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ORIGINAL ARTICLE

Cefazolin versus fluoroquinolones for the treatment of community-acquired urinary tract infections in hospitalized patients

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Abstract

Literature for the treatment of hospitalized patients with community-acquired urinary tract infections (UTI) is limited. Previous outpatient studies do not support the use of oral beta-lactams compared with oral fluoroquinolones (FQ) due to poor clinical cure rates. However, recent studies evaluating intravenous (IV) beta-lactams in more complicated cases demonstrate promising cure rates. In addition, the use of more narrow-spectrum beta-lactams may be preferable when possible, due to a lower incidence of "collateral damage" compared with FQ. This was a retrospective, non-inferiority, single-center, cohort study evaluating the effectiveness of IV cefazolin compared with FQ for the treatment of community-acquired UTI in an inpatient setting. The primary endpoint was clinical failure, defined as the presence of one or more signs or symptoms of UTI that required a change in antibiotics, re-initiation of antibiotics for UTI treatment during the hospital stay, and re-hospitalization with a UTI diagnosis within 30 days after discharge. The secondary endpoints were a microbiological cure, hospital length of stay, inpatient antibiotic duration of treatment, emergence of resistance, and *Clostridium difficile* infection within 30 days of the end of antibiotic therapy. Overall, 73 patients were treated with either cefazolin ($n = 43$) or FQ ($n = 30$) between April 2015 to January 2016. The clinical failure rates were 2% and 7% in the cefazolin and FQ groups, respectively ($p = 0.56$). Additionally, there were no significant differences between the secondary endpoints. Treatment with cefazolin, a more narrow-spectrum agent with a potential for less "collateral damage," was non-inferior to FQ for community-acquired UTI in an inpatient setting.

Keywords Cefazolin · Fluoroquinolones · Urinary tract infection · Antimicrobial stewardship

Introduction

Current Infectious Diseases Society of America (IDSA) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) clinical practice guidelines for acute uncomplicated cystitis recommend the use of nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomycin as first-line therapy, while fluoroquinolones (FQ) and oral beta-lactam antibiotics are suggested to be used as alternative therapy [1]. Although FQ have been proven to be highly efficacious for the treatment of uncomplicated urinary tract infections (UTIs), there is a great deal of "collateral damage" associated with their use, including the risk of developing *Clostridium difficile* (*C. difficile*) infection and higher rates of colonization with multidrug-resistant organisms [2, 3]. With these considerations, guidelines recommend reserving therapy with FQ for "important uses other than acute cystitis" [1].

Oral beta-lactam agents, on the other hand, are recommended as alternative agents due to their lack of efficacy for uncomplicated UTIs compared with FQ. Hooton et al. [4] assessed clinical cure of a 3-day regimen of amoxicillin-clavulanate compared with ciprofloxacin for the treatment of acute uncomplicated UTI and found that clinical cure was significantly higher in the ciprofloxacin group compared with the amoxicillin-clavulanate group (77% vs. 58%, respectively;

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$p < 0.05$). In a similar study design, a 3-day regimen of cefpodoxime did not meet criteria for non-inferiority compared with a 3-day regimen of ciprofloxacin (82% vs. 93%, respectively; 95% CI, 3–18%), strengthening the recommendation against using oral beta-lactams for uncomplicated UTIs [5].

Although these studies do not support the first-line use of oral beta-lactam agents, limited data are available evaluating the use of intravenous (IV) beta-lactams in the hospital setting for cystitis. A recent study comparing the efficacy of ceftolozane/tazobactam to levofloxacin demonstrated higher cure rates with ceftolozane/tazobactam compared with levofloxacin (76.9% vs. 68.4%, respectively; 95% CI, 2.3–14.6%) for the treatment of complicated UTIs and pyelonephritis [6]. Another recent study found cefazolin non-inferior to ceftriaxone for a composite of symptomatic resolution of acute pyelonephritis in hospitalized patients (87% vs. 85.9%, respectively; 95% CI, 11.1–8.9%; $p = 0.83$) [7]. These two randomized, controlled trials provide promising evidence for the use of IV beta-lactams and encourage the evaluation of more narrow-spectrum IV beta-lactams such as cefazolin compared with FQ for the treatment of community-acquired UTI. In addition, as FQ resistance continues to rise in both the hospital and community setting, the use of beta-lactams may provide more reliable empiric activity for uropathogens [8].

