JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Clinical Perspectives of Multiple and Extensively Drug-Resistant Typhoid; result from a tertiary care hospital from Pakistan

Samina Fida[1], Hala Mansoor[1], Saba Saif[1], Javed Iqbal[1], Arif Qayyum Khan[1]

[1] *Department of Medicine, Combined Military Hospital Lahore Medical College, Lahore, Pakistan*

Abstract

Introduction: Typhoid fever remains a problem in developing countries, including Pakistan. The emergence of multidrug-resistant and, since 2016, of extensively drug-resistant cases is a continuous challenge for health care workers. The COVID-19 pandemic is making management more difficult.

Methodology: In the present study, a total of 52 confirmed cases of typhoid have been studied during 2019. Detailed clinical features, complications and, lab findings were studied. Typhoid culture and sensitivity were recorded and patients were treated accordingly. Patients were asked about risk factors to aim at informing prevention.

Results: Out of the 52 having blood culture positive for *Salmonella* Typhi 47 (90.4%) and *Salmonella* Paratyphi 5 (9.6%), 4 (7.7%) were sensitive to first-line (Non-resistant), 11 (21.2%) MDR and 37 (71.2%) patient were XDR. One case was resistant to azithromycin. Nausea, vomiting or, abdominal pain was present in 12 (23%), abdominal distension present in 9 (17.3%), abdominal tenderness in 8 (15.4%), hepatomegaly in 10 (19.2%) and, splenomegaly in 22 (42.3%).There were ultrasound abnormalities in 58% of patients and GI complications in 19% of patients. No significant difference was found in clinical findings and complications between resistant and non–resistant cases. Only 23-27% of patients were aware of typhoid prevention and vaccination measures.

Conclusions: The increasing prevalence of resistance and higher degree of complications seen in typhoid fever raises the concern further about prevention and effective infection management in the community as well as clinical settings. Moreover, judicial use of antibiotics is much needed in developing countries like Pakistan.

Key words: Extensively drug-resistant typhoid; XDR typhoid; Multidrug-resistant typhoid; MDR typhoid; *Salmonella* Typhi; *Salmonella* Paratyphi.

J Infect Dev Ctries 2021; 15(4):530-537. doi:10.3855/jidc.13539

(Received 24 July 2020 – Accepted 17 November 2020)

Introduction

Typhoid fever is caused by the gram-negative bacterium, *Salmonella* Typhi and less commonly by *Salmonella* Paratyphi. Although the global burden of disease has decreased from 25.9 million in the 1990s to 14.3 million cases in 2017, typhoid fever continues to be a major health problem for developing countries, with about 250,000 deaths annually [1]. Since 2016, an outbreak that started from Sindh, Pakistan of an extensively drug-resistant strain, has spread to other parts of the country like Punjab and so far, 5,200 extensively drug resistant cases have been reported [2]. This strain remains resistant to the standard first-line and second-line agents used for the treatment of enteric fever, including fluoroquinolones, and is only sensitive to macrolides and carbapenems [3,4]. The same strain of bacteria has been isolated from travelers in the United Kingdom and the United States, returning from Pakistan. Centers for Disease Control and Prevention (CDC) has issued a warning to travelers to Pakistan to take extra precautions [5]. The higher burden of disease in lower income countries is associated with poor sanitation, less food hygiene and poor vaccination whereas providing good sanitation and vaccination has decreased cases in the developed world over the number of years [6]. A similar situation exists in India where controlling typhoid fever, the emergence of resistance and maintaining hygiene and vaccination is still a big challenge [7]. A recent study from Jinnah hospital Lahore Pakistan has reported all 27 Extensively Drug-Resistant (XDR) *S.* Typhi cases resistant to amoxicillin, co-trimoxazole, chloramphenicol, ciprofloxacin, and ceftriaxone [8].

