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Clinical presentation with consequences and laboratory diagnosis of multi and extensive drug resistance in typhoid cases

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ABSTRACT

Background: Enteric fever is among the major problem in the health care settings of developing countries like Pakistan. Unjudicial use and over the counter availability of antibiotics lead to the emergence of multi drug resistant and extensive drug-resistant strains of salmonella outbreak which demonstrate severity of disease of the disease. Our objective is to determine the clinical presentation, consequences and antibiotic susceptibility patterns of Multi Drug Resistant (MDR) typhoid and Extensive drug resistance (XDR) typhoid cases. **Methods:** The study was conducted in the department of Microbiology, Dow Diagnostic Reference and Research Laboratory, Dow University of Health Sciences. All laboratory proven *Salmonella* positive cultures samples were selected from laboratory that were either fully or partially treated, or were taking anti-Salmonella. Clinical trends along with clinical outcomes were assessed from clinical presentation. Furthermore, Demographic details were noted. Detailed history about the presenting illness with examination findings and medications were recorded. **Results:** A total of 333 patients had positive blood culture for enteric fever, in which maximum number of XDR cases 84% (n=281) were observed in blood cultures followed by MDR salmonella in 16 % (n=52). Meropenem and azithromycin didn't show any resistance in our study. **Conclusion:** Our study has demonstrated that pediatric population is more vulnerable for developing salmonella infection. Carbapenems and azithromycin are among the last choices for the treatment of XDR cases. Analysis of our results imply stress on the implementation of preventive measures for spread of enteric fever including proper diagnosis, vaccination and good sanitation system

Key words: Antibiotic Resistance, Drug Resistance, Health Care, Typhoid Fever

Introduction

Salmonella is a capsulated, gram negative, flagellated bacterium that causes broad spectrum of diseases like enteric fever, gastroenteritis and bacteremia (1).

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Enteric fever is a serious illness characterized by gradually rising fever along with other systemic manifestations (2). Even in the era of advanced development in health care medicine thousands of people are at great risk to contracting *Salmonella* and developing life threatening symptoms of enteric fever which results in increase mortality.

Approximately, 11.9 and 26.9 million new cases of typhoid and paratyphoid fever reported annually, whereas 200,000 deaths occur yearly, across the globe (3-5).

Incidence of typhoid fever in pediatric age group of 5 to 15 years is 573/100,000(6). According to World health organization (WHO), most of the cases of typhoid fever occur in developing countries like Africa, Eastern Mediterranean, South-East Asia and Western Pacific Regions, whereas developed countries have a minimum number of typhoid cases which mostly occurs in travelers from these developing countries(7). Antibiotics invention revolutionized the treatment of typhoid fever but the emergence of resistance to antibiotics is a hallmark as it increases the death.

Chloramphenicol was the first drug that was used for the treatment of typhoid fever which became resistant in 1970s (8). After that, ampicillin and trimethoprim–sulfamethoxazole were the next options, also showed resistance in early 1990s followed by fluroquinolone (ciprofloxacin) resistance in which multi drug resistant strains emerged against these antibiotic groups. According to WHO, Multi Drug Resistant (MDR) typhoid defines as development of resistance in first line drugs like Chloramphenicol, ampicillin and trimethoprim–sulfamethoxazole. After the emergence of fluoroquinolones resistance,third generation cephalosporin like Ceftriaxone was the optimal choice of treatment for Multi Drug resistant *Salmonella*. But use of Ceftriaxone lead to the emergence of resistant cases which are giving rise to Extensive drug resistant XDR strains of *Salmonella* that are resistant to all drug available for treatment (9).

According to WHO, first index case of Extensive drug resistance (XDR) in Pakistan was reported in 2016 in Hyderabad. There were 5274 cases of Extensive drug resistance (XDR) typhoid fever were reported out of 8188 cases of typhoid fever between 2016 and 2019. Furthermore, an increase in typhoid cases has been detected throughout the pandemic, with greater than 20,000 cases being identified in Pakistan in June 2020(10).*Salmonella typhi* of Extensive drug resistant (XDR) strain is a new emerging strain with unique and exclusive clinical manifestation and consequences when compared to other strains of *Salmonella* like Multi Drug Resistant (MDR) strain. Unluckily there is a scarcity of clinical data including features and treatment response suffering from Extensive drug resistance (XDR) *Salmonella*. The purpose of this study is to evaluate the clinical trends their consequences and antibiotic susceptibility pattern of Extensive drug resistance (XDR) – typhoid fever.