In 2012, our institution developed a stratified antibiogram, differentiating susceptibilities based on the location cultures were collected (inpatient vs. outpatient/emergency department [ED]) to improve empiric antibiotic selection for community-acquired infections. We found our outpatient/ED *Escherichia coli (E. coli)* susceptibilities to cefazolin were 90% compared with ciprofloxacin at 82%. Based on these susceptibilities, potential increased risk of *C. difficile* infection, and concerns about the development of further resistance, institutional guidelines were updated to include cefazolin as the first-line intravenous agent for uncomplicated UTI for patients requiring hospitalization. The purpose of this study was to assess the impact of cefazolin versus FQ on community-acquired UTI treatment in an inpatient setting.

Methods

Study design and patient selection

This was a single-center, retrospective, non-inferiority study conducted at a 504-bed community teaching hospital within Atlantic Health System (AHS). Patients were identified from a pharmacy report of all patients who were prescribed cefazolin or a FQ for a UTI indication from April 2015 to January 2016. Patients included were those ≥ 18 years old, received empiric treatment with ≥ 24 h of IV cefazolin or a FQ (IV or oral) such as levofloxacin or ciprofloxacin, UTI diagnosis present on admission, pyuria (defined as > 10 WBC/mm^3), bacteriuria (≥ 10^4 colony forming units/mL), and UTI symptoms. UTI symptoms included dysuria, frequency, urgency, hematuria, suprapubic pain, flank pain, fever, nausea, vomiting, malaise, fatigue, and altered mental status.

Patients were excluded for the following: receipt of greater than one dose of another antibiotic prior to initiation of study drug, history of recurrent UTI, pregnancy, anatomical abnormalities of the urinary tract, recent instrumentation of the urinary tract, pyelonephritis, concomitant infections (besides bacteremia associated with the current UTI), neutropenia, or recent healthcare exposure. Recent healthcare exposure was defined as patients residing in a skilled nursing facility, previous hospitalization within 90 days, antibiotic exposure within 90 days, chronic dialysis within 30 days, immunosuppressive therapy within 90 days, or wound/tracheostomy/ventilator care within 30 days.

Outcomes were compared between patients treated with cefazolin and those treated with a FQ. Data collection included demographic information, length of stay, length of treatment, antibiotic administered in the ED, urine culture results, organism susceptibilities, and changes in antibiotic selection.

Outcomes

The primary outcome was clinical failure defined as at least one of the following: persistence of one or more signs or symptoms of UTI that required antibiotic modification, re-initiation of antibiotics during hospitalization for UTI treatment, or re-hospitalization with a UTI diagnosis within 30 days after discharge.

Secondary outcomes included hospital length of stay, inpatient antibiotic duration of treatment, *C. difficile* infection within 30 days from the end of antibiotic therapy, microbiological cure, and emergence of resistance to cefazolin or FQ during inpatient antibiotic treatment.

Statistical analysis

Categorical, ordinal, and continuous data between groups were analyzed using chi-squared or Fisher's exact test, Mann-Whitney *U* test, and independent two-sample *t* test, respectively. The power, ratio, and non-inferiority margin were extrapolated from previous studies [5, 6]. Thus, to test non-inferiority using 0.95 as the lower limit, ratio of 1.13, 90% power, and co-variance of 0.35, 67 patients per group were needed.

Statistical significance was considered to be $p < 0.05$, and analyses were performed using MINITAB 15.1 (MINITAB® Release 15.1.1.0; Minitab, State College, PA, USA).

