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ORIGINAL ARTICLE

Drug resistant typhoid fever; its clinical spectrum and management in different age groups.

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ABSTRACT… Objective: To describe the clinical spectrum of MDR and XDR typhoid fever in different age groups of pediatric population as the disease is generally more common in children with higher rates of complications and mortality. **Study Design:** Prospective Cross-sectional study. **Setting:** Department of Pediatric, Government Teaching Hospital Shahdara, Lahore. **Period:** July 2020 to July 2021. **Material & Methods:** 211 patients with suspected/confirmed enteric fever between 6 months to 5 years were initially enrolled. Blood culture was performed in all cases. Only culture confirmed cases (143/211) were included. Data was entered and analyzed using SPSS version 23. Quantitative variables like age group, fever defervescence time and duration of hospital stay were calculated as mean and standard deviations while qualitative variables like gender, clinical symptoms and signs, types of typhoid and response to antibiotics were calculated as percentages. Chi-square test was used taking P value <0.05 as statistically significant. **Results:** Mean age of study population was 6.8 ± 3.1 years. Majority (44.1%) of patients belonged to age group >5-10 years and were males (54.5%). Anorexia, coated tongue and hepatomegaly was prevalent among all age groups. High grade fever, loose motions and splenomegaly were common in children <5 years as were anemia, leukocytosis and enteric hepatitis. Children >5-10 years of age had more frequency of abdominal pain (P value <0.03), toxic look (P value <0.04) and leucopenia. While vomiting and thrombocytopenia were common in children >10-15 years of age. MDR typhoid was common in young children (<5 years) while XDR typhoid was common in children of >5-15 years. All MDR patients responded to ceftriaxone while XDR patients responded to either monotherapy or a combination of drugs. Age and gender did not affect antibiotic resistance in both MDR and XDR typhoid (P value >0.05). Fever defervescence time (FDT) was 3-5 days in both MDR and XDR typhoid and it was not significantly different with either monotherapy or a combination of drugs (P value 0.40). **Conclusion:** There are age related differences in clinical spectrum and lab parameters of drug resistant typhoid fever (MDR & XDR). Resistance to antibiotics in both MDR and XDR typhoid was not significantly affected by age and gender.

Key words: Age Groups, Clinical Spectrum, Clinical Response, Drug Resistant Typhoid Fever.

INTRODUCTION

Typhoid fever is an entity known since antiquity and believed to have caused epidemics[1]. It is caused by Salmonella enterica serotype typhi. Once prevalent globally, it is a rarity now in developed countries but unfortunately is endemic in Asia, Africa and Latin America. Approximately 21 million people contract typhoid annually, mostly due to consumption of contaminated food and water, out of whom up to 161, 000 die. There are 3.6 cases of typhoid per 100, 000 persons-years in South Asia including Pakistan. In Pakistan, the highest risk of developing typhoid is in the habitants of the Punjab and Sindh provinces[1] The problem is compounded due to serious issues with timely diagnosis on one hand and with appropriate treatment on the other.

There is a significantly high burden of typhoid fever in pediatric population. A systematic analysis of global burden of enteric fever done in 2017 documented that the incidence and mortality rates of enteric fever were highest among young children, with the peak age of 5-9 years and a steady decline into adulthood. Typhoid fever had a case fatality rate of 1.89 times greater than for

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paratyphoid fever.[2]

There is a substantial heterogeneity in the disease prevalence across different age groups in studies done in Asia as documented by a systemic review and meta-analysis done by Britto et al. Children <5 years of age had the most notable heterogeneity.[3] There are high rates of enteric fever in school-aged children >5 years of age as documented by most typhoid studies done in pediatric population. Nevertheless, it is becoming increasingly clear that there is also a significant disease burden in preschool children.[3] This discrepancy in disease burden in may be due to the implementation of school-based vaccination programs in some areas.

