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ORIGINAL RESEARCH

Real-World Use, Effectiveness, and Safety of Intravenous Fosfomycin: The FORTRESS Study

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ABSTRACT

Introduction: Intravenous fosfomycin (FOS) is a broad-spectrum antibiotic primarily used in combination therapy to treat severe infections caused by both Gram-positive (GP) and Gram-negative (GN) pathogens, including multi-drug resistant (MDR) bacteria. The aim of this study, the largest to date, was to evaluate the effectiveness, safety, usage patterns, and patient characteristics of FOS in a real-world setting.

Methods: Interim analysis of an ongoing, prospective, non-interventional, multicentre study in five European countries, involving centres in Germany, Italy, the United Kingdom, Greece, and Austria.

Results: A total of 716 patients were enrolled between January 2017 and November 2023 (mean age: 62.8 years, APACHE II: 18.3, SOFA: 6.7). Main indications for FOS were bacteraemia/sepsis (23.6%), complicated urinary tract infections (18.0%), and bone and joint infections (17.4%). Other indications included

Klaus-Friedrich Bodmann and Stefan Hagel contributed equally to this work.

Thomas Borrmann and Christian Mayer have shared senior authorship.

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hospital-acquired/ventilator-associated pneumonia (11.0%), complicated skin and soft tissue infections (9.1%), bacterial meningitis/central nervous system (CNS) infections (7.8%), and infective endocarditis (6.4%). Most common pathogens identified were *Staphylococcus aureus* (31.4%, including methicillin-resistant *S. aureus*), *Klebsiella* spp. (including *K. pneumoniae*) (17.2%), *Escherichia coli* (14.2%), coagulase-negative staphylococci (12.9%), other Enterobacterales (10.9%), and *Pseudomonas aeruginosa* (8.4%). In 34.6% of patients, an MDR pathogen was involved. Carbapenem resistance (CR) was high in *Klebsiella* spp. infections (59/123, 48.0%). In most patients, FOS was used in combination therapy (90.2%). The median dose was 15 g/day. Overall, clinical success and clinical response were favourable with 75.3% and 83.4% at the end of FOS treatment. Clinical success rates in infections caused by MDR or CR pathogens were 78.0% and 81.8%, respectively. Microbiological cure was achieved in 82.4% of all patients. Electrolyte imbalances were the most frequently observed adverse drug reactions, while gastrointestinal disorders were rare.
***Conclusion*:** The results from this study suggest that FOS is a safe and effective option as combination partner in the treatment of patients with severe infections caused by both GP and GN pathogens, including deep-seated infections and/or involvement of MDR bacteria.

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Keywords: Fosfomycin; *Staphylococcus aureus*; Carbapenem-resistant Enterobacterales; Bacteraemia; Infective endocarditis; MDR; *Klebsiella pneumoniae*; *Pseudomonas aeruginosa*; Sepsis; Observational study

Key Summary Points

Why carry out this study?

Comprehensive and prospectively collected data on intravenous (IV) fosfomycin from real-world clinical practice encompassing its broad spectrum of indications and pathogens are needed.

This study was conducted to evaluate the effectiveness, usage patterns, and safety of IV fosfomycin in a real-world setting across Europe.

What was learned from the study?

IV fosfomycin was mainly used as part of a combination therapy in a broad range of severe infections caused by both Gram-positive and Gram-negative pathogens.

Main indications were bacteraemia/sepsis, complicated urinary tract infections, and bone and joint infections. Most commonly identified pathogens before start of IV fosfomycin treatment were *Staphylococcus aureus*, *Klebsiella* spp., and *Escherichia coli.*

Overall, clinical success and microbiological cure were achieved in 75.3% and 82.4%, respectively (clinical success rate in infections caused by carbapenem-resistant pathogens was 81.8%).

INTRODUCTION

Antimicrobial resistance (AMR) is an increasing threat to global public health. In 2019, a study analysed the global disease burden of AMR and found an estimated 1.95 million deaths to be directly attributable to infections caused by resistant bacteria. In addition, approximately 5 million deaths were associated to AMR [1]. As a consequence, new agents, such as beta-lactam/beta-lactamase inhibitors (BLBLIs), have been introduced in recent years, accompanied by the repurposing of older substances. In this context, intravenous fosfomycin (FOS), which was introduced more than four decades ago, has recently experienced a renaissance, primarily as a combination partner to other antibiotics for the treatment of difficult-to-treat (DTR) infections caused by both Gram-positive (GP) and Gram-negative (GN) pathogens. Due to its broad spectrum of activity, FOS has been recognized as a valuable option as adjunctive to other antibiotics against multi-drug resistant (MDR) bacteria, including critical and high-priority pathogens such as carbapenem-resistant (CR) and extended spectrum beta-lactamase (ESBL)-producing Enterobacterales, CR/DTR *Pseudomonas aeruginosa*, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA), with overall favourable clinical and microbiological outcomes [2–8]. Recent studies have also indicated a role of FOS-containing regimens for infections caused by *Acinetobacter baumannii* [9–13]. In addition, two recent randomized controlled trials (RCT) have demonstrated its efficacy as monotherapy in the treatment of (bacteraemic) complicated urinary tract infections (cUTI) [14, 15].

FOS has a unique mechanism of action. Like beta-lactam antibiotics, FOS interferes with bacterial cell wall synthesis. However, unlike beta-lactams, FOS acts as phosphoenolpyruvate (PEP) analogue and irreversibly inhibits

MurA (UDP-*N*-acetylglucosamine enolpyruvyl transferase), an enzyme catalysing the initial step of peptidoglycan biosynthesis [16]. Due to its distinct mode of action, cross-resistance to other antibiotics is unlikely. The results of several in vitro studies have demonstrated that FOS exhibits high synergistic and additive interactions with various antibiotic classes, particularly with beta-lactams, but also with drugs such as daptomycin, colistin, and aminoglycosides [17]. In addition, FOS penetrates well into body tissues and fluids, reaching even difficult-to-reach compartments like the cerebrospinal fluid (CSF), abscess or bone [16]. Due to its broad antimicrobial spectrum and its pharmacokinetic properties in conjunction with its biofilm and intracellular activity [16], FOS is used for the treatment of a wide range of different indications [18]. Reflecting its versatility, FOS is included in several European clinical guidelines and expert panel opinions [19–35], including recommendations in the European guidelines for the management of endocarditis and treatment of infections caused by MDR GN bacilli [36, 37].

Despite the availability of novel therapeutics, the emergence of resistance to agents such as ceftazidime/avibactam [38–40] underlines the need for a broad armamentarium of effective antimicrobials. Although effectiveness and safety data regarding FOS have become increasingly available in recent years, prospective real-world data from clinical routine are still limited. Here, we present the results of the largest prospective study (FORTRESS) to date on FOS, evaluating its effectiveness, safety, usage patterns, and patient characteristics in a real-world setting.

METHODS

Study Population

Study participants were enrolled from the pool of patients at respective study sites who were scheduled for treatment with FOS according to clinical routine and independently from **F**os-fomycin IV f**or tre**atment of **s**everely infected patient**s** (FORTRESS) study.

The following inclusion criteria had to be met for a participant to be included in the study: male or female patients aged ≥ 18 years; treatment with FOS according to the respective (national) summary of product characteristics (SmPC); patients with bone and joint infection (BJI), complicated urinary tract infection (cUTI), hospital-acquired/ventilator-associated pneumonia (HAP/VAP), bacterial meningitis/central nervous system (CNS) infection (BM/CNSI), bacteraemia/sepsis, complicated skin and soft tissue infection (cSSTI), infective endocarditis (IE), complicated intraabdominal infection (cIAI) or other infections, each as far as covered by the respective nationally relevant SmPC; and written informed consent of the participant or legal representative.