Methods

The study was conducted in Department of Microbiology, Dow Diagnostic Reference and Research Laboratory, Dow University of Health Sciences. Written approval was taken from the institutional review board with referencenoIRB2650/DUHS/Approval/2022 /1129. Sample size of patients was 333, calculated with a 0.05 margin of error and 95% confidence level with the open EPi software. Three hundred and thirty three samples were collected from 1st September 2023 till 31st December. Prevalence of Extensive drug resistance (XDR) typhoid fever in Pakistan is 69% (8). Purposive sampling technique was used. No age limit and genders were included. All laboratory proven positive culture of *Salmonella* samples from laboratory that were either fully or partially treated, or were taking anti-*Salmonella* medications were included. Clinical trends were assessed from clinical presentation like fever along with the associated symptoms like diarrhea, headache,

and sore throat vomiting and abdominal pain. Clinical outcomes were defined as the consequences of disease like any complications as sepsis, abscess, intestinal perforation, neurological manifestation, recovered, died or loss to follow up were also evaluated. Furthermore, Demographic details were noted. Detailed histories about the presenting illness with examination findings medications were recorded.

Blood cultures were performed by using automated test system, BACT/ALERT in Department of Microbiology, Dow Diagnostic Reference and Research Laboratory (DDRRL), Dow University of Health Sciences (DUHS, according to the protocols of CLSI M100, 33th edition (11) . Gram stain was performed on positive blood cultures and inoculated for isolation on Chocolate and Sheep Blood Agar and MacConkey. Chocolate and Sheep Blood Agar incubated at 35°C for 16-24 hours in CO_2 conditions and MAC-conkeys in ambient air at 35°C for 16-24 hours.

Chocolate agar, Blood agar and MacConkey's plates were examined for macroscopic evidence of growth after 18-24 hours of incubation. Additional biochemical tests were performed for the identification of *Salmonella* along with serologic testing against which was done by *Salmonella* agglutinating sera. Organism was further confirmed by API 20E. AST was done against following antibiotics with their disc content which are Ampicillin (AMP) 10 µg, Ceftriaxone (CRO) 30 µg , Ciprofloxacin (CIP) 5 µg ,Trimethoprim - Sulphamethoxazole (SXT) 1.25/23.75 µg , and, Azithromycin(AZM) 15ug, Meropenem (10 ug) antibiotics will be interpreted as per 2023 CLSI guidelines (12). SPSS version 22.0 was used for analysis. Mean ± SD was computed for quantitative variables like Age etc. Frequency and percentages were computed for categorical variables like Salmonella antibiotic susceptibility, sex, specimen type and clinical symptoms of patients

Result

A total of 333 patients had positive blood culture for enteric fever from 1st September 2023 till 31st December, 2023. Among 333 patients, 62% (n=208) were males and 38% (n=125) were females. The mean age was 9.6±9.27 year ranging from 1 day to 54 years. The most effected population were children under 10 years of age 70% (n=233). Fig-I

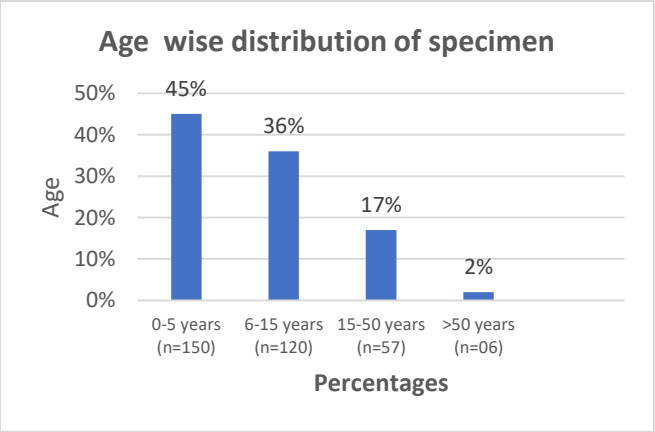

Fig-I Age wise distribution of samples

About 94% (n=313) patients were present in the outpatient department while the remaining 6% (n=20) patients seek hospital admission for further treatment. Almost all patients were presented with fever along with other signs and symptoms. Other frequently noticed symptoms, complications and outcomes were summarized in Table I.

Majority of our patient either extensive drug resistant *Salmonella typhi* (XDR) or multi drug resistant *Salmonella typhi* (MDR) are anemic and having hemoglobin level less than 12 mg/dl. White blood cell counts were seen within normal limits in most of the patients. Leukocytosis and leucopenia

were observed in one and four Extensive drug resistant salmonella patients, respectively. Neutrophilia and lymphocytosis were also observed solely extensive drug resistant *Salmonella typhi* (XDR) patient. Normal platelet count is seen in most of the admitted patients except one which has thrombocytopenia due to dengue confection. C reactive protein is greatly increased in XDR patient as compare to MDR patients. Laboratory investigations were shown in Table II.