Classically typhoid fever is associated with prolonged fever with a step ladder pattern, gastrointestinal symptoms (like nausea, vomiting, diarrhea, or constipation), headache, fatigue, malaise, loss of appetite, and cough. Fatal complications such as

intestinal perforations, gastrointestinal hemorrhages, encephalitis, and cranial neuritis may occur [9]. The main reservoir of infection is humans and the organism lives in the gut and is mostly excreted in feces and spreads to others via a fecal-oral route. It is also excreted through urine but in a negligible amount. Resistant strains are an emerging problem with Multi Drug-resistant (MDR) cases and decreased susceptibility to ciprofloxacin reported in Middle East and Asia in 2014 and after that resistance to ceftriaxone brought the challenge of extensively drug resistant typhoid [10,11]. In this paper we follow the resistance pattern are defined according to the WHO definitions, which are as follows [3]:

- Non-resistant typhoid fever: Typhoid fever caused by *Salmonella* Typhi and/or Paratyphi which are sensitive to first line drugs and third generation cephalosporins, with or without resistance to second line agents.
- Multidrug-resistant typhoid: defined as resistant to three first line drugs used to treat typhoid – chloramphenicol, ampicillin and co-trimoxazole, with or without resistance to second line agents.
- Extensively drug-resistant typhoid: defined as resistant to first- and second-line agents as well as third generation cephalosporins.

Infection caused by the MDR and XDR strains has been documented to be associated with more severe illness and higher rates of complication and death and with a higher rate of prolonged asymptomatic carrier status [12].

The goals of this study were to determine the prevalence of drug resistance in Salmonella Typhi, to identify demographic and clinical features and complications associated with typhoid fever and to identify clinical clues that might help in early diagnosis, and to look for the patterns of disease and complications in all resistant cases. We also aimed at improving knowledge of causative factors and so to inform prevention strategies.

Methodology

Study Design

The study was a cross sectional observational study of 52 patients which was conducted in Division of Medicine, Combined Military Hospital (CMH) Lahore, from April 2019 to October 2019, after approval from Institutional Review Board (IRB), CMH, Lahore (reference no 246/FRC CMHLMC). A total of 52 patients were selected from the outpatient department after calculating the sample size using 95 % confidence level, 10 % margin of error and taking frequency of typhoid as 30% (14-59%). CMH is a tertiary care hospital that receives patients from all region of Lahore and the surrounding area and also referred patients from other hospitals.

All patients with culture positive *Salmonella* Typhi and Paratyphi infection were included in the study.

All Patient with negative blood cultures, who refused to give consent and patients below 14 years of age were excluded from the study.

Data Collection

After approval of the synopsis from the ethical committee, written informed consent was taken from each patient for participation in the study, and confidentiality was maintained. Their demographic profiles (i.e. age, sex, occupation) were also noted using a structured questionnaire.

Clinical examination was performed and laboratory parameters were recorded. Patients were observed for any complications during admission time, culture and resistance patterns were observed. Patients were treated with antibiotics according to the culture and sensitivity results. Daily progress was recorded and a detailed Proforma was completed.

Statistical Analysis

Data was analyzed using SPSS-20. Quantitative variables like age, duration of fever, and laboratory test results were presented as means with standard deviation. Qualitative variables like age, gender, clinical findings, complications, antibiotic sensitivity, and resistance were presented as frequency and percentages. Cross-tabulation of clinical and laboratory findings was made with drug resistance patterns. Chi-square was used to compare the incidence of complications between drug-sensitive, multi-drug-resistant, and extensively drug-resistant strains of *Salmonella* Typhi and Paratyphi. Value of $p \leq 0.05$ was considered significant.

Results

Out of the total of 52 patients having blood culture positive for *Salmonella* Typhi 47 (90.4%) and *Salmonella* Paratyphi 5 (9.6%), 40 (76.9%) were males and 12 (23.1%) were females. The mean age was 31 ± 9 with 29 (55.8%) in young age, 23 (44.2%) in middle age. Weight was 67 kg ± 8 and height 5.7 ± 0.27. The mean duration of fever was 13.5 ± 6.6 days and response in days to antibiotic was 4.6 ± 1.0 days. Out of 52, 35 (67%) patients had high grade fever i.e. ≥ 104 °F whereas 17 (32.7%) had fever < 104 °F. 18 patients

(30.8%) were toxemic. Only 2 patients (3.8%) had a co-morbidity with one having diabetes mellitus and the other was hypertensive. 12 patients (23%) had used routine medical issue antibiotics in the last two months whereas 40 (76.9%) had not used any antibiotic in the last two months. Nausea, vomiting, or abdominal pain was present in 12 (23%), abdominal distension was present in 9 (17.3%), abdominal tenderness in 8 (15.4%), hepatomegaly in 10 (19.2%) in splenomegaly in 22 (42.3%). Blood culture and sensitivity showed maximum cases of extended drug-resistance with 4 (7.7%) patients sensitive to first-line drugs (non-resistant cases), 11 (21.2%) MDR and XDR in 37 (71.2%) patients. (Table 1)

