ORIGINAL ARTICLE

EXTENSIVELY DRUG-RESISTANT ENTERIC FEVER IN CHILDREN: SURGING THREATS OF ANTIMICROBIAL RESISTANCE AND POSSIBLE SOLUTIONS

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Background: Enteric fever is an infectious disease caused by Salmonella enterica including Salmonella Typhi and Paratyphi A and is associated with potentially serious outcomes, especially in developing countries. The study was conducted with the aim to present the clinical features, laboratory characteristics and antibiotic susceptibility in patients with culture-proven extensively drug-resistant (XDR) enteric fever and to explore drug combinations as a possible solution for the growing problem of antimicrobial resistance. M**ethods:** This descriptive cross-sectional study was conducted in the Paediatric unit of Ayub teaching hospital. Patients admitted with culture-proven XDR enteric fever were included. Patient characteristics were documented on a predesigned proforma. Response to antimicrobial agents including ceftriaxone and levofloxacin, azithromycin and meropenem and meropenem alone was assessed. Data was entered and analyzed using SPSS version 26. **Results:** A total of 53 patients participated in this study. The majority of patients 36 (67.9%) were male and above 5 years of age(n=38,71.7%). The mean age of the participants was 7.08±3.02 years. The major presenting features included fever, anorexia and pain abdomen in 53 (100%), 51 (96.2%) and 41 (77.4%) respectively. The mean duration of symptoms prior to hospitalization was 8.92±3.361 days. Of the total patients, 32(60.4%) responded to the initial therapy with ceftriaxone and levofloxacin, 11(20.8%) patients responded to meropenem alone and 10 (18.9%) patients responded to meropenem and azithromycin in combination. There was no statistically significant difference in mean duration to show response in patients receiving either of the treatments (p=0.484). **Conclusion:** Paediatric patients with XDR enteric fever mainly presented with fever, anorexia and pain abdomen and showed good response to therapy with the combination of ceftriaxone and levofloxacin inspite of the apparent resistance on blood culture and sensitivity.

Keywords: Antimicrobial; Drug resistance; Ceftriaxone

Citation: Bibi S, Gilani SYH, Siddiqui TS, Syed F, Arif MA, Haider N. Extensively drug-resistant enteric fever in children: Surging threats of antimicrobial resistance and possible solutions. J Ayub Med Coll Abbottabad 2023;35(3):424–7.

DOI: 10.55519/JAMC-03-11769

INTRODUCTION

Enteric fever is an infectious disease caused by Salmonella enterica including Salmonella Typhi and Paratyphi A and is associated with potentially serious outcomes especially in developing countries.[1] WHO estimates suggest around 20 million cases of enteric fever are reported globally every year with a mortality documented in 128000 to 161000 patients each year.[2] Pakistan has a high burden of enteric fever being estimated to be 493.5 cases per 100000 persons annually attributed mainly to poor sanitation and overpopulated cities.[3] A study reported a total of 22571 cases of enteric fever from Pakistan over a four year period(2016–2020) comprising an alarmingly high percentage(70%) of XDR enteric fever.[4] Paediatric patients aged 5–15 years are most frequently affected by enteric fever. Estimates suggest a progressive increase in the proportion of paediatric patients with enteric fever with advancing age ranging from 21% in children < 5 years to as high as 40% in Children 5–15 years old in high incidence countries and 7% and 54% in children <5 years and 5–15 years respectively in medium incidence countries.[5] The gram negative organism enters the human body through consumption of contaminated food or water. While traversing the small intestine, it invades the reticuloendothelial system and enters the blood stream. The disease manifests itself as fever of prolonged duration, headache, poor appetite, intestinal perforation, abdominal pain and rarely neurological manifestations.[6] Around 10-15% of admitted patients experience complications in the form of intestinal perforation or haemorrhage, enteric encephalopathy and shock.[7,8] Inspite of a high incidence of enteric fever in paediatric population of South East Asia, the disease in children is more difficult to diagnose owing to similarity to other pyrexial illnesses thus leading to delays in diagnosis and treatment.[9]

Salmonella typhi strains showing resistance to three first-line drugs (ampicillin, trimethoprim-

sulfamethoxazole, chloramphenicol) as well as to fluoroquinolones and third generation cephalosporins are termed as extensively drug resistant (XDR). The first cases in Pakistan were reported in November 2016, from Hyderabad Sindh.[10] Pakistan was considered a hub of the epidemic when two alerts were issued from USA and UK after confirmation of XDR Salmonella isolates in visitors returning from Pakistan in 2018 with subsequent issuance of travel advisory.[11]

The present study was designed to present the clinical features, antibiotic susceptibility and treatment responses in paediatric patients with culture proven XDR Enteric fever in our region. The results will be useful for exploring drug combinations as a possible solution for the growing problem of antimicrobial resistance in the pediatric population of our region.