Results

During the study period, 696 patients received cefazolin or a FQ for a UTI indication. A total of 73 patients were included in the study (43 in the cefazolin group and 30 in the FQ group). Among the 623 patients excluded, the most common reasons for exclusion were receipt of greater than one dose of non-study antibiotic during the same hospitalization prior to cefazolin or FQ use, healthcare-associated infections, and no bacteriuria/pyuria (Figure 1).

Patients in the FQ group were significantly younger compared with the patients in the cefazolin group (median age 79 years [IQR 64–87] vs. 88 years [IQR 80–92], respectively; $p < 0.01$). Significantly more patients in the FQ group also had a penicillin allergy and nausea/vomiting as a symptom on admission compared with the cefazolin group (50% vs. 2% [$p < 0.05$] and 16% vs. 40% [$p = 0.03$], respectively). The remaining baseline characteristics were similar between the two groups (Table 1). Uropathogens isolated were similar between groups, and the most common organism was *E. coli* (59%, Table 2). There were no patients that had concomitant bacteremia associated with the current UTI.

Primary outcome

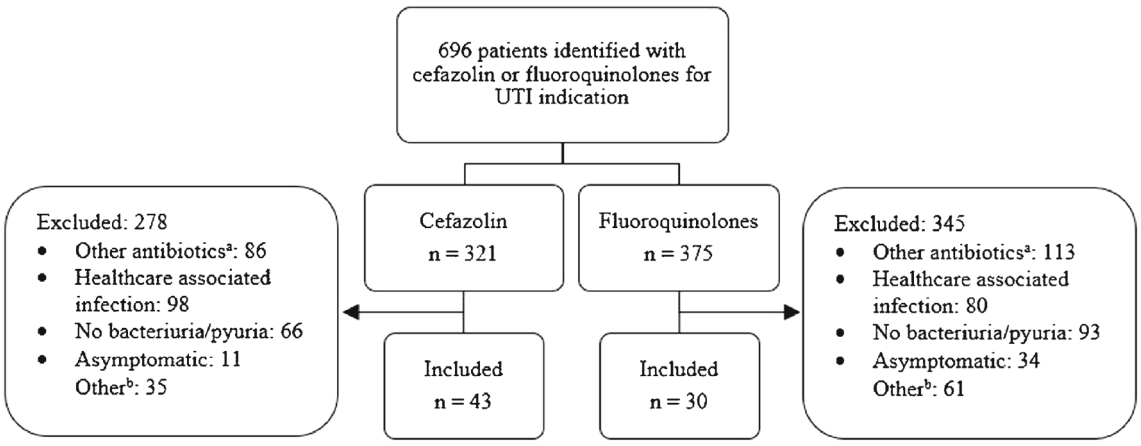
The rate of clinical failure was not significantly different between the FQ and cefazolin group (7% vs. 2%, respectively; $p = 0.56$, Table 3). One patient in the cefazolin group had a change in therapy from cefazolin to a FQ due to leukocytosis and an increase in neutrophil count on the fourth day of antibiotic therapy not attributable to other reasons. The uropathogen isolated was susceptible to both agents. Two patients in the FQ group were re-admitted within 30 days of discharge with a UTI diagnosis.

Secondary outcomes

There were no differences in secondary endpoints (Table 3). The median length of stay was 3 days, and the median inpatient antibiotic duration of treatment was two and a half days. Microbiological cure was assessed in six patients (14%) in the cefazolin group and 11 patients (36%) in the FQ group. Of these 17 patients, one patient in the FQ group did not achieve microbiological cure. The follow-up culture for this patient grew the same organism with the same susceptibilities as the initial culture.

