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## ORIGINAL ARTICLE

# Antibiotic Sensitivity Pattern in Blood Culture Positive Typhoid Fever

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### ABSTRACT

**Objective:** The objective of this study was to find out current antibiotic sensitivity pattern of *Salmonella typhi* in children admitted in Pediatric Department of Services Hospital, Lahore over a period of one year.

**Study Design:** Descriptive cross-sectional study.

**Place and Duration of Study:** Pediatric Department of Services Hospital Lahore from 1<sup>st</sup> July 2018 till 30<sup>th</sup> June 2019.

**Material and Methods:** The study was conducted in Pediatric Department of Services hospital Lahore over a period of 1 year after taking approval from hospital ethical review board. Blood cultures of all suspected patients of typhoid fever were obtained who presented in Pediatric department, were tested for their sensitivity pattern by disc diffusion method and were incubated at 37°C for at least 7 days.

**Results:** There were 114 positive blood cultures of typhoid fever. Out of these, 75 (66%) were from male children and 39 (34%) were from female children. All salmonella isolates were found to be resistant to ampicillin. Resistance to cephalosporin and fluoroquinolone was also high, being 89% to ceftriaxone and 94% to ciprofloxacin. However, antibiotic sensitivity to meropenem and imipenem was 100% and azithromycin was 98%.

**Conclusion:** In this study, increased resistance to the first line drugs: ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole along with second line drugs fluoroquinolones and cephalosporins was seen when these were used for the treatment of enteric fever. Unfortunately, we have been left with only few drugs like meropenem and azithromycin that have shown more than 98% sensitivity to the salmonella as can be inferred from this cohort.

**Key Words:** Typhoid fever, Drug resistance, Antibiotic sensitivity.

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### INTRODUCTION

Typhoid fever is a very common systemic disease especially in underdeveloped countries.<sup>1</sup> *Salmonella* enteric subspecies salmonella typhi (*S typhi*) and paratyphi (*S paratyphi*) are the most

common cause of enteric fever. Disease spreads mainly due to improper sanitation, drinking impure water and unhygienic measures. All over the world, the incidence of typhoid fever is 0.3 percent annually.<sup>2</sup> In the year 2017, 14.3 million people

suffered from typhoid and paratyphoid fever worldwide.<sup>3</sup> There was a huge epidemic of typhoid fever in the recent past in Pakistan.

After initial infection by bacteria, the organism resides in the lymphoid tissue of the ileum, producing characteristic lesions in Payer's patches and follicles. Initially these lesions get swollen, then ulcerated and finally are healed. This healing characteristically occurs without scarring, sparing intestinal lumen to be stenosed. After clinical remission, almost 5% of the patients turn into chronic carriers and secrete bacteria in stool off and on and sometimes in urine.<sup>4</sup>

The clinical manifestations are variable in typhoid fever. Antibiotic sensitivity pattern of organisms varies from country to country and even in the same country in different time periods. In spite of starting appropriate timely antibiotic therapy, chronic carrier state may persist and its reactivation during the period of immunodeficiency may contribute to drug resistance in typhoid fever<sup>5</sup>. Multidrug resistant (MDR) *Salmonella typhi* has been documented in South Viet Nam in 1992-1993.<sup>6-8</sup> These organisms were resistant to common first line antimicrobial drugs like ampicillin, cotrimoxazole and chloramphenicol, however they were sensitive to third generation cephalosporin and ciprofloxacin and other quinolones. Multidrug resistant typhoid traditionally describes resistance to all the first line antibiotics suggested by WHO (ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol). Extensively drug resistance (XDR) typhoid describes resistance to all the second line antibiotics suggested by WHO (fluoroquinolones and cephalosporins). A study at Aga Khan University, Pakistan, from 2001 to 2006 suggests that the multidrug resistance rate for *Salmonella typhi* strains has gone up from 34.2% to 48.5%, while resistance against quinolone has shot up from 1.6% to 64.1% through these years<sup>9</sup>.<sup>10</sup> Multidrug resistance (MDR) has become very common in many areas of South Asia, rising up to 13% in India and 44% in Pakistan.<sup>11</sup>

