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Efficacy of Fosfomycin-Containing Combination Therapy for Multi-Drug Resistant Gram-Negative Infections

Çok İlaca Dirençli Gram Negatif Enfeksiyonlarda Fosfomisin İçeren Kombinasyon Tedavisinin Etkinliği

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ABSTRACT

Background: Antimicrobial resistance in Gram-negative bacteria especially infections due to multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan drug-resistant (PDR) strains has narrowed therapeutic options. In the absence of many new agents, older antibiotics are being reconsidered in combination regimens. Fosfomycin, with a unique mechanism and broad spectrum, is a leading candidate in this context.

Objective: To assess whether parenteral fosfomycin-based combinations influence mortality and morbidity in hospitalized adults with MDR/XDR/PDR Gram-negative infections.

Methods: We conducted a retrospective study of adults treated between February 2019 and June 2020 in university hospital ICUs and wards. Patients received either combination therapy including IV fosfomycin (n=141) or combination therapy without fosfomycin (n=137). Demographic, clinical, laboratory and treatment data were extracted from the hospital information system.

Results: Baseline age, sex, APACHE II and SOFA scores were similar between groups, whereas the fosfomycin group had a higher Charlson comorbidity index. No significant difference was observed in 28-day or 60-day mortality between fosfomycin and control groups (p=0.568 and p=0.094, respectively); point estimates favored the fosfomycin group (28-day mortality 41.1% vs 44.5%). Mortality correlated with higher illness severity and invasive device use in both groups. Ten patients receiving fosfomycin developed hypernatremia.

Conclusion: In patients with high illness severity, comorbidity, and invasive device needs, fosfomycin-containing combinations, when used with suitable companion agents and accompanied by careful safety monitoring, constitute a rational treatment option against MDR/XDR/PDR Gram-negative infections. pharmacokinetic (PK) and pharmacodynamic (PD) data and well-designed clinical studies are required to clarify clinical efficacy and safety.

Keywords: multidrug resistant; extensively drug resistant; pandrug resistant; fosfomycin.

ÖZET

Giriş: Gram-negatif bakterilerde, özellikle ÇİD, XDR ve PDR suşlarının etken olduğu enfeksiyonlara bağlı olarak artan antimikrobiyal direnç, mevcut tedavi seçeneklerini belirgin biçimde daraltmaktadır. Yeni antibiyotiklerin sınırlı olması, mevcut ajanların kombinasyon tedavilerinde yeniden değerlendirilmesini gündeme getirmiştir. Fosfomisin, özgün etki mekanizması ve geniş spektrumu nedeniyle bu alanda öne çıkmaktadır. Çalışmanın amacı ÇİD/XDR/PDR gram-negatif enfeksiyonların tedavisinde fosfomisin içeren kombinasyonların klinik etkisini değerlendirmektir.

Yöntem: Şubat 2019–Haziran 2020 arasında üniversite hastanesinin yoğun bakımları ve servislerinde tedavi gören erişkin hastalar retrospektif olarak incelendi. Hastalar IV fosfomisin içeren kombinasyon (n=141) ya da fosfomisin içermeyen kombinasyon (n=137) tedavileri aldı. Klinik, laboratuvar ve tedavi verileri hastane bilgi yönetim sisteminden çekildi.

Bulgular: Gruplar yaş, cinsiyet, APACHE II ve SOFA skoru açısından benzerdi; fosfomisin tedavisi alan grupta Charlson komorbidite indeksi daha yüksekti. 28 ve 60 günlük mortalite açısından gruplar arasında anlamlı fark saptanmadı (sırasıyla p=0.568 ve p=0.094); nokta tahminleri fosfomisin grubunun lehineydi (28 günlük mortalite %41,1 vs %44,5). Her iki grupta da mortalite yüksek hastalık şiddeti ve invaziv araç kullanımı ile ilişkiliydi. Fosfomisin alan 10 hastada hipernatremi izlendi.

Sonuç: Komorbiditesi,ciddi hastalık yükü ve invaziv araç gereksinimi bulunan hastalarda, uygun ajanlarla birlikte ve güvenlik izlemiyle kullanıldığında fosfomisin içeren kombinasyonlar makul bir tedavi seçeneğidir. Klinik etkinlik ve güvenliği netleştirmek için PK/PD verileri ve iyi tasarlanmış klinik çalışmalar gereklidir.

