

Comparative in Vitro Analysis of Azithromycin and Fosfomycin for Typhoid Treatment in Elderly Patients: Community Medicine Insights

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ABSTRACT

Background: Due to the careless use of antibiotics, resistance is growing daily, especially in third-world nations. When treating typhoid fever, a comparison of Azithromycin with fosfomycin may be helpful.

Objective: To evaluate and compare the in vitro antibacterial efficacy, susceptibility, and resistance patterns of 15 µg azithromycin and 15 µg fosfomycin against *Salmonella Typhi*, isolates from elderly patients with uncomplicated typhoid fever.

Materials and Methods: The Antibiotic sensitivity testing was performed using the Modified Kirby Bauer disc diffusion method and Blood culture examination was done using BACTEC 9240 system. We made 2 groups Group A and Group B, Grp A treated with Azithromycin while Grp B treated with Fosfomycin.

Results: The resistance offered by Azithromycin was negligible 0 % in 50 to 60 years of age and 10% from 60 to 70 years of age respectively while the sensitivity rates were remarkable that is 55.6% in 50–60 years and 80.0% in 60–70 years.

The resistance offered by Fosfomycin was extraordinary 72 % in 50 to 60 years of age and 93% from 60 to 70 years of age respectively while the sensitivity rates were Suboptimal that is 27% in 50–60 years and 6 % in 60–70 years. The p value of less than 0.05 of these comparisons was considered as significant.

Conclusion: Azithromycin (15 µg) demonstrated superior in vitro efficacy and lower resistance than Fosfomycin in elderly patients with *Salmonella Typhi*, making it a strong treatment option for uncomplicated typhoid fever in high-resistance settings. Educating communities on typhoid prevention, symptoms, and treatment.

Keywords: *Salmonella typhi*, Antimicrobial Susceptibility, Azithromycin, Fosfomycin

INTRODUCTION

Enteric fever continues to be a prominent health concern in countries like Pakistan, where there is a lack of proper sanitation and clean drinking water, allowing for the easy spread of *Salmonella Typhi* and Paratyph¹. In Pakistan, the burden of typhoid fever is still quite high, especially in urban centers, with an estimated burden of 493 cases per 100,000 population. There is also an increasing concern of extensively drug-resistant (XDR) *S. Typhi*, which is spreading across the country after being first identified in Sindh province in 2016². The elderly population, particularly, faces a greater risk due to age-related infections, and infections they do acquire, along with pre-existing health conditions, complicate proper clinical management and recovery³. In the past few years, macrolides, cephalosporins, and even fluoroquinolones, often prescribed for infections, are losing their effectiveness and therefore, treatment options for these infections are greatly diminishing⁴. The situation is dire due as strains of XDR *S. Typhi* are increasing, particularly in the South Asian region. There is a mounting burden of the resistance crisis which highlights the necessity of changing current strategies of treatment prescribed to elderly adults⁵.

A proper and effective treatment plan for *Salmonella* must also consider the safety profile of the medicine in elderly adults.

Azithromycin is one of the more promising agents; and macrolides that inhibit protein synthesis exhibit excellent tissue penetration and have a long half-life, are well-tolerated⁶. Fosfomycin also possesses promise, as it disrupts the synthesis of bacterial cell-walls and has activity against *S. Typhi* that is multidrug resistant⁷.

In contrast, the elderly are more susceptible to the effects of aging, such as having a decreased renal and hepatic clearance⁸. Considering the elderly are more likely to use multiple medications, the pharmacokinetics of the drug is prone to alteration and increases the potential of harmful interaction.

We set out to fill this void, conducting a prospective cross-sectional descriptive study that assessed the antibacterial activity,

resistance rates, and the susceptibility patterns of *S. Typhi* isolates with azithromycin and fosfomycin in elderly patients aged 50 to 70 years. In addition, we evaluated the clinical parameters of age and gender, as well as the antimicrobial resistance with standard microbiological techniques, including blood culture with the BACTEC 9240 system and the Modified Kirby-Bauer disc diffusion technique. The aim was to determine which antibiotic was more effective with greater safety in the treatment of uncomplicated enteric fever in the vulnerable population, thus guiding future treatment protocols and techniques and strategies for preserving the effectiveness of antibiotics.

METHODS

This was a prospective cross-sectional descriptive study carried out at Ziauddin University Hospital, Karachi, in the Microbiology Department over a span of six months (January 5, 2020 – July 8, 2020). Blood samples were collected from consenting male and female in- and out-patients aged 50–70 years before any antibiotic therapy. Isolates were tested in vitro by Kirby–Bauer disc diffusion using 15 µg azithromycin (Group A) or 15 µg fosfomycin (Group B), with inhibition-zone diameters recorded. Age and gender were captured as stratification variables to assess whether susceptibility patterns differed across these subgroups, while antibiotic type remained the primary independent variable and zone size (sensitive vs. resistant) the dependent outcome (9). Blood samples for sensitivity and culture that discovered growth other than bacteria, such as yeast or fungus, were excluded, as were duplicate and repeat samples from the same patient. Authorization was given by Ziauddin Hospital's management, and written approval was obtained from the institutional ethics committee (IRB: 061118ZIMIC).

