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Original Article

Susceptibility of carbapenem-resistant *Klebsiella pneumoniae* in urinary tract infections: clinical efficacy of fosfomycin

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Abstract

Introduction: The increasing prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CR-*Kp*) limits effective treatment options. The aim of this study was to evaluate the susceptibility patterns of CR-*Kp* strains isolated from urine cultures to oral treatment options recommended by the Infectious Diseases Society of America guidelines, and ceftazidime-avibactam. Additionally, clinical data and outcomes of patients diagnosed with CR-*Kp* urinary tract infections (UTI) who were treated with fosfomycin sodium-including therapy regimens (FSITR) were analyzed.

Methodology: This retrospective cohort study included adult patients with urine culture-proven CR-*Kp* between March 2016 and October 2022. Demographic and clinical data, antibiotic susceptibility, treatment outcomes, and one-month mortality (OMM) were evaluated.

Results: A total of 179 patients were included. The susceptibility to fosfomycin tromethamol, nitrofurantoin, and co-trimoxazole (TMP-SMX) were (33.7%; 55/163), (7.7%; 13/167), and (11.1%; 20/179), respectively. All strains were resistant to ciprofloxacin. The susceptibility data compared until 2020 (pre-COVID-19) and afterwards, revealed TMP-SMX susceptibility (4.9% vs 24.1%, $p = 0.0001$) increased significantly. Susceptibility data for ceftazidime-avibactam were available for 22 isolates and 59% of the isolates were sensitive. OMM of the 179 patients with CR-*Kp* in urine cultures was 37.4% (67/179). There were 9 FSITR cases. Among those, microbiological eradication was achieved in 87.5% (7/8) and OMM was 44.4% (4/9).

Conclusions: Clinical experience may be feasible and needed to assess the efficacy of nitrofurantoin and TMP-SMX. Fosfomycin-including regimens may serve as a salvage treatment option for CR-*Kp* UTI in selected patients. However, the retrospective and single-center design of the study should be considered as a limitation.

Key words: carbapenem; resistance; antibiotherapy; urinary tract; Enterobacteriaceae.

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Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections in terms of both community-acquired and healthcare-associated infections. Gram-negative bacteria, specifically Enterobacterales, are common causes of UTIs [1]. The concerning escalation in drug resistance has led to an increase in the need for alternative treatments due to cost and side effects [1,2].

In 2019, approximately 1.3 million deaths were directly caused by antimicrobial-resistant bacterial pathogens worldwide [2]. The increasing prevalence of carbapenem-resistance among Enterobacterales (CRE) limits effective treatment options and poses challenges

for appropriate antimicrobial treatment. Clinicians face many difficulties in treatment due to the resistance profile of CRE. The latest Infectious Diseases Society of America (IDSA) guidelines suggest nitrofurantoin, co-trimoxazole (TMP-SMX), ciprofloxacin, or levofloxacin for uncomplicated cystitis caused by CRE. However, oral fosfomycin is suggested as an alternative treatment option only for *E. coli* [3]. In contrast, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend the use of old antibiotics that have shown *in vitro* susceptibility for treating uncomplicated UTIs [4]. However, both guidelines highlight the limitations and uncertainties in treating CRE-related UTIs, particularly when oral treatment options are limited or ineffective. This underscores the need for real-life clinical data on alternative options such as intravenous fosfomycin sodium, especially in settings with relatively restricted access to novel antimicrobials.

Although there is growing evidence on the use of oral fosfomycin for UTIs, data regarding the use of intravenous fosfomycin sodium—particularly for CR-*Kp* UTIs—remain limited, especially in settings with restricted access to novel antimicrobials. Nitrofurantoin and fosfomycin may serve as alternative treatments to double-carbapenem or colistin-based therapies for UTIs caused by CRE; although the availability, reimbursement, and susceptibility to any of these agents may vary from country to country. Aminoglycosides, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are preferred treatment options for pyelonephritis and UTIs caused by CRE [3,4]. This study aimed to evaluate the susceptibility of CR-*Kp* strains isolated from urine cultures to oral fosfomycin, TMP-SMX, ciprofloxacin, nitrofurantoin, and ceftazidime-avibactam. Furthermore, the clinical outcomes of patients who received fosfomycin sodium including therapy due to CR-*Kp* UTI were evaluated to assess the effectiveness of intravenous fosfomycin sodium in a real-life cohort with limited treatment alternatives.

