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Optimizing Antibiotic Use for Urinary Tract Infections: A Qualitative Assessment of Regular Prescribing Practices

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Purpose: Optimizing antibiotic use is essential for overcoming antibiotic resistance. In this study, we identified strategies for improving antibiotic use for urinary tract infections (UTIs).
Materials and Methods: This retrospective study was conducted between July 2022 and June 2023 to evaluate the effect of quarterly qualitative assessments of antibiotic prescriptions for inpatients with UTIs. Appropriateness was evaluated based on antibiotic selection, dosage, administration route, and duration, and feedback was shared with medical staff to enhance prescription practices. Evaluations were performed at 3-month intervals, with the first quarter as baseline. Changes in appropriateness were analyzed using linear regression.
Results: Overall, 1473 antibiotic prescriptions from 638 patients were analyzed. Third-generation cephalosporins were the most prescribed class. For lower UTIs, significant improvements were observed in treatment duration (40.8%, p=0.050), administration route (22.9%, p=0.039), and dosage (10.5%, p<0.001), thereby increasing the proportion of appropriate prescriptions from 28.6% to 68.0% (p=0.010). For upper UTIs, significant improvements were observed in dosage (6.7%, p=0.032) and duration (20.2%, p=0.032), with the proportion of appropriate prescriptions increasing from 55.9% to 79.0% (p=0.043). Overall, qualitative assessments and feedback improved prescribing appropriateness from 47.1% to 75.5% (p=0.013) without adverse effects on mortality or length of stay.
Conclusion: Regular qualitative assessments of antibiotic prescriptions significantly improved prescriptions for UTIs without negative outcomes. These findings support the role of qualitative assessments in antibiotic stewardship; however, further studies are required to evaluate their long-term impact and broader applicability.

Key Words: Antibiotic stewardship, antibiotic prescribing, healthcare intervention, prescription appropriateness, qualitative assessment, urinary tract infections

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INTRODUCTION

Over the past few decades, antibiotics have saved numerous lives by effectively treating various infections. However, the misuse and overuse of antibiotics have accelerated the emergence of antibiotic-resistant bacteria.[1,2] The global burden of antibiotic-resistant infections is gradually increasing each year, affecting millions of people worldwide. One report estimated that deaths attributable to antibiotic resistance could reach 10 million annually by 2050. Furthermore, few new antibiotics have been developed to combat antibiotic-resistant bacteria since the 1980s.[3-5] Antibiotic resistance is also a serious concern in South Korea.[6,7] The number of carbapenem-resistant *Enterobacterales* infections was 38405 in 2023, which is more than three times the number in 2018.[8] The annual socioeconomic cost of multidrug-resistant bacteremia was $294.5 million in 2017.[9]

The antibiotic stewardship program (ASP) is a set of coordinated actions designed to optimize antibiotic use and address the current public health threat of antibiotic resistance. ASPs are associated with significant reductions in resistance rates to major pathogens.[10-14] While many hospitals focus on controlling antibiotic consumption as part of their ASPs,[15-17] this approach may not fully address the complexity of antibiotic resistance. Incorporating qualitative assessments of antibiotic prescriptions can enhance the effectiveness of ASPs by identifying inappropriate prescriptions that may not be captured by monitoring antibiotic consumption alone. Such assessments provide physicians with tailored feedback, offering opportunities to improve antibiotic prescribing practices.[18]

In this study, we evaluated improvements in antibiotic appropriateness for UTIs by conducting qualitative assessments of antibiotic prescriptions for inpatients with urinary tract infections (UTIs).

MATERIALS AND METHODS

Study design and setting

This retrospective study was conducted at a university-affiliated hospital in South Korea. Throughout the study period, the hospital continued to implement the institutional ASP established prior to the study, along with the new ASP intervention introduced in this study. Three infectious disease specialists work at the hospital, all of whom participate in the ASP. The hospital maintains institutional guidelines exclusively for the prophylactic use of antibiotics to prevent surgical site infections. The ASP primarily operates through the pre-authorization of antibiotics classified as restricted. Data on antibiotic consumption are collected and reported to the ASP committee biannually. Additional details of the ASP are summarized in Supplementary Table 1 (only online).