The sample size was calculated to be 54 per group using the WHO Sample Size Calculator and the Meropenem sensitivity statistics of 87% margin of error, 9%, and 95% confidence interval¹⁰.

This calculation ensures that the study will have sufficient precision to estimate the sensitivity of Meropenem within ±9% of the true population value at a 95% confidence level^{11, 12, 13}.

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Prior to the initiation of any antibiotic treatment, peripheral venous blood cultures were collected after proper aseptic practice. The sample was incubated in BACTEC 9240 blood culture instrumentation with a blood-to-broth ratio of 1:10 for five days at 35.5 °C ± 1.5 °C. The BACTEC machine is based on the detection of germ growth through fluorescence sensing technology¹⁴.

A Gram-stained smear of the broth was used to determine the extent of microbial growth that could be identified by the device's flag and sound. The bacteria were then subcultured on 5% sheep blood agar, chocolate, and Mac-Conkey agar plates and incubated at 37°C for 2days for isolation. To exclude any possibility of mishandling during plate preparation, sheep blood agar, chocolate, and Mac-Conkey agar plates were pre-incubated. Sheep blood agar as well as chocolate agar was incubated in a capnophilic chamber with 5–10% CO₂, and Mac-Conkey agar plates were stored in an aerobic incubator at 37°C. Gram staining, oxidase and catalase tests, motility, triple-sugar iron (TSI) fermentation, colony morphology, and, as a final confirmation, biochemical tests of the analytical profile index (API 20 E) were some of the routine microbiological methods employed for the identification of the *S. typhi* clinical isolates.

By using Modified Kirby Bauer disc diffusion technique on Muller-Hinton agar, according to CLSI guidelines, the antibiotic susceptibility pattern of the isolate was investigated in two treatment arms—one with azithromycin (Group A) and the other with Fosfomycin(Group B)The Muller-Hinton agar plates were maintained at 35°C ± 2°C in an aerobic atmosphere for 18 to 24 hours¹⁵. The data was entered and inspected using the Statistical Package for the Social Sciences, version 20. Data were displayed as frequency and as a percentage. They employed the Chi-squared test. The p-value of less than 0.05 was reflected as significant.

RESULTS

This study was conducted in Ziauddin University Hospital in Karachi on 200 participants of ages between 50 and 70 years for

the period of 6 months to compare the efficacy of Azithromycin and Fosfomycin against Salmonella Typhi.

Group receiving Azithromycin was named as Group A, while Group receiving Fosfomycin was named as Group B. Chi-Square Test was applied. p-value ≤0.05 is considered as Significant.

Group A (15µg of azithromycin): indicates that both age groups had a larger proportion of sensitive patients (55.6% in 50–60 years and 80.0% in 60–70 years). The resistance offered by Azithromycin was negligible 0 % in 50 to 60 years of age and 10% from 60 to 70 years of age respectively.

Group B (15µg of Fosfomycin): The resistance offered by Fosfomycin was extraordinary 72 % in 50 to 60 years of age and 93% from 60 to 70 years of age respectively while the sensitivity rates were Suboptimal that is 27% in 50–60 years and 6 % in 60–70 years. The p value of less than 0.05 of these comparisons was considered as significant. The p value 0.01 and 0.02 was significant for both age groups

According to a gender-based analysis, Group A (Azithromycin 15µg) had 60% sensitive and 0% resistant males and 50% sensitive and 0% resistant females, with no resistance seen in either gender. Group B (Fosfomycin 15µg): 20% of females were sensitive, 80% were resistant, and both sexes showed high resistance. Males were 25% sensitive and 75% resistant. There are notable variations in susceptibility between the two treatment groups for both genders, as indicated by the p-values (0.01 for males and 0.02 for females).

The comparison of antibiotic sensitivity between male and female patients in both groups showed no statistically significant difference (p > 0.05). In Group A (Azithromycin), males had slightly higher sensitivity (60%) compared to females (50%), while in Group B (Fosfomycin), sensitivity was low in both genders (25% in males vs. 20% in females).

The Chi-Square Test was applied. p-value ≤0.05 is considered as Significant. Group A (Azith-Azithromycin 15µg): Refers to the antimicrobial susceptibility test using Azithromycin with a 15µg disc. Group B (Fosfo-Fosfomycin 15µg): Refers to the antimicrobial susceptibility test using Fosfomycin with a 15µg disc.

