Original Article

Emerging Trends of Resistance of Typhoid Fever in Paediatric Population: A Hospital Based Study

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ABSTRACT

OBJECTIVE: To evaluate the current trends of typhoid fever resistance in the local community.
METHODOLOGY: This descriptive cross-sectional study, conducted at UMDC/ Creek General Hospital from February to August 2019. Patients of Korangi and Landhi included. A total of 68 patients included, diagnosed clinically and positive blood cultures. The data was analyzed on SPSS 20.0.
RESULTS: The average age of patients in this study was 5.16±3.449 years and weight of about 15.88±7.77 Kg. M:F ratio was approximately 1:1. Outpatient admissions were 49(72.1%) and emergency admissions were 19 (27.9%). The duration of symptoms was about 10.91±5.092 days. Out of these 68 patients, 57 (83.8%) had a history of medication for the same disease. The most common co-morbid was un-boiled water intake (66%), followed by malaria (12%). The most common clinical presentations were persistent fever (100%), anorexia (83.8%) and abdominal pain (80.9%). Blood culture and sensitivity showed that MDR/XDR is present in 60 (88.2%) patients. Sensitivity to first-line drugs was found in 1/10th of the study population while sensitivity to Meropenem and Azithromycin was approximately 90%. The complication occurred only in 2 patients (2.9%). Almost all patients recovered and there is no recurrence of symptoms in any of the patients following treatment with fever clearance time of 5.26±1.32 days only.
CONCLUSION: This study revealed extensive drug resistance strains of Salmonella typhi in the studied population. This study reported increased use of unhealthy drinking water intake and prior medication which is one of the causes of this emerging resistance.

KEY WORDS: Typhoid fever, Enteric Fever, Resistance, Multidrug resistance (MDR), Extensive drug resistance (XDR)

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INTRODUCTION

Typhoid fever is one of the most common clinical presentations in out-patient clinics of General Practitioners and Pediatricians. Salmonella Typhi is the most common cause of typhoid fever and is responsible annually for almost over eleven million cases and about 129000 deaths globally[1]. This gram-negative bacterium transfers via the fecal-oral route, hence it is common in areas where there is no proper sanitation and provision of clean water[2]. Over two years (2016-2018), the Pakistan Health Authorities reported about 5,274 cases of the outbreak of multidrug resistance (MDR) and few extensive drug resistant (XDR) strains of typhoid fever in the province of Sindh only out of total 8,188 documented cases[3]. More than 80% of these extended drug resistances (XDR) were documented in the Sindh province only and affecting children under 15 years of age and surprisingly 18 % of which were under 2 years. A Study on the typhoid fever outbreak spread in Pakistan has documented about one-third of Typhi isolates in Karachi are ceftriaxone and quinolone-resistant have been reported[4,5]. Pakistan is developing economically and widely available antibiotics that are over the counter taken by people (without a prescription), resulting in a high incidence of developing a resistant strain of these microorganisms. Over the counter medication (antibiotics) practiced for the treatment of fever without precise diagnosis has altered the clinical presentation of typhoid fever. Currently, Progressive and persistent fever, associated with chills, anorexia, loose stools, abdominal pain, hepatosplenomegaly, and toxicity are not typically presentations. Complications, such as intestinal perforation, peritonitis are uncommon but reported within 3 weeks of clinical manifestation whereas encephalopathy, intestinal hemorrhage, and hepatosplenomegaly are the most common late complications[6,7].

Ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol were used primarily for the treatment and labeled as first-line treatment options. Resistance against these antibiotics is considered as multidrug resistance (MDR). Fluoroquinolones have been used preferably in regions with MDR infection so its resistance and sporadically resistant to ceftriaxone or azithromycin is also recently been reported[8]. The

quinolones (ciprofloxacin) have been successfully used in the treatment of typhoid fever in adults as well as in children. However, increased resistance against it has been documented in Pakistan.[4] With the advent of MDR strains of Salmonella Typhi, resistance against ciprofloxacin is on the surge.[9] The Emergence of this MDR/ XDR typhoid fever in the pediatric population resulted in severe clinical illness including toxicity, hepatomegaly, hypotensive shock, and even death.

Though, many studies have been done to indicate the prevalence of multidrug-resistant typhoid fever in Pakistan. Studies had been done to evaluate prevalence of the disease burden and prevalence of MDR typhoid in Karachi[5,11,14,20], however none has focused on Korangi/ Landhi area which has approximately 1,625,225 population (census 2017). In our study, we try to find out the trend present in our local community of Korangi/Landhi as to suspect earlier and treat accordingly to prevent its disastrous outcomes.

