# Cephalosporins for Outpatient Pyelonephritis in the Emergency Department: COPY-ED Study

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**Study objective:** The primary objective of our study was to compare the effectiveness of oral cephalosporins versus fluroquinolones and trimethoprim/sulfamethoxazole (TMP-SMX) for the treatment of pyelonephritis in patients discharged home from the emergency department (ED).

**Methods:** This was a multicenter, retrospective, observational cohort study of 11 geographically diverse US EDs. Patients aged ≥18 years diagnosed with pyelonephritis and discharged home from the ED between January 1, 2021 and October 31, 2023 were included. The primary outcome was treatment failure at 14 days defined as a composite outcome of the following: (1) recurrence of urinary symptoms, (2) repeat ED visit or hospitalization for a urinary tract infection, (3) receipt of a new antibiotic prescription for urinary tract infection. Secondary outcome was appropriateness of empiric treatment based on urine culture susceptibility.

**Results:** Among the 851 patients who met inclusion criteria, 647 patients received a cephalosporin, and 204 patients received an Infectious Diseases Society of America guideline-endorsed first-line treatment (fluroquinolones, TMP-SMX). Overall, baseline characteristics were similar between the 2 cohorts. Rates of treatment failure were not significantly different in the cephalosporin group compared with the fluroquinolone/TMP-SMX groups (17.2% of cephalosporin vs 22.5% of fluroquinolone/TMP-SMX group, difference=5.3%, 95% confidence interval −0.118 to 0.01). After adjusting for potential confounders, cephalosporin use was not associated with treatment failure (odds ratio=0.22, 95% confidence interval 0.03 to 1.95). There was no difference in rates of appropriate empiric treatment based on urine culture susceptibility.

**Conclusion:** Oral cephalosporins were associated with similar treatment failure rates compared with Infectious Diseases Society of America guideline-endorsed treatments for the treatment of pyelonephritis in ED patients discharged home. [Ann Emerg Med. 2025;85:240-248.]

Please see page 241 for the Editor's Capsule Summary of this article.



0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2024.10.013

## INTRODUCTION

### Background

Urinary tract infections (UTIs) account for more than 3 million emergency department (ED) visits annually and remain one of the most common indications for antibiotics.[1-3] Societal costs of UTIs, including health care costs and lost wages, are approximately $3.5 billion annually in the United States.[1,4] Additionally, UTIs are associated with a significant cause of morbidity, contributing to recurrent infections, sepsis due to a urinary source, antibiotic-related adverse events, and hospitalizations.[1,4]

The 2010 Infectious Diseases Society of America (IDSA) guidelines recommend fluoroquinolones as first-line therapy for acute pyelonephritis if the prevalence of *Escherichia coli* resistance is <10%.[5] However, since the guideline's publication, *E coli* fluoroquinolone-resistance rates now exceed 20% in many geographic regions in the United States.[6,7] Additionally, fluoroquinolones are increasingly associated with serious adverse events as well as collateral damage through the promotion of bacterial resistance.[5,8] Trimethoprim-sulfamethoxazole (TMP-SMX) has also been used for decades for the treatment of acute uncomplicated pyelonephritis. However, *E coli* resistance rates have exceeded 20% in most US communities for many years and IDSA guidelines recommend against its use as

**Editor's Capsule Summary**

*What is already known on this topic*

There is increasing *Escherichia coli* resistance to both fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX).

*What question this study addressed*

What are the 14-day failure rates between patients given cephalosporins and those given guideline-endorsed fluoroquinolones or TMP-SMX for outpatient pyelonephritis care after an emergency department visit?

*What this study adds to our knowledge*

In a retrospective cohort study of 851 patients with presumed pyelonephritis, failure rates were similar for the cephalosporin and flouroquinolone or TMP/SMX treatment groups.

*How this is relevant to clinical practice*

These data support the use of oral cephalosporins in the outpatient treatment of pyelonephritis.

first-line treatment.[5] Due to the increasing prevalence of fluoroquinolone and TMP-SMX resistance, which now exceed thresholds recommended for abandoning empiric administration of these antimicrobials, IDSA guidelines stress the need to evaluate alternative regimens.[5]

Oral cephalosporins may represent a cost-effective alternative for the treatment of acute pyelonephritis and are recommended by the IDSA guidelines as a second-line treatment option in combination with a dose of a long-action intravenous antibiotic (eg, ceftriaxone) being administered before discharge.[5] However, due to the lack of evidence to support the use of cephalosporins for acute pyelonephritis, the IDSA guidelines highlighted the lack of comparative effectiveness research as a significant research gap with top priority for future research. The primary objective of our study was to determine the effectiveness of oral cephalosporins compared with guideline-endorsed antimicrobial treatment across geographically diverse ED patients for the treatment of outpatient pyelonephritis.

