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**ORIGINAL PAPER**

# Current clinical use of intravenous fosfomycin in ICU patients in two European countries

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## Abstract

**Purpose** In Europe, intravenous fosfomycin (IV) is used particularly in difficult-to-treat or complex infections, caused by both Gram-positive and Gram-negative pathogens including multidrug-resistant strains. Here, we investigated the efficacy and safety of intravenous fosfomycin under real-life conditions.

**Methods** Prospective, multi-center, and non-interventional study in patients with bacterial infections from 20 intensive care units (ICU) in Germany and Austria (NCT01173575).

**Results** Overall, 209 patients were included (77 females, 132 males, mean age: $59 \pm 16$ years), 194 of which were treated in intensive care (APACHE II score at the beginning of fosfomycin therapy: $23 \pm 8$). Main indications ($\pm$ bacteremia or sepsis) were infections of the CNS (21.5%), community- (CAP) and hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP, 15.3%), bone and joint infections (BJI, 11%), abdominal infections (11%), and bacteremia (10.5%). Most frequently identified pathogens were *S. aureus* (22.3%), *S. epidermidis* (14.2%), *Enterococcus* spp. (10.8%), *E. coli* (12.3%) and *Klebsiella* spp. (7.7%). At least one multidrug-resistant (MDR) pathogen was isolated from 51 patients (24.4%). Fosfomycin was administered with an average daily dose of $13.7 \pm 3.5$ g over $12.4 \pm 8.6$ days, almost exclusively (99%) in combination with other antibiotics. The overall clinical success was favorable in 81.3% (148/182) of cases, and in 84.8% (39/46) of patients with $\geq 1$ MDR pathogen. Noteworthy, 16.3% (34/209) of patients developed at least one, in the majority of cases non-serious, adverse drug reaction during fosfomycin therapy.

**Conclusion** Our data suggest that IV fosfomycin is an effective and safe combination partner for the treatment of a broad spectrum of severe bacterial infections in critically ill patients.

**Keywords** Intravenous fosfomycin · Non-interventional study · Intensive care · Gram-positive · Gram-negative · Multidrug resistance

## Introduction

Fosfomycin is a bactericidal broad-spectrum antibiotic active against a variety of Gram-positive (GP) and Gram-negative (GN) pathogens including 'problem bacteria' such as carbapenemase- or extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant enterococci and multidrug-resistant (MDR) *Pseudomonas aeruginosa* [1–5], supported by synergistic effects with

many other antibiotics [6, 8]. Due to the unique chemical structure, cross-resistance and -allergies with other antibiotics have not been reported so far [7]. Fosfomycin exhibits advantageous pharmacokinetic properties making it particularly useful for complicated deep-seated, even biofilm-associated infections such as respiratory tract, bone or central nervous system (CNS) infections [7, 9–14]. Fosfomycin can be used without any age limitations. However, due to the high sodium load (1 g fosfomycin contains 14 mmol (320 mg) sodium), electrolyte imbalances such as hypernatremia or hypokalemia might occur [6, 15].

Fosfomycin was included in the WHO list of essential medicines for treatment of adults and children within the RESERVE group of antibacterial medicines [16, 17].

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Prospective, randomized, controlled clinical trials with fosfomycin in mono- and combination therapy, though having been initiated recently, are still ongoing. Currently, data on the efficacy and safety of intravenous (IV) fosfomycin in the daily clinical practice are still limited. In addition, fosfomycin is used for indications for which no randomized controlled trials would likely to be feasible due to constraints regarding time and study design.

Here, we present real-life efficacy and safety data on the current clinical use of IV fosfomycin in two countries with longstanding experience from the largest prospective non-interventional study conducted to date.

## Patients and methods

### Description of the study

The present trial is a prospective, open-label, multi-center, and non-interventional study (NIS-FOM; NCT01173575). According to international recommendations, fosfomycin was administered or prescribed based on license approval [18]. The unbiased assignment of a patient to a specific therapeutic strategy was made in best knowledge by investigators in advance, and always met current clinical practice and standards.

