

# Antibiotic Resistance Pattern of Salmonella Species in Children in a Tertiary Care Hospital

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## Author's Contribution

<sup>1,2,3,4,5</sup> Conception of study

<sup>1,2,3,4,5</sup> Experimentation/Study conduction

<sup>3,4,5</sup> Analysis/Interpretation/Discussion

<sup>1,4,5</sup> Manuscript Writing

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## Abstract

**Objective:** To determine the recent antibiotic resistance patterns of Salmonella species in children in a tertiary care hospital.

**Materials and Methods:** This descriptive cross-sectional study was conducted in the Department of Pediatrics of Akbar Niazi Teaching Hospital, Bhara Kahu, from 18<sup>th</sup> March 2020 to 31<sup>st</sup> January 2021. A total of one hundred and seventy-eight (n=178) patients of either gender having age between 1 month to 12 years who had signs and symptoms of enteric fever and positive blood culture report of Salmonella species were enrolled in this study through non-probability, consecutive sampling. The demographic characteristics of patients along with the antibiotic sensitivity pattern of the Salmonella species were recorded on the predesigned proforma and analyzed through SPSS version 25.

**Results:** Out of the total of 178 patients, reports of blood cultures of 164(92.1%) patients showed Salmonella Typhi while those of 14(7.9%) patients showed Salmonella Paratyphi. Out of the total of 178 Salmonella cases, 11(6.2%) were extensively drug-resistant and 58(32.6%) were multidrug-resistant. All XDR cases were of Salmonella Typhi. Out of 14 Salmonella Paratyphi, 2(14%) were MDR but no XDR Salmonella Paratyphi was found. Nalidixic acid had the highest resistance (96.4%) followed by sulphamethoxazole (65.5%). Azithromycin had the least resistance (0%) followed by imipenem (1.8%), piperacillin-tazobactam (1.9%), and meropenem (2%). Resistance of ceftriaxone was 20.8% and that of ciprofloxacin was 28.2%.

**Conclusion:** No resistance of Salmonella species against azithromycin was found in our study. The presence of XDR typhoid fever cases and the rising resistance of Salmonella species to ceftriaxone and carbapenems are very alarming. To prevent this resistance, we should reserve carbapenems for complicated cases of resistant typhoid fever only. Minocycline and piperacillin-tazobactam are two other good cost-effective drugs in resistant typhoid fever.

**Keywords:** Typhoid fever, Salmonella, ceftriaxone, meropenem, azithromycin, piperacillin, tazobactam, minocycline.

## Introduction

Typhoid fever is an endemic febrile illness in Pakistan having 2<sup>nd</sup> highest incidence rate in the world after India.<sup>1</sup> In 2017, 14.3 million cases of typhoid fever occurred all over the world resulting in 1,360,000 deaths.<sup>2</sup> In Pakistan its incidence in children is 413 per 100,000 population and 6700 deaths per year.<sup>3</sup> Children are more susceptible to typhoid fever as compared to adults. The 2016 outbreak of extensively drug-resistant (XDR) typhoid fever cases in Hyderabad in Sindh province of Pakistan has caused immense concern in physicians and health authorities all over the world. According to the latest statistics, 10,365 XDR cases of typhoid fever have occurred so far in Hyderabad and Karachi alone.<sup>4</sup> There are few cases of XDR typhoid fever found in the United Kingdom, USA, and Canada in 2017 and 2018. All of them were children having ages from 4 to 12 years and had a history of travel to Pakistan.<sup>5,6</sup> In 2018, the government of Pakistan has done serious efforts to break this chain of transmission of XDR *Salmonella* species by vaccinating 118,000 children with typhoid conjugate vaccine in Hyderabad.<sup>7</sup>

Since then *Salmonella* antibiotic surveillance has increased in Pakistan as well as all over the world and various studies have been published on this topic in recent years. Multidrug-resistant (MDR) *Salmonella* having resistance against 1<sup>st</sup> line drugs (ampicillin, chloramphenicol, and trimethoprim-sulphamethoxazole) is now becoming XDR by acquiring resistance against fluoroquinolones and ceftriaxone as well. As a result, morbidity and mortality of XDR typhoid fever cases have also increased.<sup>8</sup>