METHODOLOGY

This research was a descriptive, cross sectional study conducted at United Medical and Dental College/ Creek General Hospital Korangi Karachi from February to August 2019 after Institutional Ethics Committee approval. This study focuses population of Korangi/Landhi presented in outpatient department or emergency department of a tertiary care and teaching hospital, informed consent from each parent/caregiver was taken. After analyzing the eligibility criteria, and obtaining an informed consent from parents/ care givers, a total 68 patients were included in this study using a non-probability consecutive sampling technique. The patients presented in the emergency department/ out-patient department, diagnosed clinically as well as with positive blood culture for salmonella typhi/ Para-typhi. Whereas, those who refused to consent, had evidence of other complicated or progressive diseases, and residing besides Korangi/ Landhi were excluded.

The subsidence of symptoms following antibiotic therapy and without relapse of symptoms within four weeks of follow-up is acknowledged as cured. Fever clearance time, adverse drug reaction, the recurrence of symptoms, and cure rate were considered along with signs and symptoms at every weekly follow-up visit (4 weeks).

Data analysis was done using SPSS version 20. Mean ± Standard deviation were calculated for quantitative variable while frequency and percentages for qualitative variables. Stratification was done for age, gender, culture & sensitivity, and presence/ absence of resistance. A post-stratification chi-square test was applied. P-value $\leq$0.05 will be considered statistically significant.

RESULTS

In this study, about 68 patients were enrolled meeting the inclusion criteria with an average age of 5.16±3.449 years and an average weight of about 15.88±7.77 Kg. The male to female ratio was approximately 1:1. About two-thirds of these patients are admitted through outpatient department 49 (72.1%) and one third through accident and emergency department about 19 (27.9%). The duration of symptoms at the time of presentation was about 10.91±5.092 days. Out of these 68 patients, 57 (83.8%) patients have a history of medication for the same disease. Table I. The most common co-morbid in our study was un-boiled water intake (66%) followed by malaria (12%) as shown in Figure I.

The most common clinical presentation is our patients were persistent fever (100%), anorexia (83.8%) and abdominal pain (80.9%). The frequency of other associated sign and symptoms is shown in Figure II.

Blood culture and sensitivity showed that multidrug/ extensive drug resistance is present in 60 (88.2%) patients out of 68 patients. Sensitivity to first-line drugs is found in 1/10th of the study population while sensitivity to Meropenem and Azithromycin was approximately 90% as shown in Table II.

The complication rate was very low affecting only 2 patients (2.9%). Almost all patients recovered and there is no recurrence of symptoms in any of the patients following treatment with fever clearance time of 5.26±1.32 days only.

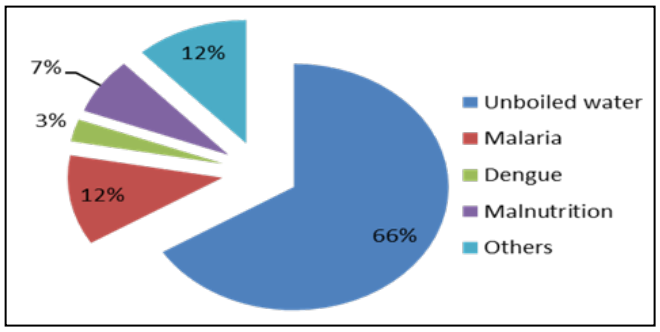
TABLE I: DESCRIPTIVE ANALYSIS OF DEMOGRAPHIC, AND CLINICAL CHARACTERISTICS OF MDR DIAGNOSED PATIENTS

Variables (n= 68)		Mean±SD/Frequency
Age (years)		5.16±3.449
Weight (kg)		15.88±7.77
Duration of symptoms (days)		10.91±5.092
Hx of Medication	Yes	57 (83.8%)
	No	11 (16.2%)
Mode of Admission	OPD	49 (72.1%)
	Emergency	19 (27.9%)
Gender	Male	31 (45.6%)
	Female	37 (54.4%)

DISCUSSION

Typhoid fever has been inflicting the world since so long and over the counter medication without proper diagnosis and use of broad-spectrum antibiotics in adult as well as pediatric population renders to develop resistance. In late twenty centuries, strains of Salmonella Typhi, resistant to 1st line of drug therapy

FIGURE I:
COMORBID ASSOCIATED WITH MDR TYPHOID



has been reported in endemic areas including Pakistan[4,10,11].

In this study, we found prior medication from quacks and over the counter medication purchased by parents to treat fever due to the prevalence of poor health-seeking behavior in more than 80% of the patient which has been documented in all regions of the world except Europe and Central Asia[11]. This study and other studies[4,12] indicate that children under 5 years are the most common sufferers of typhoid fever. The weight and sexual orientation of the study population do not correlate with disease severity and its associated complications. Typhoid fever typically

