COMPARATIVE EFFICACY OF MEROPENEM VERSUS MEROPENEM COMBINED WITH AZITHROMYCIN IN TREATING EXTENSIVELY DRUG-RESISTANT UNCOMPLICATED TYPHOID FEVER

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How to cite this article

Ahmad F, Anwar J, Ahmad HMUAA, Khalid S. Comparative Efficacy of Meropenem Versus Meropenem Combined with Azithromycin in Treating Extensively Drug-Resistant Uncomplicated Typhoid Fever. J Gandhara Med Dent Sci. 2026;13(3):64-70. https://doi.org/10.37762/jgmds.13-3.905

Date of Submission: 08-04-2026
Date Revised: 21-06-2026
Date Acceptance: 23-06-2026

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ABSTRACT

OBJECTIVES

To compare the effectiveness of treating children with meropenem monotherapy vs meropenem plus azithromycin for cases of unexplained typhoid fever that have developed resistance to other drugs.

METHODOLOGY

This study aimed to compare the clinical efficacy and safety of meropenem alone versus meropenem combined with azithromycin in treating pediatric patients with XDR uncomplicated typhoid fever in a randomised controlled trial (ClinicalTrials.gov Identifier: NCT07445282). Over 6 months, a randomised controlled trial was conducted at the Department of Pediatric Medicine at Sheikh Zayed Hospital in Rahim Yar Khan. Ninety children, aged six months to under five years, with blood-culture–confirmed XDR S. Typhi were included and randomly divided into two groups. Group A received meropenem IV (20–40 mg/kg every 8 hours), and Group B received meropenem and azithromycin by mouth (20 mg/kg/day). The main goal was the average time it took for the fever to go down. We used SPSS version 25.0 to analyse the data, setting the p-value to 0.05.

RESULTS

The mean time to defervescence was significantly shorter in the combination group (5.4 ± 2.1 days) than in the meropenem group (6.5 ± 2.8 days; p = 0.02). In the combination group, 93.3% of patients saw clinical improvement, while in the monotherapy group, only 82.2% did (p = 0.04). The dual regimen significantly reduced the mean time to ovulation and the frequency of clinical alterations, without a significant increase in adverse events, compared with the monotherapy or the combination therapy in young children with severe drug-resistant (XDR) straightforward fever.

CONCLUSION

This study provides substantial evidence for optimising antibiotic therapy in pediatric XDR tachycardia by systematically assessing the clinical outcomes of two therapeutic regimens. The results are anticipated to enhance clinical practice, inform antibiotic stewardship initiatives, and support the global effort to mitigate antimicrobial resistance.

KEYWORDS: *XDR, Salmonella Typhi, Pediatric patients, Meropenem, Azithromycin*

INTRODUCTION

Particularly in low- and middle-income nations, typhoid fever poses a significant threat to public health.[1,2] An annual infection affecting millions of people is caused by the Gram-negative, facultatively intracellular bacterium Salmonella enterica serovar Typhi (S. Typhi), which causes this fever.[3,4] Typhoid fever is a major concern in regions of Africa, the Eastern Mediterranean, and South and Southeast Asia despite a decline in global cases during the past several decades.[5,6] Typhoid fever must be continuously monitored, and efficient treatment techniques must be developed because it continues to be a leading cause of illness and death. Traditional antibiotics such as sulfamethoxazole, ampicillin, and chloramphenicol have historically been successful in treating typhoid fever.[7] However, therapeutic options have become significantly more limited due to the proliferation of S. typhi strains that are resistant to many drugs.[8,9] A strain of Salmonella, extensively drug-resistant S. typhimurium, can evade treatment with the five most common antibiotics used to treat typhoid disease. The initial instance of XDR typhoid infection was documented in Pakistan's Sindh province in 2016. The illness has since spread extensively across the nation and even into neighbouring countries.[10] Genomic studies have alarmingly demonstrated that XDR S. Typhi isolates harbour IncY plasmids and multidrug resistance transposons, rendering them resistant even to ceftriaxone, the last reliable oral agent for treating typhoid.[11,12] This means that doctors can only use

