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Original Article

Treatment of 21st Century typhoid fever in children with mono vs combination drug therapy: An open-label randomized comparative trial.

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Abstract

Background: The treatment of 21st Century XDR typhoid fever is potentially life-threatening and endemic in Pakistan, presents a therapeutic challenge as currently there is no universal treatment strategy whether to use monotherapy with meropenum or a combination of meropenum and azithromycin. Our objective was to compare the efficacy of both therapies in complicated XDR typhoid fever in children, regarding defervescence, bacterial clearance time, resolution of complications, hospital stay, and relapse.

Methodology: This open-label randomized comparative trial was conducted over 18 months at the Department of Pediatrics, Kemari, Clifton and North Campuses, Ziauddin University Hospital Karachi, Pakistan, in which children (aged 6 months to 18 years) with positive blood culture for XDR enteric fever, were recruited into 2 parallel treatment groups (meropenum) and (meropenum+azithromycin combined). Primary outcome viz clinical improvement (resolution of defervescence, complications, and hospital stay) and lab improvement (negative repeat blood culture, 5 days post-treatment), as well as secondary outcome i.e. treatment failure, adverse drug reactions, and relapse of typhoid within 2 weeks post-treatment were monitored.

Results: In the combination group, there was a quicker resolution of fever (5.40 ± 2.17 days vs 6.55 ± 2.77 days in the monotherapy group) as well as complications (3.42 ± 1.97 days vs 4.31 ± 2.71 days in the monotherapy group), resulting in shorter hospital stay (6.94 ± 2.63 days vs 8.08 ± 3.16 days in monotherapy group). 20% had treatment failure in the monotherapy group with a relative risk of 3.55 times more than that in the combination group.

Conclusion: Combination therapy with meropenum and azithromycin is more efficacious in treating complicated XDR typhoid fever in children than meropenum alone.

Keywords

Complicated XDR (Extended Drug-Resistant) Typhoid Fever, Meropenum, Azithromycin, Efficacy.

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Introduction

Enteric fever is a systemic, potentially life-t-hreatening illness, caused by Salmonella Enterica serovar Typhi[1] that warrants immediate antibiotic therapy[2]. Globally, the estimated disease burden is 19.1-20.6 million included 350 culture-proven cases in the USA alone (CDC REPORT) and 2,00,000-6,00,000 deaths per annum, of which approximately 90% of the latter are born by Asia as 400 million people, (23% of the total population) reside in areas notable for water, sanitation and hygiene (WASH) issues[3]. Pakistan, unfortunately, is included in 5 of the countries with a very high burden of Enteric Fever, scaling endemic proportions[4], the latest GDB survey (Pakistan, 2016) showing as high as 574,424 cases of Typhoid or 301 cases per 1 lac population (61% involving children less than 15 years old) and 7811 deaths due to typhoid, (accounting for 68% of children less than 15 years old)[5].

Although antimicrobial resistance has been spreading globally over the past 2 decades with a dominant MDR or multi-drug resistant haplotype of S. Typhi the H58 strain, (resistant to all the first-line drugs used for Enteric Fever; Chloramphenicol, Ampicillin, cotrimoxazole, and Quinolones)[6]. The emergence of an extremely resistant mutant H58 S. Typhi superbug, classified as XDR or extended drug-resistant, Plasmid borne and chromosome resistance genes that collectively harbor resistance to all of the drugs conventionally used for Typhoid Fever including third-generation cephalosporin, initially reported by WHO in Hyderabad, Pakistan in 2016[7,8]. It then took on epidemic proportions over the last 3 years, with 5274 cases (more than 60%) of XDR typhoid fever, out of a total of 8188 cases of typhoid fever from November 2016 up to December 2018[9], with newer cases on the rise[10]. It has jumped international boundaries, with XDR strains of Salmonella Typhi reported amongst travelers returning to the UK, USA, and even a toddler returning to Toronto(Summer 2018)[9,11]. XDR strains of Salmonella typhi have also been recorded from India, Bangladesh[12], the Philippines, Iraq, and Guatemala6. This antimicrobial resistance leaves extremely limited options, as it shows sensitivity only to Carbepenem and oral Azithromycin[7,13].

