Culture positivity and antibiotic sensitivity pattern of typhoid fever in children aged 1 to 10 years: A 10-year retrospective study from a tertiary care centre of Eastern India

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Abstract

Background: Over the last few decades there has been a change in the trend of antibiotic sensitivity of *Salmonella typhi* from being sensitive to first line drugs like chloramphenicol, ampicillin and cotrimoxazole to developing multi-drug resistance. Most strains are presently sensitive to third generation cephalosporins and azithromycin but are developing resistance against fluoroquinolones.

Objectives: To determine the culture positivity and antibiotic sensitivity pattern of *Salmonella typhi*

Method: This retrospective **s**tudy was conducted at the Institute of Child Health, Kolkata from July 2014 to December 2020. Nine hundred and twenty children aged 1-10 years were included in the study, all with fever for more than 5 days. These children were suspected to have typhoid fever clinically i.e., with history, suggestive physical examination and after excluding other common febrile illnesses with routine blood test as per hospital protocol. Blood culture was done to confirm the diagnosis of typhoid fever, determine the proportion of blood culture positive cases and to find out the antibiotic susceptibility of *Salmonella typhi* in our hospital set up. Children were included in the study irrespective of prior antibiotic treatment.

Results*:* Of the 920 children, 55% were male and 45% were female; 15% cases were between 1-2 years of age and 85% were between 2-10 years of age; 53% cases were culture positive. In our study *S typhi* was fully sensitive to ampicillin, chloramphenicol, cefixime, ceftriaxone and azithromycin. It was highly sensitive to cotrimoxazole. It was highly resistant to ciprofloxacin and nalidixic acid

Conclusions*:* There was complete sensitivity of *Salmonella typhi* to third generation cephalosporins and azithromycin. It was also sensitive to older, less commonly used antibiotics like chloramphenicol, cotrimoxazole and ampicillin. There was increased resistance to fluroquinolones.

(Key words: *Salmonella typhi*, Blood culture, Antibiotic sensitivity)

Introduction

Typhoid fever is a multisystem infection caused by *Salmonella enterica serovar typhi*. Each year around 27 million cases get affected worldwide with around 1% mortality[1]. Majority of these cases are from the developing countries of Asia[2]. Over the last few decades there has been a change in the trend of antibiotic sensitivity of *Salmonella typhi* from being sensitive to first line drugs like chloramphenicol, ampicillin and cotrimoxazole to developing multi-drug resistance (MDR). Most strains are presently sensitive to third generation cephalosporins and azithromycin but are developing resistance against fluoroquinolones[3,4].

Diagnosis of typhoid fever may be initially challenging due to its varied presentation[4]. Blood culture is the gold standard for diagnosis and the highest yield is in the 1st week of illness (90%) and is 75%, 60% and 25% in 2nd, 3rd and 4th week respectively[5,6]. However, due to inadequate laboratory facilities, cost and technical difficulties to obtain a good culture sample from smaller children, culture is not frequently done in developing countries. Positivity of blood culture may be further compromised by prior antibiotic usage. Sensitivity and specificity of the Widal test being low, in most

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cases, treatment is empirical[6]. This leads to improper and inadequate use of antibiotics and the development of MDR typhoid.

In the last two decades MDR *Salmonella typhi* has become a serious threat[7]. These strains are resistant to ampicillin, chloramphenicol and cotrimoxazole. Thus, the antibiotics of choice are 3rd generation cephalosporins and fluoroquinolones[8]. Unfortunately, due to indiscriminate use of these drugs in the last few years, resistance has emerged against fluoroquinolones. There are no recent studies regarding the antibiotic sensitivity pattern of salmonella typhi from this part of India.

Objectives

To analyse the antibiotic sensitivity pattern of *Salmonella typhi* and also to document the changing sensitivity pattern over a period of 10 years.

Method

This retrospective **s**tudy was conducted at the Institute of Child Health, Kolkata from July 2014 to December 2020. Nine hundred and twenty children aged 1-10 years were included in the study, all with a history of fever for more than 5 days. These children were suspected to have typhoid fever clinically i.e., with history, suggestive physical examination and after excluding other common febrile illnesses with routine blood test as per hospital protocol. Widal test was done routinely. Blood culture was done to confirm the diagnosis of typhoid fever, determine the proportion of blood culture positive cases and to find out the antibiotic sensitivity pattern of *Salmonella typhi* in our hospital set-up. Children were included in the study irrespective of prior antibiotic treatment.

