Original Research

Comparing Outcomes for Outpatients Treated With Cephalexin for Uncomplicated Cystitis: Is QID Dosing Necessary?

Urgent Message: Patients commonly seek unscheduled care for urinary tract infections (UTIs). Cephalexin is among the most frequently prescribed antibiotics for acute UTI treatment, however, dosing regimens lack standardization. In this small observational study, similar rates of clinical cure and adherence were observed with cephalexin 500 mg dosed every 12 hours vs every 6 hours in patients with cystitis, calling into question whether QID (4 times per day) dosing is necessary.

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Abstract

Background: Cephalexin, a first-generation oral cephalosporin, is commonly prescribed for cystitis with various dosing frequencies; lower-frequency dosing can improve patient adherence. There is still incomplete consensus regarding the optimal dosing regimen when cephalexin is used for this indication.

Methods: This observational study included patients discharged from an emergency department (ED) and urgent care (UC) center from November 2023 to February 2024. All patients were diagnosed with cystitis with growth of a urinary organism with presumed or confirmed susceptibility to cefazolin, a surrogate marker for cephalexin susceptibility. Patients were treated with 500 mg every 12 hours (q12h) or 6 hours (q6h) for at least 5 days. Notable exclusions were reduced creatinine clearance, recently treated culture-confirmed urinary tract infection (UTI), select urinary tract abnormalities, or concomitant infection. Chi-square, Fisher's exact, Wilcoxon rank sum, or t-tests were used to compare groups on selected baseline characteristics.

The primary objective was to compare clinical cure—defined as complete or near-complete resolution of symptoms upon finishing cephalexin—between groups, which was assessed via telephone survey 2-5 days post-antibiotics. Secondary outcomes included patient adherence, healthcare utilization due to worsening of symptoms within 14 days of prescription start, and adverse reactions. Healthcare utilization was defined as a patient presenting to an ED, UC, or medical clinic with complaints of urinary symptoms, UTI, cystitis, pyelonephritis, or bacteremia with urine source.

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Results: One hundred thirty-seven patients were screened, and 47 patients were included in the demographic and healthcare utilization analysis with 36 receiving q12h and 11 receiving q6h cephalexin dosing. Fifteen patients consented and were included for the telephone survey. Common reasons for exclusion included pyelonephritis (37.8%) and creatinine clearance <50mL/min (25.5%). Median ages in the q6h group and q12h groups were 56 (52–61) and 36 (22–55.5) years, respectively, and over 90% of patients in each group were female. Of those surveyed, clinical cure was achieved in all, and adherence was high in both groups. One patient returned to a healthcare facility within 14 days in the q12h group and 2 in the q6h group (p=0.13). Adverse effects of nausea, vomiting, and diarrhea were similar between groups.

Conclusions: In this small observational study of patients treated for cystitis with cephalexin 500 mg q12h vs 500 mg q6h, clinical cure rates were similar, and adherence rates were overall high in both groups.

Introduction

Urinary tract infections are one of the most common bacterial infections for which patients seek acute care, with cystitis being more common than pyelonephritis.[1] For patients with cystitis, the most recent 2010 Infectious Diseases Society of America guidelines recommend the use of nitrofurantoin and trimethoprim-sulfamethoxazole as first line therapies.[2] However, in recent years, there has been an increase in the use of beta-lactams, including first generation cephalosporins like cephalexin, for the treatment of UTIs based on evidence of urinary penetration and coverage of *Enterobacterales* (eg, *E. coli*), the most frequent cause of UTIs in the United States.[2,3,4] Cephalexin is a generally well-tolerated, cost-effective oral antibiotic, however, despite its common use for the treatment of cystitis, the ideal dosing regimen remains unknown.[5]

Beta-lactams exert time-dependent antimicrobial activity, so efforts are made to maximize the time above the minimum inhibitory concentration of the causative pathogen by using more frequent dosing intervals, which is the basis for q6h dosing of cephalexin. However, the US Food and Drug Administration's (FDA) recommendation for cephalexin dosing in the treatment of cystitis is 500 mg q12h, based on results from a single study from the 1980s.[6,7] Since then, no high-quality studies addressing the ideal dosing frequency of cephalexin for cystitis have been published. While a dosing frequency of q6h for the treatment of cystitis may present a more ideal pharmacokinetic profile, it may make adherence more difficult in the outpatient setting.[8,9] Patient adherence is an important consideration when evaluating antibiotic treatment regimens. Poor adherence may result in treatment failure or contribute to antimicrobial resistance. For other indications, there are conflicting results on whether decreasing the frequency of administrations impacts adherence; some studies have shown no difference while others have shown improved adherence.[10,11,12]

Several recent studies have described higher rates of treatment failure when using q12h dosing. However, due to these studies' retrospective, observational designs, adherence was not able to be assessed, and the populations studied were restricted to uncomplicated cystitis.[7,13,14] The purpose of this research was to assess differences in clinical cure for culture-confirmed cystitis with 2 different dosing regimens of cephalexin and assess patient adherence.