Individuals were excluded from participation if they met one or more of the following exclusion criteria: previous participation in the study; patients participating in an interventional clinical trial; patients with known hypersensitivity to FOS or any of the excipients; terminally ill patients; patients with "do not resuscitate order"; palliative treatment approach; failure of > 3 of the following organ systems: respiratory system, nervous system, cardiovascular system, liver, coagulation, kidney; manifest HIV disease (AIDS); FOS treatment as 4th line treatment or at later stage; patients with involvement of fungi or mycobacteria in the targeted infection.

Study Design

The present study is a prospective, international, multicentre, non-comparative, non-interventional clinical study conducted at different clinics to document and evaluate the effectiveness and safety of the treatment of severely infected patients with FOS under real-life conditions (NCT02979951). The study was conducted in accordance with the Helsinki Declaration of 1964 (and its amendments), and was approved by all ethics committees or other authorities according to national/local requirements (Supplementary Table S13). Written informed consent was obtained from each

patient or the patient's legally acceptable representative before any study-specific activity was performed. In Austria, an informed consent waiver was approved for patients who were incapacitated.

Data Collection

An electronic case report form ("eCRF") was used to collect data. Recorded data included demographic/medical history, and pattern of FOS usage, as well as microbiological and clinical data.

Sample Size

The FORTRESS study aimed to enrol a total of 1500 participants across multiple study sites in various countries, currently including sites in Germany, Italy, Greece, Austria, and the United Kingdom (UK). Recruitment commenced in January 2017. For this current report, the database lock of the respective interim analysis was November 2023, with a total of 716 patients with finalisation of documentation from 37 centres comprising the full analysis (FA)/safety-evaluable (SE) population.

Definitions and Outcomes

The primary endpoint of this study was clinical success, a composite endpoint defined as either clinical cure or clinical improvement, analysed at end of FOS treatment (EOT). Clinical cure and clinical improvement were defined as either resolution of signs and symptoms or partial resolution of signs and symptoms (as assessed by the treating physician), plus concomitant microbiological cure or no additional antibiotic therapy for the targeted infection necessary (i.e., both clinical and microbiological criteria must be fulfilled). Microbiological cure was defined as either the elimination of the relevant pathogen(s) at the relevant site(s) of infection (i.e., at least one negative culture) or in case of "no sample available/indicated due to sufficient clinical response" pathogen elimination was considered.

Secondary endpoints included clinical response (additional endpoint as described in the statistical analysis plan), microbiological cure, clinical success, clinical cure, and clinical improvement at initial response (IR), EOT, test-of-cure (TOC), and, if applicable, i.e., for patients treated for BJI, follow-up. IR was assessed ≤ 7 days after start of FOS treatment. TOC was timed by the investigator for concluding evaluation of the treatment success of the current infection and might correlate with the end of hospital stay but was defined to be not earlier than EOT.

Safety analysis included sodium and potassium levels (documented daily, if available), adverse events (i.e., non-serious, serious, death), adverse drug reactions (ADRs, i.e., causal relationship between the study drug and a documented AE is at least a reasonable possibility, based on medical evaluation by the study physician) [41], serious ADRs (SADRs) [41, 42], and dropouts due to treatment failure or due to AEs.

The subgroup of patients with bacteraemia/sepsis was defined as either proven bacteraemia or allocation of the term "bacteraemia/sepsis" as the applicable kind of infection by the investigator at start of FOS treatment.

For the subgroup analysis of patients with bacteraemia caused by *S. aureus*, high-risk bacteraemia was defined as either endocarditis, unknown focus, or pneumonia as the source of infection [43]. For patients allocated to other indications (i.e., not documented within the bacteraemia/sepsis "eCRF"), e.g., HAP/VAP or IE, but with concomitant *S. aureus* bacteraemia or bacteraemia caused by carbapenem-resistant (CR) pathogens, the focus of infection was considered to be the source of bacteraemia.

Antimicrobial susceptibility testing was performed according to local practices/guidelines.

Statistical Analysis

Descriptive statistics (mean, standard deviation, quartiles, minimum and maximum) was performed for continuous variables. Counts and frequencies are given for dichotomous variables. All statistical analyses were carried out by means of software SAS (version 9.4).

Table 1 Demographic and baseline characteristics

	716 patients
Demography/characteristic[a]	
Age (years)	
Mean (SD)	62.8 (14.75)
Median	65.0
95% CI (mean)	[61.68; 63.85]
Range	18–93
Gender, *n* (%)	
Female	262 (36.6)
Male	454 (63.4)
Patients in ICU, *n* (%)	370 (51.7)
APACHE II score (mean) (*n* = 84)	18.3
SOFA score (mean) (*n* = 35)	6.7
Sepsis, *n* (%)	258 (36.0)
Septic shock, *n* (%)	42 (5.9)
Mechanical ventilation, *n* (%)	168 (23.5)
Concomitant fungal infection, *n* (%)	17 (2.4)
Creatinine clearance (ml/min), mean (SD) (*n* = 521)	77.7 (47.6)
Concomitant treatment, *n* (%)	582 (81.3)
Co-morbidities (any), *n* (%)	693 (96.8)
Cardiovascular	476 (66.5)
Renal	253 (35.3)
Renal replacement therapy	*55 (21.7)*
Endocrinologic	252 (35.2)
Electrolyte disorders	226 (31.6)
Respiratory	210 (29.3)
Oncologic	128 (17.9)
Immunosuppressive	120 (16.8)
Hepatic	109 (15.2)
Orthopaedic	100 (14.0)
Traumatic injury/fractures	60 (8.4)
Other	273 (38.1)

Table 1 continued

	716 patients
Antibiotic treatment (IV) during current hospital stay prior to FOS therapy, *n* (%)	574 (80.2)
Targeted therapy, *n* (%)	390 (54.5)
Empiric therapy, *n* (%)	249 (34.8)
Information missing, *n* (%)	77 (10.8)

[a]Multiple entries possible

APACHE II acute physiology and chronic health evaluation II, *CI* confidence interval, *FOS* intravenous fosfomycin, *ICU* intensive care unit, *SD* standard deviation, *SOFA* sepsis-related organ failure assessment score, *n* number of patients; percentages in italics are relative to the total number of patients in that category

RESULTS

Data from a total of 716 patients were analysed. Of the 716 patients, 427 were enrolled in Germany (13 study sites), 236 in Italy (14 study sites), 21 in the UK (4 study sites), 16 in Greece (4 study sites), and 16 patients in Austria (2 study sites).

Demographic Data and Baseline Characteristics

Demographic and baseline characteristics of the population are summarised in Table 1 and Table S1 (Supplementary). The mean age of patients was 62.8 years, ranging from 18 to 93 years, with approximately two-thirds of patients being male (454/716, 63.4%). At the time of starting FOS treatment (baseline), 51.7% of patients were treated in intensive care units (ICU). The average APACHE II and SOFA scores were 18.3 and 6.7, respectively, indicating a generally critically ill patient population (data retrieved from 84 and 35 patients with available documentation, respectively). A considerable number of patients (298/716, 41.6%) presented with sepsis or septic shock and 23.5% required mechanical ventilation before start of FOS treatment.

In total, 163 of 716 patients (22.8%) were considered immunocompromised (Supplementary Table S1). Additionally, 66.5% and 35.3% of patients had cardiovascular and renal co-morbidities (e.g., congestive heart failure or renal insufficiency), respectively. Noteworthy, 31.6% presented with electrolyte imbalances at baseline. In most cases (390/716, 54.5%), patients received targeted FOS treatment, while empiric therapy was used in 34.8% of patients (249/716). Most patients received intravenous (IV) antibiotic pre-treatment during the current hospital stay prior to FOS start (574/716, 80.2%).

Demographics and baseline characteristics of subgroups of patients treated for infective endocarditis and *S. aureus* bacteraemia are displayed in Tables S2 and S3 (Supplementary), respectively. Most patients with IE had left-sided IE (33/46, 71.7%) and abscesses were found in 17.4% of all cases. Overall, foreign body involvement was frequent (Supplementary Table S2). The main sources of *S. aureus* bacteraemia were endocarditis (32/125, 25.6%), SSTI (18/125, 14.4%), or an unknown focus (13/125, 10.4%). Catheter-associated bacteraemia accounted for 4.8% (6/125) of cases. Taking into account the source of infection, 40.8% of all cases were considered high-risk bacteraemia (Supplementary Table S3).