## MATERIALS AND METHODS

### Study Design and Setting

We conducted a multicenter, retrospective observational cohort study at 11 geographically diverse, US hospital EDs that participate in the Emergency Medicine PHARMacotherapy Research NETwork.

### Selection of Participants

Patients were identified based on primary diagnosis of uncomplicated or complicated pyelonephritis using International Classification of Diseases (ICD)-10 codes: ICD-10, N10, and N39.0 between January 1, 2021 and August 1, 2023. All patients aged ≥18 years who had a primary or secondary diagnosis of uncomplicated or complicated pyelonephritis in the ED, reported symptoms of a UTI, and were discharged home on oral antimicrobial treatment were included. Exclusion criteria were as follows: pregnancy, suspected or confirmed acute bacterial prostatitis, orchitis, epididymitis, or chronic bacterial prostatitis as determined by history and/or physical examination, urinary tract surgery within 7 days prior to their ED visit or urinary tract surgery planned during the study period. For patients with multiple ED visits during the study period, only the first visit was included in the study.

### Measurements

All data variables were defined a priori and were available for abstraction from the electronic medical record. Data collected included patient-specific characteristics (eg, age, sex, medical history, and laboratory test results), signs and symptoms (eg, fever, dysuria, flank pain, and frequency/urgency) of UTI, risk factors for antimicrobial resistance, urine microbiological results and susceptibilities, antimicrobial treatments administered in the ED, and antimicrobial treatments prescribed at discharge from the ED. Data were abstracted at each site by a trained data abstractor with an audit of a random sample of charts (~10%) completed by each site's principal investigator to ensure accuracy of the data collected. All site institutional review boards approved the study. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.[9]

### Definitions

Pyelonephritis was defined as patients reporting urinary symptoms in addition to a fever (temperature >38 °C), chills, flank pain, or costovertebral-angle tenderness.[10] Complicated pyelonephritis was classified in patients if they were male or had a pre-existing anatomical condition or current immunocompromising condition that may increase their risk of treatment failure or serious outcomes.[6,7,11] Pre-existing urinary tract anatomical conditions included the following: urinary obstruction, neurogenic bladder, history of kidney stones, and moderate to severe renal insufficiency (eg, creatinine clearance <30 mL/min, hemodialysis dependence). Immunocompromising conditions included

active cancer, current use of immunosuppressants (eg, renal transplant), and HIV infection. We classified patients without criteria for complicated pyelonephritis as uncomplicated infections.

A positive urine culture was defined as a specimen with $\geq 10^4$ CFU/mL bacteria isolated in the urine culture and with $\leq$2 microorganisms isolated in the urine culture.[12,13] The following pathogens were considered to be contaminants: *Lactobacillus*, non-saprophyticus coagulase-negative *Staphylococcus*, *Corynebacterium* species; or $\beta$-hemolytic streptococci. In addition, if a urine culture grew >2 microorganisms, it was considered to be contaminated. Because the clinical laboratories at each institution did not report oral cephalosporin resistance to Enterobacterales, we used the Clinical and Laboratory Standards Institute recommended cefazolin breakpoint of an minimum inhibitory concentration of $\leq$16 μg/mL to define cephalosporin resistance.[14]

Antimicrobial resistance risk factors were defined as having one of the following: hemodialysis dependence, urinary tract abnormality (eg, long-term urinary catheter, nephrolithiasis, neurogenic bladder, and nephrostomy tubes), receipt of intravenous or oral antimicrobial treatments in the prior 90 days, history (within the past 12 months) of multidrug-resistant pathogen (blood or urine culture site), or residence in a long-term care facility.[7,12] Multidrug-resistant pathogens were defined as one of the following pathogens: methicillin-resistant *Staphylococcus aureus*; vancomycin-resistant enterococci; extended spectrum $\beta$-lactamase-producing Enterobacterales; carbapenem-resistant Enterobacterales; *Pseudomonas aeruginosa; Stenotrophomonas maltophilia*; *Acinetobacter* spp.; AmpC $\beta$-lactamase-producing Enterobacterales; or a single microorganism with resistance to antibiotics from 3 different classes within the past 12 months.