Methodology

This retrospective cohort study was conducted according to the strengthening the reporting of observational studies in epidemiology (STROBE) criteria [5]. The hospital records of patients who were consulted by the infectious diseases and clinical microbiology consultants (IDCMC) during night shifts, and had carbapenem-resistant *Klebsiella pneumoniae* (CR-*Kp*) growth in urine cultures between March 2016 and October 2022, were reviewed retrospectively. Demographic features; comorbidities; bacterial etiology in urine cultures; and susceptibility to oral fosfomycin, TMP-SMX, ciprofloxacin, nitrofurantoin and ceftazidime-avibactam were evaluated. In case of multiple UTI episodes, only the first UTI episode fulfilling the study inclusion criteria, was included in the study.

Bacterial identification was performed with matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF MS, bioMerieux, Marcy-I'Étoile, France); antibiotic susceptibility tests for ciprofloxacin, TMP-SMX; nitrofurantoin, and fosfomycin were performed by the VITEK2 system (bioMerieux, Marcy-I'Étoile, France); and the ceftazidime-avibactam sensitivity test was performed by disc diffusion test (Oxoid, Basingstoke, England). The ceftazidime-avibactam sensitivity data were available only for samples collected after February 2021, as reimbursement for the drug was approved in Turkey at that time, and sensitivity testing was conducted starting from that period in the hospital. All antibiotic susceptibility data were evaluated according to the European Committee on Antimicrobial Testing (EUCAST) criteria [6]. The version 5 criteria for nitrofurantoin after 2015 and the version 10 criteria for fosfomycin tromethamol after 2020 were used since related susceptibility breakpoints were not available in the versions thereafter.

The data and outcomes of all adult (aged > 18 years) patients with urine culture-proven CR-*Kp* UTI and treated with intravenous fosfomycin sodium including therapy after consultations by the IDCMC in night shifts between March 2016–October 2022 were extracted for evaluation of the clinical efficacy of fosfomycin sodium. Demographic, clinical, and laboratory findings, as well as information on the response to treatment and outcomes were obtained retrospectively. Cases aged < 18 years were excluded.

The diagnosis of UTI was based on the isolation of CR-*Kp* in at least one urine culture, and having laboratory findings and clinical symptoms of UTI. Lower UTI was classified as symptoms including increased frequency, urgency, hematuria, or suprapubic pain. Upper UTI was defined with the presence of fever, flank pain, nausea, or vomiting, along with systemic infection indicators such as leukocytosis and elevated acute phase reactants [7].

All-cause mortality during the one-month period (OMM) was defined as death from any cause within 30 days following the start of intravenous fosfomycin sodium including therapy. Relapse was defined as a documented infection in the same patient during the 30

day follow up after the end of fosfomycin sodium including treatment, and reinfection was defined as a documented infection with a different microorganism in urine culture within the same 30 day follow up period.

All the clinical and laboratory data were reconfirmed by the authors to ensure consistency in retrospective data extraction.

Statistical analyses, including the Chi square test for categorical variables, were performed with the IBM Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp, Armonk, NY, USA).

The study was approved by the local institutional review board (approval no: 2023-042-423-3T34, 9 March 2023).