Discussion

This is the first study to compare a narrow-spectrum IV beta-lactam to a FQ for the treatment of community-acquired cystitis in hospitalized patients. IDSA and ESCMID have developed guidelines for uncomplicated cystitis and pyelonephritis in pre-menopausal women, which primarily address young women in the outpatient setting [1]. There are currently no guidelines that address elderly individuals that are hospitalized for cystitis, which was the primary population that was evaluated in our study with an overall median age of 86 years. With the current black box warnings and recent FDA safety alerts recommending limiting FQ use, it is imperative to consider the alternative treatment options, especially in the elderly population who is more susceptible to adverse events [9]. Although our study did not evaluate adverse effects during therapy, we did not observe a difference in clinical failure rates between the two treatment groups suggesting that cefazolin may be an option for the treatment of cystitis for hospitalized patients, depending on local susceptibility patterns.



[a]>1 dose of non-study antibiotic administered during the same hospitalization prior to cefazolin or fluoroquinolone use.[b]Pregnant, pyelonephritis, recent instrumentation, anatomical abnormalities, concomitant infections, sepsis, susceptibility discrepancies, antibiotics ≤ 24h

Fig. 1 Selection of patients based on inclusion and exclusion criteria

Table 1 Baseline characteristics

Characteristic	Cefazolin ($n = 43$)	Fluoroquinolones ($n = 30$)	p value
Age, years, median (IQR)[a]	88 (80–92)	79 (64–87)	0.01
Gender, female	34 (79)	24 (80)	1
Penicillin allergy	1 (2)	15 (50)	< 0.0001
Symptoms of UTI			
Urinary symptoms[b]	15 (35)	17 (57)	0.09
Fever	8 (17)	10 (33)	0.18
Nausea/vomiting	7 (16)	12 (40)	0.03
Malaise/fatigue	26 (61)	21 (70)	0.46
Altered mental status	29 (67)	13 (43)	0.06
Emergency department antibiotics	35 (81)	17 (57)	
Cefazolin	21 (60)	3 (18)	0.003
Ceftriaxone	8 (23)	3 (18)	1
Fluoroquinolones	2 (6)	10 (59)	< 0.0001
Other[c]	5 (14)	1 (6)	0.65
Antibiotic resistance on first culture			
Cefazolin	3 (7)	6 (20)	0.15
Fluoroquinolones	8 (19)	7 (23)	0.77
Antibiotics switched due to susceptibilities	2/3 (67)	5/7 (71)	1

Data presented as n (%) unless otherwise specified

[a] *IQR* interquartile range

[b] Urinary symptoms: dysuria, frequency, urgency, hematuria, suprapubic pain, flank pain

[c] Other: azithromycin, amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, tobramycin

In addition, there are no current recommendations for the treatment of UTI in male patients who are not catheterized. Although oral FQ are recommended for the treatment of bacterial prostatitis based on their high prostate concentrations, these pharmacokinetic parameters are not of concern for cystitis when selecting an antibiotic and most beta-lactams have high urinary concentrations [10]. Although only 21% of the study population was male, we did not observe any treatment failures in males that received cefazolin in this study. Further studies are needed to confirm these results in this population.

Table 2 Urine culture organism distribution

	Cefazolin ($n = 43$)	Fluoroquinolones ($n = 30$)	p value
Escherichia coli	25 (58)	18 (60)	1
Klebsiella pneumoniae	4 (9)	4 (13)	0.709
Other Enterobacteriaceae	6 (14)	3 (10)	0.728
Group B *Streptococcus*	3 (7)	0 (0)	0.264
Other gram-positive organisms	3 (7)	3 (10)	0.685
Polymicrobial	2 (5)	2 (7)	0.166

These findings support our current institutional guidelines to empirically prescribe cefazolin to inpatients requiring antibiotics for community-acquired cystitis. Although our study did not observe any differences in endpoints assessing "collateral damage," by recommending cefazolin as first-line therapy we hope to reserve FQ use for more severe infections or as an oral option for pseudomonal infections.