Between July 2022 and June 2023, the hospital's ASP team conducted a qualitative assessment of antibiotic use in inpatients with UTIs to improve prescribing practices. All inpatients with positive urine culture results during the study period were consecutively reviewed for eligibility. Patients were excluded if they met any of the following criteria: age <16 years, isolation of three or more bacterial species in urine culture, presence of infections other than UTIs, candiduria, lack of documented symptoms or signs of UTIs, or asymptomatic bacteriuria. Lower UTI was defined as the presence of one or more of the following features: urinary frequency, urgency, dysuria, suprapubic pain, or gross hematuria. Upper UTI was defined as the presence of upper UTI findings on imaging tests or one or more of the following symptoms or signs that cannot be explained by other causes: fever, flank pain, or costovertebral angle tenderness.[19] Acute prostatitis was classified as an upper UTI, considering clinical characteristics of the disease. Each patient was included in the study only once; subsequent UTI episodes occurring in the same patient during the study period were excluded. Patients aged ≥16 years were considered adults at the study hospital, as adolescents of this age often exhibit clinical UTI features similar to those of adults. The study population was selected based on this age cut-off.

The Institutional Review Board of the Yonsei University Health System Clinical Trial Center approved this study (Approval no. 9-2023-0127). Owing to the retrospective nature of this study, patient consent was waived.

Qualitative assessment of antibiotics prescribed for UTIs

The qualitative assessment evaluated the appropriateness of antibiotic selection, dosage, administration route, and duration in patients with UTIs, using previously established criteria (Supplementary Table 2, only online).[20] Antibiotic selection was assessed by categorizing antibiotics as empirical or definitive. The selection was considered appropriate if the chosen antibiotic aligned with the recommendations in the national[21] and institutional guidelines (Supplementary Table 3, only online), was adjusted based on antibiotic susceptibility test results, and had not previously caused allergic reactions in the patient. Antibiotic dosage was considered appropriate if prescribed according to guidelines and adjusted based on the patient's renal function.

The administration route of antibiotics was considered appropriate when administered via the routes recommended in the guidelines. Injectable antibiotics were considered appropriate for patients with lower UTIs who could not take oral medications or had intestinal absorption issues. However, injectable antibiotics were considered inappropriate for patients with lower UTIs who had no issues with oral medication absorption. Antibiotic duration was evaluated based on guideline-recommended periods (3–7 days and 7–14 days for lower and upper UTIs, respectively). For cases requiring an extended treatment period (e.g., renal abscess or prostatitis) or where specific reasons for extension were documented, the researchers (JES and YCK) determined the appropriate treatment duration. Ultimately, if all prescribed antibiotics were deemed appropriate for selection, dosage, route of administration, and duration, the patient was considered to have received appropriate antibiotic treatment for the UTI.

Intervention

A qualitative assessment was conducted quarterly, during the month following the 3-month data collection period, for patients with positive urine culture results. For example, data on patients with positive urine cultures between July and September were assessed in October. The qualitative assessment results were reported to the hospital leadership within 1 week of completing the evaluation. Subsequently, the results were categorized by clinical department and shared with the relevant medical staff via email. In summary, the baseline period was from July to September 2022, the intervention was introduced in October 2022, and the post-intervention period spanned from October 2022 to June 2023.

The emails included a summary of findings and department-specific recommendations. This strategy aimed to improve antibiotic use for UTIs in each clinical department, which commenced mid-quarter (Supplementary Fig. 1, only online).

Statistical analysis

Baseline characteristics are presented as mean±standard deviation and numerical values (%) for continuous and categorical variables, respectively. Analysis of variance and Pearson's chi-square tests were used to compare the clinical characteristics across the study period. Antibiotic prescriptions were qualitatively assessed by UTI type at 3-month intervals, with the first quarter serving as the baseline. Changes in appropriateness over time were analyzed using linear regression, with each indicator as the dependent variable and the quarter as the independent variable. In addition, we evaluated temporal trends in appropriateness across clinical departments using the same linear regression method. To evaluate the effectiveness of the assessment, quarterly evaluations were conducted for the proportion of patients with appropriate antibiotic use, antibiotic duration, hospital stay length, and mortality. Linear regression analysis was used to determine the temporal trends. Statistical significance was set at $p<0.05$. All statistical analyses were performed using R V.4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical characteristics of patients

A total of 1734 patients with positive urine culture results were eligible for this study. Of these, 1096 were excluded based on the exclusion criteria, and 638 (193 with lower UTIs and 445 with upper UTIs) were included in the qualitative assessment (Fig. 1).