Table I. Clinical characteristics, complications, and outcome of patients

Variables	Total (n=333)				Percentage %
Clinical signs & symptoms on presentation	XDR (n=281)		MDR (n=52)		Total (n=333)
	Outpatient (n=266)	Inpatient (n=16)	Outpatient (n=47)	Inpatient (n=4)	
Fever	266	16	47	4	100%
Abdominal pain	9	4	4	2	5.7%
Headache	10	6	2	0	5%
Vomiting	8	4	3	1	4.5%
Diarrhea	6	5	1	1	4%
Cough	9	1	3	0	4%
Body ache	2	2	0	0	0.6%
Hepatomegaly	0	2	0	1	0.9%
Splenomegaly	0	1	0	1	0.60%
Rose spots	0	1	0	0	
Variables	Total (n=333)				Percentage %
Clinical signs & symptoms on presentation	XDR (n=281)		MDR (n=52)		Total (n=333)
	Outpatient (n=266)	Inpatient (n=16)	Outpatient (n=47)	Inpatient (n=4)	
Complications					
Intestinal perforation	0	4	0	0	1.2%
Neurological manifestation (Altered mental status)	0	2	0	1	0.9%
Sepsis	0	1	0	0	0.30%
Abscess (Splenic abscess)		1	0	0	0.30%
Outcome					
Recovered	266	16	47	4	100%
Death	0	0	0	0	0%

Table II: Lab investigations of admitted patients

Admitted Patient (n=20)	Hemoglobin (12-16 g/dl)	White blood cells (WBCs) (4.5-11.0 x 10^9/L)			Differential Leukocyte count		Platelet (150-400 x 10^9/L)	C-reactive protein (CRP) mg/dl
		<4	4-12	>12	Neutrophil (40-60%)	Lymphocytes (20-40%)		
Patient 1*	10	------	11.9 x 10^9	-------	55%	35%	199 x 10^9	12
Patient 2	12.2	------	5.6 x 10^9	-------	50%	35%	256 x 10^9	90
Patient 3*	11	------	10.6 x 10^9	-------	61%	33%	110 x 10^9	36
Patient 4	9.8	------	6.2 x 10^9	-------	30%	65%	186 x 10^9	101
Patient 5	7.6	------	9.1 x 10^9	-------	27%	67%	494 x 10^9	165
Patient 6	10.1	------		17.9 x 10^9	61%	31%	324 x 10^9	100
Patient 7	12.6	------	6.0 x 10^9	-------	42%	44%	199 x 10^9	83
Patient 8*	10.4	-------	8.5 x 10^9	-------	49%	36%	621 x 10^9	14
Patient 9	12.1	1.4 x 10^9	-------	-------	66%	23%	165 x 10^9	46
Patient 10	14.4	-------	6.5 x 10^9	-------	35%	62%	490 x 10^9	90
Patient 11	7.8	-------	4 x 10^9	-------	76%	16%	530 x 10^9	189
Patient 12	6.7	-------	7 x 10^9	-------	52%	38%	250 x 10^9	30
Patient 13	8.8	-------	-------	16.5 x 10^9	34%	58%	670 x 10^9	72
Patient 14	9.6	-------	-------	19.2 x 10^9	22%	13%	325 x 10^9	210
Patient 15	11.5	-------	9.6 x 10^9	-------	61%	32%	666 x 10^9	150
Patient 16*	10.4	-------	5.4 x 10^9	-------	54%	36%	126 x 10^9	60
Patient 17	9.2	-------	10.2 x 10^9	-------	33%	59%	429 x 10^9	96
Patient 18	8.5	-------	8 x 10^9	-------	37%	53%	87 x 10^9	39
Patient 19	8.3	-------	-------	22 x 10^9	54%	39%	533 x 10^9	77
Patient 20	12	-------	4.4 x 10^9	-------	47%	30%	296 x 10^9	120

***Grey column indicates MDR patients and non grey are XDR**

Maximum number of extensive drug resistant cases 84% (n=281) were observed in blood culture followed by MDR salmonella was 16 % (n=52). Antibiotic sensitivity and resistance pattern against salmonella was shown in Table III.

Treatment was challenging in the cases of Extensive and multi drug resistant salmonella. In our study, Azithromycin and meropenem was prescribed as a monotherapy in 78% (n=201) and 21% (n=43) patients, respectively. Almost 13 % (n= 7) received Ceftriaxone, which are mostly the cases of MDR. Combination therapy of azithromycin and meropenem was given in 22% (n=56) of patients and is beneficial for most of the XDR patient.