Indications

Overall, FOS was most frequently used in patients with bacteraemia/sepsis (169/716, 23.6%), cUTI (18.0%), and BJI (17.3%). Other indications included HAP/VAP (11.0%), cSSTI (9.1%), BM/CNSI (7.8%), and IE (6.4%). Importantly, patients treated for infections other than bacteraemia/sepsis may also have suffered from concomitant bacteraemia and/or sepsis/septic

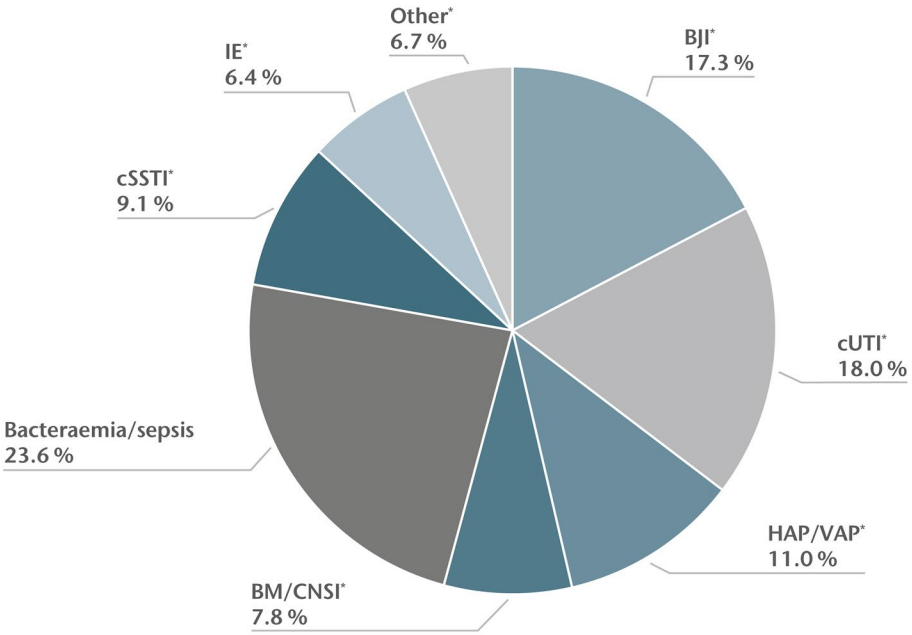

Fig. 1 Indications of IV fosfomycin use. * ± bacteraemia and/or sepsis/septic shock, *BJI* bone and joint infection, *BM/CNSI* bacterial meningitis/CNS (central nervous system) infection, *cSSTI* complicated skin and soft tissue infection, *cUTI* complicated urinary tract infection, *HAP/VAP* hospital-acquired/ventilator-associated pneumonia, *IE* infective endocarditis, *n* number of patients

shock. The indications for FOS usage are presented in Fig. 1.

As envisaged, country-specific differences in the use of FOS were identified. In order of frequency, the main indications in Germany were bacteraemia/sepsis (80/427, 18.7%), BJI (78/427, 18.3%), and BM/CNSI (54/427, 12.6%). While bacteraemia/sepsis was also the most common indication in Italy (82/236, 34.7%), the second and third most frequent indications were cUTI (74/236, 31.4%) and BJI (38/236, 16.1%) (Supplementary Table S4). In contrast to Germany, however, where bacteraemia/sepsis cases were mostly caused by GP pathogens (mainly staphylococci), patients treated for this indication in Italy had bacteraemia predominantly caused by GN pathogens, particularly by *Klebsiella* spp. (Supplementary Table S5). In Greece and the UK, most patients were treated for HAP/VAP (11/16, 68.8%) and cUTI (11/21, 52.4%), respectively. In Austria, FOS was mainly used for BJI (6/16, 37.5%).

Microbiological Findings

Table 2 summarises the microbiological findings before start of FOS therapy. Overall, *S. aureus* was the most common pathogen identified (225/716, 31.4%), with the majority being methicillin-susceptible *S. aureus* (MSSA), followed by *Klebsiella* spp. (17.2%, including *K. pneumoniae*), *E. coli* (14.2%), coagulase-negative staphylococci (CoNS) (13.0%), other Enterobacterales species (10.9%), *P. aeruginosa* (8.4%), and enterococci (8.1%). Infections were frequently caused by MDR pathogens (248/716, 34.6%). Carbapenem resistance was common in *Klebsiella* spp. (59/123, 48.0%) and *P. aeruginosa* (15/60, 25.0%) infections, but rare in infections involving *E. coli* (1/102, 1.0%). The incidence of methicillin resistance was similar in *S. aureus* and CoNS (16.4% and 18.3%, respectively) (Table 2). In 2.4% of patients, a concomitant fungal infection was identified at baseline (Table 1).

Table 2 Microbiological evaluation at baseline

Isolated pathogens[a]	**716 patients** ***n*** **(%)**
S. aureus	225 (31.4)
MSSA	192 (85.3)
MRSA	37 (16.4)
Klebsiella spp.	123 (17.2)
Escherichia coli	102 (14.2)
CoNS	93 (13.0)
Staphylococcus epidermidis	*67 (72.0)*
Other coagulase-negative staphylococci	36 (38.7)
Other Enterobacterales	78 (10.9)
Enterobacter spp.	*30 (38.5)*
Proteus spp.	*26 (33.3)*
Citrobacter spp.	*11 (14.1)*
Serratia spp.	*10 (12.8)*
Salmonella spp.	*2 (2.6)*
P. aeruginosa	60 (8.4)
Enterococcus spp.	58 (8.1)
E. faecalis	*28 (48.3)*
E. faecium	*28 (48.3)*
Streptococcus spp.	32 (4.5)
Acinetobacter spp.	7 (1.0)
Other gram-positive pathogens	12 (1.7)
Other gram-negative pathogens	15 (2.1)
Anaerobes[b]	8 (1.1)
Type of infections	***n*** **(%)**
Monomicrobial infection	443 (61.9)
Polymicrobial infection	173 (24.2)
Culture negative/no indication-relevant sample/no sample	100 (14.0)
Antibiotic resistance[a]	***n*** **(%)**
MDR	248 (34.6)
Methicillin resistance	53 (7.4)
S. aureus (*n* = 225)	*37 (16.4)*
CoNS (*n* = 93)	*17 (18.3)*
Vancomycin resistance	13 (1.8)
E. faecalis (*n* = 28)	*2 (7.1)*
E. faecium (*n* = 28)	*8 (28.6)*
Carbapenem resistance	79 (11.0)
Klebsiella spp. (*n* = 123)	*59 (48.0)*
E. coli (*n* = 102)	*1 (1.0)*
P. aeruginosa (*n* = 60)	*15 (25.0)*
ESBL-producing	62 (8.7)
Klebsiella spp. (*n* = 123)	*28 (22.8)*
E. coli (*n* = 102)	*22 (21.6)*
Other	75 (10.5)

[a]Multiple entries possible [b] obligate anaerobic

CoNS coagulase-negative staphylococci, *ESBL* extended-spectrum beta-lactamase, *FOS* intravenous fosfomycin, *MDR* multidrug-resistant, MRSA methicillin-resistant *S. aureus*, MSSA methicillin-susceptible *S. aureus*, *spp.* species, *n* number of patients, percentages and numbers in italics are relative to the total number of patients in that category or the number of patients given in brackets, baseline = before start of FOS treatment

The majority of patients enrolled in Germany and Austria had predominantly infections caused by at least one GP pathogen, whereas patients from Italy, Greece, and the UK had mainly infections with GN causative agents FOS (Supplementary Table S5). Overall, most patients had infections caused by one pathogen (443/716, 61.9%), whereas 24.2% of patients had polymicrobial infections (Table 2). However, in 100 patients, no pathogen was identified (14.0%) (Table 2).

