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THE LAST LINE OF DEFENSE: EVALUATING THE EFFICACY OF MEROPENEM AND FOSFOMYCIN AGAINST MULTIDRUG-RESISTANT SALMONELLA TYPHI

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ABSTRACT

There is an urgent need to assess and repurpose current medications due to the concerning increase in antimicrobial resistance, especially in multidrug-resistant (MDR) Salmonella Typhi. In many endemic areas, traditional first-line medications have become ineffective, which has led to research into carbapenems like meropenem and older medications like fosfomycin as possible last-resort therapies.A total of 200 people, between the ages of 20 and 40 participated in a six-month cross-sectional study at Ziauddin University Hospital in Karachi. The modified Kirby-Bauer disk diffusion method was used to analyze blood cultures from patients suspected of having typhoid fever for antibiotic susceptibility. Two therapy groups were examined: Group B received 15 µg of fosfomycin, and Group A received 10 µg of Meropenem. The Chi-square test was used to compare susceptibility patterns by gender and age ($p < 0.05$ as significant).

In contrast to fosfomycin (50% and 36% in the corresponding age groups; $p = 0.03$), meropenem showed greater overall susceptibility (72% in 20–30 years, 60% in 30–40 years; $p = 0.04$). For both antibiotics, a gender analysis showed no statistically significant variations in medication efficacy. Fosfomycin demonstrated limited age-dependent efficacy with considerable resistance, particularly in elderly patients, but meropenem maintained moderate effectiveness across demographics.When it comes to treating MDR Salmonella Typhi, Meropenem works better than Fosfomycin, particularly in younger adults. Age is a more important factor in determining susceptibility than gender.

Key Words: MDR Salmonella Typhi, Meropenem & Fosfomycin

INTRODUCTION

The global escalation of antimicrobial resistance (AMR) has necessitated a critical reassessment and strategic repurposing of existing antibiotics to combat increasingly resilient bacterial pathogens(1), mainly in the contest against multidrug-resistant (MDR) bacteria(2). Among the most concerning of these pathogens is Salmonella Typhi (S. Typhi), the etiological agent of typhoid fever, which remains a significant public health burden, particularly in low- and middle-income countries(3).

Typhoid and paratyphoid fevers—collectively known as enteric fevers—continue to pose serious threats to public health, especially in endemic regions such as South Asia and sub-Saharan Africa. In 2015 alone, approximately 17 million cases were reported globally, underscoring the urgent need for effective control measures(4, 5).

Historically, S. Typhi infections were effectively treated with first-line antibiotics such as ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole(6). However, the emergence and proliferation of multidrug-resistant (MDR) S. Typhi strains—defined by simultaneous resistance to these three agents—has significantly compromised treatment efficacy (7). Compounding the issue is growing resistance to fluoroquinolones and third-generation cephalosporins, driven largely by the widespread and often inappropriate use of antimicrobials (8).

The therapeutic landscape for treating MDR enteric fever is thus narrowing, particularly in resource-limited settings where access to advanced diagnostics and newer antimicrobial agents remains constrained(9). In this challenging context, older antimicrobials such as fosfomycin and carbapenems, particularly meropenem, have gained renewed attention as potential salvage therapies(10). Meropenem, a broad-spectrum carbapenem with potent activity against Gram-negative bacteria, is increasingly employed for severe MDR infections (Venuti et al., 2023). Meropenem, a broad-spectrum carbapenem with potent activity against Gram-negative bacteria, is increasingly employed for severe MDR infections(11). Fosfomycin, a phosphonic acid derivative with a unique mechanism of action, has demonstrated promising in vitro activity against various multidrug-resistant organisms and may exhibit synergistic effects when used in combination therapies(12).

This study aims to evaluate the antibacterial efficacy of meropenem and fosfomycin—individually and in combination—against MDR S. Typhi strains. By investigating both clinical data and in vitro findings (13), (14). this research seeks to assess the potential of these agents as critical components in the treatment arsenal against resistant enteric infections. In an era marked by limited therapeutic options, a deeper understanding of these last-resort antibiotics is imperative to guide clinical decision-making and global AMR containment strategies.

METHODS

This invitro study was conducted in the Department of Microbiology at Ziauddin University Hospital, Karachi, over a six-month period from January 4, 2020, to July 10, 2020. The study population consisted of both male and female participants, aged between 20 and 40 years, selected from inpatient and outpatient departments. Informed consent was obtained from all individuals prior to sample collection.

Inclusion and Exclusion Criteria: Only initial blood culture samples showing bacterial growth were included. Repeat samples from the same patient and those with non-bacterial growth (e.g., fungal or yeast contaminants) were excluded to ensure data integrity.

Ethical Approval: The study was approved by the Institutional Review Board of Ziauddin Hospital (IRB: 0611118ZIMIC), and administrative permission was also obtained.

Sample Size Calculation: Using the WHO Sample Size Calculator, with an assumed meropenem sensitivity rate of 87%, a 9% margin of error, and a 95% confidence interval, the minimum required sample size was calculated to be 54 isolates per treatment group.

