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ORIGINAL ARTICLE

Frequency of antibiotic resistance in enteric fever both naïve and treated patients in our population.

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ABSTRACT… Objective: To assess the antibiotic resistance in enteric fever in our population. **Study Design:** Observation study. **Setting:** OPD and indoor patients in three tertiary care hospitals of Lahore. **Period:** May 2018 to September 2018. **Material & Methods:** We selected patients with symptoms and signs of enteric fever randomly in our out door and ER departments. Blood cultures were sent before start of any antibiotic. Patients with Positive culture were enrolled for this study. **Results:** We enrolled 180 patients, including 123 (68.3%) male patients and 57 (31.7%) were female patients. We divided these patients in three groups, below 25 years 38(21.1%) patients, from 26 to 50 years 98(54.4%), and above 50 years 44(24.4%) patients. Out of 180 patients 138(76.7%) patients took antibiotic before coming to us, 42 (23.3%) were naïve patients. We found 108 (60%) patient having quinolone resistance and 72 (40%) were sensitive to floroquinolones, 88 (48.9%) patients were cephalosporin resistant and 12 (6.7%) were macrolide resistant. We did not check the sensitivity of chloramphenicol, ampicillin and nalidixic acid as it is already proven resistance of these antibiotics. Among all patients quinolones resistance was much higher and resistance against cephalosporin is also increasing and few cases were found to be resistant to even macrolides, although resistance against macrolides is low up to now. **Conclusion:** Antibiotic resistance is gradually increasing rapidly even against those drugs which were proven very effective against salmonella typhi and paratyphi infections. Younger population (26-50years) had much more resistance than below 25 and above 50 years patients. Due to such prevalence of antibiotic resistance, few antibiotics are left for the treatment of enteric fever, which lead not only to high morbidity and mortality in these patients but a great financial burden for developing countries like Pakistan. Patients with positive blood culture of salmonella were included in this study. Patients with other causes of fever, malaria, Tb, respiratory infections, and with negative blood culture.

Key words: Antibiotic Resistance, Blood Culture, Enteric Fever, Multi-drug Resistance, Salmonella Bacteria.

INTRODUCTION

Enteric fever is one of the common gastrointestinal infections with systemic clinical manifestations caused by Salmonella typhi and Salmonella paratyphi. The mode of transmission remains the oro-fecal route while humans are considered the only reservoir of this infection. Clinical symptoms predominantly manifest within 14 days of infection, commonly in the form of abdominal pain, loose stools, vomiting and fever. This infection may occur with atypical findings and included in the differential of fever of unknown origin. Enteric fever is a global health issue with number of morbidity and mortality. It is one of common infections in our population especially during summer and rainy season. According to recent data upto 21 million typhoid cases and 128,000-161,000 typhoid related deaths occur annually worldwide.[1,2] Mortality rate goes as high as 30% in untreated or inappropriately treated cases, however if treatment started timely mortality can be reduced to less than 1%.[3] It has been estimated that only in USA 35,000 deaths occur due to resistant salmonella species.[4] multi-drug resistant (MDR) and an extended drug resistant (XDR) enteric fever has caused increased morbidity and mortality in Asia and Africa.[5,6]

In 1940, first effective antibiotic was discovered to properly treat enteric fever. With passage

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of time newer and more effective drugs were discovered but on the other hand, enteric fever is caused by quickly evolved bacterium that has developed defenses against these drugs. The number and proportion of enteric fever cases which developed resistance to one or more drugs is gradually increasing globally and even more newer antibiotics that were very effective for enteric fever treatment, now becoming less effective and even becoming resistant.

