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ORIGINAL ARTICLE

Current Sensitivity Pattern of Salmonella Species in Children Presenting at a Tertiary Care Hospital

MUHAMMAD RAFIQUE[1], SHARMEEN NASIR[2], AMBER KAMRAN[3], WASEEM JAMALVI[4], AMMARAH JAMAL[5]
[1-5]Department of Pediatrics, Dow University of Health Sciences.
Correspondence to: Muhammad Rafique, Email: drmuhammadrafique@yahoo.com, Cell: 0334-3522001

ABSTRACT

Background: Enteric fever is a common and treatable pediatric bacterial infection, but emerging drug resistance has been a real challenge for treating physicians. Since 2016, Pakistan is facing the epidemic of Extensively drug resistant (XDR) salmonella typhi.

Objective: To determine the clinical presentation and current pattern of sensitivity of salmonella species in children diagnosed with enteric fever.

Study Design: Descriptive, Cross sectional

Place and Duration of Study: Pediatric department of Dr. Ruth K. M. Pfau Civil Hospital Karachi, from July to December 2022.

Methods: Medical records of patients 1 month to 12 years of age, diagnosed as enteric fever on positive blood culture for salmonella, were inducted into the study by non-probability convenient sampling. The clinical manifestations of patients and sensitivity and resistance patterns of salmonella were recorded. Data was analyzed using SPSS version 22.

Results: A total of 140 children had enteric fever, out of which 60.7% were male. Mean age of the patients was 4.48+2.47 years. Most common symptom was fever in 140 (100%), followed by anorexia in 97 (69.2%) and abdominal pain in 70 (50%). Blood culture reports showed Extensive drug resistance in 105 (75%), Multi drug resistance in 3 (2.14%) and Non-resistance in 7 (5%). Salmonella Typhi isolates were sensitive to Carbapenems in 140 (100%), Azithromycin 139 (99.2%) and Piperacillin/Tazobactam in 60 (42.8%).

Conclusion: XDR enteric fever is still the most common resistance pattern identified in admitted patients with enteric fever. Large scale public health measures and antibiotic stewardship are required to fight this disease.

Keywords: Typhoid fever, Salmonella Typhi, Drug resistance, Infection, Epidemic

INTRODUCTION

Typhoid fever or Enteric fever is a multi-systemic infectious disease and an important public health problem in underdeveloped countries[1,2]. The incidence of enteric fever is highest in preschool children and comparatively have a higher rate of complication and severity in this age group[3]. Worldwide, enteric fever is estimated to cause 17.8 million cases and approximately 129000 deaths annually.[4] It is mostly prevalent in developing countries including South Asia with an estimated 1.2 billion infections and 700,000 annual deaths[2,4]. Low standard of living, poor access to sanitation, contaminated water source [4], poor hygiene practices, lack of vaccination and overcrowding are responsible for endemicity of the disease[1]. Clinical outcome is affected by many factors including age, duration of illness before starting treatment, choice of antibiotic, previous exposure, vaccination history, virulence of the bacterial strain and quantity of inoculum ingested.[5]

Enteric fever is caused by Salmonella Enterica Serovar Typhi and Paratyphi[6]. The commonest presentation is high grade fever. Other presentations are anorexia, vomiting, abdominal pain, diarrhea and lethargy[1]. Complication usually occurs in 2nd to 4th week of the illness[3]. Central nervous system, gastrointestinal, renal, and hepatic complications are commonly seen in 10-15% of hospitalized patients[3]. Blood culture and culture positivity from other anatomic sites is mainstay for diagnosis[7]. Delay of diagnosis and treatment are responsible for greater risk of mortality in patients having enteric fever. Mean time of defervescence of fever is from 4 days to 7 days.

Treatment with appropriate antibiotic is lifesaving in enteric fever but has become difficult nowadays due to emerging resistance of the bacteria against traditionally used antimicrobial agents[2]. Over the last two decades we have witnessed the salmonella species getting resistant to various antibiotics one after the other, starting from the 1st line drugs to quinolones, being labelled as Multidrug resistant (MDR) typhoid. In November 2016, Pakistan faced the outbreak of cephalosporin resistant cases of typhoid fever which was labelled as Extensively drug resistant (XDR) typhoid[8]. These strains were sensitive to carbapenems and azithromycin which are not the traditionally used and indicated antibiotics for typhoid fever. This rise in antibiotic resistance and change in sensitivity pattern led to increased hospitalization and treatment cost as carbapenems can only be administered parentally, as well as increase in morbidity and mortality[2].

