Original Article

A Pattern of Drug Resistance of Salmonella in Patients having Suspected or Confirmed Typhoid Fever in District Bannu and Adjacent Areas

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ABSTRACT

Objective: To determine the drug resistance pattern of salmonella in patients with suspected or confirmed typhoid fever in District Bannu and adjacent areas.

Study Design: Descriptive case series study

Place and Duration of Study: This study was conducted at the DHQ Teaching Hospital (DHDTH) in Bannu, Khyber Pakhtunkhwa, from July 2022 and ending in December 2022.

Methods: The research included 55 individuals who were either diagnosed with typhoid fever or were suspected of having it (according to the case criteria) and brought to the Department of Medicine at DHQ Teaching Hospital (DHDTH) Bannu in Khyber Pakhtunkhwa. Their blood samples were collected for Blood Culture Sensitivity per standard protocols. They were sent to the laboratory (Shifa International Hospital Ltd Islamabad) to see the pattern of salmonella drug resistance.

Results: In Pakistan, typhoid fever is a common occurrence. Treatment of Salmonella typhimurium has become more difficult due to the rise of the disease's multidrug and extensively drug-resistant strains. This research aimed to identify medication resistance patterns among salmonella species in our area so that doctors can better treat typhoid in this day and age of widespread antibiotic resistance. In all, 55 individuals volunteered to have their blood samples taken and analyzed for C/S results. There were 50 positive results and 5 negative (no growth) for isolation. In these 50 cases, 9 samples revealed growths Other than salmonella (like pseudomonas aeruginosa, E.coli-MDR, group B strep, klebsiella pneum, and even MRSA in 2 samples), while Salmonella typhi were isolated in 41 blood samples.

Conclusion: Out of these 41, only 6 samples (14.63%) showed Non-resistant salmonella typhi (sensitive to 1st line drugs and 3rd generation cephalosporins, while intermediate sensitivity to 2nd line drugs), and 28 samples (68.29%) showed growth of Extended Spectrum Beta-Lactamase positive (ESBL) salmonella typhi (resistant to third generation cephalosporins), but early results also showed resistance to 1st line and 2nd ine drugs, while 7 samples (17.07%) showed samonella typhi XDR (resistant to 1st line, 2nd line drugs and 3rd generation cephalosporins, BUT sensitive to Azithromycin/Carbapenems). Our results revealed that drug-resistant salmonella (ESBL/XDR) is a big and hidden health challenge in our set up that needs proper attention from healthcare professionals and the Government.

Key Words: Drugs Resistance, Salmonella, Typhoid Fever, District Bannu.

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INTRODUCTION

Typhoid and Paratyphoid fevers are collectively called 'Enteric Fever', caused by Salmonella species (Gram Negative Rods). The specific strain of Salmonella that causes typhoid fever is serovar Typhi, while the specific strain of Salmonella that causes paratyphoid fever can be A, B, or C.S. Paratyphi causes a milder version of the fecal-oral transmitted systemic sickness that S. Typhi causes. There is no difference between the clinical symptoms caused by S. Typhi and Paratyphi. The symptoms and signs of typhoid fever can range from a simple sickness with low-grade fever to potentially lethal complications such as gastrointestinal haemorrhages, intestinal perforation, encephalitis, cerebral neuritis, severe sepsis, or septic shock, among others.

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Case Definition of Typhoid:

Suspected case of Typhoid Fever	At least five days before presentation, the patient must have had a documented fever (38°C or above), stomach symptoms, and a rising trend in temperature. The patient must also have no other obvious causes for the fever, such as a urinary tract infection (UTI), pneumonia, an abscess, etc. OR This case fits the diagnostic criteria for typhoid fever and has been associated with another confirmed disease.
Confirmed case of Typhoid fever	Someone who has a high temperature (38 °C or above) for three days or more and who has S. Typhi isolated from blood or bone marrow cultures.

Typhoid fever is often diagnosed by isolating the organism by culture, most often using blood C/S. It is believed that cultures are completely unique. To make a conclusive diagnosis, a blood culture must be sent out before administering antibiotics. Before starting empirical treatment for typhoid, blood cultures should be obtained. Patients who are not feverish or who are already on antibiotics can still have their blood cultures taken. When the blood culture comes back negative, it takes approximately 7 days after the sample is submitted. On the other hand, if the blood culture comes back positive, it takes about 3 to 4 days to get a report that includes the identification of the organism and antibiotic sensitivity testing. If the fever has not subsided after seven to ten days of treatment, a second blood culture may be necessary as a negative culture does not rule out typhoid. There is also an increase in liver transaminase (ALT) levels to levels double the normal range. Typhoid fever cases do not include serological tests like Typhidot and Widal, and such tests are not advised to diagnose intestinal fever[1].

