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X-DR (DRUG RESISTANT) TYPHOID FEVER IN CHILDREN.

Muhammad Sohail[1], Zahid Mahmood Anjum[2], Jaweeria Masood[3], Iram Iqbal[4], Jawaria Khalid[5], Hina Ayesha[6]

1. MBBS, FCPS
Senior Registrar Paediatrics
Children Hospital and ICH,
Faisalabad.
2. MBBS, FCPS
Assistant Professor
Children Hospital and ICH,
Faisalabad.
3. MBBS, FCPS
Assistant Professor
Children Hospital and ICH,
Faisalabad.
4. MBBS, FCPS
Senior Registrar Paediatrics
Children Hospital and ICH,
Faisalabad.
5. MBBS, FCPS
Senior Registrar Paediatrics
Children Hospital and ICH,
Faisalabad.
6. MBBS, FCPS
Professor Paediatrics
Faisalabad Medical University.

Correspondence Address:
Dr. Muhammad Sohail
136-B Sheikh Colony,
Jhang Road Faisalabad.
arshadsohail66@gmail.com

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ABSTRACT… Objectives: To study antibiotic sensitivity pattern of Salmonella typhi in children with enteric fever. **Study Design:** Prospective, Consecutive sampling. **Setting:** Children Hospital and Institute of Child Health, Faisalabad. **Period:** 6 Months June 2019 to November 2019. **Material & Methods:** All admitted children of age 1-16 years with strong clinical suspicion of typhoid fever and with no comorbidities were included in this study. Blood cultures and other relevant investigations were performed to rule out other causes of fever. After identification of organism as Salmonella typhi, antibiotics susceptibility testing was done by disk diffusion technique and zones of inhibition were interpreted according to clinical and Lab standard (CLSI) guidelines. **Results:** Out of 60 patients maximum children were < 5 year and >10 year of age. Maximum cases were admitted during July to September. Male to female ratio was 1.6:1. We were able to send blood cultures of 31 cases (51%) only. Out of them 14 cases (45%) were found culture positive. All culture positive (100%) were found sensitive to meropenem. 92.8% were found sensitive to azithromycin and 7.1% were found sensitive to amikacin. Overall 16 cases treated with meropenem, 10 cases (16%) with azithromycin and one with amikacin. However, 33 cases (55%) responded to ceftriaxone alone. **Conclusion:** Sensitivity pattern of Salmonella typhi revealed significant proportion of multidrug and extensive drug resistant strain. So, continue surveillance is needed in this regard to find actual burden of XDR typhoid fever. We recommend local district administration and health authorities to launch an awareness campaign regarding sanitation, good hygiene, use of safe of water and mass vaccination of children with conjugated vaccine against typhoid. Alongwith above measures antibiotic stewardship should be started.

Key words: Children, Drug Resistance, Typhoid Fever, Antibiotic Sensitivity.

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INTRODUCTION

Enteric fever caused by Salmonella enterica serovar typhi (S.Typhi) is serious and occasionally fatal disease, more prevalent in developing countries attributed to poor sanitation facilities and lack of clean drinking water supply. Approximately 21.6 million people are infected by S.Typhi yearly leading to around two hundred thousands deaths with more than 90% burden of morbidity and mortality shared by Asian countries.[1,2] India and Pakistan are ranked first and second in Enteric fever prevalence respectively.[3]

Drug resistance is emerging as a great problem in managing cases of enteric fever leading to increasing cost of treatment, morbidity and complications.[3,4,5] It started in early 70's.[5] Over past 2 decades, emergence of MDR (chloramphenicol, amoxicillin, TMP) strains has necessitated use of fluroquinolones as drug of choice with cephalosporins as alternative.[6] But recent reports of XDR (chloramphenicol, amoxicillin, TMP, fluroquinolones and ceftriaxone) strains of Salmonella in areas of Sindh (Pakistan) have been alarming.[7,9,10] International Surveillance has also identified XDR strains in patients in UK, USA and Canada with all of them having travelled to Pakistan in recent past.[8,9]

Pakistan health authorities have reported an outbreak of extensively (XDR) typhoid fever that begin in Hyderabad district of Sindh province in November, 2016.[11] Since then, number of patients with XDR typhoid fever are remarkably increasing.

We think that XDR typhoid fever is not confined to Sindh Province only and is spreading all over the Pakistan, we have observed a surge of typhoid fever cases in our setup.