Multi-drug resistant (MDR) enteric fever is defined as having resistance to three first line antibiotics, chloramphenicol, ampicillin and co-trimaxazole first appeared in 1970.[7,8]

In response to MDR- Enteric fever, floroquinolones became the drug of choice to treat enteric fever from1990 to on-ward.[9] Due to frequent use of floroquinolones leading to emergence of floroquinolone resistant-strains which are wide spread in parts of Asia and especially in our country. As it is known floroquinolones are widely used to treat enteric fever even on counter-sale of these drugs, which further added to resistance against these drugs in our population producing floroquinolones resistant strains enteric fever. After the prevailing resistance against floroquinolones, third generation cephalosporins were considered as drugs of choice to treat this infection, unluckily with passage of time, Even most cases of enteric fever are now resistant to 3rd generation cephalosporin.

The recent emergence of a new form of super-bug extensively drug-resistant (XDR) typhoid fever in 2016 in Pakistan developed in some areas of Karachi, also reported to WHO.[10] This strain of salmonella was only sensitive of Azithromycin and carbapenems. Now a day resistance against azithromycin is also emerging. Emerging resistance has spread geographically due to factors such as increasing travel connectivity, affecting those in endemic regions and travelers alike.[11] Due to XDR-strains the rate of morbidity and mortality is increasing.

As we know antibiotic resistance is increasing all over the World but it is an alarming situation in developing countries like Pakistan, so we decided to conduct this study to know the prevalence of resistance in our population.

To assess the efficacy of antibiotics for the treatment of typhoid fever to reduce incidence of resistance and also reduce economic burden.

MATERIAL & METHODS

This observational study was conducted at three tertiary care hospitals; Fatima Memorial hospital, Saadan Hospital and Alshafi hospital in the departments of Medicine, in collaboration with the department of Microbiology from May 2018 to September 2018. This study was approved by ethical review boards of hospitals (FMK-15/08/2022-IRB-1078). All information was entered in the structured, easily understandable questionnaire for patients. We attached performa to all patients with treatment files in two languages both English and Urdu after their written consent. We selected patients randomly having symptoms and signs of enteric fever, in three tertiary care hospitals having proper set up of laboratory, two blood samples were drawn from two different sites and sent for culture and sensitivity. Patients with Positive isolates of salmonella typhi or paratyphi were included in our study.

Patients of age above 18 and upto 65 years were included in our study. We divided these patients in three categories regarding age of patients. First group was below age 25 years, second group was having patients with age from 26 – 50 years and third group had patients age above 50 years. Antibiotic resistance was assessed in all three groups of patients by seeing the sensitivity of antibiotics in culture reports. We categorized these patients in two groups regarding the use of antibiotics before presenting to us and naïve patients. All the data were analyzed in the SPSS version 25.

As it had been established the resistance against of three primary drugs (chloramphenicol, trimethoprim-sulphamethaxazole, and ampicillin), for this we did not check the sensitivity of these drugs. The drugs which are commonly used and considered as drugs of choice (floroquinolones

and third generation cephalosporins) for the treatment of typhoid fever were assessed for resistance.

Inclusion Criteria

We selected those patients which had positive blood culture for salmonella typhi in blood samples.

Exclusion Criteria

All patients who had fever of other causes, pregnant women, respiratory infections and patients with blood culture negative for salmonella typhi.

RESULTS

A total of 180 patients, 68.3% (n=123) were male and 31.7% (n=57) were female patients. We divided these patients in three groups, age below 25 years, 38(21.1%) patients, from 26 to 50 years 98(54.4%), and above 50 years 44(24.4%) patients. Out of 180 patients, 138(76.7%) patients took antibiotic before coming to us, 42 (23.3%) were naïve patients. We found 108 (60%) patient having quinolone resistance and 72 (40%) were sensitive to floroquinolones, 88 (48.9%) patients were cephalosporin resistant and 12 (6.7%) were macrolide resistant. Antibiotic resistance was highest among patients with age from 26-50 years. Similarly resistance was predominantly more in patients who had already took antibiotics before presenting to us. Antibiotic resistance was more in male patients as compared to female patients. These patients had taken antibiotics either from the counter sale or used under dose and short duration of time than as has been recommended.

