ORIGINAL ARTICLE

Clinical Spectrum, Laboratory Profile and Antibiotic Susceptibility Pattern of Children with Enteric Fever at a Tertiary Care Hospital of Karachi

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ABSTRACT

Objective: To describe the clinical, laboratory and antimicrobial susceptibility profile of enteric fever patients hospitalized at a tertiary care children hospital of Karachi.

Study Design: Cross Sectional Study.

Place and Duration of Study: The study was conducted in three medical units of National institute of child health (NICH) Karachi from September 01, 2018 till February 28, 2019.

Materials and Methods: Patients of enteric fever diagnosed by positive blood culture for *Salmonella enterica Serovar Typhi,* hospitalized at National Institute of Child Health (NICH) Karachi were included. Clinical history and physical examination findings were recorded in Performa and routine laboratory tests and treatment was done according to hospital protocol. Outcome of patients was recorded in terms of alive or died. Data entry and analysis was done in SPSS 24.0. Descriptive statistics were applied for statistical analysis.

Results: Total 76 patients with culture proven typhoid were enrolled in the study including 39(51.3%) males and 37(48.7%) females. Mean age of children was 5.7± 2.81 years. Mean duration of fever in these patients was 19.04±8.39 days. Common symptoms were abdominal pain (64.5%), diarrhea (43.4%), vomiting (48.7%) and decreased appetite (67.1%). Antibiotic resistance profile showed 98.7% to chloramphenicol and trimethoprim-sulfamethoxazole, 96% resistance to ampicilline, 94.7% to cefixime and ceftriaxone, 82.2% to ciprofloxacin, 2.63% to azithromycine and no resistance to meropenam. All children were discharged with mean duration of hospital stay 8.296±3.33 days.

Conclusion: There are high rates of resistance against commonly used antibiotics for the treatment of enteric fever, including fluoroquinolones and cephalosporins leaving only extremely limited and costly options for treatment and prolonged length of hospital stay due to need of intravenous therapy.

Key Words: *Antibiotic Resistance, Cephalosporins, Enteric Fever, Salmonella Typhi.*

Introduction

Enteric fever is one of the important cause of morbidity and mortality in countries with middle to low income especially in south east Asia.[1-3] In Global Burden of Disease 2010, enteric fever was included which accounted to cause 12.2 million illnesses and 190200 deaths.[3,4] In 2015, it was estimated 17 million cases of typhoid and paratyphoid fever with highest incidence seen in South Asia and other areas like Southeast Asia and Sub-Saharan Africa.[5,6,7]

The clinical features of enteric fever are variable and may mimic any other febrile illness like influenza, malaria or dengue fever, which may cause delay in the diagnosis and start of appropriate therapy.[1] However most persistent feature is high grade continuous fever.[1]

Although a number of serological tests are available for diagnosis of typhoid fever but gold standard for the diagnosis is blood culture.[6]

Resistance to antimicrobials has been emerged in Salmonella species. In 1970, main stay of treatment was chloramphenicol.[3] First epidemic of enteric fever which was resistant to chloramphenicol was reported in 1972.[8,9] By late 1980, multiple drug resistance (MDR) enteric fever defined as resistance to the traditionally used three first line antimicrobial drugs (chloramphenicol, ampicillin, trimethoprim and sulfamethoxazole) was reported from many countries.[9] This led to the use of fluororuinolones (ciprofloxacin) as recommended first line therapy.[8] By early 2000, the increasing non susceptibility to

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flouroquinolones including intermediate and full resistance occurred and in 2006 , 55% cases of salmonella were resistant to ciprofloxacine.[10,11]This led to the use of third generation cephalosporins (ceftriaxone) as first line recommended therapy.[1,5] Most recently, an epidemic of extensively drug resistant (XDR) typhoid strain has been reported from Sindh, Pakistan, where resistance has been found to first line three antimicrobial drugs (chloramphenicol, ampicillin , trimethoprim and sulfamethoxazole), along with resistance to fluoroquinolone and also to 3rd generation cephalosporins.[10]In case where MDR and fluoroquinolone resistance is present, azithromycine has shown good efficacy by multiple trials, but by its widespread use in suspected cases of enteric fever, there is risk of emergence of resistance to it as well.[9]

Mortality due to enteric fever in pre-antibiotic era was 10-30%, but with the use of effective antibiotics, it has been reduced to <1%.[2] Reported mortality rate from Pakistan is less than 2 % from enteric fever.[3]

Considering high burden of enteric fever in developing countries like Pakistan and recent epidemic of XDR typhoid, we conducted this study at a tertiary care hospital of Karachi (Sindh, Pakistan) to assess clinical, laboratory profile and to check for antibiotic resistance pattern of *S. typhi* so that local data may be generated about recent trends on antimicrobial resistance in enteric fever cases and to modify local empirical treatment strategies and research priorities regarding typhoid fever.