Where available, baseline isolates were reported susceptible to FOS in 53.4% of patients (350/655), whereas 7.9% were documented as non-susceptible. For approximately half of patients, in vitro susceptibility data were not available.

Table 3 IV fosfomycin usage

Characteristic[a]	716 patients *n* (%)
Therapy	
Monotherapy	64 (8.9)
Combination therapy	646 (90.2)
1 partner antibiotic	*424 (65.6)*
2 partner antibiotics	*161 (24.9)*
≥ 3 partner antibiotics	*61 (9.4)*
Missing	6 (0.8)
Rationale for FOS treatment	
Insufficient efficacy of potential alternatives	124 (17.3)
Insufficient tolerance of potential alternatives	14 (2.0)
Contraindication of potential alternatives	33 (4.6)
Insufficient efficacy/treatment failure of pre-treatment	151 (21.1)
Side effects of pre-treatment	12 (1.7)
Nosocomial infection	152 (21.2)
Difficult-to-treat infection	376 (52.5)
Favourable tissue penetration	202 (28.2)
Other	40 (5.6)
Line of treatment	
Patients treated in 1st line	208 (29.1)
Patients treated in 2nd line	369 (51.5)
Patients treated in 3rd line	137 (19.1)
Patients treated in 4th line	2 (0.3)
Duration of FOS treatment (days), mean (SD)	13.6 (10.2)
Total duration of antibiotic treatment (days), (SD)[b]	18.8 (19.3)
Duration of FOS treatment (days), mean (SD), by indication	
Bacteraemia/sepsis	14.1 (9.3)
BM/CNSI	13.8 (7.6)
BJI	18.1 (12.4)
cSSTI	15.6 (11.1)
cUTI	8.1 (6.2)
HAP/VAP	10.7 (5.3)

Table 3 continued

Characteristic[a]	716 patients *n* (%)
IE	18.5 (16.0)
Estimated time from first (suspected) diagnosis to start of FOS treatment (days), mean (SD)	5.7 (9.9)
Targeted daily dose (g), median (range; 95% CI)[c]	15.0 (2–24; 14.58–15.26)

[a]Multiple entries possible

[b]Including pre-treatment of patients for the documented infection until the end of IV fosfomycin treatment (Note: For 10 patients, information on the duration of pre-treatment was not available)

[c]Average targeted daily dose

BM/CNSI bacterial meningitis/CNS (central nervous system) infections, *BJI* bone and joint infection, *CI* confidence interval, *cSSTI* complicated skin and soft tissue infection, *cUTI* complicated urinary tract infection, *FOS* intravenous fosfomycin, *g* grams, *HAP/VAP* hospital-acquired/ventilator-associated pneumonia, *IE* infective endocarditis, *IV* intravenous, *SD* standard deviation, *n* number of patients; percentages and numbers in italics are relative to the total number of patients in that category

Usage of IV fosfomycin

Table 3 displays the pattern of FOS usage. The median daily targeted dose of FOS was 15 g (with targeted doses up to 24 g), considering also dosing adjustments based on patients' renal status. In this context, the targeted dosage was found to be comparable in patients with infections caused solely by GP or GN pathogens or polybacterial infections. However, there were notable differences in the median targeted daily dose between Germany, Italy, and the UK (15 g, 16 g, and 15 g, respectively) and Austria and Greece (24 g and 20 g, respectively). Patients were treated with FOS for an average of 13.6 ± 10.2 days. However, treatment duration was strongly dependent on the indication (Table 3). The mean time from diagnosis to start of FOS therapy was 5.7 days.

In the present study, FOS was used almost exclusively in combination therapy (646/716, 90.2%), except for patients with cUTI, where it was used as monotherapy in 36.4% (47/129) of patients (mainly in Italy). Antibiotic combination partners were BLBLIs (25.3%), carbapenems (21.9%), penicillins (15.2%), vancomycin (13.8%), newer generation cephalosporins (i.e., 3rd generation upwards) (11.2%), 1st/2nd generation cephalosporins (11.0%), and daptomycin (7.8%) (Table 4 and Supplementary Table S6). Newer agents like ceftazidime/avibactam (n = 50), meropenem/vaborbactam (n = 9), or cefiderocol (n = 6) were used as companion antibiotic in a considerable number of patients, predominantly in Italy. Main antibiotics used in combination with FOS per indication and subgroup are summarised in Table 5.

Overall, 208 patients (29.1%) received FOS as first-line treatment, while in the majority of patients it was used in second line (369/716, 51.5%) (Table 3). In Italy and Austria, the proportion of FOS as first-line option was higher as compared to the other countries and was lowest in the UK. As first line-treatment, FOS was employed most frequently in patients with cUTI (65/129, 50.4%), followed by cSSTI (23/65, 35.4%) and BM/CNSI (17/56, 30.4%).

Clinical and Microbiological Outcome

Clinical and microbiological outcomes at EOT (i.e., clinical success, clinical response, clinical failure, and microbiological cure) are summarised in Table 6. Overall, clinical success and microbiological cure was achieved in 75.3% (539/716) and 82.4% (590/716) of patients,

Table 4 Antibiotics/antibiotic classes used in combination with IV fosfomycin

Antibiotic class/antibiotic[a, b]	716 patients *n* (%)
Beta lactam/beta-lactamase inhibitor combination	181 (25.3)
Piperacillin/tazobactam	*93 (51.4)*
Ceftazidime/avibactam	*50 (27.6)*
Ampicillin/sulbactam	*22 (12.2)*
Carbapenems	157 (21.9)
Meropenem	*146 (93.0)*
Penicillins	109 (15.2)
Flucloxacillin	*91 (83.5)*
Vancomycin	99 (13.8)
3rd/4th/5th/next-generation cephalosporins	80 (11.2)
Ceftriaxone	*25 (31.3)*
Ceftazidime	*17 (21.3)*
Cefepime	*14 (17.5)*
Cefiderocol	*6 (7.5)*
1st/2nd generation cephalosporins	79 (11.0)
Cefazolin	*69 (87.3)*
Daptomycin	56 (7.8)
Fluoroquinolones	37 (5.2)
Aminoglycosides	28 (3.9)
Linezolid	23 (3.2)
Colistin	16 (2.2)

[a]Multiple entries

[b]possible start of combination partner maximal 1 day after IV fosfomycin start

n number of patients; percentages and numbers in italics are relative to the total number of patients in that category

respectively. Clinical response was observed in 597 of 716 patients (83.4%), while 5.6% (40/716) had clinical failure at EOT. The overall in-hospital mortality rate was 10.6% (76/716) (Table 6). Clinical and microbiological outcomes at other timepoints are provided in Table S7 and Table S8 (Supplementary).

Clinical success was most frequent in patients with cUTI (109/129, 84.5%), followed by BM/CNSI (46/56, 82.1%), cSSTI (49/65, 75.4%), bacteraemia/sepsis (124/169, 73.4%), BJI (90/124, 72.6%), IE (32/46, 69.6%), and HAP/VAP (50/79, 63.3%) (Table 6). In subgroups of patients with bacteraemia caused by *S. aureus* (both MSSA and MRSA) or CR pathogens (mainly *Klebsiella* spp., including *K. pneumoniae*), clinical success and response rates were 69.6% and 78.4% and 86.4% and 95.5%, respectively. When compared to the composite primary endpoint, clinical response rates were generally higher,