carbapenems or macrolides to treat the disease. The growing use of broad-spectrum antibiotics like meropenem has raised concerns about the potential for further resistance and the long-term effectiveness of current treatment plans.[13] Meropenem, a carbapenem-class beta-lactam antibiotic, works by stopping the synthesis of bacterial cell walls. It works well against Gram-negative bacteria, particularly drug-resistant strains of Salmonella typhimurium.[9,14] Nevertheless, monotherapy with meropenem carries the risk of relapse and treatment failure, especially in infections caused by intracellular pathogens that circumvent host defences.[13,15] To mitigate this limitation, combination therapy utilising meropenem and azithromycin has garnered attention as a promising alternative regimen. Azithromycin, a macrolide antibiotic, inhibits bacterial protein synthesis and exhibits superior intracellular penetration compared with most beta-lactams.[16] Meropenem inhibits cell wall synthesis, while azithromycin inhibits the ribosome. Together, these two drugs may have a synergistic effect, killing bacteria, speeding clearance, and lowering the risk of relapse. Meropenem with azithromycin increases bactericidal action against XDR S. aureus, according to in vitro and preclinical research. Typhi-producing bacteria kill faster than either drug alone.[17,18] Small observational clinical studies and case reports indicate a shorter duration of fever resolution, enhanced clinical recovery, and fewer treatment failures with the combination regimen.[19] Nonetheless, substantial clinical evidence from randomised controlled trials comparing the efficacy of meropenem monotherapy versus meropenem combined with azithromycin in pediatric populations remains scarce. Since children are the demographic most impacted by typhoid fever in endemic regions, it is crucial to formulate evidence-based treatment protocols for this population. The rise of XDR typhoid fever could undo years of progress in controlling typhoid and is a big problem for both public health and clinical management. It is therefore important to find antibiotic regimens that work, are safe, and are readily available. To address this knowledge gap, this study compares the effectiveness of treating children with meropenem monotherapy vs meropenem with azithromycin for cases of unexplained typhoid fever that has developed resistance to other drugs. The main goal of the study is to determine how long it takes for body temperature to return to normal and remain below 100 degrees Fahrenheit for at least 48 hours. This is called the mean time to defervescence. Secondary endpoints include overall clinical improvement, treatment failure rate, and adverse event incidence. This study aims to provide substantial evidence for optimising antibiotic therapy in pediatric XDR typhoid fever by systematically assessing the clinical outcomes of two therapeutic regimens. The results are anticipated to enhance clinical practice, inform antibiotic stewardship initiatives, and support the global effort to mitigate antimicrobial resistance.

METHODOLOGY

This single-centre, parallel-group, open-label randomised controlled trial (ClinicalTrials.gov Identifier: NCT07445282) was conducted at the Department of Pediatric Medicine, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan. The study was carried out over six months from January 2025 to June 2025 after approval of the study protocol by the Institutional Review Board of Sheikh Zayed Medical College and Hospital, Rahim Yar Khan (Approval No. 110). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participating children prior to enrollment. Children aged 6 months to less than 5 years, of either gender, presenting with blood culture–confirmed extensively drug-resistant (XDR) typhoid fever were included in the study. XDR typhoid fever was defined as an infection caused by *Salmonella enterica* serovar Typhi strains resistant to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins (including cefixime and ceftriaxone) in the absence of clinical complications. Children were excluded if they had complicated typhoid fever, such as intestinal perforation, gastrointestinal bleeding, encephalopathy, or shock; known hypersensitivity to meropenem or azithromycin; coexisting infections requiring additional antimicrobial therapy; chronic illnesses such as malnutrition or immunodeficiency; or congenital or acquired heart disease. The sample size was calculated using the OpenEpi sample size calculator.[20] The calculation was based on a power of 70% and a confidence level of 90%, using previously reported mean defervescence times of 5.40 ± 2.17 days for combination therapy and 6.55 ± 2.77 days for meropenem monotherapy. The estimated sample size was 90 participants, with 45 children in each treatment group. Participants were recruited using a consecutive sampling technique until the required sample size was achieved. Eligible participants were randomly assigned in a 1:1 ratio to one of two treatment groups using a computer-generated randomisation sequence. Allocation concealment was ensured using sealed opaque envelopes containing the treatment assignments. Due to the nature of the interventions, blinding of participants and investigators was not feasible; therefore, the trial was conducted as an open-label randomised controlled trial. Participants were allocated to the following groups: Group A (Meropenem monotherapy): Patients received intravenous