Culture & Sensitivity Testing Of Samples: Peripheral venous blood samples were collected aseptically prior to the initiation of any antimicrobial therapy. Samples were incubated in the

BACTEC 9240 automated blood culture system at 35.5 ± 1.5°C for up to five days. This system utilizes fluorescence-based detection to signal microbial growth.

Once flagged as positive, samples underwent Gram staining followed by subculturing onto 5% sheep blood agar, chocolate agar, and MacConkey agar. To prevent contamination during media preparation, all agar plates were pre-incubated. Blood and chocolate agar plates were incubated in a capnophilic environment containing 5–10% CO_2, while MacConkey agar was incubated aerobically at 37°C for 48 hours.

Bacterial Identification: Presumptive identification of Salmonella Typhi was performed using standard microbiological procedures, including Gram staining, oxidase and catalase testing, motility assessment, triple sugar iron (TSI) agar reactions, and colony morphology evaluation. Final confirmation was achieved through biochemical profiling using the API 20E identification system.

Antibiotic Susectibility Testing (AST): Susceptibility patterns of S. Typhi isolates were determined using the modified Kirby-Bauer disk diffusion method on Mueller-Hinton agar, following Clinical and Laboratory Standards Institute (CLSI) guidelines. Two treatment arms were established: Group A tested susceptibility to meropenem, and Group B to fosfomycin. Plates were incubated at 35 ± 2°C under aerobic conditions for 18 to 24 hours (Irfan et al., 2024).

Data Analysis: Data entry and statistical analysis were performed using SPSS version 20. Descriptive statistics, including frequencies and percentages, were used for data presentation. Associations between categorical variables were evaluated using the Chi-squared test. A p-value < 0.05 was considered statistically significant.

RESULTS

This six-month, cross-sectional study evaluated the comparative in vitro efficacy of meropenem and fosfomycin against multidrug-resistant (Salmonella Typhi) isolates obtained from 200 adult patients (aged 20–40 years) at Ziauddin University Hospital, Karachi. Patients were divided into two treatment groups: Group A received meropenem (10 µg), and Group B received fosfomycin (15 µg). Antimicrobial susceptibility was assessed using the modified Kirby-Bauer disk diffusion method, and data were analyzed using the Chi-squared test. A p-value < 0.05 was considered statistically significant.Group A was designated as the group receiving Meropenem, and Group B was designated as the group receiving Fosfomycin. They used the Chi-Square Test. A p-value of less than 0.05 is regarded as significant.

1. Age-Dependent Susceptibility Patterns

A total of 100 isolates were tested per drug group. The results revealed significant age-related differences in antimicrobial susceptibility:

Meropenem (Group A)

Among patients aged 20–30 years, 72% of S. Typhi isolates were susceptible, while 28% were resistant. In the 30–40-year age group, susceptibility dropped to 60%, with resistance increasing to 40%. The observed difference between age groups was statistically significant ($p = 0.04$), indicating age-associated variation in response to meropenem.

Fosfomycin (Group B)

Susceptibility rates were lower and more variable. In the 20–30-year age group, 50% of isolates were susceptible, while in the 30–40-year age group, susceptibility declined further to 36%. The difference was statistically significant ($p = 0.03$), suggesting that fosfomycin efficacy decreases with age in this population.

Table 1: Age-Specific Antimicrobial Susceptibility Patterns

Drug Group	Age Group	Total (n)	Susceptible Frequency (%)	Resistant Frequency (%)	p-value
Meropenem (10 µg)	20–30 years	50	36 (72%)	14 (28%)	
	30–40 years	50	30 (60%)	20 (40%)	**0.04***
Fosfomycin (15 µg)	20–30 years	50	25 (50%)	25 (50%)	
	30–40 years	50	18 (36%)	32 (64%)	**0.03***

* Statistically significant at $p < 0.05$

2. Gender-Based Susceptibility Patterns

An analysis of susceptibility by gender revealed no statistically significant differences for either antimicrobial agent:

Meropenem (Group A)

Among male patients, 70% of isolates were susceptible, compared to 62% in female patients. Although a slightly higher efficacy was observed in males, the difference was not statistically significant ($p = 0.27$).

Fosfomycin (Group B)

The susceptibility rates were nearly identical between sexes—44% in males and 42% in females—with no statistically significant difference ($p = 0.84$), indicating that gender had no apparent impact on fosfomycin resistance patterns in this study.

Table 2: Gender-Specific Antimicrobial Susceptibility Patterns

Drug Group	Gender	Total (n)	Susceptible – Frequency (%)	Resistant – Frequency (%)	p-value
Meropenem (10 µg)	Male	50	35 (70%)	15 (30%)	
	Female	50	31 (62%)	19 (38%)	0.27
Fosfomycin (15 µg)	Male	50	22 (44%)	28 (56%)	
	Female	50	21 (42%)	29 (58%)	0.84

*** Statistically significant at $p < 0.05$**

DISCUSSION

The increasing prevalence of multidrug-resistant (MDR) Salmonella Typhi presents a significant challenge in clinical practice, particularly in endemic regions where empirical antibiotic use remains widespread (15). This study evaluated the comparative efficacy of two key antimicrobial agents meropenem and fosfomycin against MDR S. Typhi, while analyzing demographic trends in susceptibility across age and gender.