Results

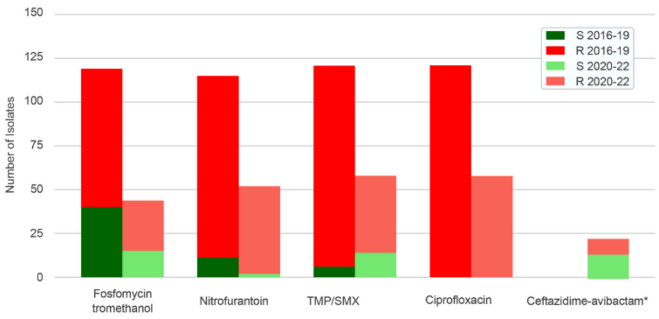
General characteristics of the cohort

Antimicrobial susceptibility data for 179 CR-*Kp* strains from 179 patients (77 (43%) females and 102 (57%) males) were included in the study. The mean age was 62.68 ± 16.33 years (range: 18–90). Of these, 116 patients (64.8%) had comorbidities, including diabetes mellitus (n = 59), hypertension (n = 67), cardiovascular disease (n = 33), or chronic renal failure (n = 34). Additionally, 149 patients (83.2%) had a history of antibiotic use within the last month. All patients had urinary catheters in place.

Antibiotic susceptibility data

Susceptibility data for fosfomycin tromethamol and nitrofurantoin were obtained for 163 and 167 strains, respectively. Susceptibility data for TMP-SMX and ciprofloxacin were available for all 179 patients. Fosfomycin tromethanol susceptibility was 33.7% (55/163), nitrofurantoin susceptibility was 7.7% (13/167), and TMP-SMX susceptibility was 11.1% (20/179). No ciprofloxacin-sensitive isolates were found (0/179). Ceftazidime-avibactam sensitivity data were available for 22 strains, and 59% (13/22) were sensitive to ceftazidime-avibactam.

Figure 1. Overall susceptibility data of the study isolates



*Ceftazidime-avibactam susceptibility data were available from 2021; **Detailed susceptibility percentages and statistical analyses are described in the results section. TMP/SMX: trimethoprim-sulfamethoxazole; S: sensitivity; R: resistant.

When the susceptibility data until 2020 (pre-coronavirus disease 2019, COVID-19) was compared with the data after 2020 (post-COVID-19), fosfomycin tromethanol (33.6% vs. 34%, p = 0.954) and ciprofloxacin (100% vs. 100%, p = 1) susceptibility were stable, nitrofurantoin susceptibility (9.5% vs. 3.8% p = 0.201) decreased non-significantly, and TMP-SMX susceptibility (4.9% vs. 24.1%, p = 0.0001) increased significantly. The overall susceptibility data are presented in Figure 1.

Evaluation of susceptibility data based on ceftazidime-avibactam susceptibility

Among the isolates that were susceptible to ceftazidime-avibactam (n = 13), the resistance rates to fosfomycin, nitrofurantoin, TMP-SMX, and ciprofloxacin were 60% (3/5), 100% (10/10), 69.2% (9/13), and 100% (13/13), respectively. Among the isolates resistant to ceftazidime-avibactam (n = 9), the same resistance rates were 87.5% (7/8), 100% (9/9), 55.5% (5/9), and 100% (9/9), respectively (p > 0.05). No statistically significant differences were found in susceptibility to other oral antibiotics between ceftazidime-avibactam susceptible and resistant isolates.

Mortality

All-cause OMM rate among the 179 patients with CR-*Kp* in urine cultures was 37.4% (67/179).

Clinical efficacy of fosfomycin sodium

Intravenous fosfomycin sodium was administered to 9 patients (5 females, mean age 56.8 ± 19 years, range 23–84), 78% (7/9) of whom required intensive care unit (ICU) monitoring. All the patients met the criteria for upper UTI and received fosfomycin sodium as part of a salvage therapy regimen. Eight patients (89%) had an additional infectious focus besides UTI (Tables 1 and 2). All the patients had recent antibiotic use within 3 days prior to treatment.

Fosfomycin tromethamol susceptibility was observed in 66.6% (6/9) of patients (susceptibility and minimum inhibitory concentration (MIC) values are presented in Table 3). Blood cultures were performed in 77.8% (7/9) of cases, and no bacteremia was detected. Ceftazidime-avibactam susceptibility was tested i n 5/9 patients, and 2 were found susceptible.

