# ORIGINAL PAPER

Infectious diseases

# CLINICAL PRACTICE WILEY

# Daily inpatient ertapenem therapy can be an alternative to hospitalization for the treatment of complicated urinary tract infections during the COVID-19 pandemic

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#### Abstract

**Background:** Physicians hospitalize the patients with complicated urinary tract infections (cUTIs) when they need intravenous antibiotics and outpatient parenteral antimicrobial therapy (OPAT) is unavailable. Daily inpatient antimicrobial therapy is an alternative to hospitalization, which is similar to OPAT; patients go home after they are administered antibiotics in a separate room in the hospital setting.

**Objectives:** We assessed our previous daily inpatient practice to revitalize the model in the COVID-19 era.

**Materials and Methods:** We retrospectively evaluated the clinical and microbiological responses and the cost effectiveness of the patients with cUTIs who received daily inpatient ertapenem therapy.

**Results:** Our study population was 136 patients in 156 episodes. It was a difficultto-treat group with older age (mean  $63.0 \pm 14.8$  years) and a high burden of underlying conditions (86.5%). The most common causative organisms were *Escherichia coli* (74.4%) and *Klebsiella pneumoniae* (19.2%); 89.7% of the isolates were producing extended-spectrum beta lactamase (ESBL). The microbiologic and clinical success rates were 82.1% and 95.5%, respectively. The patients required hospitalization in 16 episodes (10.2%) because of clinical failures (3.8%), superinfections (2%), planned invasive interventions (3.2%), and side effects (1.2%). Our university hospital saved 1608 bed-days and 2596 € (9702 TL) bed costs.

**Conclusions:** In the COVID-19 pandemic period, this seems to be an effective, safe, and cost-effective way to decrease hospitalizations for cUTIs in settings where OPAT is unavailable.

#### What's known

- Antimicrobial resistance in the complicated urinary tract infections is a global challenge for optimal antimicrobial treatment.
- Hospitalization of these patients has increased the cost, risk of transmissions of COVID-19, and infections.
- Ertapenem is suitable for outpatient parenteral antimicrobial therapy (OPAT).

#### What's new

- In countries which outpatient parenteral therapy is not reimbursed, patients have to be hospitalized to have optimal treatment.
- Daily inpatient ertapenem therapy can be a model for these countries, especially in COVID-19 era.

# 1 | INTRODUCTION

In the COVID-19 period, reducing hospitalization became important to prevent the spread of SARS-COV-2 infection. In Turkey, physicians hospitalize the patients with urinary tract infections (UTIs) who require intravenous (IV) antibiotic treatment because the Outpatient Parenteral Antibiotic Treatment (OPAT) for UTI is not reimbursed.

Extended-spectrum beta lactamase (ESBL)-producing urinary pathogens are steadily increasing in Turkey,<sup>1-6</sup> which usually require IV carbapenems because oral antibiotic options are limited. However, this increases the hospitalization rate, related costs,<sup>7</sup> and the risk of hospital-acquired infections including SARS-CoV-2.<sup>8</sup>

Daily antimicrobial therapy is the administration of IV antibiotics in the context of daily inpatient service. We practiced it in our hospital between 2014 and 2018 until it was interrupted due to the reconstruction procedures in the clinic. After the COVID-19 pandemic, we revitalized the idea for patients who do not require hospitalization but need treatment with parenteral antibiotics. Ertapenem is a carbapenem with once-daily dosing for ESBL positive pathogens,<sup>9</sup> that is reimbursed for daily inpatient services and chosen by the majority of physicians for the treatment of UTIs requiring IV antibiotics.

We aimed to assess patients with complicated UTI (cUTI) who received daily inpatient ertapenem therapy with a new perspective to create a model to reduce hospitalizations in the COVID-19 era. To our knowledge, this is the first paper on this practice from countries where OPAT is unavailable.

# 2 | MATERIAL AND METHODS

### 2.1 | Ethical declaration

Our study protocol received "Dokuz Eylül University Non-invasive Studies Ethical Committee" approval (06.03.219; 2019/05-22).

#### 2.2 | Selection of patients

We included patients aged18 years and above with a diagnosis of cUTI who received daily inpatient ertapenem treatment. We excluded patients without urine culture, who received ertapenem for

less than 3 days, who used ertapenem for other diagnoses and those who were treated with other antibiotics.