### Outcomes

Our primary outcome was the rate of outpatient treatment failure of cephalosporins compared with IDSA guideline-endorsed first-line treatments (fluoroquinolones, TMP-SMX) at 14 days as recommended by the US Food and Drug Administration Guidance for conducting UTI studies.[13] Treatment failure was defined if the patient had one of the following within 14 days of discharge from the ED: (1) receipt of a new antimicrobial prescription for UTI based on worsening of symptoms, adverse drug reaction, or identified resistance on urine culture and susceptibility; or (2) recurrence of symptoms (as documented in the electronic medical record); or (3) ED or urgent care visit with a primary diagnosis of UTI; or (4) hospital admission with the primary diagnosis of UTI. Secondary outcomes included a comparison of the rate of treatment failure between groups of patients who received a first or second-generation cephalosporin (eg, cephalexin, cefadroxil, and cefuroxime), third-generation cephalosporin (eg, cefpodoxime and cefdinir), or fluoroquinolone/TMP-SMX, rates of appropriate empiric antimicrobial treatment based on urine culture and susceptibilities, rates of treatment failure based on the duration of treatment prescribed.

### Statistical Analysis

Frequencies of cephalosporins, fluoroquinolones or TMP/SMX, or other treatments were reported for varying patient demographics, clinical histories, UTI characteristics, and risk factors. Culture-positive uropathogens frequencies were stratified by cephalosporin versus fluoroquinolones or TMP/SMX. Frequencies of the specific oral antibiotic prescribed at discharge were also determined. To characterize the average duration of treatment, the mean and SD were determined for each oral antibiotic prescribed at discharge. Z-test for proportions were used to determine differences in proportion for primary and secondary outcomes based on antibiotic type received. Logistic regression models were built to assess associations between antibiotic received and outcomes while accounting for various confounders (eg, sex, whether a patient was considered complicated, whether a previous intravenous or oral antibiotic was used in last 90 days, and urinary tract abnormalities). Data management and statistical analysis were performed using R (R version 4.4.0, https://www.R-project.org).

## RESULTS

Among the 909 patients who met inclusion criteria, 647 patients comprised the cephalosporin group, and 204 patients comprised the guideline-endorsed first-line treatment (fluoroquinolones, TMP-SMX) group (Figure). Overall, baseline characteristics, UTI characteristics, and antimicrobial resistance risk factors were similar between the cephalosporin and fluoroquinolone/TMP-SMX cohorts (Table 1). *E coli* resistance was reported in 7.3% in the cephalosporin group, 29% in the fluoroquinolone group, and 12.6% in the TMP-SMX group. Cephalexin (n=274) was the most prescribed cephalosporin with the average treatment duration of all cephalosporin being 9.1±2.3 days. The average treatment duration for fluoroquinolones and TMP-SMX was 7.3±1.1 days and 9.01±2.9 days,

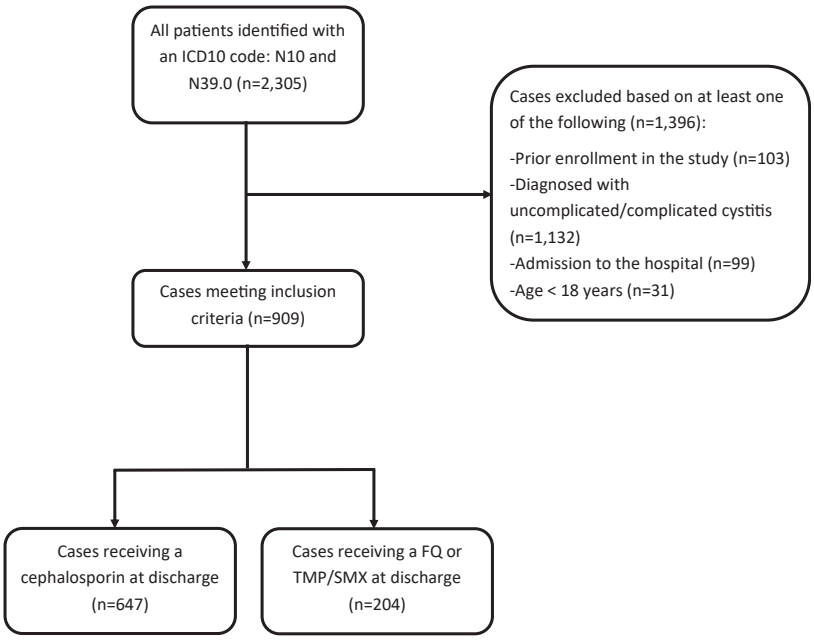


**Figure.** A flow diagram of outpatient pyelonephritis treatment. *FQ*, fluroquinolone; *ICD*, International Classification of Diseases; *TMP/SMX*, trimethoprim-sulfamethoxazole.