Before the emergence of XDR, ceftriaxone and cefixime was the mainstay of complicated and uncomplicated typhoid fever in children respectively[8], while other drugs Quinolones, Azithromycin were recommended as the second line[14,15]. The alarming increase in drug resistance among Gram-negative bacterial infections (including S. Typhi) offers a great challenge to modern medicine although its rate differs greatly among different geographic regions (e.g. up to 70% in some hospitals in India vs. less than 7% in European countries), international migration inevitably results in the globalization of infectious diseases, thus facilitating its spread[5,16].

Currently, no universal strategy exists for the treatment of complicated XDR typhoid fever in children[17-19]. Keeping in mind the limited intracellular penetration of meropenum[20] as compared to azithromycin which accumulates intracellularly even late in the lysosomes[21] and the promising effect of combination drug therapy of azithromycin along with third-generation cephalosporin in adults[22] clinicians are using meropenum alone[23] or in combination with azithromycin in such cases[24,25]. To standardize antibiotic stewardship, the rationale of our study is to determine the true efficacy of meropenum alone or in combination with azithromycin in the treatment of XDR complicated Typhoid fever.

Methodology

This open-label randomized comparative trial included children (aged 6 months to 18 years), both genders, attending outpatient/ ER department of pediatrics, from all three campuses of Ziauddin University Hospital, Karachi, from June 2019 to December 2020. The study protocol was approved by the institutional ethical review committee (Reference no: 0980419HRPED) and registered on ClinicalTrials.gov (NCT04154722).

The patients with suspected complicated XDR enteric fever were examined by a consultant pediatrician/senior pediatrics resident. Those who were severely ill requiring ventilator/two inotrope supports or severely malnourished/immunocompromised were

excluded from the study. 3-5 ml of a venous blood sample was drawn from each patient for blood culture and dispatched to the pathology department (for testing using BACTEC technique, following the steps in figure 1) for susceptibility towards Ampicillin, TMP/SMX, Ceftriaxone, Aztreonam, Fosfomycin, Ciprofloxacin, Azithromycin, and Meropenum performed according to guidelines[26] at the time of admission before starting antibiotic therapy.

