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Reducing Ciprofloxacin Prescribing for Acute Uncomplicated Cystitis: A Pilot Study in an Antimicrobial Stewardship Program

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Abstract:

Objective: Previous studies have shown the inappropriateness of antimicrobials for acute uncomplicated cystitis (AUC). Fluoroquinolones are among the most commonly prescribed antimicrobials, despite an increasing trend of fluoroquinolone-resistant Enterobacterales. To address this issue, we implemented an antimicrobial stewardship (AMS) program to improve the care of patients with AUC.

Material and Methods: A retrospective pre-post intervention study was conducted at Maharaj Nakorn Chiang Mai Hospital. The AMS intervention included the development of hospital-specific empirical treatment guidelines for AUC and bi-monthly educational sessions for general practitioners at outpatient clinics, supported by printed algorithms posted in exam rooms. The pre-intervention period was from March 1, 2021 to August 31, 2021, and the post-intervention period was from October 1, 2021 to March 31, 2022.

Results: Of the 47 enrolled patients, 28 participated in the pre-intervention period and 19 in the post-intervention period. Clinical characteristics were similar between the groups, except for a higher proportion of patients with urinary frequency in the post-intervention period. Antimicrobial appropriateness increased significantly from 0% in the pre-intervention period to 89.5% in the post-intervention period, driven by improvements in appropriate choice (7.1% vs 94.7%), appropriate dose (32.1% vs 94.7%), and appropriate duration (14.3% vs 94.7%). Treatment failure rates were low and did not differ between the 2 periods (7.1% vs. 5.3%).

Conclusion: The appropriateness of antimicrobial treatment improved significantly after the introduction of the AMS, mainly due to the decrease in ciprofloxacin prescribing. Continued AMS efforts in outpatient settings are recommended to maintain appropriate prescribing practices.

Keywords: antimicrobial stewardship, cystitis, quasi-experimental study, uncomplicated cystitis, urinary tract infection

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Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections encountered in outpatient settings, with approximately 8.3 million cases treated annually and 6.3 million outpatient visits each year in the U.S.[1]. Most UTIs are caused by *Escherichia coli* (75.0–95.0%), followed by *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus*[2,3]. The use of fluoroquinolones has increased[4–7], paralleling resistance trends, particularly in *E. coli*[8,9]. In 2019, 68.0% of *E. coli* isolated from urine were ciprofloxacin-resistant[10]. Increased use of fluoroquinolones also raises the risk of community-acquired *Clostridiodes difficile* infection by over 6 times[11].

The inappropriate use of antimicrobials is a major driver of resistance, encompassing incorrect drug choice, dose, and duration[12]. In the U.S.A., 68.0% of UTI treatments were inappropriate, with errors in duration (50.9%), choice (35.1%), and dose (12.4%)[13]. Similarly, a study in Thailand found that 91.3% of empiric antibiotic treatments for acute uncomplicated cystitis (AUC) were inappropriate[14]. Antimicrobial stewardship (AMS) programs, including education and guideline development, have shown promise in improving antimicrobial appropriateness[14,15]. This study aimed to evaluate the impact of AMS implementation on the appropriateness of antimicrobial use in patients with AUC, identify associated factors with appropriate prescribing, and assess rates of treatment failure.

Material and Methods

This retrospective pre-post intervention pilot study was conducted at Maharaj Nakorn Chiang Mai Hospital, a 1400-bed teaching hospital in northern Thailand. The pre-intervention period covered March 1, 2021 to August 31, 2021, while the post-intervention period covered October 1, 2021 to March 31, 2022. Patients included in the study were females aged 18 years or older who were diagnosed with AUC, had a urine specimen collected for bacterial culture, and were empirically prescribed antimicrobials in the designated outpatient clinic. Patients were excluded if they were pregnant, had structural urinary abnormalities, recent antimicrobial therapy or hospitalization, recurrent UTIs (≥6 episodes per year), renal replacement therapy, urinary catheters, were kidney transplant recipients, or resided in nursing homes.

Definition

AUC was defined as the presence of symptoms such as dysuria, urinary frequency, or urgency in the absence of fever or flank pain, with or without laboratory confirmation of bacteriuria. Antimicrobial appropriateness was defined based on the fulfillment of all the following criteria: selection of the correct drug, appropriate dosing, and proper duration of the therapy, in accordance with hospital treatment guidelines. Among culture-proven cases, concordant therapy was defined as empiric antimicrobial treatment that was active against the identified pathogen based on in vitro susceptibility testing. Treatment failure was defined as recurrent cystitis symptoms requiring retreatment within 30 days of completing the initial therapy, or progression to acute pyelonephritis, or bacteremia.

