

Assessment of Determinants Leading to Salmonella Resistance to Ciprofloxacin in Patients Presenting with Typhoid Fever

Salmonella Resistance to Ciprofloxacin in Typhoid Fever

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ABSTRACT

Objective: To determine the frequency and common factors leading to ciprofloxacin resistance to salmonella among patients presenting with typhoid fever.

Study Design: Descriptive / Cross Sectional Study

Place and Duration of Study: This study was conducted at the Department of Medicine, Qazi Hussain Ahmad Medical Complex, Nowshera from 23-01-2018 to 22-07-2018.

Materials and Methods: Through a Descriptive Cross Sectional Study Design, a total of 195 patients with typhoid fever were selected in a consecutive manner from Medical Wards and tested for resistance of salmonella to ciprofloxacin and common risk factors leading to it such as prior use of ciprofloxacin and recurrent typhoid fever were also scrutinized.

Results: The mean age of patients was 29.4 ± 11.56 years with 63% male gender predominating the overall sample of typhoid fever. On disc diffusion (Kirby Beur) method salmonella resistance to ciprofloxacin was found in 72 (36.9%) of patients with 36-45 years of age group most commonly affected age group (47%) and male (72.2%) commonly affected gender. The distribution of common factors leading to salmonella resistance to ciprofloxacin are: 46 (63.9%) had history of prior use of ciprofloxacin and 26 (36.1%) had recurrent typhoid fever.

Conclusion: As in many other parts of the world, salmonella resistance to ciprofloxacin is also common in our local population and the most common factor responsible for it is prior use of ciprofloxacin.

Key Words: Typhoid fever, ciprofloxacin, salmonella.

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INTRODUCTION

Typhoid fever is an important determinant of morbidity and mortality in many developing countries of the world especially in Asia¹ It is estimated that world over 16 to 33 million cases of typhoid fever cause deaths of 500,000 to 600,000 yearly². Indian subcontinent is considered to have the highest incidence of typhoid fever world-wide³.

Typhoid fever is a systemic infection. It is caused by the bacterium "Salmonella enterica" serotype "typhi"⁵. Pakistan is thus one of the hyper-endemic areas for this disease⁶.

This bacterium is disseminated through oro-fecal route after ingestion of infected food or water by the feces or urine of the infected people⁶. Typhoid Fever is diagnosed through blood culture. Serological investigations are in use but having low sensitivity and specificity. As blood culture takes many days, it is usual to start treatment in any patient with suspected typhoid fever on the basis of clinical findings and positive serology⁷.

Typhoid fever can cause complications in many parts of the body. However the most serious complications are intestinal hemorrhage and perforation. Typhoid ileal perforation is recognized as a dominant reason of morbidity and mortality in patients with typhoid fever⁸. In order to prevent these complications and hence morbidity and mortality of this disease, it is important to diagnose the disease early and then to start appropriate antibiotic⁹.

The choice of drug for typhoid fever treatment is a fluoroquinolone like ciprofloxacin. However recent studies have shown that ciprofloxacin resistance salmonella is increasing due to the widespread and irrational use of ciprofloxacin in many different conditions¹⁰. It is estimated that prevalence of ciprofloxacin resistance may be as high as 38 percent in Pakistan¹¹. In a recent study in Ontario, Canada,

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decreased susceptibility of salmonella to ciprofloxacin was found in 80% of patients. Majority of these patients belonged to Indian subcontinent¹². Another study carried out in India regarding anti-microbial resistance of salmonella typhi showed reduced susceptibility to ciprofloxacin in 24% of cases¹³. So there are dramatic geographic variations in ciprofloxacin resistance salmonella.

There are some factors that may lead to ciprofloxacin resistance salmonella like irrational use of ciprofloxacin in about 40% of cases and recurrent typhoid fever in about 14% of cases¹⁴. The optimal management of typhoid fever depends on understanding of local pattern of resistance to different drugs¹⁵.

Although patients with suspected typhoid fever are empirically treated with ciprofloxacin but no research has been formulated on ciprofloxacin resistance in local population. My study will determine the frequency of ciprofloxacin resistance in patients with typhoid fever which is important for us because ciprofloxacin resistance has vast geographical variation and also to identify common factors involved which will contribute to local magnitude of the problem. The study results will be compared with previous national and international data, so as to provide guidance for an improved empirical treatment in our local population with typhoid fever.