Over the time during our clinical practice, we noticed that there is returning sensitivity of salmonella species to the 1st and 2nd line drugs in some cases, along with persistence of XDR. This reflected that studies are needed time to time for updating drug sensitivity against microbes to decrease the morbidity and mortality associated with disease. Moreover, knowledge of the pattern of disease and its appropriate sensitivity can help not only in early diagnosis but also starting effective treatment early in the course of disease, which can reduce complications. Keeping this background in mind, we designed this study to determine the clinical presentation and current pattern of sensitivity of salmonella species in children diagnosed with enteric fever at a public sector, tertiary care hospital of Karachi, Pakistan.

METHODOLOGY

We performed a cross sectional study at the Department of Pediatrics, Dr. Ruth K.M Pfau Civil Hospital Karachi from July to December 2022 for a total of 6 months. Ethical approval from the Institutional Review Board (IRB) of Dow University of Health Sciences was taken prior to the study. Using the frequency of Extensively drug resistance (XDR) typhoid to be 69% in Karachi[8], with a confidence interval of 95% and absolute precision of 8%, 129 patients of enteric fever were needed for the study using open epi version 3.01.

All patients 1 month to 12 years of age, of both genders, admitted at the Department of Pediatrics with clinical suspicion of enteric fever and/or with a blood culture report showing growth of salmonella typhi were included in the study, by non-probability consecutive sampling. Complete blood count (CBC) and blood culture (if not sent before admission) were sent to the Central Laboratory of Dr. RKMP Civil Hospital Karachi on the first day of admission. In the lab if Salmonella isolates grew in culture, they were tested for antimicrobial susceptibility for 10 antibiotics namely, Chloramphenicol, Ampicillin, Trimethoprim/ Sulphamethoxazole (TMP/SMX), Ceftriaxone, Cefixime, Ciprofloxacin, Meropenem, Imipenem, Azithromycin and Piperacillin/Tazobactam. All patients were admitted to the inpatient department and intravenous ceftriaxone was started in a dose of 75mg/kg/day. A predesigned proforma was used to collect the

demographic, clinical and laboratory data. Demographic data included age and gender, clinical data included signs and symptoms including duration and defervescence of fever, complications if any and outcome, while laboratory data included sensitivity or resistance to one or more antibiotics. Resistance of salmonella isolates was classified as per the World Health Organisation (WHO) classification devised in 2018.

Non-resistant Typhoid fever: If the salmonella isolates are sensitive to 1st line drugs (ampicillin, chloramphenicol, and Trimethoprim/ sulphamethoxazole TMP/SMX) and third generation cephalosporin with or without resistance to 2nd line drugs (quinolones).

Multi-drug resistant (MDR) Typhoid fever: If the salmonella isolates showed resistance to 1st line drugs (ampicillin, chloramphenicol, and Trimethoprim/ sulphamethoxazole TMP/SMX), without resistance to cephalosporins.

Extensively drug resistant (XDR) Typhoid fever: If the salmonella isolates are resistant to all recommended antibiotics for typhoid fever.

After getting the blood culture report, antibiotic was prescribed according to the sensitivity report. Patient's data was anonymized to ensure privacy. Data was analyzed using SPSS version 22. Descriptive statistics were applied. Numerical variables were expressed as mean ± standard deviation (SD) while categorical variables like were expressed as frequencies and percentages.

RESULTS

A total of n=140 patients were diagnosed with culture proven enteric fever. Out of these, n=85 (60.7%) were male while rest were female. Mean age of the patients was 4.48+2.47 years (minimum 7 months and maximum 12 years). Only 12 (8.57%) patients were vaccinated for typhoid. Only 3 (2.1%) patient had a household contact with another patient with enteric fever.

Mean duration of symptoms before coming to hospital was 13.9+6.9 days and majority of the patients n=107 (76.4%) patients had taken antibiotics prior to coming to the hospital, out of which 106 (99.0%) had taken third generation cephalosporin while only 1 (0.93%) had taken amoxicillin/clavulonic acid (Table I).