Studies done in Jamshoro and Karachi in the paediatric population in the year 2018 demonstrated high resistance against ceftriaxone, fluoroquinolones, ampicillin, and chloramphenicol.<sup>3,9</sup> A retrospective study was done by Saeed et al. at Shifa International Hospital, Islamabad from 2015 to 2018 in both children and adults validated the existence of XDR *S. Typhi* all over Pakistan.<sup>8</sup>

The main reason for increasing *Salmonella* resistance is the lack of availability of blood culture in primary and secondary level government hospitals of Pakistan. Although it is available in private laboratories throughout Pakistan but it is quite expensive. As result physicians have to prescribe antibiotics empirically without experience and knowledge of recent trends of antibiotic susceptibility patterns of *Salmonella* in their population.

As knowledge of physicians is increasing regarding XDR typhoid fever which is still susceptible to azithromycin and carbapenems (imipenem and meropenem), physicians have increased their prescription of azithromycin due to its advantage of availability in oral form as well and its cost-effectiveness which has increased its chances of resistance in future.

Although few studies have been done regarding antibiotic resistance of *Salmonella* in adults in Islamabad and northern Punjab but no such study in children has been done here so far.<sup>10,11</sup> Therefore we carried out this study in children to fill this gap in knowledge. Our research aims to determine the recent antibiotic resistance patterns of *salmonella* species which will enable us to determine the percentage of MDR and XDR typhoid fever cases in our population and will also increase our knowledge of the current resistance of *Salmonella* species to individual antibiotics used for the treatment of typhoid fever in children.

## Materials and Methods

After seeking permission from the research and ethics committee of Akbar Niazi Teaching Hospital, Bhara Kahu, this descriptive cross-sectional study was conducted in the Paediatric department of Akbar Niazi Teaching Hospital, Bhara Kahu from 18<sup>th</sup> March 2020 to 31<sup>st</sup> January 2021. Patients from 1 month to 12 years of age of either gender presenting to OPD or admitted in Pediatric ward or Pediatric ICU with signs and symptoms of typhoid fever and positive blood culture of *Salmonella* species were included in this study. Patients with signs and symptoms of typhoid fever but a negative report of blood culture and patients with other infections were excluded from this study.

Total 178 patients were taken as a sample size by using OpenEpi sample size calculator with the following statistical parameters; 95% confidence level, the anticipated proportion of ampicillin resistance against *Salmonella* species = 87.1% and alpha error = 5%.

Initially, all the patients with signs and symptoms of typhoid fever were recruited through non-probability, consecutive sampling & written informed consent was obtained from parents/guardians before enrollment in the study. A 3 to 5ml of venous blood sample was collected in BACTEC PEDS Plus bottles using aseptic technique and sent to microbiology laboratory of the hospital. Blood subcultures were performed on McConkey agar (Oxoid, Basingstoke, UK) and blood

agar (Oxoid, Basingstoke, UK) for 24 hours at  $35 \pm 2^\circ\text{C}$  as per standard methods. Standard biochemical tests were used for differentiating between members of gram-negative enterobacteriaceae. Serotyping was performed by type-specific antisera. Then antimicrobial susceptibility was performed by the disc diffusion method of Kirby Bauer on Muller Hinton agar according to the latest Clinical & Laboratory Standards Institute guideline which include ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, nalidixic acid, ciprofloxacin, levofloxacin, cefixime, ceftriaxone, piperacillin-tazobactam, meropenem, imipenem, azithromycin and minocycline.<sup>12</sup>

Later on, those patients whose blood culture came out to be negative were excluded from the study. The demographic characteristics of patients i.e. age, gender, and residential address along with antibiotic susceptibility pattern of the Salmonella species were recorded on the predesigned proforma.