Of 25 centers which agreed to participate, 20 recruited patients between June 2010 and June 2016. Database lock was in November 2016 after finalization of documentation of the last patient including queries in October 2016.

The NIS-FOM study including ICF was approved by the ethics committees of participating study centers. Before approval by each study center, the study was approved on 20th August 2010 (Bonn, referral no. 140/10) by the ethics committee at the "coordinating" investigator's study center who signed the study protocol (Medical Department of the University of Bonn). Before inclusion into the study written informed consent was obtained from every single patient or patient's parent(s)/legal guardian(s).

It was the responsibility of the study sites and/or health insurances to bear or reimburse all costs of antimicrobial therapy including IV fosfomycin within the scope of the study, as this reflected antibiotic standard of care within the study center. There was no funding by the manufacturer with regards to study medication. Despite this, every study center received an appropriate and defined expense allowance for each patient documentation including queries.

### Patient enrollment and populations

All consecutive patients of the participating study centers who received treatment with IV fosfomycin were enrolled, provided that informed consent was obtained. Treatment with fosfomycin and the course of infection were followed in terms of clinical and microbiological treatment success and safety until discharge or death, if possible. Any indication for fosfomycin treatment was sufficient for inclusion of patients. Patient enrollment was delayed due to an IV fosfomycin shortage from 2011 to 2013.

All documented patients who received at least one dose of intravenous fosfomycin comprise the *intention-to-treat* (ITT) population or 'safety population'. All documented patients who received at least one dose of IV fosfomycin and had an evaluable clinical efficacy endpoint form the clinical *per protocol* (cPP) population or 'clinical effectiveness population'. All documented patients who received at least one dose of IV fosfomycin and had an evaluable microbiological efficacy endpoint form the microbiological *per protocol* (mPP) population or 'microbiological effectiveness population'.

### Recorded data

An internet-based electronic case report form (eCRF) was used to gather data on the clinical and microbiological efficacy of fosfomycin after intravenous therapy. All data were (pseudo)-anonymized by the investigators at each study center and verified by double-entry procedure.

Recorded data included demographic characteristics, admission and definite diagnosis, height, weight, body mass index (BMI), medical history and treatment indication, intensive care, fosfomycin dose, duration and dosing schedule, pathogens isolated, susceptibility pattern and MDR status, diagnostic methods with respect to infection, relevant concomitant diseases and risk factors, laboratory parameters, APACHE score at baseline and after fosfomycin treatment, body temperature, antimicrobial pretreatment, concomitant antimicrobial agents and duration of hospital stay.

### Microbiology and culture procedures

All microbiological, culture and susceptibility testing procedures were performed according to the local standard operating procedures of the respective centers.

### Definitions and outcomes

Overall clinical success was defined either as clinical cure or clinical improvement. Microbiological success was defined as eradication of the underlying pathogen.

Clinical cure was defined as resolution of signs and symptoms of infection and/or no additional antibiotic therapy necessary. Clinical improvement was defined as improvement of signs and symptoms of infection and/or improvement of signs and symptoms of infection and administration of additional antibiotic therapy.

**Table 1** Description of the demographic and baseline characteristics

| Characteristic | $n$ | % |
|---|---|---|
| Age (years) | $59.1 \pm 16.4$ | |
| Gender (m/w) | 132/77 | 63.2/36.8 |
| BMI (kg/m$^2$) | $28.3 \pm 6.9$* | |
| Intensive care patients | 194 | 92.8 |
| Patients with risk factors for bacterial infections | 136 | 65.1 |
| APACHE II (III) score at begin of fosfomycin therapy | $23 \pm 8$[#]/$104 \pm 18$** | |
| Patients with antibiotic pretreatment | 153 | 73.2 |
| Patients with identified pathogen before start of fosfomycin therapy | 150 | 71.8 |

Data are mean ± standard deviation; * 192 patients; [#] APACHE II (in 71 patients); ** APACHE III (in 19 patients)

Criteria for evaluation included efficacy and safety measurements. The primary efficacy endpoint was clinical success. Secondary efficacy endpoints included the number of patients with cure of infection, improvement of infection, unaltered infection, clinical treatment failure, pathogen eradicated, and microbiological treatment failure.