Implementation of the intervention

The AMS intervention included the development of hospital-specific, empirical treatment guidelines for AUC based on international guidelines[2], the primary literature[16], and local antimicrobial susceptibility data. According to the hospital's local antibiogram, *E. coli*, the most common causative organism of AUC, showed 100% susceptibility to amoxicillin/clavulanate, 92.8% to ceftriaxone, 28.6% to ciprofloxacin, and 42.8% to trimethoprim/sulfamethoxazole. If nitrofurantoin or fosfomycin are not an option, amoxicillin/clavulanate or cefixime are therefore recommended as alternative regimens, as shown in Figure 1. General practitioners at outpatient clinics received bi-monthly educational sessions focusing on appropriate antimicrobial selection, antimicrobial susceptibility patterns, and guideline adherence. Clinical decision support tools, including printed treatment algorithms, were distributed and posted in outpatient examination rooms to assist clinicians in selecting the appropriate therapy. Prescription patterns were monitored, and feedback was provided to clinicians on their prescribing practices in order to encourage adherence to AMS recommendations.

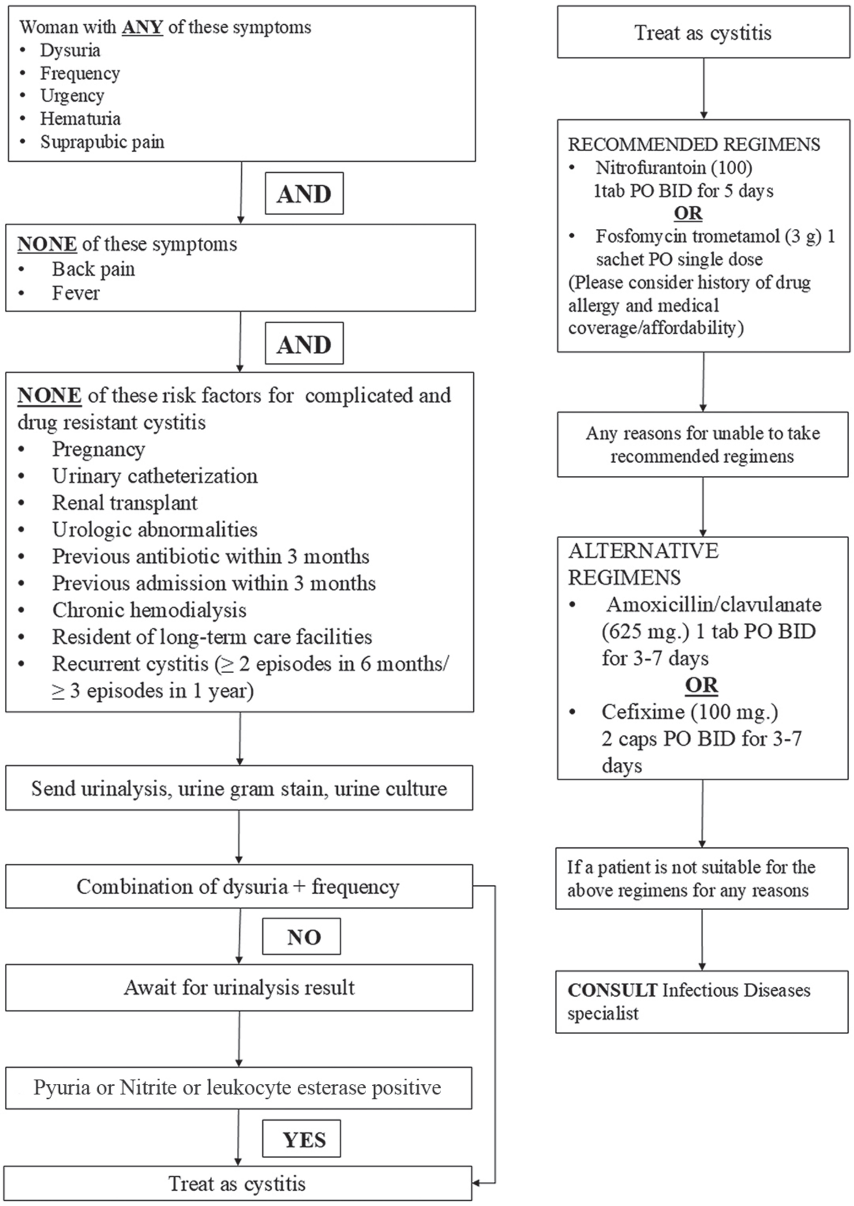

Figure 1 Treatment guidelines for patients with acute uncomplicated cystitis attending the general practitioner outpatient clinic between October 1, 2021 and March 31, 2022