Materials and Methods

This cross-sectional study was conducted in three medical units of National Institute of Child Health (NICH) Karachi over the period of 6 months, from 1st September 2018 till 28th February 2019. The study was conducted in compliance with ethical standards on human subject research, Informed consent was obtained from all patients' attendants. The study was approved by Institutional ethical review board (IERB) of NICH.

National Institute of Child Health is one of the largest tertiary care children hospitals of Pakistan that provides health care service to pediatric patients mainly from Sindh, Balochistan and South Punjab. Patients hospitalized in NICH during the study period with enteric fever proven by a positive blood culture for *Salmonella typhi* were included. Children with clinical suspicion of enteric fever but negative blood culture were excluded. Similarly, patients who left hospital against medical advice before completion of treatment were also excluded.

After explaining about the nature of the study informed consent was taken from parents or guardians. Patients' history and physical examination's findings were recorded in a semi-structured performa by principal investigator and co-investigators from their respective wards. Results of routine laboratory tests including Complete Blood Picture, Serum Urea, Creatinine, Electrolytes and Liver Function Tests were also recorded in Performa.

Blood Culture and sensitivity testing was performed at the microbiology laboratory of NICH. Five ml blood sample of each child suspected for enteric fever was drawn and inoculated in blood culture bottle aseptically and sent to laboratory. At microbiology laboratory blood culture bottles were sub-cultured after every 18-24 hours for 3-days, Identification of *S. typhi* was based on conventional biochemical tests and serotyping. Sensitivity testing was performed using Kirby Bauer disk diffusion method as per CLSI guidelines.

Other laboratory tests as needed according to the condition of child were also sent to laboratory as per NICH protocol. Antibiotic treatment started according to the hospital protocol and was recorded. Outcome of patient along with total duration of hospital stay was recorded. Outcome was recorded in terms of either recovered or died.

All data was entered and analyzed through statistical package for social sciences (SPSS) version 24. Descriptive statistics were applied. Frequency and percentages were calculated for qualitative variables including clinical signs and symptoms, previous history, drug sensitivity pattern etc. Mean± S.D was calculated for quantitative variables including age, fever history, duration of hospitalization, duration of antibiotic treatment, Biochemical Test Results Etc.

Results

Total 76 patients with culture proven enteric fever were enrolled in the study including 39(51.3%) males and 37(48.7%) females. Mean age of children was 5.7± 2.81 (range 0.83-12) years. Only 5 (6.5%) patients were from interior Sindh while 71 children (93.5%) were from Karachi.

Mean duration of fever in these patients was

19.04±8.39 days with minimum 4 days and maximum 45 days history of fever. Thirty-six (47.37%) had fever duration of >20 days. Other common symptoms among these patients were abdominal pain, diarrhea, vomiting and decreased appetite. Frequency of different clinical symptoms along with mean duration at the time of hospitalization are summarized in table I.

History of treatment before hospitalization with duration is presented in table II, which shows most of the patients already had a history of using cephalosporins, fluoroquinolones and some had also taken antimalarial treatment.

Hematological and biochemical findings of patients are presented in table III. Ultrasound (USG) abdomen was done in 63(82.9%) cases, out of which, USG was normal in 50 cases (79.4%). Major finding on sonography was hepatosplenomegaly and lymphadenopathy found in 11(17.5%) cases, 1(1.6%) had cholecystitis, and 1(1.6%) had ascites with hepatosplenomegaly.

All 76 children's blood culture was positive for *Salmonella enterica Serovar Typhi*. Antibiotic sensitivity profile of isolates is shown in figure 1 which showed high rates of resistance against all commonly used antibiotics for typhoid including fluoroquinolones and cephalosporins. However, none of the isolates showed resistance against meropenem.

In the hospital, antibiotics were started according to culture and sensitivity. Most of the patients were treated with intravenous meropenem with mean duration of 7.95±2.79 days out of which <7 days treatment was given in 10(25.6%) patients, 7-10 days treatment was received by 27(69.2%) patients while 2(5.1%) required treatment for >10 days to become afebrile. Thirty-three (43.4%) children were treated with azithromycin (mean duration of 6.23±1.38 days).

