



Study of antibiotic resistance in patients of enteric perforation in a tertiary care hospital.

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ABSTRACT... Objective: To study the clinical outcomes and determine the antibiotic resistance in patients of enteric perforation in a tertiary care hospital. **Study Design:** Cross Sectional study. **Setting:** Department of General Surgery at Nishtar Hospital, Multan. **Period:** May 2017 to December 2019. **Material & Methods:** Sample size was calculated to be 97 with a confidence level of 95% and margin of error of 10%. We collected data from 100 patients. All the surgeries were done by the same team of consultant surgeons. The abdomen was closed by the same surgical team using the same surgical technique to avoid any bias. All the continuous variables were reported as mean \pm standard deviation. The antibiotic resistance was compared with the number of patients with wound infections, burst abdomen, ICU admissions and number of in-hospital stay days. Categorical variables were compared using Chi square test for Independence. The number of in-hospital stay days were compared using Student t-test. The results were compiled using SPSS version 20. **Results:** Our result indicated that a patient had a greater chance of having a burst abdomen and wound infection if there was resistance to ciprofloxacin or ceftriaxone. Similar results were obtained for ICU admissions. There was a significantly longer in-hospital stay observed for patients who were resistant to the standard regimen of Ceftriaxone. **Conclusion:** It seems only rationale that the patients susceptible should be treated with Imipinem for 2 weeks as the empirical therapy rather than the standard empirical therapy of ceftriaxone and ciprofloxacin. The blood cultures can be sent before starting Imipinem and treatment management plan changed if the culture results are sensitive for the empiric antibiotics.

Key words: Antibiotic Resistance, Enteric Perforation, Infectious Diseases.

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INTRODUCTION

Typhoid fever has been deemed as the most prevalent bloodstream infection in the South Asian region.^{1,2} The disease is caused by *Salmonella enterica typhi* and *Paratyphi. A*. Regardless of the measures to control the disease, this has posed as a burden on public health in South Asia. Some seven million people are estimated to be effected by this calamity every year with 75000 losing the battle; though this figure is thought to be an understatement, mainly due to limited population surveillance systems.³⁻⁵ Patients in surgical department usually present with the complications of typhoid fever; intestinal perforation being the most sinister of the lot. It usually occurs in the third week of infection and

may require resection or exteriorization.^{6,7}

Multiple drug resistance has been a major problem in the treatment of Typhoid and other infectious diseases. Initially Chloramphenicol was used for the treatment of typhoid fever. It had a success in the beginning but the cases of resistance started to emerge in 1960s and 1970s.⁸⁻¹⁰ Shortly after, in 1972 there were reports of multiple drug resistance typhoid fever. They weren't just resistant to chloramphenicol but also showed resistance against ampicillin and trimethoprim-sulfamethoxazole.¹¹⁻¹³ In 2017, certain reports have suggested the presence of strains of *Salmonella typhi* in Sindh, Pakistan, that are not only resistant to the first line drugs

used against typhoid fever but stand tall against the likes of fluoroquinolones and third generation cephalosporins.¹⁴⁻¹⁶ Hence called XDR (extended drug resistance) *Salmonella typhi*.

OBJECTIVE

To study the clinical outcomes and determine the antibiotic resistance in patients of enteric perforation in a tertiary care hospital. The sampling technique used was non probability consecutive sampling. The patients included were the ones who have perforation due to typhoid fever.

Cross sectional study. This study was conducted at General Surgery Department of Nishtar Hospital, Multan. From May 2017 to December 2019. This was a cross sectional study.

MATERIAL & METHODS

Approval from ethical review board was obtained. The sampling technique used was non probability consecutive sampling. The patients included were the ones who have perforation due to typhoid fever. Patients of all ages and both genders were included. Patients who had been taking antibiotics for the fever or the ones having perforation for any other case were excluded. Sensitivity was checked was for Ampicillin, Trimethoprim Sulfamethoxazole, Third generation cephalosporins, Flouroquinolones and Meropenems.

Sample size was calculated to be 97 with a confidence level of 95% and margin of error of 10%. We collected data from 100 patients. A written informed consent was taken from all patients before surgery.

