

## Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients: a prospective evaluation

A. Michalopoulos<sup>1,2</sup>, S. Virtzili<sup>1</sup>, P. Rafailidis<sup>2,3</sup>,  
G. Chalevelakis<sup>2</sup>, M. Damala<sup>4</sup> and M. E. Falagas<sup>2,3,5</sup>

1) Intensive Care Unit, 'Henry Dunant' Hospital, Athens, Greece, 2) Department of Medicine, Tufts University School of Medicine, Boston, MA, USA, 3) Department of Medicine, 'Henry Dunant' Hospital, Athens, MA, USA, 4) Department of Microbiology, 'Henry Dunant' Hospital, Athens, Greece and 5) Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece

### Abstract

Intensive care unit (ICU)-acquired infections as a result of multi-drug-resistant Gram-negative pathogens remain a serious problem in critically ill patients. Adult ICU patients who received intravenous fosfomycin were prospectively examined to assess its safety and effectiveness as an adjunct to the antimicrobial therapy of life-threatening infections caused by carbapenem-resistant *Klebsiella pneumoniae*. Fosfomycin was administered intravenously in 11 patients for treatment of hospital-acquired infections caused by carbapenem-resistant *K. pneumoniae*. Fosfomycin (2–4 g every 6 h) was administered in combination with other antibiotics. The mean  $\pm$  SD duration of treatment was  $14 \pm 5.6$  days. All patients had good bacteriological and clinical outcome of infection. All-cause hospital mortality was two out of 11 (18.2%) patients. No patient experienced adverse events related to the administration of fosfomycin. Intravenous fosfomycin may be a beneficial and safe adjunctive treatment in the management of life-threatening ICU-acquired infections caused by carbapenem-resistant *K. pneumoniae*.

**Keywords:** Carbapenem-resistant *Klebsiella pneumoniae*, colistin, fosfomycin, ICU-acquired infection, mortality, ventilator-associated pneumonia

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**Corresponding author and reprint requests:** A. Michalopoulos, Edison 9, Edison Hill, Pallini, 15351. Athens, Greece  
**E-mail:** amichalopoulos@hol.gr

The incidence of infections caused by multidrug-resistant (MDR) Gram-negative bacteria has increased worldwide during the last decade [1–3]. There are reports dealing with intensive care unit (ICU)-acquired infections caused by MDR *Klebsiella pneumoniae* [4,5]. The shortage of new antimicrobial agents has led clinicians to reconsider the potential value of old antibiotic compounds (e.g. polymyxins, fosfomycin, tetracyclines, etc.) in the treatment of MDR Gram-negative bacterial infections.

The present study aimed to examine the effectiveness and safety of fosfomycin administered in critically ill patients suffering from ICU-acquired infections caused by carbapenem-resistant *K. pneumoniae* (CRKP).

We prospectively enrolled all patients who received intravenous fosfomycin (IF) for treatment of ICU-acquired infections caused by CRKP from 1 May 2008 to 15 December 2008 in the ICU at 'Henry Dunant' Hospital, in Athens. The study was approved by the Institutional Review Board of the hospital.

The daily dosage of IF was 4 g administered via a central venous catheter four times daily in patients with normal renal function. In elderly patients (>70 years) and in patients with renal failure, the daily dosage was 2 g administered four times daily. All patients received Infectofos® fl 2 g containing 2.64 g fosfomycin-sodium (Infectopharm Arzneimittel und Consilium GmGH, Heppenheim, Germany).

Data for several variables, including demographics, reason for ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score upon ICU admission and comorbidities, were recorded in patients receiving IF. Renal and liver function tests were recorded just prior to the initiation of IF and every day during the entire treatment period. The dosage of IF, the duration of treatment and any adverse event related to IF, as well as data regarding bacteriological and clinical response of infections, ICU length of stay and patient outcome, were also recorded.

