. *Bull Soc Med Hop Paris* 1896;13:561-6.
8. Brodie J. Antibodies and the Aberdeen typhoid outbreak of 1964. I. The Widai reaction. *J Hyg (Lond)* 1977;79:161-80.
9. Olopoenia LA, King AI. Widai agglutination test-100 years later: Still plagued by controversy. *Postgrad Med J* 2000;76:80-4.
10. Sinha A, Sazawal S, Kumar R, Sood S, Raddaiah VP, Singh B, *et al*. Typhoid fever in children aged less than 5 years. *Lancet* 1999;354:734-7.
11. Devaranavadagi RA, Srinivasa S. A study on clinical profile of typhoid fever in children. *Int J Contemp Pediatr* 2017;4:1067-73.
12. Kapoor JP, Mohan M, Talwar V, Daral TS, Bhargava SK. Typhoid fever in young children. *Indian Pediatr* 1985;22:811-3.
13. Sood SC, Taneja PN. Typhoid fever, clinical picture and diagnosis. *Ind J Child Health* 1961;10:69-76.
14. Chowta MN, Chowta NK. Study of clinical profile and antibiotic response in typhoid fever. *Indian J Med Microbiol* 2005;23:125-7.
15. Joshi BG, Keyal K, Pandey R, Shrestha BM. Clinical profile and sensitivity pattern of *Salmonella* serotypes in children: A hospital based study. *J Nepal Paediatr Soc* 2011;31:180-3.
16. Ganesh R, Janakiraman L, Vasanthi T, Sathiyasekeran M. Profile of typhoid fever in children from a tertiary care hospital in Chennai-South India. *Indian J Pediatr* 2010;77:1089-92.
17. Walia M, Gaiand R, Paul P, Mehta R, Aggarwal P, Kalaivani M. Age-related clinical and microbiological characteristics of enteric fever in India. *Trans R Soc Trop Med Hyg* 2006;100:942-8.
18. Siddiqui FJ, Rabbani F, Hasan R, Nizami SQ, Bhutta ZA. Typhoid fever in children: Some epidemiological considerations from Karachi, Pakistan. *Int J Infect Dis* 2006;10:215-22.
19. Walia M, Gaiand R, Mehta R, Paul P, Aggarwal P, Kalaivani M. Current perspectives of enteric fever: A hospital based study from India. *Ann Trop Paediatr* 2005;25:161-74.
20. Papaevangelou V, Syriopoulou V, Charissiadou A, Pangalis A, Mostrou G, Theodoridou M. *Salmonella* bacteraemia in a tertiary children's hospital. *Scand J Infectious Dis* 2004;36:547-51.
21. Patankar N, Shah I. Age related clinical and laboratory manifestations of enteric fever in children. *JK Sci* 2009;11:119-22.
22. Mathura KC, Choudhary D, Simkhada R, Pradhan M. Study of clinical profile and antibiotic sensitivity pattern in culture positive typhoid fever. *KUMJ* 2005;3:376-9.
23. Briedis DJ, Robso HG. Epidemiologic and clinical features of sporadic *Salmonella* enteric fever. *Can Med Assoc J* 1978;119:1183-7.
24. Vala S, Shah U, Ahmad SA, Scolnik D, Glatstein M. Resistance patterns of typhoid fever in children: A longitudinal community-based study. *Am J Ther* 2016;23:e1151-4.
25. Madhulika U, Harish BN, Parija SC. Current pattern in antimicrobial susceptibility of *Salmonella typhi* isolates in Pondicherry. *Indian J Med Res* 2004;120:111.
26. Chandane P, Gandhi A, Bowalekar S. Study of antibiotic susceptibility pattern of *Salmonella typhi* in children suffering from enteric fever. *Ann Trop Med Public Health* 2017;10:440-3.
27. Mannan A, Shohel M, Rajia S, Mahmud NU, Kabir S, Hasan I. A cross sectional study on antibiotic resistance pattern of *Salmonella typhi* clinical isolates from Bangladesh. *Asian Pac J Trop Biomed* 2014;4:306-11.
28. Rather TA, Hussain SA, Bhat SA, Shah SN, Arshid S, Shah Nawaz M. Antibiotic sensitivity of *E. coli* and *Salmonella* isolated from different water sources in Kashmir, India. *Comp Clin Path* 2013;22:729-31.

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