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Sensitivity Pattern for Isolates of Salmonella Typhi on Blood Culture in Children with Enteric Fever

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ABSTRACT

Background: Typhoid or Enteric fever (EF) is caused by salmonella typhi (ST) and major health concern in several developing countries. Understanding of occurrence of the ST and pattern of antibiotic sensitivity have great significance for prescription of the correct antibiotic treatment. **Objective:** To determine the antibiotic sensitivity pattern in children with positive blood culture for salmonella typhi. **Study Design:** Cross sectional study. **Settings:** Department of Pediatrics, Faisalabad Medical University / Allied Hospital, Faisalabad Pakistan. **Duration:** 1 Year from Jan 2019 to Dec 2019. **Methods:** 196 children age 1 – 12 years, of both gender, presenting in outpatient department (OPD) and inpatient department (IPD) with fever for ≥ 3 days were included through Non-probability consecutive sampling technique. Blood culture was sent and antibiotic sensitivity of ST isolates noted in terms of drugs sensitivity, multidrug resistance and extensively drug resistance. Data analyzed using SPSS software V.20. **Results:** In this study, the mean age of children was 6.15 ± 3.37 years. There were 105 (53.6%) male children while 91 (46.4%) were females children. The mean duration of fever was 5.62 ± 1.66 days. There were 127 (64.8%) children who were taking treatment for fever before presenting for culture and confirmation of typhoid fever. Total 103 (52.6%) children had drug sensitivity to antibiotics on blood culture, 44 (22.5%) had multidrug resistance (MDR) while 49 (25%) had extensively drug resistance (XDR). **Conclusion:** Frequency of MDR and XDR typhoid cases have significantly increased.

Keywords: *Blood culture, Enteric fever, Salmonella Typhi, Sensitivity pattern, MDR, XDR.*

INTRODUCTION

Enteric or typhoid fever is an endemic disease in several developing countries, especially in Indo-Pak sub-continent.[1] The complications of enteric fever are highest in the Asian continent having rate of 93% of fever episodes occurring in this area. Acceding to the estimate, the incidence of typhoid is 110 cases / 100,000 population in Southeast Asian countries. This is the 3rd highest incidence of the disease in any region of the world. Pakistan is also situated in this region with high probability.[2] The development in the standards of the public health care cause the significant reduction in the occurrence of the enteric fever in the counties of developed region.[3] Currently, owing to the changing trend in the clinical presentation of enteric fever and also the development of the multidrug resistance of the individuals, enteric fever has become a very problematic disease to be correctly diagnosed and appropriate therapy.[4] The use of chloramphenicol, ampicillin and cotrimoxazole have become infrequent. Additionally, development of increasing resistance to fluoroquinolones is a growing challenge.[5] Shrestha *et al*., reported that out of 130 blood culture samples of salmonella species, the sensitivity to Ciprofloxacin and Ofloxacin were 5.4% each whereas the sensitivity to Chloramphenicol, Cotrimoxazole, Gentamycin and Azithromycin were 100%. Nalidixic Acid Resistance Salmonella typhi strains were 87.7%.[6]

From Pakistan, Laghari *et al*., conducted a similar study. They observed that there were 81.1% children who were diagnosed with typhoid due to salmonella typhi and 18.9% had isolates of S. paratyphi, cefixime showed 60.9%

sensitivity while ceftriaxone showed 65.8% sensitivity to antibiotics. Sensitivity of ciprofloxacin was observed in 50.1% isolates of S. typhi.[7]

Though literature, an extensive disparity was observed for the trend of antibiotics sensitivity in few isolates of Salmonella Typhi (S. typhi), as recommended in several studies which were conducted in various regions of the world. Understanding of occurrence of the S. Typhi and pattern of antibiotic sensitivity have great significance for prescription of the correct antibiotic treatment which would help decreasing treatment failure rates, duration of hospitalization and cost of treatment. Thus, this would help to better understanding of the antibiotic sensitivity against bacterium involved in typhoid fever in children.

