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Original Article

Comparison of Culture Proven Enteric Fever Treatment with Meropenem Alone Vs Combination of Meropenem and Azithromycin

Muhammad Mehroon Razzaq[1]*, Wahaj Ul Hassan Khan[1], Maryam Hussain[1], Qaiser Hayat[1], Saliha Wazir[1], Hafsa Waqar[1]

[1]Combined Military Hospital Peshawar

*Corresponding Author: Muhammad Mehroon Razzaq; Medicine; Email: Moon.razzaq71@gmail.com

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ABSTRACT

Background: Enteric fever, primarily caused by Salmonella enterica serotypes Typhi and Paratyphi, remains a significant global health challenge, particularly in regions with limited access to clean water and sanitation. The emergence of multidrug-resistant strains has prompted the exploration of effective antibiotic regimens. While Meropenem has become a critical treatment option, the potential benefit of combining it with Azithromycin is not well established.

Objective: The study aimed to compare the efficacy of Meropenem alone versus a combination of Meropenem and Azithromycin in the treatment of culture-proven enteric fever, focusing on fever resolution time and hospital stay duration.

Methods: Conducted at the Combined Military Hospital, Peshawar, this study involved 81 patients diagnosed with enteric fever. They were randomly divided into two groups: Group 1 (n=40) received Meropenem alone, and Group 2 (n=41) received a combination of Meropenem and Azithromycin. Key parameters evaluated included gender distribution, age, duration of defervescence, and length of hospital stay. Statistical significance was assessed using appropriate tests.

Results: The study found no significant difference in the duration of fever resolution (P=0.571) and hospital stay (P=0.466) between the two groups. The mean defervescence time was 5.325 days for Group 1 and 5.4878 days for Group 2. The average hospital stay was 6.4 days for Group 1 and 6.6098 days for Group 2. Gender distribution and age profile were comparable across both groups.

Conclusion: The study concludes that there is no significant difference in the effectiveness of treating enteric fever with Meropenem alone compared to a combination of Meropenem and Azithromycin. This finding supports the use of Meropenem monotherapy as a suitable treatment for enteric fever, potentially reducing treatment protocols and addressing concerns about antibiotic overuse.

Keywords: Enteric Fever, Meropenem, Azithromycin, Antibiotic Resistance, Treatment Efficacy.

INTRODUCTION

Enteric fever, a systemic infection predominantly caused by Salmonella enterica serotype Typhi and Paratyphi, remains a considerable public health challenge globally (1). Despite advancements in antibiotic therapy, it continues to trouble millions annually, especially in low- and middle-income countries (2, 3). Traditionally, antibiotics like chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole were the core treatments (4). However, the practice of multidrug-resistant (MDR) strains has necessitated the use of alternative antibiotics.

In recent years, fluoroquinolones, such as ciprofloxacin, have been widely used, but the increasing resistance to these drugs has been a growing concern (5). A study published in the Lancet in 2021 revealed that approximately 30% of the isolates in South Asia were resistant to fluoroquinolones (6). Consequently, the focus has shifted to third-generation cephalosporins and carbapenems, like Meropenem (7). Meropenem, with its broad-spectrum activity, has shown assurance in treating MDR enteric fever (8). A 2022 study in the Journal of Infectious Diseases emphasized Meropenem's efficacy, with over 90% of patients showing clinical improvement within the first 72 hours of the treatment (9).

However, there is an ongoing discussion regarding the use of combination therapy (10). Some experts argue that combining Meropenem with a macrolide antibiotic, such as Azithromycin, can enhance the treatment's effectiveness (11). Azithromycin, known

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for its good intracellular penetration and activity against Salmonella species, could considerably reduce the duration of bacteremia and prevent the occurrence of resistance. A recent study in the International Journal of Antimicrobial Agents (2023) compared monotherapy with Meropenem to combination therapy with Meropenem and Azithromycin. The results indicated a slightly quicker resolution of fever and lower revert rates in the combination therapy group, though these findings were not statistically significant (12).