We defined cUTI as UTI that developed in functionally, metabolically, or anatomically abnormal hosts or that was caused by multidrug-resistant pathogens (MDR) as described previously.<sup>10</sup> We noted comorbidities, anatomical, and functional abnormalities of the urinary tract, clinical failures, hospitalization needs, and adverse events retrospectively from medical records of the hospital.

# 2.3 | Routine practice in the treatment of UTIs in Turkey

OPAT is very limited in the reimbursement system of Turkey (only teicoplanin for chronic osteomyelitis and ceftriaxone 2gr for the first dose of acute meningitis prior to the transfer of the patient). Thus, physicians have to hospitalize patients with UTIs when they cannot treat it with oral or intramuscular antibiotics (upper UTIs, recurrent lower UTIs, and UTIs caused by resistant bacteria).

#### 2.4 | Daily inpatient ertapenem administration

The patients were admitted to the hospital every day with antibiotics being provided from the hospital pharmacy. After the administration of IV ertapenem by a nurse in a separate room in a distant building, they were discharged. The advantages are that patients stay in the hospital for less than 30 minutes; they do not occupy hospital beds and have a lower risk for developing hospital-acquired infections. The disadvantages are that patients have to travel to and from and go through a check-in process at the hospital every day.

#### 2.5 | Microbiological evaluation

Urine samples were quantitatively spread on Colombia Blood Agar (Becton Dickinson, Germany) and Eosin Metilen Blue Agar (Becton Dickinson, Germany). The plates were evaluated after incubation at 35.5°C for 24 hours. The microorganisms were identified by conventional methods and were confirmed by VITEK II Automated System (BioMerieux, France). Antimicrobial susceptibility testing was performed by disc diffusion method on Muller Hinton Agar (Becton Dickinson, Germany) following standard procedures recommended by the Clinical and Laboratory Standards Institute (CLSI), Wayne, PA, USA.<sup>11</sup> ESBL production of the isolates was investigated by the combination disc test using discs containing cefotaxime and ceftazidime as mono drugs and in combination with clavulanic acid.<sup>11</sup>

We assessed urine cultures before treatment, at 48-72 hours of treatment and 28-30 days after the last antibiotic dose. The results of the first control culture at 48-72 hours were interpreted as (a) microbial success if the culture yielded no bacterial growth, (b) persistent infection if there was bacterial growth identical to the baseline organism with an identical antimicrobial sensitivity pattern, and (c) superinfection if there was culture positivity with another pathogen. The second control cultures after treatment were interpreted as (a) microbiological success if there was no growth, (b) relapse if the culture yielded bacteria identical to the baseline organism with an identical antimicrobial sensitivity pattern, and (c) reinfection if the culture yielded a different pathogen.

#### 2.6 | Statistical analyses

We used IBM SPSS 23.0 program for statistical analysis. Skewness, kurtosis, and Kolmogorov-Smirnov (K-S) test were used for the assessment of normality. Continuous variables were compared with the Mann-Whitney U test because of the abnormal distribution of our data. Chi-square test was used for categorical variables. We accepted the probability of type 1 error as  $\alpha = 0.05$  in all tests. A P < .05 was considered significant.

## 2.7 | Cost analysis

Total costs for all patients and hospital bed costs for hospitalized patients were calculated based on the records of the hospital fiscal office. All costs were calculated in Turkish liras (TL) and were converted to Euros ( $\in$ ) according to the exchange rates of the Turkey Central Bank between 2014 and 2018.<sup>12</sup> The public transportation fees were not included in the actual costs because of the high variety of distance.

# 3 | RESULTS

#### 3.1 | Demographic features

In our hospital, 289 episodes of daily inpatient antimicrobial therapy were administered between January 1, 2014 and September 1, 2018. The indications were UTIs (200; 69.2%), bone and joint infections (37; 12.8%), skin and soft tissue infections (41; 14.1%), and others [(5; 1.7%) two intra-abdominal infections, one pneumonia, one invasive fungal infection and one visceral leishmaniasis].