All the patients received combination therapy, primarily including fosfomycin sodium and

Table 1. Susceptibility data of infecting strains and underlying diseases of the CR-*Kp* UTI cases who received fosfomycin sodium regimens. Clinical characteristics, underlying diseases, and infection details of CR-*Kp* UTI cases treated with fosfomycin sodium regimens. Patient demographics, comorbidities, urine culture results, AST, coinfections, ICU admission status, and other relevant clinical data are summarized.

Case	Gender/Ag	Comorbidities	Bacteria in urine	Antibacterials found to be	Coinfections	ICU
1	F/50	Diabetes mellitus, hypertension	*K. pneumoniae*	None	Nosocomial pneumonia (*A. baumannii*), cerebral toxoplasmosis	Yes
2	M/75	Diabetes mellitus, hypertension	*K. pneumoniae*	Fosfomycin, TMP-SMX, amikacin	Nosocomial pneumonia (*K. pneumoniae*)	Yes
3	F/68	Diabetes mellitus	*K. pneumoniae*	None	Shunt infection (*K. pneumoniae* + *E. faecalis*)	Yes
4	F/36	No comorbidities	*K. pneumoniae*	Meropenem, ceftazidime-avibactam	No coinfection	No
5	M/52	Diabetes mellitus, hypertension, HIV	*K. pneumoniae*	Fosfomycin	COVID-19 pneumonia, stage 4 decubitus ulcer	Yes
6	F/23	Amyloidosis, epidermolysis bullosa, chronic renal failure	*K. pneumoniae*	TMP-SMX	Nosocomial pneumonia	Yes
7	M/57	Diabetes mellitus, lung cancer	*K. pneumoniae*	Fosfomycin, ceftazidime-avibactam, TMP-SMX	COVID-19 pneumonia + nosocomial pneumonia (*E. cloacae*)	No
8	M/67	Diabetes mellitus, hypertension	*K. pneumoniae*	Fosfomycin	Nosocomial meningitis (*S. hominis*)	Yes
9	F/84	Diabetes mellitus, hypertension	*K. pneumoniae*	Fosfomycin	Nosocomial pneumonia	Yes

AST: antimicrobial susceptibility testing; CR-*Kp*: carbapenem-resistant *Klebsiella pneumoniae*; F: female; M: male; HIV: human immunodeficiency virus; ICU: intensive care unit; TMP-SMX: trimethoprim-sulfamethoxazole; UTI: urinary tract infection. *K. pneumoniae: Klebsiella* pneumoniae *A. baumannii: Acinetobacter baumannii; E. faecalis: Enterococcus faecalis; S. hominis: Staphylococcus hominis.*

meropenem (88.9%, details in Tables 1 and 2). The mean duration of fosfomycin therapy was 10.7 ± 4.29 (5–17) days.

Microbiological response

Urine culture results on days 3–5 were available for 6 patients (66.6%), and microbiological eradication was achieved in 83% (5/6). In the subgroup of fosfomycin-sensitive isolates, eradication was achieved in 100% (5/5) within 3–5 days. One resistant isolate did not achieve eradication in this timeframe, and the patient's regimen was revised to meropenem and ertapenem including double-carbapenem therapy. Follow-up was unavailable for two other resistant isolates.

At the end of treatment, 87.5% (7/8) of patients with follow-up urine cultures achieved microbiological eradication. One patient died on day 7 without a follow-up urine culture. Among the patients with fosfomycin-resistant isolates, 66.6% (2/3) achieved eradication. All the patients with fosfomycin-sensitive isolates (5/5) achieved eradication. Three patients were receiving vasopressor support when the fosfomycin sodium

Table 2. Treatment details and outcome of the CR-Kp UTI cases who received fosfomycin sodium including regimens.