Patient characteristics are described in Table 1. The mean age of the patients was 64.06 years, and 79.2% of the patients were female. The number of patients with a Charlson comorbidity score ≥3 was 178 (27.9%). The quick sequential organ failure assessment score was 0.76±0.99, and the rate of intensive care unit admission was 3.4%. The most common reason for performing urine culture tests was the presence of urinary symptoms, followed by fever and gross hematuria. *Escherichia coli* was the most frequently identified organism. The proportion of patients with concomitant bacteremia and UTIs was 10.3% (n=66).

The clinical characteristics of the patients were compared across periods following qualitative assessment and are presented in Supplementary Table 4 (only online). No significant temporal differences were observed in patient demographics, comorbidities, disease severity, reasons for urine culture, causative pathogens, or types of UTIs, except for gross hematuria as a reason for urine culture.

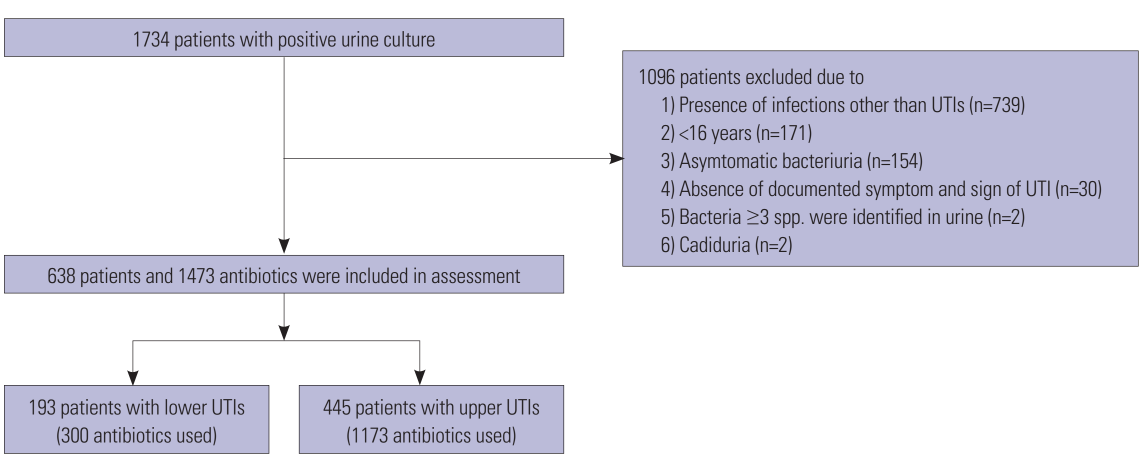

Fig. 1. Study flowchart. UTI, urinary tract infection.

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Antibiotic prescriptions in UTIs

A total of 1473 antibiotics were prescribed to 638 patients with UTIs, including 300 antibiotics to 193 patients with lower UTIs and 1173 antibiotics to 445 patients with upper UTIs (Fig. 1). In patients with lower UTIs, third-generation cephalosporins were the most frequently prescribed antibiotic class, followed by fluoroquinolones, for both empirical and definitive treatments (Supplementary Fig. 2, only online). Similarly, third-generation cephalosporins were the most frequently prescribed antibiotic class for upper UTIs. Among antibiotics used for upper UTI treatments, β-lactam/β-lactamase inhibitors were the second most frequently used empirical antibiotic class, while fluoroquinolones were the second most used definitive antibiotic class.