meropenem at a dose of 20-40 mg/kg every 8 hours. Group B (Combination therapy): Patients received intravenous meropenem at a fixed dose (20-40 mg/kg every 8 hours) and oral azithromycin at 20 mg/kg/day. All medications were administered in the pediatric ward under direct medical supervision. Patients were monitored daily for clinical improvement, temperature changes, and any adverse drug reactions during treatment. A typhoid fever infection caused by Salmonella manifests as an axillary temperature of 100°F or higher. No clinical problems associated with strains of Typhi that are resistant to chloramphenicol, ampicillin, trimethoprim - sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins.[21] The key metric for success was the average time to defervescence, the time it takes for a patient's fever to drop below 100°F and remain below that temperature for at least 48 hours after starting antibiotic treatment.[22] Resolution of fever accompanied by improvement in appetite, activity level, and overall clinical condition without development of complications. Patient demographics and baseline clinical data were documented using a structured information collection form. This data included patient age, gender, weight, temperature, and length of sickness prior to admission. Blood samples were obtained for culture and antimicrobial sensitivity testing according to standard laboratory procedures. Patients' body temperature and clinical status were monitored twice daily during hospitalisation. Information regarding time to defervescence, clinical improvement, adverse drug reactions, and complications was recorded. Patients were followed until they became afebrile and clinically stable for discharge. The data were entered and analysed using SPSS version 25.0, a statistical package designed for the social sciences. For data that follow a normal distribution, quantitative variables such as time to defervescence were presented as means ± standard deviations. Data that did not follow a normal distribution were presented as means with interquartile ranges. Frequencies and percentages were used to display categorical information, such as gender. We checked for normality of distribution using the Shapiro-Wilk test. To compare variables with normal distributions between the two groups, the independent-samples t-test was used. For non-normally distributed variables, the Mann-Whitney U test was employed. To eliminate bias, demographic stratification by age, gender, and socioeconomic position was carried out. Significance was determined by a p-value that was less than or equal to 0.05.

RESULTS

Table 1: Clinicopathological Characteristics of the Study Participants (n = 90)

Variable	Group A (Meropenem only) n = 45	Group B (Meropenem + Azithromycin) n = 45	p-value
Age (months)	32.4 ± 10.2	33.1 ± 9.6	0.68
Gender (Male/Female)	25 / 20	27 / 18	0.65
Weight (kg)	12.1 ± 3.4	12.4 ± 3.2	0.74
Baseline temperature (°F)	102.3 ± 1.1	102.5 ± 1.0	0.59
Duration of illness before admission (days)	5.8 ± 1.9	6.0 ± 1.7	0.63
Mean time to defervescence (days)	6.5 ± 2.8	5.4 ± 2.1	0.02*
Clinical improvement rate (%)	82.2	93.3	0.04*
Adverse effects(%)	6.7	8.9	0.71

*Statistically significant difference between groups ($p \leq 0.05$)

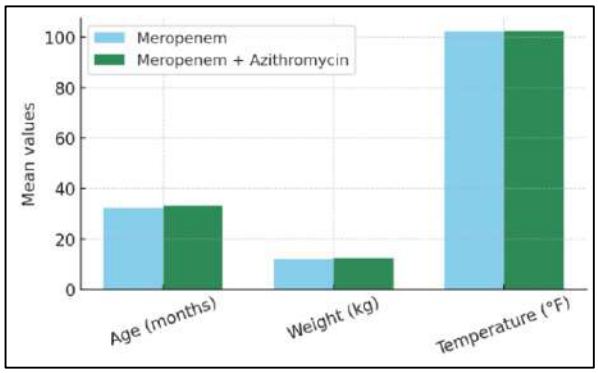

Figure 1: Bar Chart Representing Baseline Clinicopathological Characteristics (Age, Gender, Weight, Temperature) of Participants in Both Groups

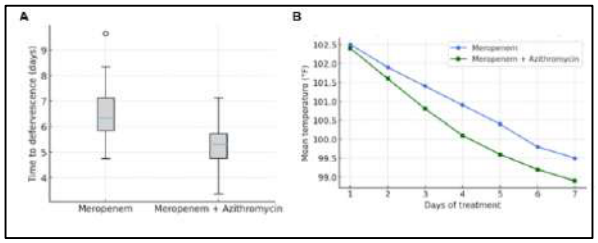

Figure 2: Comparison of Fever Resolution Between Treatment Groups

(A) Box plot showing the mean time to defervescence (days) in patients treated with meropenem monotherapy and those receiving meropenem plus azithromycin combination therapy. (B) Line graph illustrating the daily mean body temperature (°F) during the treatment period for both groups. P<0.05