Case No	Treatment and duration of fosfomycin* including therapy	Day 3–5 urine microbiologic response	Antibiotic modification during follow-up	End of treatment urine culture result	One month follow up result	Vasopressor support during the start of fosfomycin including therapy
1	TMP-SMX + Tigecycline+ Meropenem + Fosfomycin (14 days)	No data available	No	Bacterial eradication	Survived No relapse/reinfection	No
2	Meropenem + Ertapenem+ Fosfomycin (8 days)	Bacterial eradication	No	Bacterial eradication	Survived No relapse/reinfection	No
3	Meropenem + Ertapenem+ Colistin + Fosfomycin (14 days)	No data available	No	Bacterial eradication	Survived Reinfection due to *C. glabrata*	Simultaneously with fosfomycin including therapy
4	Meropenem + Fosfomycin (14 days)	*K. pneumoniae*	Meropenem + Ertapenem	Bacterial eradication after meropenem-ertapenem	Survived Relapse	No
5	Meropenem + Fosfomycin (5 days)	No data available	No	No data	Exitus on day 7 of treatment due to COVID-19	Fosfomycin including therapy was started on the 5th day of
6	Polymyxin B + Fosfomycin (11 days)	Bacterial eradication	No	Bacterial eradication	Exitus on day 11 of treatment due to pneumosepsis	After 10 days of fosfomycin including therapy
7	Meropenem + Colistin+ Fosfomycin (5 days)	Bacterial eradication	No	Bacterial eradication	Exitus on day 5 of treatment due to COVID-19	No
8	Meropenem + Colistin+ Fosfomycin (17 days)	Bacterial eradication	No	Bacterial eradication	Exitus on day 16 of treatment due to nosocomial meningitis	Fosfomycin including therapy was started on the 5th day of
9	Meropenem + Ertapenem+ Fosfomycin (9 days)	Bacterial eradication	No	Bacterial eradication	Survived No relapse/reinfection	No

Treatment regimens including fosfomycin sodium, microbiological responses during treatment, antibiotic modifications, urine culture results at the end of therapy, one-month follow-up outcomes, and vasopressor support status in CR-Kp UTI patients. * Fosfomycin was administered intravenously at a dose of 3 × 4 g to all patients. Dose adjustment was performed in cases of impaired renal clearance.** MIC values of fosfomycin tromethamol and meropenem in AST are shown in Table 3. COVID-19: coronavirus disease 2019; CR-*Kp*: carbapenem-resistant *Klebsiella pneumoniae*; TMP-SMX: trimethoprim-sulfamethoxazole; UTI: urinary tract infection; MIC: minimum inhibitory concentration.

including treatment was initiated, and 1 patient required vasopressor therapy on the 10th day of fosfomycin sodium including treatment.

One-month mortality

The overall OMM was 44.4% (4/9), with a mean time to death of 9.75 days (on day 7, 11, 5 and 16). All the isolates from these 4 patients were sensitive to fosfomycin tromethamol. Notably, no deaths occurred among those with fosfomycin-resistant isolates, whereas 66.6% (4/6) of patients with susceptible isolates died. Among those with susceptible isolates, OMM was 75% (3/4) for those requiring vasopressor support at the start or during treatment.

All cases except one had at least one comorbidity. While 4 of 8 cases who had at least one comorbidity expired during 1-month follow up, the case who had no comorbidity did not have OMM (4/8 vs. 0/1). Notably, fosfomycin sodium including therapy was revised in the case without comorbidity which referred to clinical failure.

OMM was 40% (2/5) among patients with control urine culture data available on days 3–5 and confirmed microbiological eradication. One patient whose culture persisted bacterial yield survived.

Two of the 9 patients were monitored in wards (not in the ICU) and OMM was 50% among them (1/2). On the other hand, OMM was 42.8% (3/7) among the ICU cases.

Discussion

UTIs are among the most common infectious diseases that lead to antibiotic use [3]. Carbapenem resistance among Gram-negative bacteria, including *K. pneumoniae*, is evolving in many parts of the world [3,8]. It is essential to be aware of the local antimicrobial susceptibility data when selecting antibiotics to treat anticipated CRE infections empirically. Treatment of carbapenem-resistant bacteria is more expensive, carries a higher risk of adverse effects, and may require a longer treatment duration. Therefore, morbidity and mortality rates are higher, and treatment success is lower [3,8].

