Fosfomycin vs Ertapenem for Outpatient Treatment of Complicated Urinary Tract Infections: A Multicenter, Retrospective Cohort Study

Noah Wald-Dickler,1,2 Todd C. Leo,1 Soodtida Tangraphaphorn,1 Susan M. Butler-Wu,1,4 Nina Wang,1 Tyler Degener,1,2 Carolyn Kan,1,2 Matthew C. Phillips,1,2 Edward Cho,1,2 Catherine Canamar,1 Paul Holtom,1,2 and Brad Spellberg1

1Los Angeles County - University of Southern California Medical Center (LAC-USC Medical Center), Los Angeles, California, USA, 2Department of Medicine, Keck School of Medicine of USC, Los Angeles, California, USA, 3Clinical Practice Assessment Unit, McGill University, Montreal, Quebec, Canada, and 4Department of Pathology, Keck School of Medicine of USC, Los Angeles, California, USA

Background. We sought to determine the comparative efficacy of fosfomycin vs ertapenem for outpatient treatment of complicated urinary tract infections (cUTIs).

Methods. We conducted a multicenter, retrospective cohort study involving patients with cUTI treated with outpatient oral fosfomycin vs intravenous ertapenem at 3 public hospitals in Los Angeles County between January 2018 and September 2020. The primary outcome was resolution of clinical symptoms 30 days after diagnosis.

Results. We identified 322 patients with cUTI treated with fosfomycin (n = 110) or ertapenem (n = 212) meeting study criteria. The study arms had similar demographics, although patients treated with ertapenem more frequently had pyelonephritis or bacteremia while fosfomycin-treated patients had more retained catheters, nephrolithiasis, or urinary obstruction. Most infections were due to extended-spectrum β-lactamase–producing E. coli and Klebsiella pneumoniae, 80%–90% of which were resistant to other oral options. Adjusted odds ratios for clinical success at 30 days, clinical success at last follow-up, and relapse were 1.21 (95% CI, 0.68–2.16), 0.84 (95% CI, 0.46–1.52), and 0.94 (95% CI, 0.52–1.70) for fosfomycin vs ertapenem, respectively. Patients treated with fosfomycin had significant reductions in length of hospital stay and length of antimicrobial therapy and fewer adverse events (1 vs 10). Fosfomycin outcomes were similar irrespective of duration of lead-in intravenous (IV) therapy or fosfomycin dosing interval (daily, every other day, every third day).

Conclusions. These results would support the conduct of a randomized controlled trial to verify efficacy. In the meantime, they suggest that fosfomycin may be a reasonable stepdown from IV antibiotics for cUTI.

Keywords. complicated urinary tract infections; ertapenem; fosfomycin.

Rising rates of community-acquired resistance to the fluoroquinolones, as well as the spread of extended-spectrum beta-lactamases (ESBLs), have resulted in increasing difficulty in treating urinary tract infections with oral agents [1–4]. In some centers, up to 90% of ESBL-producing Enterobacteriales are fluoroquinolone-resistant, and half or more are resistant to trimethoprim-sulfamethoxazole (TMP-SMX) [5]. No other Food and Drug Administration–approved oral options remain for the indication of complicated urinary tract infections (cUTIs) caused by such pathogens. Patients with these infections therefore typically receive intravenous (IV) antibiotics even if clinically stable and tolerating oral intake.

Fosfomycin has been used for many decades in Europe for a variety of infections. In the United States, it is only approved for single-dose oral administration for uncomplicated cystitis. However, given the complexity and inherent safety concerns associated with prolonged IV therapy, there is renewed interest in using multiple-dose oral fosfomycin regimens off-label to treat cUTI. Pharmacokinetic data support every 24–48-hour dosing to maintain fosfomycin levels above target minimum inhibitory concentrations (MICs) in urine [6]. Furthermore, recent case series describe 65%–80% cure rates for oral fosfomycin for the treatment of cUTI [7, 8], and case reports highlight successfully treated prostatitis with prolonged oral fosfomycin [9]. We sought to define the relative efficacy of fosfomycin vs intravenous therapy by conducting a multicenter, retrospective cohort study to compare outcomes of patients with cUTIs treated with oral fosfomycin or IV ertapenem.