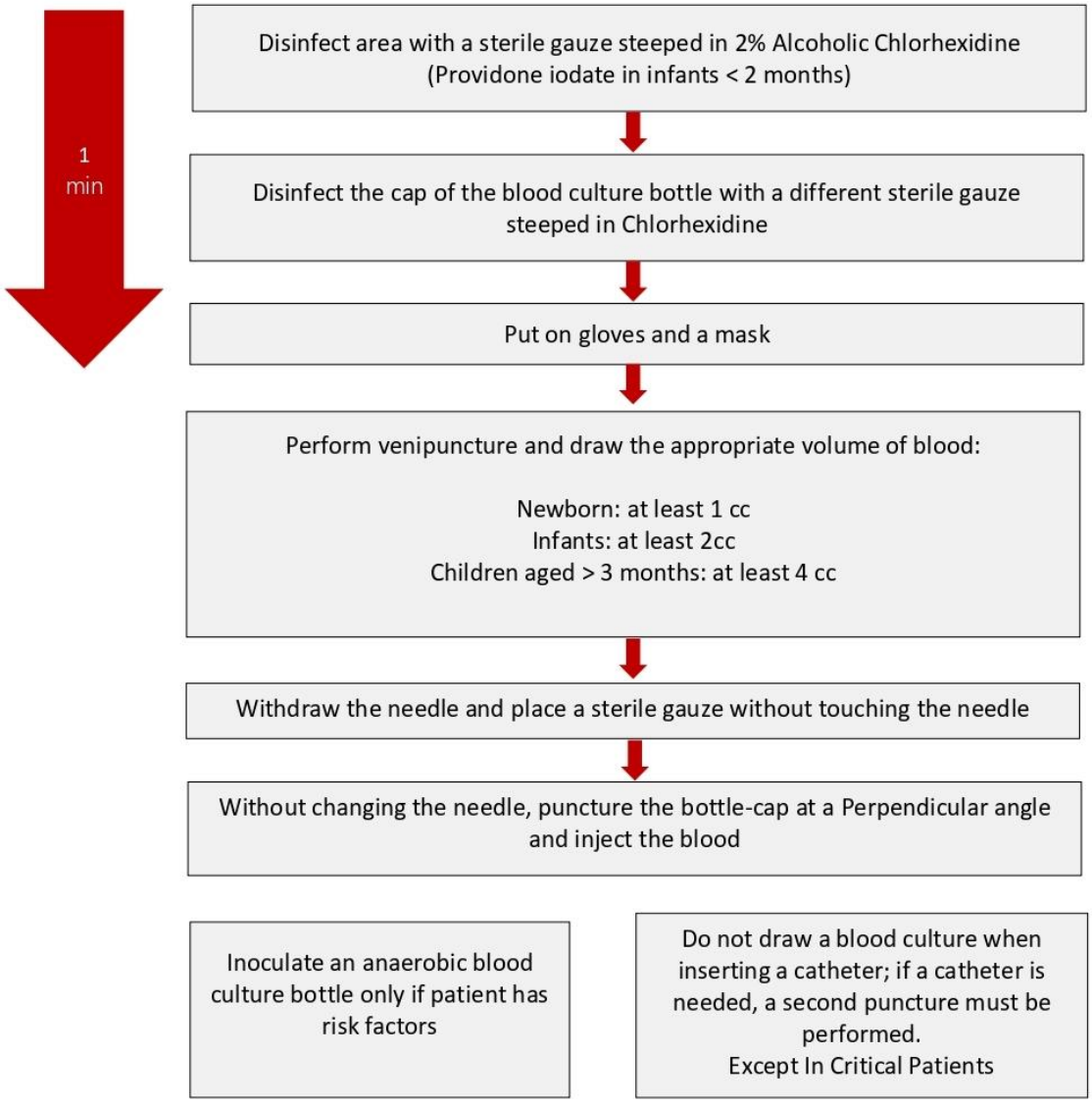

Figure 1: Steps to be followed to draw blood culture[27]

All patients were initially given Inj. Ceftriaxone (75 mg/kg/day IV) as empirical therapy according to Typhoid treatment guidelines. After getting the initial blood C/S report at 48-72 hours confirm XDR typhoid cases showed sensitivity to Meropenum and azithromycin alone (n=130), were divided into

two groups A and B through, non-probability consecutive sampling with concealed allocation using sequentially numbered, sealed, stapled, opaque, envelopes containing treatment groups A or B, by making the patient's attendant choose the envelope by the ward nurse (under supervision of a senior doctor) to decide the patient's treatment regime for total 10 days. The envelopes were internally lined with Aluminium foil to prevent transparency in bright light. To prevent undermining the concealment of the allocation sequence, each participant's biodata was written on the envelope and this data was transferred onto the allocation card inside the envelope with the help of carbon paper within the latter, and a video was made of the allocation process with the participant details visible on the sealed envelope. The video was then checked by a co-researcher to ensure the secrecy of allocation was not breached.

Group A (80 patients) was given Inj. Meropenum alone 60 mg/kg/day (in 3 divided doses) IV, while Group B (50 patients) was given Inj. Meropenum 60 mg/kg/day (in 3 divided doses) IV along with azithromycin 20 mg/kg/day in 2 divided doses, orally (syrup form). Supportive investigations including CBC, UCE, SGPT, and urine RE were also sent. X-Ray chest, urine C/S, ultrasound abdomen, CSF D/R, CSF C/S, CT abdomen advised as required in selected cases with findings were mentioned in the Proforma. Treatment response and failure were labeled if the patient required ICU admission due to worsening of complications after 48 hours (Figure 2; CONSORT diagram).

Patients data including age, sex, typhoid vaccine status, signs and symptoms (as per operational definitions), were obtained, after taking informed written consent from the guardians/caretakers. All patients were monitored for relapse and adverse drug reactions during treatment. In case of non-resolving complications by any regime, the treatment modality was changed according to the sensitivity of other drugs with consultation from the Infectious disease department. Steroids were added in selected cases according to the guidelines (IV Dexamethasone 3 mg/kg initial dose followed by 1 mg/kg every 6 hours for 48 hours). Exclusion criteria were followed strictly to avoid confounders.