Anahtar kelimeler: çok ilaca dirençli; aşırı ilaca dirençli; tüm ilaca dirençli; fosfomisin.

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Introduction

Antimicrobial resistance is a major global health threat, contributing to excess mortality, longer hospital stays, and higher costs. The incidence of MDR, XDR and PDR strains of *Pseudomonas aeruginosa, Acinetobacter baumannii* and *Klebsiella pneumoniae* continues to rise (1). Given the constraints of newly developed antibiotics, there is increasing interest in the utilization of older antibiotics as part of combination therapies (2). Fosfomycin is a broad-spectrum antimicrobial agent that exerts its activity by blocking bacterial cell wall formation through inhibition of the enzyme UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), a key catalyst in peptidoglycan synthesis (3-5). It demonstrates favorable tissue distribution and exhibits immunomodulatory effects on lymphocytes and neutrophils. Due to its pharmacokinetic and pharmacodynamic properties, it is frequently utilized in combination regimens to reduce the expression of specific penicillin-binding proteins and mitigate nephrotoxicity caused by other antimicrobial agents (4,6). Given its chemical structure and mechanism of action, fosfomycin poses a minimal risk of cross-resistance with other antimicrobials (7). *In vitro* studies have demonstrated that fosfomycin has synergistic effects when used in combination with other antimicrobial agents to treat MDR-gram-negative bacterial infections (8-11).

The limitation of available treatment options has brought combination therapies, incorporating agents like polymyxin, fosfomycin, and tigecycline, to the forefront of therapeutic strategies (12). However, intravenous (IV) fosfomycin monotherapy is not advised for systemic infections because of the risk of resistance development during treatment (13,14,15). The use of polymyxins, fosfomycin, and tigecycline in infections caused by Acinetobacter spp. remains a matter of debate due to intrinsic resistance; however, these agents have gained attention as alternative treatment options for *Acinetobacter baumannii* infections(16,17,18). The objective of this study was to assess the influence of parenteral fosfomycin-based combination therapy on mortality and morbidity among hospitalized patients with multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) Gram-negative infections.

Materials and Methods

Study design and setting

Retrospective observational cohort of adults (≥18 years) hospitalized in intensive care units (ICUs) and wards of a university hospital between February 2019 and June 2020. A total of 357 patients were screened, but 278 with accessible clinical data were included in the study.

Treatment groups and allocation rationale

Patients were allocated to one of two cohorts: a fosfomycin group, receiving combination regimens that included intravenous (IV) fosfomycin (n=141), and a control group, receiving combination regimens without fosfomycin (n=137). Allocation reflected real-world practice and was determined by illness severity (APACHE II, SOFA, and PITT where applicable), the in-vitro susceptibility of companion agents, treating physician judgment, and drug availability; no randomization was performed. Combination therapy in the fosfomycin arm typically entailed adding fosfomycin to at least one agent with in-vitro activity against the index isolate, whereas in infections due to PDR isolates, fosfomycin was added as salvage therapy.

Inclusion and Exclusion Criteria

Adults with culture-confirmed MDR/XDR/PDR infections due to *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, or *Acinetobacter baumannii* who required combination antimicrobial therapy were eligible for inclusion. Patients were excluded if they had polymicrobial infection, received <72 hours of antimicrobial therapy, or had missing key data.

Data sources and variables

Demographic and clinical data, laboratory parameters, source of infection, device use, and details of antimicrobial regimens were retrieved from the hospital information system and medical records. Comorbidity burden was measured by Charlson index; illness severity by APACHE II and SOFA; PITT score was calculated in bacteremia.