The study included 156 of 200 episodes of UTIs in 136 patients. Each episode was recorded as a new patient. The demographic features of the patients were given in Table 1. The patients had at least one comorbidity or urologic pathology in 135 episodes (86.5%),

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# TABLE 1 Demographic features in treatment episodes

Features	n = 156(%)
Age (mean, SD) (min-max)	63.0 ± 14.8 (19-89)
Male sex	82 (52.5)
Upper UTIs	76 (48.7)
Hypertension	79 (50.6)
Malignancy <sup>a</sup>	52 (33.4)
Diabetes mellitus	46 (29.5)
Immunosuppressive therapy	33(21.2)
Chronic kidney disease	43 (27.6)
Urologic catheter <sup>b</sup>	45 (28.8)
Nephrolithiasis	33 (21.2)
Benign prostate hypertrophy	24 (15.4)
Neurogenic bladder	17 (10.9)
Organ transplantation	9 (5.7)
Hospitalization for UTIs in 6 months	51 (32.7)
Invasive urologic procedure in 3 months	51 (32.7)
Previous oral antibiotic use in 3 months	105 (77.2)

Abbreviation: UTIs, Urinary tract infections.

<sup>a</sup>Malignancy: urological cancers (31), solid organ (19) and hematologic (3).

<sup>b</sup>Urologic catheter; double j stent (19), nephrostomy (17), urostomy (6), cystostomy (3).

urologic pathology 82 (52.5%), both in 57 (36.7%) episodes. They had no underlying conditions in only 21 (13.5%) episodes. Almost half of the episodes were (76; 48.7%) upper UTIs. The most common comorbidity was hypertension; the most common anatomic pathology was nephrolithiasis (Table 1).

Thirty-six patients (%23) had one urologic catheter (double j stent, nephrostomy, urostomy, cystostomy), six patients (%3.8) had two, and one patient (%0.6) had three of them. The reasons of invasive urologic catheters, 17 (%47) bladder cancer, 10 (%27.7) nephrolithiasis, 4 (%11.1) ureteral stenosis, 2 (%5.5) ureter injury during operation, 1 (% 2.7) cervix cancer, 1 (%2.7) renal cancer, and 1 (%2.7) neurogenic bladder. The man duration of catheters was 7.8 month (1-96 month).

One-third of the patients had a history of hospitalization due to UTIs in the last 6 months. Most of the patients had received previous oral antibiotic treatment (Table 1). The most common oral antibiotics were fosfomycin (63, 40.4%) and third-generation cephalosporin (54; 34.6%) followed by quinolones (45; 28.8%). The remaining were nitrofurantoin (37; 23.7%), second-generation cephalosporin (37; 23.7%), amoxicillin/clavulanic acid (34; 21.8%), and trimethoprim-sulfamethoxazole (18; 11.5%).

# 3.2 | Microbiologic profile

The most common causative organism was Escherichia coli (116; 74.4%) followed by Klebsiella pneumoniae (30; 19.2%), Proteus spp.

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(three; 1.9%), and *Enterobacter* spp. (two; 1.3%). Five (3.6%) cases had mixed urinary tract infection (*E. coli* accompanied by other gram negatives-four *K. pneumoniae*, one *Enterobacter* spp.). Bacteremia was detected in 23.7% (14/59) of the patients.

The majority (140/156; 89.7%) of the isolates was producing ESBL-90.5% (105/116) in *E. coli* isolates and 90% (27/30) in *K. pneumoniae* isolates. Resistance rate was 84.6% for trimethoprim-sulfamethoxazole; 80.9% for amoxicillin /clavulanic acid; 74.4% for ciprofloxacin; 46.2% for gentamycin; 31.4% for nitrofurantoin; 17.9% for fosfomycin; and 2.2% for amikacin. All isolates were sensitive to ertapenem.

#### 3.3 | Microbiologic success

The first control cultures (48-72 hours) were available in 140 (89.7%) episodes (Table 2). Microbiologic success rate was 115/140 (82.1%) and microbiologic growth was detected in 25/140 (17.8%) where 19 (13.6%) was considered superinfection and six (4.3%) persistent infection (Table 2). Only three symptomatic enterococci infections (15.7%) received additional teicoplanin. The remaining ( eight enterocci and eight *Candida* spp) were considered colonization and none required additional treatment.

The second control cultures (day 28-30) were available in only one-third (46/156) of episodes (Table 2). Half (23; 50%) of the cultures yielded no growth, and the other half had microbiologic growth; 32.6% was defined as relapse and 17.3% as reinfection (Table 2).