METHODS

Data Collection

We searched the common, Cerner-based electronic medical record (EMR) for relevant patients cared for at the 3 Los Angeles County - University of Southern California Medical Center (LAC-USC Medical Center), Los Angeles, California, USA between January 2018 and September 2020. We conducted a multicenter, retrospective cohort study involving patients with cUTI treated with outpatient oral fosfomycin or IV ertapenem.
Angeles County Department of Health Services acute care safety net hospitals: Los Angeles County + University of Southern California Medical Center, Harbor-University of California Los Angeles (UCLA) Medical Center, and Olive View-UCLA Medical Center. The EMR query was generated for patients with positive urine cultures who also received discharge prescriptions for ertapenem or fosfomycin between January 2018 and September 2020. Antimicrobial susceptibility testing and ESBL detection were performed using VITEK AST-GN73 cards (bioMérieux, Marcy-l’Étoile, France). Fosfomycin susceptibility testing (by disk diffusion) was performed only on ESBL-positive E. coli urine isolates. Ertapenem susceptibility testing (gradient diffusion, E-test) was performed on physician request. Urine cultures included specimens obtained from in- and out-catheterization, indwelling catheters, and clean catch specimens. Charts were manually abstracted to confirm diagnoses and receipt of intended antibiotics, as well demographics, cUTI risk factors, and outcomes. The study was approved with waiver of informed consent by the University of Southern California Biomedical Research Institutional Review Board.

Definitions

cUTI was defined as a positive urine culture with (1) documented symptoms including dysuria, urinary frequency, or suprapubic pain with an indwelling catheter, renal stone, urinary obstruction, ureteral stent, or renal transplant or (2) the presence of flank pain or tenderness, with fever or leukocytosis.

Patients were assigned to the fosfomycin arm if they received oral fosfomycin at hospital discharge, regardless of initial IV therapy. Repeat fosfomycin- or ertapenem-treated cUTI episodes were considered separate events, so the same patient may have been included multiple times, including in either arm (depending on which drug the individual cUTI episodes were treated with). Relapse was defined as recurrence of urinary tract infection (UTI) symptoms within 3 months of initial diagnosis with urine culture demonstrating the same organism as the initial episode.

Inclusion and Exclusion Criteria

We included all adult patients meeting the above cUTI diagnostic criteria who received ertapenem or fosfomycin, either as monotherapy or in sequence, following upfront alternative IV therapy. Children under 18 years old were excluded. Both women and men were included, although men with clinical diagnosis or symptoms of prostatitis were excluded. Additionally, we excluded patients clinically diagnosed with asymptomatic bacteriuria, uncomplicated cystitis, epididymo-orchitis, and non-UTI infections.

Outcomes

The primary end point was clinical treatment success, defined as resolution of signs and symptoms of infection without relapse, at 30 days after cUTI diagnosis (eg, date of the index urine culture for that episode of infection). Additional predefined secondary outcomes included resolution of symptoms at last documented follow-up (with lack of documented follow-up imputed as success) and microbiologically confirmed 3-month UTI relapse rates. Relapse required re-presentation for symptoms of cUTI with a repeat urine culture growing an isolate identical to the prior isolate. We also compared length of hospital stay and adverse event frequency between groups, as well as treatment outcomes, by fosfomycin dosing interval and length of IV lead-in therapy.

Statistical Analysis

Data were checked for normality of distributions. Continuous variables were compared using the Student t test and dichotomous variables with the chi-square (χ²) or Fisher exact test, with α = .05 for significance.

Using STATA 16.1 (STATACorp, College Station, TX, USA), we conducted multivariable logistic regression for the outcomes of 30-day clinical success, resolution of symptoms at last follow-up, and absence of relapse at 3 months. Multivariable analysis was chosen given the multiple, recorded, clinically relevant predictors we believed a priori to be important potential covariates for treatment failure, including age, biologic sex, diabetes mellitus, type of infection, presence of bacteremia, presence of a Foley catheter at discharge, kidney stones, E. coli as the predominant organism, duration of treatment before hospital discharge, and duration of postdischarge treatment. Adjusted odds ratios were estimated with 95% CIs (Table 4).

RESULTS

A total of 386 episodes of outpatient fosfomycin- or ertapenem-treated cUTIs were identified in patients with a positive urine culture. Sixty-four episodes were excluded due to failure to meet study inclusion criteria (Figure 1), leaving 322 eligible cUTI episodes for analysis during the study period: 110 in the fosfomycin arm and 212 in the ertapenem control arm. One hundred thirteen episodes (68 in the ertapenem arm and 45 in

![Patient selection flowchart](image)
the fosfomycin arm) happened in patients with multiple cUTI occurrences.