There are several limitations to this study. Previous studies measured clinical cure based on symptom resolution at a follow-up visit and microbiological cure. Due to the retrospective nature of this study, we were unable to assess clinical cure at a follow-up visit. Furthermore, symptom resolution was not always documented in the medical record and as such, we chose to evaluate clinical failure during hospitalization as our primary endpoint. There were also two patients in the cefazolin group and five patients in the FQ group that had antibiotics changed due to susceptibility results despite clinical improvement in symptoms. Since these patients had documented improvement in symptoms, they did not meet our pre-defined criteria for clinical failure or exclusion from analysis. We were also unable to fully assess microbiological cure since follow-up cultures were performed in only 23% of patients. Although previous studies evaluated

Table 3 Study endpoints

Characteristic	Cefazolin ($n = 43$)	Fluoroquinolones ($n = 30$)	p value
Primary endpoint			
Clinical failure	1 (2)	2 (7)	0.56
Signs of UTI that require additional antibiotics	1 (2)	0	1
Re-initiation of antibiotics during a hospital stay for UTI	0	0	1
30-day re-hospitalization for UTI	0	2 (7)	0.17
Secondary endpoints			
Hospital length of stay, days, and median (IQR)	3 (2–5)	3 (2–6)	0.88
Inpatient antibiotic length of treatment, days, and median (IQR)	3 (2–5)	2 (2–4)	0.39
C. difficile within 30 days[a]	0 (0)	0 (0)	1
Microbiological cure (if available)	6/6 (100)	10/11 (90)	1
Emergence of resistance (if available)			1
Cefazolin	0/0 (0)	0/1 (0)	
Fluoroquinolones	0/0 (0)	0/1 (0)	

Data presented as *n* (%) unless otherwise specified

[a] 30 days from the end of antibiotic treatment

microbiologic cure, follow-up cultures are not routinely recommended in clinical practice in patients with symptomatic improvement [11]. In addition, we may not have captured readmissions for UTI or *C. difficile* presenting to outside facilities. Lastly, the robust inclusion and exclusion criteria yielded small sample size and the study was not adequately powered to detect differences in the primary and secondary endpoints.

Many broad-spectrum agents were used, such as piperacillin/tazobactam, ceftriaxone, and ampicillin/sulbactam, that may have impacted the results. To minimize this impact, we excluded patients who received more than one dose of non-study antibiotics. A majority of patients in both groups had non-specific symptoms that could indicate another source of infection or worsening of co-morbidities rather than the emergence of a UTI. However, by only including patients that received ≥ 24 h of the study antibiotic and confirming the UTI with objective markers such as bacteriuria and pyuria, we tried to minimize the impact of these confounding variables.

Based on these results, we identified several areas of future improvements. We observed that only 50% of the patients in the FQ group had a penicillin allergy. These results support the opportunity to provide education on the use of FQ as empiric therapy for only those with a true penicillin allergy in the setting of a community-acquired UTI.

In this study, the cefazolin susceptibilities for Enterobacteriaceae were analyzed using a previous Clinical and Laboratory Standards Institute (CLSI) breakpoint of ≤ 8 mg/L. However, updated CLSI guidelines recommend a breakpoint of ≤ 16 mg/L for Enterobacteriaceae when isolated in the urine [12]. Most automated susceptibility testing systems do not distinguish site-specific susceptibilities for Enterobacteriaceae at this time, and microbiology laboratories would need to perform internal validations to use these new breakpoints for urine cultures. Our institution has not validated these urine-specific breakpoints, and the clinical impact of a potential change remains unknown.

Overall, from this study, we conclude that cefazolin is similar to FQ for the treatment of community-acquired UTI based on the clinical failure rates. In addition, local susceptibility patterns to uropathogens should guide empiric treatment.

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Compliance to ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This is a retrospective study that has been reviewed by the institutional review board prior (IRB) to the beginning of the study. A letter from the IRB has been attached in the supplementary section.

Informed consent Informed consent was not required for this study as it was a retrospective study and no interventions were taken that would impact patient care. In addition, informed consent was not required according to per institutional policies and no identifying details were revealed regarding patients.

Transparency declarations None to declare.

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