Clinical efficacy outcome variables were clinical/microbiological efficacy on day $7 \pm 1$, day $14 \pm 1$ and at discharge. The primary efficacy outcome variable was the efficacy at the first assessment day after end of fosfomycin treatment. For cases with missing data, the last observation was carried forward.

For safety analysis the number of patients with adverse events (AEs), adverse drug reactions (ADRs), serious adverse events (SAEs), number of deaths, and tolerability were recorded.

The term 'difficult-to-treat' infection was used according to common definitions in the literature for deep-seated infections associated with a poor penetration of antibiotics (e.g., CNS infections, bone and joint infections or foreign body associated infections with or without abscess involvement), infections where previous antibiotic (standard) treatment has already failed or infections in patients with high risk of complications (co-morbidities, co-medication, and drug allergies) [19, 20].

## Statistical analysis

The statistical analysis was performed using the statistical software SPSS v. 23.0 (IBM). Continuous variables were expressed by mean ± standard deviation or median and interquartile range (IQR) as appropriate.

## Results

Overall, 209 patients were included (ITT population), for which an evaluable clinical endpoint was attained in 182 cases (cPP population) and an evaluable microbiological endpoint in 90 cases (mPP population). In detail, 172 of the patients were enrolled in 19 German study centers and 37 in one Austrian study center.

### Demographic and baseline characteristic

Patients enrolled were predominantly critically ill, with an APACHE II (III) score at the beginning of fosfomycin treatment of $23 \pm 8$ (data from 71 patients). Virtually all patients were treated in intensive care (92.8%), while 65.1% ($n = 136$) had pre-existing risk factors for bacterial infections such as diabetes mellitus, smoking, immunosuppression/corticosteroids, chronic renal insufficiency, liver cirrhosis and intensive antibiotic pretreatment within the last month. Most patients (71.8%) had received a targeted therapy and 73.2% ($n = 153$) a prior therapy with other antibiotics. The patients' demographic and clinical characteristics are presented in Table 1.

### Description of the infection and microbiological data

Main indications for fosfomycin administration were infections of the CNS ($n = 45$, 21.5%), pneumonia including CAP, HAP and VAP ($n = 32$, 15.3%), BJI ($n = 23$, 11%), abdominal infection (SAI, $n = 23$, 11%), endocarditis (all with sepsis or bacteremia, $n = 9$, 4.3%), complicated urinary tract infection (cUTI, $n = 8$, 3.8%) and sepsis or bacteremia ($n = 22$, 10.5%), half of them just with signs of infection or bacteremia but unknown focus. Multiple infections with more than one focus or infections that could not be assigned to one of the other categories were found in 33 (15.8%) patients (see Fig. 1). Overall, 57 (27.3%) patients developed a clinically and microbiologically confirmed sepsis or bacteremia during
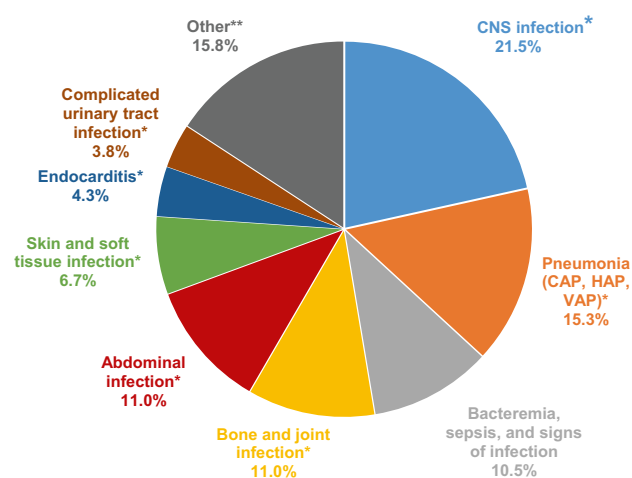
**Fig. 1** Types of infection ($n = 209$); *$\pm$bacteremia or sepsis; **multiple infections or infections that could not be assigned to one of the other categories