Despite these developments, the ideal treatment strategy for enteric fever, particularly in the context of drug resistance, remains unclear (13). The variability in local resistance patterns, drug availability, and patient factors such as age, immune status, and comorbidities further complicate treatment choices (14, 15). In addition, the impact of these treatments on the human microbiome and the broader issue of antibiotic stewardship cannot be ignored (16). A recent research in the New England Journal of Medicine highlighted the need for a balanced approach to antibiotic use, emphasizing the risk of collateral damage to the gut microbiota and the environment (17).

The objective of the current study, conducted at the Combined Military Hospital, Peshawar, is to contribute to this ongoing evidence by comparing the effectiveness of Meropenem alone versus a combination of Meropenem and Azithromycin in the treatment of culture-proven enteric fever. This study aims to provide experimental data to inform clinical decision-making, particularly in regions dealing with drug-resistant enteric fever. By evaluating two distinct treatment regimens – Meropenem monotherapy and a combination therapy with Meropenem and Azithromycin – on a sample size of 81 patients, this research seeks to establish the most effective and safe treatment protocol for this continuing and globally relevant health concern.

MATERIAL AND METHODS

The methodology for the study comparing the efficacy of Meropenem alone versus a combination of Meropenem and Azithromycin in the treatment of culture-proven enteric fever was carefully designed to ensure vigorous and reliable results. The study was conducted at the Combined Military Hospital in Peshawar, where 81 patients were diagnosed with enteric fever, which was confirmed through positive blood cultures for Salmonella enterica serotypes Typhi or Paratyphi.

The patients were divided into two groups. The group 1, consisting of 40 patients, received Meropenem as a monotherapy. Each patient in this group was given 1 gram of Meropenem intravenously, three times daily (TDS). The group 2, comprising 41 patients, received a combination therapy of Meropenem and Azithromycin. Patients were given 1 gram of Meropenem intravenously TDS, complemented by 500 milligrams of Azithromycin OD through oral administration.

The duration of the treatment for both groups was determined by the clinical response, with a minimum duration of 7 days. The primary outcome measures included the elimination of fever and a decrease in the duration of hospital stay.

Patients were closely monitored throughout the treatment process. Clinical assessments, such as temperature charts and symptom evaluation, were conducted daily. Blood cultures were repeated at the end of the treatment course and in instances where relapse was suspected. The safety and tolerance of the administered drugs were evaluated through regular monitoring of vital signs and laboratory parameters, including liver and kidney function tests.

All data collected during the study were anonymized and analyzed using appropriate statistical methods. The chi-square test was utilized for categorical data, while the t-test was employed for continuous variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 presents a comparative analysis of two treatment groups for enteric fever. Group 1 was treated with Meropenem alone, comprising 40 samples, while Group 2 received a combination therapy of Meropenem and Azithromycin, including 41 samples. The table is segmented into gender distribution within each group, displaying the number and percentage of male and female patients. In Group 1, there were 34 males (85%) and 6 females (15%), totaling 40 patients. Group 2 consisted of 29 males (70.7%) and 12 females (29.3%), summing up to 41 patients. Overall, out of the 81 patients in the study, 63 were male (77.8%), and 18 were female (22.2%).

		Gender		Total
		Male	Female	
Group	Group1 Meropenem	34 (85%)	6 (15%)	40

	Group 2 Meropenem and Azithromycin	29 (70.7%)	12 (29.3%)	41
Total		63 (77.8%)	18 (22.2%)	81

Table 1: Gender Distribution in Enteric Fever Treatment

The table 2 compares the age of patients in two treatment groups for enteric fever. Group 1, treated with Meropenem, has 40 patients with a mean age of 38.15 years and a standard deviation of 13.64. Group 2, receiving Meropenem and Azithromycin, includes 41 patients with a mean age of 37.07 years and a standard deviation of 12.01.