MATERIALS AND METHODS

This study was conducted in the in the Department of Medicine, Qazi Hussain Ahmad Medical Complex, Nowshera from 23-01-2018 to 22-07-2018. Through a Descriptive Cross Sectional Study Design, a total of 195 patients using proportion of ciprofloxacin resistance salmonella as 24%¹³, 95% confidence level and 6% margin of error using WHO sample size calculation, with typhoid fever were selected in a consecutive manner from Medical Wards and tested for resistance of salmonella to ciprofloxacin and common risk factors leading to it such as prior use of ciprofloxacin and recurrent typhoid fever were also scrutinized.

Inclusion Criteria:

- All patients with typhoid fever with salmonella positive blood cultures.
- Both genders (male and females) were included.
- All patients with age greater than 13 years.

Exclusion Criteria:

- Patients with co-morbid conditions like diabetes mellitus, AIDS, transplant recipients. Detected on the basis of patients previous medical history.
- The above conditions act as confounders and if included, will institute bias in the results.

Data Collection Procedure: Data was collected through specially designed proforma. Informed written consent was sought from all the patients. Final approval from the ethical review committee was taken. All

admitted patients in department of medicine, whether from OPD or casualty were included in the study presenting with typhoid fever with IgM positive and having salmonella positivity on blood cultures. A detailed relevant history was taken from the patients. Special enquiry was made about the prior ciprofloxacin use and past history of typhoid fever.

10ml of venous blood sample was taken from every patient under strict aseptic technique. The blood was immediately injected into blood culture bottle and sent to hospital laboratory for the detection of ciprofloxacin resistance to salmonella. Among those patients in whom ciprofloxacin resistance to salmonella is detected were carefully scrutinized for the detection of common factors leading to it (recurrent typhoid fever and history of prior use of ciprofloxacin)

All patients were started on empirical antibiotics and blood culture and sensitivity report were followed. All the above information including name, age, gender and address were recorded in a pre-designed Performa. Exclusion criteria was strictly followed to control confounders and biases. All the laboratory procedures are conducted under strict supervision of single expert "Pathologist" having experience minimum of 5 years.

Data Analysis: Data was collected through specially designed Performa and analyzed using SPSS 13. Frequencies, percentages were calculated for categorical variables like gender, ciprofloxacin resistance to salmonella and common factors (recurrent typhoid fever and history of prior use of ciprofloxacin). Mean and SD was calculated for numerical variables like age. Ciprofloxacin resistance and common factors were stratified among age and gender to see the effect modifications. Results are presented in the form of tables and charts.

RESULTS

A total of 195 patients of typhoid fever were enrolled in the study. There were 123 (63%) male and 72 (37%) females.

The mean age of the patients was 29.4 ± 11.56 years. While distributing the sample of typhoid patients in different age groups, we found that in the age group 13-25 years there were 48 (24.6%), in the age group 26-35 years there were 102 (52.3%), in the age group 36-45 years there were 34 (17.4%) while in the age group 45+ years there were only 11 (5.6%) patients. (Table 1). On Disk Diffusion method (Kirby Bauer) out of 195 patients with typhoid fever, 72 (36.9%) patients were found to have salmonella Resistance to ciprofloxacin and out of which 52 (72.2%) were males and 20 (27.8%) were females (Table 2).

On stratification we found that out of total 123 males, 52 (42.3%) were having salmonella resistance to ciprofloxacin and out of total 72 females with typhoid fever 20 (27.8%) were resistant to Ciprofloxacin

showing resistance pattern in more in male as compared to females. (Table 3).

While stratifying the salmonella resistance to ciprofloxacin, out of total 48 patients in the age group 13-25 years 7 (14.6%) were resistant, in the age group 26-35 years out of total 102 patients 45 (44%) were resistant, in the age group 36-45 years out of total 34 patients 16 (47%) were resistant and in the age group 45+ years out of total 11 patients 4 (36.4%) were resistant. (Table 4)

Out of 72 patients with salmonella resistance to ciprofloxacin, history of prior use of ciprofloxacin was found to be the most common factor leading it with total 46 patients in that group (63.9%) while recurrent typhoid fever contributed 26 (36.1%) of the resistance. (Table 5)

While stratifying the common factors among gender, we found that in among total 52 male patients with ciprofloxacin resistance to salmonella, 33 (63.5%) patients had used ciprofloxacin in the past while 19 (36.5%) had history of recurrent typhoid fever. Among 20 female patients with ciprofloxacin resistance, 13 (65%) had history of ciprofloxacin use in the past while 7 (35%) had history of recurrent typhoid which shows that gender has no effect on factors. (Table 6)