Ethical issues: Approval for the study was obtained from the Institutional Ethics Committee for Biomedical and Health Research, Institute of Child Health, Kolkata, India (No. ICH/ IECBMHR/ 20/ 2022 dated 29.06.2022). As this was a retrospective study informed consent was not a possibility.

Statistical analysis: Data entry was done in Microsoft Excel and was statistically analysed using SPSS software. Descriptive statistical data like means, medians and standard deviations were calculated for continuous variables.

Results

Table 1 shows the gender distribution of cases.

Table 1: ***Gender distribution of cases***

Gender	Culture positive cases n (%)	Culture negative cases n (%)	Total number of cases studied n (%)
Male	280 (57.4)	224 (51.8)	504 (54.8)
Female	208 (42.6)	208 (48.2)	416 (45.2)
Total	488 (100.0)	432 (100.0)	920 (100.0)

There was no statistically significant difference of gender between the study population and culture positive cases and no gender predilection of typhoid fever in our study.

Table 2 shows the age distribution of cases.

Table 3 shows the distribution of culture positive cases among the total study population.

Table 2: ***Age distribution of cases***

Cases	Mean age (years)	Median age (years)
Culture positive cases	4.85	4.8
Total number of cases	4.87	4.8

Table 3: ***Distribution of culture positive cases among total study population***

Age (years)	Culture positive cases n (%)	Culture negative cases n (%)	Total number of cases n (%)
<2	88 (64.7)	48 (35.3)	136 (100.0)
2-10	400 (51.0)	384 (49.0)	784 (100.0)
Total	488	432	920

To compare the number of culture positive cases in children less than 2 years of age and 2-10 years of age we did Chi square test. The result was not significant ($p>0.05$). Whilst 65% of cases <2 years of age were culture positive compared to 51% of cases 2-10 years of age, this was not statistically significant.

Table 4 is a comparison of the duration of fever at presentation in culture positive and negative cases.

Table 4: ***Comparison of duration of fever at presentation in culture positive and negative cases***

Group	Average duration of fever in days	p-value
Culture negative cases (n=432)	9.59 ± 2.97	p= 0.24
Culture positive cases (n=488)	8.44 ± 2.72	

There was no significant difference between mean duration of fever between study population and culture positive cases (p= 0.24).

Table 5 and Figure 1 show the pattern of antibiotic sensitivity of *Salmonella typhi* among culture positive cases.

Table 5: ***Pattern of antibiotic sensitivity of S typhi among culture positive cases***

Drug sensitivity pattern	Ampicillin	Cotrimoxazole	Chloramphenicol	Azithromycin	Cefixime	Ceftriaxone	Ciprofloxacin	Nalidixic acid
Sensitive	488 (100.0)	464 (95.0)	488 (100.0)	488 (100.0)	488 (100.0)	488 (100.0)	24 (05.0)	32 (06.5)
Resistant	0	24 (05.0)	0	0	0	0	464 (95.0)	456 (93.5)
Total	488	488	488	488	488	488	488	488

In this study *Salmonella typhi* was fully sensitive to ampicillin, chloramphenicol, cefixime, ceftriaxone and azithromycin. It was found to be highly sensitive to cotrimoxazole. It was highly resistant to ciprofloxacin and nalidixic acid.

Table 6 shows the use of prior antibiotics among culture positive and negative cases. For the test of significance Chi Square test was done. The Chi-square statistic was 7.7123. The p-value was 0.005485. This result is significant at p <0 .05.