**Patient and Infection-Related Characteristics**

Demographic features were similar between groups (Table 1). The ertapenem group had significantly more bacteremia and pyelonephritis without PCNTs (but not PCNTs), while the fosfomycin group had more indwelling catheters, nephrolithiasis, and other urinary obstructions (eg, benign prostatic hypertrophy, chronic obstruction requiring in- and out-catheterization, or penile edema).

*E. coli* was the predominant pathogen in both groups, followed by *Klebsiella pneumoniae*; combined, these 2 pathogens accounted for 115/130 (88.4%) and 208/322 (64.6%) of all isolates in the fosfomycin and ertapenem arms, respectively (Supplementary Table 1). High percentages of urine cultures included at least 1 ESBL-producing organism: 99/117 (84.6%) and 194/213 (91.0%) in the fosfomycin and ertapenem arms, respectively. High rates of resistance to TMP/SMX and ciprofloxacin were also encountered, with rates of resistance to TMP/SMX significantly higher in the fosfomycin arm (Supplementary Table 2).

**Clinical Outcomes**

Patients treated with fosfomycin and ertapenem had similar 30-day clinical success rates overall (72/110 [65.4%] vs 157/212 [74.1%]; *P* = .1) and across all comorbidity subgroups (Table 2). There were no significant differences in symptom resolution at last follow-up or in relapse rates, either overall or in any comorbidity subgroup (Table 2). However, the lowest success rates were seen in patients with persistent indwelling catheters (whether bladder or PCNTs) at hospital discharge. While the failure rates among these patients did not differ whether treated with fosfomycin or ertapenem, there were more patients with retained catheters at discharge in the fosfomycin cohort. Of note, in-hospital catheter exchange was not recorded among those patients discharged with urinary catheters given a lack of reliable clinical documentation.

**Therapy Before Fosfomycin Stepdown**

There was significant heterogeneity in duration of initial antibiotic therapy before definitive therapy with either fosfomycin stepdown or IV ertapenem. We sought to determine whether variations in upfront IV lead-in therapy duration

---

**Table 1. Demographics by Treatment Arm**

|                  | Fosfomycin (n = 110) | Ertapenem (n = 212) | P Value |
|------------------|----------------------|---------------------|---------|
| Race             |                      |                     | .5      |
| Asian            | 2 (2)                | 8 (4)               |         |
| Black            | 3 (3)                | 14 (7)              |         |
| White            | 11 (10)              | 21 (10)             |         |
| Hispanic         | 92 (84)              | 163 (77)            |         |
| Other            | 2 (2)                | 6 (3)               |         |
| Gender           |                      |                     | .8      |
| Female           | 63 (57)              | 125 (59)            |         |
| Male             | 47 (43)              | 87 (41)             |         |
| Age, mean ± SD, y| 52.9 ± 15.9          | 55.2 ± 16.8         | .2      |
| cUTI type        |                      |                     |         |
| Bladder catheter at diagnosis | 27 (24) | 31 (15) | .03 |
| Pyelonephritis, no PCNT | 48 (44) | 139 (66) | <.001 |
| PCNT             | 15 (14)              | 32 (15)             | .7      |
| Cystitis with nephrolithiasis | 5 (5) | 1 (<1) | .02 |
| Other urinary obstruction | 11 (10) | 5 (2) | .004 |
| Other cUTI | 4 (4)                | 4 (2)               | .3      |
| Comorbidities    |                      |                     |         |
| Diabetes mellitus| 48 (43.6)            | 99 (46.7)           | .6      |
| Urinary obstruction | 55 (50.0) | 93 (44) | .3      |
| Renal abscess    | 2 (1.8)              | 7 (3.3)             | .4      |
| Nephrolithiasis (all cUTI types) | 25 (22.7) | 35 (16.5) | .1      |
| Bacteremia       | 7 (6.4)              | 82 (38.7)           | <.0001  |
| Bladder catheter at discharge | 31 (28.2) | 40 (18.9) | .08 |
| Renal transplant | 0 (0)                | 7 (3.3)             | .05     |
| Mean time to last follow-up (range; IQR), d | 297.0 (0–982; 26–552) | 334.2 (0–1016; 26–617) | .5      |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CHF, cUTI, complicated urinary tract infection; IQR, interquartile range; PCNT, percutaneous nephrostomy tube.