MATERIAL AND METHODS

This descriptive cross-sectional study was conducted in Paediatric unit of Ayub teaching hospital over a period of three years from 1st July 2019 to 30th June 2022. Ethical approval was obtained from the institutional review board. All paediatric patients aged >1 month to 16 years, admitted with culture proven extended drug resistant enteric fever were included in the study by nonprobability convenience sampling. Patients with clinical suspicion of enteric fever but negative blood cultures were excluded from the study. Patients characteristics like age, gender, presenting complaints, duration of symptoms and haematological parameters were documented on a predesigned *Proforma*. All patients with clinical suspicion of enteric fever and not previously received ceftriaxone were started on combination of intravenous ceftriaxone and levofloxacin while awaiting blood culture results. Patients who had already received ceftriaxone for five or more days with optimal dosing prior to hospitalization were started on meropenem. Azithromycin was added when patient showed no response to meropenem after five days of treatment. Patients who showed no response after five days of treatment with Ceftriaxone and Levofloxacin were also switched to meropenem. Response to antimicrobial agents like ceftriaxone and levofloxacin, meropenem alone or in combination with azithromycin was assessed. Response was considered in terms of resolution of fever. Duration in days taken to show response were documented. Data was entered and analyzed using SPSS version 26.

RESULTS

A total of 53 patients including 36 (67.9%) male and 17 (32.1%) female with culture proven XDR enteric fever were included in this study. The study population comprised 15(28.3%) patients below 5 years of age and 38 (71.7%) above 5 years. The mean age of the participants was7.08±3.02 years. Mean duration of symptoms prior to hospitalization was 8.92±3.361 days. Majority of the patients presented with a normal total leukocyte count (n=41, 77.4%) while thrombocytopenia was documented in 27 (50.9%) patients. (Table-1) The major presenting features were fever in 53 (100%), pain abdomen in 41(77.4%) and anorexia in 51(96.2%) patients. This was followed by headache in 23 (43.4%), diarrhoea in 22(41.5%) and vomiting in 14(26.4%) patients. One patient presented with enteric encephalopathy. (Table-2) Of the total patients, 32(60.4%) responded to the initial therapy with ceftriaxone and levofloxacin. A total of 11 (20.8%) patients responded to meropenem alone and 10(18.9%) patients responded to meropenem and azithromycin in combination. (Table-3) The mean duration to show response was 5.64±1.00 days. There was no statistically significant difference in mean duration to show response in patient receiving either of the treatments (p=0.484). Patient characteristics like age group, gender, platelet counts and total leukocyte count were assessed in relation to the treatment and the difference was not found to be significant (p>0.05) (Table 4)

Table 1: Patient characteristics (n=53)

Patient Characteristics	Mean±SD
Age (years)	7.08±3.02
Weight (kg)	21.90±8.20
Duration of symptoms(d)	8.92±3.361
Duration of treatment before hospitalization (d)	5.16±1.57
Duration to show response(d)	5.64±1.00
Haemoglobin (g/dl)	9.88±1.55
WBC Count (/cmm)	5824.33±2300.17
Platelets count (/cmm)	165169.81±86356.09

Table-2: Presenting Features (n=53)

Patient characteristics		Frequency (%)
Gender	Male	36(67.9)
	Female	17 (32.1)
Age groups	Up to 5 years	15 (28.3)
	>5 years	38 (71.7)
Platelet counts	Low	27 (50.9)
	Normal	26 (49.1)
Total leukocytes count	Low	12 (22.6)
	Normal	41 (77.4)

Table-3: Response to antimicrobial agents

Presenting complaints	Frequency (%)
Fever	53 (100)
Anorexia	51 (96.2)
Pain abdomen	41 (77.4)
Headache	23 (43.4)
Diarrhoea	22 (41.5)
Vomiting	14 (26.4)
Seizures	1 (1.8)
Antimicrobial Response to	**Frequency (%)**
Ceftriaxone plus Levofloxacin	32 (60.4)
Meropenem alone	11 (20.8)
Meropenem plus Azithromycin	10 (18.9)