Enteric perforation was defined as hole in the anti-mesenteric part of the wall of distal ileum. Symptoms include severe abdominal pain and tenderness. Diagnosis of perforated ileum will be made using Plain supine x-rays of the abdomen (presence of air in the abdominal cavity on x-rays) along with the presenting symptoms (severe abdominal pain) and physical examination (presence of abdominal distension and tenderness) of the patient.¹⁷⁻¹⁹

All the surgeries were done by the same team of consultant surgeons. The abdomen was closed by the same surgical team using the same surgical technique to avoid any bias. I (the investigator) was assistant in all procedure. Patients follow-up was done after 1 week, 2 weeks and one month of discharge. All the gathered information was noted on a proforma.

Antibiotic resistance was checked on samples of blood culture which will be taken before the first dose of antibiotic. Patients were treated with empirical therapy of ceftriaxone and ciprofloxacin²⁰ until the results of sensitivity were received. The blood sample were sent to the Nishtar Pathology laboratory.

Patients were closely followed up for burst abdomen while they were admitted in the ward and for wound infection according to the Southampton scoring system.^{21,22} The wound infection was observed subsequently on follow up visits as well. Patient was asked to have a follow up check-up weekly for one month after discharge.

The burst abdomen includes the patients in which the continuation of the disease process led to the giving way of the abdominal layers or a perforation proximal to the ileostomy lead to re exploration of the patient

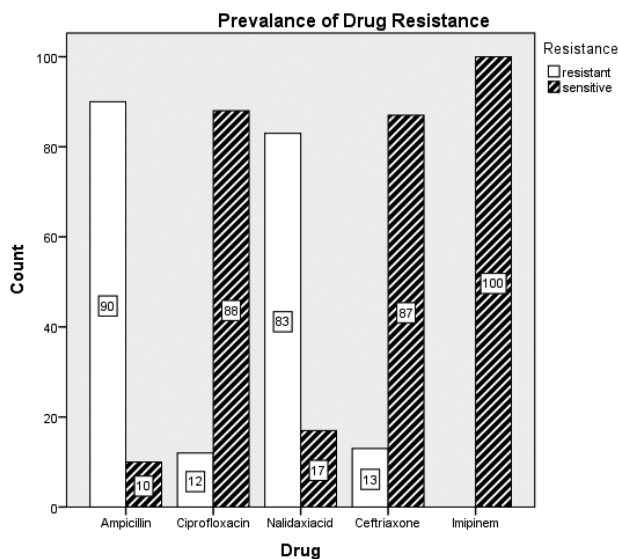
All the continuous variables were reported as mean \pm standard deviation. The antibiotic resistance was compared with the number of patients with wound infections, burst abdomen, ICU admissions and number of in-hospital stay days. Categorical variables were compared using Chi square test for Independence. The number of in-hospital stay days were compared using Student t-test. The results were compiled using SPSS version 20.

RESULTS

The prevalence of drug resistance for different groups is demonstrated in Figure-1.

To assess the length of hospital-stay in patients, Student t test was applied. There was a significantly longer in-hospital stay observed

for patients who were resistant to the standard regimen of Ceftriaxone.



Our result indicated that a patient had a greater chance of having a burst abdomen if there was resistance to ciprofloxacin or ceftriaxone.

Similarly, the rate of wound infection, as assessed by Southampton Scoring²³, was higher in patients with ciprofloxacin & ceftriaxone resistance.

Similar results were obtained for the rate of surgical wound infection & the ICU admissions.

ICU admissions were also comparable to these aforementioned results. The fact that resistant patients failed to respond to the empiric therapy, led to multiple complications of typhoid fever. These complications also included re exploration due to another perforation in the terminal ileum.

