

Original Article

Retrospective evaluation of intravenous fosfomycin in multi-drug resistant infections at a tertiary care hospital in LebanonTala Ballouz¹, Rony M Zeenny², Nisrine Haddad², Nesrine Rizk¹, Souha S Kanj¹¹ *Division of Infectious Diseases, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon*² *Department of Pharmacy, American University of Beirut Medical Center, Beirut, Lebanon***Abstract**

Introduction: Fosfomycin has re-emerged as a possible therapeutic alternative for the treatment of resistant bacterial pathogens. Its main mechanism of action is the inhibition of the initial step of cell wall synthesis and is active against both Gram-positive and Gram-negative bacteria. However, its clinical effectiveness against multidrug resistant bacteria remains largely unknown. Therefore, we aim to evaluate the clinical and microbiological effectiveness of intravenous fosfomycin as well as its safety in a tertiary care teaching hospital in Lebanon.

Methodology: This is a retrospective chart review of adult patients who had presented to the hospital and were treated with intravenous fosfomycin for at least 24 hours for any type of infection between 2014 and 2019.

Results: Among 31 episodes treated with intravenous fosfomycin, 68% had an overall favorable clinical response. In 84% of the episodes, fosfomycin was administered in combination with other antibiotics, commonly tigecycline. Of those with available cultures at end of therapy, 73% achieved microbiological success. No relapse was documented within 30 days of completion of therapy. In the episodes secondary to resistant pathogens, the rates of favorable clinical outcome and microbiological success at the end of therapy were 71% and 73%, respectively. Fosfomycin resistance developed in two cases and mild adverse events occurred in 65% of the episodes during the course of treatment.

Conclusions: Fosfomycin is a safe and effective option in the treatment of multi-drug resistant infections. Nevertheless, careful stewardship is important to maintain its efficacy and to reduce the risk of selection of antimicrobial resistance.

Key words: Antimicrobials; Fosfomycin; Lebanon; Middle East; resistance; E-coli.

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Introduction

Antimicrobial resistance (AMR) is a major public health issue worldwide, threatening our ability to adequately prevent and treat infections [1–3]. With very few antimicrobials available in the pipeline, a prominent strategy in managing resistant bacteria is repurposing of older antibiotics, such as Fosfomycin [4]. Fosfomycin is a bactericidal antibiotic active against a wide range of Gram-positive and Gram-negative bacteria [5,6]. Specifically, it was found to be highly active against *Staphylococcus aureus* and *Enterococcus* spp and exhibits considerable activity against Gram-negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* including extended spectrum beta-lactamases (ESBL) - and carbapenemase producers [7]. Currently, only oral formulations of fosfomycin are approved for treating uncomplicated urinary tract infections (UTIs). However, intravenous (IV) fosfomycin has re-emerged as a potential treatment for various infections like UTIs, pneumonias, and skin

and soft tissue infections (SSTIs) with overall cure rates over 80% [6,8–10]. It is generally used as part of a combination regimen when first-line agents have failed to demonstrate efficacy [11]. Few clinical trials have assessed the effectiveness of IV fosfomycin [11]. In a recent phase 2 randomized trial, Kaye *et al.* reported non-inferiority of IV fosfomycin to piperacillin-tazobactam for treatment of complicated UTI, with a high cure rate and tolerability [12]. In an effort to further describe the role of IV fosfomycin in treating multi-drug resistant (MDR) infections, we aimed at evaluating the clinical and microbiological effectiveness of IV fosfomycin and its safety profile in a tertiary care center in Lebanon.

Methodology

This is a retrospective study conducted at the American University of Beirut Medical Center (AUBMC), a tertiary care center in Beirut, Lebanon. We included all adult patients (≥ 18 years) who were

treated with IV fosfomycin for at least 24 hours for any type of infection between January 2014 and June 2019. This study was approved by the Institutional Review Board of the American University of Beirut (IRB_BIO-2019-0203). The requirement for informed consent was waived because of the retrospective nature of the study. A standardized spreadsheet was used to collect information on patients' demographics, clinical characteristics (e.g. comorbidities, infection requiring IV fosfomycin), data related to the use of fosfomycin (e.g. empirical versus targeted use, dose, side effects) and outcomes. Fosfomycin dose and duration were determined by the treating infectious diseases physician based on the type and severity of the infection. MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories. Extensive-drug resistance (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer categories [13]. Susceptibility of Enterobacteriales to fosfomycin was interpreted using Clinical and Laboratory Standards Institute (CLSI) cut-off points [14]. Cut-off points for *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are not determined.