Statistical analysis

Data are presented in numbers (%), means, and S.D. Data comparisons between the groups were performed using Student's t-test, Mann-Whitney U-test, chi-square test, or Fisher's exact test, where appropriate. A two-tailed test with a significance level of p-value<0.05 was used to determine statistical significance. A univariate logistic regression analysis was performed to identify factors associated with antimicrobial appropriateness. Variables with a p-value<0.10 in the univariate analysis were then tested in a multivariate logistic regression model using a stepwise backward procedure. All statistical analyses were performed using Stata Statistical Software, version 14 (Stata Statistical Software: Release 14 (Stata Corporation, College Station, TX, 2015).

Results

A total of 47 patients were included, with 28 in the pre-intervention period and 19 in the post-intervention period. Baseline characteristics were comparable between the 2 periods, except for a higher proportion of patients with urinary frequency in the post-intervention group than in the pre-intervention period (68.4% vs 28.6%). The most common presenting symptoms were dysuria (78.7%), suprapubic pain (66.0%), and urinary frequency (44.7%) (Table 1).

Table 1 Demographics, clinical characteristics, and laboratory findings of patients with acute uncomplicated cystitis

Characteristics	Pre-intervention period (N=28)	Post-intervention period (N=19)	p-value
Age in years (mean±standard deviation)	47.4±14.8	38.5±15.5	0.053
Comorbidities	18 (64.3)	7 (36.8)	0.081
Diabetes mellitus	4 (14.3)	1 (5.3)	0.635
Hypertension	7 (25.0)	1 (5.3)	0.119
Dyslipidemia	8 (28.6)	2 (10.5)	0.168
Chronic lung disease	1 (3.6)	0 (0.0)	1.000
Cardiovascular disease	1 (3.6)	0 (0.0)	1.000
Obesity (body mass index ≥25 kg/m^2)	9/27 (33.3)	2 (10.5)	0.092
Others	10 (35.7)	6 (31.6)	0.769
History of sulfa-drug allergy	1 (3.6)	0 (0.0)	1.000
Symptoms and signs			
Dysuria	22 (78.6)	15 (78.9)	1.000
Frequency	8 (28.6)	13 (68.4)	0.007
Urgency	1 (3.6)	3 (15.8)	0.289
Suprapubic pain	17 (60.7)	14 (73.7)	0.357
Hematuria	4 (14.3)	6 (31.6)	0.276
Suprapubic tenderness	14 (50.0)	13 (68.4)	0.137
Laboratory findings			
Urinalysis			
Pyuria (urine white blood cells >10 cells/high-power field)	11/27 (40.7)	11/19 (57.9)	0.370
Positive nitrite	4 (14.3)	1 (5.3)	0.387
Positive leukocyte esterase	23 (82.1)	19 (100)	0.067
Urine gram stain found bacteria	10/14 (71.4)	14/19 (73.7)	0.886
Urine culture found bacteria	17 (58.6)	13 (68.4)	0.589

Table 1 (continued)

Characteristics	Pre-intervention period (N=28)	Post-intervention period (N=19)	p-value
Uropathogens			
Escherichia coli	14 (50.0)	8 (42.1)	0.767
Staphylococcus saprophyticus	2 (7.1)	2 (10.5)	1.000
Klebsiella pneumoniae	0 (0.0)	1 (5.9)	0.404
Enterococcus faecalis	0 (0.0)	1 (5.9)	0.404
Contaminants	1 (3.6)	1 (5.9)	1.000

Data are presented in numbers (%) unless otherwise specified

Table 2 Outcomes after the implementation of antimicrobial stewardship programs in patients with acute uncomplicated cystitis

Outcomes	Pre-intervention period (N=28)	Post-intervention period (N=19)	p-value
Antimicrobial appropriateness	0 (0.0)	17 (89.5)	<0.001
Appropriate choice	2 (7.1)	18 (94.7)	<0.001
Appropriate dose	9 (32.1)	18 (94.7)	<0.001
Appropriate duration	4 (14.3)	18 (94.7)	<0.001
Outcomes			
Concordant antimicrobial therapy	4/16 (25)	10/12 (83.3)	0.002
Treatment failure	2 (7.1)	1 (5.3)	1.000
Antimicrobial prescription			
Norfloxacin	4 (14.3)	0 (0.0)	0.137
Ofloxacin	3 (10.7)	1 (5.3)	0.638
Ciprofloxacin	18 (64.3)	0 (0.0)	<0.001
Amoxicillin/clavulanate	2 (7.1)	7 (36.8)	0.021
Amoxicillin	1 (3.6)	0 (0.0)	1.000
Cefixime	0 (0.0)	8 (42.1)	<0.001
Fosfomycin	0 (0.0)	3 (15.8)	0.060