Similarly, there is a notable difference in prevalence of clinical symptoms, signs and complications among different age groups like infants and young children has more frequency of diarrhea (>2.5times) as compared to older children and adults. Similarly, typhoid hepatitis, clinically tender hepatomegaly are commonly seen in young children. While pain in abdomen and nausea are more common in older children but these are difficult to assess in young children.[3,4,5]

In addition, XDR typhoid patients has increased frequency of abdominal pain, diarrhea, vomiting, body aches and malaise as are increased days of hospitalization, complications and mortality.[7] Fatima et al documented that non-XDR typhoid (MDR and drug sensitive typhoid) in common in young children with predominance of male patients in XDR vs non-XDR cases (64% and 62%, respectively).[9]

Due to emerging drug resistant strains especially extended drug resistant typhoid (XDR), treatment of typhoid fever has become more challenging with very few options left for treatment. The only options left for the management of XDR typhoid are meropenem, azithromycin and tigecycline with azithromycin being the only feasible and effective oral antibiotic for the XDR strains.[6] This is a cause of major concern as there are increasing rates of isolation of XDR strains of salmonella typhi documented by various studies in Pakistan.[7,8]

In the global literature, there are limited number of retrospective and prospective studies done in pediatric population to describe their clinical, lab characteristics and management strategies across different age groups with culture proven enteric fever.[1] So it is very important to describe the clinical spectrum of MDR and XDR typhoid fever in different age groups of pediatric population as the disease is generally more common in children with higher rates of complications and mortality especially in pre-school children.[4,10] Mass vaccination of infants and young children along with better hygiene practices and safe drinking water can reduce the number of cases of enteric fever in endemic regions.

The objective of our study was to determine the age-related differences in clinical spectrum, lab parameters and clinical response to antibiotics in different age groups of pediatric population in drug resistant typhoid fever (MDR and XDR)

MATERIAL & METHODS

This was a prospective cross sectional study conducted at Government Teaching hospital Shahdara, Lahore, Pakistan from July 2020 to July 2021. Ethical approval was taken from ethical committee of our hospital (5529/GTHS/Admin) dated 10-07-2020. Patients were selected by non-probability consecutive technique. Children, between 6 months to 15 years of age, fulfilling the operational definition of suspected/confirmed typhoid fever presenting in OPD/admitted in the hospital were initially enrolled in the study.

Confirmed Typhoid Fever	A patient with persistent fever (38 °C or above) lasting 3 or more days and S. Typhi isolated on blood or bone marrow culture.[19]
Probable/Suspected case of typhoid fever	A patient with documented fever (38°C and above) for at least 5 days prior to presentation, with rising trend in fever and having no other focus to explain the cause of the fever (e.g. UTI, pneumonia, abscess etc.) OR A clinically compatible case that is epidemiologically linked to a confirmed case of typhoid fever[19]

Table-I. Operational definitions of typhoid fever

A detailed history and thorough clinical examination was performed in each case after taking informed consent from the parents or guardian. All details were recorded on a pre-designed pro-forma. Baseline investigations including complete blood count (CBC), liver function tests (LFTs), urine complete examination, abdominal ultrasound and chest radiograph were done in all patients. Blood culture was sent in each case using aseptic technique. Sample for blood culture was taken in pediatric blood culture bottle (Becton Dickinson) and incubated at 37^0C for 7 days in Bactec 9240 automated blood culture analyzer. Blood volume drawn from the patients was 3 to 5 ml for children < 5 years, 5 to 10 ml for children 5-12 years, and 10 to 15 ml for children > 12 years as per typhoid management guideline 2019.

Total 211 patients were initially enrolled as suspected/confirmed typhoid fever. 143/211 patients (67.7%) turned out to be culture positive. In 52/211 (24.6%) patients, cultures could not be done. 6 patients (2.8%) were excluded from the study as parents did not give the consent for further investigations. 10 patients (4.7%) left against medical advice (LAMA) before receiving blood culture results. Only blood culture confirmed cases (n=143) of typhoid fever were included in the study. Data was entered and analyzed using Statistical Package of Social Sciences (SPSS) version 23. Quantitative variables like age group, degree and duration of fever, CBC parameters, fever defervescence time (FDT) and duration of hospital stay were calculated as mean and standard deviations while qualitative variables like gender, clinical symptoms, signs, complications, types of typhoid and response to different antibiotics were calculated as frequency and percentages. Chi-square test was applied to check the association between age group and other variables, taking P value <0.05 as statistically significant.