METHODS

This cross-sectional study was conducted at Department of Pediatrics, Allied Hospital, Faisalabad Pakistan in the duration of 1 Year from Jan 2019 to Dec 2019.

Sample size of n = 196 (blood culture positive enteric fever) by using Confidence level, 1-α = 95 %, Margin of error = d = 0.07 and drug sensitivity i.e. P = 50 %. Non-probability consecutive sampling technique was used.

Children age 1 – 12 years, of both gender, presenting in OPD or IPD with fever (temperature > 101oF) for ≥ 3 days with any two or more of the clinical manifestations of vomiting, loose motion, pain abdomen, seizures, altered sensorium, hepatomegaly, splenomegaly, coated tongue and rash, with or without any complication of Enteric fever, with positive blood culture for ST, which is defined as per CLSI guidelines 10. The sample is to be sub-cultured onto MacConkey agar. Non-lactose-fermenting colonies of bacterium processed and biochemical reactions are identified and confirmed by grouping and type-specific Salmonella anti-sera were included in the study. Parents not consenting for participation in the study were excluded from the study.

The study was conducted after permission from institutional ethical review committee. A total of 196 patients with culture proven S. Typhi fever fulfilling the eligibility criteria were enrolled after informed written consent from the parents explaining the study purpose. Demographic characteristics including age, gender, duration of fever, and on treatment when blood culture was sent were noted on the proforma. Antibiotic sensitivity of S. Typhi isolates was noted as per CLSI breakpoints. Patients were categorized to sensitive (if sensitive to first line drugs), MDR and XDR cases.

Antibiotic sensitivity done by using Mueller Hinton agar medium by applying disc diffusion method against antibiotics i.e., ampicillin (10µgm), cotrimoxazole (25µgm), ciprofloxacin (5µgm), ceftriaxone (30µgm), chloramphenicol (30µgm), azithromycin (15µgm), meropenem (30µgm) and nalidixic acid (30µgm). The disk strength and zone-size interpretation done by CLSI guidelines[8] 2018.

Drug sensitive typhoid:[9] Salmonella Typhi sensitive to first line drugs i.e. ampicillin, co-trimoxazole and chloramphenicol is labelled as drug sensitive typhoid.

Multidrug Resistant (MDR) typhoid:[9] Salmonella Typhi resistant to first line drugs i.e. ampicillin, co-trimoxazole and chloramphenicol is labelled as MDR typhoid.

Extensively drug resistant (XDR) typhoid:[9] MDR cases who are also resistant to Ciprofloxacin and Cephalosporin (Ceftriaxone) are labelled as XDR typhoid.

Data was entered in and analyzed using Statistical Package for Social Science (SPSS) software version 20, (IBM Corp, Chicago, USA). Numeric variables like age and duration of illness were described using mean ± standard deviation. Qualitative data like gender, on treatment before blood culture, vaccinated for typhoid, sensitivity to different drugs and typhoid fever categories – drug sensitive, MDR, XDR were described as frequency and percentage.

Table 1: Antibiotic sensitivity Breakpoint Chart

Antibiotic	Sensitivity area (in mm)
Ampicilin	≥ 17
Cotrimoxazole	≥ 16
Chloramphenicol	≥ 18
Ciprofloxacin	≥ 13
Ceftriaxone	≥ 23
Azithromycim	≥ 13
Imipenem	≥ 23
Meropenem	≥ 23

