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Clinical Response of Meropenem versus Meropenem and Azithromycin in Extensively Drug-Resistant Salmonella

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ABSTRACT

***Objectives*:** To compare the clinical response of Meropenem versus a combination of Meropenem and Azithromycin in Extensively Drug-Resistant Salmonella.

***Study Design*:** Quasi-experimental study.

***Place and Duration of Study*:** Tertiary Care Hospital, Malir Pakistan, from Mar to Sep 2023.

***Methodology*:** A total of 100 patients (50 in the Meropenem group and 50 in the Meropenem and Azithromycin group) who were diagnosed with typhoid fever secondary to extensively drug-resistant salmonella were included. The duration of hospital stay, post-therapy C-reactive protein, time for defervescence, and complete clinical response were compared between the groups.

***Results*:** Median age was 29(49–16) years. There were 78(78%) males and 22(22%) females. Median weight of patients was 75(90–55) kg. Median duration of fever was 6(14–1) days. Median baseline C-reactive protein was 44(167–13) mg/dl. Complete clinical response in Meropenem alone group 49(98%) was significantly higher as compared to Meropenem + Azithromycin group 38(76%), (p=0.001). Similarly, duration of hospital stay and time to defervescence were also significantly shorter in the Meropenem alone group (p<0.001).

***Conclusion*:** Meropenem alone is better than the combination of Meropenem + Azithromycin, with a shorter hospital stay, lesser time to defervescence, and better clinical response.

***Keywords*:** Azithromycin, Drug Therapy, Extensive Drug Resistance, Meropenem, *Salmonella Typhi*.

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INTRODUCTION

Salmonella typhi (*S. typhi*), an organism that is gram-negative, rod-shaped, and flagellated, is the cause of enteric fever. Enteric fever is an issue of public health in poor nations and imposes a significant cost on the health system in these countries.[1] Transmission occurs through faeco-oral route by using contaminated water and food. An estimated 14.3 million cases of enteric fever occur yearly, and more than 135,000 deaths are reported worldwide each year.[2] According to the findings of a study conducted in India on more than 1200 adult patients, enteric fever accounted for 4% of cases of febrile illness.[3] It has been determined through epidemiological research that out of the sixteen Asian nations where typhoid fever is prevalent, the people living in the provinces of Punjab and Sindh in Pakistan are most at risk of acquiring enteric fever.[4] Antibiotics are required for the treatment of patients with enteric fever.

At present, a significant threat to the effective management of typhoid fever is the emergence of multi-drug resistant (MDR) and extensively drug-resistant (XDR) strains of *Salmonella typhi*.[5] Studies have reported rising prevalence of MDR strains (34.2% - 48.5%) and quinolone resistance (1.6% - 64.1%).[6] As a result, last-line antibiotics now available for managing XDR strains of enteric fever include Azithromycin, carbapenems, and tigecycline.[7] Meropenem and Azithromycin are frequently used for this purpose, either singularly or in combination, according to the clinical setting and patient's condition. In this instance, a study revealed that the clinical response was more significant when patients were treated with a single antibiotic instead of a combination medication. The time for defervescence was also shorter when patients were treated with a single antibiotic.[8] Similarly, another study reported that Meropenem alone was better than the combination of Meropenem and Azithromycin for the treatment of XDR typhoid with a complete clinical response of 100% and 89.7%,

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respectively.[9] On the other hand, another such study reported that complete clinical response was much higher with the combination of Meropenem and Azithromycin as compared to Meropenem alone [26.9% vs 5.1%, respectively].[10]

Owing to such opposing results regarding the clinical response of Meropenem alone versus a combination of Meropenem and Azithromycin in the treatment of infection caused by XDR salmonella, makes it imperative that further studies should be conducted in this regard to find out the best possible regime for the management of XDR salmonella infection. Therefore, this study was conducted to compare the clinical response of Meropenem versus a combination of Meropenem and Azithromycin in extensively drug-resistant (XDR) salmonella.

METHODOLOGY

The quasi-experimental study was conducted at Tertiary Care Hospital, Malir Pakistan, from March to September 2023 (ERB #: 115/2023/Trg/ERC dated 1st Dec 2023). The sample size of 100 was calculated using the WHO sample size calculator by assuming the anticipated frequency of complete clinical response in Meropenem alone a group of 5.1% and anticipated frequency of complete clinical response in Meropenem and Azithromycin group of 26.9% using the WHO sample size calculator.[10]

Inclusion criteria: We included patients were aged between 18-60 years, who were either male or female, who were diagnosed with a case of enteric fever secondary to XDR *Salmonella typhi* [defined as *S. typhi* strains resistant to Chloramphenicol, Ampicillin, co-Trimoxazole, and Fluoroquinolones, as well as third-generation Cephalosporins][11] by blood cultures and sensitive to both Azithromycin and Meropenem.