The data was then entered and analyzed using SPSS version 25. Mean $\pm$ SD for age was calculated. Frequencies and percentages were calculated for categorical variables such as gender, age groups, place of residence, Salmonella species, and resistance of Salmonella species to antibiotics.

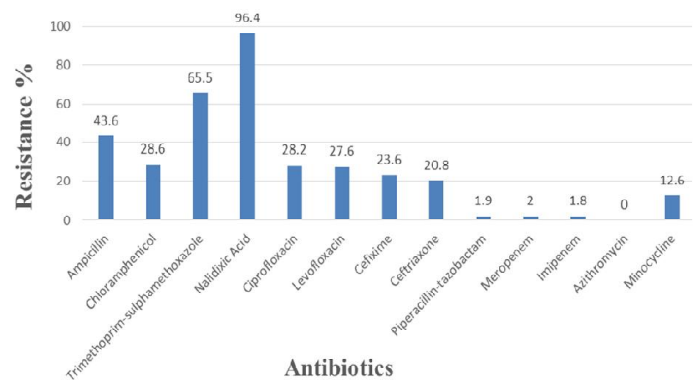
## Results

In our study, a total of 178 patients were enrolled, out of which 124(70%) of the patients were hospitalized and 54 (30%) were treated on an OPD basis. Reports of blood culture showed Salmonella Typhi (*S. Typhi*) in 164(92.1%) patients and Salmonella Paratyphi (*S. Paratyphi*) in 14(7.9%) patients. Out of a total of 178, 11(6.2%) Salmonella species were XDR and 58(32.6%) were of MDR. All XDR cases were of *S. Typhi*. Out of 14 *S. Paratyphi*, 2(14%) were MDR but no XDR *S. Paratyphi* was found. Characteristics of patients are shown in table 1.

The resistance percentage of Salmonella species is shown in figure 1. Nalidixic acid had the highest resistance (96.4%) followed by sulphamethoxazole (65.5%). Azithromycin had the least resistance (zero%) followed by imipenem (1.8%), piperacillin-tazobactam (1.9%), and meropenem (2%). Minocycline, belonging to a tetracycline group is another oral drug showing low resistance (12.6%) which can be used in children having age 8 years or above.

**Table 1: Characteristics of patients (n= 178)**

Characteristics	Mean $\pm$ SD
Age (years)	7.69 $\pm$ 3.518
<b>Variables</b>	<b>n (%)</b>
<b>Gender</b>	
Male	119 (66.9%)
Female	59(33.1%)
<b>Age groups</b>	
$\leq 5$ years	52 (29.2%)
6-10 years	72(40%)
>10 years	54 (30.3%)
<b>Residential Address</b>	
Bhara Kahu	111(62.4%)
Other nearby areas (Islamabad, Murree)	67(37.6%)



**Figure 1: Antibiotic Resistance Percentage of Salmonella Species**

## Discussion

A total of 178 children were enrolled in our study out of which 119(66.9%) were male and 59(33.1%) were female. This is comparable to the results of studies done by Laghari et al.<sup>3</sup>

The highest number of cases of typhoid fever in our study belonged to the age group of 6 to 10 years which is different from the findings of Laghari et al where incidence is higher in pre-school children of age 2 to 5 years.<sup>3</sup>

In our study reports of blood, the culture showed *S. Typhi* in 164(92.1%) patients and *S. Paratyphi* in 14(7.9%) patients which is similar to findings of studies done by Laghari et al. and Patil and Mule.<sup>3,13</sup>

In our study, out of a total of 178 patients, 11(6.2%) were XDR typhoid fever cases and 58(32.6%) were MDR typhoid fever cases. XDR cases (5.01%) of the study done by Saeed et al. in Islamabad in both children and adults are comparable to our study but MDR cases (62.7%) are double than those of our study.<sup>8</sup> XDR and ceftriaxone-resistant typhoid cases

were very negligible (0.01%) before 2016 as shown by a study done on retrospective data from 2012 to 2014 from all over Pakistan.<sup>14</sup>