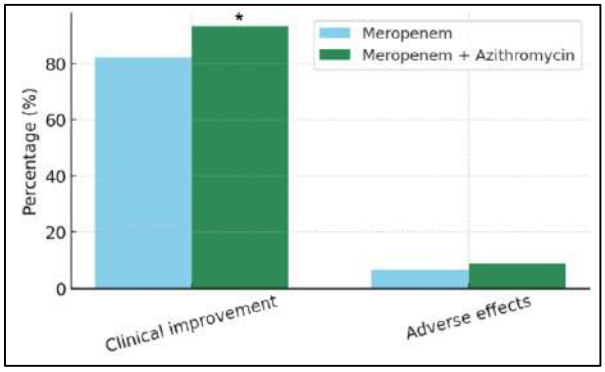

Figure 3: Clustered Bar Chart Showing Clinical Improvement Rates and Incidence of Adverse Effects in Both Treatment Groups

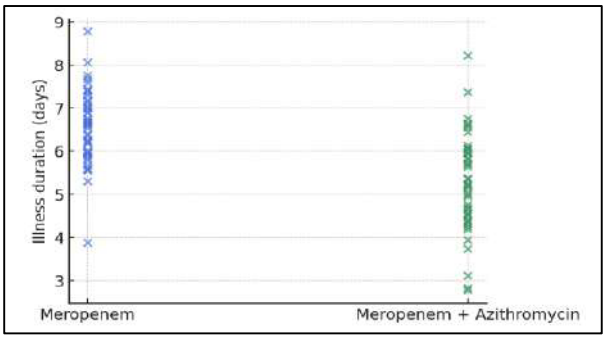

Figure 4: Scatter Plot Showing Correlation Between Treatment Type and Duration of Illness (in days)

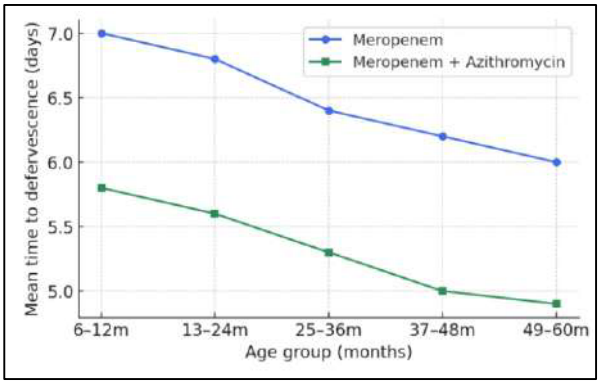

Figure 5: Subgroup Analysis Comparing the Mean Time to Defervescence across Age Groups and Genders for Both Treatment Regimens

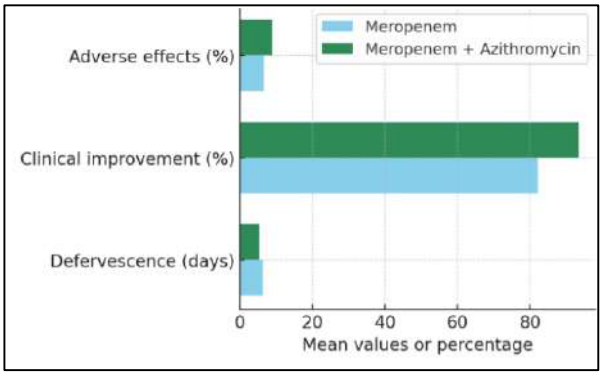

Figure 6: Summary Infographic Representing Overall Comparative Outcomes, Including Mean Defervescence Time, Clinical Improvement Rate, and Adverse Effect Profile Between Treatment Groups

DISCUSSION

Our results show that the dual regimen substantially decreased the mean time to ovulation and the frequency of clinical alterations, without a significant increase in adverse events, compared with meropenem monotherapy or meropenem plus azithromycin in young children with severe drug-resistant (XDR) straightforward typhoid fever. These results indicate that combining a carbapenem with a macrolide may provide synergistic benefits for eradicating challenging S. Typhi infections in environments with limited resources and high resistance. Our results align in part with observational and retrospective studies that have evaluated treatment of XDR typhoid in Pakistan and similar settings.[23,24] Qureshi et al. studied 81 culture-confirmed XDR typhoid patients treated with azithromycin, meropenem, or both and found that the average time to defervescence was similar across all three treatments (6.7–7.1 days), with only small differences in failure rates between groups.[25] Their data thus suggested that monotherapy with either antibiotic might suffice in some cases, although the risk of failure was nonzero. In contrast, our controlled design more clearly demonstrates a benefit of combination therapy in accelerating fever clearance.[26] Other smaller and hospital-based series also report mixed results. A hospital-based study of 120 XDR typhoid cases showed that 37.5% received both azithromycin and meropenem, but recovery rates were similar across groups, with occasional treatment failures in the combination arm.[24,27] While these real-world data emphasise the feasibility of both regimens, they lack the controlled randomisation and rigorous endpoints of our trial. Similarly, retrospective reviews such as the PLoS Neglected Tropical Diseases case series reported comparable therapeutic responses across