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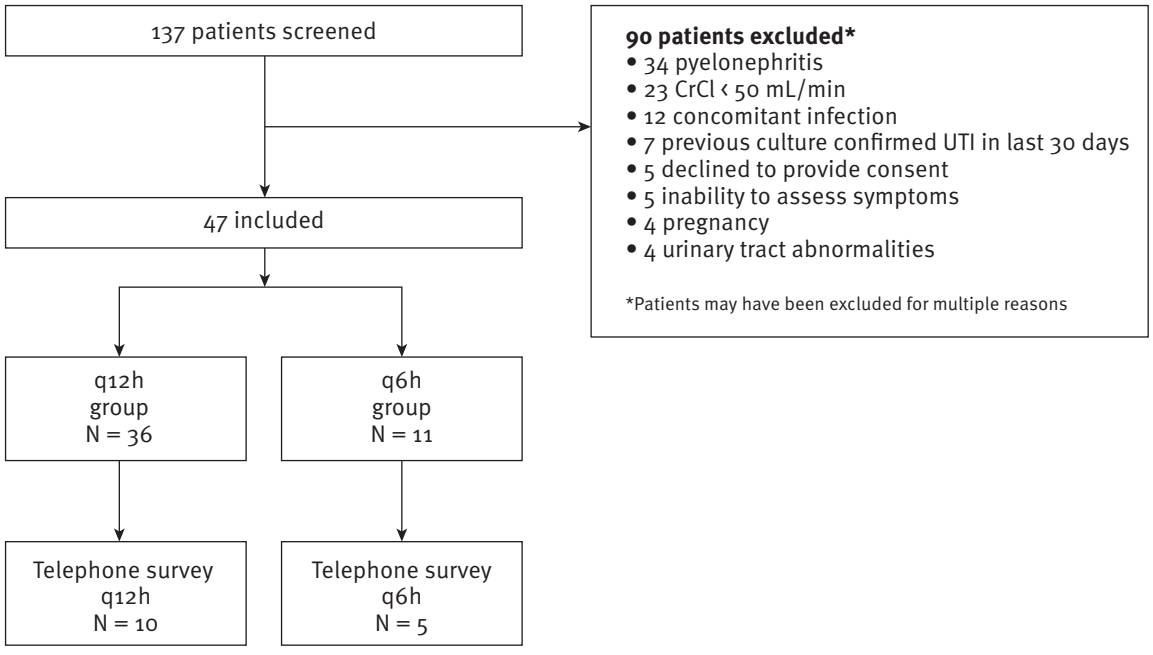
Methods

Selection and Description of Participants

This was an observational, survey-based study evaluating patients discharged from an ED or UC center associated with The Ohio State University Wexner Medical Center in the metropolitan area of Columbus, Ohio, with an encounter diagnosis of "cystitis" or "UTI" who were prescribed a course of cephalexin of at least 5 days duration between November 3, 2023, and February 28, 2024. Patients were screened twice weekly using an automatically generated report in the electronic health record (EHR). Patients were considered for inclusion if they were empirically treated with cephalexin for cystitis or were determined to have cystitis and then treated with cephalexin after urinary culture was finalized via an existing pharmacist culture-call-back process. Patients were only included if they had growth of a urinary organism with presumed or confirmed susceptibility to cefazolin, a surrogate marker for cephalexin susceptibility. Cephalexin regimens prescribed were 500 mg either

Figure 1. Patient Encounter Inclusion Process



q12h or q6h for at least 5 days in duration and were chosen at the discretion of the initial diagnosing prescriber or the culture-call-back pharmacist.