The following Drugs are commonly used for Typhoid Fever[2]:

1st Line Drugs: Chloramphenicol, Ampicillin, Trimethoprim-Sulfamethoxazole (co-trimoxazole =Septran).

2nd Line Drugs: Fluoroquinolones (Ciprofloxacin, Levofloxacin).

3rd Generation Cephalosporins: Cefixime (for uncomplicated typhoid fever) & Ceftriaxone (for complicated typhoid).

The duration of treatment is oral, 7-10 days if clinically stable, and 10-14 days, and I/V, if clinically unstable.

Based on Drug susceptibility patterns, the confirmed cases of typhoid fever are classified as:

1- Responsive to or not resistant to drugs two, extremely drug-resistant (XDR), and three, multi-drug-resistant (MDR), or 4- Typhoidal fever caused by the Extended Spectrum Beta-Lactamase gene.

Virus-Infected Typhoid	Throat infections caused by Salmonella typhimurium (S. Typhi) or Salmonella paratyphi type A, B, or C that are susceptible to penicillin and other first- and third-generation cephalosporins, with or lacking resistance to these antibiotics.
Multi-Drug Resistant Typhoid Fever	The most common types of typhoid fever are those caused by Salmonella typhimurium (S. Typhi) and Salmonella paratyphi (S. Paratyphi A, B, or C), which can be resistant to several first-line medicines but are susceptible to third-generation cephalosporins..
Highly Resistant Typhoid Fever	The pathogens responsible for typhoid disease, Salmonella typhimurium, have developed resistance to the first three generations of antibiotics. Highly susceptible to azithromycin and carbapenems
ESBL positive Typhoid Fever	The bacteria that cause typhoid, Salmonella typhimurium, are resistant to third-generation cephalosporins but can be susceptible to first-line antibiotics like chloramphenicol or cotrimoxazole, or second-line antibiotics like fluoroquinolones.

*Carbepenems: Imipenem, Meropenem, Ertapenem.

Countries with poor socioeconomic status, such as India, Bangladesh, and Pakistan, continue to suffer from typhoid as a dominant health concern[3]. With an estimated 493.5 cases per 100,000 in 2018, Pakistan has the highest typhoid rate among South Asian countries[4]. In 2016, a new extended drug resistance (XDR) typhi outbreak started in Hyderabad Sindh, which led to a dramatic increase in cases in Pakistan[4]. Due to the ineffectiveness of the previously used medicines, such as fluoroquinolones and third-generation cephalosporins, a newer and stronger antibiotic class called carbapenems, tigecycline, and azithromycin, was required to treat this new strain[5,6]. For China, the reported adult proportion of enteric fever was 3.8 and the number of typhoid cases per 100,000 people, as determined by blood culture, was 29.20; for India, it was 66.0; and for Pakistan, it was 52[7]. Worldwide, over 111,000 people die each year from typhoid fever, with an estimated 9 million cases in 2019, according to the World Health Organisation. People without access to clean water and proper sanitation are more likely to contract typhoid, and children are particularly vulnerable. The summer and monsoon seasons see a spike in its occurrence.

Various factors have impacted this spread of Typhoid in Pakistan like the presence of XDR strains of Typhoid, COVID-19 outbreaks and simultaneous antibiotic

therapy (Azithromycin), socioeconomic disparities, and illiteracy[8].

Pakistan is experiencing an increase in cases of XDR-Typhoid fever. Since the first case of XDR-TF was reported in Sindh in late 2016, a significant number of cases of Typhoid Fever (TF) confirmed by blood cultures are resistant to normal treatment[9]. Karachi recorded 14,360 XDR-TF cases between January 2017 and June 2021, per the Weekly Field Epidemiological Report published by the National Institute of Health (NIH) Islamabad. Five thousand seven hundred forty-one instances of XDR-TF were documented across Sindh province (excluding Karachi) between 2016 and 2021, with District Hyderabad accounting for 69.5% of those cases[10]. When Pakistan included the typhoid conjugate vaccine (TCV), which is recommended by the World Health Organisation (WHO), in its routine immunisation programme in 2019, it was the first country to do so[9]. The use of azithromycin and Meropenem should be limited to XDR cases of typhoid and prescribed by Registered Medical Practitioners (RMPs) only, according to the Advisory for prevention and treatment of typhoid, including XDR, by the Field Epidemiology & Disease Surveillance Division (FEDSD), NIH, Islamabad. Other drug options should be utilised for other infections. Additionally, typhoid can be prevented through increasing community knowledge and vaccination, specifically the Typhoid Conjugate Vaccine Typhibar, which provides extended immunity[11].