Table 5 Main companion antibiotics by indication/subgroup

	n (%)
Indication/antibiotic[a, b]	
Bacteraemia/sepsis (*n* = 169)	
Meropenem	30 (17.8)
Piperacillin/tazobactam	25 (14.8)
Flucloxacillin	24 (14.2)
Ceftazidime/avibactam	19 (11.2)
cUTI (*n* = 129)	
Piperacillin/tazobactam	23 (17.8)
Ceftazidime/avibactam	12 (9.3)
BJI (*n* = 124)	
Flucloxacillin	27 (21.8)
Piperacillin/tazobactam	17 (13.7)
Cefazolin	16 (12.9)
Vancomycin	13 (10.5)
Daptomycin	13 (10.5)
HAP/VAP (*n* = 79)	
Meropenem	28 (35.4)
Piperacillin/tazobactam	16 (20.3)
Vancomycin	9 (11.4)
Colistin	8 (10.1)
cSSTI (*n* = 65)	
Meropenem	19 (29.2)
Cefazolin	12 (18.5)
Vancomycin	11 (16.9)
Flucloxacillin	10 (15.4)
BM/CNSI (*n* = 56)	
Meropenem	39 (69.6)
Vancomycin	38 (67.9)
Flucloxacillin	8 (14.3)
IE (*n* = 46)	
Flucloxacillin	16 (34.8)
Cefazolin	15 (32.6)
Daptomycin	12 (26.1)
Vancomycin	6 (13.0)
Gentamicin	5 (10.9)
Subgroup/antibiotic[a, b]	
S. aureus bacteraemia[c]	
MSSA bacteraemia (*n* = 105)	
Flucloxacillin	55 (52.4)
Cefazolin	29 (27.6)

Table 5 continued

	n (%)
MRSA bacteraemia (*n* = 22)	
Daptomycin	6 (27.3)
Vancomycin	5 (22.7)
Bacteraemia due to CR pathogens (*n* = 22)[c]	
Ceftazidime/avibactam	17 (77.3)

[a]Multiple entries possible

[b]Start of combination partner maximal 1 day after FOS start

[c]Patients with allocation of the term "bacteraemia/sepsis" (due to *S. aureus* or CR pathogens) as the applicable kind of infection by the investigator at start of FOS treatment and/or positive blood culture for the respective pathogen in patients allocated to another indication (only monobacterial infections were included)

BJI bone and joint infection, *BM/CNSI* bacterial meningitis/CNS (central nervous system) infection, *CR* carbapenem-resistant, cSSTI complicated skin and soft tissue infection, *cUTI* complicated urinary tract infection, *FOS* intravenous fosfomycin, *HAP/VAP* hospital-acquired/ventilator-associated pneumonia, *IE* infective endocarditis, *n* number of patients; percentages and numbers are relative to the total number of patients per indication/subgroup given in brackets

most pronounced in the cSSTI, HAP/VAP, and BM/CNSI groups, respectively (Table 6).

Noteworthy, patients treated with a high-dose regimen (i.e., > 16 g of FOS targeted daily dose) showed better clinical success than those treated with doses of ≤ 16 g per day, particularly in patients presenting with BM/CNSI, bacteraemia/sepsis, cSSTI, or IE (Table 6). Microbiological cure rates exceeded 80% in the majority of indications/subpopulations and were highest in patients treated for IE (95.7%), cUTI (89.1%), CR GN bacteraemia (86.4%), BM/CNSI (85.7%), and *S. aureus* bacteraemia (85.6%) or treated with FOS in combination with daptomycin (91.1%) or ceftazidime/avibactam (86.0%) (Tables 6 and 7).

With regards to the aetiology of infections, patients infected with *Klebsiella* spp. and *P. aeruginosa* showed similar clinical response rates (90.8% and 89.7%, respectively). Similarly, there was no difference in clinical outcomes in MSSA and MRSA infections (Table 6). Notably, successful clinical response was independent of carbapenem resistance in infections caused by GN bacteria, as shown by the comparative outcomes.

Safety

A summary of the safety analysis is displayed in Table 8. In total, 58.2% patients experienced any kind of adverse event (AE), including patients who experienced more than one AE and/or serious AEs (SAE), and 79 patients died. However, none of the deaths were related to FOS treatment. Regarding reactions related to the study drug, 243 patients (33.9%) had at least one non-serious ADR and in 59 patients SADRs (8.2%) were reported. Details can be found in Table S11 (Supplementary).

The most frequently reported ADRs (including SADRs) were hypokalaemia (189/716, 26.4%) and hypernatraemia (109/716, 15.2%). However, in most patients, dose adjustment of FOS due to ADRs was not required, and only in a minority of patients FOS was discontinued due to possibly drug-related electrolyte imbalances. In line with this, most cases of hypokalaemia and hypernatraemia were assessed to be mild (50.8% and 74.3%, respectively) or moderate (41.8% and 22.0%, respectively) (Table 9). The ranges of actual measured potassium and sodium levels on patient level are shown in Table S12 (Supplementary). Other ADRs included relatively rare cases of gastrointestinal disorders and two cases of suspected resistance development (Supplementary Table S11).

DISCUSSION

To our knowledge, FORTRESS represents the largest prospective, non-interventional multicentre study on FOS and describes the pattern and characteristics of clinical use, microbiology of infections, clinical and microbiological

Table 6 Clinical and microbiological outcomes by indication, subgroups, main pathogens, and most frequently used combination partners at EOT

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
All patients[a]	716[b]	539 (75.3)	597 (83.4)	40 (5.6)	590 (82.4)
Indication[a]					
Bacteraemia/sepsis[c]	169	124 (73.4)	140 (82.8)	11 (6.5)	137 (81.1)
Treated with daily dose > 16 g[d]	26	22 (84.6)	24 (92.3)	0 (0)	22 (84.6)
Treated with daily dose ≤ 16 g[d]	143	102 (71.3)	116 (81.1)	11 (7.7)	115 (80.4)
cUTI	129	109 (84.5)	115 (89.1)	4 (3.1)	115 (89.1)
Treated with daily dose > 16 g[d]	15	11 (73.3)	13 (86.7)	0 (0)	11 (73.3)
Treated with daily dose ≤ 16 g[d]	114	98 (86.0)	102 (89.5)	4 (3.5)	104 (91.2)
Patients treated in monotherapy	47	40 (85.1)	42 (89.4)	2 (4.3)	41 (87.2)
BJI	124	90 (72.6)	99 (79.8)	9 (7.3)	101 (81.5)
Treated with daily dose > 16 g[d]	18	15 (83.3)	15 (83.3)	0 (0)	15 (83.3)
Treated with daily dose ≤ 16 g[d]	106	75 (70.8)	84 (79.2)	9 (8.5)	86 (81.1)
Spondylodiscitis	53	33 (62.3)	40 (75.5)	6 (11.3)	37 (69.8)
PJI	25	21 (84.0)	22 (88.0)	3 (12.0)	23 (92.0)
Long bone osteomyelitis	10	7 (70.0)	7 (70.0)	0 (0)	8 (80.0)
Diabetic foot osteomyelitis	7	4 (57.1)	5 (71.4)	0 (0)	5 (71.4)
Osteomyelitis – other	29	25 (86.2)	25 (86.2)	0 (0)	28 (96.6)
HAP/VAP	79	50 (63.3)	59 (74.7)	8 (10.1)	53 (67.1)
Treated with daily dose > 16 g[d]	24	16 (66.7)	19 (79.2)	2 (8.3)	16 (66.7)
Treated with daily dose ≤ 16 g[d]	55	34 (61.8)	40 (72.7)	6 (10.9)	37 (67.3)
cSSTI	65	49 (75.4)	56 (86.2)	3 (4.6)	51 (78.5)
Treated with daily dose > 16 g[d]	16	14 (87.5)	15 (93.8)	0 (0)	15 (93.8)
Treated with daily dose ≤ 16 g[d]	49	35 (71.4)	41 (83.7)	3 (6.1)	36 (73.5)
BM/CNSI	56	46 (82.1)	52 (92.9)	2 (3.6)	48 (85.7)
Treated with daily dose > 16 g[d]	32	28 (87.5)	30 (93.8)	1 (3.1)	29 (90.6)
Treated with daily dose ≤ 16 g[d]	24	18 (75.0)	22 (91.7)	1 (4.2)	19 (79.2)
IE	46	32 (69.6)	32 (69.6)	2 (4.3)	44 (95.7)
Foreign body involvement	35	24 (68.6)	24 (68.6)	2 (5.7)	34 (97.1)
W/o foreign body involvement	11	8 (72.7)	8 (72.7)	0 (0)	10 (90.9)
With abscess involvement	8	6 (75.0)	6 (75.0)	0 (0)	8 (100)