The World Health Organization issued a list of antibiotic-resistant bacteria in 2017 which placed CRE in the critical priority group, indicating an urgent need for the development of new antibiotics [8].

According to the latest IDSA guidelines, nitrofurantoin, TMP-SMX, ciprofloxacin, or levofloxacin are the preferred treatment options for uncomplicated cystitis caused by CRE, although the likelihood of susceptibility to these agents is low.

Table 3. MIC (mg/L) values of fosfomycin tromethamol and meropenem.

Case No.	Fosfomycin tromethamol	Meropenem
1	R (MIC ≥ 256)	R (MIC ≥ 16)
2	S (MIC ≤ 16)	R (MIC ≥ 16)
3	R (MIC ≥ 256)	R (MIC ≥ 16)
4	R (MIC ≥ 256)	R (MIC 32)
5	S (MIC 32)	R (MIC ≥ 16)
6	S (MIC 32)	R (MIC 32)
7	S (MIC 32)	R (MIC 32)
8	S (MIC 32)	R (MIC ≥ 16)
9	S (MIC 32)	R (MIC ≥ 16)

MIC values (mg/L) of fosfomycin tromethamol and meropenem for CR-*Kp* isolates from UTI patients. Isolates are categorized as resistant (R) or susceptible (S) based on MIC breakpoints. CR-*Kp:* carbapenem-resistant *Klebsiella pneumonia*; MIC: minimum inhibitory concentration; UTI: urinary tract infection.

Alternative treatment options for uncomplicated cystitis caused by CRE include aminoglycoside, oral fosfomycin (for *E. coli* only), colistin, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol. TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis and complicated urinary tract infections (cUTI) caused by CRE, if susceptibility is demonstrated. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol are also preferred treatment options for pyelonephritis and cUTIs. Aminoglycosides are alternative treatment options [3]. However, oral fosfomycin is not suggested for pyelonephritis due to poor oral bioavailability [9]. A study conducted in Turkey by Onal *et al*. reported that combination therapy, carbapenem long-lasting infusion, and double carbapenem therapies resulted in higher microbiologic eradication rates in UTIs caused by CRE [10]. Intravenous fosfomycin may also be used for pyelonephritis. Therefore, the susceptibility patterns of the four oral treatment options and ceftazidime-avibactam were evaluated in the CR-*Kp* UTI cohort.

Data on fosfomycin susceptibility in CRE are scarce, and even more so among CR-*Kp*. A study by Patel *et al*. in 2017 found that 72.34% (34/47) of isolates in the CRE subgroup were susceptible to fosfomycin [11]. The susceptibility rate was higher in extended-spectrum beta-lactamase (ESBL) producing isolates subgroup (92%). Additionally, another study found that 82.6% of the isolates were susceptible to fosfomycin, although this study also included *E. coli* [12]. The present study focused solely on CR-*Kp* and only 33.7% of the study isolates were found to be susceptible to fosfomycin. Kandemir *et al.* conducted a study in Turkey and reported that 23 out of 52 CR-*Kp* strains were resistant to fosfomycin in 2021 [13]. According to another study from Turkey, the

susceptibility of fosfomycin in CR-*Kp* was 61.8%, which contrasts with the findings of this study [14]. The primary reason for the decrease in susceptibility rate is likely to be the inclusion of only CR-*Kp* isolates in this study.

Only 7.7% of the isolates in this study were susceptible to nitrofurantoin. Data on nitrofurantoin susceptibility among CR-*Kp* are quite limited. Although there are few studies on nitrofurantoin susceptibility in CRE or CR-*Kp*, several studies have been conducted on multidrug-resistant (MDR) or ESBL-producing *E. coli*, which have yielded varying results regarding susceptibility [15]. Shanmugam *et al.* reported 51% susceptibility to nitrofurantoin among CR *E. coli* [16]. For instance, a study in China analyzed 242 CRE strains, and, similar to the findings of this study, they found that 92% of the isolates were resistant to nitrofurantoin [17].