A previous study in Pakistan showed increase in resistance against ciprofloxacin. Antibiotic resistance is increasing with evolving multi-drug resistant strains of salmonella.<sup>12</sup> Antibiotic resistance patterns are a major problem for health care workers and authorities who are dealing with

such cases. The objective of this study was to find out the antibiotic resistance and sensitivity pattern of *Salmonella typhi* in children presenting in our hospital. We would hence, be able to formulate antibiotics policy for management of MDR and XDR typhoid fever in our setting.

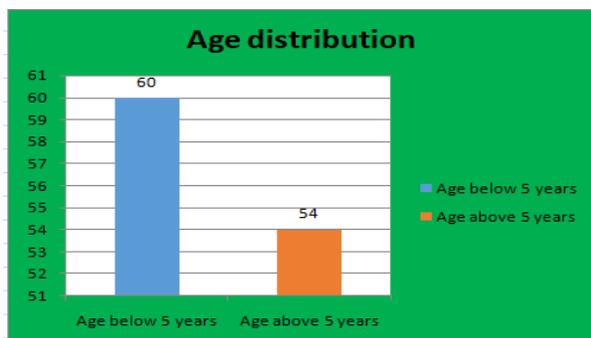
## MATERIAL AND METHODS

This cross-sectional study was conducted in Pediatric Department of Services hospital Lahore from 1<sup>st</sup> July 2018 till 30<sup>th</sup> June 2019. After ethical approval from hospital ethical review board, blood cultures were taken from all patients who were suspected of typhoid fever. Those who had already taken antibiotics were excluded from the study. Case definition of suspected typhoid fever was insidious onset of sustained fever along with headache, relative bradycardia, constipation or diarrhea and non-productive cough.<sup>13</sup> Of 350 suspected cases of typhoid fever, blood sample were taken in two separate blood culture bottles from two different sites at the same time following strict aseptic measures. The isolates of *S. typhi* were tested for sensitivity to nine antimicrobial agents that incubated imipenem, meropenem, azithromycin, ceftriaxone, ciprofloxacin, chloramphenicol, trimethoprim, cefotaxime and ampicillin by disc diffusion method<sup>14</sup> and all blood cultures were incubated at 37°C for at least 7 days. The strains were identified as sensitive, intermediate and resistant as per the diameter of zone of inhibition. The data was recorded in SPSS version 20 and Data was summarized using percentages and frequencies.

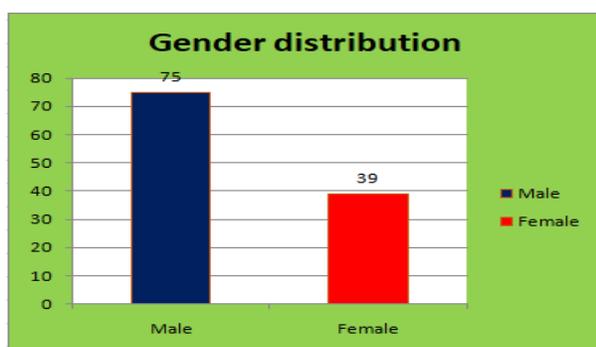
## RESULTS

Out of 350 suspected cases of typhoid fever, 114 (32.5%) turned out to be positive for *S. typhi*. Among positive cases of typhoid fever, 75 (66%) were male and 39 (34%) were female. Among them 60 (53%) were above 5 years of age and 54 (47%) were below 5 years of age. Results are shown in figure 1 and figure 2. According to the blood culture sensitivity reports, there was 100% sensitivity to imipenem and meropenem while 98% sensitivity to azithromycin. However, there was poor sensitivity to other conventional drugs being used in treatment of enteric fever with complete resistance to ampicillin. Resistance to cephalosporins and fluoroquinolones was also high being 89% to ceftriaxone and 94% to

ciprofloxacin (table 1).