Table 6 continued

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
Concomitant sepsis/septic shock	21	15 (71.4)	15 (71.4)	1 (4.8)	19 (90.5)
Treated with daily dose > 16 g[d]	10	9 (90.0)	9 (90.0)	0 (0)	10 (100)
Treated with daily dose ≤ 16 g[d]	36	23 (63.9)	23 (63.9)	2 (5.6)	34 (94.4)
Other infections	48	39 (81.3)	44 (91.7)	1 (2.1)	41 (85.4)
Treated with daily dose > 16 g[d]	6	5 (83.3)	5 (83.3)	1 (16.7)	6 (100)
Treated with daily dose ≤ 16 g[d]	42	34 (81.0)	39 (92.9)	0 (0)	35 (83.3)
Subpopulation[d]					
All patients with sepsis/septic shock at baseline	298	211 (70.8)	232 (77.9)	29 (9.7)	235 (78.9)
Immunocompromised patients	163	131 (80.4)	145 (89.0)	10 (6.1)	137 (84.0)
Non-immunocompromised patients	553	408 (73.8)	452 (81.7)	30 (5.4)	453 (81.9)
Patients treated with daily dose > 16 g[d]	147	120 (81.6)	130 (88.4)	4 (2.7)	124 (84.4)
Patients treated with daily dose ≤ 16 g[d]	569	419 (73.6)	467 (82.1)	36 (6.3)	466 (81.9)
Pathogens[a, e, f]					
E. coli	99	78 (78.8)	84 (84.8)	3 (3.0)	83 (83.8)
Enterobacter spp.	30	24 (80.0)	25 (83.3)	2 (6.7)	25 (83.3)
Klebsiella spp.	119	97 (81.5)	108 (90.8)	2 (1.7)	100 (84.0)
Proteus spp.	26	22 (84.6)	25 (96.2)	0 (0)	22 (84.6)
P. aeruginosa	58	45 (77.6)	52 (89.7)	2 (3.4)	47 (81.0)
MRSA	37	27 (73.0)	30 (81.1)	4 (10.8)	32 (86.5)
MSSA	189	141 (74.6)	152 (80.4)	9 (4.8)	163 (86.2)
CoNS	88	69 (78.4)	74 (84.1)	6 (6.8)	77 (87.5)
Enterococcus spp.	54	39 (72.2)	45 (83.3)	4 (7.4)	45 (83.3)
GP pathogens[g]	269	204 (75.8)	223 (82.9)	17 (6.3)	235 (87.4)
GN pathogens[h]	238	192 (80.7)	211 (88.7)	10 (4.2)	198 (83.2)
GP plus GN infections (polybacterial)	86	68 (79.1)	72 (83.7)	3 (3.5)	74 (86.0)
CR pathogens	77	63 (81.8)	68 (88.3)	2 (2.6)	64 (83.1)
MDR pathogens	241	188 (78.0)	204 (84.6)	16 (6.6)	206 (85.5)
Combination partners[a, f]					
Meropenem	146	108 (74.0)	121 (82.9)	11 (7.5)	113 (77.4)
Vancomycin	99	75 (75.8)	85 (85.9)	9 (9.1)	80 (80.8)

Table 6 continued

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
Flucloxacillin	91	64 (70.3)	70 (76.9)	5 (5.5)	75 (82.4)
Piperacillin/tazobactam	93	65 (69.9)	80 (86.0)	3 (3.2)	71 (76.3)
Cefazolin	69	46 (66.7)	51 (73.9)	4 (5.8)	57 (82.6)
Daptomycin	56	43 (76.8)	44 (78.6)	6 (10.7)	51 (91.1)
Ceftazidime/avibactam	50	42 (84.0)	45 (90.0)	0 (0)	43 (86.0)

[a] ± bacteraemia and/or sepsis/septic shock

[b]Overall in-hospital mortality: 10.6% (76/716)

[c]Clinically suspected or microbiologically ensured

[d]Initial targeted daily dose

[e]Without involvement of fungi, viruses, or other non-bacterial microorganisms

[f]Multiple entries possible

[g]Patients presenting with infections caused solely by GP pathogens

[h]Patients presenting with infections caused solely by GN pathogens

BJI bone and joint infection, *BM/CNSI* bacterial meningitis/CNS (central nervous system) infection, *CoNS* coagulase-negative staphylococci, *CR* carbapenem-resistant, *cSSTI* complicated skin and soft tissue infection, *cUTI* complicated urinary tract infection, *GN* gram-negative, *GP* gram-positive, *HAP/VAP* hospital-acquired/ventilator-associated pneumonia, *IE* infective endocarditis, *MDR* multi-drug resistant, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-susceptible *S. aureus*, *EOT* end of IV fosfomycin treatment, *w/o* without, *n* number of patients

Table 7 Clinical and microbiological outcomes in patients with bacteraemia caused by *S. aureus* or CR pathogens at EOT

	Cases, *n*	Clinical success, *n* (%)	Clinical response, *n* (%)	Clinical failure, *n* (%)	Microbiological cure, *n* (%)
Bacteraemia[a]					
S. aureus bacteraemia[b]	125	87 (69.6)	98 (78.4)	7 (5.6)	107 (85.6)
MRSA	22[c]	14 (63.6)	16 (72.7)	4 (18.2)	18 (81.8)
MSSA	105[c]	73 (69.5)	82 (78.1)	3 (2.9)	89 (84.8)
Due to CR pathogens[b]	22[d]	19 (86.4)	21 (95.5)	0 (0)	19 (86.4)

[a]Without involvement of fungi, viruses, or other non-bacterial microorganisms

[b]Patients with allocation of the term "bacteraemia/sepsis" (due to *S. aureus* or CR pathogens) as the applicable kind of infection by the investigator at start of FOS treatment and/or positive blood culture for the respective pathogen in patients allocated to another indication (only monobacterial infections were included)

[c]In-hospital mortality: 16.2% for MSSA bacteraemia cases (17/105) and 18.2% for MRSA bacteraemia cases (4/22), respectively

[d]In-hospital mortality: 9.1% (2/22)

CR carbapenem-resistant, *FOS* intravenous fosfomycin, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-susceptible *S. aureus*, *EOT* end of IV fosfomycin treatment, *n* number of patients

Table 8 Summary of safety analysis

Classification[a]	716 patients *n* (%)
AE (any)[b]	417 (58.2)
Non-serious ADR[c]	243 (33.9)
Serious ADR (SADR)[c]	59 (8.2)
Death[d]	79 (11.0)

[a]Multiple entries possible

[b]Patients with at least one AE or serious AE

[c]Considered as being possibly causally related to FOS treatment

[d]None related to FOS treatment

ADR adverse drug reaction (non-serious), *AE* adverse event, *FOS* intravenous fosfomycin, S*ADR* serious ADR, *SAE* serious AE, *n* number of patients

Table 9 Summary of reported electrolyte imbalances

Electrolyte disorder[a]	716 patients *n* (%)
Hypokalaemia[b, c]	189 (26.4)
Severity per reporter	
Mild	*96 (50.8)*
Moderate	*79 (41.8)*
Severe	*13 (6.9)*
Not reported	*1 (0.5)*
FOS dose not changed	*171 (90.5)*
FOS withdrawn due to ADR	*11 (5.8)*
Hypernatraemia[b, c]	109 (15.2)
Severity per reporter	
Mild	*81 (74.3)*
Moderate	*24 (22.0)*
Severe	*4 (3.7)*
FOS dose not changed	*95 (87.2)*
FOS withdrawn due to ADR	*12 (11.0)*

[a]Multiple entries possible

[b]Including ADRs and SADRs (on patient-level)

[c]Considered as being possibly causally related to FOS treatment

ADR adverse drug reaction (non-serious), *FOS* intravenous fosfomycin, *SADR* serious ADR, *n* number of patients; percentages and numbers in italics are relative to the total number of patients in that category

effectiveness, and safety in 716 patients enrolled from five European countries. Overall, patients included in the present study had a high burden of underlying co-morbidities, particularly cardiac and renal disorders, and generally presented with severe illness. Furthermore, a considerable proportion of patients exhibited a suppressed immune status, and nearly half of all participants were concurrently diagnosed with sepsis or septic shock.