Table 1:

Features of patients with enteric fever	N(%)
Male Gender	85 (60.7%)
Mean age of presentation in years (Mean ± SD)	4.48+2.47
Mean duration of symptoms in days (Mean ± SD)	13.9+6.9
Vaccinated for typhoid	12 (8.57%)

Table 2: Clinical features of patients with Culture proven Enteric fever.

Symptoms	n (%)
Fever	140 (100%)
Anorexia	97 (69.2%)
Abdominal Pain	70 (50%)
Vomiting	60 (42.8%)
Myalgia	37 (26.4%)
Diarrhea	37 (26.4%)
Bleeding	03 (2.1%)
Arthralgia	03 (2.1%)
Signs:	n (%)
Hepatomegaly	103 (73.5%)
Anemia	90 (64.2%)
Coated tongue	90 (64.2%)
Splenomegaly	20 (14.2%)
Jaundice	10 (7.14%)

Most common symptom of enteric fever was fever in 140 (100%) of the patients followed by anorexia in 97 (69.2%) and abdominal pain in 70(50%) of the patients. Hepatomegaly was the most common sign on examination in 103 (73.5%) patients, followed by anemia and coated tongue in 90 (64.2%) each (Table II). Mean duration of defervescence of fever was 6.6+4 days while average length of hospital stay was 11.8+4.44 days. One patients developed osteomyelitis, while another developed meningitis with brain abscess as complication. One patient each was interestingly found to have vivax malaria and dengue fever coexistent with enteric fever. Majority of the patients 138 (98.5%) got discharged while 2 patient (1.4%) left against medical advice before completion of treatment.

Complete blood count report of the patients showed mean hemoglobin of 8.75+1.63 gm/dl, mean total leucocyte count was 7.2+3.8/ul and mean platelet count was 222,000+146/ul. The blood culture reports showed that all the Salmonella Typhi isolates were sensitive to carbapenems n=140 (100%), while they were Non-resistant in n=7 (5%) cases, MDR in 3 (2.14%) and XDR in 105 (75%) cases. We noticed two more resistant patterns not fitting in the above three categories given by WHO. These were isolates showing sensitivity to one of the three 1st line drugs in 13 (9.2%) and isolates showing sensitivity to quinolones in 12 (8.5%) while both groups being resistant to 3rd generation cephalosporin (Figure 1). The details of individual drug sensitivities are shown in Table III.

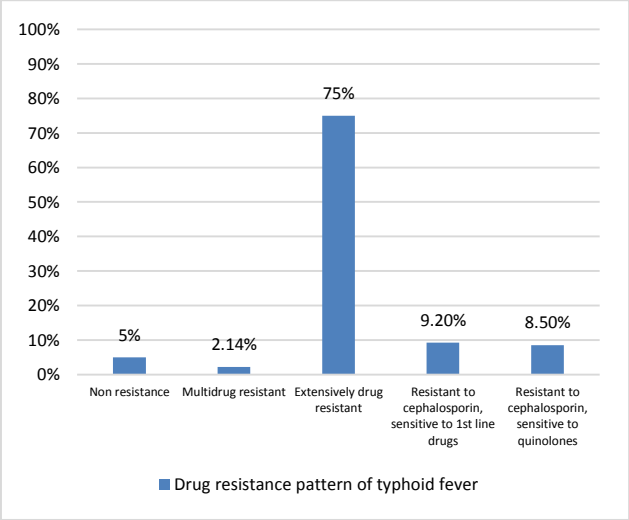

Figure 1: Drug resistance patterns of Typhoid Fever

Table 3: Sensitivity pattern of Salmonella Typhi against individual drugs.