Data are presented in numbers (%)

Urine cultures showed that *E. coli* was the predominant pathogen, isolated in 22 cases (46.8%). Susceptibility of *E. coli* to ciprofloxacin, gentamicin, and trimethoprim/sulfamethoxazole was 68.2%, 72.7%, and 54.4%, respectively, while susceptibility to amoxicillin/clavulanate, piperacillin/tazobactam, ceftriaxone, cefepime, carbapenems, and amikacin was ≥95%. Other pathogens included *Staphylococcus saprophyticus* and *Enterococcus faecalis*. Three out of 4 *S. saprophyticus* were susceptible to trimethoprim/sulfamethoxazole.

Ciprofloxacin prescriptions decreased from 64.0% in pre-intervention to 0% in post-intervention (p-value<0.001). Concurrently, cefixime prescriptions increased from 0% to 42.1% (p-value<0.001), and amoxicillin/clavulanate prescriptions increased from 7.1% to 36.8% (p-value=0.021) (Table 2).

Table 3 Demographics, clinical characteristics, and laboratory findings of patients with acute uncomplicated cystitis between those receiving appropriate and inappropriate antimicrobials

Variables	Antimicrobials appropriateness (N=17)	Antimicrobials inappropriateness (N=30)	p-value
Age in years (mean±standard deviation)	39.4±16.2	46.3±14.9	0.144
Comorbidities	7 (41.2)	19 (63.3)	0.142
Diabetes mellitus	1 (5.9)	4 (13.3)	0.640
Hypertension	1 (5.9)	7 (23.3)	0.228
Dyslipidemia	2 (11.8)	8 (26.7)	0.289
Chronic lung disease	0 (0.0)	1 (3.3)	1.000
Cardiovascular disease	0 (0.0)	1 (3.3)	1.000
Obesity (body mass index ≥25 kg/m^2)	2 (11.8)	9/29 (31.0)	0.172
Others	6 (31.6)	10 (33.3)	0.892
Symptoms and signs			
Dysuria	13 (76.5)	24 (80.0)	1.000
Frequency	11 (64.7)	10 (33.3)	0.038
Urgency	2 (11.8)	2 (6.7)	0.613
Suprapubic pain	13 (76.5)	18 (60.0)	0.343
Hematuria	5 (29.4)	5 (16.7)	0.460
Suprapubic tenderness	12 (70.6)	14 (46.7)	0.113
Laboratory findings			
Urinalysis			
Pyuria (urine white blood cells >10 cells/high-power field)	10 (58.8)	12 (41.4)	0.253
Positive nitrite	1 (5.9)	4 (13.3)	0.637
Positive leukocyte esterase	17 (100)	24/29 (82.3)	0.142
Urine gram stain found bacteria	12/17 (70.6)	12/16 (75.0)	1.000
Urine culture found bacteria	12 (70.6)	18 (60.0)	0.468
Uropathogens			
Escherichia coli	7 (58.3)	15 (83.3)	0.560
Staphylococcus saprophyticus	2 (16.7)	2 (11.1)	0.613
Klebsiella pneumoniae	1 (8.3)	0 (0.0)	0.362
Enterococcus faecalis	1 (8.3)	0 (0.0)	0.362
Antimicrobial prescription			
Norfloxacin	0 (0.0)	4 (13.3)	0.281
Ofloxacin	0 (0.0)	4 (13.3)	0.281
Ciprofloxacin	0 (0.0)	18 (60.0)	<0.001
Amoxicillin/clavulanate	6 (35.3)	3 (10.0)	0.054
Amoxicillin	0 (0.0)	1 (3.6)	1.000
Cefixime	8 (47.1)	0 (0.0)	<0.001
Fosfomycin	3 (17.6)	0 (0.0)	0.042
Being in the post intervention period	17 (100)	2 (6.7)	<0.001

Data are presented in numbers (%) unless otherwise specified

Concordant antimicrobial therapy increased significantly from 25% in pre-intervention to 83.3% in post-intervention (p-value=0.002). Despite improved prescribing practices, treatment failure rates remained low and comparable between the 2 periods (7.1% vs 5.3%, p-value=1.000), reflecting the generally mild nature of AUC.