*Other urinary obstruction includes intermittent catheterization, benign prostatic hypertrophy without catheter, or penile edema due to CHF.

*Other cUTI includes indwelling ureteral stent (n = 1 for fosfomycin), multiple rapid recurrences failing prior nonfosfomycin therapy (n = 3 for fosfomycin), ongoing ureteral fistula without catheter in place (n = 1 for ertapenem), or cystitis with bacteremia without obstruction, catheters, or clinical evidence of pyelonephritis (n = 3 for ertapenem).
affected fosfomycin treatment outcomes. Thus, we compared 4 fosfomycin-treated subgroups: fosfomycin without upfront IV lead-in (n = 15), those treated with IV therapy for 1–3 days (n = 38), 4–5 days (n = 44), or ≥6 days (n = 13) before oral fosfomycin stepdown. Clinical success at 30 days, resolution at last follow-up, and relapse did not significantly differ irrespective of IV therapy lead-in duration (Table 3).

**Fosfomycin Dosing Intervals**

Three different fosfomycin dosing regimens were used, with fosfomycin administered daily (n = 29), every other day (n = 59), or every third day (n = 22). Thirty-day clinical response, resolution at last follow-up, and relapse did not significantly differ across the 3 dosing regimens (Table 3).

**Multivariable Adjustment**

Given heterogeneity across disease types—for example, more pyelonephritis and bacteremia in the ertapenem cohort and more catheter-associated infections and retained catheters at discharge in the fosfomycin arm—we ran an adjusted analysis. After multivariable adjustment, infection in the setting of PCNT relative to pyelonephritis predicted decreased clinical success, with an odds ratio at 30 days of 0.5 (95% CI, 0.3–0.9) and at last
follow-up of 0.4 (95% CI, 0.20–0.81) (Table 4). Nephrolithiasis also predicted decreased clinical success at last follow-up and relapse, with an odds ratio of clinical success of 0.5 (95% CI, 0.3–1.0) and of relapse of 0.43 (95% CI, 0.23–0.80). In contrast, increasing age predicted increased clinical success at 30 days, with an odds ratio of 1.02 (95% CI, 1.01–0.03). No other variables were significantly associated with outcome.

In the multivariate model, accounting for the above variables, adjusted odds ratios for 30-day clinical success, symptom resolution at last follow-up, and relapse were 1.21 (95% CI, 0.68–2.16), 0.84 (95% CI, 0.46–1.52), and 0.94 (95% CI, 0.52–1.70) for fosfomycin vs ertapenem, respectively (Table 3).

### DISCUSSION

Traditionally, patients with cUTIs caused by bacteria resistant to fluoroquinolones, β-lactams, and TMP-SMX have been treated with alternative IV agents. However, prolonged IV therapy is associated with numerous adverse effects and longer hospitalizations for many infections, including osteomyelitis [10], bacteremia [11], and infective endocarditis [12]. While oral fosfomycin is of interest in treating UTIs, there are no comparative data to enable assessment of its relative efficacy compared with IV therapy for cUTIs. Our results are reassuring that patients treated with fosfomycin, either as initial or subsequent stepdown therapy, had similar outcomes compared with those receiving definitive therapy with ertapenem. Furthermore, patients treated with fosfomycin had significantly reduced hospitalizations and overall antimicrobial treatment durations, less exposure to indwelling catheters, and numerically fewer adverse events.

Our study supports findings from other publications [8, 13–15] and, by including an active control group of IV therapy, expands on the scope of prior work by suggesting oral fosfomycin as a potentially viable treatment option for cUTI treatment. There were subtle differences in clinician therapy choice, with a preference for IV ertapenem among conventionally “sicker” patients, such as those with bacteremia, suggesting greater clinician comfort with IV agents in these settings. However, outcomes were favorable even in the presence of bacteremia or other complicated clinical situations for which fosfomycin is typically avoided, including pyelonephritis and the presence of urinary tract tubes and catheters. Of note, irrespective of drug treatment, patients with bacteremia and pyelonephritis had higher clinical cure rates and were more common in the ertapenem cohort, while patients with indwelling catheters had lower clinical cure rates and were more common in the fosfomycin cohort. As bacteremia did not independently correlate with worse outcomes, while retained catheters did, the imbalance in underlying risk factors between the cohorts tended to disadvantage fosfomycin therapy. Nevertheless, overall unadjusted outcomes were not significantly different between...
coHORTS, and multivariate adjustment further elucidated similar outcomes in patients treated with fosfomycin vs ertapenem.