respectively (Table 2). Dosing regimens for each antimicrobial prescribed at discharge are listed in Table E1 (available at https://www.annemergmed.com). Intravenous antimicrobials were administered prior to ED discharge in 60.4% of the cephalosporin cohort and 46.6% of the fluoroquinolone/TMP-SMX cohort (Table 2), with ceftriaxone being the most commonly administered intravenous antibiotic in both cohorts (86.8% of the patients). Intravenous antimicrobial administration per study site are presented in Figure E1 (available at https://www.annemergmed.com). Additionally, details regarding the antimicrobial regimens and culture susceptibility patterns are presented in Table 2 and Table 3, respectively.

The composite primary outcome of treatment failure at 14 days was not significantly different in the cephalosporin group compared with the fluoroquinolone/TMP-SMX group (17.2% of cephalosporin vs 22.5% of fluoroquinolone/TMP-SMX group, difference=5.3%, 95% confidence interval [CI] –0.12 to 0.01) (Table 4). Treatment failure at 14 days per study site are listed in Figure E2 (available at https://www.annemergmed.com). After adjusting for potential differences in baseline characteristics (eg, receipt of intravenous antibiotics before discharge), receiving a cephalosporin upon ED discharge was not significantly associated with treatment failure (odds ratio [OR]=0.22, 95% CI 0.03 to 1.95). Similarly, within the secondary outcome analysis there was no significant difference found in treatment failure when comparing first/second-generation cephalosporins with third-generation cephalosporins (16.9% vs 17.4%, difference=0.5%, 95% CI –0.07 to 0.05), first/second-generation cephalosporins with fluoroquinolone/TMP-SMX (16.9% vs 22.5%, difference=5.6%, 95% CI –0.13 to 0.01), or third-generation cephalosporins with fluoroquinolone/TMP-SMX 17.4% vs 22.5, difference=5.1%, 95% CI –0.12 to 0.02) (Table 5). There was no significant difference in treatment failure in patients who received shorter courses than recommended by the IDSA guidelines in the cephalosporin group (<10 days—18.0% vs ≥10 days—16.6%, 95% CI –0.046 to 0.074), fluoroquinolone group (<7 days—33.3% vs ≥7 days—25.0%, 95% CI –0.171 to 0.338), or TMP-SMX group (<10 days—22.7% vs ≥10 days—15.4%, 95% CI –0.085 to 0.231).

After adjusting for gender, complicated infections, previous use of intravenous or oral antibiotics, and urinary tract abnormality, the odds of treatment failure at 14 days was not statistically different in patients who received fluoroquinolone or TMP/SMX (adjusted OR 1.275 [95% CI 0.86 to 1.9]) compared with cephalosporins. In addition, patients who received a fluoroquinolone or TMP/SMX did not have a statistically significant higher odds of requiring a new antibiotic prescription based on antibiotic resistance as reported on the urine culture and susceptibilities report than those