RESULTS

Mean age of our study population was 6.8 ± 3.1 years. Majority (44.1%, n=63) of patients belonged to age group >5-10 years in our study. Males were 54.5% (n=78) and females were 45.1% (n=65). Prolonged history (≥14 days) of persistent fever before admission was present in 53.1% (n=76) patients with a mean duration of fever of 15 ± 8.4 days. High grade fever (≥103^oF) at admission was documented in 35.6% (n=51) patients with mean temperature of 102.13±1.2^oF.

Majority of patients presented in summer season and were from poor socioeconomic class. There was positive family history of enteric fever 1 month prior to the illness of patient in 3.5% (n=5) patients. None of patients was vaccinated for typhoid and intake of street food from vendors was a common practice in our patients. 55.9% (n=80) patients took antibiotics before admission with no clinical improvement. Among these patients, majority took oral cefixime which was more common in young children <5 years of age (P value < 0.02).

Anorexia, coated tongue and hepatomegaly on examination were equally prevalent among all age groups. High grade fever at admission, loose motions and splenomegaly were common in children <5 years of age as were anemia, leukocytosis and enteric hepatitis. Children >5-10 years of age had more frequency of abdominal pain (P value <0.03), toxic look at admission (P value <0.04) and leucopenia. While children >10-15 years of age had increased frequency of vomiting and thrombocytopenia as compared to other age groups.

Mean total leukocyte count was 8.4±5/mm^3 with 73.6% patients having normal leukocyte count. Leukocytosis was present in 18.1% and leukopenia in 8.3% patients. Mean hemoglobin was 10±2.1 g/dl. Thrombocytopenia was present in 25.8% (n=37) patients. Enteric hepatitis was reported in 9.7% (n=14) patients as a complication of enteric fever, more common in young children <5yrs of age (57.1%, n=8) and it was significantly associated with hepatomegaly (P value <0.003). 45.4% (n=65) patients had sonographic evidence of significant mesenteric lymph nodes (MLNs) on abdominal ultrasound done within 1-2 days of admission with size ranging from 10-40mm.

Variable	1-5 yrs age (N=59)		>5-10 yrs age (N=63)		>10-15 yrs age (N=21)	
Symptoms	**N**	**%age**	**N**	**%ages**	**N**	**%ages**
High grade fever at admission	36	**61%**	32	50.7%	10	47.6%
Anorexia	55	**93%**	60	**95.2%**	20	**95.2%**
Abdominal pain	22	37.2%	38	63%	10	47.6%
Vomiting	26	44%	28	44.4%	14	66.6%
Loose motions	15	25.4%	11	17.4%	2	9.5%
Absence of cough	46	**78%**	55	**87.3%**	17	**81%**
Constipation	5	8.4%	4	6.3%	1	4.7%
Rose spots	0	0	0	0	1	4.7%
Jaundice	1	4.7%	0	0	0	0
Signs						
Toxic look	15	25.4%	21	33.3%	4	19%
Coated tongue	49	**83%**	53	**84%**	16	**76%**
Pallor	27	45.7%	27	42.8%	5	23.8%
Hepatomegaly	31	**52.4%**	33	**52.3%**	13	**61.9%**
Splenomegaly	15	25.4%	12	19%	5	23.8%
Labs						
Leukocytosis	14	23.7%	12	19%	2	9.5%
Leucopenia	3	05%	9	14.2%	0	0
Anemia	47	**79.6%**	38	60.3%	7	33.3%
Thrombocytopenia	10	17%	19	30%	8	38%
Enteric hepatitis	8	**13.5%**	5	7.9%	1	4.7%
Mesenteric lymphadenopathy	21	35.5%	33	52.3%	11	52.3%

Table-II. Frequency of symptoms and signs of enteric fever in different age groups

Salmonella typhi was isolated in all the blood cultures out of which majority of isolates were MDR (65%, n=93) while 32.9%, n=46 isolates were XDR. One strain was drug sensitive i.e it was sensitive to ampicillin, chloramphenicol and co-trimoxazole. There were increased rates of positive blood culture in children >5-10 years of age and having toxic look at admission (P values 0.03 and 0.04 respectively). Loose motions and coated tongue were significantly more common in XDR typhoid patients (P values 0.03 and 0.01 respectively).