Keeping in mind the above facts and figures regarding Typhoid and its drug resistance, the following study was conducted on a small population, to determine the pattern of drugs resistance of salmonella in patients having suspected or confirmed typhoid fever in our local set up in District Bannu and adjacent areas.

METHODS

Bannu, Khyber Pakhtunkhwa, Department of Medicine, DHQ Teaching Hospital (DHDTH), for six months, from July 2022 to December 2022.

Sample Size: 55 patients who either suspected or confirmed typhoid fever (as per the case definition of typhoid).

Sampling Technique: Consecutive, Non-probability Sampling.

Inclusion Criteria:

1. Any patient who presents with acute febrile illness with temp >38C of more than 3 days of duration ,without any focus of infection, fulfilling the case definition of suspected/confirmed Typhoid fever
2. Patients with Negative MP (on thick and thin smear), Dengue serology and acute viral Hepatitis.
3. Patients with normal Chest X-ray, and Urine R/E, normal leukocyte count/leukopenia.
4. Patients of both genders and any race.
5. Age between 15 to 70 years.

Exclusion Criteria: To avoid recall bias, the study did not include patients who did not meet the inclusion criteria, were terminally sick, were unwilling to participate, were taking antibiotics that would alter culture results, or were intellectually retarded. They would bring bias into the study outcomes if they were included as confounders..

Data Collecting Procedure: Obtaining approval from the hospital's ethics and research committee or board allowed the study to proceed. The study enrolled all patients who met the inclusion criteria according to operational definitions and presented to the Department of Medicine, DHQ Teaching Hospital Bannu through the emergency room or the outpatient department. The initial step in counselling all patients was to go over the goals of the study and the specific blood test that would be administered. Clear answers were provided to all questions pertaining to the study. All patients were given a thorough explanation of the study's goals and methods, and those who were interested in participating were asked to sign an informed consent form. Participants were instructed on the correct way to draw blood samples for C/S testing. I assure you that all information gathered from participants will be treated with the utmost confidentiality and will be utilised exclusively for research purposes. Using conventional techniques, two sets of blood samples were taken from each patient in the study population. These samples were then transferred to the Laboratory at Shifa International Hospital Ltd in Islamabad to examine the pattern of treatment resistance among salmonella species. Using a flowchart as a data collecting tool, we recorded all of the relevant information, including age, gender, whether the growth was isolated on culture, and the sensitivity (S) and resistance (R) to ten antibiotics tested against salmonella. The first three medications are from the first line: chloramphenicol, ampicillin, and co-trimoxazole. The second line contains ciprofloxacin. The third line has two cephalosporins, cefixime and ceftrioxone, azithromycin, and three carbepenems. Every single patient was placed into one of many groups. This pre-made Proforma took down all detail, including names, ages, genders, addresses, and lab results. The analysis was limited to a full Proforma. Rigorous exclusion criteria were used to prevent bias and confounding variables in the study.

Statistical Analysis: Data obtained was entered into SPSS version 23 and analyzed in analytical statistics. Mean + SD were calculated for numerical variables like Age. Frequencies and Percentages (%) were calculated for categorical variables such as Gender, Culture positivity, Type of microorganism isolated, and Pattern of resistance noted. These were stratified among age and gender to see the effect modifiers. All results were presented in the form of tables.

RESULTS

This study was conducted at the Department of Medicine, DHQ Teaching Hospital, Bannu, Pakistan. In this study, 55 patients were enrolled with suspected or confirmed typhoid fever, to determine the pattern of drugs resistance of salmonella in our set up.

Table 1 represents patients distribution according to age and gender in study population (n=55).