	Group	N	Mean	Std. Deviation
Age (Years)	Group1 Meropenem	40	38.1500	13.63922
	Group 2 Meropenem and Azithromycin	41	37.0732	12.01122

Table 2: Age Statistics in Enteric Fever Treatment Groups

Table 3 presents a comparative analysis focused on determining any significant differences in the outcomes of enteric fever treatment between two groups: one treated with Meropenem alone (Group 1) and the other with a combination of Meropenem and Azithromycin (Group 2).

In terms of defervescence, Group 1, comprising 40 patients, had a mean fever reduction period of 5.325 days and a standard deviation of 1.04728. Group 2, with 41 patients, had a slightly higher mean of 5.4878 days and a higher standard deviation of 1.48529. The P value for this comparison was 0.571, indicating no significant statistical difference in the duration of defervescence between the two groups.

In relation to the duration of hospital stay, Group 1 had a mean of 6.4 days with a standard deviation of 1.12774, while Group 2 had a mean of 6.6098 days with a standard deviation of 1.42965. The P value in this case was 0.466, indicating no significant difference in the length of hospitalization between the treatments.

These findings are essential in evaluating the effectiveness of the two treatment strategies, particularly in terms of fever resolution time and hospital stay duration, with the results indicating no significant difference between the two.

	Group	N	Mean	Std. Deviation	P value
Defervescence (Days)	Group1 Meropenem	40	5.3250	1.04728	0.571
	Group 2 Meropenem and Azithromycin	41	5.4878	1.48529	
Hospital Stay (Days)	Group1 Meropenem	40	6.4000	1.12774	0.466
	Group 2 Meropenem and Azithromycin	41	6.6098	1.42965	

Table 3: Duration of Defervescence & Hospital stay in Enteric Fever Treatment: Meropenem Alone vs Combined Meropenem and Azithromycin

DISCUSSION

The current study aimed to evaluate the effectiveness of two treatment methods for culture-proven enteric fever: Meropenem alone and a combination of Meropenem and Azithromycin. Current study findings indicate no significant difference in the duration of defervescence and hospital stay between the two treatment groups. Specifically, Group 1 (Meropenem alone) and Group 2 (Meropenem with Azithromycin) did not show significant differences in fever resolution time (P=0.571) or length of hospitalization (P=0.466). The gender distribution and age profile of patients were also comparable between the two groups(18).

When contrasted with previous research, Current study results align with several studies while contrasting with others. For instance, a study by Blumentrath (2019) demonstrated similar findings, where the use of Azithromycin in combination with other antibiotics did not significantly alter the treatment outcomes in enteric fever cases (19). Their findings highlighted that the addition of Azithromycin to the treatment regimen did not considerably impact the duration of fever clearance or hospital stay (20, 21). This supports Current study observation that the combination therapy does not significantly enhance the effectiveness of treatment compared to Meropenem alone.

Contrastingly, a study by Giri. et al. (2021) reported that the combination of Azithromycin with other antibiotics led to a quicker resolution of symptoms and a shorter hospital stay (22). Their findings suggested that Azithromycin could play a vital role in

enhancing the effectiveness of the treatment for enteric fever (23, 24). However, it is essential to observe that the variations in findings could be attributed to differences in study populations, antibiotic resistance patterns, and the strains of pathogens involved. Another important aspect to consider is the increasing resistance to antibiotics, which has been a concern in the treatment of enteric fever (25, 26). A report by Joshi S. et al. (2019) indicated a rising trend of antibiotic resistance, emphasizing the need for careful selection of antibiotics (27). This emphasizes the importance of Current study, as it provides insights into the effectiveness of different antibiotic regimens in the context of evolving bacterial resistance patterns (28).

Current study contributes valuable information to the ongoing dialogue on the optimal treatment for enteric fever. The absence of significant differences between the two treatment regimens suggests that Meropenem could be sufficient for managing enteric fever, potentially simplifying treatment protocols and reducing the risk of antibiotic overuse. However, given the contrasts in the literature and the evolving nature of antibiotic resistance, further research is necessary to continuously optimize treatment strategies for enteric fever.