While stratifying the common factors among different age groups, we found that different factors have different relations with the age groups. In the age group 13-25 years out of total 7 resistant cases 2 (28.6%) had history of prior use of ciprofloxacin while remaining 5 (71.4%) had recurrent typhoid fever. In the age group 26-35 years out of total 45 resistant cases 34 (75.6%) had history of prior use of ciprofloxacin while remaining 11 (24.4%) had recurrent typhoid fever. In the age group 36-45 years out of total 16 resistant cases 9 (56.3%) had history of prior use of ciprofloxacin while remaining 7 (43.7%) had recurrent typhoid fever. In the age group 45+ years out of total 4 resistant cases 1 (25%) had history of prior use of ciprofloxacin while remaining 3 (75%) had recurrent typhoid fever. (Table 7).

Table No. 1: Age-Wise Distribution of Sample (n=195) [DMJK1]

Age Ranges [In Years]		Percentage
13-25	48	24.6%
26-35	102	52.3%
36-45	34	17.4%
45+	11	5.6%
Total	195	100%

Table No. 2: Salmonella Resistance to Ciprofloxacin (N=195)

Salmonella Resistance	No of Patients	Percentage
Yes	72	36.9%
No	123	63.1%
Total	195	100%

Table No. 3: Gender Wise Stratification of Salmonella Resistant Patients (n=72)

Gender	Total No of Patients	Resistant Cases	Percentage
Male	123	52	42.3%
Female	72	20	27.8%
Total	195	72	

Table No. 4: Age-wise stratification of resistant cases (n=72)

Age ranges [in years]	Total No of Patients	Resistant Cases	Percentage
13-25	48	7	14.6%
26-35	102	45	44%
36-45	34	16	47%
45+	11	4	36.4%
Total	195	72	

Table No. 5: Common factors leading to resistance (n=72)

Risk factor	No. of cases	Percentage
History of Ciprofloxacin Use	46	63.9%
Recurrent Typhoid Fever	26	36.1%
Total	72	100%

Table No. 6: Gender wise stratification of common factors (n=72)

Gender	Resistant Cases	Prior use of Ciprofloxacin	Recurrent Typhoid Fever
Male	52	33 (63.5%)	19 (36.5%)
Female	20	13 (65%)	7 (35%)
Total	72	46 (63.9%)	26 (36.1%)

Table No. 7: Age wise stratification of common factors (n=72)

Age Range	Resistant Cases	Prior use of Ciprofloxacin	Recurrent Typhoid Fever
13-25	7	2 (28.6%)	5 (71.4%)
26-35	45	34 (75.6%)	11 (24.4%)
36-45	16	9 (56.3%)	7 (43.7%)
45+	4	1 (25%)	3 (75%)
Total	72	46 (63.9%)	26 (36.1%)

DISCUSSION

Typhoid fever caused by "Salmonella enterica", Serovar typhi (*S. typhi*), remains a significant problem in developing countries¹⁴. It is approximated that, typhoid fever causes more than 20 million cases and 700,000 deaths worldwide every year¹⁵. In developing countries, the antibiotics most easily available for treatment of typhoid are chloramphenicol, ampicillin, and cotrimoxazole¹⁴. In *S. typhi* plasmid-incoded resistance to these three drugs were reported from South-East-Asia.

The rate of drug resistant *Salmonella typhi* is increasing rapidly, notably in the Indian subcontinent and South-East Asia. Ciprofloxacin has remained the drug of choice for enteric fever for the last many years¹⁶. However, isolates of *Salmonella enterica* Serovars typhi and Paratyphi A with decreased susceptibility to fluoroquinolones have now appeared in the subcontinent, Vietnam and Tajikistan, and the treatment failures with fluoroquinolones have also been noted¹⁷.

The public health community has a suspicion about the probability that animals which are given antibiotics are then utilized by humans may play a role in resistance of human pathogens.^{18,19}

Several antibiotics are important to human medicine because they are effective against resistant pathogens. Fluoroquinolones are among these important antibiotics, so the emergence of fluoroquinolone-resistant *Salmonella Typhi* is potentially an alarming problem. A recent survey by the National Health Research Institute of Taiwan found that five antibiotics important to human medicine, including a fluoroquinolone (ciprofloxacin), have been widely added to animal feed for years²⁰.

The emergence of fluoroquinolone resistance would change the policy for the treatment of *S. Typhi* infections. Because the majority of *S. Typhi* isolates are also resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, the third-generation cephalosporins are now the only antibiotics with reliable activity against²¹.