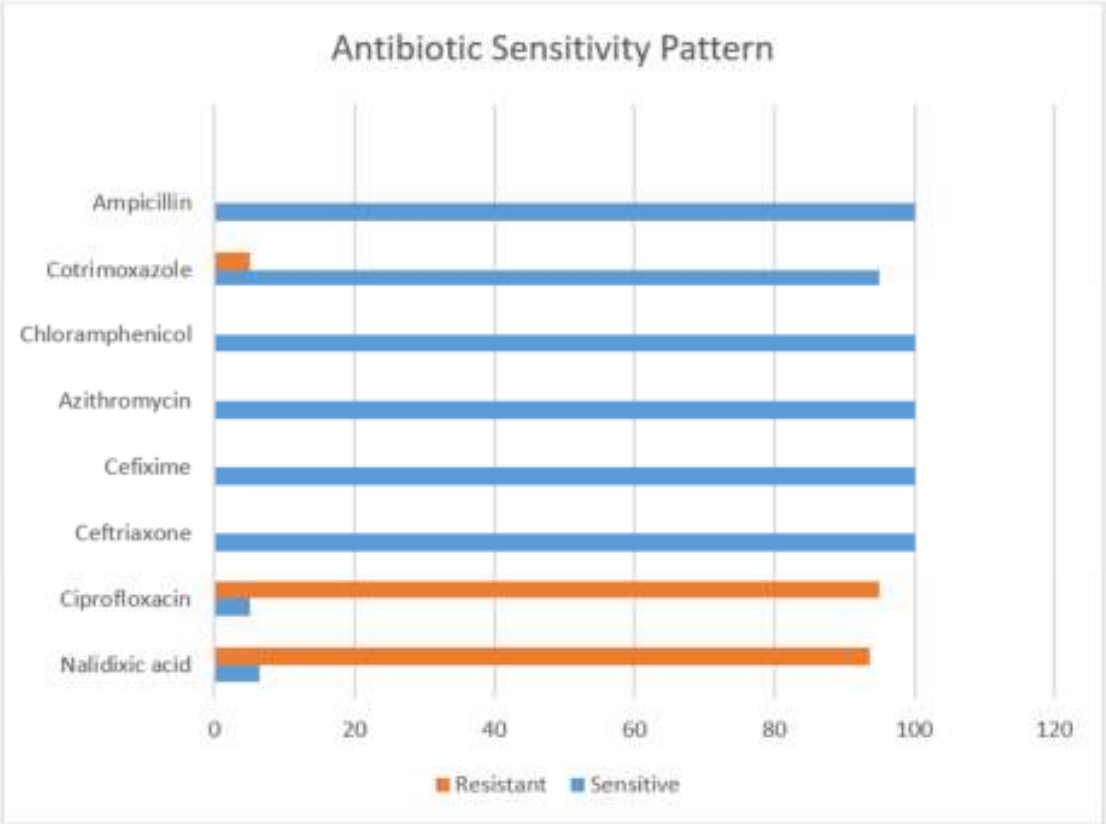

Figure 1: ***Pattern of antibiotic sensitivity of S typhi among culture positive cases***

Table 6: ***Use of prior antibiotic among culture positive and negative cases***

Category	Culture positive cases n (%)	Culture negative cases n (%)
Cases who had received prior empirical antibiotic therapy	248 (50.1)	328 (76.0)
Cases who had not received prior empirical antibiotic therapy	240 (49.9)	104 (24.0)
Total	488 (100.0)	432 (100.0)

Discussion

In our study, out of total 920 children 504 (54.8%) were male and 416 (45.2%) were female. Among total 488 blood culture positive cases, 280 (57.4%) were male and 208 (42.6%) were female. However, we did not find any significant gender difference like most of the previous studies.

We included children aged 1 to 10 years with a mean age of 4.87 years and grouped them as less than 2 years and 2-10 years. We excluded infants from our study. In present study we found that 136 (14.8%) cases were 1-2 years old and 784 (85.2%) were 2 to 10 years old. Among total 488 culture positive cases, 88 (18%) were 1-2 years old and 400 (82%) were 2 to 10 years old. We observed that 64.7% had culture positivity in children less than 2 years of age compared to 50% in the older group. However, this was not statistically significant. The mean age of our study group was 4.87 years which is similar to studies by Sinha A, *et al*[3] who found 44% of cases to be 1-5 years of age and by Siddiqui F, *et al*[9] who found 52% of cases in the 1-5-year age group and 24% in the 5-10-year age group. Our result was in contrast to a study from Ghana by Marks F, *et al*[10] in children aged 0-15 years, where the highest proportion of blood culture positive cases (21.3%) was in the 0-2-year age group. This may be due to a smaller sample size in comparison to other studies.