Exclusion criteria: We excluded the patients with an obvious source of other infection, *S. paratyphi* strains growing on blood culture, who failed to seek complete treatment or post-treatment follow-up and were hypersensitive to either study drug.

The study population was selected using the lottery method (Figure).

Written consent, which the study participants signed, was an essential prerequisite. Once selected, baseline characteristics, including age, gender, weight, duration of fever, and C-reactive protein (CRP), were documented. Venous blood samples of 7.5–10ml were taken to be sent for blood culture and sensitivity to identify XDR Salmonella strains and ensure their sensitivity to Meropenem and Azithromycin. The sample was sent to the internal laboratory of the hospital to prevent any financial burden on patients. Once identified, patients were started on treatment after they were divided into two groups through blocked randomization. Patients who were assigned to group-A were treated with injection Meropenem 20mg/kg intravenously, three times a day for 14 days. Patients in group-B were given tablet Azithromycin at 5mg/kg once daily per oral plus injection Meropenem 20mg/kg intravenously for 14 days. In both these groups, duration of hospital stay, post-therapy CRP, time for defervescence (defined as time from first recording of fever till return of body temperature to less than 38^0C for more than 48 hours), and complete clinical response (defined as complete resolution of fever as well as negative blood cultures, sent after day 10 of therapy, within 14 days of therapy) were assessed and documented.

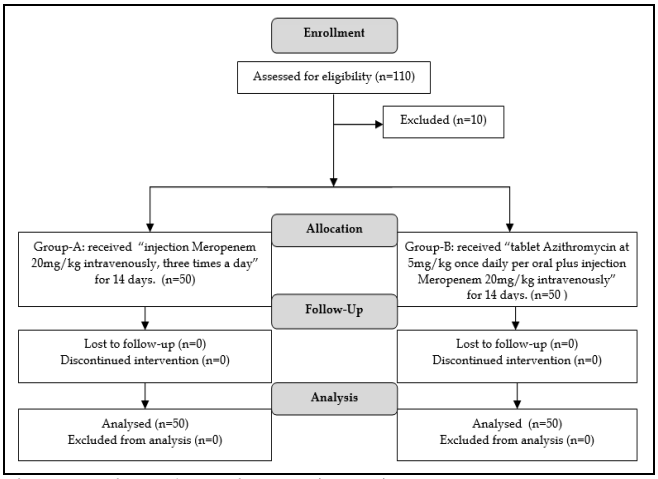

Figure: Patient Flow Diagram (n=100)

Data was analyzed using Statistical Package for the Social Sciences (SPSS) 22.00. Data normality was checked by using the Shapiro-Wilk test. Quantitative data (age, weight, duration of fever, CRP, duration of hospital stay, and time to defervescence) were not distributed normally and were represented by the median interquartile range (IQR). Qualitative data (gender and complete clinical response) was represented using percentages and frequency. Mann Whitney U-test was used to compare the duration of hospital stay, post-therapy CRP, and time for defervescence between Groups. A Chi-square test was used to compare complete clinical responses between Groups. The *p*-value of ≤0.05 was considered as statistically significant.

RESULTS

A total of 100 patients [50 in each group] were included in this study. The median age of study participants was 29(49–16) years. There were 78(78%) males and 22(22%) females. The median weight of patients was 75(90–55) kg. The median duration of fever was 6(14–1) days. The median baseline CRP was 44(167–13) mg/dl. The comparison of baseline characteristics between groups is tabulated below in Table-I.

Table-I: Comparison of Baseline Characteristics in Study Groups (n=100)

Characteristics	"Meropenem Alone Group (A) (n=50)	"Meropenem + Azithromycin Group (B) (n=50)	*p*-value
Median Age	28.50(49.00–17.00) (years)	29.00(45.00–16.00) (years)	0.658
Gender			
Male Female	42(84.00%) 8(16.00%)	36(72.00%) 14(28.00%)	0.148
Median Weight	78.00(89.00–55.00) kg	69.00(90.00–55.00) kg	0.301
Median Duration of fever	5.00(10.00–1.00) days	6.50(14.00–2.00) days	0.004
Median Baseline CRP	44.00(167.00–16.00) mg/dl	53.50(141.00–13.00) mg/dl	0.189

After therapy, the complete clinical response in Meropenem alone Group 49(98.00%) was significantly higher than that in Meropenem + Azithromycin Group 38(76.00%) (p=0.001). Post-therapy completion parameters are demonstrated below in Table-II.