FIGURE II: CLINICAL PRESENTATION OF DIAGNOSED PATIENTS

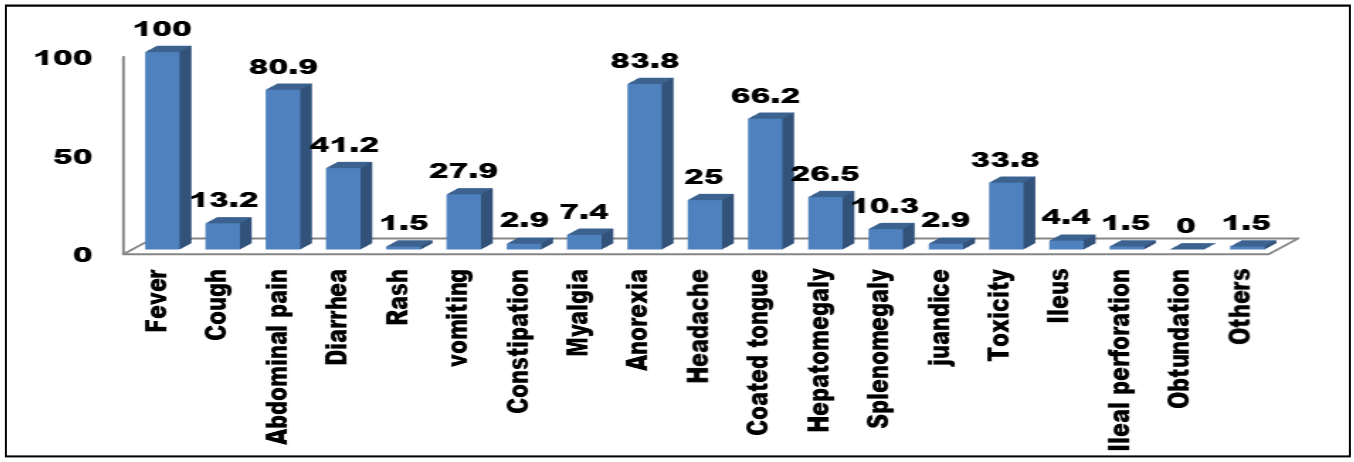


TABLE II: STRATIFICATION OF DATA WITH RESPECT TO RESISTANCE, CULTURE AND SENSITIVITY

Variables (n= 68)	Mean ± SD/ Frequency		P-value
MDR/XDR	Yes	60 (88.2%)	
	No	8 (11.8%)	
C/S Sensitivity	Meropenum, Azithro-mycin	60 (88.2%)	
	Amikacin, Gentamy-cin, Meropenum, Azithromycin	6 (8.8%)	
	Ceftriaxone, Meropenaum, Azithromycin	2 (2.9%)	<0.001*
Complica-tions	Yes	2 (2.9%)	
	No	66 (97.1%)	
Cured patient		68(100%)	
Recurrence of symptoms	No	68 (100%)	
Fever clear-ance time		5.26±1.323	

**MDR= multi drug resistance, *XDR= extensive drug resistance*

clears out typically in 7 days (3-12 days) with use of appropriate susceptible antibiotic[13,14].

Salmonella Typhi has feco-oral transmission, and incidence can be reduced by using preventive measures to reduce the spread. Our study has reported the highest numbers of patients (60%) were consuming unboiled/unfiltered water which may contribute to the resistance. Contamination of water and non-adherence to hygienic practices are risk factors in Pakistan. Some local brands of drinking mineral water have been reported to be contaminated[15].

Outcomes such as relapse and mortality were not reported in all studies including this study, leading to an incomplete representation. Although no mortality is seen in our study but previously mortality with Multidrug-resistant typhoid fever epidemics is reported about 7-16% which was eight times higher than with non-resistant typhoid fever[16].

In our study and previous blood culture studies in Sindh reported strains of salmonella typhi, sensitive to azithromycin and carbapenems (Meropenem)[17]. Azithromycin is the antibiotic of choice for non-complicated cases and well documented as effective comparable to quinolones[17,18]. Meropenem is reserved for severe disease[17,19].

Several pieces of research were undertaken and over

long periods to identify the clinical patterns and antibiotic susceptibility in different areas of metropolitan cities of Pakistan including Karachi. Our study focused on a particular community (Korangi/ Landhi) as the trend of antibiotic sensitivity has changed dramatically in the studied population. This study reflects a rough number of resistances of typhoid cases as most of patients are not presented in hospital and GPs and other health care provider would treat them empirically. The emergence of the new extended drug-resistant strain is shocking and need abrupt intervention to prevent its disastrous outcomes as sensitivity is limited to some moderately tolerable drugs such as azithromycin. Besides, the use of vast-spectrum antibiotics such as Meropenem may lead to incurable strains resulting in severe complications or epidemics. An effort has been underway to limit over the counter usage of Azithromycin as well as public awareness of vaccination against typhoid fever, especially in the pediatric population.

CONCLUSION

This study found emerging extensive drug resistance strains of salmonella typhi in the studied population. Although not significant complication rate is seen, however, its correlation with unhealthy drinking water and prior medication has raised concern about its future implication and complication which can be managed with adequate early preventive (vaccination), diagnostic and therapeutic approach.

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AUTHOR CONTRIBUTIONS

Hanif S: Idea conceived
Bai S: Data Analysis
Ur-rehman E: Data collection
Memon MH: Data collection
Ashfaq M: manuscript writing
Rajesh: Supervision of study

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