Table 1.MDR/PDR/XDR Definitions and organism specific class list

	Enterobacteriaceae	*Acinetobacter spp*	*Pseudomonas aeruginosa*
Antimicrobial Category	Antimicrobial Agent		
Aminoglycosides	Gentamicin Tobramycin Amikacin Netilmicin	Gentamicin Tobramycin Amikacin Netilmicin	Gentamicin Tobramycin Amikacin Netilmicin
Antipseudomonal penicillins + b-lactamase inhibitors	Piperacillin-tazobactam	Piperacillin-tazobactam	Piperacillin-tazobactam
Carbapenems	Ertapenem Imipenem Meropenem Doripenem	Imipenem Meropenem Doripenem	Imipenem Meropenem Doripenem
Cephalosporins	Cefazolin Cefuroxime Cefotaxime or ceftriaxone Ceftazidime Cefepime	Cefotaxime Ceftriaxone Ceftazidime Cefepime	Ceftazidime Cefepime
Fluoroquinolones	Ciprofloxacin	Ciprofloxacin Levofloxacin	Ciprofloxacin Levofloxacin
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	Trimethoprim-sulphamethoxazole	
Glycylcyclines	Tigecyclin		
Monobactams	Aztreonam		Aztreonam
Penicillins	Ampicillin		
Penicillins + b-lactamase inhibitors	Amoxicillin-clavulanic acid Ampicillin-sulbactam	Ampicillin-sulbactam	
Phenicols	Chloramphenicol		
Phosphonic acids	Fosfomycin		Fosfomycin
Polymyxins	Colistin	Colistin Polymyxin B	Colistin Polymyxin B
Tetracyclines	Tetracycline Doxycycline Minocycline	Tetracycline Doxycycline Minocycline	

This research was conducted as a retrospective observational analysis. Data on clinical and laboratory parameters, along with details of therapeutic regimens, were retrieved from the hospital information system and patient medical records. Underlying diseases of patients were evaluated using the Charlson comorbidity index and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The PITT bacteremia score was calculated for patients with bacteremia while the Sepsis-Related Organ Failure Assessment (SOFA) scores were calculated for intensive care unit patients.

Microbiology and Antimicrobial susceptibility testing

Species identification was performed using MALDI-TOF MS (bioMérieux, France). Antimicrobial susceptibility testing (AST) was conducted per The European Committee on Antimicrobial Susceptibility Testing (EUCAST)recommendations, using Kirby–Bauer disk diffusion method. Colistin susceptibility determined by broth microdilution, as recommended. Results were interpreted according to EUCAST breakpoints (v.15.0).

In Turkey, EUCAST is the reference standard for AST interpretation. For Gram-negative pathogens, clinical breakpoints for intravenous fosfomycin are limited/not established for many organisms, which constrains susceptibility reporting and may influence prescribing. As routine fosfomycin susceptibility testing was not available at our institution, treatment decisions were guided by illness severity, the in-vitro activity of companion agents, clinician judgment, and local availability—a limitation we explicitly acknowledge.

Definitions and endpoints

MDR/XDR/PDR classifications followed Magiorakos et al., 2012 (19) and were applied using the antimicrobial categories listed in Table 1. Accordingly, an isolate non-susceptible to at least one agent in ≥3 antimicrobial categories was classified as MDR; non-susceptibility to at least one agent in all but two or fewer categories as XDR; and non-susceptibility to all agents across all categories as PDR. The specific categories and representative agents employed for *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are provided in Table 1.

Clinical response was defined as improvement in signs/symptoms together with favorable trends in inflammatory markers (white blood cell count, C-reactive protein, and procalcitonin). Clinical failure was defined as recurrent culture growth, the need to modify antibiotic therapy due to non-response, or death. Microbiological cure was defined as clearance of post-treatment cultures; persistent or repeat growth after or during therapy constituted microbiological persistence.

Baseline disease severity was assessed using the Charlson Comorbidity Index and APACHE II; the Pitt bacteremia score was calculated for patients with bloodstream infection, and SOFA scores were recorded for ICU patients. The primary endpoint was 28-day mortality among adults hospitalized with resistant Gram-negative infections receiving combination therapy (with or without fosfomycin). Secondary endpoints included 60-day mortality, clinical and microbiological response, and adverse events.

Ethical Approval

The study was approved by the Ethics Committee of Ankara Medical Faculty on 8 June 2020 with decision number 16-340-20.