Consistent with our results, a recent pharmacokinetic analysis found favorable urine levels of fosfomycin after daily or every-other-day oral dosing [6]. Fortuitously, most ESBL-producing E. coli isolates have low fosfomycin MICs, below achievable urine levels [16]. While CLSI breakpoints for fosfomycin susceptibility are not available for non-E. coli bacteria, our study showed encouraging clinical success with fosfomycin in UTIs caused by other bacterial species alone or as co-pathogens in E. coli– and Klebsiella pneumoniae–predominant polymicrobial infections. Consistent with these pharmacologic data, and similar to a prior observational study of fosfomycin for pyelonephritis and cUTI [8], we found no difference in clinical success related to fosfomycin dosing variations. However, this finding should be interpreted with caution given low numbers when evaluating subgroups of patients by fosfomycin dosing intervals.

Our study has several important limitations, including its retrospective nature. However, unlike prior fosfomycin observational-only investigations, our study is strengthened by inclusion of a direct standard-of-care ertapenem comparator. Given limited numbers, extrapolation and applicability of our results to immunocompromised patients should be done with caution and warrants further randomized, prospective studies.

We were also limited to data recorded in our EMR and cannot exclude the possibility of missed follow-up for cUTI recurrence outside our system. However, average length of documented follow-up was >10 months in both groups, allowing identification of relapse and complications, and in a safety net health care system like ours, patients are less likely to receive care at outside institutions given limited insurance. Additionally, given our health system’s single EMR, capturing all urine cultures and subsequent hospitalizations and emergency department and clinic visits, we were less likely to miss future relapses during the study period. Our analysis was also strengthened by 100% confirmation of reported outcomes by manual chart review with no missing data elements, rather than relying on administrative data.

Finally, comparably favorable fosfomycin success rates may represent possible confounding by indication due to preselected cUTI populations at low risk of failure: primarily postdischarge,

### Table 4. Multivariable Adjustment for Outcomes

| Clinical success at 30 d (primary end point) | Odds Ratio | 95% CI     |
|--------------------------------------------|------------|------------|
| Fosfomycin treatment                       | 1.21       | 0.68–2.16  |
| Age                                        | 1.02       | 1.01–1.03  |
| Male                                       | 0.76       | 0.45–1.27  |
| Diabetes mellitus                          | 1.34       | 0.81–2.23  |
| Bacteremia                                 | 1.40       | 0.75–2.58  |
| Bladder catheter at discharge              | 0.97       | 0.43–2.19  |
| Nephrolithiasis                            | 0.73       | 0.40–1.35  |
| *E. coli* vs other pathogens               | 1.36       | 0.74–2.49  |
| Duration of IV pretreatment                | 1.00       | 0.91–1.11  |
| Duration of postdischarge treatment        | 1.01       | 0.98–1.04  |
| Duration of total therapy                  | 0.41       | 0.13–1.33  |
| cUTI type (relative to pyelonephritis)     |            |            |
| PCNT                                       | 0.50       | 0.25–0.98  |
| Catheter associated                        | 0.68       | 0.27–1.67  |
| Other cUTI                                 | 0.71       | 0.29–1.75  |
| Resolution of symptoms at last follow-up   | 0.84       | 0.46–1.52  |
| Fosfomycin treatment                       | 1.01       | 0.99–1.03  |
| Male                                       | 1.29       | 0.74–2.26  |
| Diabetes mellitus                          | 1.06       | 0.61–1.82  |
| Bacteremia                                 | 1.13       | 0.59–2.20  |
| Bladder catheter at discharge              | 0.69       | 0.30–1.60  |
| Nephrolithiasis                            | 0.53       | 0.28–0.99  |
| *E. coli* vs other pathogens               | 1.30       | 0.69–2.48  |
| Duration of IV pretreatment                | 1.06       | 0.96–1.17  |
| Duration of postdischarge treatment        | 1.01       | 0.97–1.05  |
| Duration of total therapy                  | 1.14       | 0.33–3.96  |
| cUTI type (relative to pyelonephritis)     |            |            |
| PCNT                                       | 0.40       | 0.20–0.81  |
| Catheter associated                        | 0.66       | 0.26–1.68  |
| Other cUTI                                 | 1.01       | 0.37–2.76  |
| Absence of relapse at 3 mo                 | 0.94       | 0.52–1.70  |
| Fosfomycin treatment                       | 1.00       | 0.98–1.02  |
| Male                                       | 0.91       | 0.53–1.56  |
| Diabetes mellitus                          | 1.01       | 0.59–1.73  |
| Bacteremia                                 | 1.44       | 0.74–2.77  |
| Bladder catheter at discharge              | 0.57       | 0.25–1.3   |
| Nephrolithiasis                            | 0.43       | 0.23–0.80  |
| *E. coli* vs other pathogens               | 1.07       | 0.57–2.03  |
| Duration of IV pretreatment                | 1.01       | 0.92–1.11  |
| Duration of postdischarge treatment        | 1.02       | 0.98–1.06  |
| Duration of total therapy                  | 2.88       | 0.82–10.10 |
| cUTI type (relative to pyelonephritis)     |            |            |
| PCNT                                       | 0.50       | 0.26–1.01  |
| Catheter associated                        | 0.83       | 0.33–2.08  |
| Other cUTI                                 | 1.05       | 0.40–2.76  |