**Table 2** Microbiological spectrum (data from mono- and polybacterial infections)

| Pathogen | $n$ (%) |
|---|---|
| *Staphylococcus aureus* | 58 (22.3) |
| *Staphylococcus epidermidis*/coagulase-negative staphylococci | 37 (14.2) |
| *Escherichia coli* | 32 (12.3) |
| *Enterococcus* spp. | 28 (10.8) |
| *Klebsiella* spp. | 20 (7.7) |
| *Enterobacter/Citrobacter* spp. | 17 (6.5) |
| *Pseudomonas aeruginosa* | 12 (4.6) |
| *Streptococcus* spp. | 9 (3.5) |
| *Proteus* spp. | 6 (2.3) |
| *Serratia* spp. | 4 (1.5) |
| Other Gram-negative pathogens | 19 (7.3) |
| Other Gram-positive pathogens | 9 (3.6) |
| Anaerobes | 9 (3.5) |

the course of infection. One or at least two organ systems ($\pm$ bacteremia) were affected in 161 (77%) and 37 (17.7%) patients, respectively.

Many infections were polybacterial ($n = 77$, 36.8%), whereas 60 patients (28.7%) had infections by only one pathogen. In 72 (34.4%) patients, no bacteria or other definite causality for infection could be identified. The majority of pathogens was GP (141 isolates, 54.2%). GN pathogens were found in 110 isolates (42.3%) and other anaerobes in 9 isolates (3.5%). Fungi were found in 31 patients (14.8%). The full microbiological spectrum of the 260 isolates is shown in Table 2.

In total, 51 patients (24.4%) presented infections due to at least one MDR pathogen. ESBL-producing bacteria were found in four isolates. The resistance pattern of *S. aureus* was not consistently reported for all isolates. In detail, only 28 monobacterial *S. aureus* infections were assessable, 75% (21/28) caused by methicillin-sensitive strains (MSSA), while MRSA was isolated in 25% (7/28) of cases.

## Mode and duration of therapy

The average daily fosfomycin dose was $13.7 \pm 3.5$ g, generally split into 2–4 single doses. Total daily fosfomycin doses ranged between 3 and 24 g, as indicated. The majority of patients ($n = 166$) received 15 g per day or less (standard dose group), and 41 patients received more than 15 g per day (high-dose group). The average fosfomycin dose for patients with infections due to GP pathogens was $13.2 \pm 7.0$ g/d and $13.6 \pm 6.9$ g/day for infections due to GN pathogens. For two patients, the fosfomycin dose was not reported. The mean treatment duration was $12.4 \pm 8.6$ days, strongly depending on the indication: average treatment duration was 20 days in BJI and sepsis, and 6 days in cUTI.

Fifty-six patients (26.8%) received fosfomycin as first-line therapy, particularly for infections of a single organ system (49/161, 30.4%). For infections of two or more organ systems, fosfomycin was used less frequently as the first-line treatment (6/32, 6.2%). As a first-line therapy, fosfomycin was employed most frequently in patients with CNS infections (25/45, 55.5%), followed by cUTI (4/8, 50%), endocarditis (2/9, 22.2%), abdominal infections (5/23, 21.7%), bacterial pneumonia (6/32, 18%), BJI (4/23, 17.4%), and sepsis or bacteremia with unknown entry (1/11, 9.1%). In patients with skin and soft tissue infections (SSTI), fosfomycin was used at least as second-line option.

Fosfomycin was nearly exclusively used in combination therapy (207 patients, 99%) and predominantly combined with a beta-lactam, glycopeptide, metronidazole and/or a quinolone (Table 3). Most patients were treated with one (80 patients), two (72 patients) or three (30 patients) combination partners. More than three concomitant antibiotics were administered in 25 patients.

Combination regimens of the three most frequently reported indications are shown in Table 4.

A carbapenem was the preferred combination partner for fosfomycin, except in patients with CNS infections. Here, fosfomycin was predominantly combined with a third- or fourth-generation cephalosporin.