Table 1: Age-Group-Specific Antimicrobial Susceptibility

Age Group	Susceptibility	Group A (Azith-15µg)	%	Group B (Fosfo-15µg)	%	p-value
50-60 Years	Sensitive	50	(55.6%)	15	(27.3%)	0.01
	Resistant	0	(0.0%)	40	(72.7%)	
60-70 Years	Sensitive	40	(80.0%)	3	(6.7%)	0.02
	Resistant	10	(20.0%)	42	(93.3%)	
Total		100	(100%)	100	(100%)	

Table 2: Pattern of Antimicrobial Susceptibility by Gender

Gender	Susceptibility	Group A (Azith-15 µg)	Group B (Fosfo-15 µg)	p-value
Male	Sensitive	60 (60.0%)	20 (25.0%)	0.01
	Resistant	0 (0.0%)	60 (75.0%)	
Female	Sensitive	30 (50.0%)	10 (20.0%)	0.02
	Resistant	0 (0.0%)	40 (80.0%)	
Total		100 (100%)	100 (100%)	

Table 3: Comparison of Sensitivity between Male and Female Patients

Group	Gender	Sensitive (n. %)	Resistant (n. %)	p-value
Group A (Azith-15 µg)	Male	60 (60.0%)	0 (0.0%)	0.32
	Female	30 (50.0%)	0 (0.0%)	
Group B (Fosfo-15 µg)	Male	20 (25.0%)	60 (75.0%)	0.76
	Female	10 (20.0%)	40 (80.0%)	

DISCUSSION

This study presents a methodologically sound, cross-sectional comparison of the in vitro efficacy of Azithromycin and Fosfomycin against Salmonella Typhi isolates in elderly patients. Conducted on a well-defined sample of 200 participants aged 50–70 years, the study applied the Chi-Square test for statistical analysis, ensuring an appropriate approach to categorical comparisons by age and gender. The results clearly demonstrate significantly higher sensitivity to Azithromycin across both age groups, with minimal

resistance (0–10%), whereas Fosfomycin showed markedly lower sensitivity and alarmingly high resistance rates—up to 93.3% in patients aged 60–70 years. These findings were statistically significant (p < 0.05), affirming the robustness of the observed differences. Antibiotic selection for uncomplicated enteric fever in elderly population is crucial since medication efficacy and resistance patterns might differ greatly by age and gender¹⁶.

These results support earlier reports indicating the rising

resistance to Fosfomycin in South Asia, particularly in aging populations where immune response is often compromised¹⁷.

The findings of this study demonstrate no significant difference in antibiotic sensitivity between male and female patients, with Azithromycin showing substantially higher effectiveness and no resistance in both genders compared to Fosfomycin, which exhibited low sensitivity and high resistance rates.

These results align with recent studies by Mehreen et al. and Hidayatallah^{18, 19} which also reported strong in vitro activity of Azithromycin against *Salmonella Typhi* across different demographic groups, emphasizing its continued reliability in elderly populations.

Conversely, Fosfomycin's poor performance in this study is supported by²⁰ who noted rising resistance to Fosfomycin, and Ford et al. (2023), who highlighted limited efficacy in older adults.

However, some studies offer differing views: Khalifa²¹ found Fosfomycin effective when used in combination therapy, suggesting its potential in multi-drug regimens. Overall, these mixed findings highlight the need for localized antibiotic stewardship and further research on gender-specific responses in elderly patients.

Azithromycin's consistent performance echoes findings from prior research^{18, 22}, which supports its continued use as a first-line treatment for enteric fever in elderly patients due to its favorable pharmacokinetics and safety profile. Conversely, Fosfomycin's declining effectiveness may reflect emerging resistance patterns, underscoring the need for judicious use and regional surveillance.

Despite these trends, some studies suggest that Fosfomycin could still be beneficial in combination therapies or in regions with low baseline resistance²³. Thus, while Azithromycin appears more suitable as a monotherapy in elderly patients with uncomplicated enteric fever, Fosfomycin may retain a role in tailored or multi-drug regimens²⁴.

Clinically, these findings have important implications: elderly patients are at higher risk of complications from delayed or ineffective treatment, and an effective, low-resistance option like Azithromycin could help reduce hospital stays and improve outcomes. These data emphasize the need to prioritize evidence-based antibiotic stewardship in vulnerable populations.

The study indicates that azithromycin showed better in vitro sensitivity among both male and female patients compared to fosfomycin, although the difference between genders was not statistically significant. This indicates azithromycin could be an improved drug of choice for enteric fever in older patients, irrespective of gender.

From a clinical perspective, these findings are important. Older patients typically present with non-typical symptoms and are at higher risk for certain complications like intestinal perforation. Early and effective antibiotic treatment is thus crucial. Favourable pattern of resistance, good tissue penetration and very good safety profile of Azithromycin make it a good fit for the treatment of uncomplicated enteric fever in our group present study. However, the high level of resistance of Fosfomycin within this cohort does not support the use of the agent as monotherapy and suggests the importance of continued monitoring and stewardship initiatives. Monitoring typhoid cases in elderly populations to inform public health interventions.

CONCLUSIONS

When compared to Fosfomycin (15 µg), in this study Azithromycin (15 µg) had significantly better in vitro activity and lower resistance rates against *Salmonella Typhi* in the patients from 50–70 years age groups. Sensitivity of azithromycin was remarkably high in all age and sex groups. Azithromycin is still reported to be a good treatment option for uncomplicated typhoid fever especially in

areas with multidrug resistance despite the emergence of antibiotic resistance in aged patients.

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