Primary outcome was clinical response at end of therapy (EOT). Patients were determined to have a favorable clinical response if they achieved complete clinical success with resolution of signs/symptoms of infection, or if they had clinical improvement but additional treatment was required for reasons not related to the primary infection. Otherwise, patients were determined to have clinical failure.

Table 1. Patient Demographics.

Variable (N = 28)	N (%)
Age, mean (SD)	56.43 (17.66)
Gender: Male, N (%)	20 (71)
Comorbidities	
Hypertension	9 (32)
Dyslipidemia	7 (25)
Diabetes mellitus	5 (18)
Coronary artery disease	3 (11)
Chronic kidney disease	1 (4)
Chronic obstructive pulmonary disease	1 (4)
Liver disease	1 (4)
Malignancy	13 (46)
Hematologic	9 (32)
Acute myeloid leukemia	4 (14)
Acute lymphoblastic leukemia	1 (4)
Diffuse large B cell lymphoma	2 (7)
T cell lymphoma	1 (4)
Hodgkin Lymphoma	1 (4)
Oncologic	4 (14)
Colorectal cancer	2 (7)
Squamous cell cancer of the mandible	1 (4)
Bladder cancer	1 (4)

N: number; SD: standard deviation.

Secondary outcomes included microbiological response, development of fosfomycin resistance, adverse events including *Clostridium difficile* infection, and mortality (all-cause and attributable). In those with available follow-up cultures, microbiological response was determined at 72 hours and EOT. Microbiological success was achieved in case of sterile follow-up cultures during or after the course of IV fosfomycin. In case of polymicrobial infections, response was based on the primary site of infection. Relapse was defined as recurrent infection with the same initial organism after a bacterial response to IV fosfomycin within 30 days of EOT. Reinfection was defined as recurrence of infection within 30 days of EOT due to an organism distinct from that isolated before therapy. Attributable mortality was defined as death occurring during or within 30 days of hospitalization related to the infection for which fosfomycin was administered and with no other causes identified.

Descriptive statistics were used. Continuous variables were presented by mean values and standard deviations (SD) if normally distributed and as median and interquartile ranges (IQR) if not. Categorical variables were presented by numbers and percentages.

Results

Characteristics of the population

In total, 41 patients received IV fosfomycin during the study period, of which 13 were excluded: six patients were younger than 18 years, six received fosfomycin for less than 24 hours and one patient was still admitted at the time of data collection. We included 28 patients with 31 admissions: two patients received IV fosfomycin more than once. Patients were predominantly male (71%) with a mean age of 56.43 years (± 17.66). The majority of patients (27/28) had at least one comorbidity with hypertension being the most common (32%) (Table 1).

Infection and treatment characteristics

Prior to the infection, patients had been hospitalized for a median duration of 7 days (IQR 0-18). Fosfomycin was used to treat blood-stream infection (BSI) (64%), UTI (16%), pneumonia (10%) and febrile neutropenia (10%). Administration of fosfomycin was mostly guided by culture results (77%). It was given empirically in seven cases due to history of carbapenem-resistant Enterobacteriaceae (CRE) (n = 5) and as salvage therapy (n = 2).

A total of 30 organisms were identified in 28/31 clinical episodes. All were Gram-negative bacteria and 93% of episodes were monomicrobial. Figure 1 shows

the distribution of the isolated organisms with 54% being Enterobacterales. 14/30 of the strains were MDR and 14/30 were XDR. 78% of *Acinetobacter baumannii* and 50% of *Pseudomonas aeruginosa* and *Enterobacter* sp. were XDR (Figure 2).

Fosfomycin was started within a mean of 5.11 days (± 2.63) from the date of cultures. Fosfomycin dose and duration were determined by the treating infectious diseases physician based on the type and severity of the infection. In those with normal creatinine clearance, the usual dosing regimen ranges from 12-16 grams per day, administered in 2-4 divided doses. Higher daily doses (up to 24 grams) were used in severe infections. Mean daily fosfomycin dose was 13.17 grams (± 5.60) for a median duration of 8 days (IQR 6-15). Fosfomycin was administered almost always (n=26) in combination with other antibiotics, mostly tigecycline (n=8) and amikacin (n=3), based on sensitivities. Patients with BSI and pneumonia received fosfomycin for an average duration of 11.5 and 10 days, respectively; whereas those with UTI and febrile neutropenia with no focus received it for an average of 6 and 7 days, respectively. Fosfomycin treatment was completed in 21/31 cases. Three patients died while on treatment and in the remaining cases, fosfomycin was not completed due to change in therapy, side effects, or development of resistance.

