



Acute rise in Multiple Drug Resistance Typhoid fever in Children in Rural Sindh: an Alarming Situation

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Abstract: Objective: Evaluation of the frequency of antimicrobial drug resistance in *Salmonella typhi* among children of rural Sindh.

Study Design: Cross sectional / observational study

Place and Duration: At Department of Pediatric medicine Civil Hospital Mirpurkhas, Sindh from January 2019 to July 2019

Methodology: With approval of ethical committee and informed consent from parents/attendant blood samples (5ml) of 55 children with age between 0 to 15 years are obtained at outpatient department (OPD) or admitted in the ward with suspected enteric fever. The blood samples were used to obtain bacterial culture and antibiotic sensitivity was performed at diagnostic and research laboratory (DRC) of Liaquat University of Medical and Health Sciences (LUMHS). Blood culture and Antibiotic Susceptibility testing was performed according to standard protocol of Clinical Laboratory Standard Institute (CLSI) guidelines.

Results: Among study population (n=55), 32 (58.2%) were in age group 0 to 5 years, 20 (36.4%) in age group of 6 to 10 years while only 3 (5.5%) were in the age group of 11 to 15 years. While regarding gender, 29 (52.7%) were male while 26 (36.4%) were females. *S. typhi* exhibited high resistance against ampicillin (93% n=51) and cotrimazole-trimethoprim (91% n=50). About 82% (n=46) of culture was observed resistant to ciprofloxacin, whereas 84% (n=46) showed resistance to ceftriaxone, 84% (n=46) were resistant to cefixime. Out of these 55, 45 (82%) showed antimicrobial sensitivity to meropenem, 34 (62%) to azithromycin, 10 (18%) to ciprofloxacin, 09 (16%) to cefixime and ceftriaxone each, while only 05 patients showed sensitivity to (9%) to cotrimazole-trimethoprim and 04 (7%) to Amoxicillin/clavulanic acid.

Conclusion: Multiple drug resistance in *S. typhi* is high alert situation in our setup and needs prompt initiatives to combat.

Keywords: Antibiotic resistance, Children, *Salmonella typhi*, Typhoid fever

1. INTRODUCTION

Enteric fever (typhoid fever) is a common bacterial infection caused by *Salmonella enterica* serovar *typhi*. A similar less severe disease is caused by *Salmonella paratyphi* A. The route of transmission of this gram-negative rod is from person to person by direct contact through saliva, oral-fecal route and indirect contact by using contaminated eating utensils. Clinical manifestation of typhoid fever comprises mild illness with low grade fever, malaise, dry cough and abdominal discomfort to multiple life threatening complications. About 5-15% infected people become life-long carriers for this bacteria (WHO, 2003).

Typically Pakistan is located in South Asia which ranks third in incidence with 110 cases/100,000. About seven million people affected and 75,000 deaths/year from typhoid were reported from this area. The natives of two thickly populated provinces of Pakistan i.e. Sindh and Punjab are at highest risk of developing typhoid among sixteen countries in Asia where typhoid is persistent despite of advancement in preventive measures (Ochiai *et al.*, 2008). Therefore it is the major issue of health concern worldwide. Still these statistics are belittled because of scarce population-based surveillance systems and reliable diagnostic methods. But multiple hospital-based studies from different parts of country have showing rising incidence of typhoid fever (Qamar *et al.*, 2018; Rasheed, *et al.*, 2019).

Globally, since last two decades an increasing trend of typhoid fever cases is assumed because of antimicrobial resistant (AMR), multi-drug resistant (MDR) and extensive drug resistant (XDR) strains of *Salmonella enterica* serovar *Typhidue* to irrational use of antibiotics. XDR strains are even resistant to fluoroquinolones and third generation cephalosporins along with first line drugs against *S. typhi*. Mostly patient belonging to poor strata attending OPD at Government Hospitals who already compromising health with poor sanitation and hygiene moreover poverty render them unable to approach appropriate or quality healthcare. In this scenario the attending pediatricians with choice of few and high cost antibiotics is facing highly challenging situation. Therefore this study was conducted to assess the frequency of antimicrobial drug resistance typhoid fever among children of rural Sindh (Hussain *et al.*, 2019; WHO, 2003).