## Clinical/microbiological efficacy and emergence of resistance

Overall clinical success was 81.3% (Table 5) and microbiological success was 70% (Table 6). No emergence of

**Table 3** Fosfomycin combination partners with number of patients per class (*n* = 209)

| Combination partner | Number of patients | % |
|---|---|---|
| Carbapenem | 102 | 48.8 |
| Glycopeptide | 66 | 31.6 |
| 3rd- or 4th-generation cephalosporin | 58 | 27.8 |
| Penicillins + beta-lactamase inhibitor | 30 | 14.4 |
| Metronidazole | 26 | 12.4 |
| Quinolone | 23 | 11.0 |
| Penicillin | 22 | 10.5 |
| 1st- or 2nd-generation cephalosporin | 13 | 6.2 |
| Linezolid | 13 | 6.2 |
| Aminoglycoside | 13 | 6.2 |
| Macrolide | 12 | 5.7 |
| Sulfonamide | 11 | 5.3 |
| Daptomycin | 10 | 4.8 |
| Colistin | 7 | 3.3 |
| Rifampicin | 7 | 3.3 |
| Tigecycline | 6 | 2.9 |
| Other | 9 | 4.3 |

**Table 4** Fosfomycin combination partners in subgroups of patients with bacterial pneumonia, abdominal infection and CNS infection (all without sepsis or bacteremia)

| Combination partner | Number of patients (%) |
|---|---|
| Patients with bacterial pneumonia (CAP, HAP or VAP) | 25 (100) |
| Carbapenem | 15 (60.0) |
| Glycopeptide | 7 (28.0) |
| 3rd- or 4th-generation cephalosporin | 6 (24.0) |
| Colistin | 5 (20.0) |
| Quinolone | 4 (16.0) |
| Patients with abdominal infection | 22 (100) |
| Carbapenem | 18 (81.8) |
| 3rd- or 4th-generation cephalosporin | 4 (18.2) |
| Glycopeptide, penicillin + BLI or metronidazole | 3 (13.6) |
| Patients with CNS infection | 44 (100) |
| 3rd- or 4th-generation cephalosporin | 34 (77.3) |
| Carbapenem | 11 (25.0) |
| Metronidazole | 11 (25.0) |
| Glycopeptide | 10 (22.7) |

*HAP* hospital-acquired pneumonia; *CAP* community-acquired pneumonia; *VAP* ventilator-associated pneumonia; *BLI* beta-lactamase inhibitor; *CNS* central nervous system

**Table 5** Clinical efficacy endpoints (*n* = 209)

| Efficacy endpoint | *n* | % | % (cPP) |
|---|---|---|---|
| Cure | 63 | 30.1 | 34.6 |
| Improvement | 85 | 40.7 | 46.7 |
| Failure | 19 | 9.1 | 10.4 |
| Unchanged | 15 | 7.2 | 8.3 |
| Not reported | 3 | 1.4 | |
| Not assessable* | 24 | 11.5 | |

*cPP* clinical *per protocol* population

*According to physicians' assessment, no definite classification. Last documented observation carried forward independently of previous assessments at earlier time points (e.g., day 7 or 14)

**Table 6** Microbiological efficacy endpoints (*n* = 209)

| Efficacy endpoint | *n* | % | % (mPP) |
|---|---|---|---|
| Eradication | 63 | 30.1 | 70 |
| Microbiological treatment failure | 27 | 12.9 | 30 |
| Not reported | 3 | 1.5 | |
| Not determined | 47 | 22.5 | |
| Not assessable | 69 | 33.0 | |

*mPP* microbiological *per protocol* population

resistance against fosfomycin was observed during fosfomycin treatment.

In patients with infections of a single organ system, clinical success was achieved in 82.1% (115/140) of patients. With infections of two or more organ systems, clinical success was just slightly lower (75%, 24/32). The highest clinical success rate of 90% (9/10) was found in patients with signs of infection or bacteremia, but unknown focus. Eradication could be achieved in all patients with BJI, SSTI and endocarditis. The clinical and microbiological success per indication is shown in Table 7.

Clinical success rates in the standard and high-dose groups were virtually identical (81.1% vs. 81.3% (cPP)). In two patients with clinical cure, fosfomycin dosage was unknown.