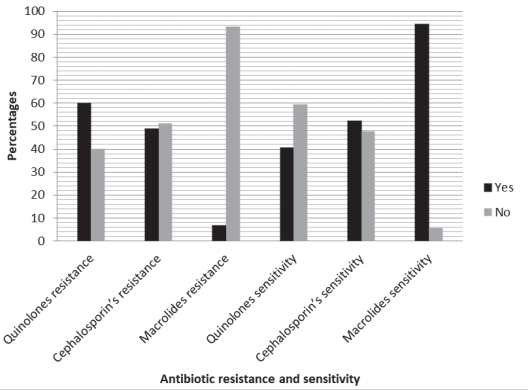

Figure-1. Antibiotic resistance and sensitivity among the patients with and without the history of antibiotics.

Antibiotic	Route of Administration	MDR	XDR
Chloramphenicol	Oral, intravenous	X	X
Co-trimoxazole	Oral, intravenous	X	X
Ampicillin	Oral, intramuscular, intravenous	X	X
Ciprofloxacin	Oral, intravenous	X	
Ceftriaxone	Intramuscular, intravenous	X	
Azithromycin	Oral		
Meropenem	Intravenous		
Tigecycline	Intravenous		

Abbreviations: MDR, multiple drug resistance; XDR, extensively drug resistant.

Table-I. Treatment options for different resistance classes of S. Typhi

Variables		Frequency	Per-centage
Age category	Less than 25 years	38	21.1
	26 to 50 years	98	54.4
	Above 50 years	44	24.4
Gender	Male	123	68.3
	Female	57	31.7
Antibiotic History	Yes	138	76.7
	No	42	23.3
Quinolones resistance	Yes	108	60
	No	72	40
Cephalosporin's resistance	Yes	88	48.9
	No	92	51.1
Macrolides resistance	Yes	12	6.7
	No	168	93.3
Quinolones sensitivity	Yes	73	40.6
	No	107	59.4
Cephalosporin's sensitivity	Yes	94	52.2
	No	86	47.8
Macrolides sensitivity	Yes	170	94.4
	No	10	5.6

Table-II. Distribution of demographic and history of antibiotics of subjects

Variable		Antibiotic History		P-Value
		Yes	No	
Quinolones resistance	Yes	97(53.9)	11(6.1)	0.0001
	No	41(22.8)	31(17.2)	
Cephalosporin's resistance	Yes	72(40.0)	16(8.9)	0.117
	No	66(36.7)	26(14.4)	
Macrolides resistance	Yes	10(5.6)	2(1.1)	0.735
	No	128(71.1)	40(22.2)	
Quinolones sensitivity	Yes	41(22.8)	32(17.8)	0.0001
	No	97(53.9)	10(5.6)	
Cephalosporin's sensitivity	Yes	67(37.2)	27(15.0)	0.080
	No	71(39.4)	15(8.3)	
Macrolides sensitivity	Yes	129(71.7)	41(22.8)	0.457
	No	9(5.0)	1(0.6)	

Table-III. Comparison of antibiotic resistance and sensitivity among the patients with and without the history of antibiotics

Variable		Gender		P-Value
		Male	Female	
Quinolones resistance	Yes	76(42.2)	32(17.8)	0.515
	No	47(26.1)	25(13.9)	
Cephalosporin's resistance	Yes	62(34.4)	26(14.4)	0.631
	No	61(33.9)	31(17.2)	
Macrolides resistance	Yes	10(5.6)	2(1.1)	0.344
	No	113(62.8)	55(30.6)	
Quinolones sensitivity	Yes	47(26.1)	26(14.4)	0.415
	No	76(42.2)	31(17.2)	
Cephalosporin's sensitivity	Yes	61(33.9)	33(18.3)	0.338
	No	62(34.4)	24(13.3)	
Macrolides sensitivity	Yes	114(63.3)	56(31.1)	0.173
	No	9(5.0)	1(0.6)	

Table-III. Comparison of antibiotic resistance and sensitivity with respect to gender