Table 1. Characteristics of Patients with UTIs Included in the Qualitative Assessment of Antibiotic Use (n=638)

Variables	Value
Demographic data	
Age (yr)	64.06±57.25
Sex, female	505 (79.2)
BMI (kg/m²)	23.39±4.14
Charlson comorbidity score ≥3	178 (27.9)
qSOFA score	0.76±0.99
ICU admission	22 (3.4)
Reasons for urine culture	
Urinary symptoms	379 (59.4)
Fever	368 (57.7)
Unknown shock	40 (6.3)
Altered mental status	45 (7.1)
Pyuria identified in urine analysis	38 (6.0)
Gross hematuria	87 (13.6)
Species isolated urine culture	
E. coli	491 (77.0)
K. pneumoniae	47 (7.4)
Enterococci	32 (5.0)
Proteus spp.	20 (3.1)
Citrobacter spp.	14 (2.2)
Other*	46 (7.2)
Concomitant bacteremia	66 (10.3)
Type of UTI†	
Lower	193 (30.3)
Upper	445 (69.7)

BMI, body mass index; qSOFA, quick sequential organ failure assessment; ICU, intensive care unit; UTI, urinary tract infection.
Data are presented as n (%) or mean±standard deviation.
*Other organisms include *Klebsiella* spp. (n=10, excluding *K. pneumoniae*), *Enterobacter* spp. (n=7), *Pseudomonas* spp. (n=7), *Providencia* spp. (n=7), *Serratia* spp. (n=6), *Acinetobacter* spp. (n=5), *Morganella* spp. (n=5), *Aerococcus urinae* (n=3), *Staphylococcus aureus* (n=2), *Streptococcus agalactiae* (n=2), and *Myroides injenensis* (n=1). A total of 55 isolates were identified from 46 patients, as multiple organisms were isolated from some patients; †Acute prostatitis was classified as an upper UTI.

Changes in the appropriateness of antibiotics prescribed for UTIs

The appropriateness of antibiotics prescribed for lower UTIs is described in Table 2. The baseline appropriateness rates for "antibiotic selection, empirical," "antibiotic selection, definite," "antibiotic dose," "route of administration," and "duration of antibiotic use" were 98.5%, 75.9%, 83.5%, 70.1%, and 62.5%, respectively, between July and September 2022. During the study period, significant changes were observed in the appropriateness of the "antibiotic dosage" (a 10.5% increase; beta coefficient=2.93; p<0.001), "route of administration" (a 22.9% increase; beta coefficient=5.85; p=0.039), and "duration of antibiotic use" (a 40.8% increase; beta coefficient=8.61; p=0.050). The proportion of patients who received appropriate antibiotic prescriptions for lower UTIs increased from 28.6% to 68.0%, representing a 138.0% increase (beta coefficient=12.64; p=0.010).

Table 3 presents the appropriateness of antibiotic prescriptions for upper UTIs. Baseline appropriateness rates between July and September 2022 were 100%, 87.6%, 92.0%, 100%, and 72.9% for "antibiotic selection, empirical," "antibiotic selection, definite," "antibiotic dose," "route of administration," and "duration of antibiotic use," respectively. The greatest improvement was observed in the appropriateness of "duration of antibiotic use" (a 20.2% increase; beta coefficient=5.38; p=0.032), followed by "antibiotic dose" (a 6.7% increase; beta coefficient=2.23; p=0.032) during the study period. Overall, the proportion of patients who received appropriate antibiotic prescriptions for up-

Table 2. Qualitative Assessment of Antibiotic Prescriptions in Lower Urinary Tract Infections

	2022.07–2022.09	2022.10–2022.12	2023.01–2023.03	2023.04–2023.06	Beta coefficient	*p*
Appropriateness of antibiotic prescriptions						
Appropriate selection						
Empirical	67/68 (98.5)	56/56 (100)	54/56 (96.4)	50/50 (100)	0.08	0.936
Definite	22/29 (75.9)	14/17 (82.4)	7/9 (77.8)	12/15 (80.0)	0.78	0.639
Appropriate dosage	81/97 (83.5)	63/73 (86.3)	58/65 (89.2)	60/65 (92.3)	2.93	<0.001
Appropriate administration route	68/97 (70.1)	52/73 (71.2)	53/65 (81.5)	56/65 (86.2)	5.85	0.039
Appropriate duration	35/56 (62.5)	33/43 (76.7)	38/44 (86.4)	44/50 (88.0)	8.61	0.050
Appropriate antibiotic use per patient	16/56 (28.6)	18/43 (41.9)	22/44 (50.0)	34/50 (68.0)	12.64	0.010

Data are presented as number/total n (%). The appropriateness of each antibiotic was evaluated individually when multiple antibiotics were administered to a single patient. The appropriateness of treatment duration was assessed at the patient level, and the overall appropriateness for each patient was determined by combining the evaluations of individual antibiotics and treatment duration. The qualitative assessment intervention was initiated after the first quarter (2022.07–2022.09). The regression coefficient reflects the change per quarter.

per UTIs increased from 55.9% to 79.0%, reflecting a 41.3% increase (beta coefficient=8.52; *p*=0.043).