RESULTS

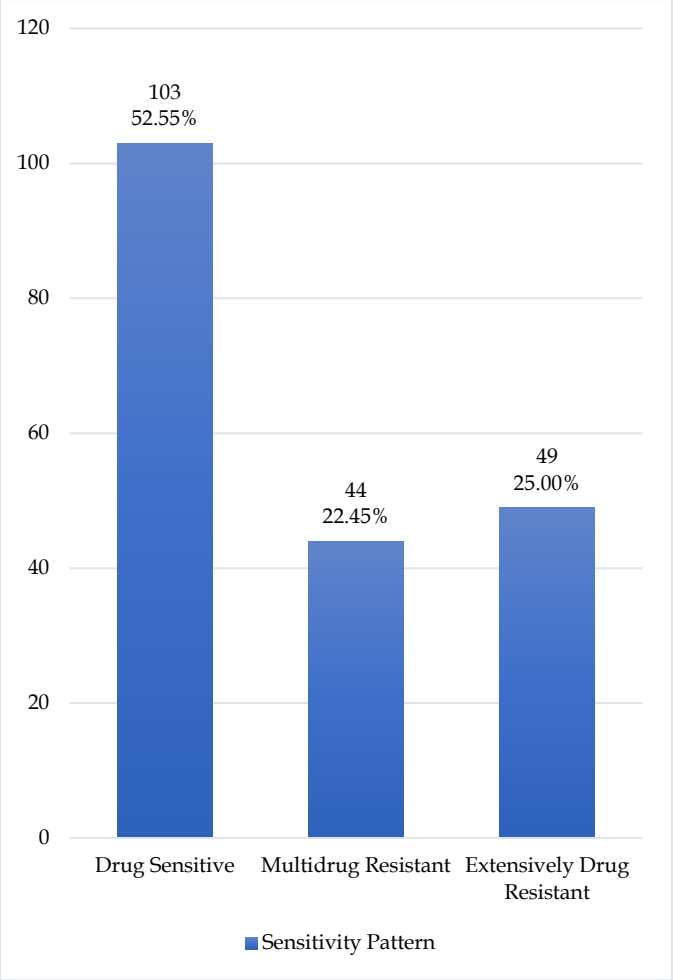
In this study, the mean age of children was 6.15 ± 3.37 years. There were 105 (53.6%) male children while 91 (46.4%) were females children. The mean duration of fever was 5.62 ± 1.66 days. There were 127 (64.8%) children who were taking treatment for fever before presenting for culture and confirmation of typhoid fever Table 2.

In the study, 103 (52.6%) children had drug sensitivity to antibiotics on blood culture, 44 (22.5%) had multidrug resistance while 49 (25%) had extensively drug resistance. Figure 1.

Table 2: Demographics of patients

Number of Patients (N)		196
Age (years)		6.15 ± 3.37
Gender	**Male**	105 (53.6%)
	Female	91 (46.4%)
Duration of fever (days)		5.62 ± 1.66
On treatment before culture		127 (64.8%)
Vaccinated of typhoid		15 (7.7%)

Figure 1: Drug sensitivity pattern of S. Typhi



On stratification of data for age of children, there is no difference in antibiotic sensitivity pattern whether children aged <6 years or >6 years (p >0.05). Similarly, data is stratified for gender of children and it is noticed that there is no difference in antibiotic sensitivity pattern among both gender (p >0.05). The difference is also insignificant whether children have fever for 3-5 days or 6-8 days, whether on treatment or were not taking treatment. (Table 2)

Table 2: Drug sensitivity pattern of S. Typhi with respect to confounders

		Sensitivity			Total (n=196)	p-value
		Drug Sensitive (n=103)	Multidrug Resistant (n=44)	Extensively Drug Resistant (n=49)		
Age (years)	1-5	48	13	26	87	0.097
	6-10	47	23	17	87	
	>10	8	8	6	22	
Gender	Male	53	21	31	105	0.267
	Female	50	23	18	91	
Duration of fever (days)	3-5	56	20	18	94	0.118
	6-8	47	24	31	102	
On Treatment	Yes	64	30	33	127	0.712
	No	39	14	16	69	
Vaccinated	Yes	6	4	5	15	0.587
	No	97	40	44	181	

DISCUSSION

Typhoid or enteric fever is one of the commonest bacterial infection of bloodstream in countries of South Asia. It is normally developed due to presence of Salmonella enterica serovars Typhi & Para typhi A.[4] It is still a highly prevalent disease that imposes a great burden of health all over the world. It is estimated that around 21.6–26.9 million people develop typhoid every year while 216,000 mortality occurs because of Salmonella Typhi.[10]