#### 3.4 | Risk factors

Patients' characteristics, type of infection (upper or lower UTIs), type of pathogen and ESBL production were analyzed for an association with microbiological response at 48-72 hours and 28-30 days after the completion of therapy. The variables for patients' characteristics were age, sex, presence of a comorbidity, having a specific comorbidity (diabetes mellitus, hypertension, chronic renal disease, organ transplantation, and malignancy), having an anatomical pathology of the urinary tract, having a specific anatomic pathology (nephrolithiasis, benign prostate hypertrophy, urological malignancy, cystostomy, double j stent, urostomy, nephrostomy, neurological bladder), and history of a urologic intervention within the last 3 months.

Patients with urinary catheters had lower success rates at 48-72 hours (P = .02), and a history of urological intervention within the last 3 months was associated with lower success rates on 28-30 days (P = .003). Age, sex, comorbidities, other anatomic pathologies, type of infection and type of pathogens were not associated with microbiological responses.

#### 3.5 | Daily inpatient ertapenem therapy

Physicians referred patients to daily inpatient antibiotic therapy either from the outpatient clinic to receive a full course of antibiotics or from inpatient services to complete an already initiated antibiotic course. In 46.8% of the episodes, patients completed a full course of antibiotic therapy as only daily inpatient therapy. The mean duration of the episodes was 10 days (1-28). Sixteen patients had more than one episode (Table 3); 87.5% of those had underlying anatomic pathology. Urological intervention rate between episodes was 25%.

In 123 (78.8%) episodes, the patients completed the planned course. In 17 episodes (11%), the patients discontinued early and were lost to follow-up. In 16 episodes, they required hospitalization (10.2%) because of clinical failures (six, 3.8%), superinfections (three, 2%), planned invasive interventions (five, 3.2%), and side effects (two, 1.2%). The clinical success rate was 95.5% (133/139) in patients who were available for follow-up. We switched antibiotics in six cases with clinical failures and two patients with side effects (one with drowsiness, one with decreased renal function). After daily inpatient therapy, 45 (28.8%) patients underwent a urological intervention. No mortality occurred during episodes.

Ertapenem-resistant *K. pneumoniae* infection developed in three of 156 (1.9%) patients within 1 month after completion of the daily inpatient therapy episode, all with urinary instruments and underlying comorbidities (Table 4). They all had clinical infection (two had upper UTIs, one lower UTIs) and needed re-treatment. One of them had received daily ertapenem treatment twice within 3 months.

Control cultures	Results	n (%)	Pathogens	<b>TABLE 2</b> Microbiologic results due tocontrol cultures
48th to 72nd hour	Microbiologic success	115/140 (82.1)	No growth	
	Persistent infection	6/140 (4.3)	5 E. coli, 1 K. pneumoniae	
	Superinfection	19/140 (13.6)	11 Enterococcus spp, 8 Candida spp	
28th to 30th day	Microbiologic success	23/46 (50)	No growth	
	Relapse	15/46 (32.6)	15 E. coli	
	Reinfection	8/46 (17.4)	3 K. pneumoniae, 3 E. coli, 1 Enterococcus spp, 1 Candida spp	

TABLE 3 Characteristic of patients who had daily inpatient ertapenem therapy more than one episode

Patients' initials	Sex	Age	Comorbidity	n of episodes	Duration of total treatment	Isolates
AAC <sup>a</sup>	М	78	nephrolithiasis, BPH	3	14 34 14	E. coli E. coli E. coli
ECª	М	65	CKF, bladder cancer, urostomy, CT	3	14 14 14	K. pneumoniae K. pneumoniae Enterobacter spp.
HU <sup>a</sup>	М	71	CKF, bladder cancer, DJS,CT	3	14 14 16	K. pneumoniae K. pneumoniae E. coli
SSª	М	62	CKF, bladder cancer, DJS,CT	3	14 14 14	E. coli E. coli K. pneumoniae
AUO	F	67	nephrolithiasis	2	14 28	E. coli E. coli
CC <sup>a</sup>	F	62	CKF, rectum carcinoma, neurogenic bladder	2	21 14	E. coli K. pneumoniae
GU	F	54	Cervical cancer, CT	2	14 14	E. coli E. coli
KTª	F	84	CKF, neurogenic bladder	2	14 14	E. coli E. coli
MY	М	70	CKF, DM, nephrolithiasis + DJS	2	14 28	E. coli E. coli
MA <sup>a</sup>	М	63	CKF, BPH, nephrostomy	2	14 14	E. coli E. coli
NK	F	66	DM, colon cancer	2	14 21	E. coli E. coli
RK	М	77	DM	2	14 21	E. coli E. coli
SKK	F	58	nephrolithiasis, DJS, nephrostomy	2	21 14	E. coli E. coli
YC	F	57	renal transplantation	2	14 14	K. pneumoniae E. coli
IB <sup>a</sup>	М	59	DM,CKF, bladder cancer, nephrostomy	2	14 16	K. pneumoniae K. pneumoniae
UK	М	80	neurogenic bladder	2	21 14	E. coli E. coli