The first encounter meeting inclusion criteria per patient during the study timeframe was included in the study. Exclusion criteria were: current pregnancy; incarcerated status; diagnosis of upper tract UTI (ie, prostatitis or pyelonephritis); history of previous culture-confirmed cystitis or pyelonephritis within the past 30 days; known urinary tract abnormalities or obstructions as documented in the EHR (hydronephrosis, nephrostomy tubes, indwelling urinary catheters, nephrolithiasis, urinary tract tumors); and current treatment for a concomitant infection at a different site. Patients were additionally excluded if the cephalexin prescription was not picked up, there was an inability to assess patient symptoms at follow-up (such as history of dementia), or if there was renal impairment with calculated creatinine clearance (CrCl) <50 mL/min.

Data Collection and Measurements

The primary outcome was rate of clinical cure among patients with cystitis who were discharged from either the ED or UC with either q6h or q12h cephalexin dosing frequencies. Clinical cure was defined as complete or near complete resolution of UTI symptoms upon finishing a course of cephalexin lasting at least 5 days in duration, which was assessed 2-5 days post-antibiotic therapy. Safety endpoints included adverse events reported or documented during therapy. Secondary outcomes included patient adherence, adverse effects, and additional healthcare visits within 14 days of the prescription start date. Additional healthcare system utilization was defined as a patient presenting to an ED, UC, or physician's office within 14 days with chief complaint of urinary symptoms, UTI, cystitis, pyelonephritis, or bacteremia with a urinary source. Attempts to contact all included patients were made 2-5 days post-antibiotic therapy. If patients were unable to be contacted after 3 attempts, they were still assessed for demographics and utilization of the healthcare system within 14 days.

The telephone survey incorporated validated tools to assess clinical cure and adherence. For clinical cure, a modified version of the Urinary Tract Infection-Symptom and Impairment Questionnaire (UTI-SIQ-8) was utilized to assess symptom severity. The UTI-SIQ-8 is a comprehensive questionnaire that assesses severity of dysuria, urgency, urinary frequency, and lower abdominal pain, including the impairment it may have on a patient's life.[15] Adherence was assessed through the utilization of a validated Brief Medication Questionnaire

Table 1. Baseline Characteristics and Patient Demographics

Characteristic	q12h group (n = 36)	q6h group (n =11)	P-value
Female, n (%)	35 (97.2)	10 (90.9)	0.417
Age, median [IQR], yr	36 [22 – 55.5]	56 [52 – 61]	0.39
Weight, median [IQR], kg	75.8 [62.3 – 88.5]	87.6 [70.5 – 88.9]	0.27
Creatinine Clearance, mean (SD), mL/min	109 (36.8)	87.4 (19.2)	0.11
Duration of therapy, median [IQR], days	5 [5 – 7]	7 [5 – 7]	0.02
UC encounter, n (%)	24 (66.7)	9 (81.8)	0.46
Complicating Factors			
Complicated Patients, n (%)	7 (19.4)	3 (27.3)	0.43
Renal Transplant, n (%)	1 (2.78)	0 (0.00)	0.99
Nephrolithiasis, n (%)	3 (8.33)	0 (0.00	0.99
Diabetes, n (%)	2 (5.56)	3 (27.27)	0.076
Immunocompromised, n (%)	1 (2.78)	0 (0.00)	0.99
Bacteria	**q12h group (n = 36)**	**q6h group (n = 11)**	**Total, n (%)**
E. Coli, n (%)	24 (66.6)	9 (81.8)	33 (70.2)
S. saprophyticus, n (%)	1 (2.8)	0 (0.0)	1 (2.1)
Group B Strep. Species, n (%)	3 (8.3)	0 (0.0)	3 (6.4)
K. pneumoniae, n (%)	4 (11.1)	1 (9.1)	5 (10.6)
Proteus Species, n (%)	0 (0.0)	1 (9.1)	1 (2.1)
Other, n (%)	2 (5.6)	0 (0.0)	2 (4.3)
Multiple species, n (%)	2 (5.6)	0 (0.0)	2 (4.3)

N - number; IQR – interquartile range; SD – standard deviation; q12h – every 12 hours; q6h – every 6 hours

(BMQ), which is a self-report tool for adherence screening.[16] The BMQ also includes a section regarding barriers to adherence, such as patient's specific concerns with medication efficacy, which was not the focus of this research study, so it was omitted.

The Ohio State Biomedical Sciences Institutional Review Board approved this protocol (Study ID 2023H0336) and necessary amendments on October 29, 2023. Patient consent was obtained verbally upon contact for the telephone survey 2-5 days after finishing antibiotics. For patients who were unable to be contacted for the telephone survey, they were included based on waiver of consent for retrospective review of demographic characteristics and healthcare utilization.