There is one mortality of XDR typhoid fever case in our study due to enteric meningitis and disseminated intravascular coagulation despite starting meropenem in that 12-year-old female child. In our study, all XDR cases were sensitive to azithromycin and carbapenems. A study done by Aziz et al. on XDR Salmonella cases in Karachi showed 67% cases were resistant to azithromycin and 55.5% are resistant to meropenem which is quite alarming and different from our study.<sup>15</sup>

Our study showed nalidixic acid had the highest resistance (96.4%) followed by sulphamethoxazole (65.5%) which is similar to findings of the study (95.4% resistance against nalidixic acid) done by Ali et al.<sup>10</sup>

Our study shows azithromycin had the least resistance (0%) followed by imipenem (1.8%), piperacillin-tazobactam (1.9%), and meropenem (2%) which is similar to statistics of the study done by Siddiqui et al.<sup>9</sup> Study done by Vala et al. in children in western India found very high (63%) resistance to azithromycin which varied a lot from our study.<sup>16</sup>

The resistance of Salmonella species to cefixime & ceftriaxone is rising nowadays as shown by 23.6% & 20.8% resistant cases respectively in our study. This is of marked concern because they are currently recommended 1<sup>st</sup> line empirical therapies for typhoid fever. It is still quite low from resistance to cefixime (60.9% and 75.2%) and ceftriaxone (65.8% & 76.2%) reported by Laghari et al. and Siddiqui et al. respectively.<sup>3,9</sup> Studies done in 2014 in Pakistan and Bangladesh showed 0% resistance to ceftriaxone and 0 and 1% resistance to cefixime respectively which is quite low from our study done in the year 2020.<sup>10,17</sup> According to our study, cefixime and ceftriaxone which are currently recommended empirical therapies for typhoid fever nowadays are still sensitive enough (23.6% & 20.8% resistance respectively) to be used as 1<sup>st</sup> line empirical therapy in typhoid fever in our population. This is quite different from a study done in Karachi by Hiba et al.<sup>9</sup>

In our study ciprofloxacin, which was used as 1<sup>st</sup> line empirical drug in the treatment of typhoid fever before ceftriaxone showed 28.2% resistance which is quite low than its resistance (50% and 100%) reported by Laghari et al and Siddiqui et al. in their studies.<sup>3,9</sup> Study done in children in western India and Bangladesh found 5% and 2% resistance to ciprofloxacin respectively which are far lower than that of our study.<sup>16,17</sup>

In our study resistance of chloramphenicol is 28.6% which is almost similar to the resistance of 3<sup>rd</sup> generation cephalosporins and ciprofloxacin as mentioned above. This is higher than its resistance reported by Patil and Mule (5.6%) in India but lower than its resistance reported by Siddiqui et al (89.1%) in Karachi.<sup>13,9</sup>

Two unique things of our study are that we include the susceptibility of piperacillin-tazobactam and minocycline in our study which shows resistance in 1.9% and 12.6% cases of typhoid fever respectively. Findings of antibiotic susceptibility of Salmonella species against these two antibiotics are not present in any other study that we come across during our literature review. Both these drugs are included in the latest Clinical & Laboratory Standards Institute guideline.<sup>12</sup> The resistance of piperacillin-tazobactam is almost equal to the resistance of Salmonella species to carbapenems. Piperacillin-tazobactam is a relatively cheap drug as compare to carbapenems which can decrease the overall cost of treatment of resistant complicated cases. Minocycline is available in oral form and licensed for use in children of 8 years and above. Its resistance is quite low as compare to other orally available drugs (ampicillin, trimethoprim-sulphamethoxazole, ciprofloxacin, levofloxacin, and cefixime) used for the treatment of typhoid fever except for azithromycin.

## Conclusion

No resistance of Salmonella species against azithromycin was found in our study. The presence of XDR typhoid fever cases and the rising resistance of Salmonella species to ceftriaxone and carbapenems are very alarming. To prevent this resistance, we should reserve carbapenems for complicated cases of resistant typhoid fever only. Minocycline and piperacillin-tazobactam are two other good cost-effective drugs in resistant typhoid fever.

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