Fig. 2 illustrates temporal trends in the appropriateness of antibiotic prescriptions for UTIs at the individual patient level by clinical department. For lower UTIs, emergency medicine demonstrated a significant improvement in appropriateness, increasing from a baseline of 37.5% to 81.8% (a 118.2% increase; beta coefficient=14.49; *p*=0.034) (Supplementary Table 5, only online). For upper UTIs, significant improvements were observed in both internal medicine and emergency medicine. In internal medicine, appropriateness increased from 54.7% at baseline to 85.5% (a 56.2% increase; beta coefficient=11.27; *p*=0.036), while in emergency medicine, it rose from 17.6% to 80.0%, representing a 353.3% increase (beta coefficient=22.60; *p*=0.050).

Effects of qualitative assessment of antibiotics prescribed in UTIs

The proportion of patients who received appropriate antibiotic treatment for UTIs increased steadily from 47.1% between July and September 2022 to 75.5% between April and June 2023 (*p*=0.013) (Table 4). During the study period, no increase in

Table 3. Qualitative Assessment of Antibiotic Prescriptions in Upper Urinary Tract Infections

	2022.07–2022.09	2022.10–2022.12	2023.01–2023.03	2023.04–2023.06	Beta coefficient	*p*
Appropriateness of antibiotic prescription						
Appropriate selection						
Empirical	142/142 (100)	124/125 (99.2)	162/162 (100)	129/129 (100)	0.08	0.742
Definite	148/169 (87.6)	117/136 (86.0)	154/169 (91.1)	130/141 (92.2)	1.90	0.158
Appropriate dosage	286/311 (92.0)	245/261 (93.9)	323/331 (97.6)	265/270 (98.1)	2.23	0.032
Appropriate administration route	311/311 (100)	261/261 (100)	331/331 (100)	270/270 (100)	-	-
Appropriate duration	86/118 (72.9)	73/97 (75.3)	106/125 (84.8)	92/105 (87.6)	5.38	0.032
Appropriate antibiotic use, by each patient	66/118 (55.9)	56/97 (57.7)	92/125 (73.6)	83/105 (79.0)	8.52	0.043

Data are presented as number/total n (%). The appropriateness of each antibiotic was evaluated individually when multiple antibiotics were administered to a single patient. The appropriateness of treatment duration was assessed at the patient level, and the overall appropriateness for each patient was determined by combining the evaluations of individual antibiotics and treatment duration. The qualitative assessment intervention was initiated after the first quarter (2022.07–2022.09). The regression coefficient reflects the change per quarter.