**Table 1.** Demographic and clinical characteristics.

| Demographics and Clinical Characteristics | Cephalosporins (n=647) | FQs or TMP/SMX (n=204) |
|---|---|---|
| **Demographics** | | |
| Age, y, median (IQR) | 36.0 (18-92) | 33.0 (18-88) |
| Sex, n (%) | | |
| Female | 556 (85.9%) | 170 (83.3%) |
| Male | 85 (13.1%) | 33 (16.2%) |
| **Clinical history, n (%)** | | |
| Diabetes | 88 (13.6%) | 12 (5.9%) |
| Chronic kidney disease | 32 (4.9%) | 10 (4.9%) |
| Advanced liver disease (cirrhosis/ESLD) | 5 (0.8%) | 1 (0.5%) |
| Dialysis dependence | 2 (1.0%) | 2 (1.0%) |
| **Pyelonephritis classification, n (%)** | | |
| Uncomplicated | 466 (72%) | 149 (73%) |
| Complicated | 173 (26.7%) | 53 (26%) |
| **Complicating characteristic, n (%)*** | n=173 | n=53 |
| Male | 66 (38.2%) | 21 (39.8%) |
| Diabetes | 42 (24.3%) | 9 (17.0%) |
| Obstructing stone | 25 (14.5%) | 9 (17.0%) |
| Immunosuppression | 12 (6.9%) | 6 (11.3%) |
| Pregnancy | 10 (5.8%) | 0 (0%) |
| Neurogenic bladder | 7 (4.0%) | 3 (5.7%) |
| Chronic indwelling catheter | 6 (3.5%) | 3 (5.7%) |
| Nephrostomy tubes | 5 (2.9%) | 2 (3.8%) |
| **Pyelonephritis symptoms, n (%)** | | |
| Flank pain | 504 (77.9%) | 157 (77%) |
| Dysuria | 333 (51.5%) | 103 (50.5%) |
| Fever | 202 (31.2%) | 65 (31.9%) |
| Suprapubic pain | 193 (29.8%) | 61 (29.9%) |
| Frequent/urgent urinary symptoms | 184 (28.4%) | 57 (27.9%) |
| Fatigue/malaise | 73 (11.3%) | 13 (6.4%) |
| Altered mental status | 6 (0.9%) | 1 (0.5%) |
| **Risk factors for antimicrobial resistance, n (%)** | | |
| Previous IV or oral antibiotic use in the last 90 d | 82 (12.7%) | 52 (25.5%) |
| History of multidrug-resistant pathogen | 15 (2.3%) | 6 (2.9%) |
| ≥3 different classes | 9 (1.4%) | 1 (0.5%) |
| Extended-spectrum beta-lactamase | 4 (0.6%) | 2 (1%) |
| Methicillin-resistant *Staphylococcus aureus* | 3 (0.5%) | 2 (1.0%) |
| Vancomycin-resistant *Enterococci* | 1 (0.2%) | 0 (0%) |
| *Pseudomonas aeruginosa* | 0 (0%) | 2 (1.0%) |
| Urinary tract abnormality (eg, catheter) | 43 (6.6%) | 20 (9.8%) |
| Nephrolithiasis | 22 (3.4%) | 2 (1.0%) |
| Long-term or intermittent urinary catheter | 19 (2.9%) | 10 (4.9%) |
| Neurogenic bladder | 4 (0.6%) | 3 (1.5%) |
| Residence in a long-term care facility | 3 (0.5%) | 1 (0.5%) |
| Hemodialysis dependence | 3 (0.5%) | 2 (1%) |
| Nephrostomy tubes | 2 (0.3%) | 4 (2%) |
| Renal transplant | 1 (0.2%) | 3 (1.5%) |
| **Any IV antibiotic at discharge, n (%)** | 397 (60.4%) | 95 (46.6%) |

*ESLD*, end stage liver disease; *FQ*, Fluroquinolone; *IQR*, interquartile range; *TMP/SMX*, trimethoprim-sulfamethoxazole.
*Totals may not sum to n total due to missing values within category.

with cephalosporin (adjusted OR 1.614 [95% CI 0.829 to 3.143]).

## LIMITATIONS

Our study has several limitations that must be addressed. First, the retrospective design may have impacted completeness of clinical data obtained during the ED visit. Also, this limits the ability to control for confounding baselines demographic variable that may impact the incidence of the primary outcome (eg, receipt of intravenous antibiotics prior to discharge, received previous treatments for a UTI). However, we purposely selected data points that are likely to be accurately reported and are easily abstractable from the electronic medical record. Second, UTI diagnosis is associated with high rates of diagnostic error in the ED which could have impacted study population.[15] To decrease the rate of misdiagnosis, we used a combination method of ICD-10 diagnosis code for pyelonephritis and determined if the patient had symptoms of UTI documented in the electronic medical record increasing our likelihood of only including patients who had a true diagnosis of pyelonephritis. Third, patients could receive care at facilities outside of the study sites before or after their ED visit. If patients presented elsewhere with conditions that met criteria for the primary outcome, it would not be documented, and could lead to a falsely low incidence of our primary outcome. Fourth, due to the retrospective nature of our study, there was no practical way to determine the true susceptibility of each oral cephalosporin prescribed. Therefore, we used the cefazolin as