In cases involving MDR pathogens, clinical and microbiological success rates were 84.8% (39/46 (cPP)) and 81.5% (22/27 (mPP)), respectively. Clinical and microbiological success rates in infections due to MRSA were 100% (6/6 (cPP)) and 66.7% (4/6 (mPP)), in MSSA 76.2% (16/21 (cPP)) and 100% (9/9 (mPP)), respectively.

If fosfomycin was combined with either a carbapenem, cephalosporin or a penicillin, pooled clinical success rates were 80.8%, 87.5%, and 85.7%, respectively (Table 8).

**Table 7** Clinical and microbiological success per indication

| Indication | Clinical success (cPP) | | Microbiological success (eradication, mPP) | |
|---|---|---|---|---|
| | n | % | n | % |
| All patients | 148/182 | 81.3 | 63/90 | 70.0 |
| CNS infections* | 33/37 | 89.1 | 9/11 | 81.8 |
| Pneumonia (CAP, HAP, VAP)* | 23/27 | 85.2 | 7/13 | 53.8 |
| Bacteremia, sepsis, and signs of infection | 17/20 | 85.0 | 7/10 | 70.0 |
| Bacteremia with unknown focus and signs of infection | 9/10 | 90 | 4/5 | 80.0 |
| Bone and join infections* | 18/21 | 85.7 | 13/13 | 100.0 |
| Abdominal infections* | 16/22 | 72.7 | 3/10 | 30.0 |
| Skin and soft tissue infections* | 10/12 | 83.3 | 8/8 | 100.0 |
| Endocarditis** | 6/9 | 66.7 | 4/4 | 100.0 |
| Complicated urinary tract infections* | 6/7 | 85.7 | 5/6 | 83.3 |
| Infection due to MDR pathogens | 39/46 | 84.8 | 22/27 | 81.5 |
| Infection due to GP pathogens# | 49/65 | 75.4 | 23/33 | 69.7 |
| Infection due to GN pathogens# | 20/25 | 80.0 | 10/13 | 76.9 |
| Infection due to GP and GN pathogens (polybacterial)# | 35/37 | 94.6 | 23/21 | 90.5 |
| Infection due to MSSA | 16/21 | 76.2 | 9/9 | 100 |
| Infection due to MRSA | 6/6 | 100 | 4/6 | 66.7 |
| Infection without identified pathogens | 44/55 | 80.0 | | |

*MDR* multidrug-resistant, *GP/GN* Gram-positive/-negative; *MS-/MRSA* methicillin-susceptible/methicillin-resistant *S. aureus*

*± Sepsis or bacteremia, **all with sepsis or bacteremia, #microbiologically confirmed (=targeted therapy)

**Table 8** Clinical success of fosfomycin in combination therapy (combinations of fosfomycin with one other concomitant antibiotic only)

| Class | n (ITT) | Combination partner (n ITT) | % Clinical success (n cPP) |
|---|---|---|---|
| Carbapenems | 30 | Meropenem (27) | 80.8% (21/26) |
| | | Imipenem (3) | |
| Cephalosporins | 23 | Cefotaxime (13) | 87.5% (14/16) |
| | | Cefuroxime (5) | |
| | | Cefazolin (2) | |
| | | Ceftriaxone (2) | |
| | | Ceftazidime (1) | |
| Penicillins | 15 | Piperacillin/tazobactam (8) | 85.7% (12/14) |
| | | Flucloxacillin (5) | |
| | | Amoxicillin/clavulanic acid (1) | |
| | | Ampicillin/sulbactam (1) | |

*n* no. of patients; *ITT* intention-to-treat population, *cPP* clinical per protocol population

## Safety

In total, 70 adverse events (AEs) were reported in 63 patients (30.1%). In seven patients, two AEs were reported, but no

**Table 9** Summary of safety analysis (adverse events, adverse drug reactions* and death)

| Classification | n | n(patients) | % (ITT) |
|---|---|---|---|
| AE(total) | 70 | 63 | 30.1 |
| Non-serious ADR* | 36 | 31 | 14.8 |
| Serious ADR* | 3 | 3 | 1.4 |
| Death | 15 | 15 | 7.2 |