Statistical Analysis

All statistical analyses were carried out using IBM SPSS Statistics version 23 (trial edition). Continuous variables with a normal distribution were expressed as mean ± standard deviation, while those without normal distribution were presented as median values with ranges (minimum–maximum). Categorical data were displayed as frequencies and percentages. Comparisons of mean values between groups were assessed using one-way analysis of variance (ANOVA), and the Kruskal–Wallis test was applied for median comparisons. Relationships between categorical variables were evaluated using Pearson's chi-square or Fisher's exact test, depending on data suitability. A p-value below 0.05 was considered statistically significant.

Results

A total of 141 patients receiving fosfomycin-containing combinations and 137 patients receiving combination therapies without fosfomycin were analyzed. The gender distribution was 44.2% female and 55.8% male, with a mean age of 64.2 years in the fosfomycin group and 62.8 years in the control group. There was no statistically significant difference between the groups in terms of gender, age, APACHE II, and SOFA scores (Table 2).

Charlson comorbidity index was 4.9 ± 2.7 in the fosfomycin group and 2.4 ± 1.6 in the control group. In terms of 28-day mortality, the increase in the Charlson comorbidity index of the patients in the fosfomycin group was statistically significant ($p<0.001$). The mean APACHE II scores between the control and fosfomycin groups were higher in patients who died within 28 days and were $p<0.002$, respectively.

A statistically significant difference was observed ($p<0.001$) in the mean SOFA scores for 28-day mortality of the control and fosfomycin groups. In the control

Table 2. Comparison of Sex, Age, APACHE II, and SOFA Between Fosfomycin and Control Groups."

	GROUPS		
	Control group n(%)	Fosfomycin-Containing Combination Regimens n(%)	P value
Number of patients	137	141	
Female/ Male	62(%50.4)/ 75 (%48.4)	61(%49.6)/ 80(%51.6)	0.738
Age	62.84±17.53 66 (20-100)	64.20±18.35 68 (20-97)	0.375
APACHE II Score	16.28±6.36 15 (2-34)	16.03±7.15 16(0-34)	0.736
SOFA Score	5.24±3.03 5 (0-14)	4.74±3.36 4 (0-13)	0.151

group, the median value of the 28-day mortality SOFA score was six whereas in survivors, the median was 4 (ranging from 0 to 11). For the fosfomycin group, the median value of the 28-day mortality SOFA score was 7 (ranging from 0 to 13), while in survivors, the median was 3 (ranging from 0 to 12). In both groups, a high SOFA score was associated with mortality (<0.001 ,<0.005). The distributions of *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* across both treatment arms are presented in Table 3.

Bacteremia was identified as the most common infectious focus, detected in eighty-eight patients (31.7%). *A. baumannii* was observed more frequently in the fosfomycin group, while *K. pneumoniae* was more prevalent in the control group. Both differences were statistically significant (p < 0.001). In the control group, 9 patients (14.8%) with *A. baumannii* experienced 28-day mortality, which was also statistically significant (p = 0.007). The mortality rate in patients with *K. pneumoniae* was 80.3 (n=49) in the control group, which was statistically significant (p = 0.015).

Among the 278 isolates, 43 (15.5%) were classified as MDR, 143 (51.4%) as XDR, and 92 (33.1%) as PDR. When stratified by treatment arm, the control group comprised 18 MDR (13.1%), 87 XDR (63.5%), and 32 PDR (23.4%) isolates, whereas the fosfomycin group included 25 MDR (17.7%), 56 XDR (39.7%), and 60 PDR (42.6%) isolates. Overall, the fosfomycin arm exhibited a higher proportion of PDR isolates and a lower proportion of XDR isolates compared with the control arm.

There was no statistically significant difference between the groups due to the 28-day and 60-day mortality rates (p = 0.568 and p = 0.094, respectively). The control group had 13 (21.3%) patients with 28-day mortality, while the fosfomycin group had 24

Table 3. Distribution of Microorganisms by Treatment Group

Microorganism	Control group n(%)	Fosfomycin-Containing Combination Regimens n(%)	Total n(%)
Acinetobacter baumanni	31 (%22,6)	56 (%39,7)	87(%31,2)
Klebsiella pneumoniea	97 (%70,8)	70 (%49,6)	167(%60,0)
Pseudomonas aeruginosa	9 (%6,6)	15 (%10,6)	24(%8,6)
	137	141	278

(41.4%). In both groups, patients who went to intensive care unit (ICU) had significantly higher 28-day and 60-day mortality rates (p<0.001). Among ICU patients, the 60-day mortality rate was 27.8% in the control group, while it was 60% (n=6) in the fosfomycin group (p<0.003).