In the present study, only 11.1% of the isolates were susceptible to TMP-SMX. A study by Luterbach *et al*. reported a susceptibility rate of 29% for their CRE isolates [18]. Another study conducted in 2021 found that 24.6% of CRE isolates were susceptible to TMP-SMX [19]. In the present study, the sensitivity rate for isolates collected after 2020 was 24.1%. The increase in TMP-SMX susceptibility was statistically significant. The potential decrease in hospital admissions and reduced use of cotrimoxazole during the COVID-19 period might have contributed to the observed increase in sensitivity. Additionally, the limited use of TMP-SMX at the hospital could also be a factor in this heightened sensitivity. However, it is worth noting that all isolates in this study were found to be resistant to ciprofloxacin. A study by Zhan *et al.* reported a resistance rate of 78.5% for ciprofloxacin in their isolates [20].

The IDSA guidelines recommend ceftazidime-avibactam as one of the first-line treatment options for CR-*Kp*. In a study conducted at our hospital, it was found that 73.5% of all CR-*Kp* isolates were sensitive to ceftazidime-avibactam [21]. The present study also showed that 59% of the CR-*Kp* isolates were sensitive to ceftazidime-avibactam. Ceftazidime-avibactam reimbursement was approved for use in Turkey at the end of 2019, but only for ICU cases. Therefore, susceptibility data have been available only since then, resulting in limited data. Notably, aztreonam, meropenem-vaborbactam, imipenem-relebactam or cefiderecol have never been available in Turkey.

As mentioned above, there are several studies in the literature related to the *in vitro* activity of fosfomycin against MDR urinary pathogens. Nevertheless, there is a paucity of clinical data regarding its clinical activity in CR-*Kp* UTI. In the case of non-availability of new beta lactam-beta lactamase inhibitors such as in our center, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend fosfomycin in combination therapy based on the susceptibility pattern of the isolate [4]. Similarly, López-Montesinos and Horcajada, in their narrative review, emphasize the promising role of both oral and intravenous fosfomycin in the management of complicated UTI, while underlining the necessity for further randomized clinical trials to support its routine use [22]. Los-Arcos *et al.* reported that lower UTI caused by resistant Gram-negative pathogens, including CRE, respond well to an oral fosfomycin tromethamine regimen of 3 g every 48–72 hours for varying durations [23]. Another study on oral fosfomycin found treatment success rates of 38% for CRE and 55% for MDR strains [24]. Favorable clinical and microbiological outcomes were observed in 55% of patients in approximately 60 cases of CRE infection, mostly in ICU, treated with a combination of antibiotics, including fosfomycin disodium [25]. Babiker *et al*. reported that 14 patients with CR-*Kp* UTI caused by MDR pathogens were treated with fosfomycin, achieving an 80% microbiological and 94% clinical cure rate on day 14 [26]. In the present study, all cases had complicated upper UTI and received intravenous fosfomycin rather than oral fosfomycin. A retrospective study conducted by Neuner *et al*., reported overall microbiological cure rate of 59% among 41 patients who received fosfomycin treatment for UTIs caused by MDR pathogens. The study reported a microbiological response rate of 46% (6/13) for CR-*Kp* [27]. On the other hand, Pullukcu *et al*. studied lower UTIs caused by extended-spectrum beta-lactamase-producing *E. coli*, and observed a microbiological success rate of 78.5% (49/52) with oral fosfomycin treatment [28]. The present study specifically focused on CR-*Kp* isolates, and no case received fosfomycin sodium monotherapy. However, fosfomycin sodium including regimens resulted in 88% microbiological eradication. The relatively high microbiological eradication rate observed in this study may be attributed to the administration of fosfomycin sodium in combination with other antibiotics, rather than its use as a monotherapy. Overall, OMM was 44% (4/9) corresponding to 56% survival or favorable outcome, which are compatible with the previously published data. The relatively increased OMM may be associated with co-infections such as meningitis and COVID-19, as well as the high number of patients in our cohort (4/9;