Data were analyzed using SPSS version 21.0, frequencies and percentages were computed for categorical variables like gender, typhoid vaccination status, signs and symptoms, adverse events, relapse. Quantitative variables like age, duration of signs and symptoms, fever clearance time, and bacteremia clearance time were presented as mean ± standard deviation. Chi-square and student t-test/ANOVA were used to assess group differences, where p-value≤0.05 with a confidence interval of 95% was considered statistically significant. Sample proportion was calculated based on the treatment response in two groups using mono vs combination drug therapy i.e. P1=82%[22]; P2=96%[22]; power of test 80%.

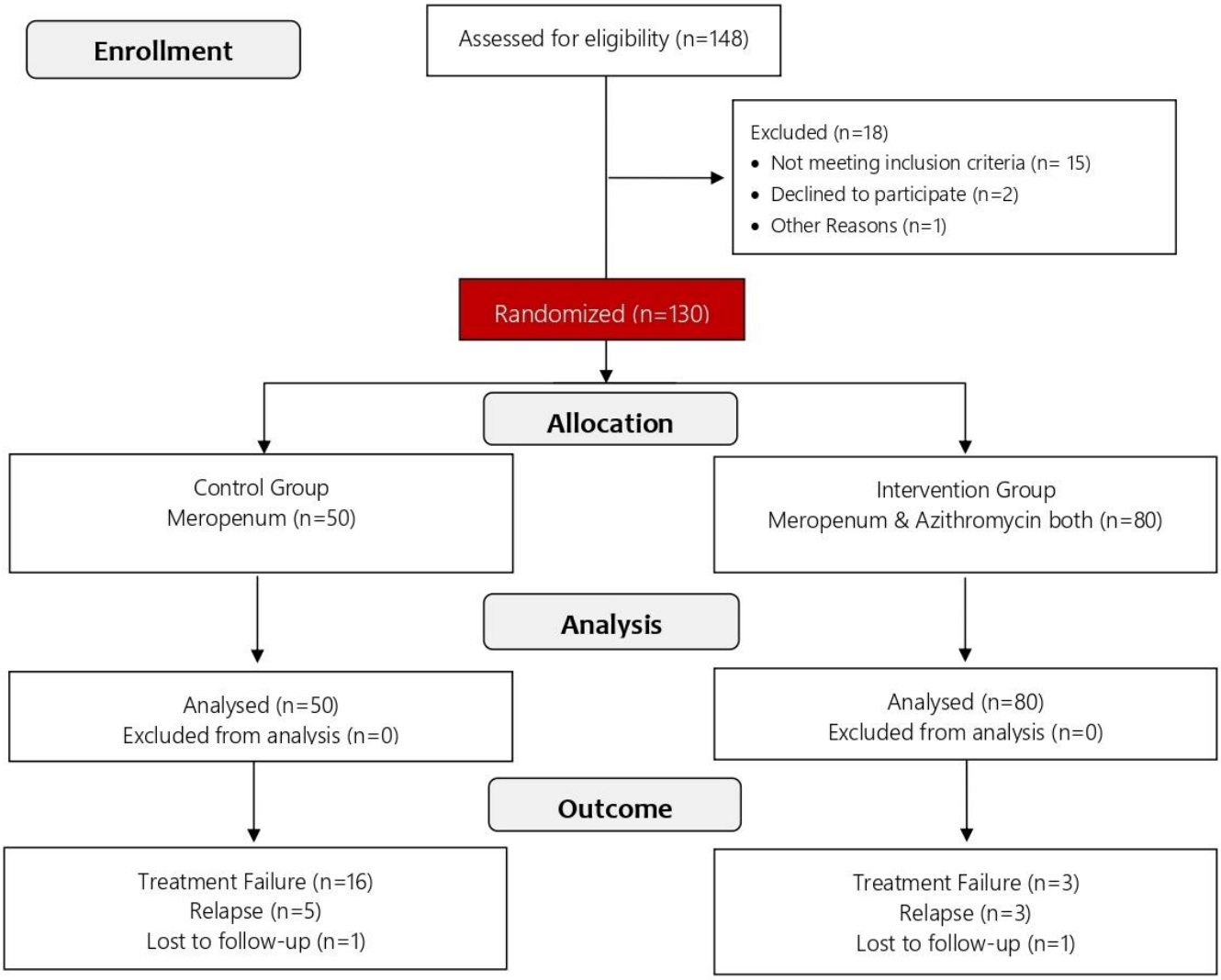

Figure 2: CONSORT Diagram describing the flow of participants throughout the study.