The mean mortality time in the control group was 14 (19.79±12.41) days after diagnosis, whereas it was 15 (17.34±9.28) days in the fosfomycin group.

In the control group patients with moderate-severe chronic kidney disease, moderate-severe chronic liver disease, leukemia and metastatic solid tumors had significantly higher 28-day mortality rates (p = 0.034, p = 0.021 and p = 0.007, respectively). Patients with PVD, dementia and connective tissue disease in the fosfomycin group exhibited a higher 60-day mortality rate. In the fosfomycin group, also patients with mechanical ventilation, NG catheter, CVC, and TPN use 72 hours before infection had higher 28 day mortality rates. This difference was statistically significant (p=0.008, p<0.001,p=0.009, p<0.001, respectively).

There was no significant difference in 28-day mortality, duration of intensive care unit stay, total hospitalization, history of surgical intervention and antibiotic use in the last 3 months between the groups. However, a significant difference was observed in urinary catheter use within the past 3 months and 28-day mortality (p = 0.017). In the control group, 38 patients (62.3%) had urinary catheters in the last 3 months, compared to 40 patients (69%) in the fosfomycin group. Regarding 60-day mortality, duration of intensive care unit stay, total hospitalization, history of surgical intervention, and antibiotic use, there was no significant difference between the groups, except for a statistically significant difference in urinary catheter use within 3 months and 60-day mortality (p = 0.030).

CRP and procalcitonin values were measured at the initiation of treatment, 48-72 hours, and 14 days after treatment. The control group had a mean baseline CRP level of 132 mg/L and a mean procalcitonin level of 1.03 ng/ml, while the Fosfomycin group had a mean baseline CRP level of 115 mg/L and a procalcitonin level of 0.6 ng/ml.

In the fosfomycin-containing arm, 19.8% (28/141) received meropenem + fosfomycin; 16.3% (23/141) received colistin and fosfomycin; 16.3% (23/141) received meropenem, colistin and fosfomycin;and 11.3% (16/141) received meropenem, colistin, tigecycline and fosfomycin.
In the control arm, the most common regimen was meropenem and colistin (31.3% [43/137]), followed by meropenem, colistin and tigecycline (13.8% [19/137]), meropenem and tigecycline (8.0% [11/137]), and meropenem and ertapenem (7.2% [10/137]).

There was no significant correlation between the median CRP levels at baseline and 28- or 60-day mortality rates between the groups (p = 0.119). However, there was a statistically significant difference between the median CRP levels at 48-72 hours and the 28- and 60-day mortality rates (p = 0.002 and p = 0.264, respectively). Additionally, a statistically significant difference (p<0.001 and p:0.016, respectively) was found when comparing the median CRP levels at day 14 with 28-day and 60-day mortality in the control and fosfomycin groups.

Statistically significant differences were observed in the median procalcitonin levels at baseline, after 48-72 hours, and on day 14, with respect to 28-day mortality in the control and fosfomycin groups (p<0.001). A statistically significant difference (p > 0.05) was observed in the median values of procalcitonin measured at baseline, after 48-72 hours, and on day 14 when comparing 60-day mortality in the control and fosfomycin groups.

Patients in the control group with 28- and 60-day mortality were diagnosed with central catheter-associated bloodstream infection, showing a higher incidence than in the fosfomycin group, and this difference was statistically significant (p<0.001).

At the fifth day of treatment, clinical response rates were low in both the control and fosfomycin groups, with 10 (16.4%) and 9 (15.5%) patients, respectively, experiencing 28-day mortality (p<0.001). There was a statistically significant difference in 28-

day mortality rates between the control and fosfomycin groups for patients with microbiological response at 72 hours and those with a microbiological cure at the end of treatment (p<0.001). Cure rates were lower in patients with a fatal outcome in both groups. However, there were no statistically significant differences in relapse rates between the groups when analyzing the association with 28-day mortality (p = 0.582). Ten out of 141 patients in the fosfomycin group experienced hypernatremia, a side effect associated with fosfomycin.