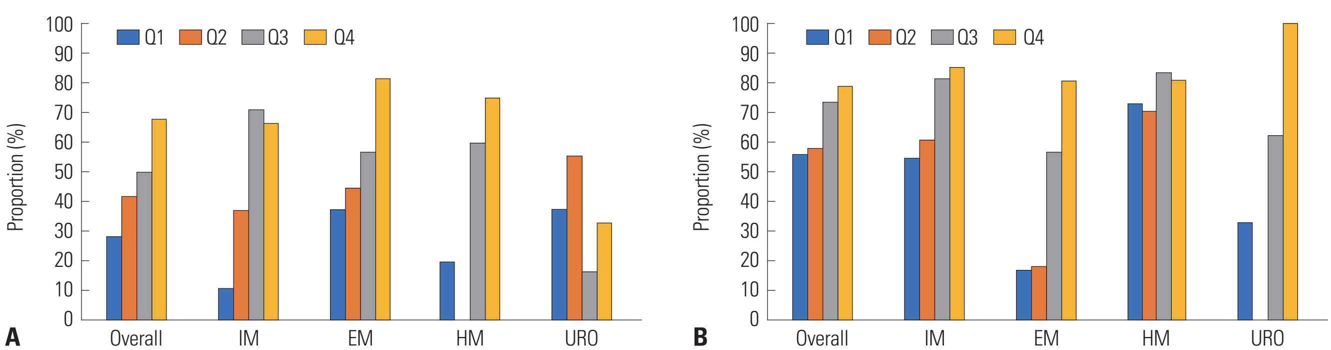

Fig. 2. Trends in individual patient-level antibiotic appropriateness for (A) lower and (B) upper UTIs across clinical departments. UTI, urinary tract infection; IM, internal medicine; EM, emergency medicine; HM, hospital medicine; URO, urology.

Table 4. Effects of Qualitative Assessment of Antibiotics Prescribed in UTIs

	Proportion of patients who received appropriate antibiotic treatment for UTIs (%)	Duration of antibiotic use (DoT/1000 patient-days)	Length of hospital stay (days)	Mortality n (%)
Time period				
2022.07–2022.09	47.1	52.6	15.59±16.61	4 (2.3)
2022.10–2022.12	52.9	41.4	10.45±9.86	3 (2.1)
2023.01–2023.03	67.5	47.0	11.43±11.50	0 (0.0)
2023.04–2023.06	75.5	41.8	13.05±15.94	2 (1.3)
Regression coefficient	9.967	-2.699	-0.665	-0.516
p	0.013	0.341	0.618	0.366

UTI, urinary tract infection; DoT, days of therapy.
Standard deviation is not applicable for DoT, as this variable is expressed as a rate per 1000 patient-days rather than as a patient-level measurement. The qualitative assessment intervention was initiated after the first quarter (2022.07–2022.09). The regression coefficient reflects the change per quarter.

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mortality or length of stay was observed. Additionally, the analysis of antibiotic consumption for UTIs over time showed a decreasing trend (regression coefficient: -2.699); however, this trend was not significant (p=0.341).

DISCUSSION

In this study, we demonstrated that regular qualitative assessments can significantly improve the appropriateness of antibiotic prescriptions for UTIs. Our intervention resulted in a steady increase in the use of appropriate antibiotics, without corresponding increases in mortality or length of hospital stay. Although antibiotic consumption for UTIs showed a decreasing trend over time, this trend was not significant.

Two primary approaches exist for evaluating antibiotic use: quantitative and qualitative assessments.[18] Quantitative assessments measure the amount of antibiotics used, and most ASP activities to date have focused on reducing antibiotic consumption. A qualitative assessment was used to evaluate the appropriateness of antibiotic prescriptions. Although some studies have conducted qualitative evaluations,[22-24] data on hospital ASP activity implementations based on such evaluations are lacking. Appropriate antibiotic use is crucial as it can reduce adverse drug events, mitigate the development of antibiotic resistance, and ultimately improve patient outcomes.[25-27] Therefore, developing a sustainable and effective strategy for the qualitative assessment of antibiotic prescriptions, tailored to the specific circumstances of each medical institution, is essential. Our results would provide valuable insights into the implementation of qualitative evaluations and ASP activities in healthcare settings.

Currently, no standard exists for the qualitative assessment of antibiotic prescriptions. Therefore, evaluation methods can vary depending on the target disease or type of antibiotic used. We chose UTIs as the target disease for qualitative antibiotic prescription assessment as they are a prevalent and significant health concern worldwide.[22,23,28] Additionally, inappropriate prescriptions of antibiotics are frequently observed in UTIs, with up to 40% of patients with UTIs known to receive unnecessary broad-spectrum antibiotic prescriptions.[29] To determine the appropriateness of antibiotic use for UTIs, we modified the criteria and definitions developed in a previous study.[20] Moreover, we aimed to identify a method for improving antibiotic use through qualitative assessment. The major advantage of our approach is that it provides prescribers with autonomy over their prescriptions, which effectively encourages their participation in antibiotic stewardship while reducing conflicts.