We are conducting this study with objective to evaluate antibiotic sensitivity pattern in patients presenting with clinical suspicion of enteric fever at Children hospital, Faisalabad which will help us to formulate management guidelines for drug resistant patients and to stress on need of vaccination against S.Typhi.

MATERIAL & METHODS

This was Prospective, consecutive sampling conducted for 6 months. Study was conducted from June 2019 to November 2019 at Children Hospital and Institute of Child Health, Faisalabad.

Inclusion Criteria

- Patients having febrile illness more than five days and there is no other observed cause of fever.

Exclusion Criteria

- Age less than one year and more than sixteen year.
- Patients having other comorbidities were also excluded from study.

After admitting the patients blood culture and sensitivity, CBC and other relevant investigations were carried out to exclude other causes of fever like Malaria, Dengue, UTI etc. Those patients who received antibiotics for more than 5 days their blood culture was not sent. Blood samples were cultured on blood agar and MacConkey agar plates. After identification of organism as Salmonella Typhi, antibiotic susceptibility testing was done by disk diffusion technique and zones of inhibition were interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Isolates were tested for ampicillin, co-trimoxazole, ceftriaxone, cefixime, chloramphenicol, ciprofloxacin, amikacin, azithromycin and meropenem susceptibility. We were able to send culture of 31 patients only due to one or more reason. All patients were given intravenous ceftriaxone 75mg/kg/day in two divided doses empirically after sending blood culture. The patients whose culture sent were later treated according to sensitivity pattern if they have not responded to empirical therapy. However, culture negative and all those patients whose culture were not sent and who did not respond to intravenous ceftriaxone after 7 days were switched to meropenem or azithromycin depending upon susceptibility patterns. No complication was observed in any patient. All patients were treated successfully.

Frequencies and percentages were calculated for gender and XDR isolates. Mean was calculated for age distribution of culture positive patients.

RESULTS

We studied 60 patients admitted with clinical suspicion of enteric fever from June 2019 – November 2019.Out of these 60 patients, 37 patients (61.6%) were males and 23 (38.4%) were females. Among them 47 (78.3%) patients were urban residents while 6 (10%) and 7 (11.6%) were from peri-urban and rural areas respectively. Maximum cases were admitted during July to September. Most common presentation was fever (100%), abdominal pain (68.33%), vomiting (60%) followed by Diarrhea (25%) (Table-I) Common signs seen were tachycardia (75%), pallor (25%), Hepatosplenomegaly (16.6%), coated tongue (8.3%), Hepatomegaly (10%) and Splenomegaly (1.6%) (Table-II).

Out of 31 patients, 14(45%) were culture positive and 17 (55%) were culture negative. Among 14 culture positive patients, 12 patients (85.7%) turned out to be XDR strains of Salmonella typhi, only sensitive to Meropenem and Azithromycin. One patient (7.1%) was sensitive to Meropenem only and one patient (7.1%) to Amikacin and Co-trimoxazole only (Table-III) Mean age of culture positive patients was 7.2 years (Table-IV). All these 14 patients were empirically treated with ceftriaxone. Those who didn't responded to empirical therapy switched to Meropenem or azithromycin depending upon susceptibility patterns.

Of the remaining 46 culture negative patients

(including 29 patients whose cultures were not sent), 33(71.7%) patients responded to ceftriaxone alone. Out of remaining 13 patients, 10 patients (76.9%) responded to azithromycin and 3(23.1%) patients responded to meropenem only. None of these 46 patients developed any complication and were discharged.

Overall sensitivity/response rate of 60 patients to various antibiotics was observed as, ceftriaxone 33/60(55%), meropenem 16/60(26.6%), azithromycin 10/60(16.6%) and amikacin 1/60(1.6%).

Symptoms	Percentage
Fever	100%
Abdominal pain	68.33%
Vomiting	60%
Diarrhea	25%
Anorexia	13.33%
Constipation	1.6%

Table-I. Symptoms observed in patients

Signs	Percentage
Tachycardia	75%
Pallor	25%
Hepatosplenomegaly	16.6%
Hepatomegaly	10%
Coated Tongue	8.3%
Splenomegaly	1.6%

Table-II. Signs observed in patients

Antibiotic	Number (n=14)	Percentage
Meropenem	14	100%
Azithromycin	13	92.8%
Ceftriaxone, Cefixime	0	0%
Ampicillin, Ciprofloxacin	0	0%
Chloramphenicol	0	0%
Amikacin, Co-trimoxazole	1	7.1%