**Table 2.** Discharge antibiotics.

| Antibiotic | | n (%) | Length of Therapy Mean (SD) | Length of Therapy Median (IQR) |
|---|---|---|---|---|
| Cephalosporin | Combined (n=647) | 391 (60.4) | 9.05 (2.29) | 10 (7-10) |
| | Cephalexin | 274 (42.3) | 8.68 (2.21) | 10 (7-10) |
| | Cefdinir | 230 (35.5) | 9.14 (2.3) | 10 (7-10) |
| | Cefuroxime | 54 (8.3) | 8.75 (1.72) | 10 (7-10) |
| | Cefpodoxime | 50 (7.7) | 11.34 (2.3) | 10 (10-14) |
| | Cefadroxil | 38 (5.9) | 8.57 (1.77) | 10 (7-10) |
| | Cefixime | 1 (0.2) | 7 (N/A)* | 7 (7-7) |
| FQ or TMP/SMX | Combined (n=204) | 95 (46.6) | 8.26 (2.69) | 7 (7-10) |
| | Sulfamethoxazole/trimethoprim | 96 (47.1) | 9.01 (3.00) | 10 (7-10) |
| | Ciprofloxacin | 80 (39.2) | 7.75 (2.03) | 7 (7-7) |
| | Levofloxacin | 28 (13.7) | 7.07 (2.56) | 7 (5-7) |

*FQ*, Fluroquinolone; *TMP/SMX*, trimethoprim-sulfamethoxazole.
*Unable to calculate SD due to a count of 1.

a surrogate to define oral cephalosporin susceptibility which may have underreported true resistance to cephalexin, and overreported resistance to the third-generation cephalosporins (eg, cefpodoxime or cefdinir). Finally, although we included 11 EDs representing various geographic regions across the United States, the generalizability of our findings to other regions not included in our study and other practice settings (eg, urgent care or ambulatory clinics) may be limited.

## DISCUSSION

To our knowledge, our study is the first multicenter study to evaluate the effectiveness of cephalosporins for outpatient treatment of pyelonephritis in patients discharged home from the ED. Although cephalosporins yield high urinary concentrations, there has been controversy as to whether the pharmacokinetics and pharmacodynamics of cephalosporins result in adequate drug concentrations in the kidney tissue to

**Table 3.** Pathogens identified from urine cultures and susceptibilities.

| Uropathogen | n | % of Total Sample | Cephalosporins (n=647) N | Cephalosporins (n=647) % | FQs or TMP/SMX (n=204) N | FQs or TMP/SMX (n=204) % |
|---|---|---|---|---|---|---|
| Enterobacterales | | | | | | |
| *Escherichia coli* | 341 | 40.1 | 268 | 41.4 | 73 | 35.8 |
| *Klebsiella pneumoniae* | 19 | 2.2 | 13 | 2.0 | 6 | 2.9 |
| *Proteus* spp. | 12 | 1.4 | 10 | 1.5 | 2 | 1.0 |
| *Enterobacter aerogenes* | 11 | 1.3 | 8 | 1.2 | 3 | 1.5 |
| *Klebsiella oxytoca* | 7 | 0.8 | 3 | 0.5 | 4 | 2.0 |
| *Enterobacter cloacae* | 5 | 0.6 | 3 | 0.5 | 2 | 1.0 |
| *Citrobacter* spp. | 4 | 0.5 | 2 | 0.3 | 2 | 1.0 |
| Non-Enterobacterales | | | | | | |
| *Staphylococcus saprophyticus* | 19 | 2.2 | 12 | 1.9 | 7 | 3.4 |
| *Enterococcus* spp. | 8 | 0.9 | 5 | 0.8 | 3 | 1.5 |
| *Staphylococcus aureus* | 5 | 0.6 | 4 | 0.6 | 1 | 0.5 |
| *Pseudomonas aeruginosa* | 3 | 0.4 | 2 | 0.3 | 1 | 0.5 |
| Multidrug resistant | | | | | | |
| Other* | 16 | 1.9 | 9 | 1.4 | 7 | 3.4 |
| ESBL-producing pathogen† | 6 | 0.7 | 4 | 0.6 | 2 | 1.0 |
| CRE-producing pathogen† | 0 | 0 | 0 | 0 | 0 | 0 |

*CRE*, Carbapenem-resistant Enterobacterales.
*Other = pathogens not commonly isolated in the urinary tract but are considered pathogenic (eg, *Aerococcus urinae*, *Stenotrophomonas maltophilia*, etc).
†The multidrug-resistant pathogens presented consist of a subset of the Enterobacterales pathogens.