FOS was used across a wide range of indications/infections caused by both GP and GN pathogens, including polybacterial infections, with various types of underlying resistance mechanisms. In line with results from a systematic review, the four main indications were bacteraemia/sepsis, BJI, cUTI, and HAP/VAP [4]. The most common bacteria identified were staphylococci, followed by *Klebsiella* spp., *E. coli*, other Enterobacterales, and *P. aeruginosa*. Infections caused by *Klebsiell*a spp. and *P. aeruginosa* were often associated with carbapenem resistance, while ESBL was the predominant MDR mechanism in *E. coli*. No difference was observed in the rate of methicillin resistance in *S. aureus* and CoNS.

In accordance with published data [4, 44, 45], FOS was primarily used in combination with other antibiotics, often beta-lactam antibiotics, and mainly employed as a second-line treatment option. Notably, a considerable number of patients also received FOS as a first-line therapy and/or empirically, and it was used predominantly in DTR infections, when previous treatment had failed or due to its favourable pharmacokinetic properties. In this context, its use as adjunctive may have also been motivated by its synergistic/additive interactions with many antibiotics and/or its biofilm activity [16, 17, 46]. Differences in local epidemiology and clinical experience with FOS were reflected in the observed country-specific use of the drug, although datasets were more robust for Germany and Italy due to the larger sample size. Similar to

the findings of the study by Putensen et al. [45], patients enrolled from Germany and Austria had infections predominantly caused by GP pathogens (mainly staphylococci). In contrast, and in accordance with the results of a retrospective study, infections in Italy were most frequently due to GN agents, especially *Klebsiella* spp. [44]. In this context, while the median dose of FOS in the current study was 15 g/day, the median doses in Italy and Greece, where FOS was mainly used to treat GN infections, were higher at 16 g/day and 20 g/day, respectively. In line with this, a recent review found that several studies evaluating FOS for the treatment of GN infections reported doses in the range of 16–24 g/day [47].

Overall, clinical success and microbiological cure at EOT was achieved in 75.3% and 82.4%, respectively; in-hospital mortality was 10.6%. Notably, even in patients with sepsis/septic shock at baseline, clinical success and clinical response were reported in 70.8% and 77.9% of patients, respectively, indicating a beneficial role of FOS as adjunctive in the treatment of both GP and GN infections in critically ill patients.

Across all indications, the clinical response rate in the present study was comparable to the results of previous studies [45, 48], but higher than those reported in other real-world studies examining FOS [44, 49–52]. In a prospective study conducted in Germany and Austria, Putensen et al. reported overall clinical success in 81.3% of ICU patients and success rates for infections mainly caused by GP pathogens such as BM/CNSI (89.1%), cSSTI (83.3%), BJI (85.7%), and IE (66.7%) [45], which are comparable to the findings of the present study. Consistent with other studies, FOS was mainly combined with daptomycin or a beta-lactam for the treatment of IE and achieved high rates of microbiological cure in this indication (95.7%) [7, 25, 53, 54]. Considering the substantial number of patients with IE with foreign body involvement and/or concomitant sepsis/septic shock in the FORTRESS patient collective, clinical and microbiological outcomes appear favourable and reinforce the idea that FOS may be particularly beneficial in subpopulations of more severely ill patients with foreign body-associated or deep-seated infections.

Unlike Putensen et al. [45], the majority of other studies have described the effectiveness of FOS in the treatment of infections caused predominantly by CR/MDR GN bacteria [44, 49–52, 55]. Anastasia et al. conducted a retrospective study in Italy and reported a successful clinical outcome in 66% of patients treated with FOS, with CR *K. pneumoniae* being the most frequent causative agent [44]. In comparison, the clinical response rate in patients infected with CR pathogens (77.6% *Klebsiella* spp.) in our study was 88.3%. Possible explanations for the differences in outcomes could be the substantially higher proportion of *Acinetobacter* spp.-related infections and the inclusion of patients with concurrent SARS-CoV-2 infection in the retrospective study, as well as differences in FOS dosing [44]. In bacteraemia caused by CR bacteria (86.4% due to *Klebsiella* spp.), clinical response in our study was 95.5%. In this context, previous studies on CR *K. pneumoniae* bacteraemia reported about 75% success with FOS-containing regimens [2, 51], and the results of two retrospective studies suggest that combination therapy with FOS could reduce mortality in severe GN bloodstream infections [6, 8]. In agreement with published data [2, 44], ceftazidime–avibactam was a frequent combination partner in infections caused by CR Enterobacterales (CRE) in our study. Noteworthy, although CR *A. baumannii* (CRAB) involvement was rare in the present study (i.e., $n = 7$), recent data, particularly from Italy, indicate that IV fosfomycin may be also a valuable agent for the treatment of severe CRAB infections [10, 11, 13, 56]. In this context, in two studies by Russo and colleagues, the combination of cefiderocol plus FOS was associated with survival at day 30 [10, 56].

Another common cause of bacteraemia is *S. aureus*. Clinical success at EOT in patients with MRSA bacteraemia treated with FOS combination therapy in the current study was slightly lower in comparison with MSSA bacteraemia. Two recent RCTs compared the efficacy of FOS-containing regimens to a monotherapy with the respective combination partner in the treatment of MSSA (flucloxacillin plus FOS vs. flucloxacillin) and MRSA bacteraemia (daptomycin plus FOS vs. daptomycin) [7, 57]. Although combination therapy was not significantly better than

monotherapy in terms of respective endpoints in the overall population in these RCTs, both studies demonstrated faster microbiological clearance of the FOS-containing regimens. It is worth noting in this context that results of two clinical studies suggest that mortality and metastatic complications are associated with the duration of bacteraemia [58, 59]. The lack of a significant benefit observed for combination regimens compared to monotherapy in both studies may be attributed to the overall clinical condition and the source of bacteraemia of enrolled patients. In this context, in the SAFO trial, most patients in both arms had a qSOFA score of < 1 at baseline, and a considerable number of bacteraemia cases were catheter-related [57]. Similar baseline characteristics were described by Pujol et al., with most patients having a Pitt score of 1, indicating a relatively moderately ill patient population. However, results of this RCT showed that more severely ill patients (Pitt score > 1) particularly benefited from combination therapy with FOS [7]. Furthermore, results from another study indicated that the focus of bacteraemia may impact clinical outcome, as high-risk sources of bacteraemia (i.e., unknown focus, endocarditis, pneumonia) were associated with higher mortality than catheter-related infections [60]. In the present study, the proportion of high-risk bacteraemia was relatively high. Together with data from a post hoc analysis of an observational study that showed that combination therapy with either rifampicin or FOS was associated with better long-term outcome in *S. aureus* bacteraemia patients with implanted intravascular devices, combination therapy with FOS may be particularly beneficial in more severely ill patients and/or involvement of foreign bodies/deep foci. RCTs are desired to confirm a benefit in these patients.

FOS, albeit predominantly used in combination regimens, showed favourable clinical response and microbiological cure as monotherapy in the treatment of cUTI, in agreement with results from two recent RCTs [14, 15]. Our data support the use of FOS alone in the treatment of cUTI caused by non-CRE, where it could serve as a carbapenem-sparing alternative.

The overall rate of microbiological cure in the present study was 82.4%, which is higher than in other recently published studies on FOS [2, 45, 48–50]. Considering the wide range of indications treated in our study, including difficult-to-reach sites, combination therapy with FOS appears to be beneficial even in infections with a deep focus. As demonstrated in several pharmacokinetic studies, FOS penetrates well into tissues/body sites, including bone, heart tissue, and the CSF [16, 61–64], which may explain its considerable use in this study in patients with IE, BM/CNSI, and BJI (226/716 patients, 31.6%).