Table III Antibiotic sensitivity and resistance pattern against salmonella

Antibiotics (n=333)	Resistance	Sensitivity
Ciprofloxacin (5µg)	333 (100%)	0(0%)
Trimethoprim-Sulfamethoxazole (1.25/23.75µg)	327(98%)	7 (2%)
Ampicillin (10µg)	325 (97%)	8 (2%)
Ceftriaxone (30µg)	285 (85%)	48 (14) %
Azithromycin (15µg)	0(0%)	333(100%)
Meropenem (10µg)	0 (0%)	333 (100%)

Discussion

Enteric fever is one of the significant problems in the health care system of developing countries including Pakistan. Unjudicial use and over the counter availability of antibiotics lead to the emergence of extensive drug resistant and multi drug resistant strains of salmonella

which is the hall mark of the disease. It is hypothesized that endemic MDR H58 clone got an ESBL-encoding AMR plasmid, possibly from an E. coli strain or another enteric bacterial donor(13).

In our study, enteric fever is more prevalent in males as compared to females which is consistent with the Ashraf Hussain M et al and Zakir M et al (14, 15). This might explain by the fact that males are more likely to involve in outdoor activities and exposed to environmental hazards as compared to females which mostly stay at home (16). The children under the age of 10 years was the dominant group affected by the enteric fever which was also observed in other studies (17, 18). This might be explained by the fact that children were more prone to develop infections due to low immunity and need lower bacterial doses for establishment of infection (19). Our study demonstrated greater number of typhoid cases were presented in outpatient department as compared to hospital wards or emergencies which is coincide with the findings of Zakir M et al (20) and contradict with the study of Ashley T et al in which more patients seek hospital admission (21). Most prominent clinical feature of enteric fever observed in our study is fever followed by abdominal discomfort, vomiting, diarrhea and cough which are parallel with the findings of various analysis (6, 22). Common complications observed in our patients in chronological order were intestinal perforation, neurological manifestation like altered mental status, sepsis and splenic abscess which was also in line with the various studies (23, 24). Fortunately, no death was reported and most of the patients were recovered in our study. Fida S et al and Herekar.F reported similar outcome but Shahid S et al reported four death in extensively resistant typhoid fever in her study (6, 12, 24).

In our study high frequency of anemia recorded which is also comparable with a study by Anabire, N. G et al (25). Anemia could be attributed to malnutrition and suspected cases of intestinal hemorrhage. Few admitted patient with XDR have leucopenia and thrombocytopenia which is consistent with the many studies (26,27). This might be due to bone marrow suppression and hemophagocytosis in enteric fever. Some of our XDR patient had lymphocytosis and Neutrophilia which is also shown by Song. W et al (28).

Our analysis demonstrated higher numbers of (84%) XDR cases which were also in agreement with the interpretations of WHO report (29). Our study also observed 16% MDR cases which is compatible as prevalence of MDR is between 10-80% worldwide in endemic areas (30). Ampicillin and Trimethoprim-Sulfamethoxazole also has higher resistant pattern in our analyses. . We also analyzed complete resistance against ciprofloxacin which was also reported by various other studies (23). High resistance to fluoroquinolones was also observed in different parts of the world especially from South Asia, which also support our findings (24). Our analysis reported high Ceftriaxone resistance which is alarming and seen in more than 85% of cases. Khan M also demonstrated 100% resistance against Ciprofloxacin, Chloramphenicol, Ceftriaxone, Ampicillin and Cotrimoxazole (22). Complete resistance of Ceftriaxone are also reported globally (31). Evaluation of susceptibility pattern of meropenem and azithromycin in our study demonstrated the sensitivity of 100% in both, which is in consistent with Tayyaba et al who had identical susceptibility

of XDR S.Typhi strains to both azithromycin (95%) and meropenem (97%)(32).

Treatment is challenging in the cases of XDR as options of treatment is restricted to carbapenems and azithromycin. In our study, combination and monotherapy of azithromycin and meropenem show significant result in the recovered patient. Qureshi et al also reported similar treatment strategies (33). Herekar F also evaluated the favorable effect of azithromycin and meropenem mono or combination therapy in XDR patients while in MDR cases, Ceftriaxone was mainly used (24).

Conclusion

Our study has demonstrated that pediatric population is more vulnerable for developing salmonella infection. Carbapenems and azithromycin are among the last choices for the treatment of XDR cases. Analyses of our results imply stress on the implementation of preventive measures for spread of enteric fever including proper diagnosis, vaccination and good sanitation system.

Recommendations

.Concerns about the rising rates of resistance and the growing costs of antibacterial prescriptions have focused the attention of the medical community and the public on the need for sensible use of antibacterial agents and new antibiotic invention.

Conflict of interest: None.

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