Table 2 and Figure 1 show individual antibiotic resistance patterns. Ampicillin sensitive cases were 7 (13.5%) and resistant cases were 45 (86.5%), ciprofloxacin sensitive cases were only 3 (5.8%) and resistance was seen in 48 (94.25) cases, chloramphenicol sensitivity was seen in 4 (7.7%) patients and resistance in 48 (92.3%) patients. Cotrimoxazole sensitivity was in 4 (7.7%) and resistance in 48 (92.5%) patients. Ceftriaxone sensitivity was in 14 (26.9%) patients and resistance in 38 (73.1%) patients. Azithromycin resistance was reported in one patient which later one was reconfirmed by minimal inhibitory concentration (MIC) (level 64). All cases were sensitive to meropenem.

Patients were treated according to antibiotic sensitivity for 14 days and observed for complications.

In laboratory investigations, mean hemoglobin level was 12.8 ± 1.9, total leukocyte count (TLC) 4.4 ± 1.1. In liver function tests, mean bilirubin level was 19.8 ± 23.7 micromole/L. Mean alanine transaminase (ALT) was 65 ± 57, 3 IU/L, aspartate transaminase (AST) 73.8 ± 67.7 IU/L, alkaline phosphatase was 201 ± 145.6, gamma-glutamyltransferase (GGT) 88 ± 50.6 and, albumin was 3.7 ± 0.57. In renal function tests (RFTs), urea was 6.6 with SD ± 4.9 and creatinine 91.2 ± 23 micromole/L. During admission patients were followed for complications and it was observed that gastrointestinal (GI) complications were the most common ones including hepatitis in 12 (23.1%), peritonitis in 6 (11.5%) and cholecystitis 1 (1.9%) of patients. One (1.9%) patient developed pleural effusion and 1 (1.9%) developed pneumonia, 5 (9.6%) patients had acute kidney injury (AKI) and 1 (1.9%) had hypernatremia (sodium > 145 meq/L). Two (3.8%) patients developed shock, 2 showed bone marrow suppression and one had arthritis (1.9%). No complications developed in rest of the patients (Table 3).

Figure 1. Antibiotic sensitivity and resistance in typhoid.

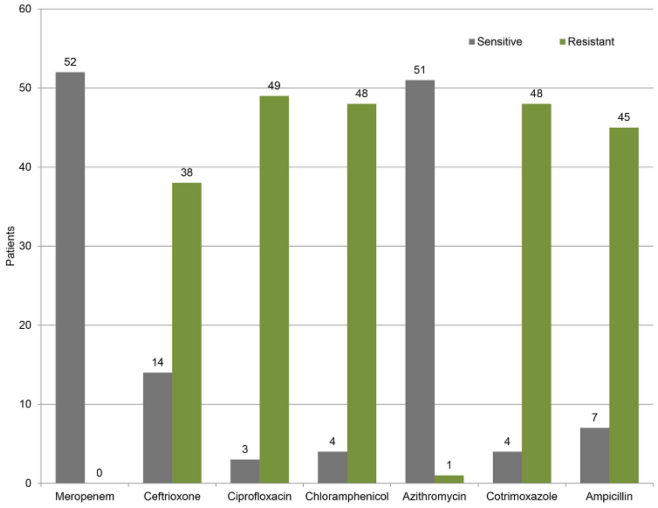

Table 1. Antibiotic sensitivity and resistance patterns in typhoid cases.

	Frequency	Percent	Valid percent
Non resistant	4	7.7%	7.7%
MDR	11	21.2%	21.2%
XDR	37	71.2%	71.2%
Total	52	100.0	100.0

MDR: multi-drug-resistant; XDR: extensively-drug-resistant.

Table 2. Antibiotic sensitivity and resistance in typhoid cases.

Antibiotic	Sensitive	Resistant
Meropenem	52 (100%)	0
Ceftriaxone	14 (27%)	38 (73%)
Ciprofloxacin	3 (5.8%)	49 (94.2%)
Chloramphenicol	4 (7.7%)	48 (92.3%)
Azithromycin	51 (98%)	1 (2%)
Cotrimoxazole	4 (7.7%)	48 (92.3%)
Ampicillin	7 (13.5%)	45 (86.5%)

Table 3. Clinical features, lab findings, complications and antibiotic resistance patterns of 52 confirmed typhoid patients (N = 52).