Patients admitted to the hospital or visiting the emergency department with lower UTIs are frequently treated with intravenous (IV) antibiotics, despite guidelines recommending oral antibiotics.[21,30] Our study also revealed that IV antibiotics were frequently used inappropriately in patients with lower UTIs during the initial evaluation, particularly in the emergency department, without justifiable reasons. UTIs can be effectively treated using oral antibiotics, even in severe cases, as studies have shown no difference in outcomes compared to that of injectable therapy.[31] Moreover, oral antibiotic use can help minimize hospital stays, lower healthcare costs, and reduce the risk of complications associated with IV therapy.[26,32,33] To decrease the prescription rate of IV antibiotics for lower UTIs, we emphasized the effectiveness and safety of oral antibiotics in messages sent to emergency departments. Consequently, the inappropriate antibiotic administration route for lower UTIs was significantly improved.

The appropriateness rates for all individual criteria were higher for upper UTIs than for lower UTIs; however, the overall appropriateness at the patient level was not as high. Accordingly, we decided to send repeated messages to clinicians after the initial evaluation to remind them of the comprehensive treatment principles for upper UTIs. We ensured that prescribers adhered to the appropriate duration of antibiotic use. Current guidelines recommend a treatment duration of 7–14 days for upper UTIs.[21,30] Furthermore, several studies have shown that a shorter treatment duration is effective.[34,35] Despite this evidence, clinicians believe that prolonged antibiotic treatment is warranted for patients with UTIs who experience recurrence. However, extended antibiotic use can often alter the microbiome in the gut and urine, which can ultimately lead to subsequent infections caused by drug-resistant bacteria and *Clostridioides difficile*.[36] Treating UTIs with effective antibiotics for an appropriate duration is important as it not only resolves the current infection but also reduces the risk of future challenges in treatment.[35] Although we did not demonstrate significant changes in the appropriate duration, the duration of antibiotic use decreased from 52.6 to 41.8 days of therapy per 1000 patient-days.

This study had some limitations. First, the 1-year observation period may have been insufficient to capture the long-term effects of our intervention. Notably, there was a trend toward reduced antibiotic duration and length of hospital stay after the intervention; however, these reductions did not reach statistical significance. Further investigations with a longer observation period are warranted to confirm the durability and significance of these effects. Second, the retrospective study design introduced the possibility of selection bias. Additionally, potential confounders may influence antibiotic prescriptions. However, there were no changes in hospital policies during the study period that could have affected the study results. Third, this study was conducted at a single center, which limits the generalizability of the findings to other populations and treatment settings. These results may vary when applied to other institutions, as differences in patient populations, healthcare practices, and ASPs could influence the outcomes. We are currently conducting a multicenter study to validate these findings and enhance their generalizability. Fourth, this study did not evaluate *Clostridioides difficile* infection rates or the occurrence of multidrug-resistant organisms as outcomes. Finally, the definition of an upper UTI included nonspecific symptoms (e.g., fever and shock), which led to the inclusion of a substantial number of patients with such symptoms. Therefore, the findings should be interpreted with caution. However, we only included cases in which an attending physician diagnosed a UTI, initiated antibiotic treatment, and the clinical documentation met predefined criteria. Throughout the study period, we consistently applied these criteria to minimize bias related to diagnosis.

In conclusion, we demonstrated that regular qualitative assessments can effectively improve the appropriateness of antibiotic use for UTIs. Although our findings highlight the potential of qualitative evaluations in antibiotic stewardship, further research is warranted to confirm the long-term and generalizable impact of such interventions.

DATA SHARING STATEMENT

The datasets used for the current study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization: Yong Chan Kim. Data curation: Hyo Won Park and I Ji Yun. Formal analysis: Seok-Jae Heo. Funding acquisition: Yong Chan Kim. Investigation: Seok-Jae Heo. Methodology: Yong Chan Kim and Yongseop Lee. Supervision: Yee Gyung Kwak and Yong Chan Kim. Visualization: Seok-Jae Heo. Writing—original draft: Yong Chan Kim and Yongseop Lee. Writing—review & editing: Je Eun Song, Yongseop Lee, Jong Hoon Hyun, Yoon Soo Park, Bongyoung Kim, Yee Gyung Kwak, and Yong Chan Kim. Approval of final manuscript: all authors.

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