*Considered as being related to fosfomycin

*AE* adverse event, *ADR* adverse drug reaction

patient experienced more than two AEs. Thirty-nine AEs were considered being related to the study drug (adverse drug reactions, ADR), three of which were assessed as serious. One of these three patients developed a multiple organ failure, another an acute respiratory insufficiency in pneumonia and a terminal cystic fibrosis, both with fatal outcome and both considered being unlikely related to fosfomycin. The third serious ADR was a severe hypokalemia that did not lead to discontinuation of fosfomycin treatment, however. A summary of the safety analysis is shown in Table 9.

Most common adverse events were hypernatremia ($n = 31$, 14.8%) and hypokalemia ($n = 13$, 6.2%). A causal relationship to fosfomycin was suspected in 22 (10.5%) patients with hypernatremia and five (2.4%) with hypokalemia. Of

**Table 10** Overview of adverse events

| AE | $n_{related}$ (% (ITT)) | $n_{not\ related}$ (% (ITT)) |
|---|---|---|
| Hypernatremia | 22 (10.5%) | 9 (4.3%) |
| Hypokalemia | 5 (2.4%) | 8 (3.8%) |
| Diarrhea | 3 (1.4%) | |
| Nausea | 2 (1%) | |
| Transaminases increased | 1 (0.5%) | |
| Pyrexia | 1 (0.5%) | |
| Allergic reaction | 1 (0.5%) | |
| Hyponatremia | 1 (0.5%) | |
| Hyperkalemia | | 1 (0.5%) |
| Not specified | 1 (0.5%) | |

*AE* adverse event; *ITT* intention-to-treat population

note, one and six patients, respectively, had hypokalemia or hypernatremia prior to fosfomycin treatment. Only four patients developed hypokalemia concomitantly with hypernatremia. In one patient, occurrence of an AE was formally documented, but not further specified. An overview of all AEs is shown in Table 10.

In eight patients, fosfomycin treatment was discontinued due to an adverse event, with hypernatremia being the cause in six of these cases. In the remaining two cases, therapy was stopped either due to an allergic reaction or pyrexia and nausea.

## Discussion

To date, this study is the largest non-interventional study focusing on the use of intravenous fosfomycin in the daily clinical practice. In total, 209 critically ill patients were enrolled, presenting with severe, life-threatening infections. Severity of illness of our patients was higher as of those reported in a previous study [39].

In our study, we found a broad use of IV fosfomycin against both GP and GN pathogens with a higher proportion of Gram-positives (54.2%). The widespread spectrum of indications ranging from infections predominantly caused by Gram-negatives such as cUTI to others most often associated with GP pathogens such as CNS infections, BJI or endocarditis, indicate that fosfomycin has been used across different sites of infection. High in vitro activity against several 'problem bacteria', in particular *S. aureus* and *S. epidermidis,* is clinically reflected by the large number of staphylococcal infections (36.5%) treated in NIS-FOM [21, 22]. Despite several alternative therapeutic options, fosfomycin was mostly used in MSSA infections [23, 24]. This might suggest that severe *S. aureus* infections with deep focus might represent entities not yet adequately covered by standard therapy [25].

In contrast to studies solely reporting on the use of IV fosfomycin as a last-resort option in infections due to MDR GN pathogens such as carbapenemase-producing *Enterobacteriaceae* or ESBL-producers [26, 33, 38, 39], data from this two-country study suggest that only in 24% of all patients the indication for fosfomycin use was an infection caused by MDR pathogens. More often it was used as a combination partner against other difficult-to-treat infections with limited therapeutic options or where the first-line treatment had already failed. In difficult-to-treat infections, even in those with biofilm involvement, IV fosfomycin has become a valuable combination partner supported by its advantageous pharmacokinetic properties [26–28, 30]. Its chemical properties allow fosfomycin to penetrate deep into tissues, even into bones and the CNS, which might explain the preferred use in CNS infections (22.3%) such as brain abscesses or bacterial meningitis, BJI (14.2%), or sepsis (10.5%) [11, 13, 29].