Antibiotic	Sensitivity of Salmonella isolates	
	Complete sensitivity	Intermediate sensitivity
1st line drugs:		
Chloramphenicol	13 (9.2%)	-
Ampicillin	8 (5.7%)	-
Trimethoprim/Sulphamethoxazole	20 (14.2%)	-
2nd line drugs:		
Ciprofloxacin	12 (8.5%)	7 (5%)
Ceftriaxone	10 (7.1%)	-
Cefixime	8 (5.7%)	-
3rd line drugs:		
Meropenem	140 (100%)	-
Imipenim	140 (100%)	-
Azithromycin	139 (99.2%)	-
Piperacillin / Tazobactam	60 (42.8%)	-

DISCUSSION

Enteric fever is still a common pediatric infectious disease, despite the efforts of health authorities to carry out mass vaccination campaigns against typhoid and including it in Expanded Program of Immunization of Pakistan. It accounts for a large number of hospital admissions as well as financial and social burden over the family and healthcare system. Superimposed on this changing sensitivity patterns are another challenge for the treating physicians. This article describes the current sensitivity patterns of salmonella typhi species causing enteric fever in pediatric age group.

Out of a total of 140 patients, majority were male with a mean age of 4.48 years. In other studies from various areas of Pakistan mean age of 5.7 years, 6.1 years and 9.8 years has also been reported[9,10 and 11]. Only 8.5% of the children were vaccinated for typhoid by word of the attendant. Similar discouraging results were shared by Memon et al where none of the children with enteric fever were vaccinated for typhoid[12]. The myths of parents and caretakers related to vaccines and thus not getting their children vaccinated is still a major factor leading to rampant spread of infectious diseases like enteric fever and measles in a developing country like Pakistan.

The most common manifestations of enteric fever in our cohort were fever, along with anorexia, abdominal pain and vomiting. The mean duration of illness was 14 days. These are the classic manifestations of enteric fever and similar findings have been documented by other researchers from the same city[13,14]. The blood culture report revealed that majority of our patients (75%) had extensively drug resistant typhoid (XDR). The situation was similar in a large prospective study done from 2016 till 2019 at a private sector hospital[13]. The findings are same from our study which is in 2022 at a public sector hospital. This reflects that XDR salmonella typhi is persistently circulating in our water supplies and infecting our children.

An interesting fact which surfaced in our study is that only 2% cases were MDR, 5% were non-resistant while we came across two new groups of sensitivities. Those salmonella which were sensitive to one of the three 1st line drugs and those which were sensitive to quinolones while being resistant to cephalosporin. This is a small proportion but it gives us a ray of hope of returning sensitivity of salmonella species to 1st line drugs and/or quinolones, possibly because their use if now decreased as compared to cephalosporin and azithromycin. Another interesting finding was the high sensitivity of salmonella for piperacillin/tazobactam, though it is not a traditionally used antibiotic for enteric fever. Other researchers have also reported sensitivity of small proportion of salmonella with amikacin and/or gentamicin[15,16].

Carbapenems were still found to be 100% sensitive to salmonella species and azithromycin in 99% in our study population. Another study from Karachi performed in 2021 reveals 15% resistance to azithromycin and carbapenems[15-18]. It would be alarming if the resistance to these drugs increases. Thus, it is the duty of all physicians to apply antibiotic stewardship in their daily practice and avoid unnecessary use of these broad spectrum antibiotics in conditions where narrower spectrum antibiotics can be used, to break this cycle of resistance.

Typhoid conjugate vaccine (TCV) is another option to reduce the spread of the disease and a study conducted in Hyderabad, Pakistan showed that it is 95% effective against culture proven typhoid and 97% effective against XDR typhoid[19]. Pakistan, in 2019, became the first country to include TCV in its routine immunization program[20]. Along with this, in 2019, a two week TCV vaccination campaign was launched in Sindh with a target to vaccinate 10 million children and another similar campaign was then launched in Punjab in 2021[21]. Unfortunately, despite these massive efforts, majority of patients in our study were unvaccinated for TCV and this is the reason why cases of XDR enteric fever are still persisting and daily encountered in our clinical practice.

CONCLUSION

Extensive drug resistance is the most common resistance pattern identified in admitted patients with enteric fever. XDR Enteric fever is still a significant problem in pediatric population despite the massive efforts taken by the government in the form of vaccination. Physicians need to implement antibiotic stewardship in their day to day practice to avoid facing resistance to available drugs.

Recommendations: Medical professionals and health ministry should take steps to increase awareness of our population regarding vaccines and basic hygienic measures including hand washing and use of boiled water for drinking.

Limitations of Study: This was a single center study in a public sector hospital. Larger population based or multicenter studies are needed to identify the culprits leading to non-vaccination of the affected children.

Conflicts of Interest: None

Funding Source: None

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