Discussion

The problem of infections caused by resistant microorganisms is a global concern. There is currently no standardized approach for determining which antimicrobial classes or groups should be used to define MDR, XDR, and PDR (21,22). To ensure reliable collection and comparison of epidemiological surveillance data between healthcare institutions and countries, universal definitions are needed to identify and classify bacteria that are resistant to multiple antimicrobial agents (19,21,22). In our study, we established definitions of MDR, XDR, and PDR by reviewing the literature. In recent years, growing attention has been directed toward the synergistic potential of fosfomycin in combination with other antimicrobial agents, particularly against resistant strains for which therapeutic alternatives are scarce.

A study was conducted in Turkey involving 147 MDR and PDR carbapenemase-producing Enterobacteriaceae. The study found that 76.19% of the strains were resistant to colistin and 67.35% were resistant to fosfomycin, indicating high resistance rates for both antibiotics(22). It is unclear what the fosfomycin resistance rates were in our study, as fosfomycin susceptibility testing was not performed in our hospital. Patients were treated according to their susceptibility.

In Turkey, EUCAST serves as the reference standard for antimicrobial susceptibility testing (AST) interpretation. For Gram-negative pathogens, intravenous fosfomycin has limitedly defined clinical breakpoints, which constrains susceptibility reporting and may influence prescribing practices. As fosfomycin susceptibility testing was not routinely available at our institution, therapeutic decisions were guided by illness severity, the in-vitro activity of companion agents, clinician judgment, and drug availability—a limitation that we explicitly acknowledge.

A study conducted in seventeen intensive care units across Turkey, including a total of 831 nosocomial gram-negative bloodstream infections, found that the overall mortality rate of *K. pneumoniae* was 44%. The study found that mortality was associated with age over 70 years, central venous catheter use, the presence of ventilator-associated pneumonia, carbapenem resistance, and the APACHE II score (23). Our study found no statistically significant differences between the groups in terms of gender, age, APACHE II, and SOFA scores. The group receiving combination therapy with fosfomycin had statistically significantly higher rates of skin and soft tissue infections, but lower rates of central catheter-related blood and circulatory infections compared to the control group. Statistically significant differences were found when comparing the mean APACHE II and SOFA scores according to 28-day mortality in the control and fosfomycin groups (<0.001). Higher APACHE II and SOFA scores were associated with mortality in both groups.

Fosfomycin is utilized in combination with other antimicrobials for treating infections caused by MRSA, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant Enterobacteriaceae. Clinical efficacy rates reported in various studies range from 54.2% to 100.0%. It should be emphasized, however, that these rates were derived from case series or small cohort studies where fosfomycin was co-administered with other antibiotics (24). In this study, *K. pneumoniae* was identified as the causative organism in both groups. Specifically, it was found in 97 (70.8%) patients in the control group and in 70 (49.6%) patients treated with fosfomycin. *A. baumannii* was observed more frequently in the group receiving combination therapy with fosfomycin than in the control group, and both differences were statistically significant (p = 0.001).

In our study, we found that clinical response rates on the fifth day of treatment were low in both groups of patients who experienced 28-day mortality (16.4% and 15.5%, respectively). In addition, we observed lower microbiological cure rates in patients who experienced mortality in both groups. Regarding 28-day mortality, the groups showed no statistically significant difference in relapse rates (p = 0.582). Similarly, there was no significant difference in 28- and 60-day mortality between the fosfomycin and the control group (p = 0.568, p = 0.094, respectively). However, 28-day mortality was 41.1% in the Fosfomycin group compared to 44.4% in the control group. Mortality rates were lower in the combination regimens containing fosfomycin compared to the other group. At fifth day, the response rate was 56.0% in the fosfomycin group and 56.2% in the control group, indicating similar rates. Of the patients studied, 75 (53.2%) in the fosfomycin group achieved clinical cure compared to 60 (43.8%) in the control group. Although the difference was not statistically significant, the fosfomycin group had higher clinical cure rates.