44.4%) who required vasopressors and met the criteria for septic shock. Önal *et al.* also reported that despite early diagnosis and effective treatment, mortality rates were quite high in CRE infected patients with septic shock [29]. Compatible with previous reports, 75% of these vasopressor-dependent cases had 30-day mortality. Clinical outcomes appeared to be influenced by coexisting conditions such as coinfections and the need for vasopressor support. Notably, 89% of patients had an additional infectious focus beyond the urinary tract, and 44.4% (4/9) required vasopressor therapy during the treatment period. OMM rates among patients in the ward and ICU were 50% (1/2) and 42.8% (3/7), respectively. The absence of a significant difference is attributed to the limited number of subjects. On the other hand, the OMM rate reached 75% (3/4) among those with vasopressor support at the initiation or during therapy. This suggests that hemodynamic instability and severe systemic infection may worsen outcomes even when microbiological eradication is achieved.

The number of studies in the literature providing mortality data for patients with CR-*Kp* is limited. In the present study, 37.4% (67/179) of the patients died within 30 days follow-up after the urine culture positivity.

This study has several limitations, including the use of single-center data and a retrospective design, as well as the relatively low number of fosfomycin sodium including regimen receiving cases. In addition, data such as ceftazidime-avibactam susceptibility before 2021 was lacking. This inherently limits the generalizability of the findings, as well as the ability of the study to control for confounding variables. Additionally, treatment decisions and timing were not standardized, as they were based on the clinicians' judgement and available antibiotics at the time of care, which may affect the consistency and generalizability of the results. Intravenous fosfomycin sodium is predominantly used in the hospital as a salvage therapy, and therefore, most patients in this study met the criteria for septic shock. This might have led to selection bias. Besides, the majority of the patients included in the study were evaluated and treated under night shift conditions, which might also have introduced bias, as only sicker, acutely deteriorating patients were assessed and the cases seen during standard working hours were not included. Outcomes of fosfomycin sodium including combination treatments may be attributed not solely to the fosfomycin sodium, but also to the additional antibiotics incorporated in the regimen. Additionally, the clinical outcomes or molecular epidemiology could not be analyzed. Susceptibility data could be obtained only via VITEK, and not for all antibiotics, which restricts the ability to determine the clonal relationships between isolates and to elucidate the underlying resistance mechanisms, particularly in cases with fosfomycin resistance. Another critical limitation was that fosfomycin tromethamol susceptibility data were available while fosfomycin sodium susceptibility data were unavailable. Mortality analysis was performed on 30-day all-cause mortality. No autopsies were performed on any of the cases. Susceptibility data of all analyzed antibiotics were not available for all strains. However, one of the strengths of this study is that it provides a rare dataset specifically focused on the oral options for CR-*Kp* UTI from Turkey as well as the world and one of the rare datasets related to the efficacy of intravenous fosfomycin in CR-*Kp* UTI.

Conclusions

Clinical experience may be feasible and needed to see the efficacy of nitrofurantoin and TMP-SMX. Fosfomycin sodium including regimens may be used at least as a salvage treatment option for CR-*Kp* UTI in selected patients. Future research should focus on evaluating the efficacy of intravenous fosfomycin sodium in combination regimens compared to monotherapy, particularly in critically ill patients with MDR infections, to better define its optimal role in salvage therapy. In order to advance the understanding and treatment of CR-*Kp* UTIs, future research should focus on multicenter investigations employing comparative effectiveness designs, detailed molecular characterization of resistance, and pharmacokinetic/pharmacodynamic evaluations, with the goal of refining fosfomycin's role within combination therapies and optimizing clinical outcomes. Conducting well-designed multi-center clinical studies to analyze the efficacy of oral and intravenous fosfomycin, nitrofurantoin, and TMP-SMX in treating CR-*Kp* UTIs in a clinical setting is recommended.

Authors' contributions

All the authors declare that they have participated in the design, execution, and analysis of the research, and approve the final version of the manuscript.

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Conflict of interest

No conflict of interest is declared.

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