Variable		Age			P-Value
		Less Than 25	26 to 50	Above 50	
Quinolones resistance	Yes	20 (11.1)	58 (32.2)	30 (16.7)	0.347
	No	18 (10.0)	40 (22.2)	14 (7.8)	
Cephalosporin's resistance	Yes	17 (9.4)	48 (26.7)	23 (12.8)	0.793
	No	21 (11.7)	50 (27.8)	21 (11.7)	
Macrolides resistance	Yes	2 (1.1)	5 (2.8)	5 (2.8)	0.356
	No	36 (20.0)	93 (51.7)	39 (21.7)	
Quinolones sensitivity	Yes	18 (10.0)	41 (22.8)	14 (7.8)	0.334
	No	20 (11.1)	57 (31.7)	30 (16.7)	
Cephalosporin's sensitivity	Yes	21 (11.7)	52 (28.9)	21 (11.7)	0.769
	No	17 (9.4)	46 (25.6)	23 (12.8)	
Macrolides sensitivity	Yes	36 (20.0)	94 (52.2)	40 (22.2)	0.48
	No	2 (1.1)	4 (2.2)	4 (2.2)	

Table-IV. Comparison of antibiotic resistance and sensitivity with respect to age

DISCUSSION

Antibiotic resistance in enteric fever is growing concern for whole world but much concern is for developing countries especially indo-Pak region where resistance of antibiotics against salmonella is highest.[12] It puts a huge economic burden on our country but also a great threat for patients developing this infection.

Resistance of antibiotics emerged in 1948 with the first line drugs which led to development of resistant strains of salmonella typhi as early as 1950 in the UK.[13,14] Later, in 1980s cases of MDR typhoid were reported in South Asia.[15] Floroquinolones were considered drug of choice for typhoid fever after 1980s, then resistance to floroquinolones was reported as early as in 1992 in UK, ciprofloxacin and parenteral ceftriaxone have been used for a significant time with promising results. In the last decade an extended drug-resistant typhoid fever cases were reported in Hyderabad, Pakistan in November 2016. Over of a period of two years more than 5000 cases of XDR have been documented in Province Sindh of Pakistan. Few cases of XDR had been reported from UK and also from USA. In our country, frequent and injudicious use of antibiotics due to availability of these antibiotics over the counter sale, has played a major role in the development of antibiotic resistant strains of salmonella.

In our study floroquinolones showed highest

resistance against salmonella species, as it was widely used in our patients, resistance of quinolones was 60% in already taken or naïve patients, resistance was on its peak in age group from 26 to 50 years and there was predominance of males as compared to female patients. The increase of resistance of quinolones in our study is perhaps a direct consequence of their indiscriminate prescription not only for typhoid fever but also for other infections which is quite similar to other study.[16]

In this alarming situation of resistance, azithromycin remained only oral antibiotic available for the treatment of typhoid fever, which is also at risk of resistance due to use of this drug for upper and lower respiratory infections. In our study resistance against macrolides was also noted, the other options for the treatment of XDR typhoid with carbapenem, which is not cost-effective for the patients and a huge economic burden on developing countries. Our study results are similar with the study conducted which showed difficulty in the treatment of typhoid infection.[17,18]

CONCLUSION

As resistance against common infections especially against salmonella is gradually worsening, careful selection of antibiotic especially culture based, should be prescribed to reduce the further worsening of antibiotic resistance.

Further studies are required from different areas of world to assess the frequency of resistance against salmonella typhi and para-typhi. A combined disciplinary approach for proper mass education of community for proper sanitation, vaccination, and culture based antibiotics for infection especially typhoid fever can reduce economic burden not only globally and particularly for growing countries like Pakistan, and reduce morbidity and mortality of typhoid fever.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Mirza M. Ilyas Baig	Collection of data.	
2	Hafiz Abdul-Rauf	Collection of data & SPSS.	
3	Arzinda Fatima	Discussion + References.