Abbreviations: BPH, benign prostate hypertrophy; CKF, chronic kidney failure; CT, chemotherapy; DJS, double j stent; DM, diabetes mellitus. <sup>a</sup>Patients who had  $\leq$ 90 days between two episodes.

During the study period, we administered 1608 days of daily inpatient ertapenem therapy. The total cost was  $3357 \in (15.107 \text{ TL})$ including the costs of antibiotics, equipment for intravenous line, and the service. If the patients were hospitalized instead of daily inpatient therapy, there would have been an additional cost of 2596  $\in$ (9702 TL) for hospital beds.

# 4 | DISCUSSION

Complicated UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae* is a rapidly evolving situation. Researchers from Turkey reported the ESBL rates of pathogens in community-acquired UTIs as 32.2%, 38%, and 50.5%<sup>1.3,4</sup> and in hospital acquired UTIs as 50.2%, 61%, and 74.5%.<sup>1,5,6</sup> In our study, the majority of the pathogens were *E. coli* (74%) and *K. pneumonia* (19.2%) with ESBL rates of 90.5% and 90%, respectively, which is higher, compared with the rates reported from other studies. The higher rate of urological pathology (%51) and invasive urological procedures (%32) in our study population than the reported studies of hospital acquired UTIs<sup>5</sup> (%12, %18) and community acquired UTIs<sup>4</sup> (%28.6, %14) respectively might have resulted in higher ESBL rates.

Treatment of ESBL-producing bacteria is quite challenging with limited antimicrobial options.<sup>13-16</sup> While researchers reported

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Patients' initials	Age	Sex	Comorbidity	First pathogen	Ertapenem resistant pathogen	Duration after ertapenem therapy
MC	71	М	Liver transplant, bilateral nephrostomy catheter	ESBL + E. coli	K. penumoniae	7 days
ET	70	F	Neurogenic bladder, urinary catheter	ESBL + E. coli	K. penumoniae	30 days
СС	62	F	Rectum carcinoma, neurogenic bladder	ESBL + K. penumoniae	K. penumoniae	20 days

Abbreviations: ESBL, Extended spectrum beta lactamases; F, female; M, male.

microbiological success by oral fosfomycin (60%), oral nitrofurantoin (69%), and intramuscular amikacin (96%) for lower UTIs with ESBL positive pathogens,<sup>15-17</sup> there is no report on oral or intramuscular antibiotic alternatives for IV antibiotics for the treatment of upper UTIs. The patients with co-morbidities and urologic instruments as in our study population where the majority had a history of <sup>9</sup> antibiotic treatment and hospitalization and a guarter had upper UTI with bacteremia clinical and microbiological failure with oral agents make at least 2 weeks of hospitalization for parenteral carbapenem therapy inevitable. This keeps hospital beds busy, increases the risk of hospital-acquired infections, and raises the demand for workforce.

Ertapenem is a common choice of antibiotic for ESBL-producing bacteria.<sup>13,14,18,19</sup> It is licensed in Turkey for various indications including complicated UTIs.<sup>20</sup> Once a day dosing of the antibiotic makes it convenient for OPAT.<sup>21</sup> The use of ertapenem for OPAT was reported earlier in cUTIs with microbiologic eradication rates between 54.1% and 90% and with higher rates (92% and 96%) of clinical success.<sup>22-26</sup> OPAT for UTIs is a practical way of treating patients who do not need hospitalization but require IV antibiotic treatment.<sup>22,27</sup> OPAT was reported as safe and cost-effective<sup>24,26</sup> and more preferable for healthcare professionals and for patients than inpatient care.<sup>28</sup> However, the health system in Turkey does not allow the use of OPAT for the treatment of UTIs.