In our study 488 (53%) cases were blood culture positive for *Salmonella typhi* and 432 (47%) cases were culture negative. This is consistent with a study done in Nigeria in 2012 by Adabara NU, *et al*[11] where the culture positivity was 40-60% in early stage of disease. A clinical review by Bhutta ZA[12] suggested a sensitivity of 40–80% for blood culture and 55–67 % for bone marrow culture.

We found that for culture positive cases the mean duration of fever was 8.44 ± 2.72 days and for culture negative cases 9.59 ± 2.97 days. In contrast to the general belief that blood culture is usually positive in 1st week of illness, we found it to be also positive in the 2nd week. Thus, blood culture should not be discouraged if the patient presents late or with prior antibiotic treatment.

We found that *Salmonella typhi* in our set-up was fully sensitive to ampicillin (100%) and chloramphenicol (100%) and highly sensitive to cotrimoxazole (95%). Thus, there is a definite re-emergence of sensitivity of *Salmonella typhi* to all first line drugs which is being reported by several studies from different parts of India and Nepal since the last decade. Our result is very similar to the study in Nepal by Chand H, *et al*[13] in 2011 which showed 100% sensitivity to chloramphenicol and cotrimoxazole and 98.2% sensitivity to ampicillin. Another study in the same year by Kumar Y, *et al*[14] reported 95.3% sensitivity to chloramphenicol and 94.5% sensitivity to both ampicillin and cotrimoxazole. Similar results were described in 2013 by Gupta V, *et al*[15] and Choudhary A, *et al*[16]. In Kolkata, a study in 2005 by Dutta S, *et al*[17] reported increased sensitivity to all first line drugs and reversal of resistance pattern and decreased MDR *S typhi*. In that study resistance was 13% to ampicillin and chloramphenicol and 15% to cotrimoxazole. A study in 2007 by Sen B, *et al*[18] found 14% of the total isolates to be MDR. In our study MDR *Salmonella typhi* was not found. This finding is in contrast with reports published in Bangladesh by Rahaman M, *et al*[19] and in Cambodia by Kasper MR, *et al*[20] that reported a rise in MDR *Salmonella typhi* with reduced susceptibility to fluoroquinolones.

Our study and many other studies indicate a remarkable reversal in the resistance pattern of *Salmonella typhi* in Kolkata as well as in India. This reversal may be due to the emergence of de novo susceptible strains or the loss of plasmid encoding chloramphenicol, ampicillin, and cotrimoxazole resistance in the recent strains of *S typhi* or decreased use of these drugs in last 2 decades. In the present study we found 95% of *Salmonella typhi* were resistant to nalidixic acid. Sensitivity to ciprofloxacin was 5% whilst 95% were intermediate sensitive that behaved like resistant. This nalidixic acid resistant *S typhi* (NARST) is thought to be a marker of fluoroquinolone resistance. This finding is much higher than the previous studies by Kadhiravan T, *et al*[21] (2005) who determined NARST to be 78% and very similar to the study by Choudhary A, *et al*[16] and Gupta V, *et al*[15] who found 91.9% and 100% NARST respectively in 2013. However, in both studies resistance to ciprofloxacin was 13.7% which is much less than our study. Mishra R, *et al*[22] in 2015 reported 80% cases to have intermediate sensitivity to ciprofloxacin in a study from North India which is consistent with our findings. Thus, there is increased resistance to fluoroquinolones due to their over-the-counter use in the last few years. In the present study we found complete sensitivity to third generation cephalosporins and azithromycin like most of the recent studies. With these findings, use of empirical antibiotic use may have to be revised and use of first line drugs should be re-considered to prevent rise of drug resistance and complications.

Typhoid in children remains a significant health issue. Though limited with small number of sample size our study attempted to address few emerging issues of typhoid fever. A good number of children came to be culture positive even after late presentation and prior antibiotics especially in the younger age group. Re-emergence of susceptibility of *Salmonella typhi* was documented with reversal

of MDR. However, rise of fluoroquinolone resistance was threatening. Larger population-based studies are essential to assess the current situation in a deeper and more extensive manner.

Conclusions

There was complete sensitivity of *Salmonella typhi* to third generation cephalosporins and azithromycin. It was also sensitive to older and less commonly used antibiotics like chloramphenicol, cotrimoxazole and ampicillin. There was increased resistance to fluroquinolones.

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