Results

Patient's characteristics

Out of the total of 130 patients, 69(53.1%) were males and 61(46.9%) were females, with a mean age of 5.18 ± 3.0 years. The diagnosis was based on blood culture showing Salmonella Typhi or Paratyphi sensitive to Meropenum and Azithromycin. Ten patients (7.6%) had additional sensitivity with Fosfomycin. One patient also had Brucellosis along with enteric fever while only 2 patients received typhoid vaccination in the last two years.

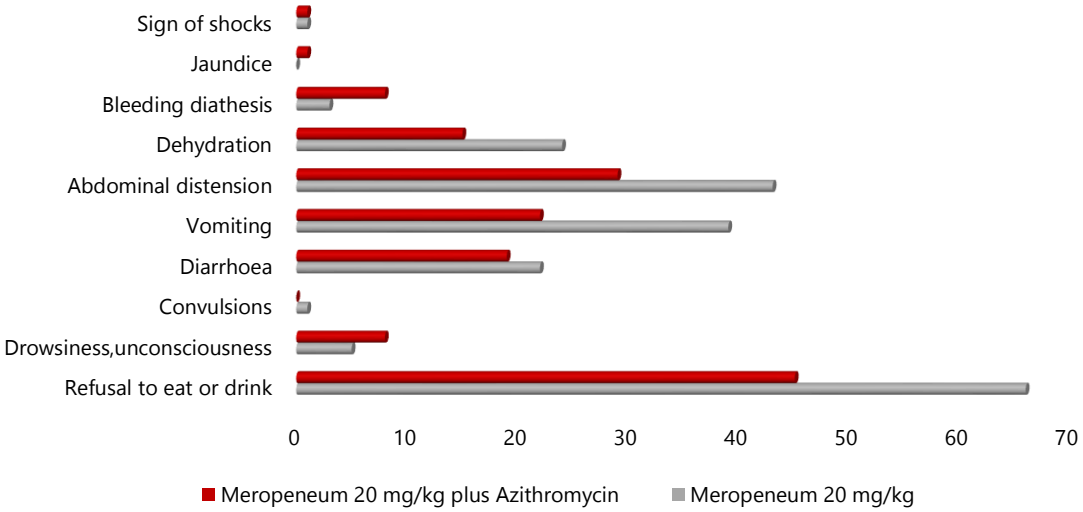

Figure 3: Frequency of complications in treatment groups.

All patients required hospitalization due to complications ranging from refusal to feed to shock with variable frequencies shown in figure 3. Among lab investigations ALT was found to be mildly elevated in both groups, while a summary of others is given in table 1.

Table 1: Laboratory parameters in both the groups.

Laboratory parameters	Meropeneum 20 mg/kg	Meropeneum 20 mg/kg plus Azithromycin
	Mean±SD	
Heamoglobin Level (gm/dl)	10.40±1.54	10.38±1.44
White blood cell count (10^9/L)	7.21±3.15	7.44±2.6
Platelets count (10^9/L)	249.27±98.83	229.01±143.36
Random Blood Sugar (mg/dl)	100.42±23.22	96.64±18.53
Serum Urea (mg/dl)	21.77±9.8	20.51±12.05
Serum Creatinine (mg/dl)	0.49±0.15	0.44±0.19
Serum Sodium (mEq/L)	134.82±3.64	134.88±4.74
Serum Potassium (mEq/L)	4.22±3.9	3.62±0.618
Serum Chloride (mEq/L)	101.85±4.26	100.77±6.82
Serum Bicarbonate (mEq/L)	21.29±2.19	21.31±3.54
Serum Alanine transaminase (units/L)	90.16±216.9	85.39±132.95

Primary outcome

Fever clearance time is 6.55 ± 2.77 days in the Meropenum group while 5.40 ± 2.17 days with a mean difference of 1.15 days (p=0.067). Out of 80 patients, 13(16.25%) have positive blood culture after 5 days of receiving antibiotics in the Meropenum group while 15 out of 50(30%) patients reveal positive blood culture in the combination group. Complications resolved in 4.31 ± 2.71 days in the Meropenum group while in 3.42 ± 1.97 days in the Meropenum and Azithro group with a Mean difference of 0.52 days (p=0.091) Hospital stay was found to be significantly shortened in the combination group with 6.94 ± 2.63 vs 8.08 ± 3.16 days in the Mero group with a mean difference of 0.53 days (p=0.036) as shown in table 2.