This study was designed to determine the frequency of salmonella resistance to ciprofloxacin and common factors leading to it. In our study a total of 195 patients presenting with typhoid fever were included. In our study, there were 63% males and 37% females. This was in contrast in a study by Wain J et al²² as in his study out of 132 patients with typhoid fever, 51.5% were males while 48.5% were female gender. The mean age group in our study was 29.4 ± 11.56 years and again it was in contrast with the study by Wain J et al²² as the range of age in his study was 7-21 years only.

On Disk Diffusion method (Kirby Bauer) out of 195 patients with typhoid fever, 36.9% patients were found to have salmonella Resistance to ciprofloxacin. Various studies have been done in the literature not only on resistance of various species of salmonella on ciprofloxacin but also on the multiple drugs. Although the proportion of this resistance is not low in our population but even higher proportion were observed in various studies like Chiu C et al²¹ reporting ciprofloxacin resistance was found in 60% of isolates of salmonella, Morris SK et al¹² reported it to be 80% in Canada. Another study from Pakistan reported salmonella resistance to ciprofloxacin to be 38%¹¹ which was a bit comparable to our study and another study from India reported this resistance of 24% somewhat less than what was observed in our study

however, another study from New Delhi India by Chandel DS²³ et al reported none of resistance of salmonella to ciprofloxacin though they found 32% isolates resistant to chloramphenicol and cotrimaxazole while another 13% to multi-drugs. A similar result of no ciprofloxacin resistance was observed by Anjum P et al²⁴ in Rawalpindi. Another local study from Pakistan by Mirza SH et al¹⁶, they reported the salmonella resistance to ciprofloxacin was observed in 65.5% of cases of typhoid fever. Yet another study by Ahmad D et al²⁵ reporting from Dhaka, a very high 90.6% of salmonella typhi isolates were found resistant to ciprofloxacin.

The above statistics explain a wide geographical variation in the resistance to ciprofloxacin and this further is supported by a strong evidence by Frost JA et al²⁶ who carried out a long study from 1991-1994 in England and Wales and showed the trend of changing resistance of salmonella to ciprofloxacin. In their study Resistance to ciprofloxacin, which increased from 0.3% in 1991 to 0.6% in 1992 and 0.8% in 1993 has doubled to 2.1% in 1994. In another study by Wain J et al²² the number of patients who were found to be having salmonella multi-drug resistance were 63% which also included ciprofloxacin. Another study by Threlfall EJ et al²⁷ 23% of *Salmonella enterica* serotype Typhi isolates from patients in the United Kingdom exhibited decreased susceptibility to ciprofloxacin, more than half were also resistant to chloramphenicol, ampicillin, and trimethoprim and important thing in their study was that most of the resistant cases had traveled to UK from India and Pakistan. The same study also reported an increasing resistance of salmonella to ciprofloxacin from 0% in 1990 to 23% in 1999.

Treatment failures with quinolones were significantly prevalent in infected patients with "nalidixic acid resistant *Salmonella typhi*" (NARST), than in those infected with "nalidixic acid sensitive *Salmonella typhi*" (NASST). Viet Nam study showed 2.1% isolates resistant to nalidixic acid with raised MICs to ciprofloxacin²². In recent years studies have been focused on fluoroquinolone resistance in *Salmonella* isolates with special reference to strains for which ciprofloxacin MICs were >0.125 mg/ml^{23,28}.

The common factors leading to salmonella resistance to ciprofloxacin reported in our study were history of ciprofloxacin use in the past (63.9%) and recurrent typhoid fever (36.1%). The reported frequency of these risk factors are bit higher if we compare them to study reported by Crump JA et al¹⁰ who observed 40% cases of ciprofloxacin resistance was caused by prior use of ciprofloxacin and 14% were caused by recurrent typhoid fever in the past. In another study reported by Ahmed D et al²⁵ from Dhaka, 88% of resistant cases to ciprofloxacin were found have used ciprofloxacin in the past.

CONCLUSION

As in many other parts of the world, salmonella resistance to ciprofloxacin is highly prevalent in our society. Prior use of ciprofloxacin and recurrent typhoid fever are the main culprits responsible for such resistance in our population. We recommend further research work over the similar objective with more comprehensive and variety of risk factors and also recommend changes in policy especially with regards to better control of endemic typhoid fever and on counter availability of antibiotics.

Author's Contribution:

Concept & Design of Study: Muhammad Khalid
 Drafting: Abdul Hannan, Nizam Muhammad Darwesh
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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