Antimicrobial appropriateness improved significantly after AMS implementation, increasing from 0% in the pre-intervention period to 89.5% in the post-intervention period (p-value<0.001). Improvements were observed in appropriate drug choice (7.1% vs 94.7%), dosing (32.1% vs 94.7%), and duration of therapy (14.3% vs 94.7%) (Table 2). Ciprofloxacin prescriptions were associated with inappropriateness due to discordance with the in vitro susceptibility results, higher than recommended dose, and longer than recommended treatment duration, as shown in Table 3. Multivariate analysis was planned to identify factors associated with antimicrobial appropriateness. However, due to zero counts in some variables, analysis could not be performed.

Discussion

This study demonstrated that AMS implementation significantly improved antimicrobial appropriateness in AUC treatment. Ciprofloxacin prescriptions decreased, while cefixime and amoxicillin/clavulanate use increased. These findings align with prior studies showing AMS-driven improvements in prescribing patterns, although differences in AMS components and outcome measures may influence the magnitude of effect[14,15]. In this study, appropriateness improved from 0% to 89.5%, largely due to reduced fluoroquinolone use, which had previously been associated with inappropriate dose and duration.

Drug susceptibility data are crucial for guideline development. Improved concordance between empirical treatment and pathogen susceptibility was observed, increasing from 25.0% to 85.0% in this study and from 74.0% to 89.0% in a study by Percival et al.[17]. However, when pre-AMS concordance is already high, improvements may be less pronounced[18]. The susceptibility of *E. coli* to ciprofloxacin in this study (68.0%) was higher than in prior reports from Siriraj Hospital, Bangkok (56.0% in 2017)[19] and NARST (32.0% in 2019)[10]. These differences may be explained by the sources and settings of urine specimen collection. The Siriraj study focused on community-acquired UTIs, including upper urinary tract infections[19]. Whereas, the NARST study analyzed a broader, more heterogeneous sample from 92 hospitals nationwide, likely including both community- and healthcare-associated UTIs[10]. This broader sampling may reflect higher antimicrobial resistance due to greater healthcare exposure, prior antibiotic use, and more complex patient populations.

Before the intervention, fluoroquinolones, including norfloxacin, ofloxacin, and ciprofloxacin, were commonly prescribed. Notably, ciprofloxacin was often used at higher than recommended doses and for extended durations, consistent with findings from other studies[2,3]. Post-intervention, nitrofurantoin and fosfomycin were designated first-line treatments, with amoxicillin/clavulanate and cefixime as alternatives. AMS implementation significantly reduced ciprofloxacin use, consistent with other AMS studies[20-22]. Despite guideline recommendations[2,3], nitrofurantoin and fosfomycin were underutilized in this study due to supply shortages for nitrofurantoin and cost constraints for fosfomycin, leading to increased reliance on beta-lactams.

In this study, treatment failure rates remained unchanged between periods, likely due to the mild nature of AUC, which often resolves spontaneously[23]. Similar findings have been reported in other AMS studies[15,20,22].

This study had several limitations. Due to COVID-related reductions in outpatient visits, the sample size was small, which may have limited the power to detect differences in treatment outcomes. Extending the study period might have helped recruit more patients. However, the power to detect improvements in antimicrobial appropriateness, which is the primary outcome, increased from 0% to 89.5%, which approached 100%. Given these results, we had sufficient evidence to guide improvements in antimicrobial use for AUC patients and therefore decided not to extend the data collection period. Second, due to the retrospective nature of the study, relying on chart reviews and International Classification of Diseases, 10th Revision (ICD-10) codes may have missed some patients with AUC, introducing potential selection bias. Third, as a single-center study, the findings may have limited generalizability.

Key takeaways from this study include the unnecessary prescribing of ciprofloxacin for AUC, despite available alternatives. One-third of *E. coli* isolates were ciprofloxacin-resistant, suggesting possible community spread of resistant strains. Ensuring access to first-line agents like nitrofurantoin and fosfomycin could reduce reliance on cephalosporins. Additionally, as urine cultures are not routinely collected for AUC treatment, systematic urine cultures in AUC cases would help track resistant trends and inform guideline updates.

Conclusion

The implementation of AMS significantly improved antimicrobial appropriateness and concordant therapy for AUC. Expanding access to first-line agents like nitrofurantoin and fosfomycin may further enhance outcomes. Sustaining these improvements requires regularly updated local susceptibility data, prompt feedback on prescribing, and regular provider training.

Ethical considerations

This study complied with the Declaration of Helsinki and was exempted from ethical review by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, due to its retrospective data collection from medical records (Exemption No. 8947/2022).

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Conflict of interest

The authors have no conflicts of interest to report.

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