**Fig 1: Age Distribution in Positive cases of Typhoid Fever.**



**Fig 2: Gender Distribution in Positive cases of Typhoid Fever.**

**TABLE 1: Sensitivity pattern of salmonella isolates to antibiotics (n=114)**

Antibiotics	Sensitive Number of Cases (%)
Imipenem	114 (100.0)
Meropenem	114 (100.0)
Azithromycin	112 (98.0)
Ceftriaxone	21 (18.0) (18 were completely sensitive and 3 showed intermediate sensitivity)*
Ciprofloxacin	6 (5.0)
Chloramphenicol	5 (4.0)
Trimethoprim	3 (2.0)
Cefotaxime	3(2.0)
Ampicillin	1(0.0)

\*Intermediate sensitivity was shown only for ceftriaxone

## DISCUSSION

Enteric fever is a great threat in our part of the world. Growing antibiotic resistance poses a great problem for clinicians and medical health

professionals. Easy availability and irrational use of antibiotics has made this problem worse. Multidrug and extensive drug resistance in enteric fever has made it difficult to treat as well as is associated with increased frequency of complications with significant morbidity and mortality. Chloramphenicol, that was used in the past for the treatment of enteric fever, got obsolete due to its side effect of bone marrow suppression. Later on, cotrimoxazole and ampicillin were used for enteric fever. But due to injudicious use of these antibiotics, enteric fever got resistant to these drugs.

Several studies have been conducted in different parts of the world showing promising results with the conventional drugs that have been used a decade ago. One study conducted in India showed improved sensitivity to chloramphenicol (98%) and to aminoglycosides (100%).<sup>15</sup> Another study conducted in Nepal showed (95%) sensitivity to chloramphenicol and (97%) sensitivity to cotrimoxazole.<sup>16</sup> In one more study in India, the antibiotic sensitivity pattern in the patients showed a high level of resistance to fluoroquinolones at 29.2%. Decreasing susceptibility of *Salmonella typhi* to ciprofloxacin has been well documented in several studies<sup>17-20</sup>, and is indicative of the effects of indiscriminate use of this group of antibiotics. However, in our current study, there is increased resistance to conventional antibiotics showing poor sensitivity to chloramphenicol (4%), fluoroquinolones (5%), cephalosporin (18%) and 100% sensitivity to imipenem and meropenem while 98% sensitivity to azithromycin.

Now-a-days azithromycin is also been used injudiciously in every infection especially after emergence of COVID 19. This is an alarming situation for all of us because we have developed multidrug resistance and extensive drug resistance in our country. The mechanism of transformation of the bacteria from MDR to XDR occurs via single step of acquiring a plasmid, conferring its resistance against all first- and second-line antibiotics. It is suggested that this particular H58 clade is responsible for the current outbreak of XDR typhoid. Its XDR variant harbors an IncY plasmid that provides resistance against fluoroquinolone, as well as the CTX-M-15 gene *bla*, which protects the organism against

ceftriaxone.<sup>10</sup> New guidelines should be made in order to deal with this distressing condition and great focus should be made on cautious use of antibiotics. It is need of the hour that we should formulate our guidelines for antibiotic use and avoid the irrational use of antibiotic in every case.

## CONCLUSION

This study showed that isolates of *S. typhi* obtained from children suffering from typhoid fever presenting to the Services Hospital, Lahore had high resistance to fluoroquinolone and third generation cephalosporin. 84% were resistant to ceftriaxone and 94% were resistant to ciprofloxacin in this cohort. Taking into view these figures, we can deduce that presence of extensively drug resistant strains is a major challenge in the management of enteric fever in children in children in Pakistan. Judicious use of antibiotics in children is warranted to prevent the rise in multidrug resistant and extensively drug resistant typhoid.

**Conflict of interest:** Nil

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