Enteric fever related complications observed among study participants included bone marrow suppression in 45(59.2%) with 35(46.1%) patients having moderate anemia (Hb<9.0g%), 14(18.4%) having leucopenia (TLC<4.5x10^3/UL), while thrombocytopenia (plt<150x10^3/UL) was present in 31(40.8%). Clinical jaundice was present in 4(5.3%), while subclinical hepatitis with raised SGPT (>40 IU) was present in 25(32.9%). Acute kidney injury (based on deranged renal function) was present in 2(2.6%). Hyponatremia (serum sodium <130meq) was seen in 7(9.2%), hypokalemia (serum potassium<3.5 meq) was seen in 9(11.8%). Other complications included cholecystitis 1(1.3%), ascites 1(1.3%), meningitis 1(1.3%), sepsis 1(1.3%), hepatomegaly 29(38.2%) and abdominal distension 19(25%).

Outcome in term of mortality was nil and all children (100%) were discharged. Mean duration of hospital stay was 8.296±3.33 days with range of 1-17 days. Hospital stay of <5 days was found in 7.4%, 5-7 days in 37%, 8-10 days in 35.2% and >10 days in 20.37%.

Table I: Clinical Features of Typhoid Patients Hospitalized at NICH.

Clinical Signs/ Symptoms	Number (%) of Patients	Mean Duration in Days (Min-Max)
Decreased appetite	51(67.1%)	6.25±1.5 (4-7)
Abdominal pain	49 (64.5)	4.75±3.05 (2-14)
Vomiting	37(48.7)	4.8±3.04 (2-13)
Diarrhea	33 (43.4)	6.33±5.82 (02-30)
Chest symptoms	3(3.9%)	
Clinical anemia	43(56.6%)	
Hepatomegaly	29(38.2%)	
Abdominal distension	19(25.0%)	
Splenomegaly	16(21.1%)	
Juandice	2(2.6%)	
Bruises	1(1.3%)	
Lymphadenopathy	1(1.3%)	
Edema	1(1.3%)	

Table II: Treatment History Before Culture and Sensitivity

Drug name	Number (%)	Mean Duration± SD (Range) days	Duration ≥7days N (%)
Ceftriaxone	39(51.3)	5.38±1.84(1-10)	14(18.4)
Cefixime	37(48.7)	5.97±2.48(7-14)	20(54)
Artemether and lumefantrine	20(26.3)	3	-
Ciprofloxacine	16(21.1)	8.25±4.16(3-17)	11(14.47)
Ampicillin Amoxicillin-clavulanate	10(13.2)	5.1±1.79(1-7)	3(3.9)

Discussion

In Pakistan enteric fever is amongst the leading causes of febrile illnesses due to bacterial pathogens.[12] There are alarming reports of

Table III: Hematological and Biochemical Features of Typhoid Patients Hospitalized at NICH

Laboratory Parameters	Mean± SD (range)
Hb (g/dl)	8.97±2.023 (4.1-13.9)
WBC (X10^3/UL)	7.19±3.55(0.5-19.6)
Platelets t(X10^3/UL)	230.5±218.2 (13.00-1060.0)
Urea (mg/dl)	21.77±15.54 (4-82)
Creatinine (mg/dl)	21.77±15.54 (4-82)
Sodium (meq/L)	135±6.4 (120-155)
Potassium(meq/L)	4.0±0.767 (2.3-5.3)
Chloride (meq/L)	96.99±17.03 (97-115)
Bilirubin (mg/dl)	0.99+0.992 (0.2-3.6)
ALT (IU/L)	70.4+64.54 (10-325)
Alkaline phosphatase (IU/L)	273.5+162.6 (64-620)

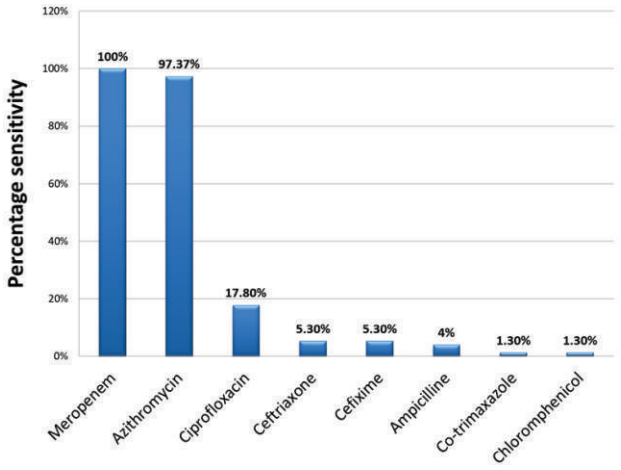

Fig 1: Antibiotic Sensitivity Profile of *S. Typhi* Isolates

antimicrobial resistance from Pakistan with need of careful selection of antimicrobials in children with enteric fever.[13]