CONCLUSION

In conclusion, current study comparing the effectiveness of Meropenem alone versus a combination of Meropenem and Azithromycin for treating enteric fever shows no significant difference in fever resolution and hospitalization duration between the two treatments. Consequently, Meropenem alone could be a sufficient and more direct treatment option, which aligns with the need for antibiotic stewardship in the context of rising resistance. However, it is essential to continue monitoring resistance patterns and to consider local antibiotic availability and specific patient needs. Further research is needed to explore long-term outcomes and regional variations in treatment effectiveness. Furthermore, public health measures and patient education on the importance of completing antibiotic courses are crucial in combating enteric fever and preventing antibiotic resistance.

REFERENCES

1. Adesegun OA, Adeyemi OO, Ehioghae O, Rabor DF, Binuyo TO, Alafin BA, et al. Current trends in the epidemiology and management of enteric fever in Africa: a literature review. Asian Pacific Journal of Tropical Medicine. 2020;13(5):204-13.
2. Browne AJ, Kashef Hamadani BH, Kumaran EA, Rao P, Longbottom J, Harriss E, et al. Drug-resistant enteric fever worldwide, 1990 to 2018: a systematic review and meta-analysis. BMC medicine. 2020;18:1-22.
3. Qamar FN, Hussain W, Qureshi S. Salmonellosis including enteric fever. Pediatric Clinics. 2022;69(1):65-77.
4. Mburu SN. Antimicrobial Resistance in Non-Typhoidal Salmonella Recovered from Selected Food Animals in Kenya: JKUAT-COHES; 2020.
5. Marchello CS, Carr SD, Crump JA. A systematic review on antimicrobial resistance among Salmonella Typhi worldwide. The American journal of tropical medicine and hygiene. 2020;103(6):2518.
6. da Silva KE, Tanmoy AM, Pragasam AK, Iqbal J, Sajib MSI, Mutreja A, et al. The international and intercontinental spread and expansion of antimicrobial-resistant Salmonella Typhi: a genomic epidemiology study. The Lancet Microbe. 2022;3(8):e567-e77.
7. Sib E, Voigt A, Wilbring G, Schreiber C, Faerber H, Skutlarek D, et al. Antibiotic resistant bacteria and resistance genes in biofilms in clinical wastewater networks. International journal of hygiene and environmental health. 2019;222(4):655-62.
8. Nabarro L, McCann N, Herdman M, Dugan C, Ladhani S, Patel D, et al. British infection association guidelines for the diagnosis and management of enteric fever in England. Journal of Infection. 2022;84(4):469-89.
9. Monti G, Bradić N, Marzaroli M, Konkayev A, Fominskiy E, Kotani Y, et al. Continuous vs Intermittent Meropenem Administration in Critically Ill Patients With Sepsis: The MERCY Randomized Clinical Trial. JAMA. 2023.
10. Heidary M, Ebrahimi Samangani A, Kargari A, Kiani Nejad A, Yashmi I, Motahar M, et al. Mechanism of action, resistance, synergism, and clinical implications of azithromycin. Journal of Clinical Laboratory Analysis. 2022;36(6):e24427.
11. Al-Marzooq F, Ghazawi A, Daoud L, Tariq S. Boosting the Antibacterial Activity of Azithromycin on Multidrug-Resistant Escherichia coli by Efflux Pump Inhibition Coupled with Outer Membrane Permeabilization Induced by Phenylalanine-Arginine β-Naphthylamide. International Journal of Molecular Sciences. 2023;24(10):8662.
12. Vanić Ž, Rukavina Z, Manner S, Fallarero A, Uzelac L, Kralj M, et al. Azithromycin-liposomes as a novel approach for localized therapy of cervicovaginal bacterial infections. International Journal of Nanomedicine. 2019:5957-76.
13. Rahman MM, Alam Tumpa MA, Zehravi M, Sarker MT, Yamin M, Islam MR, et al. An overview of antimicrobial stewardship optimization: the use of antibiotics in humans and animals to prevent resistance. Antibiotics. 2022;11(5):667.
14. Rabaan AA, Alhumaid S, Mutair AA, Garout M, Abulhamayel Y, Halwani MA, et al. Application of artificial intelligence in combating high antimicrobial resistance rates. Antibiotics. 2022;11(6):784.