Statistics

Categorical variables were examined utilizing a chi-square test unless tests of categorical variables had cells with numbers less than 5, of which a Fisher's exact test was used. A Shapiro-Wilk test was utilized to test for data distribution of continuous variables. T-tests were used to examine continuous outcomes between the 2 groups and Wilcoxon rank-sum was utilized when these variables were not normally distributed. Study data were collected and managed using REDcap electronic data capture tools.[17] Data analysis was completed using Stata Statistical Software, version 16 (StataCorp LLP, College Station, Texas, USA).

Results

A total of 137 patient encounters were screened for potential inclusion with 47 patients included and assessed via chart abstraction (36 in the q12h group and 11 in the q6h group). The most common reasons for exclusion were pyelonephritis, CrCl < 50 mL/min, and concomitant infections (**Figure 1**). All included patients were contacted for the telephone survey, and 15 were successfully reached and consented to the telephone survey assessing clinical cure.

Baseline characteristics were similar between groups (**Table 1**). Median age tended to be lower in those receiving a q12h regimen, while these patients also tended

Table 2. Outcomes

	q12h group (n = 10)	q6h group (n = 5)	P-value
Clinical Cure, n (%)	10 (100)	5 (100)	0.99
Adherence, %, mean (SD)	97.0 (6.7)	98.6 (3.2)	0.63
Any Adverse Events, n (%)	5 (50)	1 (20)	0.301
Nausea, n	3	1	0.999
Vomiting, n	0	0	-
Diarrhea, n	4	0	0.231
	q12h group (n = 36)	**q6h group (n = 11)**	
Healthcare utilization, n (%)	1 (2.8)	2 (18.2)	0.13

N – number; q12h – every 12 hours; q6h – every 6 hours

to have a higher CrCl. There were differences in duration of therapy between groups with those in the q12h group having a lower median therapy duration of 5 (5-7) days as compared to the q6h group at 7 (5-7) days (p=0.02) utilizing a Wilcoxon rank-sum test. Most patients were female, and the most common urinary pathogen was found to be *Escherichia coli* (*E.coli*) with a majority of patients included from a UC encounter.

Of those patients included in the telephone survey (n=15), clinical cure was similar between the groups with all patients in the q12h (n=10) and q6h group (n=5) reporting near complete or complete resolution of symptoms (p=0.99) determined through a Fisher's exact test. Of these patients, all had calculated adherence rates of at least 80% with adherence overall high in both groups with mean adherence of 97% in the q12h group and 98.6% in the q6h group. Adverse effects of nausea, vomiting, and diarrhea were found to be similar between groups with the most common side effect of nausea (**Table 2**).

Regarding the outcome of healthcare utilization within 14 days of prescription start date, 1 patient (2.8%) had a healthcare utilization visit in the q12h group and 2 (18.2%) in the q6h group, but results were not found to be statistically significant (p=0.13) through a Fisher's exact test.

Discussion

In this small observational study comparing those with

cystitis receiving regimens of cephalexin q12h vs q6h, there were equal rates of clinical cure with similar rates of healthcare utilization, adverse events, and adherence. Previously published studies focus on outcomes of treatment failure and exclude those who did not fit in the traditional definition of uncomplicated cystitis with similar treatment durations.[13,14]

The FDA approved dosing of cephalexin cites some of the first evidence comparing the dosing regimen of cephalexin for cystitis to the recommended q12h dosing, however despite this recommendation there remains variation in practice. The previous study by Kostas and colleagues compared 500 mg q12h to 250 mg q6h in male and female patients with UTI and found equal rates of symptomatic response and bacteriologic cure.[7] Similar to this current study, Kostas and colleagues also found high rates of symptomatic response with both groups (94% in q12h vs 93% in q6h) regardless of the regimen selected.[7]

As the use of cephalexin for cystitis has become more common in recent years, there has been renewed interest in researching the ideal regimen. A single-centered retrospective observational study from Benning and colleagues described clinical efficacy of q12h dosing in patients discharged from an ED with uncomplicated UTI through an outcome of clinical success.[13] It was determined that 81.1% of patients who received cephalexin 500 mg q12h met the criteria for clinical success, which is much lower than what was previously noted by Kostas and colleagues and this current study.[7,13] The study by Benning and colleagues posed some limitations and did not have a comparator group. Given the retrospective design, clinical success was evaluated based on subsequent presentation to a healthcare provider within the system or a change in antibiotic therapy, both of which have limitations in assessing clinical outcomes. Return visits may underestimate true clinical failure. Patients in whom culture growth was non-susceptible to empiric cephalexin therapy would not be expected to have clinical success based on the organism's resistance and may overestimate clinical failure in the study design. Given these considerations, this present study was designed to include a patient interview for clinical response as well as excluding patients who had an organism that was non-susceptible to cephalexin to account for these limitations in previous literature.