Antibiotics are the only effective way to cure typhoid fever in children. Ceftriaxone and ciprofloxacin are the two most commonly prescribed and effective antibiotics for typhoid fever. Ciprofloxacin is one of the main and impotent antibiotic to cure typhoid fever. But there are also difficulties in direct application of ciprofloxacin due to resistance of individual against few antibiotics. Few old researches observed that rate of Salmonella typhimurium resistance are approximately 35%.[11]

In this study, the mean age of children was 6.15 ± 3.37 years. There were 105 (53.6%) male children while 91 (46.4%) were females children. The mean duration of fever was 5.62 ± 1.66 days. There were 127 (64.8%) children who were taking treatment for fever before presenting for culture and confirmation of typhoid fever while 15 (7.7%) were vaccinated for typhoid. We observed that 103 (52.6%) children had dug sensitivity to

antibiotics on blood culture, 44 (22.5%) had multidrug resistance while 49 (25%) had extensively drug resistance.

Since 1970s, the first report of *Salmonella* Typhi resistance to chloramphenicol, resistance to each new antimicrobial treatment has emerged relentlessly.[12] Extensively-drug resistance, i.e., resistance to amoxicillin, chloramphenicol, and co-trimoxazole, is detected in several regions of South Asia. It was concomitant to several epidemics in late 1980s & early 1990s.[4,13] According to updated data of World Health Organization, in Pakistan, few health officials say that in 2016, epidemic of extensively drug-resistance typhoid fever, affected >5200 people.[14,15]

Typhoid fever showing extensively drug-resistance is increasing in Pakistan. It increases the dreads of failure of antibiotic treatment all over the world.[16,17] One study reported that during 2016 & 2018, 29 cases of typhoid fever have been reported to travel to or from Pakistan. Those were isolates to test antimicrobial susceptibility. Out of these 29 cases, 5 (17.2%) cases had extensively drug-resistance typhoid.[18]

Multidrug resistance in cases of enteric fever is found to be the major health problem. Immunization at massive level by using oral "live attenuated Typhi 21a" or unconjugated Vi typhoid injectable vaccine, sensible antibiotics use, improvement in the sanitation conditions at public places, disposal of clean consumable water, campaigning the safe food handling practices and public health education are important in preventing Multidrug resistance.[19]

Few studies reported a changing trend in the pattern of clinical characteristics and complications of typhoid by multi-drug resistant strains. During 2005, the resistance pattern of 71% typhi were detected. During 2009, the situation was about 90% resistance to the second-generation fluroquinolones.[20]

One study found that the frequency of multidrug resistance was 67.2% of salmonella typhi in children presented with typhoid.[21] In another study, 73.6% resistant Salmonella strains to different antibiotics were found.[22]

CONCLUSION

Incidence of MDR and XDR cases of Enteric fever has significantly increased in previous years as in our study. Quinolones are the most resistant while, azithromycin and meropenem are the most sensitive drugs. Thus, these findings and antimicrobial susceptibility patterns of ST can help to decide and prescribe appropriate antimicrobial therapy which would help reducing the rate of treatment failure, incidence of complications, hospital stay and cost of the treatment.

LIMITATIONS

Some of the suspected cases of enteric fever presenting in OPD refused to hospital admission but advised blood culture and 1st line antibiotics were prescribed. Due to lack of follow up they are not included in the study.

SUGGESTIONS / RECOMMENDATIONS

Blood culture and sensitivity of every suspected case of enteric fever must be done as baseline to detect ST and determine antibiotic sensitivity as well as to improve surveilance of EF. It will help patients by decreasing duration, cost of treatment, risk of complications of EF and need of hospitalization. Currently azithromycin is 1st line oral, reliable and affordable antibiotic, ceftriaxone and meropenem are injectable antibiotics of choice.

CONFLICT OF INTEREST / DISCLOSURE

No conflict of interest to be declared.

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