Overall, FOS use was generally safe and well tolerated. In line with previous studies, hypokalaemia and hypernatraemia were the most frequent ADRs [3, 45, 49, 51, 57, 65]. In this context, the frequency of hypernatraemia in our study is comparable to the findings of Putensen et al. and Tseng et al. [3, 45], but lower than that described in other studies [50, 65]. Conversely, lower frequencies or even no events were reported in an observational study from Canada and the SAFO trial, respectively [49, 57]. Similarly, the incidence of hypokalaemia in the present study is within the range of previous reports. Importantly, most electrolyte imbalances were mild/moderate and transient, and in only a few patients led to the discontinuation of FOS. Noteworthy, partner antibiotics or co-medications might have also contributed to electrolyte imbalances, as, e.g., the incidence of hypokalaemia associated with beta-lactam use may be as high as 40% [66, 67]. In the current study, FOS was mainly combined with beta-lactams. In addition, hypokalaemia is a common condition in hospitalised patients [68], and one-third of patients in the current study presented with electrolyte imbalances at baseline. It is noteworthy that a prolonged infusion of FOS may reduce the risk of developing hypokalaemia [69]. Despite isolated reports of AHF associated with FOS treatment [7, 15, 54, 69–71], the present study did not identify any related cases of AHF, even in patients treated for IE, where heart failure is usually the most common complication [36].

Consistent with published data [4, 7, 14, 15, 44, 57], resistance development to FOS was rare. In this context, several in vitro studies have demonstrated that FOS-containing combinations suppress re-growth of resistant

subpopulations [72–77]. Notably, even when used as monotherapy, in vivo resistance development appears uncommon, as two recent RCTs did not show any emergence of FOS resistance [14, 15].

The current study has several methodological strengths, including a prospective design, comprehensive on-site training/monitoring, and centralised remote monitoring, which collectively ensure high data quality and integrity. Moreover, the detailed documentation of baseline data thoroughly describes the initial status of the patient collective. This methodological rigor increases the reliability of the results with regards to the effectiveness and safety of FOS. Furthermore, this study was conducted in five European countries and included more than 700 patients, providing a robust dataset that reflects routine clinical practice. Unlike randomised controlled trials, which impose strict eligibility criteria, thereby often representing a less severely ill and somewhat artificial patient collective, this real-world study included a diverse patient population with a wide range of comorbidities and concurrent treatments. FOS was administered according to approved indications and dosing recommendations, ensuring that the results of the study are generally applicable to patients eligible for FOS use in clinical practice across Europe.

Limitations of the study include its non-comparative nature, which prevents a direct comparison with other treatment regimens. Second, the co-administration of other antibiotics may serve as a confounding factor, particularly concerning the interpretation of safety data. A further limitation of the present study is that the management of electrolyte imbalances was not systematically documented. However, for example, the treatment of hypokalaemia in clinical practice commonly involves potassium supplementation. In this context, attending physicians in the SAFO trial were advised to use supplementary potassium (and furosemide) as a preventive measure in patients receiving the combination of flucloxacillin plus FOS, resulting in similar rates of hypokalaemia between the two study arms [57]. Moreover, as there was no systematic inclusion of all patients receiving FOS at the study sites, a selection bias cannot be ruled out and should be considered, particularly when interpreting the mortality outcomes. Another limitation is the lack of data on whether the infection was hospital-acquired or community-acquired. However, given that a considerable proportion of isolates exhibited MDR, and that most patients had been treated for another infection prior to FOS therapy, it can be speculated that the majority of infections were of nosocomial origin. Lastly, our study provides limited information on the genetic background of mechanisms conferring resistance to carbapenems and other antibiotics.

CONCLUSION

FORTRESS provides important real-world data on the treatment patterns, patient characteristics, effectiveness, and safety of FOS from clinical practice in Europe, also highlighting notable country-specific differences in its use. In the present study, FOS was primarily used in combination therapy, both targeted and empirically, across a wide range of different infections caused by GP and GN pathogens, with overall favourable clinical and microbiological outcomes, even in deep-seated and/or difficult-to-treat infections and independent of underlying resistance mechanisms. Electrolyte imbalances were the most common ADRs observed. However, most of these were mild to moderate and not treatment-limiting. In conclusion, our data might help to improve antibiotic treatment of severely ill patients and to identify patients who would benefit most from FOS-containing regimens.

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Data Availability. The data sets generated and/or analysed during the current study are not publicly available due to InfectoPharm's internal policies. InfectoPharm will provide access to related study documents upon reasonable request from qualified researchers, and subject to certain criteria, conditions, and exceptions.

Declarations

Conflict of Interest. Klaus-Friedrich Bodmann has received honoraria from Shionogi, Advanz Pharma, Gilead, Roche, Eli Lilly, and InfectoPharm. Stefan Hagel has received honoraria from Pfizer, MSD, InfectoPharm, Philips, Advanz Pharma, Beckman Coulter, Shionogi, Thermo Fisher, and Tillots. He also participated in advisory boards for Advanz Pharma, Shionogi, and Pfizer. Alessandra Oliva has received honoraria from Advanz Pharma, MSD, InfectoPharm, and Pfizer. She also participated in advisory boards for Advanz Pharma. Stefan Kluge received research support from Cytosorbents and Daiichi Sankyo. He also received lecture fees from ADVITOS, Biotest, CSL Behring, Daiichi Sankyo, Fresenius Medical Care, Gilead, Mitsubishi Tanabe Pharma, MSD, Pfizer, Shionogi, and Zoll. He received consultant fees from ADVITOS, AstraZeneca, Fresenius, Gilead, MSD, and Pfizer. Alessandra Mularoni has received honoraria from Pfizer, Gilead, and Takeda and participated in advisory boards for Takeda and MSD. Marco Falcone received honoraria from Pfizer, Menarini, Gilead, GSK, and Thermo Fisher. Mathias W. Pletz has received honoraria from Pfizer, MSD, Sanofi, Janssen, GSK, AstraZeneca, InfectoPharm, and Shionogi. Jan T. Kielstein received speaker fees from Fresenius Medical Care, BAXTER, and DiaMed. Carlo Tascini has received honoraria from Angelini, InfectoPharm, Menarini, Correvio, Merck, Viatris, Pfizer, Thermo Fisher, Diasorin, and Biomérieux. He also participated in advisory boards for Pfizer, Viatris, and Thermo Fisher. Claudia

Spies participated in advisory boards for Takeda and Lynx Health Science. Alessandra Bandera has received honoraria from AstraZeneca, Biomérieux, Qiagen, Janssen-Cilag, and Nordic Pharma. She has also participated in advisory boards for Viiv Healthcare, Sobi, Gilead, and Angelini Pharma. Matthias G. Vossen received consulting fees and honoraria for educational talks from Astro Pharma. Abhijit M. Bal is an investigator in the UKAR trial and PROVE trial. Thomas Borrmann and Christian Mayer are employees of InfectoPharm, Heppenheim, Germany. Valentina Galfo, Simone Lindau, Nadja Käding, Michael Zoller, Sebastian Kintrup, Dirk Schädler, Francesco G. De Rosa, Szilvia Radnoti, Roberto Luzzati, Sam Allen, Loredana Sarmati, Antonio Cascio, Nikolaos Kapravelos, Chinari P. K. Subudhi, George Dimopoulos, Mario Venditti, and Claudio M. Mastroianni have nothing to declare.

Ethical Approval. The study was conducted in accordance with the Helsinki Declaration of 1964 (and its amendments) and was approved by all ethics committees or other authorities according to national/local requirements (Supplementary Table S13). Written informed consent was obtained from each patient or the patient's legally acceptable representative before any study-specific activity was performed. In Austria, an informed consent waiver was approved for patients who were incapacitated.

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