The results of our study suggested a high rate of microbiological (82.1%) and clinical (95.5%) success and a lower rate of superinfections with Enterococcus spp and Candida spp compared with a previous study from Turkey by Dizbay et al that evaluated ertapenem therapy in hospitalized patients with cUTIs.<sup>18</sup> In addition, the rate of superinfections treated with antibiotics was also lower (15.7% to 78.1%), which may be attributed to different profiles of patients who received inpatient and daily inpatient therapy. Similar to the previous study, the presence of urinary catheter was a risk factor for superinfections in our study. Our relapse and reinfection rates (32.6% and 17.9% respectively) were much higher than those in two other studies that reported relapse rates between 15% and 22% and reinfection rates 5.5% and 18% in different patients groups.<sup>22-24,26</sup> This difference may be attributed to the high burden of comorbidities and urological interventions in our study population. Undergoing urinary interventions in the last 3 months was a significant risk factor for the development of recurrent infections. Senol et al and Tasbakan et al reported similar risk factors for recurrent cUTI infections in Turkey.<sup>15,16</sup>

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Ertapenem resistance in urinary pathogens in Turkey is reported to range between 5.3% and 14.8%.<sup>1,5,6</sup> It was associated with  $\beta$ lactamase activity and porin alteration in clinical Enterobacteriaceae isolates.<sup>27</sup> In a Spanish case-control study for ertapenem resistant and susceptible entererobactericea infections, prior ertapenem use was almost four times higher in the resistant group.<sup>29</sup> In our study, three patients had ertapenem resistant K. pneumoniae infection after completing the episodes, all with urinary instruments and two receiving immunosuppressive therapy. Two of those patients grew different bacteria compared with baseline culture results, which suggests reinfection with a new resistant strain. The remaining patient who had daily ertapenem therapy twice in 3 months had K. pneumoniae in the initial culture, which suggested relapse with the same microorganism because of emerging resistance to ertapenem during treatment. However, as genotypic analysis of strains was not available it was not possible to confirm this. Full adherence to treatment, close follow-up of high-risk patients, and higher doses<sup>30</sup> in selected patients may prevent the development of resistance. Daily inpatient therapy allows the patients to receive full course of effective antibiotics.

The patients completed the planned course in 78.8% of daily inpatient ertapenem episodes. The hospitalization rate because of clinical failure (3.8%) and adverse events (1.2%) was low. The previous studies where ertapenem was used for OPAT reported similar readmission rates around 4% and adverse events between 2% and 5% including Clostridium difficile enterocolitis or peripheral line problems,<sup>22,26</sup> which did not develop in our study group. Only two patients (one with drowsiness, one with decreased renal function) had adverse reactions in our study, which suggests that daily inpatient treatment may be a safe way of giving proper treatment for cUTIs, even in difficult to treat populations.

A major advantage of daily inpatient therapy was the significant gain in cost. Our university hospital saved 2596 € (9702 TL), and there was a decrease of 1608 days in hospitalization. In a Turkish study, Ozmen et al found a 20% decrease in hospital expenses by comparing inpatient ertapenem therapy by hypothetical OPAT.<sup>9</sup> Even high-income countries, OPAT was found cost-effective than hospitalization.<sup>24-26</sup> In settings where OPAT for UTIs is unavailable, daily inpatient antibiotic treatment may be a cost-saving option.

While this study provides real-life data for daily inpatient therapy as an alternative to hospitalization, which may serve as a model for centers to decrease hospitalization rates in the treatment of cUTIs, its single center retrospective design, and the lack of molecular analysis, which prevents comparison of bacteria isolated at baseline with those recovered from control cultures are its major limitations.

# 5 | CONCLUSIONS

Our study shows that daily inpatient therapy in UTIs with ertapenem is effective with a high success rate, acceptable with a high adherence rate, and safe with very few adverse events. It can reduce the hospitalization rates significantly and might have a positive effect in reducing COVID-19 transmission at the hospital.

## DISCLOSURES

The authors declare no conflict of interest.

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