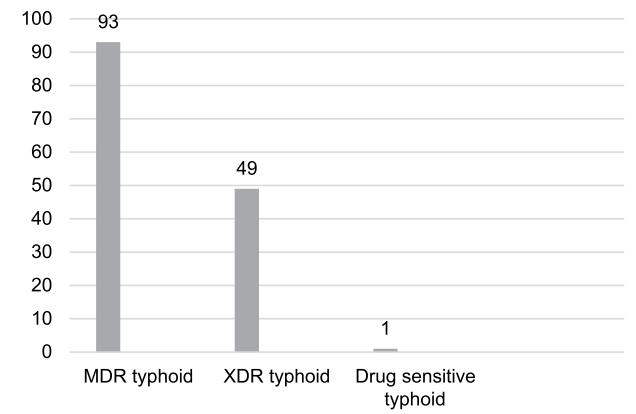

Figure-1. Percentage of different types of typhoid

In children <5 years of age, MDR typhoid was more common while XDR typhoid was more common in children >5-15 years of age. Percentage of MDR and XDR typhoid fever in different age groups is shown in a bar chart. (Figure-2)

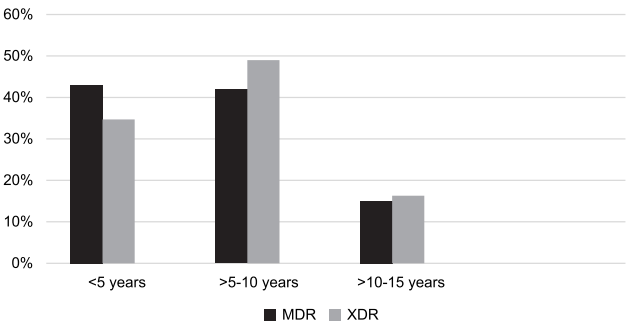

Figure-2. Percentage of MDR and XDR typhoid in different age groups

Mean duration of improvement of fever after the start of sensitive antibiotic was 4.7±2.3 days with range of 1-12 days. Anorexia was the first symptom to be resolved after the start of sensitive antibiotic in both MDR (61.8%) and XDR (77.6%) patients followed by fever and vomiting. Majority of MDR patients (98.9%, n= 92) stayed in hospital

for ≤7 days while XDR patients (85.7%, n= 42) had increased hospital stay >7-14 days (P value 0.000). All the patients were discharged in stable condition after completing the course of antibiotic and no mortality was documented due to enteric fever in our study. All the patients (100%) with MDR typhoid responded well to intravenous ceftriaxone. While the response of XDR typhoid patients to different antibiotic is as follows (Figure-3).

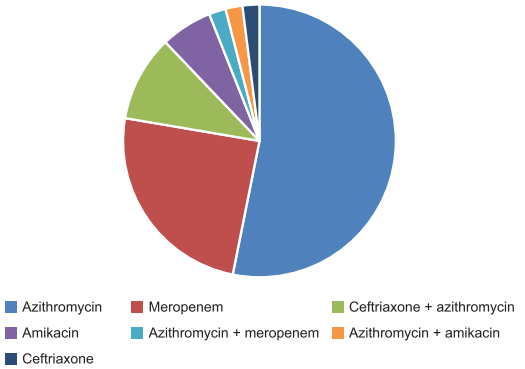

Figure-3. Response of XDR patients to different antibiotics

DISCUSSION

Typhoid fever is endemic in developing countries like Pakistan and the highest incidence is in younger children under the age of 5 years.[11] The annual typhoid incidence among 2-15 years olds is 412.9 cases per 100,000 person years with an increased incidence in 2-4 years olds which is 573.2 per 100,000 person year.[12] Since the emergence of XDR typhoid fever in Karachi Sindh, Pakistan in 2016, there are increasing number of cases of drug resistant typhoid fever especially XDR typhoid documented by various studies.[13,14,15] Anwar T et al documented that majority of drug resistant typhoid fever cases in their study were of XDR typhoid and it was more common in males, younger age group (1-6 years), poor socioeconomic class and west district of Karachi.[16] Similarly, Zakir et al documented XDR typhoid fever cases to be more prevalent in their study with increased incidence in males and 0-10 year age group.[14] This finding is similar to our study in which drug resistant typhoid (MDR and XDR) was more common in males and in children 0-10 years of age.