Table No. 1: Patients Distribution: Age and Gender wise (n=55)

		Gender		
		Male	Female	Total
Age	<20years	5	10	15
	20-40years	14	13	27
	>40years	6	7	13
Total		25	30	55

Table 2 represents cross-tabulation of culture result (Positive or Negative) and microorganism isolated (salmonella/other than salmonella).

Table No. 2: Culture-Microorganism Cross tabulation (n=55)

		Microorganism		Total
		Samonella	Other than Salmonella	
Culture	Positive Result	41	9	50
	Negative Result	0	0	5
Total		41	9	55

Table 3 represents cross-tabulation of culture result and resistance pattern of samonella typhi(NR/ESBL/XDR).

Table No. 3: Culture-Resistance Cross tabulation (n=41/55)

		Resistance			Total
		Non Resistant NR	ESBL	XDR	
Culture	Positive result	6	28	7	41
Total		6	28	7	41

Table No. 4: Resistance in study population (n=41/55)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Non Resistant (NR)	6	14.63	14.63	14.63
	ESBL	28	68.29	68.29	82.92
	XDR	7	17.07	17.07	100.0
	Total	41	100.0	100.0	

Table: 4 represents % ages of various resistance patterns of salmonella (NR/ESBL/XDR) in study population.

DISCUSSION

Typhoid is still most common and endemic in low socioeconomic countries like Pakistan[3]. There are Rising XDR-Typhoid Fever Cases in Pakistan, which has further worsen the situation[4]. Preventive measures, vaccinations, early diagnosis and prompt treatment with appropriate Antibiotic by health care providers is necessary to decrease disease burden and prevent its complications.

In this study, we have determined the pattern of drug resistance of salmonella typhi in 55 suspected or confirmed cases. Age of the patients was 15 to 70 years, with mean 31.18, and Std of 15.655. Twenty five patients (45.45%) were males and 30 (54.55%) were female, predominantly involving middle age group (20-40years), followed by young age group (<20years). Over all, Culture positivity was observed in 50 cases out of total 55 (90.9%), and salmonella isolation was obtained in 41 out of these 50 cases (74.54%). Out of 55, 50 C/S results were positive, but only 41 showed samonella isolates (Tables 2, 3). In these 41 cases, only 6 (14.63%) were non-resistant samonella, while the remaining 35 (85.36%) were resistant samonella, either ESBL (28 = 68.29%) or XDR (7= 17.07%) (Table 4). So overall resistance is 85.36%, which is very significantly high. This alarming increase in XDR typhoid cases is also in accordance with the recent study conducted in Sindh[6].

According to the results of our study, it has been established that, there is a high burden of salmonella in our set up, just like other parts of the country, and most of the cases are resistant to routinely used antibiotics.

The reasons for this high resistance is irrationale use of antibiotics, its under dose, for shorter duration, unawareness of the presence of resistance, and low education with low socioeconomic status that hinders in seeking expert opinion and proper health care.

Our current study findings revealed that typhoid is endemic here and mostly resistant in our setup.

CONCLUSION

In the light of above findings, it is concluded that typhoid is still endemic here. Most of the cases are culture proven resistant samonella typhi cases, to 1st line drugs, 2nd line drugs and 3rd generation cephalosporins. At the same time, sensitive only to Azithromycin/Carbapenems, in our set up also, which is very alarming, warranting the proper attention both from health care professionals and government. However, more detailed research is required to determine the disease's overall burden and its resistance pattern.

Recommendations: In the view of the above study, we recommend:

All the health care providers and physicians should have a high index of suspicion for drug resistant salmonella.

Do a rationale use of antibiotics in general and azithromycin/carbapenems specifically to preserve these drugs and decrease the chances of resistance against them. In suspected cases, they need to take blood cultures before prescribing antibiotics. Then, they can start empirical treatment with oral cefixime or IV ceftriaxone, depending on the severity of the disease. Based on the C/S results, they can modify treatment to switch from a broad spectrum to a narrow spectrum drug. The hidden burden of drug-resistant Salmonella must be recognized to reduce the disease's progression, consequences, and burden through early identification and appropriate treatment. There has to be an increase in immunisation programmes, telehealth, and awareness campaigns.

Author's Contribution:

Concept & Design of Study:	Raza Muhammad Khan
Drafting:	Nafidullah Khan, Tahir Ullah
Data Analysis:	Tahir Ullah
Revisiting Critically:	Raza Muhammad Khan, Nafidullah Khan
Final Approval of version:	Raza Muhammad Khan

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