Standard criteria for definitions of comorbidities, nosocomial infections, multidrug resistance and outcome parameters were employed in accordance with previous studies [6,7]. CRKP strains were tested using the disc diffusion test for susceptibility to fosfomycin. The results were interpreted as showing susceptibility of isolated *K. pneumoniae* to fosfomycin when the zone of inhibition was  $\geq 16$  mm.

The primary endpoint of the study was all-cause in-hospital mortality. Secondary endpoints included clinical and bacteriological outcome of infections and the occurrence of

any adverse event during IF. Assessment of effectiveness and safety was made at the end of fosfomycin treatment.

Eleven patients receiving IF for treatment of ICU-acquired infections caused by a CRKP susceptible to fosfomycin were studied. During this period, 658 patients (29.8% females) with a mean  $\pm$  SD age of  $66.6 \pm 13.7$  years were admitted to the ICU, with a mean stay of 3.8 days and an ICU mortality rate of 6.9%.

Table I shows the demographic and clinical characteristics of patients. The mean APACHE II score was  $23.4 \pm 4.9$ . The mean  $\pm$  SD ICU stay and mean hospital stay were  $40.5 \pm 31.7$  days and  $111.5 \pm 97.5$  days, respectively.

All patients developed multiple ICU-acquired infections as a result of Gram-negative pathogens from different sites preceding the episode caused by the CRK and received antibiotics for a prolonged period prior to the inclusion of IF.

These episodes were bacteraemia ( $n = 2$ ), ventilator-associated pneumonia (VAP) and bacteraemia ( $n = 3$ ), VAP and urinary tract infection (UTI) ( $n = 2$ ), UTI ( $n = 2$ ), bacteraemia and wound infection ( $n = 1$ ) and wound infection ( $n = 1$ ). The median time for development of infection as a result of CRKP was 27 (range 21–208) days after the patient's admission to the hospital.

Fosfomycin was administered in combination with colistin ( $n = 6$ ), gentamicin ( $n = 3$ ) and piperacillin/tazobactam ( $n = 1$ ), based on sensitivities. The mean  $\pm$  SD duration of IF administration was  $14.0 \pm 5.6$  days. There was a good bacteriological and clinical outcome of infection for all patients. All-cause hospital mortality was 18.2%. No patient developed relapse of infection because of this pathogen. All patients tolerated IF well, without renal or liver function test abnormalities. Serum urea and creatinine levels on the day just prior

**TABLE I.** Demographic and clinical characteristics for the patients studied ( $n = 11$ )

General features	Entire group
Female gender, $n$ (%)	6 (54.5)
Mean $\pm$ SD age, years	$67.5 \pm 14.5$
Previous surgery, $n$ (%)	5 (45.4)
Underlying disease	
Diabetes mellitus	3 (27.2)
Chronic obstructive pulmonary disease	3 (27.2)
Transfer from another institution, $n$ (%)	3 (27.2)
APACHE II score on ICU admission (mean $\pm$ SD)	$23.4 \pm 4.9$
Previous antibiotic courses during the same hospitalization period, median (range)	3 (2–7)
Number of organ dysfunctions, median (range)	3 (2–5)
Length of hospital stay before isolation of multiresistant <i>Klebsiella pneumoniae</i> (sensitive to fosfomycin)-associated infection, median (range) (days)	27 (7–208)
Mechanical ventilation for >48 h, $n$ (%)	11 (100)
Total length of ICU stay, median (range) (days)	31 (4–107)
Total length of hospital stay, median (range) (days)	86 (20–330)

APACHE, Acute Physiology and Chronic Health Evaluation score; ICU, intensive care unit.

to fosfomycin administration were  $91.2 \pm 54.2$  and  $1.4 \pm 0.5$  mg/dL, respectively. At the end of IF administration, these corresponding values were  $57.7 \pm 24.1$  and  $1.3 \pm 0.6$  mg/dL, respectively. No patient experienced any other adverse event related to the administration of fosfomycin. In particular, none of the patients presented signs of a hypersensitivity reaction, skin rash or venous thrombosis. No patient developed a superinfection, including *Clostridium difficile*-associated diarrhoea and pseudomembranous colitis. The main findings of this study were that all patients receiving IF had good bacteriological and clinical responses. Furthermore, no patient experienced adverse-events related to IF.