Clinical Outcome

Among 31 episodes treated with IV fosfomycin, 21 (68%) cases had an overall favorable clinical response and 14 cases (45%) reached complete clinical success at EOT. In those clinically failing, eight had persistent infections, one of which was due to the development of fosfomycin resistance in a carbapenem resistant *E. coli*. When assessed by the site of infection, 100%, 80% and 65% of pneumonia, UTIs and bacteremia, respectively, had a favorable clinical response. 67% of the cases without a documented infectious focus had clinical failure. A favorable outcome was achieved in 82% of infections caused by Enterobacterales and 75% of those

caused by *Pseudomonas aeruginosa*. In infections due to *Acinetobacter baumannii*, a favorable outcome was seen in 56% of cases. Overall in-hospital mortality was 26% and attributable mortality was 13%.

Microbiologic Outcome

Overall, there were 21 episodes with follow-up cultures at least once during or after EOT (Table 2).

At 72 hours of treatment, microbiological eradication occurred in 9/9 episodes. Subsequent

Figure 1. Frequency distribution of isolated micro-organisms (N=28).

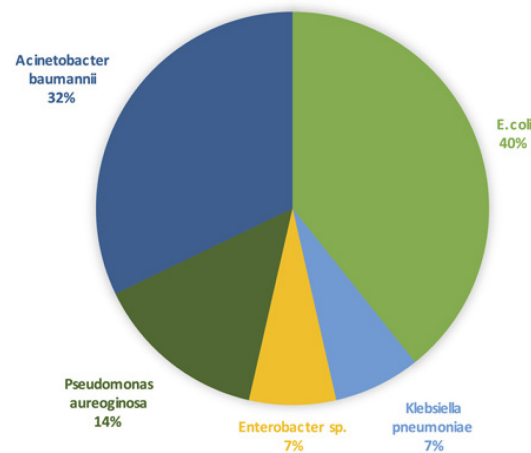


Figure 2. Frequency of multi-drug resistant (MDR) and extensively drug-resistance (XDR) among isolated bacteria.

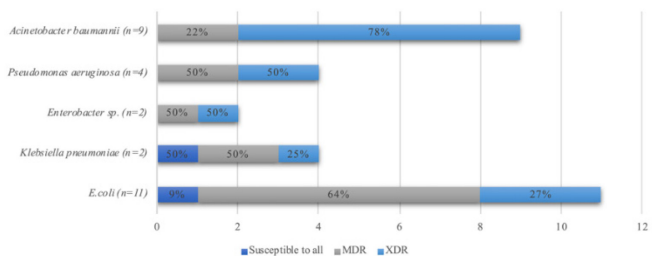


Table 2. Microbiological outcome in patients by type of infection and microbiology.

Variable, N (%)	Microbiological eradication	
	At 72 hours	At end of therapy
All patients	9/9 (100)	8/11 (73)
Blood stream infections	7/7 (100)	5/6 (83)
Urinary tract infection	1/1 (100)	3/3 (100)
Pneumonia	1/1 (100)	0/2 (0)
By organism		
Enterobacteriaceae	6/6 (100)	6/7 (86)
<i>Acinetobacter baumannii</i>	2/2 (100)	3/3 (100)
<i>Pseudomonas aeruginosa</i>	1/1 (100)	0/2 (0)

N: number.

cultures at EOT were available in 11 episodes with 73% achieving microbiological success. 2/3 episodes where fosfomycin failed microbiologically were due to *Pseudomonas aeruginosa*. Within 30 days of EOT, none of the 10 patients with available follow-up data developed a relapse. However, 5/10 presented with a re-infection with Gram-negative bacteria.

In episodes secondary to MDR or XDR pathogens, rates of favorable clinical outcome and microbiological success at EOT were 71% and 73%, respectively.