2. MATERIAL AND METHODS

This Cross sectional/ observational study was conducted in Department of Pediatric medicine at Civil Hospital Mirpurkhas Sindh from January 2019 to July 2019 after approval from ethical committee of Hospital. Mirpurkhas is the fourth biggest city of Sindh province and covers the population of about 233,916. The Civil Hospital Mirpurkhas is a tertiary care Hospital which covers patients from the city itself as well as from

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nearby small towns and villages (pakinformation, 2017). Five milliliter (5 ml) blood samples are taken after taking an informed consent from parents/attendant of 55 children with age between 0 to 15 years, examined at outpatient department (OPD) or admitted in the ward with, suspected enteric fever. The samples were subjected to blood culture and drug sensitivity at diagnostic and research laboratory (DRC) of Liaquat University of Medical and Health Sciences (LUMHS). DRC laboratory Mirpurkhas is a part of LUMHS which is biggest tertiary care Hospital in Sindh Province. All reports are from one laboratory prevent the difference of interpretation. The identification of *S. typhi* in Blood culture and Antibiotic Susceptibility testing was performed according to standard protocol of Clinical Laboratory Standard Institute (CLSI) guidelines as described previously (CLSI-M100, 2015; Mehveen Iqbal, Jan–Feb 2019). The following antibiotics disc potencies are used in susceptibility test: Ampicillin (10µg), Cotrimazole-trimethoprim, Ciprofloxacin (5µg), Ceftriaxone (30µg), Cefixime (5µg). Meropenem, Azithromycin

Data Analysis:

Results were tabularized and analysis was done with SPSS 20. Frequencies of data variables and percentages are calculated for variables like age, gender, number of resistant and sensitive drugs and symptoms.

3. RESULTS

Among study population (n=55), 32 (58.2%) were in age group 0 to 5 years, 20 (36.4%) in age group of 6 to 10 years while only 3 (5.5%) were in between the age of 11 to 15 years. Regarding gender 29 (52.7%) were male and 26 (47.27%) were females (Table 1 and Fig.1)

Table 1: Age distribution in study population (n=55)

Age in years	frequency	percentage
0-5	32	58%
6-10	20	36%
11-15	03	06%

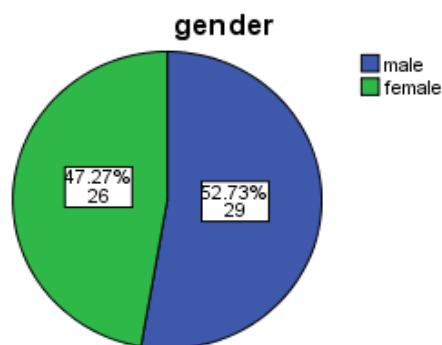


Fig.1: Gender based distribution of typhoid fever among study population (n=55)

S. typhi exhibited high resistance against ampicillin (93% n=51) and cotrimazole-trimethoprim (91% n= 50). About 82% (n=46) of *S.typhi* were observed to be resistant to ciprofloxacin whereas 84% (n=46) showed resistance to ceftriaxone, 84% (n=46) were resistant to cefixime (Table 2).

Table 2: Antibiotic resistance profile of *S.typhi* (n=55)

Drug Resistant	Frequency	Percentage
Ampicillin	51	93%
cotrimazole-trimethoprim	50	91%
Ciprofloxacin	46	83%
Ceftriaxone	46	83%
cefixime.	47	85%

Out of these 55, 45 (82%) showed sensitive to meropenem, 34 (62%) to azithromycin, 10 (18%) to ciprofloxacin, 09 (16%) to cefixime and ceftriaxone each, while only 04 (7%) to Amoxicillin/clavulanic acid and 05 patients (09%) showed sensitivity to cotrimazole-trimethoprim.

Table 3: Drugs sensitivity to *S. typhi* (n=55)

Drug sensitivity	Frequency	Percentage
Meropenem	45	82%
Azithromycin	34	62%
Ampicillin	04	7%
cotrimazole-trimethoprim	05	9%
Ciprofloxacin	10	18%
Ceftriaxone	09	16%
Cefixime	09	16%

Fever was the most common symptom observed in every patient, regarding duration of fever 21 (39%) > 05 days, 13 (23%) > 10 days, 16 (29%) > 15 days, 03 (5%) > 20 days, 02 (4%) > 25 days. All patients under study complaint for loss of appetite and some occasional abdominal cramp.