In present study, mean duration of fever was19 days, therefore most of the patients were already in third week of illness where complications of enteric fever are expected. This suggests that there is need of early suspicion and early diagnosis in order to reduce complications and reduce mortality. Common associated problems were decreased appetite, abdominal pain, clinical anemia, vomiting, diarrhea, hepatosplenomegaly, abdominal distension and chest congestion. *Thompsom et al* also found the associated symptoms of anorexia, diarrhea and cough along with high grade fever in children of enteric fever.[13]

In the present study results are alarming with 97.7% of MDR isolates, resistance to third generation cephalosporins as 93.4% and resistance to ciprofloxacin in 82.2% leading to serious limitation in therapeutic options, leaving only behind options of carbapenam and azithromycin. *Klemm* et al in 2018 has reported the emergence of extensively drug resistant *S. typhi* showing resistance to flouroquinolones and third generation cephalosporin along with resistance to three first line drugs in Sindh Pakistan.[14] Gene sequencing of MDR *S. typhi* revealed that it is haplotype H58, encoded by plasmid having additional resistant elements including extended spectrum beta lactamase and exhibited high identity to the plasmids of other enteric bacteria found worldwide highlighting ability of *S. typhi* to convert from MDR to XDR by plasmid acquisition from other enteric bacteria.[14]

In the past there have been few sporadic reports of resistance to ceftriaxone where Indian Network for Surveillance of Antimicrobial Resistance Group has reported 3% resistance to third generation cephalosporin and *Jain et al* has reported 2% resistance to it.[11,15] Similar proportions of resistance has also been reported by *Abdullah et al* from Karachi Pakistan.[16] In previous study from Pakistan, in 2014, fluoroquinolone resistance was 82% and ceftriaxone resistance was not reported.[17]

Azithromycin is another oral option which has been reported as safe and effective against *S. typhi* but it can only be use d in uncomplicated early cases of enteric fever. Resistance to azithromycin has been found in 2(2.63%) cases. Resistance to azithromycin has also been reported by *Jain et al* in New Delhi where 7.3% isolates of salmonella has shown resistance to azithromycin.[11]

Most of the patients in present study were receiving cefixime (48.7%), ceftriaxone (51.3%) and ciprofloxacin (21.1%), indicating these medications may have been started on clinical grounds by suspicion of simple MDR *S. typhi*. Many patients had a treatment history suggestive of their condition being diagnosed as upper respiratory tract infection and malaria as antimalarial was taken in 26.3% cases, and amoxicillin/amoxicillin+co-amoxiclav was given in 13.2% cases. These figures are indicating high rates of empirical antibiotic treatment without culture reports which may be a factor towards harboring of

XDR *S. typhi* and resistance to other pathogens, as we can look; intravenous ceftriaxone was received by 51.3% cases before culture reports.

Most common complications were bone marrow suppression was found in 59.2% and subclinical hepatitis in 32.9% and similar results have been reported by Iftikhar et al.[18] We didn't find any case of intestinal perforation. One of its reasons may be that we only enrolled patients admitted in all medical units while enteric fever patients with perforation are usually admitted in pediatric surgical units.

The limitations of the study are that it included only hospitalized patients. Secondly, study enrolled only blood culture proven cases, so enteric fever patients treated with negative blood culture might have been missed.

Conclusion

There are high rates of resistance against all commonly used antibiotics for typhoid including fluoroquinolones and cephalosporins. There is shift of antimicrobial susceptibility leaving only extremely limited and costly options for treatment and increases length of hospital stay due to need of intravenous therapy resulting in increased financial burden over families as well as government.

Recommendation

In settings of poor sanitation, lack of vaccination coverage and the emergence of XDR *S. typhi* suggest the appropriate policies for antimicrobial usage, need for nationwide vaccination campaigns, and Govt. based policies for provision of safe drinking water. There is also needed to revise guidelines for treatment of enteric fever in both empirical and in culture proven cases. Treatment of enteric fever patients with two or more sensitive drugs may also be considered as this policy has been implemented in cases of malaria and tuberculosis to prevent further emergence of resistance.

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