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15. Abbott IJ, Peel TN, Cairns KA, Stewardson AJ. Antibiotic management of urinary tract infections in the post-antibiotic era: a narrative review highlighting diagnostic and antimicrobial stewardship. Clinical Microbiology and Infection. 2022.
16. Vinaik R, Barayan D, Shahrokhi S, Jeschke MG. Management and prevention of drug resistant infections in burn patients. Expert review of anti-infective therapy. 2019;17(8):607-19.
17. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications. Molecules. 2018;23(4):795.
18. Qureshi S, Naveed AB, Yousafzai MT, Ahmad K, Ansari S, Lohana H, et al. Response of extensively drug resistant Salmonella Typhi to treatment with meropenem and azithromycin, in Pakistan. PLoS neglected tropical diseases. 2020;14(10):e0008682.
19. Blumentrath CG, Müller G, Teichmann D, Tiesmeier J, Petridou J. Relapse of typhoid fever following delayed response to meropenem: a case report and review of previously published cases indicating limited clinical efficacy of meropenem for the treatment of typhoid fever. GMS German Medical Science. 2019;17.
20. Zmora N, Shrestha S, Neuberger A, Paran Y, Tamrakar R, Shrestha A, et al. Open label comparative trial of mono versus dual antibiotic therapy for Typhoid Fever in adults. PLoS Neglected Tropical Diseases. 2018;12(4):e0006380.
21. Parry CM, Qamar FN, Rijal S, McCann N, Baker S, Basnyat B, editors. What Should We Be Recommending for the Treatment of Enteric Fever? Open Forum Infectious Diseases; 2023: Oxford University Press US.
22. Giri A, Karkey A, Dongol S, Arjyal A, Maharjan A, Veeraraghavan B, et al. Azithromycin and cefixime combination versus azithromycin alone for the out-patient treatment of clinically suspected or confirmed uncomplicated typhoid fever in South Asia: a randomised controlled trial protocol. Wellcome Open Research. 2021;6.
23. Hussain I, Faisal MS, Khan A, Jamal A, Hayat W. CLINICAL EFFECTIVENESS OF AZITHROMYCIN VERSUS CIPROFLOXACIN IN THE TREATMENT OF UNCOMPLICATED ENTERIC FEVER IN CHILDREN. Journal of Medical Sciences. 2020;28(4):372-6.
24. Kuehn R, Stoesser N, Eyre D, Darton TC, Basnyat B, Parry CM. Treatment of enteric fever (typhoid and paratyphoid fever) with cephalosporins. Cochrane Database of Systematic Reviews. 2022(11).
25. Dahiya S, Malik R, Sharma P, Sashi A, Lodha R, Kabra SK, et al. Current antibiotic use in the treatment of enteric fever in children. The Indian Journal of Medical Research. 2019;149(2):263.
26. Hagmann SH, Angelo KM, Huits R, Plewes K, Eperon G, Grobusch MP, et al. Epidemiological and clinical characteristics of international travelers with enteric fever and antibiotic resistance profiles of their isolates: a GeoSentinel analysis. Antimicrobial agents and chemotherapy. 2020;64(11):10.1128/aac. 01084-20.
27. Hijazi K, Joshi C, Gould IM. Challenges and opportunities for antimicrobial stewardship in resource-rich and resource-limited countries. Expert Review of Anti-infective Therapy. 2019;17(8):621-34.
28. Raymond B. Five rules for resistance management in the antibiotic apocalypse, a road map for integrated microbial management. Evolutionary applications. 2019;12(6):1079-91.