4. DISCUSSION

Multidrug resistance in *Salmonella* is defined as resistance to the first-line recommended drugs for their treatment, that include ampicillin, chloramphenicol, and cotrimoxazole (Rowe, et al., 1997). Multi-Drug Resistant (MDR) Typhoid Fever is a global alarming situation, emerged with outbreaks in numerous developing countries including Pakistan. The irrational and inappropriate use of antibiotic, quality compromised antimicrobial drugs combined with non-fulfillment of therapy course by the patients due to high cost of antimicrobials enhances the hazard of resistance. Unnecessary prescription of antibiotics for minor infections due to wish of parents for quick recovery,

inadequate knowledge of physicians in suggesting antibiotics during the treatment of typhoid fever, which may predispose resistant strains (Sharma, and Kapoor, 2005; WHO, 2003).

Among study population (n=55), 32 (58.2%) were in age group of 0 to 5 years, 20(36.4%) in 6 to 10 years while only 3(5.5%) were 11 to 15 years old. In this study frequency of typhoid fever was observed more in children of 0-5 years same age group is observed by Mahveen Iqbal and Hassan (Hasan *et al.*, 2008; Mehveen Iqbal, Jan – Feb 2019).

While regarding gender 29(52.7%) were male and 26(36.4%) were females study conducted by Sana Aziz and Ayesha had also revealed male children (61%) more affected than females (38%) and 58% male and 42% females respectively (Aziz and Malik, 2018; Saqib and Ahmed, 2000).

S. typhi exhibited high resistance against ampicillin (93% n=51) and cotrimazole-trimethoprim (91% n= 50). About 82% (n=46) of *S. typhi* was observed resistant to ciprofloxacin whereas 84% (n=46) showed resistance to ceftriaxone, 84% (n=46) were resistant to cefixime in this study. Other studies also show that *S. typhi* is resistant to first-line antibiotics including ampicillin, chloramphenicol, cotrimoxazole and ceftriaxone but meropenem and azithromycin are observed to inhibit its growth (Klemm *et al.*, 2018).

Drug sensitivity in out of 55, meropenem sensitivity is observed in 82%(45), 62% (34) to azithromycin, 18% (10) to ciprofloxacin, 16% (09) to cefixime and ceftriaxone each, while only 7% (04) to Augmentin and 9% (05) showed sensitive to cotrimazole-trimethoprim. While study conducted by Farah Naz found antibiotic resistance in about 50% *Salmonella* isolates against chloramphenicol, ampicillin and cotrimoxazole. Higher resistance against ciprofloxacin (93%) is observed. Their antibiotics sensitivity results shows: 44.52% sensitive to meropenem, 32.8% to azithromycin, 9.4% to fosfomycin, 8.02% to Amoxicillin/clavulanic acid and 3.64% to ceftriaxone (Butt, *et al.*, 2003; Qamar *et al.*, 2018).

Hence more or less similar resistance to first line drugs observed in different regions of Pakistan by various groups. Such dreadful situation is however first time noticed in our setup and need prompt effort from prevention by improving awareness and hygiene to proper prescription of antimicrobials for management.

5. CONCLUSION

Cell wall synthesis inhibitor Carbapenem (e.g. Meropenem) and protein synthesis inhibitor Azithromycin are still important antibiotics for the treatment of typhoid fever. Antibiotic resistance in pathogenic bacteria has become an important issue worldwide especially in underprivileged nations like Pakistan, where health emergency is needed to fight against MDR pathogenic bacteria.

We should drive and support vaccination campaigns for eradication of diseases instead of blindfold use of antibiotics and follow good hygiene practices. That helps in the decrease of morbidity and mortality associated with emergence of antibiotic resistance. Awareness among the society predominantly to children regarding cleanliness and use of safe drinking water and hygienic food, by various methods at their schools and community centers will be beneficial.

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