Adverse events and fosfomycin resistance

Fosfomycin resistance developed in two patients, both of which received fosfomycin in combination with other antibiotics (amikacin and tigecycline). 26 mild adverse events occurred during treatment. The most frequent adverse event was hypokalemia (n=14) and hypernatremia (n=6), which were not present before the initiation of fosfomycin. Five patients developed diarrhea, four of which tested negative for *C.difficile*. One patient developed *C.difficile* infection within a month of fosfomycin treatment. All five patients were on at least one antibiotic other than fosfomycin. None developed pulmonary edema or hypertensive crises.

Discussion

In this study, we report favorable clinical and microbiological outcomes in patients treated with IV fosfomycin. Similar to the literature, our results show that fosfomycin can be a potentially reliable treatment option for infections caused by MDR Gram-negative bacteria [6,8–12,15–17].

Fosfomycin has been classically used in UTIs. However, use of IV fosfomycin beyond the urinary tract has gained more interest due to its unique mechanisms of action and favorable safety profile. Successful treatment of SSTI, BSI and pneumonias with IV fosfomycin has been documented [10,11,15–17]. In our study, IV fosfomycin was administered in a broad range of infections caused by Gram-negative bacteria with a favorable overall clinical response of 68%. We report high clinical success rates for pneumonias, BSI and UTI similar to those reported by Dinh *et al.* [17] but lower than those reported by Putensen *et al.* (81% overall and 85% in MDR infections) [16]. On the other hand, only 33% of those receiving fosfomycin for febrile neutropenia had a favorable clinical response. However, these patients received fosfomycin as a last resort empiric therapy, did not have a documented infectious focus and were markedly ill.

In those with a documented infection, Enterobacterales, namely *E. coli*, were the most

common pathogens. 83% of the episodes caused by Enterobacterales had a favorable clinical response, compared to 75% for those caused by *P. aeruginosa* and 56% by *A. baumannii*. These results are in line with other studies. In fact, fosfomycin has demonstrated good *in-vitro* and clinical activity against *E. coli* and *K. pneumoniae* including ESBL and carbapenemase producers but is less active against MDR *P.aeruginosa* and *A.baumannii* [7,17–21].

Multiple guidelines and consensus on managing MDR infections have suggested fosfomycin as a relevant treatment option in combination with other antibiotics. Davido *et al.* reported that fosfomycin was the most prescribed last resort antibiotic in combination regimens [22]. This has been supported by *in-vitro* experiments where synergism was detected between fosfomycin and other antimicrobials such as meropenem in KPC-producing *K. pneumoniae* [18,23]. In our study, fosfomycin was used almost exclusively in combination, namely with tigecycline, which may have led to the favorable results. Furthermore, higher frequency of emerging resistance to fosfomycin has been documented when used as a single agent [11,24,25]. In contrast to most literature but similar to results by Karageorgoulos *et al.* [24], both cases in our study subsequently developing resistance had received fosfomycin as part of a combination therapy. Perhaps underdosing and persistent neutropenia explain the findings. In any case, clinicians need to be aware of the possibility of resistance development during the course of fosfomycin treatment.

All-cause and attributable mortality rates of our study population were around 25% and 13%, respectively. All those who died had a complicated stay and 88% of them had a hematological malignancy. Such a mortality rate may be expected in a severely ill and comorbid population and is within the range reported in the literature [26].

In regards to adverse effects, fosfomycin has been reported to be safe and well tolerated with electrolyte disturbances and gastrointestinal side effects being the most common [11,27]. At least one adverse event was recorded in 65% in our study. However, most patients were receiving other medications concomitantly and thus we cannot be certain that the adverse events were directly related to fosfomycin. Nevertheless, all were mild with hypokalemia and hypernatremia being the most frequent. This high frequency of electrolyte disturbances warrants careful monitoring of the fluid and electrolyte balance in patients receiving IV fosfomycin.

To our knowledge, this is the first study in the Middle East to assess the use of IV fosfomycin for resistant Gram-negative infections. However, our study has some limitations. It was a retrospective monocentric study; therefore, findings may not be applicable to other centers. The small sample size of our cohort did not allow any further analyses to identify differences between groups. Additionally, due to the retrospective nature of the study, important variables, such as timing of follow-up cultures, were not standardized. Larger comparative cohorts are warranted to analyze prescription patterns and outcomes.

Conclusions

Our results suggest that fosfomycin is a safe and effective option for the treatment of MDR organisms. This value appears to be the strongest for *E. coli* infections of various sites. However, stewardship with prudent use of antibiotics and monitoring of susceptibility patterns is important to reduce the risk of selection of AMR, if we are to keep this agent in our treatment armamentarium.

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