### Table 5. Lengths of Therapy and Hospitalization

|                     | Fosfomycin (n = 110) | Ertapenem (n = 212) | P Value |
|---------------------|----------------------|---------------------|---------|
| Average lengths of treatment and hospitalization |                      |                     |         |
| Length of inpatient stay | 4.3 ± 3.8           | 5.7 ± 3.9           | .002    |
| Duration of inpatient IV therapy       | 3.3 ± 2.1           | 4.7 ± 3.3           | <.0001  |
| Duration of therapy postdischarge     | 5.3 ± 4.1           | 7.8 ± 8.3           | .003    |
| Total duration of IV therapy          | 3.3 ± 2.1           | 12.4 ± 8.9          | <.0001  |
| Total duration of antibiotic therapy  | 8.6 ± 4.4           | 12.4 ± 9.8          | <.0001  |

Durations are reported as mean ± SD in days. Abbreviation: IV, intravenous.

Abbreviations: cUTI, complicated urinary tract infection; IV, intravenous; PCNT, percutaneous nephrostomy tube.
However, all included patients had complex disease, with high proportions of urinary obstruction, indwelling catheters, and recurrence. Fosfomycin was the only antibiotic received in 5.7% of patients, and in patients with initial IV therapy, fosfomycin constituted on average 56% of the total treatment duration. Additionally, there were no significant differences in outcomes among the 15 fosfomycin recipients who received no IV lead-in therapy compared with those who received 1 or more days of an upfront IV agent. Thus, despite heterogeneity in initial choice of upfront IV therapy, our study suggests fosfomycin stepdown efficacy that cannot be attributed solely to initial IV therapy alone, as seen in our analysis of treatment outcomes stratified by length of upfront parenteral therapy. Finally, inpatients who are being prepared for oral stepdown therapy are generally those for whom concerns for high systemic oral bioavailability may be less important.

It would not be rational to administer oral therapy of any kind to a patient too unstable to be transitioned to outpatient care.

And last, it is important to note variations in overall length of therapy, with ertapenem recipients receiving on average >4 more days of total antibiotic therapy than fosfomycin recipients. Two years before our study period, all study sites adopted an Expected Practice (EP) [17] on antibiotic duration that included a recommendation for 5–7 total days for cUTI. And despite mean antibiotic days of therapy for UTIs of all types significantly decreasing after EP implementation in the largest of the 3 study sites [18], total duration still remained >12 days. Our study suggests the safety of shorter courses for cUTI and further opportunities for improvements in antimicrobial stewardship.

In summary, we found that patients receiving off-label oral fosfomycin for UTIs—including those with pyelonephritis, bacteremia, and bladder catheters or nephrostomy tubes—have comparably favorable outcomes compared with those receiving ertapenem. Our findings support a basis for future randomized controlled trials of fosfomycin vs IV comparators as stepdown for cUTI. Meanwhile, oral fosfomycin appears worthy of broader consideration as UTI therapy outside its current narrow indication, enabling shorter lengths of IV catheter exposure and hospital stays, with similar clinical outcomes.