The broad spectrum of combination partners might be due to synergistic or additive effects of fosfomycin with many other classes of antibiotics that could be explained by inhibiting the bacterial cell wall synthesis at an earlier stage than other antibiotics (e.g., beta-lactams) [2]. Interestingly, our data indicate that fosfomycin was not used as a carbapenem-sparing treatment option, evermore discussed in the literature [31, 32]. Instead, in infections like nosocomial pneumonia (HAP, VAP) or abdominal infection (Table 4) fosfomycin was most often combined with a carbapenem. This combination is supported by synergistic effects and has recently been recommended, especially if MDR GN pathogens are involved [26, 33–36].

Although IV fosfomycin is generally considered a second-line treatment option, it was used in first-line therapy in more than a quarter of patients. Given its ability to rapidly cross the blood/brain barrier, fosfomycin may be regarded as a useful combination partner for treatment of CNS infections, e.g., when combined with a third- or fourth-generation cephalosporin [37].

The overall clinical success rate in the NIS-FOM study is the highest compared to other more recent studies on IV fosfomycin with similar design. Dinh et al. reported a favorable overall outcome in 76.8% of evaluable patients; BJI 82.6%, lung infection 67.7%, UTI 100%, endocarditis or neurological infection 83.3%, and bacteremia 57.1% [38]. According to Pontikis et al., clinical outcome at day 14 was successful in 54.2% of patients, whilst failure, indeterminate outcome and superinfection were documented in 33.3%, 6.3% and 6.3%, respectively [39]. However, in both studies the proportion of MDR pathogens was significantly higher, ranging between 70 and 100%. In NIS-FOM, clinical success rates ranged from 67% in patients with endocarditis to 89% in patients with CNS infection, emphasizing the role of fosfomycin in the treatment of GP pathogens [6]. Of note, all

patients with endocarditis developed a bacteremia or sepsis concomitantly, hampering a favorable clinical outcome [40]. In the subgroup of infections with MDR pathogen (including MRSA), clinical and microbiological success was adequate (Table 7). The reason for comparatively low clinical and microbiological success in patients with intraabdominal infections is unknown so far and needs further investigation.

Critically ill patients with impaired organ function and intensive co-medication challenge a safe and effective antibiotic treatment [42]. Pharmacokinetic interactions are common, possibly leading to discontinuation of therapy [43]. Many antibiotics, e.g., glycopeptides or colistin, are associated with serious adverse events such as nephrotoxicity, limiting their therapeutic use [44, 45]. However, our data show that IV fosfomycin was used in a large dosing range. Reported adverse events were generally non-serious and expected, without troubling drug/drug interactions. Moreover, safety results from the NIS-FOM are in line with recent reviews corroborating the good safety profile of the substance [6, 15]. Given the sodium load of IV fosfomycin, discontinuation of the drug due to accumulating high sodium levels in six cases was reasonable to prevent potentially serious electrolyte imbalances. One limitation of our study is the lack of a control group. Thus, it remains unclear how many patients would have developed hypernatremia or hypokalemia independent of fosfomycin treatment. In general, hypokalemia is a common problem in ICU patients and medication is merely one possible explanation [41]. Therefore, clinicians should be aware of disturbances in sodium and potassium homeostasis and initiate adequate measures early to avoid further complications. Altogether, fosfomycin's safety profile appears advantageous, since the generally non-serious and expected nature of adverse events constitutes no limiting factor in therapy.

## Conclusion

These results suggest that IV fosfomycin is an effective and safe combination partner in the treatment of critically ill patients with severe infections due to Gram-negative and Gram-positive pathogens, even in first-line treatment. Fosfomycin was used across different indications and sites of infection, independently of the pathogen's resistance pattern. On the other hand, IV fosfomycin is also suitable for highly specific patients and settings, when standard treatment might be inadequate due to clinical circumstances or has already failed. Thus, considering the critical medical condition of the study population and the severity of underlying infections, the high overall success rate of 81% together with an advantageous safety profile is very promising and might give rise for further prospective clinical trials.

## Compliance with ethical standards

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