**Table 4.** Outcomes.

| Outcomes | Cephalosporins (n=647) | FQs or TMP/SMX (n=204) | Difference in Proportion (95% CI) |
|---|---|---|---|
| **Treatment failure within 14 d, n (%)** | 111 (17.2%) | 46 (22.5%) | −5.3% (−12% to 1.0%) |
| **Reason for treatment failure within 14 d, n (%)** | | | |
| ED or urgent care visit for UTI | 86 (13.3%) | 29 (14.2%) | −0.9% (−6.0% to 5.0%) |
| Receipt of a new antibiotic prescription for UTI | 63 (9.7%) | 28 (13.7%) | −4% (−9.0% to 1.0%) |
| Recurrence of symptoms | 61 (9.4%) | 24 (11.8%) | −2.4% (−7.0% to 3.0%) |
| Hospital admission for UTI | 24 (3.7%) | 13 (6.4%) | −2.7% (−6.0% to 1%) |
| **Reason for receipt of new antibiotic prescription, n (%)** | | | |
| Resistance reported on susceptibility report | 29 (4.5%) | 15 (7.4%) | −3.9% (−7.0% to 1.0%) |
| Clinical status worsening | 28 (4.3%) | 11 (5.4%) | −1.1% (−5% to 2%) |
| Adverse drug reaction | 5 (0.8%) | 1 (0.5%) | 0.3% (−1% to 0.2%) |
| De-escalation after susceptibility report | 1 (0.2%) | 0 (0%) | 0.2% (−0.1% to 0.5%) |
| **Appropriate empiric treatment based on urine cultures and susceptibilities, n (%)** | | | |
| Yes | 266 (81.6%) | 83 (76.1%) | 5.5% (−7% to 8%) |

*CI*, Confidence interval.

exceed the pathogen's minimum inhibitory concentration.[16] We found that when compared with IDSA guideline-endorsed antimicrobial treatments, cephalosporins had similar rates of symptom recurrence, repeat ED visits for UTI, and prescribing of subsequent outpatient antibiotics within 14 days of discharge.

Previous studies have evaluated the use of cephalosporins for the treatment of pyelonephritis. Fosse et al[17] and Lin et al[18] explored acute pyelonephritis treatment with either a cephalosporin or fluoroquinolone/TMP-SMX and found no difference in treatment failure rates between cephalosporins and fluoroquinolone/TMP-SMX ([17% vs 17%; $P<.851$] and [15.3 vs 17.4%], respectively).[17,18] Similarly, Vogler et al[19] performed a retrospective cohort study of women discharged from the ED with acute uncomplicated pyelonephritis on either a cephalosporin or fluoroquinolone/TMP-SMX. Patients who received a cephalosporin had a significantly lower failure rate at 30 days compared with fluoroquinolone/TMP-SMX treatment (0% vs 23%; $P<.001$).[19] Although our rates of treatment failure are similar to previous reports, the past studies were limited by being single center studies with stricter inclusion criteria (eg, the majority of patients who were classified as having a complicated infection were excluded), which decreases the generalizability of their findings. In contrast to our findings, a large retrospective cohort study of outpatient adults in 31 Veteran's Affairs medical centers found that patients who received $\beta$-lactams

**Table 5.** Secondary outcomes based on cephalosporin generation.

| Secondary Outcomes | First/Second-Generation Cephalosporins* (n=366) | Third-Generation Cephalosporins* (n=281) | FQs or TMP/SMX (n=204) | Difference (95% CI) |
|---|---|---|---|---|
| Treatment failure within 14 d, n (%) | 62 (16.9%) | 49 (17.4%) | | −0.064, 0.054 |
| | 62 (16.9%) | | 46 (22.5%) | −0.125, 0.013 |
| | | 49 (17.4%) | 46 (22.5%) | −0.124, 0.021 |
| | **First/Second-Generation Cephalosporins* (n=202)** | **Third-Generation Cephalosporins* (n=124)** | **FQs or TMP/SMX (n=109)** | **Difference (95% CI)** |
| Appropriate empiric treatment based on urine cultures and susceptibilities, n (%)† | 162 (80.2%) | 104 (83.9%) | | −0.003, 0.149 |
| | 162 (80.2%) | | 83 (76.1%) | −0.049, 0.12 |
| | | 104 (83.9%) | 83 (76.1%) | −0.125, 0.051 |

*Cefazolin susceptibility was used as a surrogate to predict susceptibility for all cephalosporins.
†Total used for this test was on a smaller population due to exclusion of samples with no growth or contamination specific analysis.

had a higher rate of clinical failure or hospitalization compared with ciprofloxacin (OR=1.89; 95% CI 1.23 to 2.90; *P*=.002) and TMP-SMX (OR=1.50; 95% CI 1.00 to 2.26; *P*=.05).[20] The failure rate difference compared with our study is likely related to differences in enrolled patient population and criteria used to define uncomplicated pyelonephritis. Our enrolled population consisted primarily of uncomplicated pyelonephritis (73% of the population) in young females, in contrast to the previous study which primarily included men (75% of the population), who are, by definition, classified as having a complicated infection due to their sex.