DISCUSSION

Pakistan is one of the few regions of the world where the extensively drug resistant Salmonella Typhihas beenreported.^{23,24}

Drug	Resistance	N	Hospital Stay (days) Mean ± SD	P-Value
Ampicillin	resistant	90	8.69 ± 6.81	0.93
	sensitive	10	8.90 ± 7.74	
Ciprofloxacin	resistant	12	11.25 ± 6.97	0.17
	sensitive	88	8.36 ± 6.82	
Nalidaxiacid	resistant	83	8.96 ± 7.02	0.42
	sensitive	17	7.47 ± 6.10	
Ceftriaxone	resistant	13	13.38 ± 7.65	<0.01
	sensitive	87	8.01 ± 6.50	
Imipinem	resistant	0 ^a	.	.-
	sensitive	100	8.7100 ± 6.86713	

Table-I. Difference between in-hospital stay days based on drug resistance, checked by student t test

Drug	Burst Abdomen	Resistance		Total	P-Value
		Resistant	Sensitive		
Ampicillin	Yes	10	1	11	1.00
	No	80	9	89	
Ciprofloxacin	Yes	7	4	11	< 0.01
	No	5	84	89	
Nalidixic acid	Yes	9	2	11	1.00
	No	74	15	89	
Ceftriaxone	Yes	6	5	11	< 0.01
	No	7	82	89	
Imipinem	Yes		11	11	No data
	No		89	89	

Table-II. Comparison of burst abdomen with drug resistance by Chi Square Test

Drug Resistance vs Wound Infection					
Drug	Wound Infection	Resistance		Total	P-Value
		Resistant	Sensitive		
Ampicillin	Yes	18	3	21	0.43
	No	72	7	79	
Ciprofloxacin	Yes	8	13	21	< 0.01
	No	4	75	79	
Nalidixic acid	Yes	18	3	21	1.0
	No	65	14	79	
Ceftriaxone	Yes	11	10	21	< 0.01
	No	2	77	79	
Imipinem	Yes		21	21	No data
	No		79	79	

Table-III. Comparison of wound Infection with drug resistance by Chi Square Test

Drug Resistance vs ICU Admissions					
Drug	ICU Admissions	Resistance		Total	P-Value
		resistant	sensitive		
Ampicillin	Yes	8	1	9	1.00
	No	82	9	91	
Ciprofloxacin	Yes	5	4	9	.001
	No	7	84	91	
Nalidixic acid	Yes	8	1	9	1.00
	No	75	16	91	
Ceftriaxone	Yes	5	4	9	0.002
	No	8	83	91	
Imipinem	Yes		9	9	No data
	No		91	91	

Table-IV. Comparison of ICU Admissions with drug resistance by Chi Square Test

The result of these resistant strains has not only posed a burden on our healthcare system but has made us as clinicians unsure if the empirical therapy that we are going to start a patient is going to get the job done effectively.²⁵ The data collected in this research has shown that ampicillin and Nalidixic acid are no longer nearly enough for this battle against the resistant typhoid strains. The worrisome is the fact that resistance seem to be emerging against ciprofloxacin and ceftriaxone as well. The patients with the resistance against the empiric treatment did not only have a longer stay at the hospital but also a greater incidence of burst abdomen and a greater deal of ICU admissions. This problem of typhoid outbreak has been reported in people who have recently travelled to Pakistan. Recommendations have been made that since these strains are susceptible to imipinems and azithromycin, the susceptible patients should be treated with these

antibiotics as first line medications rather than the standard empirical treatment.²⁴

Not only this but the wound infection rates in the patients who had been infected with resistant strains of Salmonella Typhi were significant as compared with the patients with sensitive strains. The probable reason for this is the initial treatment with the empiric therapy failed to curb the infection and by the time culture results arrived and we started the patients on imipenem, the wound infection had already set in.

CONCLUSION

Majority of the patients were resistant to ampicillin and nalidixic acid. There is an emergent resistance to ciprofloxacin and ceftriaxone that render patients prone to complications and extended hospital stay. The resistance against imipenem in

Salmonella typhi is still very low.




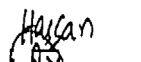

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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3	Junaid Hashmi	Manuscript writing.	
4	Waqas Anjum	Data collection and Data entry.	
5	Hasaan Rafique	Data collection and Data entry.	
6	Ali Rabbani	Proofreading.	