Meropenem, a broad-spectrum carbapenem, demonstrated superior in vitro efficacy, with significantly higher susceptibility rates in younger patients (72% in the 20–30-year group vs. 60% in the 30–40-year group; $p = 0.04$). This age-related disparity may be attributed to multiple factors, including pharmacokinetic changes, variations in immune response, or cumulative antibiotic exposure in older individuals that could select for resistant strains. The higher susceptibility observed in younger adults suggests that early, appropriate intervention with potent antimicrobials like meropenem can yield better clinical outcomes. These findings support the consideration of patient age as a variable when formulating treatment strategies for MDR enteric infections.

Gender-based analysis revealed no statistically significant difference in meropenem susceptibility between males (70%) and females (62%) ($p = 0.27$), indicating consistent efficacy across sexes. The small difference may be due to physiological factors such as renal clearance rates, body composition, or differential healthcare access. However, the lack of significance suggests that meropenem remains a reliable treatment option regardless of sex.

The results align with findings from other clinical studies that highlight the therapeutic value of meropenem in managing extensively drug-resistant (XDR) typhoid fever. For instance, Muhammad et al. (2024) reported comparable defervescence times with meropenem monotherapy or in combination with azithromycin, reinforcing its clinical utility in cases where first-line therapies fail.(16).

Shah et al. (2024) further noted that meropenem displayed higher sensitivity rates than doripenem (11.98%) and ertapenem (35.5%), underscoring its superior efficacy within the carbapenem class.(17).

Similarly, Ameen et al. (2024) observed that patients treated with meropenem alone experienced faster recovery and shorter hospital stays compared to those receiving combination therapy ($p < 0.001$)(18).

Despite its advantages, some studies caution that meropenem's limited intracellular penetration may contribute to relapse by allowing latent bacteria to persist(19).

This highlights the importance of using meropenem judiciously and in combination with drugs that can target intracellular pathogens when needed. Given its effectiveness against MDR S. Typhi, meropenem serves as a vital last-line treatment, particularly in contexts where resistance has rendered fluoroquinolones, cephalosporins, and chloramphenicol ineffective. However, its use should be guided by culture sensitivity data to mitigate the risk of emerging carbapenem resistance.

In contrast, fosfomycin demonstrated relatively poor performance, with age-dependent susceptibility patterns showing a marked decline in efficacy among older adults. In the 20–30-year age group, 50% of isolates were susceptible, whereas susceptibility fell to 36% in the 30–40-year group ($p = 0.03$). This trend may reflect increased exposure to fosfomycin, particularly through its common use in urinary tract infections, as well as the growing prevalence of plasmid-mediated resistance genes such as fosA and fosB. These findings align with reports of rising fosfomycin resistance globally (20).

The gender-based susceptibility rates for fosfomycin (44% in males vs. 42% in females; $p = 0.84$) were not significantly different, suggesting that resistance is driven more by microbial and environmental factors than by host sex. Similar findings have been reported by Rusic et al. (2024) and Amir et al. (2024), who emphasize that ecological antibiotic pressure and resistance gene dissemination are more influential than patient demographics.(21, 22).

Although fosfomycin possesses theoretical advantages—such as oral availability and a distinct mechanism of action its practical utility appears limited in the face of increasing resistance. Irfan et al. (2024) and Ullah et al. (2024) support this observation, with the latter also noting variable susceptibility depending on the local resistance profile. Overall, our findings reinforce the limited role of fosfomycin in treating MDR S. Typhi, particularly in older patients where resistance is more prevalent(23) (24).

Taken together, the results indicate that meropenem remains a more effective treatment option for MDR S. Typhi than fosfomycin, especially in younger patients. However, the growing global concern over carbapenem resistance necessitates prudent use. This underscores the importance of antimicrobial stewardship and reliance on culture-directed therapy to preserve the effectiveness of critical antibiotics.

Furthermore, the demographic analysis underscores the need for personalized treatment approaches. While gender may not significantly affect susceptibility in this setting, age-related trends suggest that treatment regimens should be tailored based on patient age and prior antibiotic exposure. Ongoing surveillance and region-specific resistance mapping are essential for optimizing therapeutic outcomes and curbing the spread of resistance.

CONCLUSIONS

Meropenem shows higher efficacy than fosfomycin against MDR Salmonella Typhi. Age significantly influences drug susceptibility, with younger patients responding better. Gender has minimal impact, emphasizing the need for age-informed antibiotic strategies. These findings support the clinical use of meropenem as a preferred treatment option in regions with high MDR Typhoid prevalence.

Conflict of Interest

All the authors declare no conflict of interest.

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