Table-III. Antibiotic sensitivity pattern of Salmonella Typhi

Age at the Time of Presentation	Frequency of Patients	Percentage of Patients
< 5years	5	35.7%
5 to 10years	4	28.5%
10 to 15years	5	35.7%

Table-IV. Age distribution of patients with XDR Salmonella Typhi (n=14)

Months	No. of Cases (n=60)	Percentage
June	08	13.3%
July	14	23.3%
August	14	23.3%
September	11	18.3%
October	08	13.3%
November	05	8.3%

Table-V. Month wise distribution of cases

Month	Number of Patients Admitted (n=60)	Number of Blood Cultures sent (n=31)	Positive Blood Cultures (n=14)	Percentage of Positive Blood Cultures
June	08	01	01	100%
July	14	06	03	50%
August	14	08	02	25%
September	11	05	02	40%
October	08	07	05	71.4%
November	05	04	01	25%
Total	60	31	14	45.1%

Table-VI. Month wise distribution of culture positive patients

DISCUSSION

Most of the studies already done on typhoid fever includes age group of 5 to 15 years. However, in studies from Bangladesh and India higher trends are seen in children younger than 5 years.[12] So, we included age group 1 to 15 years and found that the maximum children affected were in age groups less than 5 years and greater than 10 years. Perhaps it is difficult to maintain hygiene in these age groups as less than 5 years demand continue surveillance by elders and age group greater than 10 years are school going and have easy access to food stuff at school canteens.

Male to female ratio is 1.6:1 and this is very similar to a study done in Bangladesh.[13] Greater percentage of patients belong to urban areas[12]and only a small percentage was found resident of rural areas indicating poor hygienic conditions and sanitation of our urban areas, inviting attention of health authorities to promote public awareness and guide government officials to work on this.

Maximum cases were admitted during July to September. We know this period coincides with moon-soon season and increase in house fly population, hence facilitating feco-oral transmission**.** Same phenomena was observed in most of studies done in Asia.[3,14]

Most common presentation was fever (100%), abdominal pain (68.33%), vomiting (60%) followed by Diarrhea (25%) which was very similar to a study done by Habte, L., Tadesse, E., Ferede, G., et al Ethiopia at University of Gondar, Ethiopia.[15]

Common signs seen were tachycardia (75%), pallor (25%), Hepatosplenomegaly (16.6%), coated tongue (8.3%), Hepatomegaly (10%) and Splenomegaly (1.6%).[14]

In this study we were able to send culture of 51% of patients (31 cases) only. Out of them 45% of patients (14 cases) were found culture positive. Our culture positivity rate was very high as compare to studies done in other parts of Asia and Pakistan that showed a range of 5 to 33.1%.[3,16] In an analysis, based on antibiotic susceptibility from 2012-2014, prevalence of MDR salmonella typhi was 52%, fluoroquinolone resistance was 90% and there was no cephalosporin resistance.[17] But the recent trends seen in studies from 2015-2019, showed a decline in MDR strains and rising trends of resistance against cefixime and ceftriaxone.[18,19] In our study there were 100% MDR strains and only 7.1% were sensitive to amikacin and co-trimoxazole and no isolate was found sensitive to ceftriaxone, cefixime, ampicillin or ciprofloxacin.

We have reported only 14 culture positive patients. As this number is very small to make any solid conclusion. So, continue surveillance should be in place to find the actual burden of XDR typhoid fever in Faisalabad. For this, we may need collaboration with other medical institutes of Faisalabad for collection of data regarding XDR typhoid fever. Considering the reports from Hyderabad, Sindh, we recommend local district administration and health authorities to launch an awareness campaign regarding sanitation, good hygiene, use of safe water and mass vaccination of children with conjugated vaccine against typhoid which has already initiated in district Hyderabad. Along with these, injudicious use of antibiotics should be banned and it can be safely prevented by sensitising general practitioners and clinicians on the rational use of antimicrobials for typhoid fever.

CONCLUSION

Emergence and spread of XDR typhoid fever is on the rising trend. Surveillance studies are required at all levels for risk stratification and control of this disease. Our study also signifies the role of preventive measures, better health care facilities, antibiotic stewardship and vaccination, at a national level to restrict this menace.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Muhammad Sohail	1st Author	
2	Zahid Mahmood Anjum	2nd Author	
3	Jaweeria Masood	3rd Author	
4	Iram Iqbal	4th Author	
5	Jawaria Khalid	5th Author	
6	Hina Ayesha	6th Author	