More recently, Yetsko et al. conducted a retrospective, multicentered study comparing clinical treatment failure between patients receiving cephalexin 500 mg dosed q12h vs q6h in the setting of uncomplicated UTIs.[14] The primary outcome was treatment failure, defined as continuing or non-resolving symptoms, and was assessed retrospectively via EHR. Female patients who received 5–7 days of cephalexin for a cefazolin-susceptible urine culture with documented symptoms of UTI were included. With a population size of 261(173 in the q12h group and 88 in the q6h group), the investigators found that there was no difference in treatment failure between groups (12.7% in q12h group vs 17% in q6h group).[14] Although this study did include a comparator group, with similar baseline characteristics between groups, due to the retrospective chart review used in this study, adherence was unable to be assessed, and only patients who met the traditional definition of uncomplicated cystitis (ie, young, healthy, non-pregnant, and female) were included. This present study focused on the patient-oriented outcomes of reported clinical cure and adherence while including a more real-world population of patients with cystitis, such as males, immunocompromised patients, or those with more frequent UTIs.

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Within this current study, a high rate of clinical cure was observed in both groups (100%) with low rates of healthcare utilization ranging from 2.8–18.2% in the subsequent 14 days. This is in line with previous literature that sought to evaluate treatment failure and was assessed at 28 and 30 days. Although limited by a small sample size, strengths of this study included that it assessed patient-oriented outcomes and adherence in the treatment of cystitis with varying cephalexin dosing frequencies. In addition, this study included patients who did not meet criteria for simple cystitis (eg, those with diabetes, history of nephrolithiasis, and renal transplant).

Limitations

This study does have a number of important limitations. Though it sought to concurrently evaluate clinical cure by patient interview immediately after completing cephalexin, a small patient population met inclusion criteria, so the study was not powered to detect a difference. With a small population of only 15 patients included in

the final analysis, no differences were found between the groups in clinical cure, and adherence overall was found to be high. Importantly, the sample size was too small to determine if there were important subgroup differences based on patient age, organism, and co-morbidities. Additionally, due to the nature of the telephone survey, there may be recall bias and subject bias among those included, both in terms of clinical cure and adherence. It may be possible that patients in each group who may have not taken the prescription as prescribed or taken the entire course as directed were less likely to respond to a telephone survey. There were attempts to control for this by also reviewing rates of return to healthcare facilities within the study institution. Selection bias of patients may also be present in those included in the study due to the inherent patient population of the study institution and its associated care locations.

Given that this study was conducted in the ED and UC settings at a single institution, there is a potential the results might not be able to extrapolate to populations that differ. The treatment was left to the discretion of the clinician evaluating the patient; there may have been characteristics of patients in whom specific cephalexin dosing was chosen and other agents were avoided that could have meaningfully affected rates of cure. Furthermore, the sample size was inadequate to assess for potential differences in patient populations. Additionally, the decision on which cephalexin dosing regimen used was determined by the prescriber and may introduce selection bias. Adherence was similar between q6h and q12h groups, but this similarity may be predominantly attributable to small sample size, as it is likely patients will have less difficulty adhering to twice daily dosing. Overall, a majority of patients were seen in urgent care settings (66.7% in q12h group vs 81.8% in q6h group) and given the smaller sample of patients seen in the ED setting, we did not assess for differences between the ED and UC populations. As such, it is unknown if there are inherent differences in those populations that would impact clinical cure or patient adherence.

Due to the inclusion of patients who fall outside of the traditional definition of uncomplicated cystitis, this study's findings add to the knowledge base of utilizing cephalexin q12h for the treatment of cystitis. A prospective, multi-site, randomized controlled trial with a larger study population would be of great value to corroborate these findings and clarify in which patients with UTI is cephalexin 500mg q12h sufficient and for what duration of therapy.

Conclusion

In this small observational study of patients treated for cystitis with cephalexin 500 mg q12h or 500 mg q6h, rates of clinical cure as assessed by post-treatment interview were similar, and most patients were 100% adherent to the regimen they received. Post-treatment healthcare utilization was overall low in both groups. ■

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