Age in years Mean ± SD	**31 ± 9**
< 30	29 (55.8%)
31-60	23 (44.2%)
> 60	0
Weight (Kg)	67 kg ± 8
Height	5.7 ± 0.27
Symptoms and signs	
Fever duration Mean ± SD	13.5 ± 6.6 days
Fever grade	
≥ 104	36 (67%)
< 104	17 (32.7%)
Co-morbidity present	2 (3.8%)
No co-morbidity	50 (96.2%)
Antibiotic used in last 2 months	
yes	12 (23%)
No	40 (76.9%)
Nausea ,vomiting ,abdominal pain	12 (23%)
Abdominal distension	
present	9 (17.3%)
absent	43 (82.7%)
Abdominal tenderness	8 (15.4%)
Abdominal tenderness negative	44 (84.6%)
Hepatomegaly	10 (19.2%
Normal liver	42 (80.8%)
Splenomegaly	22 (42.3%)
normal non palpable spleen	30 (57.7%)
Investigations	
CBC	
Hb mean ± SD	12.8 ± 1.8
TLC mean ± SD	4.4 ± 1.1
Neutrophils	49%
Lymphocyte	40%
Eosinophils	6.4%
Monocytes	3.3%
LFTS	
Bilirubin normal (1-17 micromole/L)	38 (73.1%)
Hyperbilirbinemia (> 17)	14 (26.9%)
ALT normal (1-42) U/L	26 (50%)
Increased ALT > 42	26 (50%)
Alkaline phosphates NORMAL (60-300)	41 (78.8%)
Increased Alkaline phosphates	11 (21.240%)
Albumin normal (> 3.5 g/dL)	40 (76.9%)
Hypoalbuminemia (< 3.5 g/dL)	12 (23.1%)
RFTS	
Urea normal (< 7 mmole/L)	43 (82.7%)
Increased urea (> 7 mmol/L)	9 (17.3%)
Creatinine normal (1-110 micromole/L)	51 (98.1%)
Increased creatinine(> 110 micromole/L)	1 (1.9%)
GI complication	
Hepatitis	12 (23.1%)
Cholecystitis	1 (1.9%)
Peritonitis	6 (11.5%)
None	33 (63.5%)

Majority of the patients had abnormal ultrasound findings, 22 patients had no abnormality on ultrasound abdomen and out of the rest 30 patients 4 (7.7%) had hepatomegaly with acute parenchymla, 1 (1.9%) patient had acute parenchymal changes with normal liver size, 4 patients (7.7%) had hepatosplenomegaly, 12 (23%) patients had splenomegaly, 2 had splenomegaly with pelvic ascites, 1 (1.9%) had hepatosplenomegaly with, 5 patients (9.6%) had mesenteric lymphadenopathy and out of these 2 had splenomegaly and 2 had pelvic ascites and splenomegaly along with lymphadenopathy. One patient (1.9%) had thickening of distal ileum.

Prolonged fever with gastrointestinal symptoms, toxemia, liver function test abnormalities (12-26%), ultrasound abnormalities (58%) and GI complications (19%) were the main findings in our patients denoting main findings associated with enteric fever in patients of this region ($p < 0.05$, CI 95%).

Table 4 shows the relationship of antibiotic resistance with clinical findings and complications. Although a number of patients had positive clinical findings and complications no significant differences were found between resistant and non-resistant cases ($p > 0.5$).

Table 3 (continued). Clinical features, lab findings, complications and antibiotic resistance patterns of 52 confirmed typhoid patients (N = 52).

Respiratory complication	
Pleural effusion	(1.9%)
Pneumonia	1 (1.9%)
None	50 (96.2%)
Renal complications	
Hypernatremia (sodium > 145 meq/L)	1 (1.9%)
AKI	5 (9.6%)
None	46 (88.5%)
CVS complications	
Circulatory failure	2 (3.8%)
None	50 (96.2%)
Hematological complications	
Bone marrow suppression	2 (3.8%)
None	
Other complications	
Arthritis	1 (1.9%)
Blood Cultures	
Salmonella Typhi	47 (90.4%)
Salmonella Paratyphi	5 (9.6%)
Antibiotic Resistance	
Sensitive to first line	4 (7.7%)
MDR	11 (21.2%)
XDR	37 (71.2%)

CBC: complete blood count; Hb: hemoglobin; TLC: total leukocyte count; LFTS: liver function tests; ALT: alanine transaminase; RFTS: renal function tests; GI complications: gastrointestinal complications; AKI: acute kidney injury; CVS complications: cardiovascular complications; MDR: multi-drug-resistant; XDR: extensively-drug-resistant.