Majority (n=63, 44.1%) of our study population belonged to the age group >5-10 years with a male predominance consistent with other studies done in South Asia including Pakistan.[17,18,19] Majority (55.9%, n=80) of patients took oral or injectable antibiotics before admission to the hospital with no clinical response which is also observed by Behera et al.[20]

Most common symptoms in our study population were anorexia (94.4%), abdominal pain (49%) and vomiting (47.6%) following fever which was present in all cases. Similar findings are described by Sarswat et al.[5] Majority patients of our study population (82.5%, n=118) did not has cough similar to a multi-center study done in Pakistan, Bangladesh and Nepal under SEAP, which documented that cough was a less common symptom in enteric fever patients and sensitivity of absence of cough to diagnose enteric fever was highest among all other clinical features of enteric fever.[21] This finding was different from a systemic review and meta-analysis where cough was the most common respiratory symptom present in 72% cases.[3]

Coated tongue (82.5%) and hepatomegaly (53.8%) were most common signs on examination and were prevalent in all age groups also documented in these studies.[4,5] Prevalence of various symptoms, signs and lab investigations were age dependent like high grade fever at admission, loose motions, anemia, leukocytosis and enteric hepatitis were more common in younger children <5 years of age, also observed by Britto et al, who noted that diarrhea and enteric hepatitis were more prevalent in young children and leukocytosis was >4 times more common in children <5 years of age.[3] Similar findings were described by Azmatullah et al in their systemic review and Bhutta ZA in their study where he documented higher rates of diarrhea, anemia, shock and mortality in young children[4,22] Abdominal pain, toxic look and leucopenia were common in older children >5 years of age consistent with other studies.[3,4,5]

Anicteric hepatitis was the only complications reported in our patients. A prospective cross

sectional study documented enteric hepatitis as the most common complication (24.62%) followed by enteric encephalopathy (18.46%).[23] None of our patients had enteric encephalopathy. This may be due to the fact that severe cases of typhoid fever are referred to other hospitals as there are inadequate ICU facilities at our hospital. Similar findings are described by Malik and Pramoolsinsap C.[24,25]

Majority of XDR patients responded to azithromycin (53.1%) followed by meropenem (24.5%), combination of ceftriaxone + azithromycin (10.2%), azithromycin + meropenem (2%), azithromycin + amikacin (2%). 6 patients (6.1%) responded well to IV amikacin when started according to culture and sensitivity report. 2 patients (2%) showed clinical response to IV ceftriaxone despite having culture sensitivity report showing resistance to it. A study conducted in Lahore, Pakistan documents that age and gender of patients does not affect the resistance to antibiotics in both MDR and XDR typhoid (P value >0.05).[14]

Fever defervescence time (FDT) after the start of sensitive antibiotic was 3-5 days in majority of the cases of MDR and XDR typhoid fever and it was not significantly different with either monotherapy or a combination of antibiotics (P value 0.40). This is similar to a retrospective study where they noticed that fever defervescence time was same whether XDR patients were given Azithromycin, Meropenem alone or a combination of these two drugs.[26]

More studies are needed to know the reasons for these age-related differences in clinical spectrum, lab parameteres and clinical responses to different antibiotics because it will help to manage the cases more effectively and better policy making for prevention of typhoid fever in endemic regions. Preventive measures can include access to clean drinking water, adequate sanitation and proper waste management especially in underdeveloped regions. In addition, mass vaccination of children with typhoid conjugate vaccine should be done and public awareness campaigns focusing on hygiene practices and importance of vaccination should be routinely conducted.

CONCLUSION

There are age related differences in clinical spectrum and lab parameters of drug resistant typhoid fever (MDR & XDR). Age and gender of patients does not affect the resistance to antibiotics in both MDR and XDR typhoid (P value >0.05) and fever defervescence time was similar with either monotherapy or a combination of antibiotics.

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4	Samreen Ashraf	Data collection, Statistical analysis.	
5	Syed Mujtaba Azhar Bokhari	Data collection.	
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