Table 2: Mean difference in primary outcome between two treatment groups.

Primary outcome	Meropeneum 20 mg/kg	Meropeneum 20 mg/kg plus Azithromycin	95% CI		p-value
			Lower	Upper	
Hospital stay (days)	8.08±3.16	6.94±2.63	0.077	2.196	0.036
Resolution of complications (days)	4.31±2.71	3.42±1.97	-0.145	1.922	0.091

Secondary outcome

Adverse drug reactions were observed in only 6 out of 130 patients including diarrhea (n=1), oral moniliasis (n=1), and neutropenia/thrombocytopenia (n=4). The relative risk of adverse drug reaction is 0.33 times more in the group receiving meropenem and azithromycin as compared to those who were given Meropeneum alone. The relative risk of treatment failure is 3.55 times more in those who were given Meropeneum 20 mg/kg as compared to those who were given meropenem 20 mg/kg along with azithromycin (p= 0.03). Treatment failure in total is found to be in 19 patients (14.3%) having a relative risk of 3.55 (p=0.03). Relapse occurred in 8(6.25%) patients out of 128 as 2 patients were lost to follow up. The relative risk of relapse was found to be 1.45 (p=0.57) as shown in table 3). The risk of typhoid relapse is 1.11 times more in the group receiving Meropeneum 20 mg/kg as compared to those who were given meropenem 20 mg/kg along with azithromycin (p=0.88,non-significant).

Table 3: Results of regression analysis of treatment groups on secondary outcome.

Secondary outcome	Relative risk (RR)	95% CI of RR	p-value
Typhoid relapse	1.11	0.27-4.45	0.88
Treatment failure	3.55	1.09-11.86	0.03
Adverse drug reactions	0.33	0.06-1.75	0.33

Discussion

We analyzed the effect of combination antimicrobial therapy as a strategy to enhance therapeutic efficacy and reduce treatment failure in XDR typhoid patients in comparison to monotherapy. The two drugs that showed sensitivity for XDR typhoid were used in hospitalized patients; meropenum as monotherapy and meropenum with azithromycin as combination therapy. All patients were successfully treated with no mortality in each group. Clinical and microbiological response to treatment and organ function were similar in both groups, however, patients treated with meropenem alone had high treatment failure and relapse as compared to the combination group.

Our results revealed that in XDR typhoid along with meropenum and azithromycin, Fosfomycin had shown sensitivity in 7.65% of patients, similar to the study from Abbasi Shaheed hospital Karachi, Pakistan[26] which also showed 9.4% sensitivity to

fosfomycin, proving a good milestone in the treatment of XDR typhoid. Fosfomycin is a time-tested cost-effective antibiotic used successfully for the treatment of multidrug-resistant strain of S. Typhi[28] either alone or in combination and has a synergistic inhibitory effect on cell wall synthesis[29]. The mean age group in our study was 5.18 ± 3.0 years and 53.1% were males consistent with the findings of Qureshi et al[24] and Aziz et al[26] from Pakistan.

The main objective of the current study is to assess the response of Meropenum vs Meropenum + azithromycin for the treatment of complicated XDR typhoid fever in children. Our study suggests that the combination of meropenum and azithromycin may confer a more effective therapy, in terms of fever clearance time and hospital stay. The mean difference in fever clearance time is 1.15 days (p=0.067) between the study group i.e. 6.55 ± 2.77 days in the Meropenum group while 5.40 ± 2.17 days in the combination therapy group. Although limited data is available regarding the treatment of meropenum in typhoid fever however studies showed the usual time of defervescence for ceftriaxone was 4.3 days (range of 1-9 days)[23] and for MDR typhoid is less than 7 days. Keeping in mind the average time of defervescence for other drugs our combination group showed fever clearance within the average time whereas monotherapy with meropenum had shown more than 7 days fever clearance time.