Only hyperbilirubinemia was associated with typhoid resistance (chi square 7.5, $p = 0.02$).

Similarly, no statistically significant difference was found in renal, respiratory, cardiovascular, bone marrow complications in typhoid resistant and non-resistant (MDR and XDR) cases ($p > 0.05$).

All patients recovered and no mortality or disability was reported. Risk factors/causes responsible for

Table 4. Relationship of drug resistance with typhoid clinical findings and complications.

		Non resistant	MDR	XDR	Total N = 52	chi square	*p* value
Age	Young age	3	8	18	29	2.6	0.26
	Middle age	1	3	19	23		
	Old age	0	0	0	0		
Gender	Male	1	8	31	40	7.1	0.028
	Female	3	3	6	12		
Prior antibiotic use	Yes	1	2	9	12	0.18	0.09
	No	3	9	28	40		
Fever	≥ 104	2	7	26	35	0.75	0.68
	< 104	2	4	11	17		
Toxemia	Yes	2	5	9	16	2.5	0.28
	No	2	6	28	36		
Abdominal distension	Yes	2	3	4	9	4.8	0.089
	No	2	8	33	43		
Abdominal tenderness	Yes	1	2	5	8	0.45	0.80
	No	3	9	32	44		
Hepatomegaly	Yes	1	1	8	10	0.9	0.60
	No	3	10	29	42		
Splenomegaly	yes	3	5	14	22	2	0.35
	No	1	6	23	30		
Organism	*Salmonella* Typhi	3	8	36	45	7	0.29
	Salmonella Paratyphi	1	3	1	5		
Hyperbilirubinemia	Normal < 17	2	5	31	38	7.5	0.023
	Raised > 17	2	6	6	14		
Raised ALT	Normal ≤ 42	2	4	20	26	1.06	0.58
	Raised > 42	2	7	17	26		
Alkaline phosphatase	Normal 65-300	4	9	28	41	1.35	0.51
	Raised > 300	0	2	9	11		
AST	Normal ≤ 45	2	6	19	27	0.041	0.98
	Raised > 4 5	2	5	18	25		
Hypoalbuminemia	Normal ≥ 3.5	4	7	29	40	2.3	0.311
	Decreased < 3.5	0	4	8	12		
Urea	Normal ≤ 7	4	7	32	43	4	0.135
	Raised > 7	0	4	5	9		
Creatinine	Normal ≤ 110	4	11	36	51	0.41	0.81
	Raised > 110	0	0	1	1		
GI complications	Hepatitis	0	2	10	12	7.5	0.275
	Peritonitis	2	1	3	6		
	Cholecystitis	0	0	0	1		
	None	2	8	23	33		
Respiratory complications	Pleural effusion	0	0	1	1	4.1	0.38
	Pneumonia	0	0	1	1		
	none	4	10	36	50		
Renal complications	Hypernatremia	0	0	1	1	5.4	0.24
	AKI	0	3	2	5		
	None	4	8	34	46		
Hematological complications	Bone marrow suppression	0	1	1	2	1.1	0.57
	none	4	10	36	50		

ALT: alanine transaminase; AST: aspartate transaminase; AKI: acute kidney injury; GI complications: gastrointestinal complications; MDR: multi-drug-resistant; XDR: extensively-drug-resistant.

typhoid fever in these patients were listed and patients food and water was identified as a possible factor in 27 (51.9%), the job-related cause was found in 8 (15.4%) patients, crowding poor living conditions in 5 patients, poor sanitation in 5 (9.6%) patients, 2 patient thought that not being vaccinated was the cause of illness in them and 5 (9.6%) patients reported contact with typhoid positive patients.

During admission, patients were interviewed about their awareness of vaccines and preventive measures and the finding were that 14 (26.9%) patients were aware of the possible preventive measures for typhoid and 12 (23%) patients knew about the typhoid vaccine showing poor knowledge of prevention in patients and population.

Discussion

Enteric fever prevalence and increasing resistance are a parallel problem with COVID-19 even in 2020. Poor hygiene, poor sanitation, non-availability of clean water, flies, and contaminated food are major factors in continuously increasing cases in this part of the world. Moreover, the non-judicial and over-the-counter use of antibiotics has worsened the situation by increasing resistant cases.