It is noteworthy that recent studies report isolates of *K. pneumoniae* emerging in ICU patients that are colistin-resistant or pan-drug-resistant pathogens [4,6,8,9]. Previous studies report susceptibility of extended-spectrum- $\beta$ -lactamases (ESBL)-producing *K. pneumoniae* to fosfomycin [10]. Falagas *et al.* [11] reported that the *K. pneumoniae* strains producing both ESBLs and metallo- $\beta$ -lactamases exhibited the greatest susceptibility to fosfomycin, with a unimodal distribution of MICs, across the range 8–64 mg/L, with an MIC<sub>50</sub> of 16 mg/L and an MIC<sub>90</sub> of 32 mg/L. *Klebsiella* strains have shown a high spontaneous mutation rate for *glpT* or *uhpT* genes and this trait could affect monotherapy with fosfomycin [12].

It is considered that treatment with fosfomycin is free from the nephrotoxicity that characterizes treatment with aminoglycosides. Animal studies have demonstrated that fosfomycin has a protective effect against nephrotoxicity as a result of treatment with aminoglycosides by inhibiting aminoglycoside-induced histamine release from mast-cell destruction [13].

The present study has several limitations. The main shortcoming of the study is the small number of patients who were treated with IF, thus not permitting any definitive conclusions and not allowing examination of the comparative effectiveness and toxicity of fosfomycin when combined with other antibiotics. Furthermore, there are limitations in the validity of MIC values of fosfomycin according to the methodology used.

In addition, the disc diffusion method used has an error rate of approximately 15% compared to reference methods [14]. However, this is the first study in which the effectiveness and safety of high doses of IF were examined.

In conclusion, fosfomycin may be considered as another choice for the treatment of infections caused by CRKP in adult patients, especially in combination with other antibiotics, because of its unique mechanism of action, and its favourable safety profile.

## Transparency Declaration

The authors declare that there was no source of funding and that they have no conflicts of interest.

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## Dissemination and genetic context analysis of *bla*<sub>VIM-6</sub> among *Pseudomonas aeruginosa* isolates in Asian-Pacific Nations

M. Castanheira<sup>1</sup>, J. M. Bell<sup>2</sup>, J. D. Turnidge<sup>2</sup>, R. E. Mendes<sup>1</sup> and R. N. Jones<sup>1</sup>

1) JMI Laboratories, North Liberty, IA, USA and 2) Women's and Children's Hospital, Adelaide, SA, Australia

## Abstract

VIM-6, previously reported in two strains from Singapore recovered in 2000, was detected in 16 isolates collected in 2006 in India (12 isolates), Indonesia (two), Korea and the Philippines (one each). High genetic variability was observed among VIM-6-producing isolates (12 ribotypes and 11 pulsed-field gel electrophoresis types), but clones were observed in India and Indonesia; *bla*<sub>VIM-6</sub>-carrying integrons of 3.9 kb and 5 kb were detected, and two of five Indian hospitals yielded isolates with both integrons. These two integrons, *bla*<sub>VIM-6</sub> was located in the first position, followed by *bla*<sub>OXA-10</sub> and *aacA4*. The 5-kb integrons also harboured *aadA1* and a 331-bp open reading frame encoding a putative efflux pump.

**Keywords:** Asia-Pacific, metallo- $\beta$ -lactamases, *Pseudomonas aeruginosa*, SENTRY, VIM

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**Corresponding author and reprint requests:** M. Castanheira, JMI Laboratories, 345 Beaver Creek Center, Suite A, North Liberty Iowa 52317, IA, USA  
**E-mail:** mariana-castanheira@jmilabs.com

Acquired metallo- $\beta$ -lactamase (MBL)-producing isolates have been increasingly reported in the Asia-Pacific (APAC) region.