In Canada, a study reported that IV fosfomycin was used predominantly due to resistance to initial therapies (69.5%) and most often in combination with other agents (86.4%); similarly, microbiological success was observed in 77.4% of patients and clinical success in 62.5% (25). The Charlson comorbidity index was 4.9 ± 2.7 in the group that received fosfomycin-containing therapy and 2.4 ± 1.6 in the group that received other therapies. Although there was no statistically significant difference between the groups, it was observed that combination therapies containing fosfomycin were used more frequently in the group with higher comorbidity. Combination therapy is recommended for severe infections characterized by high morbidity and mortality. Because resistance emergence has been reported with IV fosfomycin when used as monotherapy, its use is particularly recommended within combination regimens (26).

The 28-day mortality rate was significantly higher in the control group for patients with moderate to severe chronic kidney disease, leukemia, moderate to severe chronic liver disease, and metastatic solid tumors (p = 0.027, p = 0.048, p = 0.017, p = 0.032, respectively). Among patients receiving fosfomycin-containing therapies, those with PVD dementia, and connective tissue disease had a higher 60-day mortality rate.

Intravenous fosfomycin disodium carries a substantial sodium load, which is clinically relevant in ICU patients who frequently have fluid restriction, renal dysfunction, or vasopressor-dependent shock. In this setting, fosfomycin-associated hypernatremia may worsen hemodynamic instability, contribute to delirium, and increase the risk of osmotic diuresis and acute kidney injury, thereby complicating ventilator weaning and overall ICU course. In our study ten patients in the fosfomycin group developed hypernatremia. In a study including 62 patients treated with fosfomycin, 63.7% of hypernatremia events were attributed to improper drug dilution. Accordingly, education on correct dilution practices prior to administration is essential (27).

In our study, the Charlson comorbidity index was higher, ICU stay was longer, and A. baumannii infections and PDR strains were more common in the fosfomycin group. While some of the studies have shown that combining fosfomycin with other antibiotics can improve mortality, our study did not find a significant difference in mortality between the treatment and control groups. The absence of a significant difference may be attributable to the poor prognostic factors of the patients in our study, including a high Charlson comorbidity index and older age and the fact that most patients had bacteremia.

Study Limitations

This retrospective, single-center study has inherent limitations. Fosfomycin susceptibility testing was not routinely available, PK monitoring was not performed, and molecular testing for resistance determinants was not conducted; consequently, we could not determine fosfomycin susceptibility/resistance rates, assess in vitro–in vivo correlation or dose–response, or evaluate the contribution of resistance genes to outcomes. Findings should therefore be interpreted with caution, and multicenter, prospec-

tive, PK/PD-guided studies with standardized AST and molecular characterization are warranted.

Conclusions

In this real-world cohort of MDR/XDR/PDR Gram-negative infections, fosfomycin-containing combinations showed no statistically significant difference in 28- or 60-day mortality compared with non-fosfomycin combinations, despite a higher comorbidity burden and greater *A. baumannii*/PDR prevalence in the fosfomycin group. Point estimates favored fosfomycin (28-day mortality 41.1% vs 44.5%), suggesting possible clinical equivalence or modest benefit. With respect to antimicrobial resistance, the observed pathogen mix (notably the predominance of *A. baumannii*) and the elevated PDR rates mirror the substantial constraints on available therapies that characterize routine clinical settings. Mortality correlated primarily with illness severity (APACHE II/SOFA) and invasive device exposure rather than the specific combination chosen.

Fosfomycin-containing combinations may represent a valid therapeutic strategy for patients with substantial comorbidity, high illness severity, and invasive device requirements. Appropriate companion agents should be selected, and careful safety monitoring should be implemented. From a safety standpoint, hypernatremia was observed in the fosfomycin arm (n=10). This finding underscores the need to incorporate sodium load/serum sodium monitoring and fluid management into protocols when planning fosfomycin-containing combination regimens. Fosfomycin-containing combination therapy may be a viable option for MDR/XDR/PDR Gram-negative infections; however, in-vivo evidence remains limited. Robust PK/PD studies and well-designed clinical trials are needed to confirm efficacy and safety.

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