In the present study, we have found that 71.1% cases were XDR, 21.2% MDR, and only 7.7% sensitive to the first line with one azithromycin resistant case being the only oral antibiotic available for XDR cases. This resistance pattern is expected to rise because of increased use in COVID-19. Increasing resistance has increases fever duration, toxemia, days of response to antibiotics and will help in early diagnosis and treatment but clinical, ultrasound findings and complications are not found to be associated with increasing resistance being as prevalent as in non-resistant cases. Prevention knowledge is poor and needs attention.

Since 2016 extensively drug-resistant cases starting from Sindh, increasing throughout the country including Lahore, Islamabad in 2018, and cases reported from the United Kingdom in travelers from Pakistan has marked Pakistan as one of the countries having the most alarming situation [13,14].

The CDC notes that everyone traveling to Pakistan is at risk of contracting XDR typhoid strain, and declares a level 2 alert for this outbreak with a need to follow precautions strictly [5]. In a local study from Pakistan by Hussain *et al*., ciprofloxacin resistance was 91% and it is 94.2% in our study, multidrug-resistant (MDR) cases of *Salmonella* Typhi was 76%, *Salmonella* Paratyphi in 34%, XDR in *Salmonella* Typhi were significant being 48%, whereas in our study MDR *Salmonella* Typhi was 17%, XDR *Salmonella* Typhi was 76.6%, MDR *Salmonella* Paratyphi was 60% and XDR 20%. In our study XDR cases are more than MDR [15].

In a study from Fiji by Getahun *et al*., reported: a mean duration of symptoms as 11.1 days, 96.9% patients had fever, 70% patients GI complaints, 11% patients developed complications, none were resistant to first line antimicrobials and only 0.8% resistant to ciprofloxacin (1.4% to nalidixic acid) [16]. This is in contrast to our study where we found only 7.7 % non-resistant isolates and the rest all either MDR or XDR with one case of azithromycin resistance. In our study all patients had fever and the mean duration of fever was 13.5 days, there were more resistant cases i.e. 21.2 % MDR and 71.2% XDR, 40 percent of patients had GI complaints, and 63.1 % of patients developed some complications as compared to 11 % in a study by Getahun *et al*. which attributes to the higher number of resistant cases in our study [16].

Ceftriaxone sensitivity was 100 % in Ali *et al*. in 2017 whereas it has decreased to 26.9% patients in our study [17].

Chatham-Stephens *et al*. reported that out of 169 typhoid fever cases from travelers to Pakistan, 133 (79%) were fluoroquinolone non-susceptible and 85 (50%) were MDR. During 2016–2018, 29 patients with typhoid fever reported travel to or from Pakistan and had isolates tested for antimicrobial susceptibility; among these, five patients had XDR *Salmonella* Typhi (17%) and 45% were MDR. Our study denotes that from 2018-2020 extensively drug-resistant cases have increased and more cephalosporin resistance has been reported [18].

In a local study from Karachi in 2012, there was an association between the duration of fever and temperature at presentation and being infected with multidrug-resistant *Salmonella* Typhi. Of 189 isolates 83 were found to be resistant to first-line antimicrobial therapy. There was no statistically significant difference in the clinical presentation of blood culture-sensitive and resistant *Salmonella* Typhi isolates whereas in our study no statically significant association ($p > 0.05$) was found between resistance patterns and clinical presentation or complications. Typhoid complications are increasing with increasing resistance in our patients over the years [19].

Typhoid has always been a serious issue in developing countries especially South Asia and increasing antibiotic resistance, morbidity and mortality have been a huge burden on health care and despite the

introduction of vaccination, creation of public awareness, CDC and World Health Organization (WHO) warnings and travel restrictions, recent epidemic hitting Pakistan which started from 2016 in Hyderabad extending to Punjab is continuing. Increasing resistance to first-line drugs, quinolones and now even third generation cephalosporin is an ongoing challenge in Pakistan, India, Bangladesh, Africa, and many other developing countries.

Azithromycin is the only oral available drug in this situation and resistance to this is alarming, other options are parenteral like carbapenems and tigecycline [20,21].