There are several concerns surrounding the use of cephalosporins as the primary empiric treatment of outpatient pyelonephritis. First, some oral cephalosporins (eg, cefpodoxime or cefdinir) have poor bioavailability which may limit their ability to achieve adequate renal tissue concentrations to adequately treat pyelonephritis.[21] Unfortunately, pharmacokinetic/pharmacodynamic studies evaluating the oral cephalosporins with low bioavailability (eg, cefpodoxime or cefdinir) to assess the efficacy and minimum dose for pyelonephritis have not been conducted.[16] It is still uncertain whether the low bioavailability of certain cephalosporins results in inadequate renal tissue concentrations at the currently recommended doses. Despite this concern, we found no difference in treatment failure between third-generation cephalosporins and first/second generation in our analysis. A second concern is that variations in the beta-lactam side chains across cephalosporin generations are associated with varying susceptibility patterns resulting in higher resistance rates for first/second-generation cephalosporins compared with extended-spectrum third-generation cephalosporins.[22] Because of these concerns, IDSA guidelines recommend a one-time intravenous antibiotic administration for patients receiving empiric cephalosporins.[5] In our study cohort, a higher proportion of patients in the cephalosporin group received a one-time dose of an intravenous antibiotic before they were discharged home. This could favor the cephalosporin group because fluoroquinolones and TMP-SMX have excellent bioavailability, so they are unlikely to benefit from receiving an intravenous antibiotic dose. However, our analysis did not find a difference in the rate of recurrence after controlling for the receipt of intravenous antibiotics. Our data indicate that commonly used cephalosporins appear have similar rates of treatment failure in treating pyelonephritis. However, future prospective, comparative effectiveness studies are necessary to confirm or refute our findings.

The IDSA guideline recommendation to further study cephalosporins for the treatment of pyelonephritis was primarily driven by the increasing rate of *E coli* resistance to fluoroquinolones and TMP-SMX.[5] Similar to our previous work evaluating *E coli* resistance rates in ED patients diagnosed with a UTI, we found that fluoroquinolone and TMP-SMX *E. coli* resistance was >10% which exceeds the threshold recommended by the guidelines to utilize different empiric antibiotics.[5,7,23] Although none of the EDs participating in the study have specific protocols for outpatient pyelonephritis treatment, rising *E coli* resistance rates, along with new Food and Drug Administration boxed warnings regarding serious adverse events associated with fluoroquinolones, likely prompted ED providers to adopt cephalosporins as the primary empiric treatment for pyelonephritis. The most recent update of the IDSA guidelines for pyelonephritis was in 2011, and its recommendations may no longer be as salient to modern clinical practice.[5] This was highlighted by the fact that more than 70% of the included cohort received a cephalosporin for empiric treatment.

In summary, our study found no difference in rates of treatment failure in patients treated with cephalosporins or guideline-endorsed treatments in patients diagnosed with pyelonephritis and discharged home from the ED. Cephalosporins may serve as an alternative to guideline-endorsed treatments, especially in geographic regions where high *E coli* resistance rates have been reported. Although cephalosporins were the most prescribed antibiotics, future clinical trials should determine treatment failure rates based on the specific class of cephalosporin prescribed.

*The authors wish to thank Keith Burrell, Lauren Gravert, PharmD Candidate (2025), University of Iowa.*

*Supervising editor*: Gillian R. Schmitz, MD. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

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*Author contributions*: BF and JK contributed to the study concept and design; BF, JK, CB, AM, AZ, DZ, PS, RS, JK, RF, GS, GH, BN, AK, AP, and AL involved acquisition of data. BF, JK, and DS analyzed and interpreted the data and drafted the manuscript; BF, JK, CB, AM, AZ, DZ, PS, RS, JK, RF, GS, GH, BN, AK, AP, MR, DS and AL performed the critical revision of manuscript for important intellectual content, statistical expertise, and acquisition of funding. BF takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Data sharing statement:* The entire deidentified dataset, data dictionary and analytic code for this investigation are available upon request, from the date of the article publication by contacting Dr. Brett Faine at brett-faine@uiowa.edu.

*Funding and support:* By *Annals'* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have declared that no competing interests exist. REDCap database was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002537.

*Publication dates:* Received for publication August 5, 2024. Revisions received September 17, 2024, and October 2, 2024. Accepted for publication October 14, 2024.

*Presentation information*: This work was accepted and presented at the SAEM Annual Meeting, May 14-17, 2024, Phoenix, AZ.

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