Table-II: Comparison of Post-Therapy Parameters in Study Groups (n=100)

Parameters	"Meropenem Alone Group (A) (n = 50)	"Meropenem + Azithromycin Group (B) (n = 50)	*p*-value
Median Duration of hospital stay	5.00(15.00–3.00) days	7.50(15.00–5.00) days	<0.001
Median Post-therapy CRP	12.50(63.00–1.00) mg/dl	17.00(63.00–2.00) mg/dl	0.214
Median Time to Defervescence	3.50(12.00–2.00) days	6.00(12.00–3.00) days	<0.001
Complete clinical response	49(98.00%)	38(76.00%)	0.001

DISCUSSION

The XDR *Salmonella typhi* strain is a newly identified variant under the H58 lineage".[12,13] This lineage is characterized by the presence of plasmid-mediated resistance mechanisms, including the extended-spectrum β-lactamase (ESBL) gene. These mechanisms confer resistance to various antibiotics, including first and second-line treatments.[14] Considerable seasonal changes have been observed in the association between typhoid fever and geographical regions across the globe.[15] Drug-resistant enteric fever peaks have been observed in Pakistan throughout the months of May-June and October. The occurrence of monsoon rains in Pakistan characterizes both of these periods. A hypothesis suggests a correlation between seasonality and heightened consumption of locally produced beverages and ice cream that may be contaminated during the hot season. Additionally, it is proposed that drinking water may get contaminated with rainwater following the monsoon season, increasing the chances of contracting Salmonella infection.[16]

In any case, when it comes to XDR enteric fever, antibiotic availability is quite limited, with only a few effective antibiotics being available for effectively treating such cases. Meropenem and Azithromycin are among those drugs. In this study, we observed that most patients were younger and were males. No statistical significance difference was observed between study Groups (p>0.05) regarding baseline characteristics. However, in terms of post-therapy parameters, such was not the case. It was observed that the duration of staying admitted at the hospital was significantly longer in patients who received a combination of Meropenem and Azithromycin. A similar finding was observed in a study conducted by Ishaque *et al.*,[8] who reported that this hospital stay duration was shorter in those patients who received a single antibiotic. In terms of time to defervescence, it was found that the mean time to defervescence was shorter in the Meropenem alone Group as compared to the combination therapy Group, and the difference was significant statistically (p<0.001). A similar finding was observed by Ishaque *et al.*,[8] However, contrarily, Qureshi *et al.*,[9] reported no difference between Meropenem alone and Meropenem + Azithromycin combination in terms of time to defervescence with a median time to defervescence of 6.7 days in both the Groups.

Regarding complete clinical response, both Meropenem and combination therapy proved effective in managing XDR enteric fever. Multiple studies have reported both (Meropenem as well as Azithromycin) to be highly effective treatment options for XDR Salmonella infection cases.[17-19] However, upon comparison, it was observed that patients who were treated with Meropenem alone had a much higher percentage of achieving complete clinical response as compared to those treated with combination of

Meropenem with Azithromycin. Subsequently, treatment failure was also higher with combination therapy 12(24%) as compared to monotherapy with Meropenem 1(2%). These findings were congruent with those of Ishaque *et al.*,[8] and Qureshi *et al.*,[9] but were opposite to what was observed in a study conducted by Shahid *et al.*,[10] who reported higher clinical response with combination therapy.

Severe cases of enteric fever tend to result in catastrophic patient outcomes like death.[20,21] Therefore, effective, timely, and appropriate therapy must be ensured. Based on this study, monotherapy with Meropenem is a better option than its use in conjunction with Azithromycin. It is recommended that further studies with a larger population be conducted in this regard to establish the most ideal and effective treatment regimen for treating XDR enteric fever.

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CONCLUSION

The management of XDR Salmonella infection is complex due to the limited choice of antibiotics. Meropenem monotherapy is an effective treatment option for XDR enteric fever. It should be preferred over its combination with Azithromycin because of its shorter hospital stay, less defervescence time, and better clinical response.

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Authors' Contributions:

Following authors have made substantial contributions to the manuscript as under:

MA & SA: Data acquisition, data analysis, critical review, approval of the final version to be published.

JA & NI: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AS & AN: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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