Table-4: Patient characteristics in relation to antimicrobial response

Patient characteristics		Ceftriaxone + Levofloxacin	Meropenem+/- Azithromycin	*p*-value
Gender	Male	24	12	0.173
	Female	8	9	
Age group	Up to 5 years	11	4	0.226
	>5 years	21	17	
Platelet counts	Low	17	10	0.695
	Normal	15	11	
Total Leukocyte count	Low	10	2	0.065
	Normal	22	19	
Duration to show response (Mean±SD)		5.56±0.759	5.76±1.3	0.484

DISCUSSION

Our study comprised culture proven extensively drug resistant enteric fever patients. Majority of the patients (67.9%) were male and more than 5 years old. World Health Organization (WHO) has also documented a higher incidence of enteric fever in children aged 5 years to 15 years.[12] Another study from Karachi also reported that the majority of patients (79%) with culture proven enteric fever were below 15 years of age.[13] In a study from Karachi involving XDR enteric fever patients, mean age of the participants was reported to be 8 years[14] inspite of the fact that adult patients were included in that study as well. Majority of our patients also presented in the same age group.

Fever was the most consistent clinical feature in our study being documented in 100% patients. Other features included anorexia, pain abdomen, headache, diarrhoea and vomiting in decreasing order of frequency. Similar results are also reported in the literature where fever is reported in 97–100% paediatric patients being treated initially as pyrexia of unknown origin in many cases. Diarrhoea is found less frequently in children and pain abdomen is a common complaint in older children. Enteric encephalopathy is also more commonly described in paediatric patients.[15] One patient from our study population presented with enteric encephalopathy.

The mean total leukocyte count was found to be within normal limits in our study. Similar results are also reported from another study where normal Leukocyte count was documented in 73% paediatric patients with culture proven enteric fever.[16]

In a study from Karachi on culture positive XDR enteric fever mean duration to show response was around 7 days.[14] Similar, results were also obtained from our study. In contrast to our study, they used either meropenem or azithromycin alone or in combination in their patients.

Our study documented a good response to combination of ceftriaxone and levofloxacin in XDR enteric fever patients. Data in literature is scarce about use of ceftriaxone and levofloxacin in patients with XDR enteric fever. However, there are reports of treatment failures in XDR enteric fever patients receiving meropenem and azithromycin.[14] One study reported, efficacy of fosfomycin as an add on therapy in treating XDR Enteric fever in a patient who failed to show response to monotherapy with meropenem.[17]Another report recommended the use of ceftriaxone and azithromycin or ceftriaxone and Fosfomycin as empirical therapy in suspected severe enteric fever patients keeping in view the delayed response to meropenem alone.[18] There was no significant difference in time duration to show response among patients receiving ceftriaxone and levofloxacin and meropenem±azithromycin in our study.

An important observation was that most laboratories do not routinely check for antimicrobial sensitivity of quinolones other than Ciprofloxacin in our region. Literature recommends individual testing for different quinolones due to their different in vitro activities. The varied actions of different drugs of fluoroquinolone group is also attributed to different chemical composition of their molecules including additional Fluoro group. Furthermore, the in vitro patterns may not be fully representative of the in vivo activities hence clinical trials of antimicrobials are mandatory in addition to culture and sensitivity patterns obtained from laboratory.[19]

Previously, studies comparing efficacy of ciprofloxacin to levofloxacin, the L isomer of racemic ofloxacin, in uncomplicated enteric fever have also elucidated better antimicrobial activity in the levofloxacin group again highlighting the difference in antimicrobial activity of both drugs.[20]

Studies have recommended the use of different antibiotics in combination to overcome the problem of resistance thereby utilizing the concept of synergistic effect.[21] This might be the reason for response in patients receiving ceftriaxone and levofloxacin in combination inspite of showing resistance to individual groups on culture and sensitivity.

CONCLUSION

The paediatric patients with extended drug resistant enteric fever mainly presented with fever, anorexia and pain abdomen and showed good response to

therapy with combination of ceftriaxone and levofloxacin. There was no difference in duration of response in patients who responded to combination of ceftriaxone and levofloxacin and meropenem alone or in combination with azithromycin.

Recommendations:

Further studies with larger samples involving multiple centers are recommended.

Acknowledgement: None

Disclaimer: The abstract of this paper was presented in annual scientific meeting of Pakistan Paediatric Association held on 6th August,2022.

Conflict of interest: None

Funding disclosure: None

AUTHORS' CONTRIBUTION

SB: Principal author, study design, literature search, data collection, analysis, interpretation, write-up. SYHG: Literature search, proof reading. TSS: Conceptualization of the study design. FS: Data interpretation. MAA: Questionnaire design, write-up. NH: Literature search.

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Submitted: January 29, 2023	*Revised: April 11, 2023*	*Accepted: May 13, 2023*

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