Lack of preventive measures by the government and public because of multiple factors, inadequate knowledge and practices related to prevention and vaccinations along with poverty make the situation very alarming. Antibiotics like azithromycin are prescribed and taken over the counter and so these too will soon select for resistance. The use of carbapenems and tigecycline is not affordable for a country like Pakistan and other low-income countries having resistant typhoid more prevalent. In a situation of azithromycin resistance in an XDR strain, a very serious action plan and its implementation is needed to have control over this situation otherwise it will take many lives away and eradication will become impossible.

That many extensively drug-resistant cases are associated with more prolonged fever and more complications leading to increased morbidity, mortality, and chances of carriers and relapses.

Very few patients are still aware of preventive practices and vaccines [22]. In a study from Karachi, stool samples were positive in asymptomatic food handlers for *Salmonella* Typhi [23]. We suggest that there should be more emphasis on sanitation, clean water, and food supplies, and all people working in restaurants especially food handlers should be tested and vaccinated, similarly cooks and homes, different institutes, and chefs should be tested and vaccinated. Handwashing and personal hygiene practices should be emphasized more and more. Every traveler should be vaccinated before traveling. Unnecessary and over-the-counter use of antibiotics is to be banned, monitored, and stopped efficiently. Only by those means, this much burden of that resistant and deadly disease can be managed.

Conclusions

Extensively resistant enteric fever is one of the biggest challenges in endemic areas like Pakistan and it is still not under full control and needs more serious attention for prevention, control on the spread of disease, and judicial use of antibiotics. Finding a bacterial isolate that was resistant to azithromycin is of great concern, as the antimicrobial options for XDR typhoid are already limited.

Although we did not find any statistically significant difference in clinical findings and complications between resistant and non-resistant cases of typhoid, typhoid complications overall are increasing in proportion to resistance and can bring serious consequences in the future. Public awareness on prevention and vaccination is still not satisfactory and more education programs are needed to sort this issue out.

Authors' contributions

SF conceived, designed, and did statistical analysis &editing of the manuscript. SS and SF did data collection and manuscript writing. HM and RN did statistical analysis. JI helped in review and statistical analysis. AQK did the review and final approval of the manuscript

References

1. GBD 2017 Typhoid and Paratyphoid Collaborators (2019) The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis 19: 369-381.
2. Zaki SA, Karande S (2011) Multidrug-resistant typhoid fever: a review. J Infect Dev Ctries 5: 324-37.
3. Center for Infectious disease research and policy (CIDRAP) (2018) WHO: XDR typhoid outbreak in Pakistan tops 5,200 cases. Available: http://www.cidrap.umn.edu/news-perspective/2018/12/who-xdr-typhoid-outbreak-pakistan-tops-5200-cases. Accessed: 16 july 2020.
4. Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, Wong VK, Dallman TJ, Nair S, Baker S, Shaheen G, Qureshi S, Yousafzai MT, Saleem MK, Hasan Z, Dougan G, Hasan R (2018) Emergence of an extensively drug resistant *Salmonella enterica* Serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. mBio 9: e00105-18.
5. Centers for disease control and prevention (CDC) (2019). Extensively drug-resistant typhoid fever in Pakistan. Available: https://wwwnc.cdc.gov/travel/notices/watch/xdr-typhoid-fever-pakistan. Accessed: 3 november 2020.
6. Lee JS, Mogasale VV, Mogasale V, Lee K (2016) Geographical distribution of typhoid risk factors in low and middle income countries. BMC Infect Dis 16: 732.
7. Mukhopadhyay B, Sur D, Gupta SS, Ganguly NK (2019) Typhoid fever: Control & challenges in India. Indian J Med Res 150: 437–447.
8. Rasheed F, Saeed M, Alikhan NF, Baker D, Khurshid M, Ainsworth EV, Turner AK, Imran AA, Rasool MH, Saqalein M, Nisar MA, Fayyaz ur Rehman M, Wain J, Yasir M, Langridge GC, Ikram A (2020) Emergence of Resistance to Fluoroquinolones and Third-Generation Cephalosporins in *Salmonella* Typhi in Lahore, Pakistan. Microorganisms 8: 1336.