Acknowledgments

Financial support. This work was supported by research salary support from Fonds de Recherche de Québec – Santé (T.C.L.).

Potential conflicts of interest. B.S. reports consulting fees from GlaxoSmith-Kline, IQVIA, and PPD and equity in BioAIM, ExBaq, and Mycomed, all outside the scope of the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. Given its retrospective nature, this work does not include factors necessitating patient consent. The study was approved with waiver of informed consent by the University of Southern California Biomedical Research Institutional Review Board.

References

1. Spellberg B, Doi Y. The rise of fluoroquinolone-resistant Escherichia coli in the community: scarier than we thought. J Infect Dis 2015; 212:1853–5.
2. Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum beta-lactamase-producing Escherichia coli infection in the United States. Clin Infect Dis 2013; 56:641–8.
3. Lob SH, Nicolle LE, Hoban DJ, Kazmierczak KM, Badal RE, Sahm DF. Susceptibility patterns and ESBL rates of Escherichia coli from urinary tract infections in Canada and the United States, SMART 2010–2014. Diagn Microbiol Infect Dis 2016; 85:459–65.
4. Jernigan JA, Hatfield KM, Woldford H, et al. Multidrug-resistant bacterial infections in U.S. hospitalized patients, 2012–2017. N Engl J Med 2020; 382:1309–19.
5. Ben-Ami R, Schwaber MJ, Navon-Venezia S, et al. Influx of extended-spectrum beta-lactamase-producing Enterobacteriaceae into the hospital. Clin Infect Dis 2006; 42:925–34.
6. Wenzlue Z, Bleasdale SC, Sikka M, et al. Phase I study to evaluate the pharmacokinetics, safety, and tolerability of two dosing regimens of oral fosfomycin tromethamine in healthy adult participants. Antimicrob Agents Chemother 2018; 62:e00464-18.
7. Derrington CG, Benavides N, Delate T, Fish DN. Multiple-dose oral fosfomycin for treatment of complicated urinary tract infections in the outpatient setting. Open Forum Infect Dis 2020; 7:XXX–XX.
8. Hatlen TJ, Flor R, Nguyen MH, Lee GH, Miller LG. Oral fosfomycin use for pyelonephritis and complicated urinary tract infections: a 1 year review of outcomes and prescribing habits in a large municipal healthcare system. J Antimicrob Chemother 2020; 75:1993–7.
9. Grayson ML, Macesic N, Trevillyan J, et al. Fosfomycin for treatment of prostatitis: new tricks for old dogs. Clin Infect Dis 2015; 61:1141–3.
10. Li HK, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. N Engl J Med 2019; 380:425–36.
11. Amosio-Grotton M, Madu A, Madu CN, et al. Sequential parenteral and oral ciprofloxacin regimen versus parenteral therapy for bacteremia: a pharmacoeconomic analysis. Ann Pharmacother 1996; 30:596–602.
12. Iversen K, Filemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 2019; 380:415–24.
13. Senel S, Tashbakan M, Pulukcu H, et al. Carbapenem versus fosfomycin tromethanol in the treatment of extended-spectrum beta-lactamase-producing Escherichia coli-related complicated lower urinary tract infection. J Chemother 2010; 22:355–7.
14. Neuner EA, Sekeres J, Hall GS, van Duin D. Experience with fosfomycin for treatment of urinary tract infections due to multidrug-resistant organisms. Antimicrob Agents Chemother 2012; 56:5744–8.
15. Pulukcu H, Tashbakan M, Sipahi OR, Yamanathan T, Aydilir S, Ulusoy S. Fosfomycin in the treatment of extended spectrum beta-lactamase-producing Escherichia coli-related lower urinary tract infections. Int J Antimicrob Agents 2007; 29:62–5.
16. Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin. Clin Microbiol Rev 2016; 29:321–47.
17. Seni SM, Gichone P, Vee HF Jr. Development and implementation of expected practices to reduce inappropriate variations in clinical practice. JAMA 2016; 315:2163–4.
18. Yadav K, Masuda E, Minejima E, Spellberg B. Expected practice as a novel antibiotic stewardship intervention. Open Forum Infect Dis 2019; 6:XXX–XX.