the monotherapy and combination groups for fever clearance and complication rates, though they cautioned that cost and resource constraints may influence regimen choice in practice.[28,29] In broader pediatric typhoid literature (non-XDR), studies comparing meropenem or azithromycin monotherapy indicate that both agents are safe and effective, with differences typically in the speed of response rather than the ultimate cure rate. For example, a comparative in vivo pediatric typhoid study concluded that meropenem and azithromycin had similar cure rates and complication profiles, though meropenem tended to reduce fever more rapidly.[30] Our findings echo this pattern under the more stringent XDR context, but further emphasise that adding azithromycin may enhance early bacterial clearance without compromising safety. Compared to broader reviews of antibiotic response in XDR typhoid, our trial provides more definitive insight. A systematic review of pediatric XDR typhoid cases in Pakistan showed that 29 % of children recovered on combination therapy, 27 % on azithromycin alone, and only 6 % on meropenem monotherapy, suggesting that monotherapy with meropenem alone may be insufficient in many cases.[31] That review, however, was limited by heterogeneity in patient populations, follow-up, and definitions of cure. Our randomized trial helps clarify that in a controlled setting, meropenem plus azithromycin can deliver more rapid clinical benefit. Our study's randomised design, uniform endpoint (time to defervescence maintained for 48 hours), and pediatric emphasis provide a stronger evidence base than prior observational findings. We evaluated both fever remission and adverse events, classified by age, and instituted follow-up to monitor relapses. The findings thus provide substantial data to guide antibiotic stewardship in areas affected by XDR S. Typhi, which is widespread yet for which treatment options are limited.

LIMITATIONS

There was insufficient power to assess less common outcomes, such as recurrence or death, due to the small sample size and the study's focus on time to defervescence. Furthermore, the results may not apply to patients with severe sequelae, such as intestinal perforation and shock, because the study included only individuals with uncomplicated typhoid fever. There is a risk of observer bias in the evaluation of outcomes due to the trial's open-label design. The fourth limitation is that the study only included one location, a tertiary care facility, which means that the results might not apply to other locations or populations. In addition, microbiological eradication data, such as post-treatment sterile blood cultures or molecular confirmation of relapse, were not routinely available, making it difficult to distinguish bacteriological cure from clinical recovery. Implementation of combination therapy may pose challenges in resource-limited settings due to costs, logistical constraints, and adherence issues. Finally, the follow-up period was relatively short, and longer-term follow-up would be useful to evaluate relapse rates and the potential emergence of antimicrobial resistance. Future large-scale, multicenter trials incorporating microbiological endpoints and pharmacokinetic monitoring are warranted to validate the effectiveness and safety of this treatment strategy.

CONCLUSIONS

This study provides strong evidence that combining meropenem with azithromycin is more effective than meropenem alone for treating pediatric XDR typhoid fever. This is especially true because it shortens the duration of the fever without making the treatment less safe.

CONFLICT OF INTEREST: None

FUNDING SOURCES: None

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AUTHORS CONTRIBUTION

Fawad Ahmad - *Concept & Design; Data Acquisition Data Analysis/Interpretation; Critical Revision; Final Approval*

Jamal Anwar - *Concept & Design; Data Acquisition; Data Analysis/Interpretation; Critical Revision; Supervision; Final Approval*

Hafiz Muhammad Usman Ali Ashraf Ahmad - *Data Acquisition ; Data Analysis/Interpretation; Critical Concept & Design;Revision; Final Approval*

Faryal Bashir - *Concept & Design; Data Acquisition; Data Analysis/Interpretation; Drafting Manuscript; Final Approval*

Sajida Khalid - *Concept & Design; Data Analysis/Interpretation; Drafting Manuscript; Final Approval*

The authors accept responsibility for all aspects of the work and will ensure that any concerns regarding the accuracy or integrity of any part are properly investigated and resolved.