9. Mogasale V, Desai SN, Mogasale VV, Park JK, Ochiai RL, Wierzba TF (2014) Case fatality rate and length of hospital stay among patients with typhoid intestinal perforation in developing countries: a systematic literature review. PLOS ONE 9: e93784.
10. Rahman BA, Wasfy MO, Maksoud MA, Hanna N, Dueger E, House B (2014) Multi-drug resistance and reduced susceptibility to ciprofloxacin among *Salmonella enterica* serovar Typhi isolates from the Middle East and Central Asia. New Microbes New Infect 2: 88–92.
11. Parry CM (2004) The treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever in Viet Nam. Trans R Soc Trop Med Hyg 98: 413–422.
12. Kadhiravan T, Wig N, Kapil A, Kabra SK, Renuka K, Misra A (2005) Clinical outcomes in typhoid fever: adverse impact of infection with nalidixic acid-resistant *Salmonella* typhi. BMC Infect Dis 5: 37.
13. Akram J, Khan AS, Khan HA, Gilani SA, Akram SJ, Ahmad FJ, Mehboob R (2020) Extensively Drug-Resistant (XDR) Typhoid: Evolution, Prevention, and Its Management. Biomed Res Int 2020: 6432580.
14. Rasheed MK, Hasan SS, Babar ZU, Ahmed SI (2019) Extensively drug-resistant typhoid fever in Pakistan. Lancet Infect Dis 19: 242–243.
15. Hussain A, Satti L, Hanif F, Zehra NM, Nadeem S, Bangash TM, Peter A (2019) Typhoidal *Salmonella* strains in Pakistan: an impending threat of extensively drug-resistant *Salmonella* Typhi. Eur J Clin Microbiol Infect Dis 38: 2145–2149.
16. Getahun SA, Parry CM, Crump JA, Rosa V, Jenney A, Naidu R, Mulholland K, Strugnell RA (2019) A retrospective study of patients with blood culture-confirmed typhoid fever in Fiji during 2014-2015: epidemiology, clinical features, treatment and outcome. Trans R Soc Trop Med Hyg 113: 764–770.
17. Ali A, Ali HA, Shah FH, Zahid A, Aslam, H, Javed, B (2017) Pattern of antimicrobial drug resistance of *Salmonella* Typhi and Paratyphi A in a Teaching Hospital in Islamabad. J Pak Med Assoc 67: 375–379.
18. Chatham-Stephens K, Medalla F, Hughes M, Appiah GD, Aubert RD, Caidi H, Angelo KM, Walker AT, Hatley N, Masani S, Nash J, Belko J, Ryan ET, Mintz E, Friedman CR (2019) Emergence of Extensively Drug-Resistant *Salmonella* Typhi Infections among Travelers to or from Pakistan - United States, 2016-2018. MMWR Morb Mortal Wkly Rep 68: 11–13.
19. Khan MI, Soofi SB, Ochiai RL, Khan MJ, Sahito SM, Habib MA, Puri MK, von Seidlein L, Park JK, You YA, Ali M, Nizami SQ, Acosta CJ, Sack RB, Clemens JD, Bhutta ZA (2012) Epidemiology, clinical presentation, and patterns of drug resistance of *Salmonella* Typhi in Karachi, Pakistan. J Infect Dev Ctries 6: 704-714. doi: 10.3855/jidc.1967.
20. Kaurthe J (2013). Increasing antimicrobial resistance and narrowing therapeutics in typhoidal salmonellae. J Clin Diagn Res 7: 576–579.
21. Parry CM, Thieu NT, Dolecek C, Karkey A, Gupta R, Turner P, Dance D, Maude RR, Ha V, Tran CN, Thi PL, Be BP, Phi LT, Ngoc RN, Ghose A, Dongol S, Campbell JI, Thanh DP, Thanh TH, Moore CE, Baker S (2015). Clinically and microbiologically derived azithromycin susceptibility breakpoints for *Salmonella enterica* serovars Typhi and Paratyphi A. Antimicrob Agents Chemother 59: 2756–2764.
22. Mushanyu J, Nyabadza F, Muchatibaya G, Mafuta P, Nhawu G (2018). Assessing the potential impact of limited public health resources on the spread and control of typhoid. J Math Biol 77: 647–670.
23. Siddiqui TR, Bibi S, Mustufa MA, Ayaz SM, Khan A (2015) High prevalence of typhoidal *Salmonella enterica* serovars excreting food handlers in Karachi-Pakistan: a probable factor for regional typhoid endemicity. J Health Popul Nutr 33: 27.

Corresponding author

Samina Fida, Associate Professor Medicine
Department of Medicine, CMH Lahore Medical College, Abdur Rehman Road 123/124 Tipu block Garden Town, Lahore, Pakistan
Phone: 0092323-8816994
Email: samm.doc@hotmail.com; sfida86@gmail.com

Conflict of interests: No conflict of interests is declared.