Hospital stay was shorter in the combination group with a significant p-value of 0.036, corresponding to good extracellular and intracellular drug concentration by meropenum and azithromycin respectively, conferring early treatment response, also postulated in previous studies). Bacteremia clearance time showed better results with meropenum alone vs combination therapy (relative risk 0.541, 0.2819-1.041, p-value 0.06), partially explained as meropenum has a good extracellular concentration that helps in bacteremia clearance especially when given in intermittent infusions[29] as was the case in most of our monotherapy patients, (but could be confounded by other factors like age, the severity of disease and comorbids).

The commonest complications in the studied population were gastrointestinal viz; refusal to feed, abdominal distension, vomiting, diarrhea, and jaundice in descending frequency. Bleeding diathesis and CNS complications were seen in 8.5% and 10.7% cases respectively. The above slightly higher complication rate can be justified based on the delayed start of effective antibiotics due to resistant strain. A meta-analysis was done by Espinoza et al[30] related to the occurrence of complications in relation to days of hospitalization also showed higher complication incidence including encephalopathy (18%) and gastrointestinal bleeding (14%) in cases where the duration of illness was ≥ 10 days. In both groups, the time duration for resolution of complications was the same (mean difference = 0.52 days, p=0.091).

Among secondary outcomes, we found no severe side effects with either group (p=0.33). The response to combination treatment was comparable to that observed in few case reports with multidrug-resistant strains. The risk of treatment failure was found to be 3.55 times more in those who were given Meropeneum vs those who were given meropenem along with azithromycin (p=0.03). Similarly, the risk of typhoid relapse is 1.11 times more in the group receiving Meropeneum which was although not statistically significant (p= 0.88) but overall, slightly high i.e. 6.4% as compared to other studies. Similarly, Blumentrath et al. in 2019[16] reported a case that was treated with meropenem and questioned its efficacy and reported other similar studies with inadequate response to meropenem monotherapy[30-33]. However, Tayyaba et al. in 2020, reported 96.7 %, and 95.5% treatment response to meropenem and azithromycin respectively[32], and a similar response was found by Qureshi et al.[24] for XDR typhoid. Many models were proposed by the researchers to explain the lower efficacy of meropenum in multidrug strains including lower intracellular penetration of drug, short half-life which helps bacteria evolve tolerance or persistence of dormant bacteria in the body tissues. However, if the limited intracellular penetration (more precisely, lack of intracellular accumulation)

is the only limitation of its efficacy then how could the other ß-lactam-antibiotics, including amoxicillin, ampicillin, and ceftriaxone show promising results in the past?[33-35] We assume that the variation and contradicting reports are due to the unavailability of reliable data supporting the utilization of meropenem especially in terms of its dosage, way of administration (bolus vs intermittent infusion)[31], and duration of therapy especially keeping in mind the risk factors of the patients. Furthermore, most of the data available are limited to in vitro susceptibility testing and a few case reports; a point worth considering which was also highlighted by Blumentrath et al. in 2019[16]. The strengths of our trial include the use of concealed randomization, a protocolized approach to the diagnosis and treatment of patients with suspected Enteric fever, and the use of clearly defined study outcomes.

Although it was an open-labeled trial, we minimized bias by using a standardized protocol for diagnosis, management, and outcome. Besides, we did not follow the patients for a longer time i.e. for 4 to 6 weeks to assess for relapse. Despite the good sample size and multicenter design, we could not check the response of different dosage levels and way of administration (intermittent infusion vs bolus form) that could change the outcome of treatment in both groups, since many stricken patients in our study belonged to middle or low socio-economic class, thus could not afford hospitalization and healthcare costs, therefore reducing the length of therapy was inevitable.

Conclusion

Our study concludes that combination therapy using meropenum and azithromycin is more efficacious in the therapy of XDR typhoid fever in children than monotherapy with meropenum. Further research is warranted to determine whether a combination of two antibiotic agents with different pharmacokinetic properties can augment treatment response in XDR Salmonella strains which can be envisaged in terms of lower incidence of treatment failure, relapse, and transmission, and reduce the emergence of resistant bacterial strains. Such beneficial effects would prompt a paradigm shift in the current management approach and translate into better and more efficient outcomes related to disease burden, its mortality, and morbidity.

Conflicts of Interest

The authors have declared that no competing interests exist.

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